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GENERAL PATHOLOGY

OR

THE SCIENCE OF THE CAUSES, NATURE AND COURSE OF THE PATHOLOGICAL DISTURBANCES WHICH OCCUR IN THE LIVING SUBJECT

BY

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TRANSLATED FROM

THE NINTH REVISED GERMAN EDITION

BY

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AUTHOR'S PREFACE TO THE EIGHTH EDITION.

In making my preparations for the publication of an eighth edition of my "Treatise on Pathological Anatomy," I hesitated for a long time in regard to what method of revision I should adopt. During recent years a number of manuals of pathological anatomy have been published, and the authors of these seem to have laid stress upon the point that a text-book intended for the use of medical men should deal with the subject-matter in the most concise manner possible; they believed, evidently, that compendious treatises of this nature would tend to promote the study of pathological anatomy, and would at the same time render the student's task easier. I carefully examined a number of compends of pathological anatomy which had been written from this point of view, but they failed to convince me that this was the most useful manner of treating the subject. In the first place, it is not possible, within the limits of a small compend, to treat general pathology and pathological anatomy in a scientific manner. Then, in the next place, it is extremely difficult, owing to the richness of the material at our disposal, to avoid treating the subject in such a manner that the book, when completed, shall not present the characteristics of a mere catalogue of facts, which would scarcely convey to the reader's mind a clear conception of the processes that take place in the living body when it or any of its organs are diseased, and which, furthermore, would compel the beginner merely to commit to memory those things which, by the aid of his reasoning power, he should make a permanent and useful part of his medical knowledge.

It is possible that if a compend were gotten up in the form of a catechism, it might prove helpful to a certain number of students in acquiring a knowledge of the principles of general pathology and pathological anatomy. Nevertheless I am disposed to believe that the number of those who would derive satisfaction from such a catechism must indeed be small. General pathology and pathological anatomy should constitute the foundations of that knowledge which is to enable the practitioner of medicine to interpret correctly the symptoms of disease as they present themselves before him at the patient's bedside. It must be conceded, I think, that simply a knowledge of the definitions given to the technical terms commonly employed in describing different pathological processes that take place in the living body, or merely a superficial insight into the pathological processes which affect individual organs and tissues, can scarcely suffice to furnish the practitioner with the fundamental knowledge which he requires for the satisfactory study of clinical medicine. He might be able, it is true, when called to treat a patient who presented certain well-defined symptoms of disease—as, for example, those belonging to an inflammation of an important organ—to form an approximate idea of the nature of this disease, and at the same time he

would also probably take satisfaction in the thought that he had already been instructed in regard to the occurrence of this very malady in this particular organ. But he certainly would not be able to form a clear conception of the essential nature of the entire process, or to analyze all the little pathological features which are dependent upon the peculiar construction of the organ affected; in a word, he would not be able to interpret, in its full breadth and depth, the significance of the disease under observation. In his endeavors to understand each new type of disease he would, by reason of his lack of a proper training in the fundamental principles of medicine, find his pathway constantly strewed with difficulties, and he would be forced in a slow and plodding fashion to commit to memory the sequence of symptoms as they occur in any given disease. Then, besides, he would fail to grasp the connection between the latter and other correlated symptoms. On the other hand, if he had previously received proper instruction in the fundamental knowledge required, he would at once be able to understand correctly the nature of the malady which he has been called to treat.

Bearing all these things in mind, I felt as if it were perfectly clear what my aim ought to be in preparing this new edition of my "Treatise on Pathological Anatomy." In the first place, it seemed to me that I should strive to perfect the knowledge of the mode of origin, nature, and significance of diseases as they occur in the living body, and consequently that I should make such improvements and alterations in the text as would carry out this idea. As a matter of course, in making this revision I did not forget for a moment that descriptions of histological and pathologico-anatomical alterations must continue to form the foundation-work of the book. Knowing, also, from experience how greatly good illustrations aid the reader in understanding the nature of these alterations, it seemed to me that I ought to provide a certain number of additional cuts, carefully prepared. At the same time I felt as if more space than was given to these matters in the preceding editions should be allotted to the consideration of pathological processes—their causes, their mode of origin, the course which they pursue, and their sequelæ.

In performing the task which I had thus set before me I found that extensive alterations were necessary, especially in that part of the work which treats of general pathology. On the one hand I found it necessary either greatly to alter or actually to rewrite certain chapters, while on the other I was obliged even to introduce entirely new chapters. In remodelling this general portion of the work special consideration has been given to the subjects of general etiology of diseases and pathological physiology, and in harmony with these alterations it has seemed to me advisable to change also the title of this general part. Accordingly I have abandoned the former title, "General Pathological Anatomy," and have substituted for it that of "General Pathology." The present work, it is true, does not cover the entire field of general pathology, but nevertheless it does treat of all those portions of the subject which are ordinarily taught, at least in the German universities, by the chairs of pathological anatomy and general pathology.

The section which deals with the causes, mode of origin, and course of diseases has, with the exception of a few pages, been entirely rewritten and greatly amplified; and I have gone more thoroughly in the present edition than I did in the earlier ones into the subject of the origin of diseases from poisoning and from infection, hoping thereby to provide

the beginner with a thoroughly clear and simple description of the pathological changes which take place in these diseases. Furthermore, I have given full consideration to the subject of the dissemination of pathological foci throughout the body by means of the processes known as metastasis and embolism, by means of poisoning, or by means of the extinction of certain glandular functions; and at the same time I have explained the relations of these foci to pathologically altered functions. Among the diseases which owe their origin to the extinction or modification of certain glandular functions I have given careful consideration to diabetes mellitus, to the cachexia which results from a withdrawal of the influence exerted by the thyroid gland upon the economy, to myxœdema, to cretinism, and to Addison's disease.

I have introduced special chapters on the protective mechanisms and forces, and on the healing powers of the human body; on certain inherited and acquired weaknesses or predispositions; on idiosyncrasy and immunity; and on the acquisition of immunity through the fact of one's having already experienced an attack of the disease, or through inoculation; and it is my hope that these chapters will not only supply the practical needs of the medical practitioner, but will also serve to increase the existing stock of knowledge in regard to the origin, course, and essential nature of diseases, and particularly of those which are due to infection and poisoning.

The chapter on the causes of internal diseases and on the inheritance of certain pathological conditions will, I think, be found to supply not only a clearer bird's-eye view of the subject, but also at the same time more complete information than did the same chapter in the earlier editions.

The section relating to disturbances of the circulation remains unchanged in its general features, but it has in many respects been made more complete than it formerly was; and, besides, it has been furnished with new illustrations.

In the section relating to retrograde disturbances of nutrition and infiltrations of the tissues, the chapter devoted to hypoplasia, agenesia, and atrophy and that relating to pigment-formation are the ones which have been remodelled to the greatest extent. In the section devoted to hypertrophy and regeneration I have introduced all the alterations and additions which the investigations of recent years in regard to these processes rendered necessary.

The section on inflammation has been entirely rewritten, and the definition which I now give of this process is the same as that which I suggested two years ago and published in pamphlet form. I am well aware that my views in regard to the nature of inflammation will not be generally accepted, and yet I cannot help hoping that, in giving this new explanation of pathological changes which have received such varied interpretation at the hands of different authorities, I may have succeeded in furnishing satisfactory proof that, on the basis of the views here set forth, all the different processes which play a part in inflammation may be arranged in comprehensive groups; and, furthermore, that the separation of the reparative processes of proliferation from those which belong more strictly to inflammation—which latter are characterized by a degeneration of the tissues, coupled with an exudation of pathological fluid products—is in harmony with the practical needs of the physician as well as with the unprejudiced requirements of science. In describing the healing processes which take place in the course of an inflammation,

the formation of granulations, the resorption of necrosed tissues and exudations, and the substitution in their place first of granulation tissue and then of cicatricial tissue, I have striven by the aid of numerous pictorial illustrations to make it easier for the student to understand these important processes, and at the same time I have endeavored to manage my descriptive text in such a way that it should throw light upon those diseases which are most commonly encountered in actual medical practice.

The sections which relate to tumors and malformations remain fundamentally the same as they were in the previous edition, and yet in both of these sections I have rewritten the portions which refer to the general aspects of these subjects, and at the same time I have altered, improved, and amplified many of the remaining paragraphs in these sections; this statement being particularly true of the paragraphs relating to cystomata, teratomata, and transposition of tissues.

In the section devoted to parasites I have given due weight to the results of recent investigations, at least so far as they seemed to me to be thoroughly established. I have treated the infectious granulation tumors as heretofore in the section devoted to parasitic diseases, for it would scarcely be possible to acquire a complete understanding of their nature and significance unless full account were taken of the relationship which exists between their peculiarities and the special nature of the exciting cause.

As a result of all these alterations and additions this general part of my text-book has increased in bulk; but, as I have already said, I believe that, owing to the wealth of material which must be treated in a text-book of general pathology, it would scarcely be possible to handle the subject more concisely unless important matters should be entirely omitted, and unless the idea of explaining fully the phenomena of disease in the living subject should be abandoned.

But, after all, the extent of the text which the beginner must actually study is less than one might at first suppose it to be, for the illustrations, which have been increased in number by the addition of seventy-two, and the text printed in small type occupy a good deal of space in the volume.

E. ZIEGLER.

FREIBURG IM BREISGAU, November, 1894.

AUTHOR'S PREFACE TO THE NINTH EDITION.

In the preparation of this new edition I have endeavored to take fully into account—so far, at least, as it is possible to do this within the compass of a text-book like the present one—the advances which have been made in general pathology and pathological anatomy during the last few years. At the same time I have been careful not materially to increase the bulk of the book. In order to accomplish these objects I have subjected all the chapters to a most careful revision, and wherever it seemed necessary, on account of some new light furnished by recent investigations, I have rewritten the text.

The number of the illustrations has been increased from four hundred and fifty-eight to five hundred and forty-four, in the hope that thereby the text may be rendered easier to understand. The most radical alterations will be found in Chapters IV. and VII., which have been entirely rewritten. I have arranged the different kinds of degenerations which lead to the formation of hyaline products in four groups (mucous degeneration not being included in this number): (1) The formation of colloid by epithelium and the epithelial hyaline concretions; (2) the pathological cornification of epithelium; (3) the amyloid degeneration of connective tissue and the amyloid concretions; (4) the hyaline degeneration of connective tissue and the hyaline products of connective-tissue cells. I believe that by means of this classification it will be possible to obtain a very good general idea of the different processes under consideration. In addition to the part which relates to the pathological formation of pigment I have written something in relation to the pathological absence of pigment.

I have divided the tumors into three large groups: tumors of the connective substances, epithelial tumors, and teratoid tumors and cysts; and I have subdivided the epithelial tumors into two lesser groups, in one of which the papillary epitheliomata, the adenomata, and the cystadenomata are to be placed, while in the other belong the carcinomata and the cystocarcinomata. My views in regard to the nature and origin of tumors are essentially the same now as they were when I wrote the last edition of this work; and I can find nothing in the criticisms of Lubarsch, Hansemann, and others which would lead me to alter them in any respect. Many new illustrations have been introduced in the chapter on this subject, and at the same time the descriptive text has been made to cover the ground more thoroughly than before. In these two ways, therefore, I believe that I have succeeded in presenting my views on tumors in a sufficiently clear manner. Ribbert's view, that the separation of individual cells, or groups of cells, from their physiological relationships constitutes the main cause of the development of a tumor, does not, as I have already often enough stated, commend itself to my judgment. I scarcely need to add that I am just as little able as are

others to state what is the original cause of the atypical growth of the tumor cells. The term "tumor," as is well known, comprises tissue-new growths which, so far as their origin is concerned, differ widely the one from the other; and equally numerous and various are the causes of this growth in the individual cases. In fact, more than one cause is competent to excite growth even in the malignant tumors which spread by a sort of infiltrative process. Then, again, the view that parasites cause the exuberant growth of the malignant tumors lacks as yet a solid foundation; and accordingly I have considered it wise to bring out this point in my definition of tumors. Finally, the disposition which still exists in certain quarters to classify the infectious granulation-growths among the tumors as infectious tumors, appears to me only to confuse the subject. This disposition, it must be remembered, first showed itself at a time when nothing was known in regard to the causes of these infectious granulation-growths.

The definition of inflammation which I gave in the last edition has been approved by some authorities and combated by others. The arguments brought forward by the latter do not appear to me to be valid, and accordingly I have not felt that I was called upon to modify my views. Indeed, a further study of the processes which take place in inflammation has rather strengthened me in the determination to maintain my former position; and I trust that the present revised version of this chapter on inflammation will also furnish satisfactory proof that the definition which I have given serves as an excellent standpoint from which one may view the different processes that form an essential part of inflammation. It was a source of great pleasure and satisfaction to me that, after the publication of the last edition, some of my highly esteemed colleagues notified me of their approval of this definition.

In my presentation of the doctrine of infection and of the efforts of the organism to antagonize the effects of such infection, I have been careful to consult the most recent publications on the subject, and I trust that no fact of importance has escaped my attention. In the chapter relating to bacteria I have retained the commonly accepted classification, and have introduced among them, as before—under the name of polymorphous bacilli, in the group of bacilli—those bacteria which, according to recent investigations, assume different forms as they advance in their development. To separate them from the group of bacilli would lead to a separation of pathological processes which stand closely related one to another, and consequently such a step would only render it more difficult to comprehend these processes.[1]

ERNST ZIEGLER.

FREIBURG IM BREISGAU, November, 1897.

[1] As already explained in an editorial note in the eighth edition, it has been decided to omit the bibliographical lists which are scattered throughout the original work. Their publication would require fully two hundred additional pages, and their value, to the great majority of English-speaking medical students, would be comparatively small. —*Editor's Note.*

LIST OF TRANSLATORS.

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CHAPTERS IX. and X.

Translated by Dr. B. Meade Bolton and Dr. Philip H. Hiss, Jr.

CHAPTER XI.

Translated by Dr. R. A. McDonnell.

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LIST OF ILLUSTRATIONS.

GENERAL PATHOLOGY.

CHAPTER I.

Introduction.—Health and Disease.—Problems of General Pathology and Pathological Anatomy.

§ 1. When the act of fecundation is completed, by the union of the spermatozoön with the germinal vesicle, there occur in the ovum a series of changes leading to the formation of a large number of cells, and finally to the production of an embryo, which, in the course of nine months [in the human species], reaches a definite stage of development, and is thereupon expelled from the maternal organism. When it is detached from the latter, its growth continues until completed after a series of years, the attainment of its physical maturity being followed by a long period of time in which the bodily weight remains approximately the same. After a number of years—the extent of time not going beyond a certain limit either in man or in the lower animals—the organism perishes.

In all Metazoa, in which the functions of the organism are allotted to certain cells and groups of cells, and in which, furthermore, the propagation of the species is dependent upon certain definite cells which are set loose from the maternal and paternal organisms, the parents invariably sink into death. For the maintenance of the species the individual has only this importance: it produces the germinal cells, and in the first stage of development harbors and nourishes them. Thus, if the offspring be freed from the maternal organs and be capable of existing without parental aid, the parents, if incapable of further production, have become superfluous for the maintenance of the species, and sooner or later cease to exist.

So long as the human organism lives, and is in a condition which we consider as one of **health**, its manifestations of life show a fixed character, and, within certain limits, are the same for all individuals. For example, the bodily temperature is nearly the same for all persons, and, notwithstanding the changes in the surrounding media, varies only to a slight degree. The number of heart-contractions in a minute is confined within certain limits, and, while differing somewhat according to age and sex, their frequency does not overstep certain boundary-lines for any length of time. The breathing is performed in a distinct rhythm. The ingestion of food, and its changes in the alimentary canal, are made up of a series of mechanical and chemical phenomena which are always repeated by the individual in the same way. The kidneys secrete a fluid which contains certain definite substances which are always of the same composition, and the chemical reactions going on in the body always

reproduce themselves in the same way. Again, the nervous system, central and peripheral, with its end-apparatus, acts in a certain manner, which differs very little in different individuals.

The condition of the organism which we designate as **disease** is principally characterized by the fact that some function or functions of the organism are no longer carried out in the way which, from the fact that it occurs in all human beings, is considered as normal. One therefore recognizes disease in the greater or less number of changes in the manifestations of life, and disease is nothing else than **a life the manifestations of which partly deviate from the normal.**

Nearly every function through which life manifests its relations to the external world—in the human organism, for instance, all the different and partly very complicated processes through which the organism accomplishes its nourishment, removes the products of nitrogenous metabolism from the tissues, and cares for the maintenance of the species—brings with itself also the manifestations of disease. The symptoms by which we determine that an individual is diseased are of a very manifold nature; thus it may happen that the functions of the organism are increased or diminished or destroyed, or they may in a greater or less degree deviate from the normal. It is, furthermore, very common, in a condition of illness, that at the same time not only one function, but many, may vary more or less from the normal, or even be entirely suspended. It is therefore necessary to have an extended experience, and it requires a thorough study, to enable us to recognize all the phenomena of disease and to diagnose correctly their meaning.

The **symptoms of disease** are partly **subjective** and partly **objective.** To the first group belong the feeling of uncomfortableness, debility, and sense of painful feeling in some particular part of the body or in numerous parts of the organism: dyspnœa, tightness of the chest, palpitation of the heart, loss of appetite, chills, fever, etc.—in short, a great number of phenomena which are referred partly to changes in single organs and tissues and partly to an ailing condition of the whole organism.

The objective symptoms, as well as the subjective, are partly local and partly general. The process of the digestion of food is often at fault; the contents of the bowel may be hurried along too rapidly, or may be retarded, or may not be discharged at all. The breathing is changed: at times slow, then hurried; at times shallow, then deep; over the lungs in these cases are not seldom heard abnormal sounds.

The heart-contractions are often quickened or slowed, strengthened or weakened, and often of an irregular nature; consequently the frequency and rhythm and quality of the pulse are changed. The sounds which are heard in the neighborhood of the heart may also be changed, or replaced or accompanied by new sounds. The urine often exhibits an abnormal appearance, and contains substances which are not normally found in it. In many forms of disease the sensitiveness of particular nerves is lowered; in others it is increased. In the muscles there is sometimes more or less paralysis; at other times involuntary contractions are present. In the central nervous system the greatest variety of disturbances of function may appear, determining conditions of excitation as well as those of depression or paralysis. Very often the bodily temperature, which normally rises and falls only within certain limits, is elevated, often very markedly, above the normal; and that condition which we designate as *fever* is mainly characterized by the increase of the proper warmth of the body.

The tissues of the body—that is, the cells and their derivatives, of which the tissues are composed—constitute the material substratum upon which the processes of a healthy life depend.

Diseased life is connected with the same material substratum, and what we consider as **its symptoms** are **the life manifestations of the tissues and of the organs of the human body.**

The function of a tissue is dependent upon the organization of its component parts. A kidney cannot perform any other function than the secretion of urine, and the constituents of the bile can be separated only by the liver-cells.

If the functions of any tissue manifest a change from the normal, it necessarily follows that **the organization of the tissue in question is changed.** Concerning the character of such changes experience alone gives an explanation, and experience has shown that in most cases these changes of the organization result in a *transformation of the physical make-up of the tissues*,—that organs which have functionated in a pathological manner are changed to a degree that often enables us to recognize by even macroscopical examination numerous deviations from the normal appearance.

The number of observations which have been made in relation to tissue-changes in conditions of disease is already very considerable; and especially have the improved optical appliances which the last decade has brought to our aid greatly increased our knowledge in regard to the anatomical changes of diseased organs. Since most forms of disease in man show definite changes in the organs, when we speak of disease we now usually think not only of a group of symptoms, but rather of *a group of anatomical changes;* our **conceptions of disease** have become materially **anatomical,** and we seek to know the character of a given disease by the investigation of the anatomical changes.

Still we are far from being able always to discern positively the corresponding changes of organization and structure of the tissue. Even in very severe and fatal diseases (as epilepsy, diabetes) there are times when no anatomical changes in any way commensurate with the phenomena observed during life can be proved; and numerous diseases are accompanied with functional disturbances, the seat of which we are unable to locate with any certainty.

Nevertheless we may fairly assume in these cases also that the disturbed function is grounded on changes of organization. That we do not know what these changes are has its foundation in this: either that we do not look for them in the right place, or else that our optical aids are not sufficiently powerful to bring them to light. And even when histological changes are present we are often unable to recognize their pathological nature, from the fact that our knowledge concerning the nuclei and cells of the various tissues is not so far advanced as to enable us to distinguish in all cases that which is normal from that which is pathological.

It is difficult to say whether there exist any *purely functional* (dynamic) *disturbances*, in which the tissues suffer neither physical nor chemical changes. Provisionally we accept this in all cases in which we cannot give any better information. An example of such disturbances is seen in the toxic action of nerve-poisons, concerning which we cannot say in what way they exert upon the nerve-cells and nerve-trunks a stimulant or a paralytic effect.

The **causes of sickness** may be **external** or **internal.** *The former are dependent on the numerous injurious influences exerted by the external*

surroundings, and can affect the organism as well in intra-uterine as in extra-uterine life. *The internal causes are the innate, springing from the embryonic alterations of the organization, or of any particular organ, or of several organs, and appearing either as spontaneous variations or as something inherited from progenitors.* If an organism is easily affected by a certain disease, we speak of it as being *predisposed* to that disease; if the reverse is true, we speak of it as being *immune*.

If a disease is entirely characterized by local symptoms, it is designated as a **local disease** or **disease of an organ**; when the organism appears diseased as a whole, one speaks of a **general disease**; should the morbid processes deviate for a long time from the normal, so that the whole organism seems to have become subject to essential changes, the condition is called a **constitutional disease.**

No definite separation, therefore, can be made between local and general diseases, for the reason that a disease may begin with local symptoms and, later on, lead to disturbances of the whole organism; conversely, a disease may begin with general phenomena, and disease of the organ follow.

These differences in the course of a disease depend mainly on the different ways in which the deleterious influences of the external world act. If by such means only the tissues of an organ are damaged, local diseases occur. If, on the contrary, at the outset, changes of the blood and the fluids of the system appear, by means of which the function and the organization of numerous tissues are changed; if fever appears, and the nervous system is also affected, then the picture of a general disease is produced. If, still further, one organ is more seriously damaged than another, so that consequent disturbances of function are markedly apparent, then it will be proper to speak of the general disease as being accompanied by the symptoms of a local disease.

If an organ is attacked with disease, a **generalization of the disease** may occur from the spreading of the noxious agent by continuity and contiguity; also by its being conveyed in the blood and the other fluids of the body—either producing general disease or setting up in other organs the same condition of disease that was found in the organ first attacked. And furthermore, the changes in the functions of an organ may produce functional changes in another organ, or even, as a sequence, an ailing condition of the entire body. For instance, a chronic disturbance of the secretion of the kidney may produce a change in heart-function, and, later, poisoning of the whole body, including the nervous system, by means of the harmful products of metabolism, now no longer capable of being discharged from the body in the ordinary manner.

In many general diseases which begin with general symptoms we must assume that there was a primary lesion, this, however, being so mild as to produce only slight and circumscribed disturbances of function, and consequently no symptoms capable of being recognized. For example, it is in the highest degree probable that, in an infectious disease beginning with general phenomena, the poison causing the disease multiplies somewhere in the body, and at this point causes local tissue-changes and functional disturbances. Consequently even in this class of diseases it may be said that the morbid process has a local starting-point or several local seats.

Strictly speaking, even the so-called general and constitutional diseases are not really such, inasmuch as the tissues of the organism are practically never all involved in a diseased condition. The disease has,

even in such cases, its local seats, but these are very numerous and are distributed over the greater portion of the body.

The **duration of disease** is very variable. A shock produced by a sudden fright, with the coexisting excitation of the vaso-motor nerves, is an instance of disease which may last but a few seconds. Tuberculosis, leprosy, and syphilis may give rise to sufferings lasting for years. Diseases characterized by a duration of a few weeks are called *acute*; those lasting for months or for a longer period are designated as *chronic*. Many diseases have a **typical course**—one which is repeated in every case without much variation; in others the course is markedly **irregular**. Some begin abruptly, others slowly.

The **termination of an illness** is either complete or incomplete **recovery**, or **death**. The first event is symptomatically marked by the return of the functions of the diseased organs little by little to their proper condition, until at last they do not deviate at all from the normal. In general diseases attended with fever the temperature sinks to the level of health, and the ailing condition of the body is transformed to one of well-being.

Ordinarily the return to health goes on without interruption, or at least without much deviation. Not infrequently, however, it happens that while the patient is convalescing the disease breaks out anew; in other words, there is a **relapse**.

The disappearance of the abnormal symptoms denotes a **restitution of the tissues**. The chemical processes of the body return to their normal state, the damage done to the cells is repaired, the dead cells being replaced by new ones of the same nature as the old, and the whole tissue is restored.

In many cases, after the disease has run its course, a complete restoration of the former condition of the tissues is produced. In severe sickness—that is, in severe tissue-lesions—complete anatomical restoration of the tissue is impossible; there will remain *defects* here and there, or *where a certain tissue is lost it may be replaced by another of a lower grade*. If in such cases, nevertheless, restoration of health ensues, so far as regards the functions, it is for the reason that the individual organs have a redundant amount of functionally capable tissue, so that the disappearance of a small group of cells is not appreciable. It therefore happens that, upon the destruction of certain parts, others do compensatory work, increase in size, and show a greater activity of functional power.

Thus there will be permanent disturbances of function only when the diseased organ has not enough healthy tissue to carry on the work and other organs are not capable of acting as a substitute for it, or as compensatory to it, or if the disease leaves such changes as to produce permanent disturbances of function in the same organ or in another organ having similar functional capacity.

We must regard it as an incomplete convalescence when, although the symptoms of the disease have disappeared, the harmful influence which caused the trouble is not destroyed, but remains in the body, with the possibility that sooner or later the disease will break out anew. Strictly speaking, we have not a cure, but only the **latency of the disease process**. This condition occurs most frequently in the chronic infectious diseases.

Upon the **occurrence of death** all functions of the organism cease.

The order in which the various organs of the body suspend and annul

their functions varies, in accordance with the nature of the disease. The death of the individual is absolutely determined when the functions of the heart and brain are definitively inoperative.

Through the victory of an organism over a disease the body not seldom becomes immune against the particular poison which caused the disease from which it has recovered. Often, however, on the contrary, the body, during the course of a disease, or during convalescence from it and after its disappearance, is *predisposed to certain other diseases.*

§ 2. The **scientific investigation of diseased life** may reach its conclusions from the symptoms of a disease, and practical medicine is markedly concerned in learning the meaning of morbid phenomena in each individual case observed by the physician. The exact investigation of pathological symptoms chiefly serves the purpose of determining the different forms of disease present in given cases, and of separating one disease from another; at the same time it should also furnish us with the power of penetrating into the origin of the different phenomena, and of determining their connection with the changes in the organs and tissues. So far as an investigation of disease symptoms at the sick-bed serves useful diagnostic and therapeutic purposes, it belongs to the domain of *practical medicine* and of *special pathology*, the object of which is to learn to know the phenomena, as well as the course and termination, of the individual diseases, and to find means of controlling them. If the investigation is mainly concerned in determining the nature and the origin of disease phenomena, without regard to their assignment to special forms of disease, it falls within the scope of **general pathology**, *which has for its object the acquisition of definite data concerning the nature and course of disease processes.*

Various authors, in seeking to define the field of general pathology, have sought its problems in different directions, and their arrangement of its proper constituent elements is not always confined within the same boundaries. If one faces the task without regard to its practical bearing on the subdivision of science (specialism), it inevitably follows that general pathology must be held to deal not only with the theory of the nature and the course of disease processes, but also with their causes; that it not only embraces that section of natural science which we call **pathological physiology**, but includes at the same time the **theory of the causes and nature of disease.**

As the morbid symptoms are neither more nor less than biological manifestations of pathologically changed tissues, so the **theory of the changes of the tissues in disease,** or **general pathological anatomy,** naturally falls into the domain of general pathology.

The great extent of the field embraced by general pathology, both in text-books and in the lecture courses, would make it appear reasonable that the limits of a course in general pathology should be narrowed, and that special portions of it should be relegated to the special departments to which they belong.

Notwithstanding that the theory of the symptoms of disease forms the largest portion of general pathology, it seems to be expedient to leave to special works, to lectures, and to preparatory instruction those facts which are perfected at the bedside and are readily capable of utilization for directly practical purposes.

General pathology must also undergo a further contraction in the field of the study of the causes of disease, because the latter are pur-

posely brought within the circle of consideration only so far as pathological changes are really caused through them, while the further and more extended relations to the outer world in which we find ourselves—relations which eventually can produce harmful influences upon our organism—are to be turned over to *hygiene*.

The main point of interest in general pathology lies indisputably in the **knowledge of the anatomical changes which are at the bottom of the disease processes.** But the studies in this domain do not need to be confined to the effort to ascertain the morphological characteristics of disease processes; they should rather penetrate into the questions of *how these processes are brought into existence and what is their nature.* A scientific treatment of pathological anatomy, therefore, leads necessarily also to the study of the **etiology** and the **genesis of the disease processes.** If by the study of etiology we are able to prove the cause and development of the changes induced by disease, then shall we also be able to gain an understanding of the phenomena of disease as they come under observation during life, and also at the same time to lay the foundations for an adequate knowledge of that part of general pathology which is designated by the term **pathological physiology.**

CHAPTER II.

Cause, Origin, and Course of Diseases.

I. Origin of Disease through External Pathological Influences.

1. *Origin of Diseases through Deficiency of Food and of Oxygen; by Fatigue; by Heat and Cold; by Changes of the Atmospheric Pressure; by Electrical and by Mechanical Influences.*

§ 3. From birth until death man is continually subject to the influences of the surrounding external world, some of which influences aid, while others hinder, the exercise of his functions.

As long as the human body is able to utilize its functions for the purpose of spontaneous changes of relation to the external world, and also to accommodate its functions to the external necessities of life, so long does it remain in health. If its contrivances of adjustment are no longer able to neutralize surrounding influences, and man can neither escape nor change the necessities of life, he falls into sickness or dies.

For its preservation the body requires first of all a certain amount of nutrient material, as well as a definite quantity of water and of oxygen; and while man is able to survive the loss of these agents for a short time, yet, beyond a certain degree and after a limited time, **insufficiency of oxygen, food, and water** must necessarily occasion sickness or death.

The **suppression or diminution of the supply of oxygen** to the tissues is an occurrence that can happen at all ages, and may be due either to a lack of oxygen in the surrounding medium, or to a hindrance in the transportation of the oxygen contained in the air to the lungs and the blood, or, finally, to an inability of the blood to take up the oxygen in sufficient quantity. Lack of oxygen can occur to the fœtus within the uterus, through the mother herself suffering from want of oxygen, or through premature separation of the placenta, or by means of disease changes in the placenta, or through compression of the cord, the gaseous interchange between the blood of the mother and that of the fœtus being thereby hindered. After birth an insufficient supply of oxygen can happen through hindrances occurring to the breathing-power of the lungs, or through the fact that the child itself is too weak sufficiently to expand the thorax, in order to introduce sufficient air, by means of the respiratory movements of the lungs.

If the supply of oxygen is stopped completely, either through any fluid—e.g., water—getting into the respiratory tract in place of air, or from the air-passages being closed, the individual thus affected dies in a short time from lack of oxygen, by "**choking**" or **suffocation.** If animals remain in a closed place for a certain length of time, death is found to occur as soon as the oxygen of the air reaches 2 or 3 per cent by volume, it being normally 20.8 per cent by volume (Cl. Bernard, P. Bert).

If the supply of oxygen is not entirely withdrawn, but only markedly diminished in amount—as may occur in carbon-dioxide poisoning, in which the firm combination of carbon-dioxide gas with the hæmoglobin prevents the taking up of the oxygen by the blood corpuscles—suffocation follows only after the lapse of several days. By the gradually increased shutting off of the supply of oxygen, and accumulation of carbon dioxide in the blood—as in cases of narrowing of the lumen of the larynx by inflammatory exudations and through compression of the windpipe from goitre—there occur breathlessness, cyanosis, cramps, and disturbances of consciousness, a condition which we call **asphyxia.**

If the supply of oxygen is diminished even in a small degree, but for a long time—a condition which may occur, for example, in a diminution of the blood-cells in oligocythæmia,—there will take place in the tissues of the organism degenerative processes which are characterized by an increase of the destruction of albumin, and by fatty changes in the organs, and may cause not only disease, but ultimately death.

If the body is **deprived of all nourishment and water,** then, as albumin and fat still continue to undergo decomposition, a rapid diminution in the body-weight occurs, and finally death ensues. According to Lehmann, Müller, Munk, Senator, and Zuntz, the total amount of oxidation does not go below the amount which would be observed in the same individual under favorable circumstances and when in a normal condition. There takes place a marked conversion of albumin into other products, as well as a decided loss of water. In animals death follows when about forty per cent of the body-weight has been lost, nearly half the deficiency being due to a diminution in the muscles.

Fat disappears the most rapidly, and may be reduced even to ninety-three per cent of the entire amount originally present. The diminution of substance takes place in the various parts of the organism according to the following order: liver, spleen, testicles, muscles, blood, alimentary tract, skin, kidneys, and lungs. The heart, the nervous system, and the bones show the least loss of weight, although the investigations of Lehmann, Müller, Munk, Senator, and Zuntz have shown that an absorption of the bony tissue takes place during starvation, and if water be ingested an increased amount of phosphoric acid and calcium is found to occur in the urine. In the blood the white corpuscles diminish rapidly in number (Luciani); the red blood-cells may, on the contrary, in a given quantity of blood, be increased. The organs of starved animals show, not only simple atrophy of the elementary tissues, but also in many places evidences of vascular engorgement, with here and there actual hemorrhages, areas of degeneration, and inflammatory alterations. These changes are particularly noticeable in the intestine, the liver, the kidneys, and the nervous system. As a rule, however, no very marked alterations can be demonstrated in the latter (Peri).

The fatal issue, in the case of absolute withdrawal of nourishment and water, occurs in man in from seven to twelve days; bodily exercise hastens the fatal termination. This period may be considerably extended if water is taken into the system; some individuals having lived, under these circumstances, for as long a period as thirty days, or sometimes longer, without perishing or even without the production of serious permanent effects upon their health. The introduction of water into the system produces an increase in the amount of nitrogen excreted by way of the urine.

Life can be maintained for a long time with insufficient nourishment;

there occurs, however, a certain diminution of body-weight, which may under certain circumstances lead to the most marked emaciation, and finally to death. The same thing happens when the composition of the food is unsuitable, and only a portion of the nutrient material is offered in sufficient quantity, so that the body is starved in albumin, or in fats, or in salts, or in water. Dogs deprived of all nitrogenous nourishment die in from thirty-one to thirty-four days (Magendie). If the nourishment is sufficient, but poor in albumin, there occur, after a certain length of time (in dogs after six weeks), loss of appetite and an unwillingness to take the proffered food, and digestion and assimilation in the animal are lessened (Munk). Especially is this the case if the nourishment is deprived of fat, while it holds to a lesser degree if the aliment is wanting in albumin and carbohydrates. Very likely this deficiency of absorption is chiefly dependent upon a diminution of the secretions of the digestive juices, this being especially noticeable in the bile. The excrement at last is found to be nearly without bile.

If, for experimental purposes, an animal is **deprived of all water,** while continuing to receive an ample supply of food, it will lose enormously in weight and will die in from eight to twelve days. The lesions found in the different organs will be essentially the same as those observed in cases of death from starvation. These alterations are to be attributed partly to the lack of water, partly to the insufficiency of the food taken up by the tissues, and partly to the retention of the harmful products of metabolism.

§ 4. If the **functional activity** of an organ **is exerted for a considerably longer time than that to which it is accustomed,** there will occur, sooner or later, a state of **exhaustion,** due in part to the consumption of the parenchyma of the organ, and in part to the formation of toxic nitrogenous products of metabolism, these making such an organ unfit for further continued action. In most cases the results of an overexertion manifest themselves in the muscular and nervous systems, the evidences of the existence of such a condition being a painful stiffness of the muscles involved, some mental excitement, sleeplessness, a heavy sensation in the head, the lack of appetite, a feeling of exhaustion, the unnatural breaking out of perspiration upon the surface of the body, and at times a rise in the body-temperature. If this exhaustion affects a vital organ, such as the heart, death may ensue from this cause alone. This result can take place, however, as well when the heart is unable to perform its ordinary function for a short time as when it acts for a long time in more nearly normal manner, indeed, but still under the conditions demanded of a maximum amount of work. If the wearied tissues are able to secure rest, and if a sufficient and proper amount of nourishment is supplied to them, the extra material which was lost by the unusual activity will be replaced, the effete products of metabolism which are acting detrimentally to the functions of the tissue will be removed, and the part will again become ready for a renewal of its normal activity.

If a tissue frequently becomes the seat of exhaustive functional activity, and the periods of rest are too short to admit of a complete restoration of the tissue, there will finally occur a condition of permanent insufficiency, a chronic exhaustion, which under certain circumstances may even lead to degeneration or atrophy of the affected organ. A muscle may thus become atrophied through excessive use, and a brain which, by too constant stimulation of any character without the required

periods of rest, is exhausted by its continuous activity, may finally pass into such a condition of debility and exhaustion as to make even the performance of the normal function an impossibility. By means of rest and of regulated nourishment the brain may again recover; in a high degree of exhaustion, however, the functional insufficiency may become permanent, and may find its expression eventually in anatomical changes.

If the excitation of the nervous system is very severe, there occurs under certain circumstances, by even a short continuation of the source of the irritation, a cessation of the nervous functions—a paralysis which, should it affect the functional capacity of the heart and the respiration, may lead to death; more often, however, it passes away after a short time.

In organs from which much work is required, exhaustion and insufficiency take place the more quickly in proportion as the nourishment is insufficient. Fatigue and insufficiency of the heart are most often observed when the general nourishment is poorest, as from disease of a febrile character, or when the absorption of oxygen in the blood is more or less hindered by heart-defects poorly compensated for and by diseases of the lung.

It is highly probable that overexertion renders the organism more susceptible to infections of different kinds.

If the demands upon a muscle or a gland are only slightly increased, and if at the same time the nourishing material is good and sufficient for the carrying out of such increased work, the **affected tissue becomes hypertrophied** and is thereby rendered capable of accomplishing the increased work for a time.

§ 5. **High temperatures** act in part by a *local destruction of the tissue* (burning), in part by an *overheating of the entire body*. Naturally the latter condition is possible only when the high temperature acts for a length of time sufficient to render it impossible for the organism to protect itself from the excess of temperature by giving up its heat. In dry air of from 55° to 60° C. (131° to 140° F.) even the most profuse perspiration is no longer able to hinder the body from becoming overheated, and in moist air even a lower temperature suffices.

If rabbits are placed in well-ventilated incubators in which the temperature stands at some point between 36° and 40° C. (96.5° and 104° F.), their body temperature will rise to a height which varies from 39° to 42° C. (102.3° to 107.7° F.), and at the same time both the respiration and the pulse will increase in rapidity. A very marked elevation of the body temperature may, by inducing paralysis of the nervous and contractile apparatuses, lead to the death of the animal in from one to three days; the symptoms observed under these circumstances being a decided acceleration of both the breathing and the heart's action. If the body temperature, however, does not rise more than two or three degrees C. (from three to five degrees F.) the animals may, if properly fed, continue to live for a period of from ten to thirty days, or even longer, but they will lose flesh and will eventually perish under manifestations of a progressive diminution in the amount of hæmoglobin contained in the blood and in the number of the red blood corpuscles. Degenerative changes, particularly fatty degeneration, take place in the liver, the kidneys, and the muscular substance of the heart. During the progress of the experiment the production of urea undergoes an increase.

If a man is subjected to a high temperature, an overheating of the body may take place, and finally the condition may occur which is designated by the name of **heat-stroke.** In this condition the pulse is increased, the respiration is rendered galloping and panting, the pupils are dilated, and death may take place in the same manner as in the case of an animal made the subject of experiment. The occurrence of the heat-stroke is hastened by severe bodily labor, by interference with heat-dissipation, by impermeable clothing, or by lack of water in the body.

By direct action of the rays of the sun upon the head cerebral and meningeal symptoms may be produced. This condition is characterized by hyperæmia and inflammatory exudations, and is called **sun-stroke** or **insolation.**

Local effects of heat upon the skin (**burns**), according to the time during which their action is exerted, and according to the intensity of the heat, lead to hyperæmia (first degree of a burn), or to the formation of blebs (second degree), or to tissue-eschars (third degree), or to carbonization (fourth degree). The action on the tissues depends upon the heat—first locally and then more extensively—and their destruction results from a certain degree of temperature acting for a certain length of time.

If a large part of the surface of the body, about one-third, is burned, the individual dies, even though the burning is only of a mild character and eschar-formation does not take place. An attempt has been made to explain this phenomenon in various ways. Billroth, Foà, Mendel, and others believed the cause of death to lie in the suppression of perspiration and the consequent collection of poisonous materials in the blood; others, as Sonnenburg and Falk, believed the fatal result to be due to a reflex lowering of the vascular tone. In marked cases, according to Sonnenburg, the overheating of the blood causes paralysis of the heart. On the other hand, Ponfick, Klebs, von Lesser, and others consider the fatal outcome to be chiefly due to injury and destruction of the red blood-cells. Silbermann, Welti, and Salvioli also seek the cause of death in injury to the blood, laying especial stress, however, not so much upon the destruction of the red blood-cells as upon the occurrence of stasis and coagulation of blood within the vessels of the different organs, this condition being the consequence of the injury to the blood. Kijanitzin, on the contrary, holds that a poison (ptomaïn), which acts detrimentally to the organism, is created in the bodies of those who have been burned.

The anatomical findings in those cases of burns in which an opportunity has been given for examination tend to demonstrate that—in cases in which death does not follow in a short time from the severe disturbance of the nervous system and the overheating of the body—the cause of death occurring from burns of the cutaneous surface is to be sought in the changes of the blood and in the disturbance of the circulation. The blood-changes consist in destruction of the red blood-cells, or such an injury to them as to diminish their functions and give rise at the same time to the deposit of the products of degeneration and the collection of hæmoglobin in the liver, the spleen, and the kidneys. The alterations are further characterized by a tendency of the blood to form thrombi and intravascular clots, by means of which vessels of the lesser as well as of the greater systemic circulation may be obstructed. And besides these should be mentioned the facts that both during life and

after death venous clotting and hemorrhages, as well as arterial anæmia, are occasionally observed, and that local tissue-degeneration and necroses may occur in certain organs, as, for example, in the kidney, in the liver, in the gastric and intestinal mucous membrane, in bones, and in the soft parts.

Low temperatures act in much the same manner as do high temperatures, in part through local injuries and death of the tissues, in part by chilling of the entire body. Severe and lasting refrigeration causes tissue-death; after mild chilling there occur, as a consequence of tissue-changes, the formation of blood-clots, hyperæmia, and exudations which are exceedingly rich in leucocytes. The tips of the nose and of the ears and the fingers and toes freeze most easily. After repeated chillings limited areas of the skin are apt to become red and swollen from inflammatory action, and to itch a good deal (*chilblains; perniones*).

If the entire body be strongly cooled, a condition of general paralysis finally occurs, through reduction of the normal excitability of the tissues, especially of the nervous system and of the heart. The sensorium is dulled; the heart-contraction and respiration become progressively weaker, and finally cease entirely. If, before the excitability of the tissues has entirely disappeared, the body be again warmed, the power of movement in the limbs returns gradually, and, after a certain time, consciousness is restored. In man, instances of complete recovery have been observed even after the temperature of the body has been reduced to from 24° to 30° C. (75° to 86° F.).

Besides the severe forms of local or general lowering of the tissue-temperature, there also occur, as harmful pathogenic influences, mild general or local chillings—the so-called "**colds**"—from the effects of which disease phenomena manifest themselves, partly at the seat of refrigeration and partly in other organs in distant portions of the body. For example, after widely extended refrigeration of the skin there may be produced diarrhœa, or catarrh of the respiratory system, or kidney disease; after local chilling of the skin, painful affections in the deeply seated muscles. In what manner the phenomena referred to depend upon the refrigeration is unknown, but there is no reason to deny that these manifestations of disease are caused by cold. But though many diseases formerly attributed to "catching cold" have been found to be due to infectious diseases, there still remain a number of diseased conditions for which we know no other etiology than that of refrigeration. Conditions of the body in which the skin is hyperæmic and in which perspiration is secreted seem to favor the attacks of disease caused by cold. In many individuals there seems to be a special disposition for the effects of refrigeration to manifest themselves in connection with definite tissues, so that in one person certain muscles, and in another the mucous membranes, will be the parts affected.

According to Pflüger and others, the processes of life in animals may be brought to a standstill by means of the abstraction of heat, without its being an impossibility for an awakening to take place from apparent death. This is said to happen, indeed, if an animal be frozen to a solid mass. Preyer is also of the opinion that the continuity of life can be fully interrupted by refrigeration, and describes the subjects who are thus "lifeless," but still capable of living, as *anabiotic*. Frogs are said to remain vital for many hours, even though the temperature be reduced to − 2.5° C., at which temperature the heart is frozen. According to the investigations of Koch such a return to life on the part of animals which have been frozen stiff is possible only when a portion of the water contained in the body (and not the entire mass of fluid) is converted into ice, and when at the same time the thawing-out process takes place slowly. When the latter

process occurs rapidly strong diffusion currents are developed between the water that comes from the ice crystals and the concentrated solutions of albumin in the blood and the tissues, and these currents exert a damaging effect upon the latter.

Tissues of mammals and of man do not necessarily succumb to the abstraction of heat, if it is of short duration, even though the freezing-point be reached, but may again recover.

§ 6. Sudden **lowering of the atmospheric pressure,** as occurs in the ascension of mountains and in balloon voyages, can cause conditions of great exhaustion, with marked palpitation of the heart, unconsciousness, irregular breathing, and sometimes vomiting and hemorrhages from the gums and lips. Probably these phenomena depend chiefly upon lack of oxygen (P. Bert), the capillaries of the lung being unable to take up sufficient oxygen from the highly rarefied air. According to the investigations of Schumburg and Zuntz it is also true that a given amount of labor calls for a greater supply of oxygen at an elevated place than at one situated at a low level. Owing to the demands made upon the muscles in climbing a mountain, the phenomena mentioned above appear at a less elevation than they do in a balloon ascension. Hemorrhages are probably due in part to the occurrence of fissures, through drying of the mucous membrane of the parts affected by evaporation (Hoppe-Seyler, von Recklinghausen).

According to the researches of Egger, Miescher, and others, a sojourn in high altitudes causes an increase in the number of red blood-cells in a short time, with an augmentation of the amount of hæmoglobin in the blood. Other authors (Schumburg, Zuntz) oppose this view, and maintain that the phenomenon is due in part to the thickening of the blood caused by a loss of its watery constituents, and in part to a change in the distribution of this fluid; and they attribute the favorable effects which many individuals experience from a sojourn at a high elevation among the mountains, to the stimulating influences (due largely to diminished atmospheric pressure) which affect the nervous system favorably and which excite increased metabolism.

Sojourn in diving-bells and caissons—such as are used for carrying on building operations beneath the water—in which, under certain circumstances, the **atmospheric pressure is increased** more than fourfold, causes a trifling difficulty in respiration and slight acceleration of the circulation. Upon going quickly from the compressed air to the open air there may occur fatigue, a sense of oppression in the chest, noises in the ear, cramps in the muscles, pains in the joints, hemorrhages from the nose, ears, and lungs, dilatation of the pupils, and, under certain conditions, paralysis, coma, delirium, and even death after an interval of from one to twenty days (P. Bert, Hoppe-Seyler). The cause of these phenomena is probably the sudden escape from the blood of the nitrogen which had been absorbed under pressure. According to the investigation of Heller, Mayer, and von Schrötter, the blood—when freed rapidly from the pressure exerted upon it—contains gas in a free state (almost exclusively nitrogen). Free gas, therefore, according to these authorities, circulates in the blood. According to the investigations of Leyden and Nikiforoff, degenerated areas are observed in the white columns of the spinal cord in the fatal cases associated with paralysis. In these areas of degeneration some of the individual nerve-fibres are torn apart, and, by the swelling of the axis-cylinders and the disintegration of the medullary sheaths, the tissue is markedly changed, empty spaces taking the place of the nerve-filaments.

Probably these disturbances are incident to the formation of bubbles of gas inside the spinal cord. If the gray matter is affected, the ganglionic cells may also degenerate.

Changes in the electrical condition of the atmosphere and in the magnetism of the earth have no demonstrable influence upon the body of man; on the other hand, **electric discharges**, as lightning-stroke, induce in part local burning (Fig. 1) and in part lesions of the whole body. Under certain circumstances lightning-stroke can cause laceration of the tissues of the internal organs, as of the liver and of the heart (Liman). The most frequent and important action of lightning is to cause a *paralysis of the nervous system* which gives rise to severe dyspnœa, sooner or later ending in death or gradually passing away. Only very rarely do the special nerves remain lastingly affected. Transitory paralyses occur when the lightning has not passed through the body, but has only been conducted in its neighborhood, whereby, in consequence of the sudden electrical discharge from the clouds, the body of the affected individual is quickly emptied of its electricity, or else the electricity present in the body is combined with the electricity discharged from the clouds.

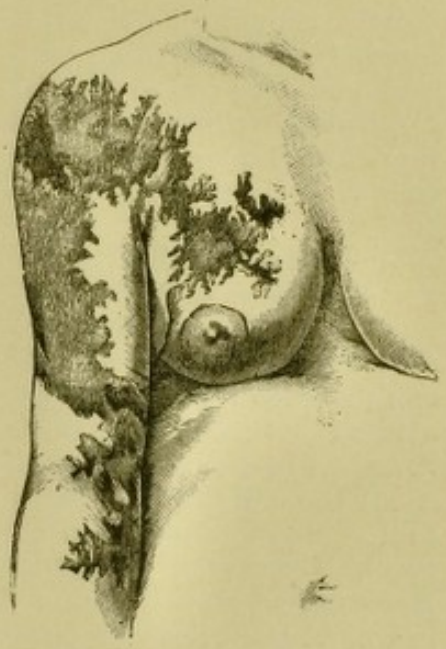


FIG. 1.—Lightning-figures on the shoulder, breast, and arm of a woman struck by lightning.

Individuals who have been struck by lightning show mild or severe burns at the points of entrance and exit, as well as destruction of the tissues in the path of the bolt. The marks of the burn are mostly red, forming peculiar ramified, zigzag lines, the so-called *lightning-figures* (Fig. 1), which are essentially a hyperæmia, and soon disappear if severe burning has not occurred.

If a **powerful electric current of high tension**, such as is generated by dynamo machines, passes through a man, either when he forms a part of the circuit or when he simply comes in contact with an uninsulated conductor, severe pathological disturbances or even death may follow. According to Kratter the lower limit of danger occurs at a tension of about five hundred volts. Alternating currents are much more dangerous than continuous ones of the same strength and tension. When the effects produced do not result in death the person injured is as a rule rendered immediately unconscious, and he remains in this condition for either a few minutes only or for several hours (Kratter). Then for several days afterward he is likely to suffer from vertigo, prostration, and headache, and often also from palpitation of the heart. At the points of contact there will be more or less pronounced evidences of burning.

When the effects are fatal, death occurs either immediately or at the end of a very few minutes—rarely after the lapse of from ten to thirty minutes. Apart from the evidences of burning at the points of contact, the changes found in the body after death are the following: evidences of suffocation and of hypervenosity of the blood, stasis of the circulation of the blood in the cavity of the chest, and often also a few scattered

small hemorrhages, which are in part the result of the suffocation and in part must be ascribed to the direct effects of the current. The cause of death in these cases is a paralysis of respiration of central origin (Kratter).

Mechanical influences are frequently productive of pathological conditions, causing those lesions which are known as *contusions*, *wounds*, *lacerations*, *fractures*, *concussions*, etc. These influences act through destruction of tissue, through changes in the organization of tissue, not externally recognizable, through lesions and ruptures of the vessels, and through irritation of the nerves. The sequelæ are destruction of tissue, disturbances of the circulation, inflammations, and growths due to proliferative processes. Frequently repeated, though trifling, mechanical traumatisms, as rubbing, cause congestive hyperæmia followed by inflammation and, if the traumatisms are continued, hyperplasia of the tissues. If large quantities of insoluble dust-particles are continuously brought to the lungs, marked changes will be noticed in the lungs themselves and, under certain circumstances, in other internal organs. One can group these changes under the name of **dust-diseases.** Continuous **pressure** and **diminution of the amount of space allowed an organ** may cause atrophy of that organ, as seen in constricted liver following tight lacing.

§ 7. Mechanical, thermal, electrical, and many chemical agents, especially those of a corrosive nature, cause: first, local injuries to those tissues which may be attacked directly; second, a *general involvement of the nervous system through the influence of the local irritation.* The trauma can produce this involvement by directly attacking the central nervous system or through the irritation of the sensory or sympathetic nerves, thus producing a number of additional nervous symptoms.

If the cerebral functions are disturbed by direct agitation of the cranial contents, and unconsciousness is the result, the condition is termed **commotio cerebri** or **concussion of the brain.** This term is given, however, when the trauma has not visibly altered the structure of the brain, at least not to a considerable extent nor in a striking manner.

Should phenomena of inhibition and paresis be produced reflexly by intense irritation of the peripheral nervous system, especially attacking the functions of the heart and the respiratory tract, the term **shock** is commonly employed to designate the entire group of symptoms observed under these conditions. The most common causes of shock are injuries to the vertebral column, abdominal cavity, or scrotum; less frequently to the extremities or to the thorax. Further, shock is caused by lightning, burns, corrosions of the skin, fear, and psychical emotions, through whatever channels they are conveyed to the brain. An individual whose nervous system is in a particularly irritable condition is especially liable to shock; conditions of alcoholic or drug narcosis inhibit its appearance.

Shock is chiefly characterized by weakened energy of the heart's action; by an irregular breathing, which leads to a decrease in the interchange of gases in the tissues; and by a lowering of the temperature (Roger). Owing to these conditions the venous blood of persons dying of shock is lighter in color than the normal venous blood (Roger). In shock consciousness generally remains, the skin and the visible mucous membranes are pale, and the pulse is small and markedly slowed, often irregular and interrupted.

In a person suffering from shock the nervous symptoms are varied. He may be agitated, and groan, shriek, and cry out with fear. This anguish of mind is associated with full breathing, and is known as *erethistic shock*. He may lie quiet, partially conscious, with sunken countenance, showing evidences of marked weakness in the sensory and motor functions. This combination of symptoms is known as *torpid shock*. In severe cases death follows from the stopping of the heart's action and the cessation of the respiration.

Shock, in its irritation of the terminal fibres of the peripheral nervous system, is closely allied etiologically to that phenomenon which we call **syncope**. Syncope, however, is to be differentiated from shock in that the chief symptom is a loss of consciousness of short duration, while the heart's action and the breathing show no marked disturbance. In syncope we have prodromes, such as giddiness, tinnitus aurium, and darkening of the visual fields, all of which are absent in shock.

Not infrequently, as the result of injuries in various portions of the body, there may arise more or less marked functional disturbances in the nervous system, which often remain after the local injuries to the tissues are entirely healed. These derangements cannot be considered in any way dependent upon anatomical changes of the peripheral or central nervous system, but must be considered as *purely functional disturbances of a psychical origin*. They are generally termed **traumatic neuroses, nervous diseases of accidental origin,** and are frequently characterized by subjective, but sometimes also by objective symptoms. To the first class of symptoms belong pains which are not necessarily localized at the seat of the injury, as, for instance, headache, chest-pains, backache, difficulty in motion, general lassitude and inability to perform mental labor, dulness of perception, disturbed vision, flittings before the eyes, giddiness, restless sleep, loss of appetite, and indigestion. To these symptoms Oppenheim and Strümpell have added psychical ill humor of a hypochondriac or melancholic character, irregularly placed patches of cutaneous anæsthesia, enfeeblement of sense of taste, hearing, or smell, motor palsies, hyperæsthesias, concentric narrowing of the visual fields, pareses, muscular spasms, tremors, acceleration of the pulse, and a tendency to sweating.

According to the opinion of the writers upon this subject, we are dealing in these cases principally with symptoms which are referable to a psychical shattering of the perceptive life, a **psychoneurosis**, which is less often caused by the traumatism and the accompanying psychical shock than by the consequent anxiety over the injury to health and loss of business. Sometimes, through disturbance of the normal relation between the mental processes, the patient's condition is changed to one that suggests *hysteria*, in part due to the spontaneous occurrence of abnormal sensations, called *hypochondria*, and in part to a neurasthenia. If volition no longer finds a way to the motor centres, hysterical palsies are established. If the normal exertion and inhibition of the will-power are broken down, so that unreasonable will-stimuli are created and reach the muscles, we have hysterical convulsions, contractures, or cramps. If the nervous irritation originating in the sensory tract does not enter the area of consciousness, we have an hysterical anæsthesia. If there are present in the consciousness images of awaited or feared objects, and if these images are intensified by the conditions of the disease into true subjective irritations of consciousness, we shall have hysterical pains and neuralgias (Strümpell).

2. *The Origin of Diseases through Intoxication.*

§ 8. *By* **poisoning** *or* **intoxication** *we mean that impairment of health, occasioned by the injury to a tissue of the body, which certain agents are capable of producing, under suitable circumstances, by reason of their chemical nature.* Those substances which are designated as **poisons** belong in part to the mineral, in part to the vegetable, and in part to the animal kingdom. Poisons are found as such in nature, or are produced artificially from organic or inorganic substances, which either may be non-poisonous themselves or may possess properties quite different from such poisons. Among the most important poisons are the products of the metabolism of animals or plants. The combinations which take place under these circumstances are formed either within the tissues of the plant or animal, or from the nutrient materials surrounding them, through the occurrence of transformations of non-poisonous elements, or of elements which exert an entirely different action.

The *poisons which belong to the mineral kingdom or which are produced from minerals* are: metallic mercury, chlorine, bromine, iodine, sulphur, and various combinations of these substances, besides many combinations of arsenic, antimony, lead, barium, iron, copper, silver, zinc, potassium, sodium, chromium, etc. The best-known poisons containing carbon which are artificially produced are: chloroform, chloral hydrate, ether, alcohol, iodoform, carbon disulphide, hydrocyanic acid, potassium cyanide, oxalic acid, nitroglycerin, nitrite of amyl, petroleum, carbolic acid, nitrobenzol, picric acid, and aniline. In general it is to be noted that modern chemistry is continually producing new substances which act as poisons.

Among the *poisons produced by plants of the higher order*, which are especially noteworthy, are: the *organic alkaloids*, such as morphine, quinine, colchicine, atropine, hyoscyamine, veratrine, strychnine, curarine, solanine, nicotine, digitalin, santonin, aconitine, cocaine, coniine, muscarine, and ergotin, all of which may cause severe poisoning even in small doses.

Lower forms of plant life, especially the bacteria, produce non-poisonous and poisonous substances in the nutrient material (albuminous bodies) *in which they develop.* Some of these substances are similar to the vegetable alkaloids, some to the ferments, and are accordingly termed *toxic cadaveric alkaloids, toxic ptomaïns, toxins, toxalbumins,* and *toxenzymes* (compare § 12; also Chapter IX.). It follows that the blood, the flesh, or any organ of a healthy animal may acquire poisonous properties, in consequence of changes which are set up in it by the influence of bacteria. Those diseases which are held to be due to sausage-, meat-, fish-, and cheese-poisonings are in part ascribable to the fact that bacteria have developed in these food-products, and out of albuminous material have produced the poisonous products of metabolism. In other cases the bacteria may have developed in the slaughtered animal during its life, so that the animal was diseased when killed; and the person eating its flesh acquires the poison, or is infected with the identical disease with which the animal was affected. Under certain conditions food which is in no way spoiled, but which contains bacteria, may be taken into the stomach and digested, and the bacteria thus liberated may develop in the alimentary tract of man and produce poisoning, by means of the toxins, toxalbumins, or enzymes which are formed by their multiplication.

Among the *animals which normally produce poisons within certain tissues of their bodies* the best known are: serpents, toads, salamanders, scorpions, Spanish flies, and many other insects which are supplied with stings. Latterly much attention has been given to the poisonous substances which are to be found in the internal organs of fishes and mollusks. There are certain forms of sea-fish that are constantly poisonous, and others also that are poisonous only at certain times; such observations have been made especially on the fish in Japanese waters. According to Saotschenko, the poison in many poisonous fishes is secreted by the glands of the skin at the roots of the dorsal and caudal fins, and may be found in their eggs. According to Remy, Miura, and Takesaki, the poisonous fish belonging to the family Gymnodontes (tetrodons) secrete poison only in the sexual organs. According to Mosso, there is found in the blood-serum of eels a poisonous substance, ichthyotoxin, which acts detrimentally if ingested into the intestines of the ordinary animals used for experimentation, and can produce death. Observations of poisoning from eating mollusks, which were made a few years ago at Wilhelmshafen, have excited considerable interest. Severe illness, with death in certain cases, followed the eating of moss-mussels (*Mytilus edulis*).

According to M. Wolff, the poison is contained in the liver of the mussels. According to Schmidtmann, Virchow, Salkowski, and Brieger, the action of the poison is similar to that of curare. According to Brieger, there can be obtained from the poisonous moss-mussels basic substances which are similar in their composition to the ptomaïns—that is, to the basic products of decomposition. How far the causes of the poisoning are to be ascribed to normal and how far to disease processes in the life of these fishes and mollusks has not been determined at the present time. From the fact that the moss-mussels were poisonous only in certain areas (Schmidtmann, Wolff) where the water was impure, and that the starfish found in the same localities were similarly affected (Wolff), it would seem probable that in a certain number of cases the poisonous action must be referred to some contaminating influence, or to pathological alterations of the natural processes of life. It is probable that the bacteria which are found in mussels which live in stagnant canal-water may be the cause of the deadly action (Lustig). In other cases the cause seems to have been connected directly with special circumstances; for instance, with the production of elements elaborated by the sexual organs.

It is difficult to give an exact definition of a poison and of poisoning, since the action of the substances considered above varies with the dose and the attenuation, as well as with the method of introduction into the tissues of the body. It is well known that even the most powerful poisons may be introduced into the tissues in small doses not only without doing damage, but even in such a manner as to produce a beneficial and curative effect upon them. On the other hand, substances which are not usually classed among the poisons, as, for instance, non-corrosive sodium salts, when introduced into the organism in large quantities or in concentrated solutions, induce phenomena which must be ascribed to the action of a poison. Furthermore, poisonous substances sufficiently diluted (phenol) may serve as foods. In the above definition I have come to the same conclusion as Kobert, and have utilized in the following paragraphs, concerning the workings of poisons, much material from his "Text-book on Intoxications," published in 1893.

Snake poison is formed exclusively in the poison glands which are located above the angle of the mouth. It consists of a greenish or yellowish fluid, the poisonous activity of which is not diminished by desiccation or by being preserved in alcohol. The active principle is a toxalbumin.

§ 9. **Poisons** may be divided according to their action into three classes: first, those which produce local changes in the tissues; second, those which produce an injurious action upon the blood; third, those which produce in the tissues anatomical alterations which are not recognizable.

The **poisons which produce pronounced local alterations in structure** injure primarily the tissues with which they come directly in contact upon entering the body. If these substances are absorbed by the juices of the body, injury may result to the most diverse organs and tissues; but they most frequently confine their action to the organ in which they are stored up, or to which they are brought for purposes of excretion, as, for instance, the liver, the intestines, or the kidneys.

The most frequent situation for the primary injurious action is the mucous membrane of the upper alimentary canal and the respiratory tract; but in many cases of poisoning the skin is the first point attacked. Very often poisons are employed as disinfectants—i.e., they are purposely used to prevent the growth of or to kill off bacteria which have come in contact with wounds. When thus used they can produce local changes in the tissues, or, through absorption by the circulatory streams, injure the internal organs or the entire body.

The first group of poisons to be discussed here is made up of those substances which produce severe changes in the tissues at the point of contact. From the similarity of the results of this contact to burns, these poisons have been called **caustics**, or **corrosive agents**. If the action of the caustic reaches the highest characteristic grade, the tissue attacked will be entirely destroyed, in one case being converted into a dry, hard crust, in another case into a moist, soft one. If the action is less severe—because of the application of a less concentrated solution of the caustic, or because the chemical substance, though applied in concentrated solution, acts incompletely, or because the tissue itself is resistant, as in the case of the skin—we have less severe changes, which are characterized by redness, swelling, inflammation, and hemorrhages. Very often one finds in the same organ diverse changes, as local sloughings or necroses, hemorrhages, inflammations, and swellings due to slight local extravasations of blood. If the condition has been present for some time, the local eschars are surrounded by a more or less widespread inflammatory areola, though in the case of some caustics the tissues are inflamed only within a limited area.

As substances which act in this manner should be mentioned the *corrosive acids:* sulphuric, nitric, hydrochloric, phosphoric, oxalic, acetic, arsenious, arsenic, osmic, lactic, trichloracetic, carbolic, and salicylic. To this class also belong the *corrosive compounds of the alkalies and alkaline earths*, as potassium and sodium hydrate (watery solutions of KHO and NaHO), caustic ammonia (NH_3 dissolved in water), ammonium carbonate, caustic lime, and barium sulphate. To this list should also be added a number of corrosive salts, as those of antimony (tartar emetic and antimony trichloride), salts of mercury (corrosive sublimate and red precipitate), nitrate of silver, chloride of zinc, sulphate of zinc, sulphate of copper and acetate of copper, aluminium acetate, potassium chromate, potassium bichromate, and chloride of iron.

Among the especially irritant *poisons derived from animals* are: cantharidin, obtained from the beetle *Lytta vesicatoria;* phrynin, contained in the secretions from the cutaneous glands (parotid) of toads; the secretions from the poison glands of snakes and scorpions; the se-

cretions from the sting-glands of bees, wasps, and hornets; the secretions from the salivary glands of stinging gnats, flies, and horse-flies; the secretions from the poison glands of the maxillary palpæ of spiders (Tarantula), which produce local necrosis or give rise to inflammation. Finally, many of the *higher plants* produce substances which, when brought in contact with the tissues, cause local irritation and inflammation. Examples are: daphne, various forms of Ranunculus, anemone, marsh-marigold, calla, dragon-root, *Croton tiglii* (producing in its seed croton-oil), buckthorn (*Rhamnus cathartica*), water-elder (*Rhamnus frangula*). These plants produce the poisonous substances either in their blossoms, or in their seeds, stems, or roots.

The character of the local changes which the substances mentioned above produce is naturally very varied, and is dependent in part upon the activity of the poison, and in part upon the place and manner of its application. Mineral salts, liquor potassæ, and strongly concentrated corrosive-sublimate solutions produce marked eschar-formations, associated with severe hemorrhagic inflammations, especially when taken into the stomach. Through the action of acids a strong demand is made upon the alkaline fluids of the body, and we find, in consequence, alterations in the respiration and the circulation. The poisons which are produced by the poison glands of snakes, and which belong to the toxalbumins, cause usually very severe local inflammations and hemorrhages, which often become widespread and sometimes occasion marked gangrene of the tissues. There are other snake-poisons which produce only slight local changes, while the systemic symptoms of poisoning are by far the most marked. There is a *volatile or gaseous class of poisons* which cause local irritation of the tissues, especially of the mucous membranes of the eye and of the respiratory tract (*irrespirable gases*). To this class belong the fumes of ammonia, chlorine, sulphuric acid, nitrogen monoxide, nitrogen dioxide, nitrogen trioxide, osmic acid, and mustard-oil. The intensity of action of these poisons varies also, often occasioning mere temporary redness, but being able also to produce severe inflammation and necroses of tissue. From the irritation of the respiratory tract coughing is produced, and by spasm of the larynx the breathing may be interfered with.

There are added, in many cases, to the local irritation and inflammation caused by the action of this class of poisons, further *effects upon the internal organs*. After the absorption of these poisons by the juices of the body, those organs suffer most, as a rule, in which the poison is retained or elaborated, although the action may extend also to those organs which do not take part in the excretion of the poison. After the application of certain poisons the lesions at the point of entrance are transient and unrecognizable. The first recognizable anatomical lesions occur in tissues to which the poison has been carried by the blood. Finally, a given poison may act as a *nerve- and heart-poison*, so that, clinically, this action appears more prominently than the local tissue-degeneration. After corrosive-sublimate poisoning, cell-necrosis takes place in the secreting portion of the kidneys, combined with marked inflammation of the colon. Salts of chromic acid, cantharidin, and many acids cause more or less marked tissue-necrosis and inflammation in the secreting portion of the kidneys and in other parts of the urinary tract.

Phosphorus, arsenic, and antimony, which are but mildly corrosive, produce tissue-degenerations, principally of a hemorrhagic or fatty nature, in the kidneys, liver, heart, muscles, and capillaries of differ-

ent organs. These changes are seen especially after phosphorus-poisoning.

If an individual is exposed for months or years to the vapor of yellow phosphorus, it may produce an inflammatory necrosis of the jaw-bones; but this necrosis takes place only when the inhalation of the vapor is combined with such conditions as putrid decompositions in the mouth, or decayed teeth.

After the long-continued use of nitrate of silver, black silver-deposits may be found in the most diverse tissues of the body—in the skin, in the kidneys, in the intestinal villi, and in the choroid plexus of the brain.

The snake-poisons possess, in addition to their local irritant action, a paralyzing effect upon the nervous system and the heart. So after snake-bite we may have death from paralysis of the centre of respiration.

Solutions of lead, when taken into the alimentary tract, may have a corrosive action on the mucous membrane, giving rise to inflammation, and producing such intestinal symptoms as vomiting, diarrhœa, constipation, and gastric cramp, associated with such nervous symptoms as anæsthesias, motor palsies, convulsions, faintings, and unconsciousness. If lead is ingested continuously for a long time, general disturbances show themselves, such as derangements of digestion, intestinal colic, pain in the limbs, anæsthesia, motor palsies, disturbances of cerebral activity, and kidney disease. These various lesions are undoubtedly dependent upon the dispersion and deposition of lead in the body, leading to the most widespread anatomical changes.

The active poisonous principles of *ergot* (*Secale cornutum*) are *sphacelinic acid* and *cornutin*. When taken in large doses, as continuously in bread, this drug causes itching, pains, cramps in the extremities, and, later on, numbness and a feeling of cold in the tips of the toes and fingers. This condition may go on to more or less widespread gangrene and sloughing of the parts, with the formation of ulcers in the intestines (*ergotism, itching disease*). In long-continued poisonings, degenerations take place in the spinal cord (Tuczek). The feeding of chickens with ergot causes gangrenous necrosis of the comb, this result being due to the occurrence of stasis and hyaline thrombosis in the blood-vessels. In experimental animals which have been fed for a considerable length of time with ergot, degenerative alterations will usually be found in the central and peripheral nervous system, in the blood-corpuscles, and in the endothelium of the blood-vessels (Grigorieff).

§ 10. *Poisons which cause changes especially in the blood*, and hence may be called **blood-poisons**, are partly gases and partly fixed substances which are absorbed. The latter are absorbed principally from the intestinal tract; they may, however, enter the body through wounds, or they may be injected directly into the blood-vessels. Sometimes these blood-poisons produce also a local action upon the tissues at the point of entrance; again, there may be joined to the action on the blood a direct influence upon the nervous system, producing death under certain circumstances, even before the action upon the blood has been recognized. Finally, it should be noted that the blood-changes induced by the poison may produce secondary diseases in the different organs, as, for instance, the kidneys, the liver, the intestines, and the brain.

The most important blood-poison is *carbon-monoxide gas*, which causes an effect upon the blood, and very frequently produces more or less serious or deadly poisonings. Most frequently the poisoning occurs

from the carbon monoxide contained in coal- or illuminating-gas. This gas may also be produced after the burning of gunpowder or gun-cotton.

The action of the carbon monoxide taken in by breathing consists largely in its combination with the hæmoglobin, forming carbo-oxyhæmoglobin. This combination decreases the amount of oxygen in the hæmoglobin and hinders the taking up of oxygen by this substance, even when the respired air contains as low as 0.05 per cent or 0.02 per cent of CO (Gruber). The blood-corpuscles are not changed in appearance by this poison. If a sudden addition of carbon monoxide reaches the nervous system, it may produce direct injury to it, giving rise to cramps and, later on, to paralysis (Geppert). In cases of poisoning lasting for a long time, the displacement of the oxygen in a large portion of the blood-corpuscles may produce tissue-asphyxia. If the poisoned individual does not die, he may suffer from disturbances of the nutrition of various organs of the body, especially of the nervous system. The poisoning itself is characterized by headache, tinnitus aurium, fainting, malaise, vomiting, giddiness, cramps, palsies, and coma. The blood itself turns a pale-violet or cherry-red color on account of the increase in carbon monoxide, and the internal organs have a bright-red color.

A second not infrequent form of poisoning is that produced by *hydrocyanic acid* (CNH), which, in combination as *potassium cyanide* (KCN), is much used in the arts. In general, hydrocyanic acid is found in unstable combination in the leaves, barks, and seeds of very many plants: bitter almonds, cherry- and peach-stones, apple-seeds, leaves from the common laurel, the rind of *Prunus padus*, the root-bulbs of many of the Euphorbiaceæ, flaxseed, etc.

Hydrocyanic acid possesses a double action. In relatively small doses it exerts a paralytic influence upon the central nervous system, and death may be produced in a short time—even in a few seconds—by paralysis of the centres of respiration or of circulation. Besides this, there is an action upon the blood and tissues, robbing them of their ability to unite with and use oxygen (Geppert), so that these organs suffocate in the presence of oxygen. According to Kobert, there is formed a cyan-methæmoglobin which appears bright red in color and produces a bright-red appearance of the cadaveric lividity.

Among the third class of poisonous substances which should be named in this connection is *hydrogen sulphide* (H_2S), which is formed in the vapor of sewers and dung-pits, and which may, when inspired in large amounts, produce sudden death by paralysis of the nervous system. By long contact with blood containing oxygen, as may usually be seen in decomposed corpses, sulphur-methæmoglobin is formed, the blood becoming greenish in color.

Apart from their direct action on the nervous system, carbon monoxide, hydrocyanic acid, and hydrogen sulphide produce deleterious effects by lowering the functional powers of the red blood-cells, through combination with the hæmoglobin.

Another large group of poisons injure the blood chiefly by destroying the red blood corpuscles and forming methæmoglobin. By methæmoglobin we understand a combination of oxygen with the hæmoglobin; the amount of oxygen present in the combination being the same as in oxyhæmoglobin. The hæmoglobin, however, has been bound up with the oxygen into a more stable chemical compound than oxyhæmoglobin. Such

an action is produced by oxidizing substances, as ozone, iodine, sodium hypochloride, chlorates, nitrites, and nitrates; by reducing agents, as nascent hydrogen, palladium hydride, pyrogallol, pyrocatechin, hydroquinone, and alloxantin; and, finally, by substances which act differently from either of these, as aniline salts, toluidin, and acetanilid. In the change from hæmoglobin to methæmoglobin through oxidizing agents, oxyhæmoglobin is present as an intervening stage.

The production of methæmoglobin can take place as well in the blood-corpuscles as in the coloring matter which has escaped into the blood-plasma; but the destruction of blood-corpuscles and the escape of hæmoglobin into the blood-plasma are not always followed by the formation of methæmoglobin. In case of such a marked destruction of red blood-cells as occurs in poisoning from phallin, helvellic acid, and arseniuretted hydrogen, only a portion of the hæmoglobin is changed into methæmoglobin. Hæmoglobin and oxyhæmoglobin have a red color, methæmoglobin a sepia-brown color.

Dissolution of the red corpuscles and the formation of methæmoglobin is seen after poisonings which have produced marked local tissue-changes, as, for instance, poisoning with acids, salts of the metals, and phosphorus; but a great number of other substances have the property of attacking the blood and changing the coloring-matter.

Phallin, a toxalbumin which is found in mushrooms (*Amanita s. Agaricus phalloides*), the *helvellic acid*, which occurs in fresh *Helvella esculenta* and is lost if the fungus is dried, and *arseniuretted hydrogen* (AsH_3) have a marked dissolving action on the red blood-corpuscles, and, in consequence, produce an increased formation of biliary pigment, as well as a deposition of the derivatives of the blood-coloring matter in the liver, kidneys, and spinal marrow.

Potassium chlorate ($KClO_3$), *pyrogallol* ($C_6H_3[OH]_3$), *hydrazin* ($H_2N—NH_2$), *toluylendiamin* ($C_6H_3[NH_2]_2CH_3$), *nitrobenzol* ($C_6H_5[NO_2]$), *nitroglycerin* ($C_3H_5[ONO_2]_3$), *amyl nitrite* ($C_5H_{11}NO_2$), *picric acid* ($C_6H_2[NO_2]_3$-OH), *aniline* ($C_6H_5[NH_2]$), *carbon disulphide* (CS_2), are distinctive in their action, in that they sometimes cause the destruction of the red blood-corpuscles in the formation of methæmoglobin, and they sometimes do not.

After a very large dose of potassium chlorate death may occur in a very few hours, through destruction of the blood-corpuscles and the action of the potassium, with the development of vomiting, diarrhœa, dyspnœa, cyanosis, and weakening of the heart. The blood in these cases is of a chocolate-brown color. In more protracted cases of poisoning with small doses we find the products of the destruction of the blood in the spleen, liver, marrow of the bones, and kidneys; and the urine may show a color varying from reddish-brown to black (methæmoglobin). The presence of delirium, numbness, coma, and cramps during the illness shows that the central nervous system is markedly affected. Pyrogallol produces similar symptoms. Hydrazin and phenyl hydrazin produce multiple ecchymoses, besides the destruction of the red blood-cells, with the production of methæmoglobin. The main feature of toluylendiamin-poisoning is the breaking up of the red blood-corpuscles, which leads to the deposition of iron-containing pigment in the spleen, liver, and bone-marrow. In cats hæmoglobin may also be excreted by way of the urine (Biondi). In picric-acid poisoning there is marked disturbance of the central nervous system, which is characterized by severe cramps, in addition to the changes in the blood and the produc-

tion of methæmoglobin. In a similar manner, aniline and carbon disulphide not only cause changes in the blood, but also act harmfully by paralyzing the nervous system.

In the *last group of blood-poisons*, as the chief representatives, are to be named *ricin*, derived from the seed of the castor-bean, and *abrin*, found in the seed of the *Abrus precatorius*, which belongs to the Papilionaceæ. These poisons cause coagulation of the blood and at the same time induce degenerative changes in the blood-vessels, the heart, the intestines, and the kidneys. *Ricin* is very virulent, and may be absorbed from wounds and from the alimentary tract, producing weakness, vomiting, colic, bloody dejecta, icterus, cramps, and anuria. In the intestine ricin is competent to cause thrombosis of the blood-vessels and ulcerations of the mucous membrane.

Abrin is also very poisonous and, when introduced into the blood in doses of a few hundredths of a milligram per kilo of the body-weight of the animal, can produce death. Upon the mucous membrane it produces, even when very dilute, coagulation in the blood-vessels, and, later on, inflammation. When the poison enters the blood it induces sleeplessness, a decrease in the warmth of the body, and bloody stools. In persons who have died from the effects of the poison the post-mortem examination reveals, according to Werhovsky, well-marked degeneration of the muscular substance of the heart, a disorganization of the blood corpuscles, hyperæmia of the abdominal organs, and hemorrhages and inflammatory areas in the intestines.

§ 11. The last group of poisons, which are generally classed together as **nerve- and heart-poisons**, are principally characterized by the fact that notwithstanding the severity of the symptoms, which show themselves in the form of irritations and palsies, anatomical changes are either not susceptible of being recognized, or at least they are not so in a manner that can be looked upon as characteristic in a given case of poisoning. This is especially the case when the poison produces death very quickly; for during the course of protracted poisoning, or chronic poisoning from small doses extending over months and years, anatomical changes very easily recognized are often found—a fact which shows that these poisons do not produce solely functional changes in the nervous system, but more frequently produce a damaging effect on the cell-protoplasm, which finds expression in degenerations.

Among the very numerous *poisons which act especially upon the nervous system*, and thus may produce death through its paralysis, belong, as the most important members: chloroform, ether, hyponitrous oxide, alcohol, chloral hydrate, opium and its alkaloid morphine, cocaine, atropine, hyoscyamine, daturine (*Stramonium-atropine*), *nicotine, coniine, cicutoxin, santonin, camphor, quinine, veratrine, colchicine, aconitine, strychnine, cytisin, and curarine.

As *heart-poisons* are to be especially noted: digitalin, helleborin, and muscarine.

Chloroform ($CHCl_3$) acts in an irritating manner when applied directly to the mucous membranes, and may produce transitory inflammations. When it is inhaled, or when it is conveyed to the blood by means of the intestinal tract, there ensues, after a short period of excitation, a diminution of the irritability of the gray and the white matter of the brain. According to Binz, a slight coagulation of the protoplasm of the ganglion cells is produced. Death may be caused by paralysis of the central nervous system, as well as through early stoppage of the heart—the latter, however, occurring only when the heart is abnormally weak or degenerated, though perhaps also when the irritation

produced by the chloroform upon the mucous membrane of the nose causes an unduly strong excitement of the inhibitory nerves of the heart. Finally long-protracted exhibition of chloroform may produce degenerative changes in various organs, as the heart, kidneys, liver, the muscles, and the blood.

Ether (diethyl ether, $C_2H_5.O.C_2H_5$) acts similarly to chloroform, yet it is less poisonous and acts less detrimentally upon the functional activity of the heart.

Hyponitrous oxide (N_2O) acts especially upon the cerebrum, destroys sensation of pain, and paralyzes consciousness; later on, the action extends to the spinal cord, the medulla oblongata, and the heart.

Alcohol (C_2H_5HO), after temporarily producing excitement, acts as a depressant and paralyzant of the brain, and produces at the same time a dilatation of the arteries of the skin, so that in a drunken person a severe chilling through the skin can easily take place. Death can follow suddenly, in a manner similar to what is observed in apoplexy; more frequently it produces a gradually deepening loss of consciousness and sensorial perception, the breathing becomes slower, the pulse small, the countenance cyanotic; complete coma and general paralysis close the picture. The immoderate use of alcohol extending over months or years may produce, on the one hand, pathological accumulations of fat in the regions where fat is normally to be found, and, on the other hand, it may cause degeneration of the glandular organs, especially the kidneys and liver, followed by overgrowth of the connective tissue, with atrophy of the liver and kidneys, and, in addition, sclerosis and atheroma of the arteries, degenerations in the brain, etc. It is, however, impossible to say at the present time in what manner, how frequently, and to what extent these symptoms belong to the use of alcohol. It is certain that the drunkard frequently suffers from indigestion, diseases of the circulation, laryngitis, pharyngitis, bronchitis, and disturbances of the cerebral functions, and that the disease of the brain which is produced by alcoholism and is called delirium tremens is marked by twitchings of the muscles, obstinate sleeplessness, anxiety, and hallucinations.

Chloral hydrate ($CCl_3.CHO.H_2O$) has a local irritating action on the mucous membranes, and a paralyzant action through the blood upon the brain, spinal cord, and heart, and thus produces sleep. When death occurs from an overdose, deep coma and relaxation of all tissues are observed, with œdema of the lungs.

Opium and *morphine* ($C_{17}H_{19}NO_3$) produce depression of the functions of the brain, leading to sleep, though in some persons this is preceded by a condition of excitation. Large doses produce unconsciousness, muscular paralysis, slowing and weakening of the action of the heart, contraction of the pupils, slowing of intestinal peristalsis, diminution in the exchange of gases in the blood, and an inhibition of the normal irritability of the respiratory centres. There are no characteristic post-mortem lesions; the blood is dark and liquid. Chronic opium-ingestion may produce disturbances in digestion, dizziness, sleeplessness, neuralgias, imbecility, impotence, anæmia, hallucinations, tremors in the hands, fever, etc., which may vary much in different individuals. The system in chronic morphinism becomes accustomed to increasingly large doses; withdrawal of the drug produces severe nervous symptoms, and, under certain conditions, dangerous collapse.

Cocaine ($C_{17}H_{21}O_4$) produces peripheral dulling of the sensibility of the terminal sensory nerve-filaments; centrally, first irritation, then paralysis. The chronic cocaine habit may produce symptoms similar to those seen in chronic morphinism.

Atropine and *hyoscyamine* ($C_{17}H_{23}NO_3$), alkaloids, which are found in the members of the order Solanaceæ (deadly nightshade, thorn-apple, and hyoscyamus), have a paralyzing action on the peripheral nerve-filaments and finally irritate and then paralyze the centres. A solution of atropine introduced into the eye produces dilatation of the pupil and paralysis of accommodation for near vision, through its action on the terminal fibres of the oculo-motor nerve in the iris. Atropine may further inhibit the secretion of glands (as the submaxillary); under its action, also, intestinal peristalsis ceases through deprivation of the necessary nerve-stimulus. Through the action of this poison on the brain we may have excitation, gaiety, laughter, leading even to insanity and madness, followed by paralysis. Post-mortem examination is negative.

Nicotine ($C_{10}H_{14}N_2$), a volatile alkaloid found in the tobacco-plant, acts upon both the peripheral and the central nervous system, producing nausea, salivation, vomiting, diarrhœa, dizziness, muscular weakness, headache, convulsions, delirium, and paralysis. Chronic nicotine-poisoning may be followed by nervous diseases and disturbances of the heart's action. According to Vas, there is both in chronic alcohol and nicotine poisoning a characteristic degeneration of the ganglion-cells, the chromatin structure becoming homogeneous.

Coniine ($C_8H_{15}N$), an alkaloid of hemlock, acts as a paralyzant of the peripheral motor terminal nerve-fibres, irritating and then paralyzing the central nervous system.

Cicutoxin, a poisonous resin extracted from the water-hemlock (*Cicuta virosa*), causes nausea, vomiting, attacks of colic, palpitation of the heart, cramps, and unconsciousness.

Santonin ($C_{15}H_{18}O_3$) produces cramps originating in the brain and spinal cord, with benumbing of the sensorium, vertigo, vomiting, salivation, and yellow vision, or xanthopsia, in which white is seen as yellow and blue as green.

Quinine ($C_{20}H_{24}N_2O_2$), the most important of the numerous vegetable alkaloids, found in the bark of cinchona and other plants of the same order, acts in a paralyzing manner upon the living protoplasm, and in relatively small doses inhibits the functional capacity for work of the cerebrum. Large doses produce death by paralysis of the centres of respiration and of the heart.

Aconitin, *colchicine*, and *veratrine* produce local irritations and, later, benumbing of the peripheral endings of the sensory nerves. On the central nervous system they act as irritants and finally as paralyzants.

Strychnine ($C_{21}H_{22}N_2O_2$), derived especially from the plant nux vomica, causes increased reflex irritability of the nerve-centres, so that the slightest external irritation produces tetanic convulsions. Death may occur in from ten to thirty minutes after the first attack of convulsions, and results through central paralysis—namely, of the vaso-motor centre.

Curarine ($C_{36}H_{35}N$), the most active principle of the arrow-poison curare, which is probably derived from the cortical portion of the roots of many plants of the Strychnia family, paralyzes in small doses the terminal fibres of the musculo-motor nerves. Larger doses paralyze the central nervous system and the vaso-motor nerves, after a temporary excitation.

Digitalin and *digitalein*, two glucosides obtained from the foxglove, act locally as irritants, and also exercise, after absorption, an irritating action on the heart, vagus-centre, and muscular fibres of the blood-vessels, so that there is produced, by the slowing of the heart, an increase in blood-pressure. Larger doses produce headache, delirium, ringing in the ears, irregularity in the frequency of the heart's action, convulsions, and coma.

Helleborin, a glucoside from hellebore, acts similarly to the preparations of digitalis.

Muscarine ($C_5H_{15}NO_3$), the poison of the fly-mushroom, acts as an irritant upon those peripheral nerve-filaments which atropine paralyzes. In poisoning by muscarine, death takes place not from paralysis of the heart, but from the intense excitation of the inhibitory centres producing stoppage of its action. In general, after the ingestion of this poison, we have salivation, vertigo, anxiety, nausea, vomiting, diarrhœa, convulsions, and finally unconsciousness. Small doses produce a condition similar to that seen in inebriation, with a state of excitation.

In the foregoing summary of poisons, which necessarily comprises but a superficial examination of a few out of the entire number of such agents, I have in general followed the arrangement in groups used by Kobert in his "Text-book on Intoxications." A deeper knowledge than that which we have at present concerning the physiological action of these poisons will probably lead in the future to another mode of classification. Loew[1] has lately attempted to make a classification of poisons according to their action on the manifestations of life—*i.e.*, upon the living protoplasm. He divides them into two large groups—namely, *general poisons*, those which, in moderate concentration, act fatally upon the entire organism; and *special poisons*, those which do not injure certain classes of organisms. The *general poisons* are characterized chiefly by their power to change the chemical character of the proteids out of which the living protoplasm is formed. Among these can be differentiated: 1, *oxidizing poisons* (ozone, chromic acid, manganic acid, hypermanganic acid, hypochlorites, hydrogen peroxide, chlorine, bromine, iodine, phosphorus, and arsenious acid); 2, *poisons having a catalytic action* (ethyl ether, chloroform, chloral, many carbohydrates, etc.), which transfer to the protoplasm the unstable condition of their molecules, and thus tend to produce chemical changes in the unstable (*labilen*) albumin; 3, *poisons acting by the production of salts* (acids, soluble mineral bases and caustic alkalies, alkaline earths, and salts of the heavy metals) which form chemical combinations in the proteid materials; 4, *substitution-poisons* (hydroxylamin, diamide, phenyl hydrazin, ammonia, carbolic acid, hydrocyanic acid, etc.), which even when greatly diluted interfere with the aldehyde- or amido-groups. *Special poisons* are classified as: 1, *toxic proteids—i.e.*, (*a*) *toxalbumins* (produced by bacteria and poisonous to animals), (*b*) *alexins* and *immunitoxins* (produced in animals physiologically or pathologically, and poisonous for bacteria), (*c*) *vegetable enzymes* (abrin and ricin, produced from phanerogams and the higher fungi, and poisonous to animals), (*d*) *animal enzymes* (produced by certain animals, snakes, fishes, and spiders, and poisonous to other animals); 2, *organic bases* (strychnine, atropine, curare, etc.) having an unknown action; 3, *poisons working indirectly*, which interfere with the processes of respiration (carbon monoxide, sulphites), or act as poisons through decomposition (nitrites, iodine combinations), or act destructively through changes in the formative conditions of organized tissues (neutral salts of the alkalies, the alkaline earths, oxalates).

[1] "Natürliches System der Gifte," München, 1893.

3. *The Origin of Diseases through Infection or Parasitism.—Miasms and Contagions.—Vegetable and Animal Parasites.*

§ 12. As we have seen in §§ 8–11, there occur, in the intoxications, morbid vital phenomena which are produced by definite chemical substances, the mode and severity of their action being dependent not merely upon the character of the poison but also upon the dose employed—that is, if the idiosyncrasies of the subjects of the poisoning and the special mode of application of the poison are not taken into consideration.

In those **diseases which arise from infection**, and therefore are called **infectious diseases**, we have, on the contrary, to deal with *diseased vital phenomena*, which, if we disregard the individual susceptibility of the infected person and the peculiar mode of entrance, into the body, of the infecting material, are dependent solely upon the character of the infecting agent; while the amount of the dose, if it possesses any significance, has at least only a subordinate one.

The explanation of this difference between intoxication and infection consists in the fact that, in the first case, intoxication, the poison does not increase within the body, while *in infection the harmful substance increases after its entrance into the organism*, so that amounts of infective material so small as to be utterly inappreciable by us suffice to produce the severest fatal diseases. The dose, or quantity, of infecting material has this influence, therefore, upon the succeeding illness—namely, that a larger amount makes the infection more probable; that is, the reproduction of the injurious material within the body takes place more rapidly, and the constantly increasing material of infection will therefore in a shorter time attain such proportions that pathological processes must develop in the tissues, and must at the same time be accompanied by recognizable symptoms.

The injurious elements which are produced by infectious diseases always find their way from the outer world into the human organism, and cause *an illness which may follow a pathognomonic course;* and from the peculiarities of this course it is possible to conclude that we are dealing with a specific variety of injurious influence—one that behaves in an entirely characteristic manner. In pregnant women the infectious matter may be transmitted from the organism of the mother to her child *in utero*.

If an infectious disease attacks a number of individuals in a given locality, it is termed either a **pestilence** or an **epidemic**.

A study of professional observations shows that, in a certain number of cases, the noxious influence producing a certain infectious disease manifests its activity in certain localities, causing sickness among the people of a given district. In other cases contact with the diseased person, or proximity only, or using something which that person has used, or still other ways—as, for instance, through dejecta or sputum upon uncleaned objects—may produce the disease. Finally, it may occur that infecting material is produced only occasionally in a given locality, and only when a patient visits that particular region and by his presence leads to the production there of the infectious material. Out of the various conditions enumerated, occasion has been taken to divide the matters which are capable of producing infectious diseases into various groups and to designate these under particular names. If

infectious material is connected with a certain locality it is called a **miasm**, and receives this name on the ground that the particular region produces the infectious material. If one particular region alone produces the disease it is termed a *local miasm*, and if present everywhere it is termed a *ubiquitous miasm*. To these miasmic diseases belong especially malaria, and also croupous pneumonia, articular rheumatism, many wound-inflammations, septic osteomyelitis, and ulcerative endocarditis.

When the infection is carried directly from man to man, and spreads through houses, villages, cities, and countries, it is termed a **contagium**, and it is consequently understood that the place in which the organism grows is within the human body, or it may be also in some inferior animal, while outside the human or animal body neither production nor multiplication of the infecting material takes place. To such contagious diseases belong smallpox, measles, scarlet fever, diphtheria, typhus fever, relapsing fever, anthrax, hydrophobia, gonorrhœa, whooping-cough, influenza, many catarrhs of the mucous membranes, tuberculosis, syphilis, glanders, and leprosy.

When an infectious material is characterized by the fact that it develops in a certain district only when a patient suffering from the disease chances to visit this particular locality and there gives rise to an outbreak of an epidemic, we have what is called a **miasmatic-contagious disease**; the assumption being warranted, under these circumstances, that the infecting matter had spread from the organism of the first patient, had then multiplied at some given spot, and finally had of itself, or with the help of certain local influences, attacked the resident population of the locality in an epidemic fashion. Such miasmatic-contagious diseases are cholera, typhoid fever, dysenteries, yellow fever, and the plague.

The nature of the causes of these miasms and contagious diseases remained concealed from the older practitioners. If such an infectious disease made its appearance in the form of a plague or epidemic its cause was sought in cosmic and telluric conditions, and it was spoken of as a *constitutio epidemica* or a *constitutio pestilens*. Only within the last few decades has our knowledge of the etiology and nature of infectious diseases made true progress, and it has been shown that infectious diseases are **parasitic diseases** *the origin of which is attributable to an increase of small living organisms within the human body*. While it is true that only some of the infectious diseases are known positively to be produced by parasites, it is most highly probable that all are due to such agency. The proofs that the causation of infectious diseases is thus related to living substances capable of reproduction—to a *contagium animatum*—are deduced principally from: first, the fact that the deleterious influence produced by a certain infectious disease, where it is once present, continues to renew itself endlessly, so that from a single case innumerable others may be infected; secondly, the fact that a minute and imponderable amount of infectious matter is sufficient to convey disease to an individual, and afterward to produce effects of the most striking character upon the organism of this individual—circumstances which could scarcely be explained in any other way than by assuming that the detrimental substance actually multiplies itself within the human body.

The attempt has been frequently made to explain the manifestations of infection through the action of noxious gases or soluble ferments.

These hypotheses, however, are wholly insufficient; for they either leave the phenomena which are observed in the course and spread of these epidemics unexplained, or else the explanations adduced are open to well-founded objections.

The parasites which are capable of causing infectious diseases belong to the lowest orders of the vegetable and animal kingdoms. Among the plants the **Schizomycetes** or **bacteria** are the most important; among the animal parasites the smallest of living protoplasmic bodies, called **Protozoa**, play a prominent part. Among the more highly organized plants are the **Saccharomycetes** and **Hyphomycetes**, whose pathogenic importance is much less than that of the bacteria. Among the animal **parasites** occurring in man are a number of **worms** (Nematoda, Trematoda, and Cestoda) and **Arthropoda** (Arachnida and Insects). Their action is, however, markedly limited, and the pathological conditions produced by them are not generally classified as infectious diseases in the true sense of that term.

For the production of a true infection a given parasite must increase and reproduce itself through a number of generations within the human body, and must spread more or less widely throughout the tissues. This definition being accepted, and at the same time the itch-insect being excluded (for it reproduces many generations in the skin), we must place in this class only the parasitic Schizomycetes, Saccharomycetes, and Protozoa. The majority of the more highly organized animal parasites live only a portion of their lives within an individual organism—i.e., within the same host. Such parasites as multiply within the invaded organs by means of the production of eggs or of formed offspring are devoid of the power to become again reproductive in the same host.

Parasitic infection—i.e., the entrance into the human body, and the increase, of a parasite—can occur in almost every portion of the body. The most usual seats of infection are the mucous membranes that are most easily accessible from without, particularly the intestinal and respiratory tracts. In many cases the parasites are introduced in the food and the drink, especially in water. The pathogenic organisms being for the greater part very small and easily suspended in the atmosphere, they are by this means carried about everywhere. They are often obtained from respired air, and are found distributed partly in the respiratory tract, partly in the alveoli of the lungs, where they remain clinging to the walls, and frequently are taken up into the tissues.

Wounds form a broad field for the entrance of small parasites. Becoming infected by means of the air, or from contact with unclean fluids or with solid objects, they thus furnish the starting-point of an infection. Finally, many parasites can attack an injured cutaneous surface, and there increase, giving rise in this manner to infectious diseases.

The belief that certain diseases, as the plague, were of parasitic origin, is very old, and found expression in the works of Kircher (1602–1680), Lancisi (1654–1720), Linné (1707–1778), and others. Confirmation of the parasitic origin of infectious diseases, however, has been obtained only in these later times. A few decades ago Henle, Liebermeister, and others put forward the belief that only upon the assumption of a *contagium animatum* could we explain the peculiarities of infectious diseases; but it is only within the last twenty years that the doctrine of their parasitic origin has obtained a really firm foundation.

The influence which **climate** exerts upon man—the effects of temperature being left out of the account—is essentially dependent upon the consideration whether or not the special micro-organisms which have the power of producing disease develop in the

soil of that particular locality. A harsh, rough, windy climate may thus be healthy, while one that is mild and subject to but slight variations of temperature may be an unhealthy one. In well-populated regions the question naturally arises whether infectious diseases are to be found among the inhabitants. Periodic fluctuation in the virulence of the noxious influence in a certain climate is partly dependent upon the fact that micro-organisms do not multiply in the same ratio at all seasons, and partly upon the fact that pathogenic micro-organisms present in the soil do not always get into the drinking-water and into the atmosphere, or at least are only occasionally brought in this manner into the human organism.

According to Pettenkofer, the spread of miasmatic-contagious diseases—as, for instance, cholera—is not to be explained by the fact that the bacteria from the dejecta of a patient are able to survive outside the body for a given length of time, and under favorable circumstances to develop, and then through drinking-water, food, or unclean hands to find their way into the mouth and the intestinal tract, and again cause cholera in the human subject. He believes, rather, that the infecting germ, having reached the soil, is capable of producing its characteristic poison only when certain temporary local conditions are present—that the poison there increases its virulence by reason of its combining with an unknown something due to certain conditions of the soil, in order to be capable of reproducing the poison of the disease. The latest researches concerning the etiology and spread of typhoid fever and cholera have not confirmed this supposition; they point, instead, to the fact that the bacteria of cholera and typhoid fever are sufficient in and of themselves, in certain cases, to produce infection. It follows from what has already been said that cholera-bacteria, when introduced into the alimentary tract of man, or into that of certain animals, may produce the disease known as cholera.

§ 13. The **disease-producing bacteria** are very small, unicellular masses of protoplasm, which appear in the form of little spheres (cocci) and fine, straight, or curved rods (bacilli and spirilla), frequently uniting among themselves to form peculiar combinations. Some of them multiply in the outer world, and thence occasionally enter the human body. Others, on the contrary, are so constituted that they cannot multiply in the outer world, and only reproduce themselves when within the human or animal body. *The pathological bacteria have therefore been classified as ectogenic and endogenic;* the first are identified with the *miasmatic diseases*, the second with the *contagious*. This division cannot, however, be strictly adhered to, since some bacteria that generally multiply only within the animal organism may, under certain conditions, develop outside these organisms; so that, in a certain sense, a contagium may become a miasm.

On the other hand, it is not necessary for the spreading of a disease caused by ectogenic bacteria that the Schizomycetes shall multiply outside the human body; there occurs more frequently an infection from individual to individual. For instance, the bacillus of anthrax can multiply in the outer world as well as in animal tissues, and the spread of the disease may occur through direct infection of one person by another, or of a human being by an animal, equally as well as by the man or animal receiving the infection from culture-media of any kind. The cocci which produce suppuration, or those of inflammation of the lungs, can infect a hitherto healthy individual directly from the outer world where they have been propagated, quite as well as from another diseased individual.

Therefore it is impossible to draw a definite boundary-line between miasms and contagions, or between ectogenic and endogenic bacteria. This distinction has, indeed, as yet no great value, except that in many infectious diseases one of these two forms predominates, and there are infections concerning which we know of but one mode of spreading. Thus, for instance, smallpox and measles, whose infecting materials have not yet been discovered, are diseases in which spreading is known to occur only through direct and indirect contagion; and similarly,

we are warranted in assuming that the poison of syphilis cannot multiply outside the human body.

Outside the human body pathogenic bacteria are found both in solids and in liquids, and also in the air. In regard to those forms which may increase outside the human body (the bacteria of cholera, of typhoid fever, of anthrax, of suppuration, and of actinomycosis), they are found to be contained in the water fouled by organic substances, in moist soils rich in organic substances, and in dead animal or vegetable tissues containing moisture. They are, besides, often present in dry earths and dried tissues, and from these can pass into the air, as well as from fluids. Thus severe wind-storms, clouds of dust, and sprinkling the streets favor their distribution. It is true that, in the drying of substances containing bacteria, some die, since they cannot survive complete desiccation. Many of the pathogenic bacteria, however, produce *a resistant form* (*spores*), and are thus able to resist thorough drying, and consequently to maintain their vitality in the air. If in this condition they come in contact with solids or fluids, and become attached to them, they may remain alive here for a long period; and if the circumstances are favorable—i.e., if they find a proper nourishing material and the necessary water, and if the temperature of the locality reaches the height necessary for their development—they may again multiply.

If bacteria which cannot, under normal conditions, propagate their kind outside the living animal tissues, exist for a long time outside the body, it is because they produce forms which withstand drying or which are not immediately destroyed by chemical products in the surrounding fluids, moist earth, or the tissues in which they lie. For a limited time these organisms can cling to the most varied objects and yet live, producing for a while the danger that individuals may become infected from objects not properly cleaned. If the bacteria live in spite of drying, the dust of the streets, of the floors and walls of houses, as well as the air itself, may contain bacteria, especially when they are thrown off in large numbers. This is especially true of the *Bacillus tuberculosis*, since in pulmonary tuberculosis the sputum, in intestinal tuberculosis the fæces, and in urogenital tuberculosis the urine, contain a great number of these organisms.

§ 14. **Bacteria** usually **enter the system** through the mucous membrane of the intestinal or the respiratory tract, or through external wounds. From a freshly made wound both pathogenic and non-pathogenic bacteria are taken up rapidly by the juices of the body and so find their way into the blood; whereas a healthily granulating, uninjured wound surface possesses the power of preventing the entrance of many varieties of bacteria. Not infrequently they enter the sound skin, by means of the openings of the hair-follicles or of the sebaceous glands. Under special conditions (coitus, operative measures, dribbling of urine) the infection may take its start from the mucous membrane of the genito-urinary tract. Certain cases of infection may be due to insects which have taken up bacteria with the diseased blood or secretions of men or animals. These insects may have become outwardly infected by the micro-organisms, and then may have deposited the latter on some denuded or ulcerated area of the human skin or mucous membrane, by means of their oral apparatus for piercing the skin and sucking the blood, or by scraping them off their legs upon such exposed spots. If the flesh of an animal containing bacteria is eaten, and if the animal

while alive was suffering from an infectious disease which also occurs in man, this particular disease may be transmitted to man, unless the bacteria have been previously destroyed.

The bacteria arrive at the point of entrance sometimes in company with chemically active substances, as in the intestinal tract, and sometimes without these substances, as in the respiratory passages and lungs; and yet at times chemical poisons may also find their way into the lungs along with bacteria, and so, too, may bacteria find access to the intestinal canal without the effective aid of any other material.

The **injurious chemical substances which accompany the bacteria** may occur as *accidental admixtures of the food*, or of the water used either for drinking purposes or for the cleansing of wounds; or they may be contained in the respired air; but they are more frequently the **products of the bacteria themselves.** All bacteria, including the non-pathogenic, produce (see Chapter IX.), within the tissues from which they derive the nourishment necessary for their growth, certain changes which are called fermentation and putrefaction processes, and which are very closely related to their life-activity and their powers of reproduction. Among these products of chemical metamorphosis are many which are injurious to the organisms of the higher animals and of man, since they are able to produce, in a manner similar to that described in the paragraphs devoted to poisons (§§ 10, 11), local tissue-degenerations and inflammations, changes in the blood, or symptoms of general poisoning, which may result in functional disturbances of the heart and nervous and respiratory systems. The most important of these substances are derived from albuminoid bodies, and belong to the **cadaveric alkaloids** or **ptomaïns.** These substances are basic bodies, many of which are poisonous to the human body, and consequently are called **toxins.** Then we have next the **toxalbumins**—that is, *active albuminoid substances* which probably are produced and cast off by the bacteria themselves (Buchner). Neuridin, cadaverin, putrescin, neurin, and methyl guanidin are basic products derived from putrefying meat, the last three being very poisonous toxins. The bacillus of typhoid fever produces a toxin (typhotoxin) which causes palsies and increases the activity of the intestinal and salivary glands. The cholera-bacteria produce, besides penta- and tri-methylendiamin and methyl guanidin, still other specific toxins, which irritate the intestine, render the blood incapable of coagulating, and produce muscular cramps. The tetanus-bacillus produces tetanotoxin, a toxalbumin which causes muscular spasms. According to Roux, Yersin, Brieger, and C. Fränkel, the diphtheria-bacillus, the anthrax-bacillus, the typhoid-bacillus, the cholera-spirilla, and the pus-cocci produce toxalbumins.

If these **toxic bacterial products** are introduced into the intestines or into wounds in considerable quantities with the bacteria, they may produce symptoms of **poisoning,** without a simultaneous infection—i.e., without increase of bacteria within the tissues. The same thing may also happen when poison-producing bacteria grow in the contents of the intestine, in wound-secretions, or in necrosed lung-tissues, and thus multiply as *saprophytes.* In these cases one cannot strictly speak of an infection, but must rather consider the disease which is making its appearance as an intoxication; at least it is in such cases impossible to draw a sharp line between pure intoxications and infections, since these bacteria, which originally increased in numbers as saprophytes, not infrequently also enter the tissues and multiply there.

Intestinal intoxications *caused by bacterial toxins and toxalbumins* occur when animal tissues or fluids decomposed by the action of bacteria are taken as food; and to these intoxications belong the greater part of the diseases termed *meat-*, *sausage-*, *fish-*, and *cheese-poisonings.* In these cases the particular poison is either introduced as such into the intestinal canal with the food, or else is formed in the intestinal tract. Decomposition and fermentation of the vegetable ingredients of diet—for instance, fermented fruit-juices, cabbage, beans, pease, etc.—exercise an injurious influence upon the intestine, or even upon the entire organism, especially if large quantities are eaten or if the offending article is used as food for a considerable period of time. In this class belongs the chronic disease known as *pellagra, Italian leprosy,* or *scurvy of the Alps,* which is met with in Italy, Spain, southwestern France, and Roumania, and is due to the eating of spoiled maize or Indian corn. This disease is characterized by gastro-intestinal affections, alterations in the skin, disturbances in the functions of the spinal cord and cerebrum, and general marasmus (Lombroso, Tuczek).

If the bacteria which have reached one of the known points of entrance are in the strict sense pathogenic, so that they give rise to an **infection,** they may multiply first in the tissues where they enter, namely, in the intestinal mucous membrane, in a wound, in the skin, etc. The **local effect** of this multiplication is dependent primarily upon the character of the bacteria (see Chapter IX.), and also in a measure upon the peculiarities of the tissue. In general, the local action is characterized by degeneration of the tissues, by inflammation, by necrosis, and also by regeneration; yet the condition varies very considerably in individual infections, so that in many instances the species of microbe causing the infection may be determined from the form of the local changes. It is difficult and sometimes impossible to determine in each case the exact mode of action of the multiplying bacteria; yet one may say that the processes of chemical metamorphosis called into activity by the multiplication of the Schizomycetes produce certain changes in the tissue-cells, the various chemical substances produced by the processes just referred to apparently possessing the power to kill the cells, or at least to induce degenerative changes in them, while in some instances the influence of these substances manifests itself in some form of increased cell-activity. In a certain sense, therefore, a *local poisoning* may be said to be produced by the localized growth of the bacterial colony; and it is certain that greater importance should be attached to the effects of this local poisoning than to the mere *withdrawal of nutritive material* effected by the consumption of nourishing substances. Nevertheless the importance of such withdrawal cannot be wholly denied, for it must be recognized that the tissue-juices are often rendered unfit for the nourishment of the tissue-cells by the chemical changes effected by the bacteria, and as a result of this the cells must necessarily suffer even if no poisonous materials are produced.

The **participation of the whole system** in a local bacterial infection must be very slight, or may even be entirely absent, so that the disease appears as a purely local one (tuberculosis). In other cases the locally produced toxins and toxalbumins find their way into the circulating fluids (i.e., into the blood) of the body, and a *general intoxication* (*toxinæmia*) is produced—i.e., a poisonous effect is exerted upon the nervous system and sometimes upon the blood itself and upon the heart, and the poison thus taken into the system may produce demonstrable changes

in the anatomical structure of the internal organs, especially the secreting glands, and sometimes also in the skin. In many diseases (tetanus, typhoid fever, septicæmia, and diphtheria) these symptoms of poisoning are especially prominent.

If healing should not take place in the original seat of the disease, it may involve the neighboring tissues through a **continuously progressing invasion of the bacteria.** Very frequently the **bacteria pass into the lymph-vessels,** or **into the blood-channels** (*bacteriæmia*), and are in this manner carried off and spread over the entire body. The result of this *metastasis of the bacteria* is the *production of new colonies* at a distance from the seat of the original one, *which new colonies possess all the characteristics that belong to the primary colonies.* There are diseases (tuberculosis and suppuration) in which the number of these **metastatic colonies** is very great, so that numerous portions of the body (glands, lungs, brain, bones, etc.) may become the seats of diseased areas. In contrast to these diseases there are infections in which there is no metastasis of the bacteria from the original seat to other organs (tetanus, diphtheria).

During the metastasis of the bacteria there is usually no increase in numbers in the circulating blood, *the latter acting rather as a vehicle* to carry the bacteria to other parts of the body; and multiplication first occurs when the bacteria have come to rest. Nevertheless in certain infections—as, for example, anthrax—*the bacteria increase enormously in the circulating blood*, and in this way act harmfully on the blood itself. Should small blood-vessels become filled by the multiplying bacteria, local disturbances in the circulation may be added to the poisoning effects just mentioned.

If the **bacteria** should be deposited secondarily in the mucous membrane of the respiratory or genito-urinary tracts, **they may multiply within these tracts** and carry on their characteristic pathological processes. In the same manner **they may multiply in the greater cavities of the body,** as the peritoneal, pleural, and subarachnoid spaces. Should a woman at the time of infection be pregnant, there are **many varieties of bacteria which may be carried to the fœtus** (the bacteria of anthrax, malignant pustule, symptomatic anthrax, glanders, typhoid fever, relapsing fever, pneumonia, and pus-diseases).

The description given above of the course pursued by the different infections can be considered as applying correctly to the typical cases, and there are many infections which run this course (typhoid fever, pyæmia, erysipelas, diphtheria, tetanus, tuberculosis, syphilis, leprosy, glanders, actinomycosis, etc.). On the other hand, there are also many deviations from such a typical course. In the first place, it frequently happens that in infectious diseases which, in general, adhere to the described type, the locality of the inception of the infection is not discoverable, either because no changes have taken place at the point of entry, or because these changes have already disappeared. Such forms are called **cryptogenic infections.** It also happens in many typical infectious diseases that the primary location of the cause of the disease is not recognizable, so that *general disease symptoms occur before any local disease can be recognized*, and the tissue-changes produced later on have more the appearance of a *secondary localization of the disease poison.* This occurs in a number of infectious diseases the causes of which are not known, as, for instance, in scarlet fever, smallpox, and measles; while in some infections, the causes of which are known to us, it is not possible to specify the point at which the first multiplication of bacteria

takes place. Thus, for example, in the case of relapsing fever, we only know that at the time of the fever the spirilla are found in great quantities in the blood; the place where they multiply, however, is not known.

Not infrequently we have a **secondary infection** accompanying one already present. In many cases the association is entirely accidental, while in other cases the anatomical changes set up by the first infection produce a local predisposition to the new invasion. To the first group would belong, for instance, a croupous pneumonia occurring in a patient suffering from tuberculosis of the lungs, while with the second group we would class an infection with bacteria which produce pus and septic intoxication, as occurs in infected wounds, and during the course of typhoid fever, diphtheria, scarlet fever, dysentery, caseous ulcerating tuberculosis, etc. So far as can be judged from the pathological events observed in recent epidemics of influenza in Europe, this disease is also one which predisposes in a marked degree to secondary infections. In certain infections—as, for instance, many forms of suppurative processes—the tissues contain, already at an early stage, two or more varieties of Schizomycetes, a circumstance which shows that in these cases we are dealing with a sort of **association of bacteria**—a **double infection.**

That decomposition produces substances which are poisonous is a fact which has been known for some years. In 1852 Beck observed that ammonium hydrosulphate, if injected into animals, possessed the septic properties found in pus and sloughs. In 1863 R. Panum secured from putrefied matter a *putrid poison*—i.e., a body which was not destroyed by cooking and steaming. The action of this poison on the body was found to be similar to the action of snake-venom and some vegetable alkaloids, producing in dogs salivation, dilatation of the pupils, diarrhœa, fever, and severe prostration.[1] Von Bergmann and Schmiedeberg found a crystalline substance in putrefying yeast which they named *sepsin*, and which produced symptoms of putrid infection in animals. By the use of glycerin, Senator, Hiller, and Mikulicz extracted, from decaying tissue-masses, a substance which exerted a similar septic action. Billroth called these poisonous substances *putrefaction zymoids*. Selmi endeavored to characterize all these substances more minutely, and he succeeded in obtaining from different cadavers a number of extracts soluble in ether or in water, which he recognized as fixed bases of alkaloidal character, and which he designated as **cadaveric alkaloids** or **ptomaïns.** Gautier, Etard, Zuelzer, Sonnenschein, Béchamp, Schmiedeberg, Harnack, von Nencki, Otto, Angerer, and others also found in decomposing tissues the same or similar cadaveric alkaloids, and their experiments with these upon animals showed that in some cases these substances produced no effect whatever, while in other cases they produced poisonous symptoms similar to those produced by curare, morphine, and atropine. Von Nencki (1876) discovered a cadaveric alkaloid (*collidin*) which, as a salt of platinum, crystallized in flat needles. He also produced it in a pure state, and made out its chemical formula. According to von Nencki, Etard, Gautier, and Baumann, and especially Brieger, have studied these ptomaïns, and the latter has produced a large number of them in a pure state, and has ascertained their physiological action. Brieger, for instance, has extracted from fibrinopeptone a poisonous substance (*peptotoxin*) which produces in animals paralytic symptoms and ultimately death. From decomposing horse-flesh he extracted three substances, crystallizing in the form of needles — namely, neuridin, neurin, and cholin, the second of which is markedly poisonous, and, like muscarine, produces salivation, alterations in the respiratory and circulatory functions, contraction of the pupils, and clonic spasms. From fish he obtained, besides neuridin, three other poisonous substances—namely, ethylendiamin, a substance similar to muscarine, and a substance called gadinin. From decaying cheese and glue he obtained the poison neurin, and from decomposed yeast, dimethylamin.

The majority of ptomaïns are not present in fresh tissues, and it is probable from this that they are derived from the breaking up of chemical combinations which are contained in the tissues. Thus, from lecithin, cholin is probably derived, and from this is then produced the poison neurin.

Cholin and neuridin, according to Brieger, are already recognizable in the fresh human brain.

[1] See Panum, "Das putride Gift, die Bakterien, die putride Infection und die Septikämie," *Virch. Arch.*, vol. lx., 1874.

When the poisonous character of a part of the ptomaïns was learned from these investigations, there was a tendency to assume that the toxic symptoms observed in infectious diseases are due entirely, or in a great measure, to the substances called toxins. By investigations conducted during the last few years by Roux, Yersin, Buchner, Brieger, and C. Fränkel, it has been established that the **toxalbumins** play a more important part than the toxins, and can therefore be called the *peculiar specific poisons of bacteria*. Of the active albuminoid substances one formerly knew only the enzymes—pepsin, trypsin, ptyalin, diastase—which produce a hydrolytic decomposition into various elements. The actively poisonous albuminoid bodies, the toxalbumins, have become known only through the study of infectious diseases in late years. Brieger and Fränkel are of the opinion that the toxalbumins which produce the poisonous symptoms are formed, by the action of bacteria, from the albuminoids of the juices of the body. Buchner, on the contrary, holds the opinion that they are produced from the cell-contents of the bacteria themselves, and brings forward, in support of this view, two facts —namely, that the diphtheria-bacillus is capable of producing its toxalbumin in urine free from albumin (Guinochet), and that the tetanus-bacillus produces its toxalbumin in a solution of asparagin and animal salts. The toxalbumins and the enzymes lose their virulence in solutions at a temperature of from 55° to 70° C. In the dry state they can withstand much higher temperatures.

It is noteworthy that, after being injected into the tissue of an animal, the toxalbumins do not act immediately, but after some hours, or even after some days. They differ, therefore, in this respect from ordinary poisons.

Should the composition of the blood be altered and the blood and body-juices be infected by the continuous introduction of harmful substances from bacterial colonies, a condition may be produced to which the term **dyscrasia from bacteria** may with propriety be applied. In this connection it should be mentioned that this name, which formerly indicated an alteration in the constitution of the blood and fluids of the body, which was formerly much used, and which played a great rôle in pathology, is employed very little at the present time.

§ 15. The **disease-producing Mucorineæ and Saccharomycetes** belong, as do the Schizomycetes, to the non-chlorophyllaceous thallophytes, and enter into the human organism in the form of inarticulated and articulated, and sometimes ramified filaments or *hyphæ*, and short oval cells, the so-called *conidia*. These organisms sometimes form peculiarly shaped seed-organs. The individual cells are much larger than those of the Schizomycetes, so that they may already be recognized by the aid of a slight magnifying power. Outside the body the *Mucorineæ* develop as moulds of various colors on the surface of all sorts of organic substances and solutions, the carbon compounds of which serve for their nourishment. The *Saccharomycetes* or *yeast-fungi* are found in fluids containing sugar, and are the cause of their alcoholic fermentation.

The spores or conidia of the Mucorineæ are to a great extent developed in special seed-organs, but they are also occasionally cast off from the ends of the stalks or filaments by a simple process of constriction, these latter constituting a specially resistant type of propagation-cells. Both varieties find their way into the air and may be widely scattered by its currents. In a similar manner the yeast-cells can be carried about in the air, in case any fermentative fluid dries up and the remaining solid product becomes reduced to dust.

As disease producers, the Mucorineæ and Saccharomycetes are much less important than the Schizomycetes, since only a few forms can be reproduced within the human body, and since those which do so multiply always develop only in a very limited area, so that the disease produced remains a purely local one. Finally, they do not produce poisons which are capable of acting upon the entire organism, or upon the nervous system, or upon the blood, but, at most, substances which act only upon the tissues in the near neighborhood of the filaments. They can, therefore, produce only **local infectious diseases.**

The points of entrance for these organisms are in general the same

as those for the bacteria. The development of fungi almost always occurs at points which are accessible from without. Very frequently they develop only in the dead material which lies upon some particular part of the skin or mucous membrane, or upon the surface of a wound. Thus the external ear, from uncleanliness, from the presence of cerumen, or from oil dropped into the canal, may become the seat of their growth. They may develop in necrosed portions of lung-tissue, or in dead epithelium and food-débris in the mouth. Through the introduction into the stomach of liquids undergoing fermentation, a further multiplication of the mould may there occur; and, besides, the stomach usually contains a small number of saccharomycetes. The action of these saprophytic growths of moulds and yeast-fungi is in general insignificant, the latter practically *nil*. The changes produced by the yeast-fungi at the spot where they multiply tend to excite inflammation. The local action is increased by the penetration of the filaments into the living epithelium, at which points they play the part thenceforth of a parasitic growth. Under certain conditions the fungi may penetrate into the connective tissues, but even then their extension is limited. Only in rare instances and under peculiar circumstances has the spread of the conidia by means of the lymph and blood been noted. When this happens, however, and conidia are deposited in other organs, they may there develop into filaments, and cause local degenerations and inflammations. But from these secondary centres no further extension takes place.

Their rôle as parasites is most strongly accentuated in the case of a few forms of filamentous fungi (favus, herpes tonsurans, pityriasis versicolor) which are encountered in the skin, for in this locality they develop in the epidermis and its adnexa, in the hair and nails, and cause there peculiar epithelial degenerations and inflammations of the papillæ and corium.

§ 16. The **production of diseases by animal parasites** can most frequently be traced to the fact that the mature parasites, or their larvæ or eggs, are introduced into the intestinal canal by means of the food or drink or by unclean fingers; and this is particularly true of those parasites whose habitat is the intestine or other structures located in the interior of the body—a circumstance which has caused them to be named *Entozoa*. Parasites that live in the outer tissues of the body—namely, the skin—and are consequently called *Epizoa*, either remain only on the outer surface of the skin, or penetrate from without into it. If the parasites pass from the intestine into the surrounding tissues, this procedure, according to Heller, is called an *invasion-disease*. Animal parasites produce only local changes; yet they may also induce symptoms of a general disease, especially when they are present in great numbers in the body, and pervade thickly either the blood or certain tissues.

Some of the **parasitic Protozoa** are harmless, inasmuch as they develop in the secretions of the mucous membranes without producing morbid conditions. Other forms, on the contrary, penetrate the living tissues and multiply within the cells, so that localized pathological conditions, characterized by the new formation of peculiar tissues, are produced (see, in Chapter IX., Coccidia-disease of the Rabbit's Liver and Epithelioma Contagiosum). Certain forms, which probably are to be classed among the Sporozoa, multiply as inhabitants and destroyers of

the red blood-corpuscles, and are the cause of the infectious disease which is called malaria. The malarial parasites develop externally to the human body, in the earth of certain localities, and are probably taken into the human body through the respired air or with the drinking-water. It is not impossible that other infectious diseases—for instance, smallpox—are caused by parasites that belong among the Protozoa.

Parasitic worms (*nematodes*, *cestodes*, *trematodes*) dwell in the human body, sometimes fully developed and capable of reproduction, at other times as larvæ; in the first case they are mostly intestinal parasites which live on the contents of the intestine, rarely sucking the blood from the intestinal mucous membrane. There are, besides, worms which develop in other regions—e.g., in the blood-vessels, in the lymphatics, in the lungs, in the pelvis of the kidneys, and in the skin. If they produce either eggs or developed larvæ, these either pass away with the dejecta or reach, through active wanderings or by being carried in the current of the blood and lymph, other organs of the body, and thus complete their first stage of development. In this new locality, however, they do not again reach the reproductive stage, but remain in the larval condition. Further development takes place only when these larvæ reach a new host.

The worms which attain the reproductive stage in man enter as larvæ with the food and drink, having made their first development in animals the flesh of which serves us as food; in some cases, however, they are derived from certain of the lower animals that do not serve as food. Others, again, develop in water or moist earth, or even in the intestinal tract of man, so that the eggs or the embryos, which pass off with the dejections, at once commence to develop again, provided they find an entrance into the human intestinal tract.

The worms which exist in man only in the larval form (as the cysticercus) develop from eggs which have come from sexually mature worms which inhabit different animals. They are taken into the intestinal tract mostly through the media of food and drink; still they may be also, under certain conditions, inhaled in air containing dust which has in it eggs capable of development, whence the eggs get into the intestinal tract and complete the first stages of development.

The intestinal parasites produce generally very little disturbance, though they may irritate the intestine mechanically. Those that suck blood (*Anchylostoma duodenale*) can, if they are present in great number, produce anæmia. The parasites which take up their abode in the tissues produce, in their immediate neighborhood, slight inflammation and proliferation of the tissues; but these changes can produce severe symptoms only when the parasites (larvæ of trichinæ) are present in the tissues in great numbers. Some act detrimentally to the parts through the fact that they reach a large size (echinococcus cysts) and thereby crowd aside and compress the neighboring organs.

In general their pathogenic significance depends essentially on their location. A parasite situated in the muscles or the subcutaneous tissues causes slight symptoms, while one located in the eye, the medulla oblongata, the heart, or any vessel, may cause severe complications, and, under certain conditions, death.

Of the **parasitic Arthropoda** (*Arachnida* and *Insects*) some come from the outer world, some from infected animals, and some from infected men. Most of them belong to the Epizoa, which have their habitat in or on

the skin and accessible mucous membranes (lice, bedbugs, flies, itch-mites), or only occasionally take their nourishment from the skin (gnats, horse-flies, fleas). A few multiply either in the skin (itch-mites) or on its surface (lice). In the internal organs is found only the larva of an arachnoid (*Pentastoma denticulatum*). In so far as the Arachnida penetrate the skin, epidermis, hair-follicles, and sweat-glands, they cause symptoms of irritation and inflammation; the bite of insects that draw blood is also followed by an inflammation in the affected region.

II. Metastasis and Embolism, and their Importance in the Etiology of Lymphogenous and Hæmatogenous Diseases.

§ 17. Injuries acting upon the body from without cause, except in certain cases (overheating of the body, lack of food and oxygen, poisoning by nerve-poisons, etc.), local tissue-changes. Should the local disease be caused by missiles, dust, poison, or parasites, these may at the same time introduce foreign substances into the altered tissues. The consequence of this is that **the primary focus of disease very frequently contains portions of the body which have been set free through tissue-changes, and also corpuscular substances which have been introduced from without,** both of which are capable, on account of their chemico-physical characteristics, of being taken up by the lymph-currents of the body, or by the blood, and carried to other localities, where they again become lodged. If the substances are insoluble they will be carried along in that form; if they are soluble they will be taken up in a state of solution, and then either be destroyed or be excreted by the excretory organs, in their original or in a changed form; or, finally, they may be deposited, once more in solid form, in some other organ or tissue of the body.

When a substance which has penetrated into the tissues, or one which has become free in the body, is taken up by the lymph- or blood-stream and carried to other parts of the body, and there deposited among the tissues, the process is called **metastasis.** If the metastasis occasions a pathological change in the tissue involved, we speak of a **metastatic disease.** Inasmuch as the latter must originate either in the lymph or in the blood, it is correct to speak of it as either a **lymphogenous** or a **hæmatogenous disease.**

As has been seen in the preceding chapter, metastases play an exceedingly important rôle in the pathological processes that occur during life, and yet they are not all of equal significance. The **importance of the metastasis** is dependent rather upon the nature of the transported material.

In the first place, the **size of the metastatic body** influences greatly the course and action of the metastasis, as very small bodies can pass through all the blood-vessels—even the capillaries—while larger bodies can be transported only through vessels the diameter of which when filled exceeds their own diameter. Should one of these bodies in any way enter either the pulmonic or the general circulation and be carried along with the blood-current, its further progress will be stopped when it reaches one of the subdivisions of a vessel which has a calibre too small to permit the body to pass, and then the latter will plug the vessel more or less perfectly. When a somewhat large particle is forcibly thrown in this manner into a vessel it is customary to speak of the

occurrence as an **embolism**, and the body that remains fixed in the vessel is called an **embolus** or a **thrombus** (Fig. 2, *b*). The effect of an embolism is generally to stop the vessel more or less completely and to interfere with the circulation; yet there are cases in which the resultant alterations in the circulation are very varied, owing to the fact that at one time either a complete or a partial compensatory circulation may be established behind the embolus, while at another time such a compensation may be entirely wanting (see Chapter III.). If the compensation is insufficient, or if it is entirely wanting, the tissues supplied by the ramifications of the plugged blood-vessel will either undergo degeneration or will die.

The **nature of the transported body** has the greatest influence upon the subsequent events of the metastasis. If it is a small, bland, insoluble body, its action on the tissues will be very slight; if it is soluble and chemically active, it may produce very marked tissue-changes. If it is made up of bacteria capable of multiplication, they can, by increasing, produce a pathological change similar to that which occurred in the original seat of infection. If they are tissue-cells capable of growth and increase, they may induce a pathological growth.

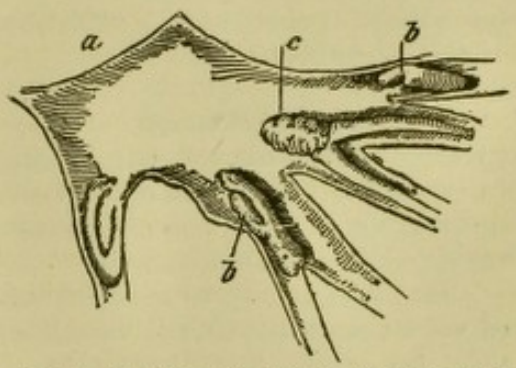


FIG. 2.—Multiple emboli in the branches of the pulmonary artery, after thrombosis of the right auricle. *A*, Arterial branch; *b*, embolus; *c*, embolus, associated with a condition of thrombosis.

Metastasis may occur in the lymph-channels as well as in the blood-vessels, and this usually takes place in the direction of the normal current; but in exceptional instances it may take place in the direction opposite to the current—that is, a **retrograde metastasis** may occur. In the lymphatic channels such a change in the direction of the current occurs when the normal escape of lymph from the territory involved is hindered by the stoppage of the lymphatics, and the lymph is thus compelled to seek other outlets. A similar condition may be produced in limited areas supplied by blood-vessels situated at the periphery of the body. Then, again, plugs may be forced back from the right side of the heart and from the vena cava, by blood-waves running in the reverse direction, into the peripheral venous branches. According to the experiments of Arnold upon dogs, foreign bodies (small particles of wheat) which were introduced into the jugular veins, crural veins, and longitudinal sinus of the dura mater, and which were too large to pass through the capillaries, were carried, by a current running in the reverse direction, not only into the trunks, but also into the smallest branches of the veins in the liver, kidneys, heart, extremities, dura and pia mater, and orbits, as well as into the posterior bronchial veins.

If there chances to be an opening in one of the septa of the heart, it is possible that particles circulating in the blood may pass directly from one side of the heart to the other, and so give rise to the condition termed a **crossed** or **paradoxical embolism.**

The transported particles start in the first place from the primary foci of disease, but it must not be forgotten that such a transported substance may a second time undergo transportation; and, further, that in a metastatic centre of disease there may be produced a fresh crop of

transportable particles, which afterward can be swept along by the blood- or lymph-current to other portions of the body. There can consequently be produced from one metastatic focus of inflammation other new metastases. Finally, it also happens that diseases plainly dependent upon some contamination of the lymph or blood—and which, therefore, may rightly be termed **lymphogenous** and **hæmatogenous diseases**—are developed without our being able to find the primary centre from which the disease started. As such centres often contain bacteria which can originate only in the outer world, one must suppose that these organisms, which ordinarily produce inflammation at the point of entrance, may under certain conditions enter the tissues, and eventually reach the blood- and lymph-channels, without causing such changes at the point of entrance, and that afterward their presence in these fluids may be discovered—a chain of circumstances which gives color to the belief that a **cryptogenic infection** *may take place, and that the metastatic disease may assume the appearance of a primary affection.* This can happen not only when pathological changes are entirely absent at the point where the bacteria entered, but also when they may at one time have been present, but afterward entirely disappeared before the time of the examination.

§ 18. **The bodies which may be subjected to transportation in the process of metastasis** can advantageously be divided into six groups, in which arrangement both the source and the nature of the transported bodies, as well as the effects of the metastases, will be found to have received due consideration.

The first group is made up of insoluble, lifeless substances composed of very small particles, which enter the body from without and which may be called **dust-particles.** The majority of them enter the body by way of the respiratory tract, and pass from the lungs into its tissues. A few may enter the tissues by unintentional or intentional wounds (tattooing). Most frequently they are particles of soot, coal, and stone, while less frequently they are metal, porcelain, tobacco, hair, and divers other dusts. In tattooing of the skin, soot, cinnabar, and other granular coloring-matters play a part.

How the tissues of the organism behave toward these bodies will be described in other places (see Chapter VI., Part III., and Chapter IV., Part IX.). It is only necessary to mention here that these dusts, sometimes in a free state, sometimes within the cells of the tissues, are deposited in the tissues at the point of entrance, or after a time in the lymphatics and lymph-glands. In the latter organs they may remain for a lifetime; but when there is a great deposit the possibility arises of their being transported to remoter spots, this occurrence being likely to take place when the lymph-glands undergo softening by reason of the great quantity of particles deposited in their substance, and excite inflammation and proliferation of the tissues in their neighborhood. As a result of this inflammation the affected lymph-glands are likely to break down and establish a communication with a neighboring vein, and this is especially apt to occur at the hilus of the lung, where eventually the contents of the gland find their way—sometimes immediately, sometimes more slowly—into the calibre of the blood-vessel, and ultimately into remoter parts of the vascular system. According to Arnold, dust in the lung can lodge directly in the wall of the blood-vessel, and thence penetrate even as far as into the intima. Then again,

particles from a broken-down lymph-gland can enter into the lymph-stream, and, if not again arrested in some lymphatic gland, may reach the blood-stream. It is also conceivable that softened lymph-glands may break directly into the thoracic duct.

As numerous experiments have shown, the dust which may gain an entrance into the blood-vessels remains in the circulating blood for an extremely short time. Thus, for example, if even a relatively large amount should be artificially introduced into a vein, at the end of a few hours it will be found to have disappeared entirely from the circulating blood. The greater part is collected in the capillaries of the liver, of the spleen, and of the bone-marrow, and is there found partly within the leucocytes and partly free, in the latter case adhering to the inner surface of the endothelial cells. After a short time there commences an emigration of leucocytes containing the particles of dust out of the blood-channels, so that the dust collects more and more in the tissues, where it is held partly within wandering cells, partly in fixed cells, and in part free for a long while—under certain conditions, even for a lifetime. In the mean time a part is carried, within the lymphatics, to more distant points and there deposited—namely, in the portal and cœliac lymph-glands. Still other dust-cells can, according to the researches of Kunkel and Siebel, reach—through the capillaries of the lungs and the parenchyma of the tonsils, and doubtless other lymphoidal apparatus, as in the intestine—the surface of one of these three cavities, and thence be discharged externally. From the liver they may be discharged by means of the bile. According to observations which one can often make on inflamed organs, the wandering leucocytes are able to transport to the surface in large numbers the foreign particles which lie among the tissues of the lungs, the intestinal tract, and other organs, and in this manner clean the tissues.

The second group of portions of the substance of the body which are occasionally transported from one spot to another by means of the blood-stream is composed of the **remains of tissues** and of **cells of the parenchyma of organs**, in addition to **dead, coagulated, and broken-up blood-constituents.** Among tissue-necroses, the elements which most frequently find their way into the circulation are **fat-drops** (Fig. 3, *b*, and Fig. 4, *b*); and this occurs especially when, through trauma or some other pathological process—as, for instance, hemorrhages—one of the tissues is destroyed. The finding of fat-drops occurs most frequently after the crushing, destruction, and violent agitation of fat-tissues, such as are found in the different panniculi adiposi and in the marrow of bones; but fat may also find its way into the circulating blood after destruction of the tissue of the liver. Of the parenchymatous cells, those which most frequently find their way into the blood come from the liver (Turner, Jürgens, Klebs, Zenker, von Recklinghausen, Schmorl, Lubarsch); less frequently are placental cells (Schmorl, Lubarsch, Leusden) and the giant cells of bone-marrow (Lubarsch) encountered. All of these are generally transported to the arteries and the capillaries of the lung; but they may also, through a retrograde action of the current, be thrown back into the veins; or, through paradoxical embolism, they may find an entrance into the arteries and capillaries of the systemic circulation. Traumatic and toxic injuries and hemorrhages in the affected tissues give rise to emboli composed of liver-cells and the giant cells of bone-marrow. Placental-cell emboli, in the form of multinuclear giant cells, are observed in puerperal eclampsia, but it is maintained by Leusden

that they are also encountered in the course of a normal pregnancy. In pathological conditions of the intima of the heart or the blood-vessels, *degenerated endothelial cells, broken-down and degenerated masses of the connective tissue of the intima, portions of the valves* and similar material may enter the blood-stream. *Fragments and disintegrated portions of blood-corpuscles* may emanate from hemorrhagic foci or even from the blood-vessels themselves (as in the case in which the blood circulating in them has begun to degenerate through the influence of some harmful agency), and in this condition they may form a part of the circulating blood. On the other hand, *coagulated masses of blood* enter the circulation when a **thrombus**—i.e., blood coagulated in the vessels (see Chapter III.)—breaks loose from its attachments, either *in toto* or in fragments.

The fate of the last-named substances is dependent upon their size and physical characteristics. All fragments that are of greater calibre

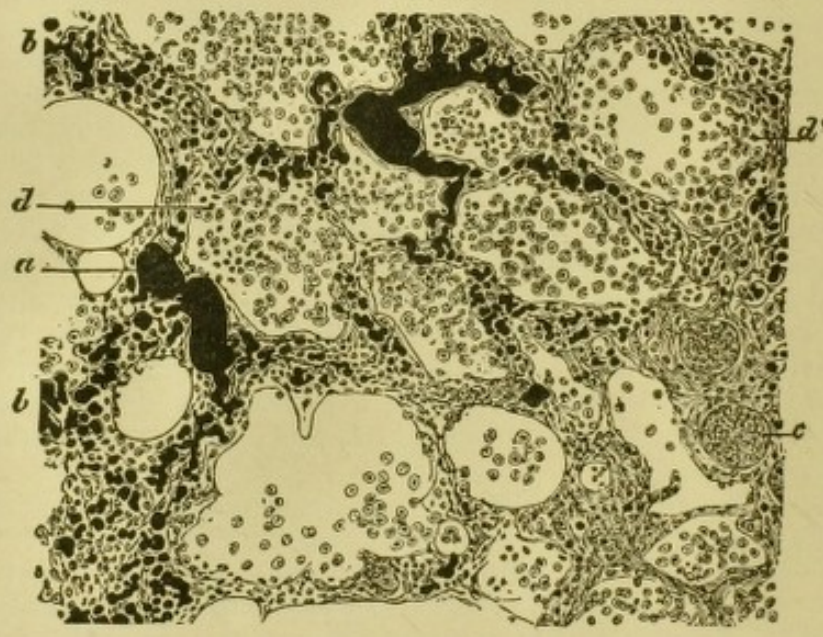


FIG. 3.—Fat-embolism of the lungs. (Flemming's mixture; safranin.) *a*, Arteries plugged by blackened fat; *b*, fat-drops in capillaries; *c*, veins; *d*, cells in the alveoli. Magnified 100 diameters.

than the capillaries remain impacted in the bifurcations of the artery (Fig. 2, *b*), and generally effect occlusion of the vessel. This usually results from thrombi dislodged from other localities, or from fragments of them. The fat-droplets, on the other hand, generally pass into the capillaries, and some remain there, while others pass through their lumina and become arrested only in some other locality. It is because the fat-droplets occasionally pass into the veins and then into the heart that we find them collected especially in the capillaries of the lungs (Fig. 3, *b*). They may go, however, still further; passing through the lung, they may reach the capillaries of the major circulation, and thence enter the intertubular and glomerular capillaries of the kidney (Fig. 4, *b*), and occasionally they are also found to some extent in the capillaries of the brain. Fat-emboli in the capillaries produce noticeable alterations in the circulation only when they are present in great numbers; but when this is the case they can produce œdema at various places in the body (Virchow). Furthermore, fat is destroyed in the progress of metabolic changes.

When transported by means of the arterial circulation, parenchyma

cells remain fixed in the arterioles or capillaries, the stoppage occurring in the former when the liver-cells enter the circulation *en masse*. At the point of impaction their presence can produce a collection of blood-plates associated with a hyaline coagulation, this occurrence taking place in the case of emboli formed of liver-cells. The cells themselves do not multiply, but may remain intact for a certain length of time (according to Lubarsch, three weeks) and then gradually die, when the protoplasm dissolves, and the nuclei swell or shrink and lose their chromatin. In multinuclear cells the dissolving is followed by a clustering together of the nuclei. The locality where fragments of thrombi, or thrombi which have become detached, are arrested is determined by the size of these masses and by that of the vessel in which they happen to be. Inasmuch as thrombi can be produced in the veins, in the right heart, and in the pulmonary arteries, as well as in the veins of the lung, in the left heart, and in the arteries of the body (see Chapter III.), it is possible for emboli to occur in any of the arteries of the major and minor circulation; and, furthermore, emboli frequently remain fixed at the bifurcation of the arteries, forming **straddling emboli** (Fig. 2, *c*). Through transportation in the reverse direction of the current, emboli may be carried out of the greater veins into the lesser. Defects in the septa of the heart may produce a paradoxical embolism.

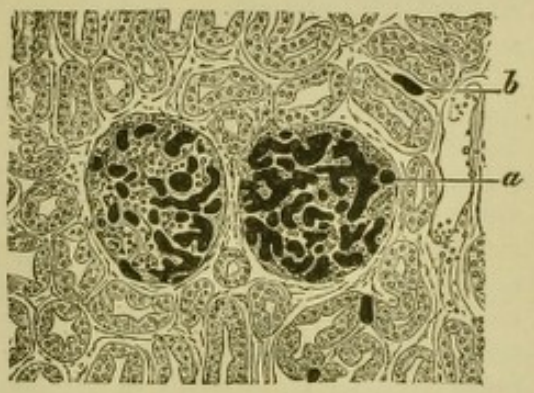


FIG. 4.—Fat-embolism of the kidney. (Flemming's mixture; safranine.) *A*, Glomeruli with (bleak) fat in the capillaries; *b*, fat-drops in the intertubular capillaries. Magnified 100 diameters.

Small collections of débris from thrombi, dead red blood-corpuscles or fragments of them, fatty-degenerated and broken-down endothelial cells, etc., in the same manner as happens to particles of dust, either become incorporated into the substance of cells or remain entirely free; in both of which conditions they are quickly removed from the circulation and deposited in the spleen, the liver, and the bone-marrow, where they undergo further changes and are destroyed. Nevertheless the products resulting from the destruction of the blood form colored and colorless deposits in the organs mentioned, and remain there as such for a considerable period of time (see Part IX. of Chapter IV.).

A third group of substances which produce metastases is composed of **living cells** which have originated in **foci of growing tissues**, and are carried to other organs through the lymphatics or through the blood-vessels, into which latter they find an entrance by a direct rupture of the walls of the vessel. This process is observed when a **tumor**, which has the characteristic of growing by a sort of infiltrative process, develops in some part of the body; and the transportation of living cells from this tumor to other spots in the body, partly by way of the lymphatics and partly by way of the blood-vessels, gives rise to the formation, by a process of proliferation, of **metastatic daughter-tumors** (see Chapter VII.). Metastasis most frequently occurs in the natural direction of the blood- and lymph-streams; but it may also be effected by *backward transportation*, which explains how a tumor which has broken into one of the larger veins of the body produces daughter-tumors in the region

drained by another vein. A backward metastasis is frequently seen in the lymphatic system, when closure of one part of the lymph-channels occasions a change in the direction of the current.

As a fourth group we may mention all those processes which are characterized by the entrance of **vegetable and animal parasites** into the circulation. If, under these circumstances, these organisms do not find conditions suitable for their further development, they are quickly eliminated from the blood-current and, under the influence of the metabolic changes, destroyed. But if they are able to reproduce themselves anywhere, they will lead to the production of **metastatic infectious foci**, which are located primarily in the vascular system, but may also force their way from there into the surrounding tissues. When the invading forces consist of bacteria, the secondary infection will have the same character as that of the primary focus (see also Chapters IX., X., and XI.). Should an embolus contain organisms which possess the power of inducing necrosis of the tissues, inflammation, and putrid decomposition, there will be produced, along with the embolism and the disturbances in the circulation which necessarily accompany it, suppuration and sloughing; or, in other words, there will be a transportation of the very same process which ran its course at the original seat of infection.

As a fifth group of metastatic processes may be classed together the following pathological occurrences: first, those cases in which **constituents of the human body, having undergone solution,** pass into the circulation, are carried to some other part of the body, and are then **deposited in the new location in a solid form;** and second, those in which **substances are taken up into the body from the outer world in a dissolved condition** and are then **deposited in the tissues in a solid form.** Most frequently it happens that the coloring-matters of the bile are taken up in solution into the blood within the liver, are then distributed to different tissues, and at the same time produce granular or crystalline deposits of *bile-pigment.* Not infrequently, *products from the destruction of red blood-corpuscles undergo solution in the blood-stream,* and are deposited, in the form of drops, granules, and crystals, in the spleen, liver, and kidneys. *Substances derived from the coloring-matter of the blood in hemorrhagic foci* may also be taken up into the circulation and distributed to various organs.

In rapid reabsorption of portions of the skeleton, *lime-salts* are brought into solution in great quantities, and may produce calcareous deposits in the mucous membrane of the lungs, the stomach, or the kidneys.[1]

Preparations of silver used medicinally for a long time may produce a deposit of fine *granules of silver* of a grayish-brown color in various organs. The tissues most frequently affected are the connective tissue of the skin, the glomeruli and connective tissue of the medullary substance of the kidney, the intima of the larger blood-vessels, the adventitia of the smaller arteries, the tissues in the neighborhood of the mucous glands, the connective tissues of the intestinal villi, the choroid plexuses of the cerebral ventricles, and the serous membranes.

The fact that the epithelial tissues and the cerebrum are unaffected shows that there is a selective tendency exhibited by the tissues, and that this selective tendency differs materially from that which is seen in

[1] The processes referred to in this and in the next four unnumbered paragraphs probably constitute the author's sixth group.—TRANSLATOR'S NOTE.

the case of a metastatic deposit of the corpuscular elements. It is well to assume that, for this excretion and precipitation of substances in solution, the chemico-physical character and the functional activity of the tissues which come into contact with the blood containing these substances exert a determining influence (compare Part XI. of Chapter IV.).

If a large amount of **air gains entrance to the right heart,** as may occur from the wounding of a large vein in the neighborhood of the thoracic cavity, or, which happens more rarely, from the opening of the veins (e.g., of the stomach) by an ulcerative process, the air mingling with the blood produces a foamy mass, which the contractions of the heart are scarcely able to drive onward. In consequence of this, the left heart contains little or no blood, the aortic pressure falls, and the individual speedily dies. Should the air enter the right heart only in slight or in interrupted amounts, air-bubbles are formed which may circulate through the entire body. Larger amounts sometimes remain for a time in the vessels of the major or minor circulation, cause their closure, and give rise to disturbances of the circulation which may in turn cause disorders of the nervous and respiratory functions. If this condition does not produce death, the air is reabsorbed after a time.

If the lung-tissue is ruptured by some traumatism or by violent coughing, crying, or vomiting, the air may enter the **connective-tissue spaces** and **lymphatics,** and may extend along these into remoter parts of the lungs, into the pleura and the mediastinum, and even out as far as the skin, thus giving rise to conditions which are termed *emphysema* of the skin, of the subcutaneous tissues, of the mediastinum, etc. Under certain circumstances the air may spread throughout a considerable portion of the subcutaneous lymph-channels and connective-tissue spaces, and when this happens the skin presents a blown-up appearance, and pressure upon it produces a crackling sound.

Arnold believes that the lymphatic glands form a sure filter for dust, and that metastases can occur only after the rupture of a lymphatic gland into a blood-vessel. This opinion, which is supported by the results of numerous experiments, seems to me to be correct for all those cases in which the gland-structure is still not too much altered. I think, however, that when the lymph-glands soften, from being overloaded with dust, they may discharge dust-containing, broken-down material through their efferent lymphatics.

As will be shown later (compare Part III. of Chapter VI.), it is an invariable fact that where foreign bodies or dead tissue-masses are present in the midst of living tissues, there wandering cells will be sure to appear, and these, so far as is possible, take up into their substance a smaller or larger quantity of whatever corpuscular materials may happen to be present. This material is then carried further on, especially to the lymphatic vessels and lymphatic glands. Very probably this material is utilized —so far as it is capable of being so utilized—for the nourishment of growing tissue-cells.*

According to Siebel and Kunkel, cinnabar and indigo granules injected into the blood-stream of a frog are rapidly taken up by the leucocytes, and in one or two hours not a granule is to be found free in the blood. At the end of twenty-four hours the granule-containing leucocytes have all passed out of the circulation and lie for the most part rolled together in the capillaries, the largest number being found in the capillaries of the spleen, liver, bone-marrow, and the lungs, while they are found in smaller numbers in the kidneys, and in still smaller numbers in the capillaries of the heart-muscle.

Already at the end of two hours a few granule-containing cells and free granules are found in the tissues outside the vessels, and after a few days they have almost entirely disappeared from the vessels. The granules are then seen partly in the wandering cells, partly in the fixed cells, as well as in the free cells of the splenic pulp (Ponfick)

*Ziegler, "Exper. Unters. über die Herkunft der Tuberkelelemente," Würzburg, 1875; Nikiforoff, "Unters. über den Bau und die Entwickelung des Granulationsgewebes," *Beiträge von Ziegler*, viii., 1890.

and of the bone-marrow. They may even still be found in these organisms weeks afterward (Hoffmann, Langerhans). Both in frogs and in dogs some of the granule-holding cells find their way into the lumen of the alveoli and bronchioles of the lungs, and are then discharged from the system by these channels. In a short time after the injection a large portion of the granules of coloring-matter are found adhering to the endothelial cells of the hepatic capillaries, while a second portion are found in the leucocytes, which later on escape from the vessels into the tissues. From this point many of them manage to enter the lympnatics of the liver and then ultimately reach the lymph-glands. Finally, a portion of the granules are cast out with the bile, but by what course they manage to enter this fluid is not known. In dogs the pigment granules also collect in the tonsils, and are carried by the leucocytes, into which they penetrate, through the epithelial covering to the outer surface.

According to the observations of Jadassohn ("Pigmentverschleppung aus der Haut," *Arch. f. Derm.*, 24 Bd., 1892) and Schmorl ("Pigmentverschleppung aus der Haut," *Centralbl. f. allg. Path.*, 4 Bd., 1893), skin pigment—both that which is normal and that which is the result of some pathological process—may be transported from this part of the body and lodged in the lymph-glands; in other words, a *pigment metastasis* may take place.

III. Secondary Local and General Diseases.—Auto-Infection.—Diseases Caused by the Cessation of the Functional Activity of Certain Glands.

§ 19. If a local tissue-change is caused by any injurious influence, a **primary local** or **organic disease** will occur, which is accompanied by a disturbance of function of the affected part or organ. If the injurious agent finds its way into the juices of the body and into the blood, without causing any noticeable changes at its point of entrance, although inside the body it induces local alterations, we may speak of the condition as a solitary or multiple **lymphogenous or hæmatogenous local or organic disease.**

The local malady may remain confined, during its entire course, to the organ originally affected, and yet it is a very common occurrence for some **secondary organic disease,** or even for a **general disease,** to develop.

One way in which *a pathological process may extend to other parts of the body* is by the process of metastasis—described already in § 18. It is in this way that not merely isolated, but also often a large number of foci of disease develop with such extraordinary frequency in the living body. In many cases *the generalization of this process* by aid of the blood- and lymph-channels is so widespread (as in tuberculosis, suppurations, and carcinomatous growths) that the majority of the organs will be found to contain such foci of disease, and that at the same time they will give unmistakable evidences of being more or less disturbed in their functional activity, according to the extent to which each is involved.

A second group of pathological phenomena owe their origin to the fact that poisonous products are generated in the primary foci of disease, and that these products, when taken up into the juices of the body and into the blood, produce upon many of the organs effects which may be designated as due to *poisoning by substances which have emanated from certain foci of disease.* This form of intoxication is, as I have already explained in § 14, of extremely frequent occurrence in the infective diseases, and gives rise not only to secondary degenerations of different organs, but also to general disturbances of the metabolic processes—such, for example, as a feverish increase in the heat of the body, and some damaging of the central nervous system,—manifestations which indicate the existence of a more or less severe general disease.

A third mode of distribution of pathological processes throughout the body becomes possible by reason of the fact that the integrity and the normal functional activity of many organs are dependent in large measure upon the function of certain other organs, and upon the further fact that the organism as a whole has need—if it is to maintain a normal condition for any considerable period of time—of the perfect functional working of all its organs. Accordingly there is a large group of *local and general diseases which owe their origin to the imperfect functional working of this or that organ.*

Finally, it is not a rare event for normal products of metabolism—which, under normal conditions, are cast out from the body or else are consumed again—to be retained in the body and to escape being consumed; in which event their influence upon the tissues of the body produces conditions which may be described as an *auto-intoxication.*

Auto-intoxications are in some measure the result of the defective functional activity of certain glands, and yet they may also develop under other circumstances; and furthermore *the disturbance of the functions of certain glands may cause, not only auto-intoxications, but also other pathological changes.*

§ 20. **Secondary diseases, which develop in consequence of certain organic affections,** occur with extraordinary frequency as a result of *pathological alterations of the blood and of the circulatory apparatus.*

The vascular system and its contained blood have relations to all the tissues, and accordingly *diminution in quantity and diseases of the blood,* as well as *pathological alterations of the blood-vessels,* very often produce diseased conditions in this or that tissue, or even in the entire body. If the amount of hæmoglobin in the blood is diminished by a decrease in the number of red blood-corpuscles (oligocythæmia), or by some pathological change in the corpuscles themselves, or, finally, if the hæmoglobin be made, by the action of carbon monoxide (§ 10), in a measure incapable of taking up the oxygen from the air, the normal amount of oxygen would no longer be carried to the tissues of the body. Consequently, if the amount of oxygen conveyed to the tissues, under the circumstances just stated, sinks below a certain point, deficient nutrition and its attendant fatty degeneration will result; in fact, in exceptional cases, this deficiency of oxygen may produce death, by causing a paralysis of the nerve-centres.

Should the arteries be closed by *thrombi* or *emboli* (compare § 17 and Chapter III.), or narrowed or actually closed by *thickening of their walls,* as happens in the arterial disease known as *arteriosclerosis,* the regions supplied by the arteries thus affected become the seat of local deficiencies in nutrition and in oxygen-supply, of *local asphyxia,* and, later, of *degenerative processes* which very frequently end in the death of the tissues involved, and sometimes also of the connective-tissue framework of the organ.

In the cerebrum and spinal cord the alterations in the blood-vessels tend to produce ischæmic softening processes (see Chapter IV.), which frequently cause paralyses, and not infrequently end in death. In the heart, the changes in the vessels produce diffuse fatty degeneration, or local softening of the heart-muscle, as a result of which the function of this organ is disturbed, or it may even become entirely insufficient. In the kidney the secreting glandular parenchyma, together with a portion of the connective tissue, undergoes necrosis and atrophy, and the loss of these substances produces local or widespread shrinkings

which are called, according to their size, embolic and arteriosclerotic atrophies.

In the stomach ischæmia of the mucous membrane produces local ulcerations; in the liver and in the muscles it induces atrophy; in short, no tissue can withstand the effects of a long-standing bloodlessness or poverty of the blood. Consequently, narrowing or closing of the arteries by clots or by changes in their walls plays an exceedingly important part in pathology, and is not only the cause of *anæmic necroses* (see Chapter IV.) and *hemorrhagic infarcts* (see Chapter III.), but also of numberless *progressive organic atrophies*. In the production of organic atrophies arteriosclerosis possesses a prominent significance, since it is a very frequent disease with the aged, resulting in tissue-degeneration in various organs. As a result of these degenerative processes, most of the organs attacked contain at a later date cicatrized patches, in which the specific tissue has disappeared, while the connective tissue is increased.

The active participation of the vascular apparatus in all *inflammatory processes* (see Chapter VI.), the *disturbances of the circulation* through alteration in the blood-vessel walls, the *displacements and changing of the vascular channels* which result in part from the *closing of old vessels by proliferating endothelial cells or by thrombi* and in part from the *formation of new vessels*, make it appear comprehensible how in all chronic inflammations the specific cells, deprived of regular nutrition, undergo degeneration, and frequently become replaced, but only to a limited extent, by connective tissue. This is especially true in the case of chronic inflammations of glandular organs.

If there is a profuse watery discharge from the *intestines* the body will suffer for lack of water; and if stenosis of the œsophagus or of the pylorus prevents the intestinal tract from habitually receiving sufficient food, or if the stomach and the intestine are no longer able to digest the alimentary materials which are brought to them, and afterward to carry them along into the juices of the body, the organism as a whole will be made poorer in albumin and fat.

If the *heart* is unable to drive out with normal vigor the contained blood, evidences of venous stasis will show themselves in the more remotely situated organs. If the *respiration* is impeded, or in any way rendered imperfect, the composition of the blood will undergo alterations. A collection of fluid in the thoracic cavity results in compression of the lung; interference with expiration while inspiration remains perfectly free gives rise to distention, and, later on, to atrophy of the lung. If a portion of the *lung* has been rendered useless by a chronic inflammatory process, the inspiratory distention of the thorax acts only upon that portion of the lung which is functionally active. The effect of this is to produce first an overdistention of this part of the lung, and eventually a condition of atrophy due to the abnormal stretching of the tissues.

By increase in the size of the *liver* compression is exerted upon neighboring organs; diseases of the parenchyma of the liver are often followed by disturbances in the circulation of blood through the organ, and at the same time by stasis in the area of distribution of the portal vein, together with abdominal dropsy.

Prevention of the outflow of *urine* from the ureters retards the secretion of urine and leads to atrophy of the kidney. A large excretion of albumin in the urine produces a diminution of the albumin in the body.

The destruction of large portions of the parenchyma of the kidney is followed by increased arterial pressure in the aorta, increase in the heart's action, and hypertrophy of that organ.

An *increased resistance in the pulmonary circulation*, on account of disease of the lungs, is often followed by dilatation and hypertrophy of the right side of the heart. *Obstacles at the aortic opening* which interfere with the emptying of blood from the left chamber lead to hypertrophy of the left ventricle. Stenosis and insufficiency of the mitral orifice cause backward pressure of the blood in the direction of the right heart. This influence may be counterbalanced by a hypertrophy of the right ventricle, or, if this compensation fails, the back pressure exerts its influence upon the veins of the major circulation.

An oblique position of the pelvis produces curvature of the spine. Stiffness of a joint and inability to use it produce atrophy of the surrounding muscles, this atrophy being due to inactivity.

Diseases of the nervous system may give rise to functional derangements and anatomical changes in every organ of the body—in glands, muscles, skin, bones, lungs, heart, intestines, etc. These changes are due in part to an increase, in part to a diminution or even an arrest, of nervous impulses; they are also due to disturbances in the circulation, and perhaps also to the withdrawal of trophic nerve-influence upon which the tissues are dependent for their nutriment. Destruction of the large ganglionic cells in the anterior gray horns of the spinal cord produces atrophy of the corresponding peripheral nerves and the muscles supplied by them. Paralyzed extremities become atrophied. Diseased conditions in the region of the respiratory and vascular centres induce disturbances of the functions controlled by these centres. Injuries of certain portions of the medulla oblongata, concussions of the brain and spinal cord, the presence of tumors in the brain, psychical affections, and poisonings of the nervous system, cause, under certain circumstances, first a rapid absorption of the hepatic glycogen into the blood, and then a secretion of a saccharine urine. Irritation of the peripheral nerves may produce abnormal reflex sensations and movements, as well as circulatory disturbances, in other parts of the body. Paralysis of both vagi, or of the branches which are given off by them, and which are called the recurrent laryngeal nerves, may be brought about by inflammatory processes or by pressure on the part of neighboring lymph-glands, etc.; and the condition is one which may be followed by inflammation of the lungs, by reason of the fact that the accompanying paralysis of the laryngeal muscles permits the entrance of foreign substances into the lung during inspiration.

The *trophoneurotic diseases of the tissues* are mentioned in the main text only cursorily, and their occurrence is set forth as only a possibility. This is done for the reason that the relations of the trophic nerve-system to the individual tissues are still imperfectly understood, and the opinions of different authors vary greatly in regard to the dependence of the tissues upon the nervous system. Many authors ascribe to the trophic action of the nervous system a far-reaching influence on the various diseased conditions to which the tissues are liable, and attribute to the motor, secretory, sentient, sensory, and reflex nerves the power of establishing the necessary connection with the nerve-centres. Others attribute the same power to special trophic nerves. Thus, for instance muscular atrophy, glandular atrophy, bone- and joint-atrophies (in tabes and syringomyelia), diverse diseased conditions of the skin characterized by thinning, exfoliation of the epithelium, loss of hair, inflammation, etc., unilateral tissue-atrophies, and also hypertrophic growths of the muscles, the glands, the skin, the bones, etc., all are attributed to affections of the nerves.

It is not to be questioned that, as the result of disturbances of innervation, there

are produced both degenerative and hypertrophic tissue-changes and inflammations; but most probably these are dependent not upon a condition of the tissues caused by the removal of or change in nerve-influence, but much more upon the increased or decreased functional activity of the tissues, or upon injury or inflammation and disturbances in circulation which have developed coincidently with the disturbances of innervation. An example of this is seen in the tissue-disturbances which are observed when there is a loss of sensibility. Golz and Ewald, who in dogs thoroughly destroyed the thoracic and lumbar portions of the spinal marrow, were successful, by the exercise of great carefulness, in preserving intact the skin of the animals thus operated upon; and consequently they are also opposed to the idea that trophic centres and nerves exist.

§ 21. **Auto-intoxications** or **self-poisonings** may take place in a variety of ways. In the first place, *poisonous products of metabolism*, which are normal both in character and in quantity, *may, through some hindrance or other, fail to be excreted in adequate quantity*, and in this way they may be carried over into the juices of the body and there be retained. In the next place, *the physiological production of poisonous substances may undergo an increase which is great enough to be considered pathological.* In the third place, it may happen that *poisonous products of metabolism*, which under normal conditions are at once decomposed and thereby converted into something harmless, *fail*—as a result of some disturbance of metabolism of either a local or a general character—*to undergo this decomposition.* Finally, it also sometimes happens that, as a result of *pathological changes in the functional activity of certain organs, or even of the entire cessation of such activity, poisonous substances make their appearance in the blood and at the same time also in the urine.*

If injurious substances resulting from the decomposition of albumin are retained in the intestinal canal, or if they are formed there in an abnormally plentiful manner, they may give rise, not only to local pathological disturbances, but also to general intoxications; and, furthermore, through the agency of the bacteria that are present in this canal, the sulphuretted hydrogen that originates from the sulphur which enters into the composition of the albuminous elements, may pass over into the blood in such large quantities that the odor of this gas can be recognized in the patients' breath, while, at the same time, the sulphuretted hydrogen itself will also be found to be present in the urine. The elements which, when taken up into the blood, are capable of producing manifestations of poisoning—such, for example, as vomiting, headache, vertigo, depression of spirits, urticaria, etc.—are, as a rule, those toxins which are derived from the decomposition of albumin through the agency of the intestinal bacteria. It is also probable that the tetany which occurs, as something exceptional, in dilatation of the stomach, owes its origin to an auto-intoxication.

If *the function of the kidneys is disordered* to such a degree that the substances which are convertible into urea are excreted in only insufficient quantities, symptoms of poisoning may manifest themselves in consequence of the retention of these substances; these symptoms consisting of a comatose condition, interrupted from time to time by convulsions, and of disturbances of the respiration—all of which taken together constitute what is designated as *uræmia*. According to von Limbeck the retained substances act like a narcotic, and the first effects of this narcosis are a dulling of the powers of sensation and an inability to sleep. According to Fleischer, the poisoning, through an irritation of the vaso-motor centre, induces a spasm of the muscular elements of the blood-vessels, and this in turn causes a high degree of cerebral anæmia. It is still an unsettled question whether the toxic effect is depend-

ent upon the action of a single element or upon that of a number of substances. According to the investigations of Bohne it is probable that the conditions described are dependent in the largest measure upon the retention of the chlorides within the organism.

Inasmuch as many substances are also eliminated by way of the intestinal tract, it is possible that some defective functional activity on the part of the intestines may thus, under certain circumstances, render it difficult for the organism to rid itself of retained poisonous substances, and in this way may lead to an auto-intoxication. Similarly, the overcharging of the blood with carbonic acid, through some interference with the exchange of gases in the lungs, may also give rise to symptoms of poisoning.

When the excretion of bile from the liver is either arrested altogether or is merely hindered in its escape, through the existence of some pathological lesion in the gall-ducts or in some other part of the liver, the constituent elements of the bile will be taken up into the blood, and there will be produced that condition to which the term *cholæmia* is commonly applied. When this happens, not only the coloring matter of the bile but also the biliary salts enter the circulating blood, and their presence in this fluid produces general lassitude, irritable temper, mental fatigue, a disposition to sleep, a slowing of the pulse rate, itching of the skin, and abnormal sensations of hearing and of taste. These effects upon the heart, the muscles, and the central nervous system are to be ascribed to the biliary salts, which in addition exert a solvent action upon the red blood-corpuscles.

If the liver has already undergone marked pathological changes, there will be disturbances in the formation not only of bile, but also of sugar and of urea in this organ; and besides, it is likely that the substances which are carried to the liver from the intestinal canal, and which under normal conditions undergo in this organ decomposition into other elements, in reality pass through it without undergoing any alteration. There are many who believe that at least the severe symptoms—such as the various forms of mental excitement, delirium, drowsiness, coma, cerebral paralysis—which occur in degenerations of the liver (icterus gravis), ought to be ascribed to the presence of these substances in the blood, and they mention, in support of their belief, the fact that under these circumstances abnormal substances (e.g., ammonium carbonate) make their appearance in the urine.

If the pancreas has undergone degeneration, considerable quantities of dextrose, acetone, and acetic acid (compare § 22)—the last two of which substances are capable of producing poisonous effects—may appear in the blood and in the urine; and consequently one is tempted to refer this pathological phenomenon to some defect in the functional activity of the pancreas.

Finally, the observation has also been made that when the thyroid gland and the suprarenal capsules (§ 23 and § 24) undergo degeneration, pathological symptoms arise which may perhaps be explained (at least in part) by the assumption that, as a result of the degeneration of these organs, certain poisonous products of metabolism cease to undergo decomposition.

The term *auto-intoxication* is not used with the same significance by all authors, many of them giving to it a wider scope than I have given in the preceding text, and even applying the term to the poisonings caused by pathogenic bacteria. In justification of this stand it may be said that these poisons have also in large part originated from

the component elements of the body. Nevertheless, it seems to me that such a widening of the significance of this term is not to be commended, inasmuch as the cause of this decomposition does not reside within the body but reaches it from the outside—in other words, a previous infection is indispensable for the establishment of the poisoning. I am therefore of the opinion that it is more correct to apply the term auto-intoxication only to those poisonings which owe their origin to products of metabolism which have come into existence either through the activity of cells belonging to the organism, or else through that of non-pathogenic bacteria which are always present in the organism (e.g., in the intestines).

According to Bouchard's view the auto-intoxications are caused chiefly by leucomaïns, i.e., by the earlier products of the retrograde metamorphosis of albuminous materials, which materials, under normal conditions, undergo decomposition, chiefly through a process of intra-organic oxidation, until they reach the form of urea, whereupon they are cast out from the body.

Chronic diseases, which are characterized by a change in the whole tone of the bodily functions, are very commonly grouped together as **constitutional diseases.** Samuel places in this category the permanent anomalies of the blood, the lymph-glands, and the nervous tissues (neuropathic predisposition), rachitis, osteomalacia, mutiple exostoses, feeble muscular development, relaxed articular bands, etc. Hoffmann ("Lehrbuch der Constitutionskrankheiten," Stuttgart, 1894) applies the term to the different forms of anæmia, the hemorrhagic diathesis, hæmoglobinæmia, rachitis, osteomalacia, chronic rheumatism, progressive ossifying myositis, the formation of multiple exostoses, obesity, gout, diabetes mellitus and diabetes insipidus, and Addison's disease. Nothnagel, in his "Handbook of Special Pathology," omits diseases of the blood from the constitutional diseases, and includes among them only rachitis, osteomalacia, gout, obesity, chronic rheumatism, arthritis deformans, diabetes mellitus and diabetes insipidus. From these examples it becomes reasonably clear that the conception of a constitutional disease is made to apply to very different conditions. As a matter of fact, the diseases enumerated are not at all characterized by constitutional anomalies; they represent, rather, the sequelæ of anomalies or diseases of certain tissues. Consequently the term "constitutional disease" is commonly employed in an entirely erroneous manner. At most it may still be applied with some fitness to obesity and gout.

§ 22. If a gland produces an **internal secretion**—that is to say, if it contributes to the great mass of the juices of the body or to the blood certain materials which are important for the normal functional activity of other organs or for the organism as a whole—the **alteration of this function** or **its complete abolishment** may cause more or less serious disturbances in the nutrition as well as in the functional activity of other organs and indeed of the entire organism. We are in the habit of attributing the power of producing such an internal secretion to the liver, the pancreas, the thyroid gland, the suprarenal capsules, the thymus and the sexual glands. Nevertheless, our actual knowledge in regard to the nature of these different secretions is still extremely scanty and hypothetical, and we are obliged to infer what influence each of these glands exerts upon the metabolic changes and the life of the organism almost entirely from the disturbances which arise when the glands in question become diseased. Among the most important of the diseases which belong in this category are *diabetes mellitus*, *thyreoprival cachexia*, *myxœdema*, *cretinismus*, and *Addison's disease*, as well as *the functional and anatomical changes which occur in the body as a result of castration.* In a certain sense it is proper to place in the same category *asphyxia*, which arises *from the failure of the lungs to perform properly their function;* for it is through the functional activity of the lungs that the requisite amount of oxygen is conveyed to the organism.

Diabetes mellitus is a disease characterized by the presence of a large amount of grape-sugar in the urine (glycosuria), accompanied by a marked increase in the total amount of urine secreted (polyuria), often also by the pathological increase of acetone and by the excretion of acetoacetic acid and β-oxybutyric acid in the urine. At the same time grape-

sugar and the acids just named are found in the blood, and frequently diminish its alkalinity. When the blood of these patients contains a large proportion of acids, headache, a feeling of anxiety, delirium, faintings, and finally arrest of consciousness (coma diabeticum) are apt to develop, and these conditions are probably attributable to intoxication by acids (Stadelmann, Minkowski).

The presence of sugar in the urine may be due to the fact that too much sugar has been taken into the body, so that a portion has entered the urine unchanged (alimentary glycosuria). Glycosuria may also occur in consequence of injuries to particular parts of the medulla oblongata (puncture of Bernard), or as the result of disease in the cerebrum (softening, epilepsy, mental affections, severe psychical derangements, tumors, parasites), or of some form of poisoning (carbon monoxide, curare, morphine, strychnine, amyl nitrite, nitrobenzol), in which the liver probably gives up its glycogen into the blood more rapidly than normal, so that a hyperglycæmia is set up.

Finally, glycosuria may occur when the kidneys are unable to hold back the slight amount of glucose which is normally present in the blood, a phenomenon which may be produced experimentally by the administration of phloridzin (von Mering) or of caffeine sulphate (Jacobi).

These alimentary, neurotic, and toxic glycosurias are, however, to be distinguished from the ordinary diabetes in that the cause of glycosuria is to be sought not in an increased conveyance of sugar into the blood or a pathological excretion of sugar contained in the blood, but rather in the fact that the diabetic patient is unable to decompose sufficiently the carbohydrates, and especially the dextrose, while the sugars which turn polarized light to the left (levulose and inulin) usually can be oxidized, if not entirely, certainly in greater amount than dextrose. In most cases, also, the power to form fats from the carbohydrates is lessened; yet there are cases in which this function is intact, and the sugars are stored up in the body as fats (diabetogenous obesity).

According to the investigations of von Mering and Minkowski, which have been confirmed by different authors, this loss of power in the organism to oxidize the sugar brought into the body, or to store it up as glycogen or fat, is to be explained by a **weakened functional action of the pancreas.** This conclusion is drawn from the fact that, after the total extirpation of the pancreas in dogs, a severe, and after a few weeks fatal, diabetes is produced, which is characterized, as diabetes is in the human subject, by polyuria, polydipsia, hyperglycæmia, glycosuria, a diminution of the glycogen in the tissues, and occasionally also by the existence of active destruction of albumin, by emaciation, by excretion of large amounts of acetone, aceto-acetic acid, β-oxybutyric acid, and ammonia, and by the appearance of a comatose condition. In support of the supposition that there is a definite relation between the disturbance of the pancreatic function and diabetes, we find in certain cases of this disease that the pancreas has undergone some alteration—that is, it is atrophied or degenerated; it should, however, be borne in mind that the anatomical examination often fails to disclose a pathological condition of the pancreas, so that we must content ourselves with the belief that the anatomical alterations which may underlie the functional disturbance of this organ are not sufficiently well marked for us to be able to demonstrate them.

A precise explanation of the causal relations existing between diseases of the pancreas and diabetes cannot be given at the present time;

yet from the foregoing experimental researches we may deduce the hypothesis that the pancreas yields a substance to the juices of the body which enables them to destroy the glucose, which power is lost after destruction of this gland. Likewise, an explanation cannot be given of the increase in the destruction of the albumins, and the attendant destruction of β-oxybutyric acid, aceto-acetic acid, and acetone. As these substances are not always found in artificially produced pancreatic diabetes (Minkowski), it would appear that they have no direct connection with the excretion of sugar, but should be considered rather as constituting a complication of diabetes. They may also accompany other diseases (poisonings, carcinoma, derangements of digestion), and are not always to be found in cases of diabetes.

The development of *diabetes* after the total extirpation of the pancreas furnishes evidence that the pancreas has an especial function which is of the greatest importance in the normal consumption of sugar in the organism. Lépine is of the opinion that there is in the blood a glycolytic ferment which is derived directly from the pancreas, and that, in diabetic patients and in dogs from whom the pancreas has been removed, the cause of the mellituria is to be sought in a decrease in the amount of this ferment. According to Minkowski, Lépine's experiments are not sufficient for the support of this theory. A satisfactory explanation of the genesis of pancreatic diabetes cannot be given at the present time.

If we remove only a part of the pancreas of a dog, no diabetes occurs, or at least the separation of sugar is much less than after total extirpation of the organ (Minkowski). In dogs under whose skin a portion of the pancreas has been ingrafted diabetes is not produced, even when the gland has been completely extirpated (Minkowski, Hédon); it recurs, however, as soon as the implanted portion is removed.

According to Minkowski, there is no direct relation between the secretory functions of the pancreas and those which aid in the assimilation of sugar.

According to von Mering and Minkowski, poisoning by phloridzin produces in man and in most animals a marked glycosuria, and symptoms similar to those seen in diabetes may be produced by a continuous administration of the poison. Since the cause of the pathological excretion of sugar lies in the kidney and thus represents a washing out of the sugars from the organism, the phloridzin diabetes cannot be identified with the ordinary diabetes—that is, the pancreatic diabetes as found in man. In dogs in which diabetes has been produced by extirpation of the pancreas, phloridzin produces an increase in the amount of sugar excreted (Minkowski).

§ 23. **Cachexia thyreopriva** is a peculiar disease which is *produced by the decrease or suspension of the function of the thyroid gland*, these conditions resulting either from defective development or from pathological changes in the gland. To Kocher belongs the honor of having discovered the cause of this disease, he having observed that it followed the total extirpation of the thyroid gland. Numerous clinical observations and experimental researches which followed this discovery have confirmed the fact that the presence of thyroid tissue is necessary for the maintenance of the integrity of the organism, and that the body, especially during its growth, requires a thyroid gland capable of performing its functions in a normal manner. Probably this gland produces a substance (thyroiodine) that serves a useful purpose in the metabolism of the body; it is also possible that it changes or destroys deleterious substances circulating in the blood.

According to experimental and clinical observations, the total extirpation of the thyroid gland produces in man, as well as in animals, after a very short time, severe morbid symptoms, which are characterized by the appearance of convulsions and cramps, and finally by palsies of the muscles, so that the condition has been called **thyreoprival tetany**. Young animals and the carnivora are especially sensitive, and dogs die mostly in a short time after the total extirpation of the thyroid.

If the loss of the tissues of this gland is borne fairly well at first, as occurs in human subjects, then after the lapse of months, or perhaps even of years, peculiar disturbances of nutrition begin to show themselves. At first these consist of a feeling of weakness and heaviness in the limbs, sensations of cold, often accompanied by pains and transient swellings of the limbs, and decreased mental activity; then, later, a **cachexia**, accompanied by anæmia, manifests itself, and at the same time pale waxy swellings of the skin, especially of the face (Fig. 5) appear, and there is a noticeable diminution of mental power, together with a decrease in muscular power; and, finally, the termination of these conditions is apt to be death. The removal of the thyroid gland in childhood produces disturbances in development, and may prevent either entirely or partially the growth of the bones in their longitudinal axes (Fig. 5). Animals (rabbits, goats) that have had their thyroid gland removed early in life fail to attain their full growth and acquire a stupid look.

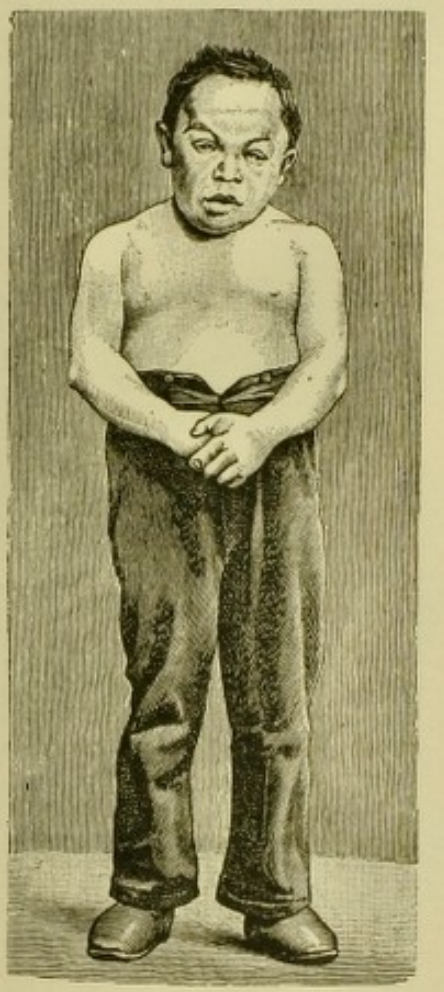


FIG. 5.—Thyreoprival cachexia, with a disturbance of the bodily and mental growth such as is observed in cretins. Age of patient, twenty-eight years; length of body, 127 cm. This condition developed after the complete extirpation of the thyroid gland in the patient's tenth year. (Consult Grundler: "Zur Kachexia Strumipriva, Mittheil. a. d. chir. Klin. zu Tübingen," i., 1884.)

In thyreoprival tetany the body-temperature is raised; in thyreoprival cachexia it is lowered.

Pathological functional changes, as well as total extirpation of the thyroid, may produce pathological conditions of the body, and both experimental and clinical observations tend to show that **myxœdema** (Ord) is a disease (Fig. 6) which is especially dependent upon changes in the thyroid gland. Myxœdema is a condition in which the external appearance of the patient reminds one of the thyreoprival cachexia; there is the same peculiarly pale elastic swelling of the facial skin (Fig. 6), which does not yield to the pressure of the finger, and which may also be accompanied by similar pale and dry swellings in other parts of the body. Later on, there is a decrease in intellectual power, which shows itself in an increasing difficulty in thinking and acting, also in dulness of tactile sensation, in retardation of muscular reaction, and in the monotonous, nasal character of the voice. Finally, marked general weakness and often symptoms of actual mental derangement appear, and the fatal termination occurs under manifestations of increasing cachexia, anæmia, and coma.

So far as may be judged from the clinical and anatomical facts observed in patients affected with this disease, it is highly probable that **cretinism** (Fig. 8), or rather the alterations in the structure and functions of the body which characterize this disease, is also dependent upon disturbances of the functions of the thyroid gland. Thus we know

that in cretinism there is always degeneration of the thyroid gland, which may manifest itself in an enlargement of the organ, together with a certain amount of alteration of its structure (goitre), or in a contracted and atrophied condition of the gland. The fact should also be stated that cretins (Fig. 8) in their general aspect remind one of those individuals whose growth has been stunted through a thyroidectomy (Fig. 5) having been performed upon them during childhood. The longitudinal growth of the hollow bones is more or less imperfect, while the soft parts are relatively well developed. The different portions of the body are unequally developed. The head, for example, is relatively large; the abdomen and neck are thick; the root of the nose is depressed, while the nose itself is broad and stumpy; the skin, especially of the

FIG. 6.—Myxœdema (case observed by Meltzer). Age of patient, thirty-seven years.

FIG. 7.—Myxœdema. The same individual (Fig. 6) three months after the pulverized thyroid gland of the sheep had been regularly administered.

face, is pale, flabby, wrinkled, and puffy, as if œdematously swollen. The mental faculties are always feeble, sometimes markedly so. The power of speech and of understanding words may be entirely absent; and only those persons in whom cretinism is but slightly marked are capable of performing work of any kind.

Since cretinism appears to be an endemic disease in certain regions, it is reasonable to suppose that an unknown local miasm, probably taken into the system in the drinking-water, acts in such a manner to cause degeneration of the thyroid gland during the time of bodily development, and injures the entire organism by disturbing the function of this gland. We have, then, a miasm the action of which produces the same effects as an operative removal of the gland; and since we call this action *epidemic cretinism*, we might also term cachexia thyreopriva *operative cretinism*. In addition, we might add myxœdema to the cretinisms, and term it a *sporadic form*, in contrast to the epidemic.

The great importance of the thyroid gland for the nutrition of the body, the cerebral functions, and the growth of bones can no longer be doubted, after the numerous clinical

observations and experimental researches which have been made. Regarding the mode of action of the thyroid gland there are, however, many opinions. If an animal, after its thyroid gland has been extirpated, is fed with that belonging to some other animal, —say, for instance, the sheep,—the injurious effects which usually are observed after a thyreoidectomy will fail to appear, or, at all events, they will not appear until we stop feeding the animal with thyroid-gland substance. In the human being the systematic administration of thyroid-gland tissues, either in a fresh state or in that of an extract, exerts a curative influence upon thyreoprival cachexia and myxœdema (see Fig. 7); and, furthermore, reports have been published which show that favorable results may also be expected from a similar treatment of children who are suffering from cretinistic disorders of bodily and mental growth. Goitres (i.e., enlarged and hypertrophied thyroid glands) which have not yet undergone some form of secondary degeneration, often diminish greatly in size under the systematic administration of thyroid-gland tissues throughout a period of several weeks. In fact, the diminution in size begins to show itself already at the end of a few days.

According to Lanz, the extirpation of the thyroid gland in hens causes the eggs which they lay to diminish in size. On the other hand, the latter will be increased in size if the hens are fed with thyroid-gland substance.

According to the investigations of Baumann the thyroid gland always contains a certain element in combination with iodine, viz., **thyroiodine** or **iodothyrin.** This substance is present in the largest quantity in individuals who are advanced in years, and in the smallest quantity in quite young children. Iodothyrin is generally combined, in the thyroid gland, with an albuminous substance and with one containing globulin, but it is also occasionally found in this gland in an uncombined form. A healthy thyroid gland is able to store up in its tissues the extremely small quantities of iodine which are ingested with certain articles of vegetable food or with the drinking-water, and then to convert them into the combination mentioned above. When preparations of iodine are administered internally or when a wound is treated with some form of the remedy, a more considerable quantity of iodine is likely to accumulate in the thyroid gland.

FIG. 8.—A female cretin, twenty-one years of age (from Virchow). Length of body, 84 cm.; length of arm, 30 cm.; circumference of skull, 52 cm.

Baumann maintains that iodothyrin is the element of chief efficacy in the composition of this gland. Its employment in the treatment of goitres, myxœdema, strumiprival cachexia, etc., produces precisely the same effects as those which are obtained from the administration of fresh thyroid-gland tissues.

According to the investigations of the same authority it may be assumed that the living organism requires iodine for its proper maintenance, and that the thyroid gland provides the needed combination of iodine in whatever quantity may be required. In regions where goitres are not encountered (North Germany, for instance) the thyroid glands are, on the average, much smaller (from 30 to 40 gm.) than they are in regions where the disease prevails (e.g., in Switzerland and in South Germany), but at the same time they contain more iodine (i.e., on the average, about 3¼ instead of 2 mgm.). Whether the absence of a sufficient amount of iodine from the food and from the drinking-water is the cause of the hypertrophied condition of the thyroid gland which is observed in cases of goitre, or whether this condition is the outcome of an injury, or whether, finally, some of the forms of the lower organisms are perhaps able to interfere with the specific function of the thyroid gland, are all questions which it is impossible at the present time to answer. Among the domestic animals, those which have a large quantity of iodine in their thyroid glands are the sheep, the cow, and the calf, whereas the quantity found in the thyroid gland of the hog is small.

Anatomical investigations fail to throw any certain light upon the question of the internal secretion of the thyroid gland. It has been proved that the colloid material produced by the cells of the gland passes on into the lymph vessels. It is probable that iodothyrin is contained in this colloid substance. According to Bruns we may attribute the diminution in size which takes place in a goitre after thyroid-gland substance or thyroiodine has been regularly administered, to the fact that in the hypertrophied gland

tissue of these goitres, which contains numerous follicles,—some of them having no colloid material in them, others only a little of it, and still others being imperfectly developed,—there are two different kinds of phenomena going on at the same time: on the one hand, an increase in the secretion of colloid takes place in the well-developed follicles, and the material thus formed is conveyed in abundance into the lymph-vessels; whereas, on the other, processes of atrophy and decay are at work in the less perfectly developed follicles. After the secretion of effective thyroid-gland substance has been going on for some time, some of the secreting follicles begin to undergo atrophy.

The investigations of Rogowitsch, Stieda, and Hofmeister show that the extirpation of the thyroid gland in rabbits causes an enlargement and a peculiar transformation of the hypophysis.

It is possible that Basedow's disease, which is characterized by a pulsating and highly vascular swelling of the thyroid gland, by projection of the eyeballs from their sockets, by accelerated heart action, and by a certain degree of excitability on the part of the patient, has some sort of relationship with a diseased condition of the thyroid gland—viz., with that of *hypersecretion* (*hyperthyreosis*); and in confirmation of this hypothesis it may be stated that the thyroid glands thus affected are noticeably rich in actively secreting gland tissue. However, it is not possible to furnish any convincing proofs in regard to the point in question.

§ 24. **Addison's disease** is a peculiar affection which ends in death after a course, on an average, of two years, and which probably is *produced by some alteration of function in the suprarenal capsules.* Its most noticeable characteristic is the appearance of a light-yellow-brown to dark-brown, diffuse, and spotted pigmentation of the skin, which first shows itself in exposed portions of the skin, as well as on the areas usually pigmented, then on the remaining superficial portions and on the mucous membranes of the mouth (melasma suprarenale). Already, before the recognizable beginning of the disease or before the pigmentation of the skin, there occur loss of appetite, nausea, pain in the epigastrium, diarrhœa, and constipation—all of them symptoms of disturbance of the gastric and intestinal functions. Then, later, these are followed by muscular weakness, and finally also by manifestations on the part of the nervous system, such as asthenia, fatigue on slight exertion, headache, dizziness, faintings, epileptic seizures, and a comatose condition. At times a recognizable increase in the amount of pigment deposited in the skin is also lacking, the disease in these cases being characterized only by the symptoms which are due to gastro-intestinal irritation, and by progressive weakness and anæmia.

According to the comprehensive statistics compiled by Lewin, alterations of the suprarenal capsules are found in about eighty per cent of all typical cases of Addison's disease. Most frequently these organs are found to be changed into a caseous or a partly cheesy and partly fibrous mass. Other lesions which might be called characteristic of Addison's disease are wanting. It can hardly be doubted that the disease of the suprarenal capsules holds a causal relation to this particular disease, so that one may describe it as a **suprarenal cachexia.** In what manner, however, the complete loss of the function of the suprarenal capsules, or simply some modification of their power, produces the injury to the organism, cannot be explained at present. It is not improbable that the suprarenal capsules produce, in a manner similar to that which has been observed in the case of the thyroid gland, a substance which is necessary to the organism. Possibly poisonous substances are also destroyed by the action of the suprarenal capsules.

The literature of *Addison's disease* is unusually rich, but, nevertheless, the very numerous clinical and experimental observations have failed to make clear the genesis of the disease and the precise importance attaching to the suprarenal capsules in the human and animal organisms. At the same time it may be confidently assumed that a

normal functional activity of the suprarenal capsules is essential to the integrity of the organism—an hypothesis which is necessitated not only by the results of clinical observation and by post-mortem examinations upon human beings, but also by the results of experimentation. Thus, for example, the extirpation of the suprarenal capsules in dogs, rabbits, cats, and guinea-pigs causes a diminution in the tension of the vascular system, muscular weakness, nervous manifestations, paralyses, coma, and also—if life is prolonged for a sufficient length of time—a falling-off in the vital powers. Tizzoni mentions also, as an additional result, abnormal pigmentation of the mucous membrane of the mouth. When an extract of suparenal capsules is administered regularly to experimental animals, an increase in the blood-pressure takes place, the pulse-rate becomes slower, the muscular contractions which result from the irritation of a nerve grow stronger, and the movements of respiration become less marked. Some authorities (e.g., Scymonowicz) attribute the increase in the blood-pressure to the effects of the extract upon the vaso-motor centre, while others (e.g., Schäfer) refer it to the effects of the same extract upon the walls of the arteries. Inasmuch as the suprarenal capsules are not anatomically altered in all cases of Addison's disease, many have been disposed to maintain that the disease is dependent upon some other local pathological alterations, as, for example, upon abnormal conditions of the sympathetic nerve and its ganglia. The conditions found thus far, however, scarcely furnish a satisfactory explanation of the disease. The fact that in a small minority of the cases the suprarenal capsules have appeared to be unaltered, cannot be accepted—even if it is conceded that a correct diagnosis was made in every one of these cases (a thing not likely to be true)—as valid evidence against the pathogenic significance of degeneration of these glands, inasmuch as an apparently normal suprarenal capsule may not have performed its functions in a normal manner.

Inflammatory and degenerative changes in the semilunar ganglia and in other parts of the sympathetic system, and also in the intervertebral ganglia, have been found frequently in Addison's disease, and have been described by a number of writers. They can be explained upon the hypothesis of an extension of the inflammation and degeneration from the suprarenal capsules to these points. To conclude from this that Addison's disease is dependent upon a lesion of the sympathetic nerves, and not of the suprarenal capsules, is not sufficiently well founded, since the suprarenal pathological alterations are constant, while those of the nerves have been found in only a few cases.

Manasse found, in preparations that were removed and placed in a chromic-acid solution while they were still at the normal blood-temperature, that the cells of the suprarenal capsules are in most intimate relation with the veins, reaching out into their lumen, and that in the vessels, but especially in the veins, a peculiar hyaline substance is found, which by the chromic-acid solution is colored brown, in much the same manner as are the surrounding parenchyma-cells. It is therefore possible that from these cells a peculiar substance is furnished to the blood. It should be stated, furthermore, that this substance is also found in arteries. It cannot be demonstrated in alcoholic preparations.

In the same category with the pathological conditions which result from the withdrawal of a glandular function are to be classed the abnormal symptoms in the growth and functions of the body which are produced by **castration**—i.e., the removal of the sexual glands. If the ovaries are removed from a woman after puberty menstruation usually ceases at once, although in rare cases it may continue for some time. Sexual desire and the erethism accompanying the culmination of the sexual act usually diminish in intensity, but in some instances they persist without noticeable diminution. Retrograde changes take place in the rest of the genital apparatus, and more particularly in the uterus. Among the different nervous manifestations which are observed in some cases, the commonest are wave-like sensations, coupled with reddening and heat of the skin, especially of the face, and with outbreaks of perspiration; all of which manifestations are particularly apt to occur during the period immediately following the castration. So far as the patient's spirits are concerned they often remain unchanged or may even grow more cheerful, especially if the castration puts an end to the severe suffering which previously existed. Now and then the patient shows some depression of spirits or even melancholia. If the ovaries are removed or destroyed in childhood the growth of the body approaches that of the male; the muscles are strongly developed, the changes in the pelvis do not take place, and the development of the breasts ceases.

Castration in a man produces no marked change in the development of the body. If, on the contrary, boys are castrated the development of the body simulates in many respects that of woman. An increased amount of fat is stored up, especially on the abdomen, while the muscular structure is only feebly developed. The external genitalia remain small, the prostate gland is not of full size, and there is no development of either beard or pubic hair. The larynx remains small, and the voice is childlike. The mental powers are devoid of strength or energy.

In castrated stags the antlers are not developed; in cocks the growth of the comb is arrested.

According to White, Kirby, Kümmel, Bruns, and others, the operation of castration, when performed upon fully grown animals, produces a diminution of the prostate gland; and also, in old men who suffer from hypertrophy of the prostate, a diminution in the size of the enlarged gland may be expected to result from the operation. Other authorities (e.g., Czerny and Socin) express a less favorable opinion in regard to the beneficial effects of the operation in cases of enlarged prostate.

How the *extirpation of the sexual glands* affects the entire body has not been determined with certainty. It is generally supposed that, by means of this operation, the trophic influence which is exerted upon the tissues by the sexual glands, through the nervous system, is withdrawn. The cessation of the menses may indeed be attributed to the fact that certain nervous stimuli have been withdrawn, and it is also likely that influences of the same character are responsible for the atrophy of the uterus. In the main, however, it is more likely that certain *chemical substances* which are formed in the sexual glands exert an appreciable influence upon the functions, increase in size, and development of the body.

According to the opinion of Brown-Séquard, all glands produce a peculiar secretion within themselves, and they contribute substances to the blood which are useful to the organism. He ascribes to the juice of the generative glands a special, exciting, tonic influence upon the organism. According to Poehl, the active principle found in these glands is *spermin*, a base which is present in many glands (thyroid, pancreas, ovaries, spleen), and which, through its catalytic action, is able to restore the oxidizing power of the blood, whenever, through any cause, it becomes reduced below the normal, and to *promote* the so-called *intra-organic oxidation*.

Zoth and Pregl, who have carried out experiments in regard to the effects of a glycerin extract of the testicles of animals, report that injections of this extract increase very materially the power of muscular contractions.

IV. Fever and its Significance.

§ 25. When disease of an organ assumes a constitutional character, or when a disease manifests this character from the very beginning, there is seen very frequently a peculiar combination of symptoms which is called **fever.** It is particularly in the infectious diseases which run their course with toxic symptoms that fever plays an active part. The characteristic mark of fever is the *increase of bodily temperature;* yet other symptoms usually accompany it, as, for example, *increased frequency of the pulse, disturbances in the distribution of the blood,* and *alterations in the interchange of gases in the lungs and in the excretion of urine.* There is usually also a subjective feeling of being ill; and yet it does not form a necessary part of the symptomatology of fever, but is rather the special effect of the infection when associated with symptoms of poisoning; the infection occurring either at the same time with the feverish increase of temperature, or a little before it, or even after it.

The study of the healthy individual teaches us that, in spite of changes in the surrounding temperature and in the external conditions, the bodily temperature maintains a mean height of 37.2–37.4° C. (98.8–99.3° F.). The normal variation in thermal condition between morning and evening is 1.0–1.5° C. (1.8–2.7° F.), the evening temperature being the higher of the two.

The raising of the temperature of the body above that of its surroundings is produced by chemical changes occurring in the organism, especially in the muscles and glands; so energetic, indeed, may be this process that a rise of 1° C. (1.8° F.) may be obtained within half an hour. This phenomenon of heat-production stands in contrast to that of heat-dissipation, the latter taking place especially through the skin, the lungs, and the excreta. Both processes—heat-production and heat-dissipation—are governed by the nervous system, and it is such regula-

tion of both phenomena that makes possible the normal constancy of body temperature.

On exposure to low temperatures the bodily heat-production is increased (essentially by the action of the muscles), while heat-dispersion is hindered by contraction of the cutaneous blood-vessels and by the inhibition of sweat-production.

On exposure to high temperatures the heat-dissipation is augmented by an increase in the frequency of respiration, by dilatation of the cutaneous arteries, and by an increase in the sweat-excretion.

In those conditions which we call **fever** *the proper balance between the production and the dissipation of heat is disturbed*, the former being excessive; and as a result *the temperature of the body becomes more or less elevated above the normal* (Figs. 9, 10, and 11). Elevations of temperature (taken in the rectum) to 38° C. (100.4° F.) are called *hypernormal;* from 38° to 38.5° C. (100.4° to 101.3° F.), *slightly febrile;* from 38.5° to 39.5° C. (101.3° to 103.1° F.), *moderately febrile;* from 39.5° to 40.5° C. (103.1° to 104.9° F.), *markedly febrile;* over 40.5° C. (104.9° F.) (even-

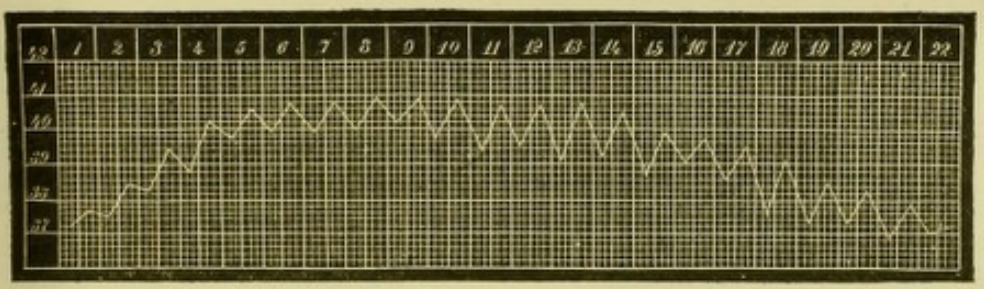


FIG. 9.—Temperature-curve in a continued remittent fever, with a slowly increasing and a very gradually decreasing temperature (typhoid fever).

ing), *highly febrile;* while any temperature over 41° C. (105.8° F.) is called *hyperpyretic.*

Four **periods** may be distinguished in fevers. The first, called the **pyrogenetic** or **initial stage,** or **stadium incrementi,** comprises the time during which the previously normal temperature reaches the characteristic height of the particular disease. This period is sometimes short—from half an hour to two hours in duration (Fig. 10)—and is then generally accompanied by a *chill;* sometimes it is longer (Fig. 9), extending over one or more days, and is then usually unaccompanied by a chill, but in some cases there may be repeated chills.

The second period is called the **fastigium,** or the **acme** of the disease; its duration is very variable, according to the disease, and may be from a few hours to many weeks. The temperature reaches one or more *acme-like crisis-points,* between which are found more or less marked *remissions.*

In the **period of decrease** or **defervescence,** or **stadium decrementi,** the temperature sinks again to normal. If this occurs rapidly, by a sudden decrease in the temperature (Fig. 10), it is called **crisis;** if it occurs gradually (Fig. 9) it is termed **lysis.** The former is usually accompanied by profuse sweating, and in a few hours, or at most in one day or a day and a half, the temperature sinks two or three degrees, or even, under exceptional circumstances, five or six degrees (Centigrade).[1]

[1] Nine or ten degrees Fahrenheit.—TRANSLATOR.

In lysis the temperature falls gradually in from three to four or more days, and may be either continuous or intermittent.

The boundary-line between the acme of the disease and defervescence is not always sharply defined, and before the latter sets in definitively, increases in temperature may occur; this phenomenon is called the **critical change,** or **perturbatio critica.** If between the fastigium and defervescence there are days of uncertainty, with occasional changes in temperature downward and upward, we have what is called the **amphibolous stage.** Sometimes there is observed a short period during which, while the temperature is somewhat lowered, it yet remains constantly above the normal; but after a few days it sinks either rapidly, or by a gradual decrease, to the normal.

In the **convalescent period** the temperature returns to the normal condition. The heat-regulating function during this time, however, is still imperfect, so that often slight increases and not infrequently subnormal temperatures are observed.

If in the course of a fever the daily variations are small, so that the difference between the maximum and minimum is no greater than under

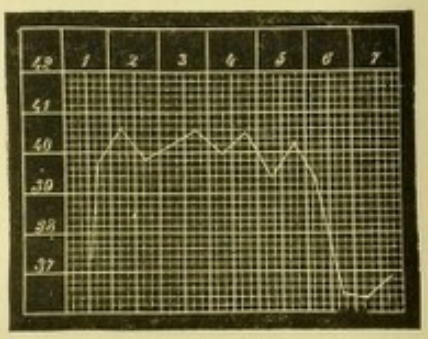


FIG. 10.—Temperature-curve of a continued fever, with rapid increase and rapid decline of temperature (pneumonia).

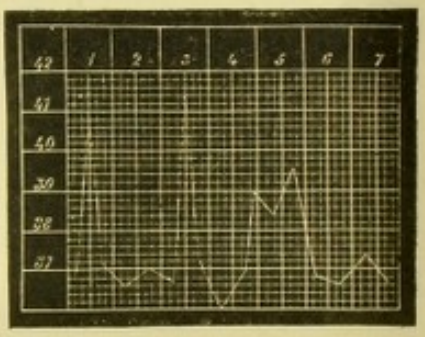


FIG. 11.—Temperature-curve of an intermittent tertain fever (malaria).

normal conditions, the fever is called a **continuous fever** (*febris continua*) (Fig. 10). If the differences are greater the fever is termed a **subcontinuous fever** (*febris subcontinua*) or a **remittent fever** (*febris remittens*) (Fig. 9), or an **intermittent fever** (*febris intermittens*) (Fig. 11). In the latter condition afebrile periods (*apyrexia*) alternate with periods of high temperature (*pyrexia*), and each *paroxysm* has its period of greatest intensity, or fastigium, and its defervescence. In the infectious disease called **relapsing fever** (*febris recurrens*) there is first a continuous fever, which after a few days falls suddenly; after about one week a second rise in temperature may occur, to be followed, after the expiration of another period of apyrexia, by a third return of the fever.

Many diseases—as, for example, typhoid, pneumonia, measles, relapsing fever, etc.—are characterized by typical temperature-curves, while others—like pleuritis, endocarditis, diphtheria, tuberculosis, phlegmon, etc.—show no typical febrile course.

The **elevation of the body-temperature** in fever is dependent, primarily, upon *an increase in the production of heat*, and this in turn is due to *an increased activity in the chemical changes which take place in the body*. The *respiratory interchange of gases*—the giving up of carbonic acid (Liebermeister, Leyden), and the taking in of oxygen (Zunz, Fink-

ler)—*is increased*, a proof that the oxidation processes and the heat-production are increased. At the same time *the excretion of nitrogenous substances in the urine* (urea, uric acid, creatinin) is increased—on the average, from 70 to 100 per cent, but under certain conditions to as much as threefold. The destruction of the albuminoid substances in the body is also increased, and this occurs even as early as in the latent period of the fever (Naunyn).

The second cause of the increase in body-heat is the *defective manner in which heat is given off by the body*. The incompleteness of the process of heat-dispersion may—even in cases in which the production of heat is no greater than it is under certain physiological conditions (for example, increased muscular activity)—bring about a pathological increase of the body-temperature.

When the fever is at its height the patient, as a rule, gives up more heat than does a person who is in health. This dissipation of heat, however, is not sufficiently rapid to offset the excess of heat produced within the body. Furthermore, the excessive production goes on continuously, whereas the dissipation of heat is an irregular process.

In the initial period the skin is pale, and the cutaneous vessels, in consequence of irritation of the vaso-motor nerves, are contracted; heat-dispersion is slight, and, under certain conditions, may even be less than normal.

Rigors occur in fever when, through the contraction of the peripheral arteries, the amount of blood, and consequently the heat-supply, furnished to the cutaneous nerves is suddenly decreased, whereas in the interior of the body the temperature is rising.

In the **second stage of the fever** the skin is frequently hot and reddened, and in certain diseases sweating occurs; the increased heat-dispersion occasioned thereby is, however, not sufficient to reduce the temperature to normal. The increased irritability of the vaso-motor nerves, or the deficient irritability of the vaso-dilator nerves (Heidenhain, Naunyn, Senator), is also present during this period, and, as a result, the skin-temperature, as well as the heat-dispersion, varies considerably. The skin is at times pale and cold, at other times red and hot, and the hands may be cold while the trunk is hot. The centres governing heat-dispersion are therefore acting faultily.

In the **period of defervescence** the relations of heat-dispersion to heat-production are altered, the former being more active than the latter. The cutaneous vessels become dilated, the skin gives out a great amount of heat from the rich supply of blood circulating through it, and, when the critical fall of the fever occurs, there is usually profuse sweating.

We do not know certainly the **cause of fever**,, but we can say this much—that fever is generally *the result of the absorption of a harmful agent into the fluids of the body*. In many cases this harmful agent comes from a demonstrable local source—for instance, from a mass of necrosed and broken-down tissue, or from some centre of erysipelatous and phlegmonous inflammation of the skin. Experimentally, fever may be produced by various procedures—for instance, by the infusion, into the circulation of the animal experimented upon, of blood from another species, by the injection of vegetable or animal substances which have begun to undergo decomposition (Billroth, Weber), and by a great variety of infections. In man we may mention particularly the *infectious diseases* as instances of a fever which is produced by peculiar microparasites which multiply within the body.

It is probable that the microparasites multiplying in the body cause —sometimes directly, and at other times by the production of unformed ferments—an increased retrograde metamorphosis of the tissues, and that at the same time substances are produced which act as *poisons* upon the nervous system. Their action may be supposed to be of such a nature that, on the one hand, through conditions of excitability, the activity of the muscles and glands and consequently the heat-producing metabolism is increased; while, on the other hand, by the lessened and disturbed functions of the nerves governing sweating, as also of the vaso-motor nerves, the increase of the heat-dispersion does not keep pace with that of heat-production; and, further, that the organism makes an effort to regulate the temperature, but is no longer able, in consequence of disturbances in the regulating apparatus, to maintain it at the normal height. To what extent the bacteria and the ferments produced by them contribute directly to the elevation of the body-temperature; how far this elevation is caused by the increased metabolism due to irritation of the nerves, and, further, how far it is caused by the disturbance of the heat-dispersion, are questions which cannot be determined; one thing, however, is certain—the causative factor is different in different cases. That, under certain conditions, changes in the nervous system, without infection of the tissue-juices, suffice to cause the production of a feverish increase in the temperature is shown by the appearance of fever in epileptic attacks, in the excitation periods that occur in the course of progressive paralysis, after severe frights, after the passage of a catheter into the bladder, etc. According to the researches made by Richet, Aronsohn, and Sachs, it is possible, in animals, by a prick which passes through the cerebral cortex and strikes the corpus striatum, to produce marked elevation of temperature, with increase in the respiratory interchange of gases and in the excretion of nitrogenous material (Aronsohn and Sachs); and the same phenomena may also be produced by electrical irritation of the same portions of the brain. Nevertheless fevers which are the result of neurotic disturbance are seldom seen, and are overshadowed in importance by those produced by different infections.

The rise of temperature in fever is usually accompanied by an **acceleration of the pulse**; but still, in some cases, the effect of the elevation of temperature can be so greatly modified by stimulation of the vagus—as, for instance, in basilar meningitis—that the frequency of the pulse is diminished. The pulse is at one time full and bounding; at another, through defective contraction of the heart, it is weak and without body.

The weakening of the contractions of the heart-muscle is dependent partly on the steadily maintained high temperature and partly on the action of the harmful substances that are produced by the morbid processes which are peculiar to the especial disease, and which exert an injurious effect upon the muscular or the nervous system.

In feverish diseases the sensation of being ill is usually very pronounced, and the patient experiences a full sensation in the head. In a severe fever there are present disturbances of consciousness, symptoms of excitation and depression, hallucinations, delirium, general apathy, involuntary evacuations, tremor of the hands, cramps (in children), etc. The muscles of the body become weak, and not infrequently they are painful. Digestion is decidedly impaired; the appetite for food is slight; the thirst, on the contrary, is increased; the mouth is dry. There is increased frequency of respiration, and upon the appearance of muscular weakness it becomes superficial. The excretion of

urine is usually diminished; the amount of urea in the urine is increased, and that of sodium chloride is decreased.

In a long-continued fever marked wasting of the body is produced, a large part of the albuminous materials of the body and of the fatty tissue being destroyed.

It is difficult to say to what extent these symptoms in individual cases depend upon the increased temperature, and to what extent upon the injury done to the organism by the particular morbid process itself, although most of the nervous disorders may be looked upon as resulting from the infection.

Death is commonly due to insufficiency of the heart, and yet it may be produced by the severity of the infection—i.e., by the changes in the bodily juices, through their action upon the nervous system; by wasting of the strength; and also by an excessive elevation of the temperature—to 43°, 44°, and 45° C. (109°, 111°, and 113° F.). It should, however, be remembered that, under certain conditions, very high temperatures may be endured for a long time without producing death, and that death resulting after a very high temperature is not always due thereto, but is more frequently to be looked upon as partly or entirely the result of the infection (compare § 5).

The discussion concerning the nature of fevers, which Galen described as *Calor præter naturam*, has within the last few decades been greatly advanced by numerous exact clinical experimental studies, and we have learned from them of the disturbances of the metabolic processes, of the increased consumption of oxygen, of the increased excretion of nitrogenous and carbon compounds, and of the changes in heat-dissipation. If, despite this, we have not as yet obtained a complete knowledge of all those morbid processes which, in any given case, produce a feverish condition, we may attribute the difficulty to the fact that the efficient cause of fever is not something uniform, but may be any one of several things, and also to the fact that the feverish increase of the bodily temperature is not always produced in exactly the same way. The increased activity in tissue-metamorphosis and oxidation in the body is not always produced in the same manner. Then, furthermore, the disturbance in the heat-dissipation, through the radiation from the skin and through water-evaporation, is not always the same; in fact it changes not only in the course of one febrile illness, but also in the diverse varieties of fever. The part which the nervous system takes in the production of the febrile increase in temperature is not the same in every case. According to Senator, there exists in fevers no harmony between regulation of heat and metabolism. One must therefore suppose that in fever heat is produced by other processes besides those which lead to the formation of urea and carbonic acid. According to Herz, heat is set free by the disarrangement in the molecules of the cell protoplasm—a change which takes place in many cells in fever patients, and which leads to the destruction of the protoplasm. Heat may also be set free by the processes of swelling and coagulation which take place in the cell-protoplasm, while at the same time the diminished activity of the regenerative processes in fevers also necessitates a decrease in the power to retain heat. Krehl and Matthes, on the other hand, maintain the doctrine that oxidations are the sole source of the heat.

V. The Natural Protective Mechanisms, Protective Forces, and Healing Powers of the Human Organism, and their Action.

§ 26. The human organism is not entirely defenceless against the many harmful influences with which men come in contact during the natural course of their lives; it possesses various forms of **protective contrivances** and **protective forces**, which are capable in many instances of warding off noxious influences, or at least of rapidly counteracting their harmful effects, so that a disease is either entirely prevented or shows itself only as a slight lesion, of much less severity than the decided illness which, according to experience, can be produced by this

particular injurious agent. As the kinds of harmful influences are numerous, so are the kinds of protection, and they act at very varying periods—i.e., sometimes even before the tissues have begun to be damaged; sometimes not until such attack has advanced to a certain degree and has begun to spread itself, in part by attacking the surrounding tissues or by sending some of its products to distant spots (metastasis), in part by poisoning the body-fluids or by deranging the bodily functions.

If the environment of the body is relatively cold or relatively warm, the *regulating powers of the organism* are at once brought into play, *increasing the heat-production and heat-dissipation, or diminishing them*, as the circumstances demand; so that the body is capable, within certain limits, of protecting itself against the influence of the surrounding temperature. If the functions of the regulating mechanism are defective—as happens, for instance, in consequence of a fit of drunkenness—a man is more liable to die from the effects of cold than he is when under normal conditions.

One cannot speak of special protecting mechanisms against gross mechanical influences, yet it is to be noted that the tissues are able, through their peculiar qualities, to suffer numberless traumatisms without themselves receiving any harm. If small, hard bodies, such as dust-particles, reach the mucous membrane of the respiratory tract or that of the intestines, the *epithelium* forms a barrier to prevent their being taken into the tissue-spaces; and, further, if they are present in a locality where there are ciliated epithelia, these, through the *movements of their cilia*, will keep them moving onward, or they will become surrounded by *mucus* produced by the epithelium and the mucous glands, and in this envelope they will be carried outside the body.

Not infrequently cells come to the outer surface of the mucous membrane, encompass the dust-particles, and carry them away within themselves, in a secretion derived from the mucous membrane. This phenomenon, which is called *phagocytosis*, is observed on the mucous membranes both of the pharynx and of the respiratory tract, as well as in the alveoli of the lung; and epithelial cells can also take part in the same work in company with the wandering cells which come out of the tissue-parenchyma to the surface, and which are derived mostly from the blood-vessels, and also from the groups of lymphadenoid tissue found in the mucous membrane. This peculiar phenomenon is made possible by the fact that the cells can, by the motion of their protoplasm, take up small particles, which, like insoluble dust, exert no injurious influence upon their protoplasm. If these cells laden with dust escape outward, the act of taking up the dust into their substance appears as a useful activity—one which aids in the cleansing of the organs from dust. On the other hand, if these dust-laden cells—as happens particularly in the lung-tissue—pass into the lymphatic channels and are laid up along the sides of the channels or are carried into the lymph-glands—in other words, if a metastasis of the dust-containing cells takes place into the internal organs (see § 18)—then the taking up of dust by these cells appears in a less favorable light, and one can speak of the act as a useful phenomenon only when one is prepared to consider the infiltration of the pulmonary connective tissue and lymph-glands with dust as less harmful than the collection of dust-particles on the inner surface of the alveoli.

When the particles, either free or contained in cells, reach the *lymph-*

glands, they are arrested at this point and stored away in the cells of these glands, so that the lymph-glands may be considered to be trustworthy *filters* which guard the blood and the internal organs from the conveyance of dust to them.

Against the action of poisons the human body possesses but feeble powers of defence. Against corrosive substances the epidermis of the outer skin and the mucus of the mucous membranes afford a certain amount of protection; and there may occur, under certain circumstances, a marked increase in the production of mucus—for instance, in the stomach—whereby the irritating action of a caustic fluid may be markedly reduced. Through the transudation of fluid from the blood-vessels upon the surface of the mucous membrane, a dilution of the corrosive solution may be produced, which modifies its action. On the other hand, the extension of the corrosive agent over a larger surface may thus be produced, and may result in a more widespread injury to the tissues.

If the poisonous substances are of such a character that, after being taken up into the juices of the body, they act injuriously upon the blood or the nervous system, a protective influence may be exerted by the organism in part through the action of the kidneys, liver, and intestine, which are sometimes able to *excrete the poison rapidly*, and in part through the occurrence of *chemical changes in the poison itself;* but this sort of protection is effective only when the processes referred to take place before any injury has been inflicted by the poison.

§ 27. The human organism possesses various kinds of **protective mechanisms** and **protective forces against the parasitic infections and intoxications**, and they play a very prominent part in all diseases caused by bacteria. According to their activity, these protective forces may be divided into four groups: the first prevents the entrance of the bacteria into the tissues; the second prevents the unlimited local spread of the bacteria which have already begun to multiply; the third prevents their passage into the blood and their transportation (metastasis) to other parts of the body; the fourth hinders the intoxication or weakens and reduces it to a low degree of power.

For the prevention of **the entrance of pathogenic bacteria into the tissues**, the latter are provided with those peculiar powers which, as we have already mentioned, are also competent to hinder the entrance of dust; and in the accomplishment of this purpose the *protective epithelial coverings* and the *mucus* play a very important part. In the respiratory tract the *movements of the ciliated epithelium* furnish efficient protection, while in the stomach the *gastric juices are poisonous* to many pathogenic bacteria. It is certain that many bacteria are not able to penetrate the unwounded external skin or the unwounded mucous membrane without some assistance favoring colonization and reproduction, and that the stomach secretions not infrequently destroy the activity of the bacteria (pneumococci, cholera-spirilla) or even kill them.

It appears, also, not only that the mucus secreted by the mucous membranes can envelop the bacteria in its substance, and in this way hinder their entrance into the tissues, but that, what is more important, the mucus acts upon the bacteria with harmful effect, either through a substance which it contains that is injurious to them, or by producing a culture-medium unfavorable to their growth. It happens thus, for instance, according to Sanarelli and Dittrich, that pus-cocci, cholera-spirilla, and pneumococci gradually lose their virulence in the mucus of the mouth and die, while diphtheria-bacilli, as it appears, are not

injured by the mucus. There are also many kinds of bacteria which soon die in the secretions of the vagina and uterus.

Many pathogenic organisms, therefore, may obtain a foothold upon the skin or upon some accessible mucous membrane, or may enter the lungs; but comparatively few among them produce an infection. Investigation has shown repeatedly that in healthy individuals there are found in the upper respiratory tract and in the mouth not only harmless bacteria—i.e., those which cannot reproduce themselves in the human tissues—but also those which can undoubtedly cause disease, as, for instance, cocci which produce pus, or those which are capable of producing croupous inflammation of the lungs. From these facts we are warranted in drawing the conclusion that the bacteria which are found upon the mucous membranes, and have perhaps multiplied at these spots, often die and are carried away without having produced infection. This is probably what happens in the case of the above-named cocci and the tubercle-bacilli; and to this number should also be added the spirilla of cholera, which suffer when in contact with the acid secretions of the stomach. Finally, we may also assume that many of the pathogenic bacteria that are inhaled into the alveoli of the lungs do not reach the reproductive stage, but die.

If a wound exists at any point the granulations which form upon its surfaces afford a comparatively safe protection against infections, for the tissue-juices which escape from these granulations and pass through their substance, weaken the virulence of, or entirely destroy, many varieties of bacteria.

If **the bacteria have succeeded in effecting a lodgment at some spot, and have begun to multiply,**—it matters not whether they effected a passage through the epithelial stratum without aid from some outside source (as in the case of typhoid-bacilli and cholera-spirilla), or whether they succeeded in reaching the connective-tissue layer by way of some small wound (as in the case of tetanus-bacilli, pus-cocci, the cocci of erysipelas, and tubercle-bacilli),—and if their further progress is characterized partly by local tissue-destruction and partly by a poisoning of the juices of the body, there may be brought into action, on the part of the general organism, certain **counter-influences** *which either restrain the further multiplication of the bacteria, or weaken or perhaps even neutralize completely the poisons produced by them.* The first-mentioned inhibitory influence must naturally be situated in the local surroundings, and depends either upon the vital action of the tissues or upon the action of certain chemical substances.

As has already been mentioned, colonies of bacteria produce local tissue-degenerations, inflammation, and proliferation of tissue—all of which are processes in which the amount and the composition of the fluid which may happen to be at the time in the locality undergo a change; and similarly the cells of the locality also become altered. Inasmuch as, in some of these cases, it is noticed that in the course of the processes just enumerated the bacteria die, and that upon their death the infection often ceases, we may safely draw the inference that the cause of the death of the bacteria is confined to the locality involved.

The prevention of the spread of the bacteria and their destruction, in the spots where they are gathered together in colonies, have been ascribed by many authors to the activity of cells which have collected at the point of infection; and at the same time they have acknowledged that the process termed **phagocytosis**—i.e., the taking up of the bac-

teria by the cells into their substance—plays a decisive part in this work. According to Metschnikoff and others, the amœboid cells of the body carry on a war against the foreign invaders, and endeavor to overpower and destroy them. Such a manner, however, of characterizing the phenomena of phagocytosis amounts simply to a poetical way of expressing one s self, and does not do justice to the essential facts. Its faultiness consists in their attributing consciousness and will-power to the amœboid cells of the body—i.e., to the leucocytes and the multiplying connective-tissue cells. These attributes, it is manifest, could not possibly belong to these cells. Scientifically considered, the gathering together of the cells at the point involved in the disease, and the subsequent phagocytosis, are simply an expression of certain forces which are natural to the amœboid cells. The latter, therefore, in obedience to these laws of their nature, perform certain definite movements when they are subjected to the influence of mechanical, chemical, or even thermal irritants. We know, from numerous investigations made by Buchner, Gabritschewsky, Leber, Massar, and Bordet, that the motile cells of the body can, by means of soluble chemical substances in certain concentrations of solution, be attracted or driven away, and sometimes injured (see the chapter on Inflammation), and, further, that the contact with hard bodies can stimulate them into pushing out protoplasmic prolongations.

These phenomena are known as **negative** and **positive chemotropismus** or **chemotaxis**, and as **tactile irritability**. We must suppose that the bacteria multiplying within the tissues act upon the amœboid cells through a chemical substance which they produce, sometimes repelling and injuring, sometimes attracting, and in the latter case affording conditions which are favorable to phagocytosis. This supposition is also in harmony with the actual behavior of the cells in the different local infections, since in one case the bacteria are quickly taken up by the cells, while in another they are left undisturbed.

If one considers *phagocytosis* of the cells, in the infections, in the light of a process natural to the life of the cell, one can then classify it only as *a specific process destined to facilitate the taking up of nourishing material;* and this interpretation would have to suffer only one exception, and that is when certain microparasites, themselves possessing amœboid motion, penetrate by their own movements into the cells.

The result of the devouring of bacteria by cells depends sometimes on the activity of the devouring cells, sometimes on the peculiar properties of the microparasite, and can either result in the death and dissolution of the parasite or in the death of the cell; sometimes, also, the bacteria live quietly in the cells, thus furnishing an example of a symbiosis of the cells with the parasites. In the first case the phagocytosis may prove to be a curative process, in that it hinders the multiplication and spread of the bacteria. In the second and third cases, on the contrary, the phenomena are useless for inhibiting the further dissemination of the parasites; in fact, there are cases (leprosy, and to a certain degree, also, tuberculosis) in which the parasites, finding therein a proper culture-medium, increase within the cells and finally destroy them. If these infected cells remain intact for a certain length of time they may wander into other regions and in this way effect a metastasis.

Phagocytosis acts as a protective agent only in a limited number of cases, yet it is not to be doubted that the phagocytes in certain infections can take up not only dead or dying, but also living bacteria not yet in-

jured by other agents, and can cause their death. If a large number of cells collect in the infected tissues, they may on this account, by filling completely the lymphatics, produce a certain mechanical obstruction to the spread of the bacteria; but the protection thus afforded is frequently insufficient.

If the bacteria, either free or enclosed in cells, pass from the lymphatics into the **lymph-glands**, these act as **filters**, as in the case of dust, and retain the bacteria; still this protection suffices only when the bacteria collected here are hindered in their reproduction and are killed by the influence of their surroundings. The destruction can be fully accomplished here, also, under the influence of phagocytosis; but this is in many instances possible only after the bacteria are weakened or have already been killed. The taking up of living bacteria by the cells does not always lead to their death; in fact, it is frequently followed by an intracellular multiplication of the bacteria.

More powerful than phagocytosis for the inhibition of the spread of bacteria and other microparasites is the action of certain **chemical substances** found in solution in the tissues. Furthermore, since saprophytic, non-pathogenic bacteria injected into living tissues can be killed in a very short time, we must suppose that *there are in the tissues substances which, by reason of their chemical powers, are poisonous to many varieties of bacteria and can cause their death rapidly.* The same explanation may also be given of the fact (mentioned by Afanassieff) that pathogenic bacteria (bacilli of anthrax, vibrio of Metschnikoff) which are transferred to the granulating surface of a wound, very soon begin to degenerate and then die. Then, again, since many pathogenic bacteria develop only locally—for example, the tetanus-bacilli, diphtheria-bacilli, and cholera-spirilla—and after a certain time die within the infected area without having spread more widely in the body, so is it very probable that the tissues of the body contain **substances which are also poisonous for many pathogenic forms of bacteria** and prevent their wider diffusion. The phenomena observed in local infections show also that these substances are generated at times in increased amounts, or are augmented in their action by newly produced poisonous substances. It is, furthermore, probable that the crowding together of cells, which takes place either in the infected area or in the neighborhood, tends to increase the production of these poisonous substances, and may thus impede the spread of the bacteria; nevertheless attention should be directed to the fact that in some infections the spread of the bacteria comes to a standstill (e.g., in erysipelas) in certain places where there has been no crowding together of cells. It is a fact that in many infections the spread of bacteria in the body by metastasis either is entirely wanting (as in tetanus and diphtheria) or at least is quite insignificant in comparison with the local infection, and is followed by relatively trifling changes (as happens, for example, in typhoid fever). Now the explanation of this fact is to be sought not so much in the circumstance that local changes in the tissues have hindered the spread of the bacteria into the lymph- and blood-vessels—for instance, by the production of peculiar chemical substances, or by the introduction of some mechanical impediment such as would result from the building of a wall of cells —as in the further fact that *there are present in the lymph and blood itself forces which are able to injure and weaken the bacteria that have been taken in, or even to destroy them.*

Some investigators have been led to believe that the **hostile action of**

the blood upon bacteria depends upon the phagocytic action of the leucocytes, and they support this idea, first, by the fact that one very frequently can recognize, after acquired infection, or after one artificially produced by the introduction of bacteria into the blood, such a phagocytosis; and also by the further fact that bacteria within the blood—very many of them contained in cells—are carried out of the blood-channels and deposited in diverse organs—for instance, in the spleen, the liver, the bone-marrow, and the kidneys—in which they die, or from which they are excreted. These observations, however, do not warrant the conclusion that phagocytosis forms in any way a protection against the spread of bacteria in the lymph and blood, since in those very cases in which the bacteria are not carried off in the blood, the phagocytosis is absent; whereas, on the other hand, an entrance of bacteria into the blood, and their multiplication within the vessels, are very often accompanied or followed by phagocytosis. Here, too, phagocytosis is a secondary phenomenon, which occurs when bacteria or protozoa are present in the blood, and, like bland dust-particles, are not able to hinder their being taken up into the bodies of the leucocytes.

When bacteria are taken up by cells they either die or continue to multiply inside the cells; and which of these two courses they will take depends upon their peculiarities and upon the condition in which they are at the time when they are taken up.

According to the researches which have thus far been made, the power which is able to prevent the increase of bacteria in the blood resides principally in **antibacterial chemical substances** which probably belong to the albuminoid bodies (Buchner), and accordingly are termed **protective albuminoid bodies** or **alexins** (the mycosozins of Hankin). The mode of production and the action of these substances are not known, and can be spoken of only hypothetically. So far as conclusions can be drawn from the behavior of the human and animal organisms in infectious diseases, we may assume that *in the human organism there are always present certain protective chemical substances, and that others, on the contrary, are produced only after infection has taken place;* so that not until a certain stage in the course of an infection has been reached is an inhibitory influence exerted upon the development of the bacteria by antibacterial poisons. Such an assumption is supported by the fact that many bacteria (typhoid-bacilli, the spirilla of cholera, and pus-cocci) possess their full power of virulence when they are first distributed throughout the body in the blood, but afterward they lose their virulence and finally die.

The protection which the *alexins of the blood* afford the organism is restricted to certain diseases—i.e., to those infections in which the multiplication of the bacteria is confined to a limited area, or in which the transported bacteria have lost considerable virulence. On the contrary, in many infections the peculiar action of the blood in causing the bacteria to undergo degeneration seems to be entirely wanting, or, when it is present, is easily overcome—as, for instance, in those infections in which the bacteria multiply in the blood itself (anthrax), and also in those in which the bacteria, though not increasing in the blood (infections of tuberculosis and lepra) show no decrease in their virulence after metastasis.

The **protective power** which the organism possesses **against the poisons produced in the tissues by bacteria** is to be found in the possibility of a rapid **excretion of the poisons,** by the kidneys, and, under certain circumstances, through the stomach, the intestines, and the skin;

and the action of these organs is sufficient, in certain cases, to prevent a fatal poisoning. Besides this, in certain infections there is evidently an antagonistic action on the part of the organism, in the sense that certain poisons are rendered inactive or are actually destroyed by **counter-poisons** or so-called **antitoxins**, or that the toxins and antitoxins combine to produce non-poisonous substances, or, finally, that the products of metabolism of the tissues protect the latter from the action of the toxins. It is furthermore possible that by the spread of bacterial products through the body in certain concentration the tissues can be made immune against the same products, or also against the products of other bacteria (see § 30).

The *antibacterial properties of the blood and lymph* in relation to certain bacteria have been established by the experimental researches of a number of authors. These experiments have shown that the destructive action of a definite kind of blood is exerted only upon certain species of bacteria, and never upon all; and that this action, at the same time, is subject to individual variations.

According to the investigations of Fodor, Petruschky, Nuttall, Ogata, Buchner, Behring, Nissen, Pansini, and others, the blood and serum from dogs, rabbits, and white rats are capable of making the anthrax-bacillus powerless, and even of killing it; yet this action is a limited one, so that after the introduction of a large number of anthrax-bacilli into the blood taken from the blood-vessels, the bacilli after a little time begin to multiply. Defibrinated blood of dogs and rabbits can destroy the cholera-spirillum and typhoid-fever bacillus; it is, however, powerless against various forms of pus-cocci and against proteus; the same statement is also true with regard to the blood-serum. Human blood or blood-serum can cause the death of typhoid-bacilli, diphtheria-bacilli, and the bacilli of glanders, but it has no effect upon the bacilli of anthrax. If the bactericidal properties of the blood are exhausted, then these bacteria grow luxuriantly in either blood or serum.

Hankin, Kanthack, Denys, Hahn, Löwit, and others, assume—on the strength of experimental investigations—that the alexins are produced by the leucocytes. Kossel believes it to be possible that the nucleinic acid present in relatively large amounts in the leucocytes plays a part in the destruction of the bacteria.

According to the opinion of Bitter, *the bactericidal substance found in organs*—that, for example, which one can derive from the lymphatic glands, the spleen, and the thymus gland—is to a certain extent different from that which is found in the blood and serum, and consequently does not originate entirely in the blood. It is certain that the bacteria-destroying power of the blood and blood-serum is not the only protective influence which can resist the spread of an infection or prevent it entirely, and can confer immunity.

According to Emmerich and Tsuboi, the bactericidal albuminoids lose their power on being mixed with alcohol and dried *in vacuo* at 40° C., as also by being heated; they recover it, however, when the dried material is dissolved in water containing from 0.05 to 0.08 per cent of potassium or sodium at 39° C., and their activity can thus be greatly increased (a thousandfold).

According to the observations of Czaplewski, the anthrax-bacilli which have been taken up into the leucocytes degenerate more slowly within the infected organism than do those which are free in the blood or the tissue-fluids. It appears, therefore, that under certain conditions the cells protect the bacteria which are contained within them from the bactericidal substances in the fluids of the body.

The *antitoxins* which render the bacterial poisons harmless, are generally first formed during the course of the infection. Nevertheless, the investigations of Wassermann, Abel, Fischl, von Wunschheim, and others have shown that they are also contained in the serum of healthy human beings. Serum which contains an antitoxin that is effective against a certain toxin—as, for example, against the toxin of diphtheria—may nevertheless serve as a medium in which the bacteria of this disease can be cultivated. The antitoxin, therefore, does not destroy the bacteria.

§ 28. The **healing powers of the human body** *are furnished by those functions of life which are fitted to compensate for the derangements and changes produced by disease, and to render harmless or to remove altogether any harmful agent that may still be present in the body.* When portions of tissue are destroyed, the *healing* consists essentially in *the removal of the altered and dead parts, and in the replacement of these by new tissue.*

If from any cause the temperature of the body is abnormally low or abnormally high, compensation is effected by a suitable regulation of the heat-production and heat-dispersion, as a result of which the temperature of the body is once more restored to its normal height. If a portion of tissue is destroyed by a traumatism, the organism can repair the defect either by the production of new tissue on the spot (*regeneration*), or by providing a marked increase in other similar tissues (*compensatory hypertrophy*).

If poisons have entered the body and have produced symptoms of poisoning, there are only two ways in which healing can result—namely, through the removal of the poison by the excretory organs, or through its being changed and made harmless within the body. At the same time the damaged tissues, under the influence of a normal nutrition, again receive a normal organization, and any defects that may remain are in due time compensated for.

In **infections** the healing processes follow directly on the *action of the protective forces;* indeed, the action of the latter constitutes the first stage of the healing process. Consequently *the protective and the healing forces are in a measure identical.* If the alexins succeed in hindering the growth of the bacteria, and then if the weakened bacteria are dissolved and destroyed in the fluids of the tissues or within the cells, the first step in the healing process will have been taken, inasmuch as the *causa efficiens* has been removed. If by the massing together of cells in the infected tissues a protective wall is formed against the spread of the bacteria, or if the latter are retained in the lymph-glands and destroyed, then these phenomena may also be looked upon as processes which usher in the healing. In a similar manner the removal of the poisons or the bacteria which have entered the blood, by way of the excretory organs—the kidneys, the liver, and the intestines—not only acts as a protection against further localization of the bacteria and against increased intoxication, but also makes possible, through the removal of the noxious materials, the restoration of the injured tissues.

In many infectious diseases the healing action of the protective agents already in the body (§ 27) is supplemented by the **appearance on the scene of new substances, foreign to the normal organism, which as bactericidal substances,** and as **antitoxins,** antagonize both the infection and the intoxication. These *antagonistic poisons* are produced either by the cells and the blood—both of which have been altered by the infection so as to perform other life-processes—or by the bacteria themselves; they spread through the body by way of the tissue-juices, and thus form an impediment to the further spread and increase of the bacteria.

These **antagonistic bodies** act in one of two ways: they either hinder the reproduction of the bacteria and kill them, or they alter and render harmless the bacterial poisons, or they combine with them to produce an inactive, non-poisonous substance. It is also possible (cf. § 30) that in the case of a few infections they render the tissues to a certain extent unsusceptible to the effects of bacterial poisons.

The cause of *healing in infectious diseases* is most frequently referable to the fact that *chemical substances produce an antagonistic action against the intoxication*, and the bacteria are prevented from any further spread and thus die out. It has been proven, however, that in many cases the bacteria survive and probably continue to produce poisonous matters, which, however, remain harmless in consequence of the presence of the antitoxins. In individual cases the theory appears admissible that a lack of proper nutritive material produces the death of bacteria; this being true, perhaps, in the case of localized areas of infection (tuberculosis), in which bacteria remain for a long while

enclosed in tissue which is dead and which, with the lapse of time, is undergoing alteration, and from which, consequently, they are unable to escape and find a new source of food.

According to the investigations of R. Pfeiffer, which have been verified by Sobernheim, Dunbar, Loeffler, and others, the blood-serum taken from animals which have been rendered immune as regards the bacilli of typhoid fever or the spirilla of cholera, and that taken from human beings who are either ill with or are convalescing from either typhoid fever or cholera, contains, besides certain antitoxins, *a specific bactericidal substance* (*lysogenous substance* of C. Fraenkel) which possesses this characteristic, viz., that when some of it is added to a virulent culture of the organisms belonging to either of the above-mentioned diseases, this culture becomes so modified in its composition that the bacteria, after being injected into the abdominal cavity of experimental animals, rapidly break up into minute globules and become dissolved.

According to the investigations of Gruber, Durham, Pfeiffer, Kolle, Sobernheim, Widal, and C. Fraenkel, the blood-serum obtained from persons who are actually ill with typhoid fever or with cholera, or who are convalescing from one or the other of these diseases, or who have even entirely recovered from such illness, exerts a damaging influence upon the bacilli of the corresponding disease; this influence being of such a nature that in bouillon cultures the bacteria cease to make their ordinary movements, roll themselves together in clumps, sink to the bottom of the vessel, and then undergo disintegration. When the serum is added to a hanging drop of bouillon culture it causes the vibriones which were previously in active motion at once to become motionless and to collect together in little heaps. Gruber is of the opinion that this phenomenon is to be explained by the swelling up and bursting of the membranous coverings of the bacteria, and he assumes that this change at once renders it possible for the alexins to destroy whatever bacteria may be present in the body. In harmony with this view he applies the name *agglutinins* to the active substances or elements contained in the serum, and he believes that he is warranted in attributing to them the chief agency in bringing about a cure of the infectious diseases and in establishing the condition of immunity in respect to the same. Pfeiffer, on the other hand, denies that any such swelling of the cell-membrane takes place, and attributes the occurrence of the phenomenon referred to above to arrested development. To the active substances, the nature of which is wholly unknown, he gives the name *paralysins*. After Gruber had demonstrated the peculiar powers possessed by the blood-serum of typhoid-fever patients, Widal (*Semaine médicale*, Paris, 1896) made the proposition to utilize this action of blood-serum upon the bacilli of typhoid fever (or upon the spirilla of cholera) as an auxiliary method of establishing the correctness of the diagnosis during the actual progress of this disease (or of cholera). As a matter of fact, the investigations of C. Fraenkel, Du Mesnil, and others have since shown that it is possible, by means of this action of the blood-serum upon cultures of typhoid bacilli, to determine—both during the course of the attack and for a long time (even several months) afterward—whether the diagnosis of typhoid fever has been correctly made.

Metschnikoff, Bordet, and others maintain that the recovery from any of the infectious diseases and the acquisition of the condition of immunity (compare § 30) are to be attributed chiefly to the activity of the leucocytes, which, as they contend, supply bactericidal substances to the juices of the body, and at the same time destroy the bacteria by taking them up into their cell-bodies. The latter performance, termed phagocytosis, plays nevertheless a subordinate rôle, for the majority of the bacteria are destroyed by the cells only after they have been damaged or killed by bactericidal substances furnished by the blood and by the juices of the tissues. In many forms of infection the bacteria are, it is true, taken up into the cells, but they do not perish within the cell-bodies. Indeed, it is highly probable that they find, in the protoplasm of the cell, a soil favorable to their development.

It has often been assumed that the **fever** present in infectious diseases is a process which favors the destruction of the bacteria, and it is not impossible that in individual cases it exerts such a beneficial influence. Thus, for example, it is easy to believe that a parasitic micro-organism that easily endures a temperature of from 37° to 38° C. (from 98.6° to 100.4° F.) may not endure one of from 40° to 41° C. (from 104° to 105.8° F.), and consequently that high fever-temperatures would be likely to hinder its powers of reproduction. The conclusion must not be drawn from this fact, however, that the fever is a useful phenomenon or one that always favors the counter-balancing of one set of pathological disturbances by another set. And even in those cases in which the metabolism which goes on during the fever produces upon the bacteria a deleterious influence, it is not permissible to consider this as something useful which should be credited to the fever. One could only say that a portion of the morbid processes taking place in the course of an infectious fever induces the formation of certain products of chemical decomposition which act in an antibacterial or an antitoxic manner.

VI. Congenital and Acquired Predisposition.—Idiosyncrasy and Immunity.—The Acquiring of Immunity.—Immunizing Inoculations.

§ 29. It is an old observation that *different individuals are diversely disposed toward external harmful agents.* In a certain number of cases this difference depends upon the *general constitution*—i.e., upon the general condition of the body; in other cases there are *local conditions* that produce these differences in behavior. Furthermore, the differences may be *congenital* and *lasting*, or they may be *acquired*, and are then often a *transient peculiarity* of the special individual.

If an individual is markedly susceptible to the action of a certain disease, this condition is termed a *predisposition* to that particular disease. If an individual shows an especial susceptibility to a particular external influence, which is much more marked than the susceptibility thereto which is seen in the majority of mankind, and so constitutes an individual peculiarity, it is termed an *idiosyncrasy.* If, on the contrary, an individual is insusceptible to the action of an injurious force, so that the symptoms of the disease do not appear even when the individual exposes himself to this particular injurious influence, the condition is termed *immunity*, and, according to its grade, it may be distinguished as a *relative* or an *absolute immunity.*

Predisposition has a great influence over the acquiring of infectious diseases, and also plays a prominent part in the causation of numerous other diseases. In one instance it is founded on general constitutional conditions, in another on those which are simply local; and besides it may be a lasting or a transient phenomenon. Mankind has a strong predisposition to measles, smallpox, scarlet fever, cholera, typhoid fever, malaria, tuberculosis, and syphilis;* and consequently, in those cases in which the protective forces against infection that belong naturally to every man prove to be insufficient, an infection would be sure to follow exposure, at least in the great majority of instances. It may also be assumed that the *grade of susceptibility* for these diseases *is not equally great in all individuals* and that *it varies in the same person at different times.* Thus in epidemics of measles certain children who are exposed to infection escape, and later in life are taken ill during some subsequent epidemic,—a circumstance which in many cases can be explained only by the supposition that the individual was for the time but slightly susceptible to measles. Excessive bodily exertion, as it appears, favors the entrance of an infectious disease into the system. Diabetes mellitus predisposes a person to tuberculous and suppurative infections.

For the acquisition of many infections a peculiar *local predisposition* is often necessary, which is gained by *local tissue-changes*, such as wounds, excoriations, and the formation of ulcers. In such cases, therefore, the disease appears as a **wound-infection.**

To this class belong many forms of suppurations, erysipelas, tetanus, hydrophobia, and, in part, tuberculosis, syphilis, glanders, anthrax, and other diseases; and although any of these diseases may occasionally be produced by infection through intact mucous membrane or skin or lung tissue, in the majority of cases a traumatic injury or an ulceration furnishes the required *locus minoris resistentiæ* from which the infection can take its start. Thus, for instance, the suppurative inflammations produced by the so-called pus-cocci are mostly diseases which

originate in wounds, excoriations, or ulcers; and in the last case they often represent secondary infections, which follow other infections that have resulted in the production of ulcers. Furthermore, they are frequently encountered in some part of the genital apparatus after parturition—i.e., in tissues which, by reason of the childbirth, are torn or crushed, or, through the rubbing off of the epithelium and the superficial layers of the connective tissue (as in the uterus), are laid open to the invasion of bacteria. Similarly, erysipelas and tetanus are diseases which ordinarily develop from small wounds, and the infection called hydrophobia is almost always caused by the bite of an animal having rabies. Finally, we may also assume that the virus of tuberculosis or of syphilis very often enters the tissues only where a local lesion has taken place.

The *predisposition to diseases which are not of an infectious origin* is manifested particularly in those morbid affections which occur as the result of overexertion, as *exhaustive conditions;* and also in those which are the result of temperature variations, such as the *diseases due to chilling of the body or to the effects of heat-stroke.* But this predisposition may also play a prominent part in still other diseases, as, for instance, in various forms of poisoning. Mental labor and psychical irritations, of which human life is full, can produce illness in predisposed individuals—i.e., in those who have a certain weakness or imperfect resisting power of the central nervous system when subjected to the demands made upon it; while in the majority of men the same amount of work will do no harm. It is well known that the functional capacity for work of the muscles is very different in different individuals, and that consequently many are easily tired; it is also known that many are very susceptible to heat and cold. Illness and death from heat-stroke occur only in a small percentage of individuals who find themselves situated in exactly the same circumstances—i.e., in those who, under the conditions named, are unable to endure the strain laid upon them. By chilling of the entire body, or of certain portions of it, which the majority of individuals can bear without receiving harm, many are made ill, and there are individuals who have an excessive susceptibility to influences of this nature.

The *weakened power of resistance* to outward influences, and the easy exhaustion from work, constitute, in many cases, an *individual peculiarity of congenital origin*—a peculiarity which sometimes appears only in childhood and is then outgrown, and sometimes persists throughout life. In other cases it is *an acquired state*, which shows itself especially in convalescence from severe illness, and gradually disappears. Under certain conditions it may prove to be a permanent sequela of the illness out of which it developed.

Idiosyncrasy in regard to certain injurious influences is generally congenital; at times, however, it is an acquired peculiarity of certain individuals, often showing itself in most peculiar ways. Thus, for example, the eating of fresh fruit, or of sugar, or of salad, produces, in certain individuals, nausea and vomiting. Others have an aversion to eating dishes prepared from liver or kidneys, and become ill if they compel themselves to eat these foods. Still others have a peculiar disease, called urticaria, after eating crawfish, lobster, strawberries, raspberries, morels, or asparagus. The disease is characterized by itchy wheal-formations, characteristic skin-lesions, or abdominal cramps and vomiting. Not a few persons are unable to drink boiled milk without

experiencing trouble therefrom. Alcohol, even in very small doses, may in certain individuals produce marked excitation, or even narcosis, or marked vaso-motor derangements. The drinking of cocoa can produce cardialgia and dyspeptic symptoms. Doses of morphine or chloroform that are borne by the majority of men without injury may produce, in certain individuals, severe symptoms or even death. A few individuals manifest a high degree of sensitiveness, on the part of the mucous membrane of the respiratory tract, to the effects of the pollen of certain grasses; and accordingly, upon the arrival of the hay-making time, through the inhalation of the pollen which are floating everywhere in the air, these individuals manifest symptoms of catarrhal inflammation of the nasal passages and the conjunctivæ, and often also of the larynx, the trachea, and the bronchial tubes. To these catarrhal symptoms, which in the severe cases may be accompanied by asthma and fever, the name of *hay-fever* or *hay-asthma* is given. Washing the skin with disinfecting fluids—as, for example, with sublimate or carbolic-acid solutions—in a strength usually borne without trouble, may cause not only local derangements of sensation and inflammation, but also, under certain circumstances, an eczema which spreads over the greater part of the body.

On what, in particular cases, the idiosyncrasy depends is not clear. In many cases we may look upon a peculiar irritability of certain portions of the nervous system as the cause of the symptoms. In acquired idiosyncrasy—with regard, for instance, to the taking of certain foods—psychical factors may play a part.

Immunity, like predisposition, is a peculiarity which plays an essential rôle in the pathogenesis of the infectious diseases, and the term "immunity" is used to characterize the behavior of an individual with regard to infection. If a person is so constitued that the parasites under consideration cannot grow in his tissues, this condition is termed immunity, in the narrow sense of the term; if the peculiarity of the individual is of such a nature that the poisons produced by the bacteria are, for him, harmless and produce no effect, one speaks of it as **insusceptibility to poisons**, and uses this term also in cases in which a person shows special powers of resistance when exposed to the influence of other poisons—as, for instance, those which come from the phanerogamous plants or from animals.

Immunity and insusceptibility to the poisons of infections and intoxications are partly congenital, partly acquired, and form, when they have existed from birth, a peculiarity which may belong to all men, or may be possessed by only a few individuals. Man is immune from various infectious diseases that are common to domestic animals—for instance, hog-cholera, symptomatic anthrax, and hen-cholera—while he is susceptible to the infection of anthrax and glanders. So far as tuberculosis and actinomycosis are concerned, he is just about as susceptible to infection as are beeves, sheep, goats, and swine. There is an apparent immunity from scarlet fever in the case of a large number of persons; and even as regards measles, small-pox, cholera, and influenza there exists in many persons a relative immunity. At all events, it happens that only a relatively small percentage of the population acquire scarlet fever, and also that, in regions where cholera and measles appear repeatedly as epidemics, a portion of the population escape—a circumstance which cannot be explained by the statement that these persons did not happen to come in contact with the infective poison which is

necessary for the production of the disease, but must be ascribed in part to the fact that their bodies were, at the time the virus entered, not receptive, or at least were only slightly so, so that the natural resistant power of the body was able to prevent the infection. It cannot, however, be determined in these cases whether this immunity was absolute and general, or whether, at the point of infection, there were special local conditions which caused the infection to be suppressed. It is an interesting fact that the escape of an individual who has been often exposed to infection during an epidemic is no guaranty that he possesses a lasting immunity, since experience has shown that infection may take place during a later epidemic or later on during the same epidemic. The immunity may therefore be temporary and at the same time only relative; and it is probable that at certain times a stronger predisposition may be present.

Concerning *natural immunity from the effects of poisons* or *natural lack of susceptibility to poisons*, we know little at the present time; still, without doubt, many poisons are poisonous only to certain organisms, and it is probable that mankind is relatively insusceptible to many poisons that are deadly to certain animals. This is true, for example, with regard to the toxic proteids and the organic bases which are derived from bacteria and also from higher animals (serpents) and plants. If one takes into consideration that many animals are slightly or not at all susceptible to poisons which act powerfully upon the human body—that, for instance, the hedgehog is not susceptible to the cantharidal poison and to the bite of poisonous snakes; that birds experience no bad effects from atropine and opium, nor goats from lead and nicotine; and, finally, that dogs, rats, and other animals used in experiments show a relatively greater resisting power to bacterial poisons and also to vegetable alkaloids than does the human being—it seems very probable that the converse may also be true. From this it would be proper to conclude that the natural insusceptibility of man to many of the infectious diseases of animals rests upon his powers to resist the toxalbumins and toxins which the bacteria belonging to these diseases produce.

The acquisition of relative or absolute immunity from poisoning by certain infecting germs and poisonous substances is generally produced by either a single infection or intoxication, or by repeated infections or intoxications, which leave behind such an effect upon the body that it is no longer susceptible to the corresponding micro-organisms or poisons—in other words, that it can no longer be made ill by these micro-organisms or poisons. Besides, it often happens that the fact of an individual's having passed through an attack of an infectious disease confers on him a relative or absolute insusceptibility to a disease which is closely related to it.

The great importance which natural predisposition and immunity possess with reference to the origin of infectious diseases is confirmed not only by the consideration of the spread of plagues among men and animals, but much more by numerous experimental researches. If a mixture of diverse bacteria is injected into an animal, only a part of them develop and produce tissue-changes; the others die. If the same mixture is injected into another animal of a different species, the bacteria which develop will be of different varieties from those which developed in the first instance. Further, a certain kind of Schizomycetes, inoculated into a certain species of mouse, produces certain death, but when the same kind is injected into another species of mouse it proves harmless. Mice are very susceptible to anthrax; rats are nearly immune. The poison of the so-called septicæmia of rabbits kills with absolute certainty rabbits and mice; guinea-pigs and rats are, on the contrary, immune, while sparrows and pigeons are susceptible to the poison. The spirilla of relapsing fever can be successfully inoculated

only in apes. Gonorrhœa, syphilis, and leprosy cannot be successfully inoculated into any species of animals.

Different animals of the same species, but of different ages, show dissimilar behavior in this regard. Young dogs are easily infected by anthrax (Koch), while old ones are not.

Diverse experiments have shown that, by suitable action upon the tissues, an existing immunity from the effects of a certain infection can be rendered powerless.[1]

According to Roger,[2] the natural immunity of rabbits and pigeons in respect to anthrax can be overcome by injecting the non-pathogenic *Bacillus prodigiosus* at the same time that the anthrax is inoculated. The effective agent in this procedure, according to this author, is a decomposition product of the *prodigiosus* that is soluble in glycerin, and that produces a modifying action on the organism.

According to Gottstein,[3] guinea-pigs may be made susceptible to the subcutaneous injection of hen-cholera bacilli, in respect to which they have a natural immunity, by previously injecting subcutaneously substances which dissolve blood-corpuscles, as hydracetin or pyrogallol; and he is of the opinion that toxic substances which make men or animals susceptible to infections act chiefly through their power of dissolving the blood-corpuscles. According to Leo,[4] white mice, which are immune in respect to glanders, may be made susceptible by mixing with their food a slight amount of phloridzin, which produces a toxic diabetes.

According to Canalis and Morpurgo,[5] pigeons may be made susceptible to anthrax by hunger. According to Lode, simple chilling of the body is capable of increasing the susceptibility to infections.

The *special diseases* to which the *new-born* frequently succumb (aside from those which begin in intra-uterine life) are dependent partly upon a pathological weakness of the entire organism (especially in those born prematurely), partly upon the particular surroundings in which they are placed. Asphyxia, which is of such frequent occurrence, may originate either from a weakness of the body or from pathological influences exerted during delivery. Infectious diseases may be acquired from infection through the cord, or through the accessible mucous membranes and the respiratory apparatus, during the passage through the parturient canal. Hemorrhages are dependent partly upon traumatic influences during birth and partly upon circulatory disturbances and infections. Icterus in the new-born is sometimes the result of a change in the mode of nutrition (reabsorption of the bile out of the meconium); sometimes, however, it is the result of infection.

Children are, according to the observations of medical men, *more susceptible than grown people to many infections;* this is particularly true, for instance, with regard to whooping-cough, diphtheria, measles, and scarlet fever. In this connection it should be noted that the slight liability or the immunity of many grown-up people is due to the fact that they became immune through having had the disease during childhood. Further, it is to be remarked that children are more exposed to certain diseases—for instance, tuberculosis—than grown people.

In advancing years hemorrhages, softening of the brain and heart, cancerous growths and the formation of gall-stones are especially frequent. Arterial diseases, designated by the term arteriosclerosis, and also gout, are seen already in the later years of middle life. This *predisposition in old age to certain diseases* depends in part upon degenerative processes, associated with early-developed senility of the tissues; in part also upon the circumstance that certain effects which years bring with them gradually accumulate, so that finally the alterations which they produce become so prominent that they lead to disturbance of function, and ultimately to recognizable morbid conditions. In general it is to be observed that many pathological symptoms of old age are secondary diseases, which show themselves only after other tissue-changes have reached a certain degree. We may mention, for example, hemorrhages of the aged, senile gangrene, and softening of the brain and heart, resulting from morbid processes in the arteries.

The *predisposition of the sexes to special diseases* depends, in the first place, upon the

[1] Sirotinin, "Die Uebertragung von Typhusbacillen auf Versuchsthiere," *Zeitschr. f. Hyg.*, i., 1886.

[2] "Contribution à l'étude expérimentale du charbon symptomatique," *Revue de méd.*, 1891.

[3] "Beiträge zur Lehre von der Septikämie," *Deutsche med. Wochenschr.*, 1890.

[4] "Beiträge zur Immunitätslehre," *Zeitschr. f. Hyg.*, vii., 1890.

[5] "Ueber den Einfluss des Hungers auf die Empfänglichkeit für Infectionskrankheiten," *Fortschr. d. Med.*, viii.

peculiar construction and special functions of the genital organs; the conditions present in pregnancy and during the puerperium furnishing a particularly favorable field for many diseases, as, for instance, infections from wounds. In general the diverse relations of the sexes to certain diseases are explained by the differences which exist between men and women as regards their respective modes of earning a livelihood, and, further, by the differences in the respective habits of the sexes.

Differences in the predispositions of different races are shown in such diseases as malaria and dysentery, to which negroes are in general less liable than Europeans. The Japanese are said to be more susceptible to beriberi than Europeans.

§ 30. **The acquiring of immunity with respect to a particular infectious disease** is a thing of frequent occurrence, and has been known for a long time past by clinical observers to be a well-established fact. This fact is established principally by the observation that the greater number of men are ill only once with any of the infections such as measles, small-pox, whooping-cough, scarlet fever, and diphtheria, and that after such an attack they remain exempt from the influence of this particular disease even when they expose themselves in all sorts of ways to the danger of contracting it. The knowledge of this fact is old, and early in the eighteenth century it gave rise, in the Orient, to attempts to produce in men immunity against the natural contagion of small-pox by the inoculation of material from the pustules of the disease. In the latter part of the last century, Jenner discovered that the disease called cowpox—i.e., a milder form of pox, which is either a special variety of disease closely allied to human small-pox, or a weaker form of the latter—also afforded-protection against the true small-pox. As a result of this observation, since the beginning of the year 1796, at first by Jenner himself, and after him by the practitioners of all the civilized world, artificial inoculations of cowpox have been carried out upon millions of men, and with the result that through these inoculations a high degree of immunity from the true small-pox has been secured, so that at the present time, in countries where vaccination is practised universally, we no longer have the extraordinarily widespread epidemics of small-pox which were constantly occurring in former years, nor does the disease any longer assume the form of a dangerous epidemic.

The investigations with regard to the causes and origin of infectious diseases which have been undertaken during the last ten or fifteen years, and which have covered such a remarkably wide extent of pathological territory, have shown that **the acquisition of immunity against a certain infectious disease is secured by a person's having once passed through an attack of that disease,** and that this mode of acquiring immunity holds good for a number of infectious diseases, especially those which run an acute course; furthermore, that this immunity is sometimes a transitory, sometimes an enduring peculiarity of the individual who has had such an attack of the disease; and, finally, that when a pregnant woman acquires immunity she may transmit it to her child *in utero*. These observations have also shown that the **inoculation,** performed either once or repeatedly, **of attenuated pathogenic bacteria**—i.e., of bacteria which, on account of their decreased virulence, produce a disease that, in contrast to the natural infection with bacteria of full virulence, is merely a trifling affair, often confined to a circumscribed area—can also bestow, upon the individual so treated, immunity with regard to the corresponding disease. It has even been demonstrated that, for the production of insusceptibility to a certain disease, **it suffices to inject certain chemical substances produced by the bacteria of that disease.**

In explaining how immunity from an infectious disease is acquired through the fact of once having had the disease, or by inoculation, we can as yet give only hypotheses; but it is a matter beyond dispute that the last few years have brought great increase to our knowledge concerning the forces which effect this immunity, and we have now reached a point where we at least know in what direction further researches should be made.

After Pasteur had, in 1880, by experimentation proved that chickens could be made insusceptible to chicken-cholera by inoculation with attenuated chicken-cholera poison, and after it had been established by the repeated researches of various authors that similar results could be obtained with anthrax, symptomatic anthrax, and hog-cholera, they believed they could explain acquired immunity by saying that, through either the inoculation or the first overcoming of the particular infectious disease, the food-material in the body had been destroyed (Pasteur, Klebs), and consequently that the bacteria which entered the body later were unable to find food for themselves. This theory, termed the *exhaustive theory*, does not agree with the observed facts, and consequently at present it is generally no longer advocated. Metschnikoff's view that, in consequence of the preventive inoculations, the mesodermic cells become accustomed to the inroads made upon their substance by the previously undisturbed virulent bacteria, and that when the latter are again introduced they quickly take them up and destroy them, cannot in any wise be considered as an hypothesis possessing scientific foundations.

According to the facts which have been ascertained by investigations concerning the natural protective powers of the body against infections, and concerning the natural mode of recovery from such infections, as also by the experiments made with regard to protective inoculation and with regard to the artificial healing of infective diseases, it is very probable that **the acquired immunity is dependent upon the presence of certain chemical substances** *which are either poisonous to the particular variety of bacteria under consideration, or in some manner or other render harmless the poisonous products formed by these bacteria.* (This is known as the *poison theory*.) It remains an unsettled question, however, whether these substances are the product of the bacteria or of the body-cells; further, whether the abolition of the poisonous action of the bacterial toxalbumins and toxins results from their destructive decomposition, or from the formation of some harmless combination of these substances, or from an immunizing of the cells with respect to these particular poisons.

Some light is thrown upon this question by the past experiences in regard to the different ways in which it is possible to obtain, not only in experimental animals, but also to a certain extent in the human being, immunity as regards certain infectious diseases. Some further light is also obtained from experiments concerning the artificial healing of infections which have already become manifest. As heretofore stated, it is possible in animals to produce, in agreement with the results obtained by Jenner's cowpox inoculation, **an immunity through the inoculation of attenuated specific disease-germs.** This has been accomplished, for instance, in anthrax, in symptomatic anthrax, in chicken-cholera, in diphtheria, and in swine-plague.

The weakening of the virulence of bacteria is produced either by the action of high temperatures or by that of chemical agents, or by the air

only; further, it is also produced by the inoculation of certain animals with the bacteria, and by long-continued cultivation of them on artificial media. Inoculation is generally carried out by injecting first markedly attenuated, then less attenuated, and finally fully virulent bacteria, along with their products, beneath the skin.

According to the investigations of numerous authors, immunity may be produced by the **injection of sterilized cultures** in which the contained bacteria are dead. The diseases which may be warded off in this manner are the following: American hog-cholera, symptomatic anthrax in cattle, diphtheria, the infectious disease produced in rabbits by the injection of the *Bacillus pyocyaneus*, and the infection produced in guinea-pigs experimentally by cholera-spirilla. Probably the immunizing substances are contained in the cell-substance of the bacteria (Brieger, Kitasato, Wassermann).

A third form of artificial immunizing, which Raynaud tried as early as in 1877, but which was first securely established by Behring in 1890, can be produced by the injection, into an experimental animal or even into man, of **blood-serum taken from animals which were previously susceptible, but which have been artificially rendered immune by means of inoculations.** The most extensive and at the same time the most successful experiments thus far made have related to *tetanus* and *diphtheria*—that is, to diseases in which the most striking feature is an intoxication by means of toxalbumins. Besides these, reports have been published of successful experiments with the blood-serum of immunized animals in cholera, swine-plague, anthrax, typhoid fever, and the plague.

The specific protection which the blood-serum affords can be secured not only by injections which are made before infection takes place, but also by injections which are made after infection has already occurred; thus justifying us in speaking of the serum not only as a *protective*, but also as a *healing serum*. Further experience has also shown that both for the prevention and for the cure of a particular infection *a certain amount of serum* is necessary, the precise amount depending, on the one hand, upon the severity of the infection, and, on the other, upon the activity of the serum itself, which increases with the completeness of the immunizing of the original susceptible individual who furnished the serum. If the injection is not made until after the infection has occurred, the amount of serum injected must be greater the longer the time which has elapsed since the infection took place.

In the case of *diphtheria* the injection of curative diphtheria-serum has now been resorted to in thousands of cases of the disease—the severe forms as well as the mild ones—and there can no longer be any doubt in regard to its beneficial effects upon the course of the disease; these effects manifesting themselves in the establishment of a rapid improvement of the patient's general condition (increasing bodily comfort, diminution in the fever-temperature, and improvement in the state of the pulse) and also in the favorable course pursued by the local disease. In *tetanus* the curative effects of the serum treatment have been well established, so far as experimental animals (e.g., guinea-pigs and mice) are concerned; but it has not yet been surely established that the same effects can be produced in the human being.

The blood-serum of immunized animals exerts its beneficial effects, without any doubt, through the presence in it of an **antitoxin**, which neutralizes the poisons produced by the bacteria. In the case of patients, therefore, who have been treated with a certain antitoxin—as,

for instance, with the antitoxin of diphtheria—there is established an **immunity from the effects of the corresponding poison**—that produced by the diphtheria bacilli, in the case supposed; and this immunity is to be ascribed to the presence, in the circulating blood, of a fixed amount of this antitoxin.

It has not yet been ascertained what is the chemical nature of the antitoxins, the presence of which in a great variety of infections and intoxications (diphtheria, tetanus, pneumonia, snake poisons, ricin, abrin) has been demonstrated. It is probable, however, that they should be classified as albuminous bodies. Their effective power is presumably that of destroying the specific bacterial poisons (Behring); it is also possible that they simply render the tissues insusceptible to the effects of these poisons (Buchner, Tizzoni, and others).

Apart from the antitoxins the blood-serum of animals or of human beings who have been rendered immune may also contain **bacterial substances** which are capable of injuring or killing the bacteria themselves; and it is claimed that this is true of cholera and typhoid fever infections (R. Pfeiffer, Gruber, Durham), and of the infections caused by the pneumococci (Emmerich).

The **origin of the immunizing substance** in the blood is still an unsolved problem. One may suppose that it is the product of an especial activity of the cells of the infected organism; yet it is very difficult to reconcile this theory with the fact that these substances which produce immunity protect only against the particular form of disease in whose course they have originated; the tetanus antitoxin, for instance, being active only against tetanus, and the diphtheria antitoxin only against diphtheria. It is better to explain the phenomena by the supposition that the antitoxins are substances which are produced by the bacteria themselves, or that the bacteria at least provide the material for the making of the antibody. Buchner is of the opinion that the antitoxins are specific bacterial cell-substances. On this theory the immunization by means of healing serum would be effected in somewhat the same manner as it is by the injection of sterilized or attenuated bacterial cultures. The distinguishing characteristics of the different modes of immunizing may then be stated as follows: in the injection of attenuated cultures (vaccine) the production of the immunizing substance occurs partly in the cultures, partly in the person inoculated; in the injection of sterilized cultures it takes place only in the cultures; and, finally, in injections of the so-called healing serum it takes place in the animal from which the serum is obtained.

If the organism itself produces the immunizing substance, it is customary to speak of this as *active immunization*. On the other hand, if already prepared immunizing substances are introduced into the organism from without, the term *passive immunization* is employed.

For the foundation researches in regard to attenuated inoculation cultures grown in culture-media outside the body we must thank Pasteur, who, in the year 1880, discovered the fact that by the inoculation of cultures of chicken-cholera bacilli, which had become attenuated by remaining for a long time in the air, chickens could be made insusceptible to this disease.

Since that time numerous experiments have been carried on with other forms of bacteria—for example, with attenuated anthrax-bacilli and with symptomatic anthrax-bacilli. The best results have been obtained from inoculations of cattle against symptomatic anthrax. The results obtained by the inoculation of anthrax have been less successful, a portion of the animals dying from the inoculation, while in others no absolute immunity was obtained against a new anthrax infection.

Sheep and cattle may be made insusceptible to *anthrax*, and most easily in the following manner (Koch): they are first inoculated with attenuated bacilli which will kill mice, but not guinea-pigs; then with bacilli which will kill guinea-pigs, but not strong rabbits.

As vaccine against *symptomatic anthrax*, bacteria should be employed which have been attenuated by heat or by chemical agents, such as sublimate solutions, thymol, eucalyptol, and nitrate of silver; and by inoculations of this character cattle may be rendered immune. At the present time heat is most commonly used in preparing the vaccine (Hess, Kitt). A piece of infected muscle is taken from an animal that has died of symptomatic anthrax, and chopped into small bits; then it is mixed with one-half its weight of water, and squeezed through a linen cloth. Finally, the fluid is again filtered through a moistened piece of linen. This virulent mass is first spread upon glass plates or flat dishes, and then transferred to a dry chamber where the temperature is kept at from 32° to 35° C. (from 89.6° to 95°F.). When thoroughly dried the virus may be scraped off and removed in the form of a powder. If one wishes to produce material for inoculation from this virulent virus, it should be triturated with double its weight of water, and this fluid is then to be steamed in a thermostat. By raising the temperature to 100° C. (212° F.) during six hours, one gets a weak immunizing material; by the action of a temperature of 85° C. (185° F.) for six hours, a more active preparation is produced. For immunizing an ox or a cow, about 0.5 gm. of a thin watery solution of the weak vaccine should be injected, preferably into the subcutaneous cellular tissue near the animal's tail; and, after the lapse of from eight to twelve days, the stronger solution should be injected in a similar manner.

Hogs, according to Pasteur, may be made insusceptible to inoculation with virulent *hog-cholera bacilli* by the employment, as vaccine material, of bacilli which have become attenuated through a series of inoculations of rabbits. According to Emmerich, rabbits may be made insusceptible to swine-erysipelas bacilli by the injection, into the veins of the ear, of small amounts of virulent bacilli-cultures diluted fiftyfold with water.

For animals susceptible to *diphtheria*, immunity may be procured, according to Behring, by the injection, into their abdominal cavity, in small amounts (2 c.c.), of cultures of diphtheria-bacilli which have been attenuated by exposing them for sixteen hours to the action of iodine trichloride (1 : 500); and then, after the lapse of three weeks, by the employment of another injection containing a diphtheria-culture (0.2 c.c.) which has been permitted to grow for four days in bouillon to which iodine trichloride (1 : 5,500) has been added. At a still later period, cultures of full strength are to be injected in increasing quantities.

According to Emmerich, rabbits may be made completely insusceptible to pneumococci by injections, first, of 0.3 c.c. of a strongly virulent bouillon-culture diluted in the proportion of 1 : 5,000, and afterward of bouillon-cultures of full virulence.

Protective inoculations against rabies are resorted to only after the individual has actually been bitten by a rabid animal, and the practice is employed chiefly in France (at the Pasteur Institute), in Russia, and in Italy. For inoculation purposes it is customary to employ the spinal cord (desiccated in dry air at a temperature varying from 23° to 25° C.—from 73.4° to 77° F.) of rabbits in whom the disease has been created artificially. By means of this drying process, continued for a period of about fifteen days, the cord gradually loses its poisonous character. According to Protopopoff, it is not so much the drying as it is the heat which diminishes the virulence of the poison. From this piece of spinal cord, possessing diminished poisonous properties, small bits are taken and rubbed up in sterilized chicken-broth. Some of this mixture is then injected beneath the skin of the person who has been bitten; only a very weak mixture being employed at first, but afterward the strength being gradually increased. It is Pasteur's opinion that the spinal cord, under the conditions we are now considering, contains partly microbes and partly a specific poison which they have produced; and that this poison, if it becomes distributed throughout the body more rapidly than are the microbes, will confer on the organism immunity from the effects of a subsequent invasion of these microbes, and especially will protect the nervous system. It is therefore necessary, if we wish to secure the desired degree of immunity, to introduce into the system as large quantities as possible of the chemical poison. The published reports of the institutes in which the Pasteur protective inoculations against rabies are made warrant the conclusion that these inoculations do actually prove effective in warding off an outbreak of rabies.

According to the observations of Chauveau and others, it is possible, in making protective inoculations, to adopt the plan of injecting virulent bacteria in very small quantities, or in such a manner that they shall not be injurious to life. In symptomatic anthrax, for example, this result may be obtained, in oxen or cows, by injecting very small quantities of the fluid into the extremity of the animal's tail; these injections not causing a fatal illness, but merely some local disturbance.

According to Afanassieff it is possible to render animals immune by inoculating the granulating surface of a wound with virulent cultures.

According to the researches of Schuetz, cattle may be rendered insusceptible to contagious pleuropneumonia by injections of the tissue-juices obtained from the lung of an animal suffering from the disease, provided the injections be made into the tail. There is produced by this means a localized inflammation, or one, at least, that is confined to the tail; and after it has quieted down, the animal will be found to be insusceptible both to the natural infection and to an infection of artificial origin.

So far as *cholera* is concerned, both animals and men may be rendered immune (according to Haffkine, Pfeiffer, Kolle, Voges, and others) by injecting into the body sterilized and weakened cultures of cholera spirilla, and the immunity thus obtained (and which lasts for only a short time) is due to the formation, within the blood, of *specific bactericidal antitoxic bodies* (compare Voges: "Die Choleraimmunität," *C. f. Bakt.*, xx., 1896 [Lit.]). On the other hand, we do not possess any specific remedy by means of which we may save the life of an animal or a man that may happen to be infected with cholera.

Immunity from the danger of being infected with typhoid fever may be secured (in the case of a human being) by the subcutaneous injection of sterilized cultures of typhoid bacilli (Pfeiffer, Kolle), and the establishment of this immunity may be recognized by the fact that the blood-serum of the person who has thus been inoculated will be found, at the end of a few days, to contain *bactericidal substances*. The immunization experiments which have been made in cases of persons who were already recognizably ill with typhoid fever have thus far, according to Brieger, Wassermann, and C. Fraenkel, given rather unsatisfactory results.

According to the accounts published by Koch (*British Medical Journal*, 1897; *Deut. med. Woch.*, 1897, No. 16; *Centralbl. f. Bakt.*, xxi., p. 526), who, during the winter of 1896–97, carried on investigations into the cattle plague in Cape Colony, it is possible to immunize cows and oxen by the subcutaneous injection of 10 c.c. of the bile taken from cattle that have died of this disease; and, furthermore, the condition of immunity becomes established (according to the same authority) not later than on the tenth day.

During the year 1890 Koch made the discovery that cultures of tubercle bacilli contain a toxin—*tuberculin*—which, when injected into the tissues of a person affected with tuberculosis, produces feverish elevations of temperature, and to some extent also local inflammations in the neighborhood of foci of tuberculous disease. For a certain length of time after this discovery had been made, the hope was entertained that in this tuberculin a remedy for the cure of tuberculosis had been found; but the trials made with it upon human beings and animals revealed the fact that it was indeed competent, after repeated injections had been made, to establish an immunity from the poisonous effects of the tuberculin, but that it was impotent to arrest the multiplication of the tubercle bacilli and also to prevent the disease from advancing; and, furthermore, that the local inflammations belonging to the disease were affected favorably by it only under certain special conditions, while in many instances the effect which it produced upon these inflammations was distinctly unfavorable (the tubercle bacilli being thereby more widely disseminated throughout the body). Notwithstanding these drawbacks, Koch's discovery has proved to be one of great importance. In the first place, it possesses some practical value as a means of detecting the presence of tuberculosis in certain cases, for the injection of tuberculin, in the case of a healthy individual, gives rise to no fever; and besides, these inoculations are now used very widely for diagnostic purposes among the domestic animals. Then, in the next place, the reports published by Koch have stimulated others to make further investigations into the question of securing immunity by injecting the toxins of different bacteria; and in this way it has come to pass that we have discovered antitoxins for diphtheria, tetanus, cholera, and typhoid fever.

Maragliano, during the last few years, has made attempts, by inoculating experimental animals (donkey, dog, horse) with the toxins derived from cultures of tubercle bacilli, to secure a serum that will cure tuberculosis. The observations thus far made, however, do not warrant the conclusion that this serum possesses the power to cure that disease in the human being. Koch, according to a communication which he published recently ("Ueber neue Tuberculinpräparate," *Deutsche med. Woch.*, 1897, No. 14), has succeeded in obtaining, from highly virulent cultures of tubercle bacilli, a substance which, as he claims, is able to confer immunity from the effects of all the constituent elements of these bacilli. In order to obtain this substance it is necessary that young cultures of tubercle bacilli should be dried in a vacuum-exsiccator and then reduced to a fine powder by trituration. The product of this triturating process is then thoroughly mixed with distilled water and placed in a centrifugal machine. The active substance is contained in the slimy deposit which forms as a result of the centrifugal action of the machine (Koch designates this slimy deposit by the letters T. R.), and the latter must again be dried and triturated, and then dissolved in water to which (for the proper preservation

of the material) twenty per cent of glycerin should be added. (The preparation is manufactured at the establishment of Meister, Lucius, and Brünning, in Höchst-on-the-Main, Germany.) In this fluid form the preparation contains 10 mgm. of solid substance in each cubic centimetre; and when it is to be used, it should be diluted by the addition of some physiological salt solution. When rather large quantities are injected, it is claimed that the animals become immunized in from two to three weeks. In treating human beings who are actually affected with tuberculosis it is well to begin with a dose of $\frac{1}{500}$ mgm. of the preparation, and then to increase the dose—the injections being made every other day—up to 20 mgm. So far as one can judge from the published reports thus far available, the T. R. preparation does not appear to exert a curative action upon tuberculosis in the human being.

The *blood-serum treatment of diphtheria*—i.e., the employment of the antitoxins contained in the blood of animals that have been rendered immune as regards diphtheria, as a means of curing that disease when it is actually in progress or of warding off a diphtheria infection—is a discovery that we owe to Behring; and I may add that thousands of observers have confirmed the favorable effects which are produced by the procedure which he had first thoroughly tested by experimental methods. In the treatment of diphtheria patients it is customary to inject at a single sitting, beneath the skin of the thigh, quite large quantities (1,000 immunization units) of the serum.

The term "normal serum"—i.e., a serum having the value of a single immunization unit—is applied by Behring to such serum as will, when mixed with a quantity of diphtheria poison equal to ten times the minimum fatal dose, and then injected, in the amount of $\frac{1}{10}$ c.c., into a guinea-pig weighing between 200 and 300 gm., surely protect the animal from contracting the disease. Sheep and horses are the animals from which it is easiest to obtain the desired quality of serum. The preparation is put up and sold in quantities varying from 500 to 3,000 immunization units.

If culture filtrates of the *tetanus bacilli* are rendered weaker by the addition of certain chemical reagents (such as iodine trichloride or iodine in combination with potassium iodide) it is (according to Kitasato, Behring, Tizzoni, and Buchner) a possible thing, by repeatedly injecting such a filtrate, of increasing virulence, to establish in animals a condition of immunity as regards tetanus; and, according to the same authorities, the blood of these immunized animals contains *an antitoxin which can surely protect experimental animals from an infection with tetanus.* The treatment of human beings who are actually suffering from this disease has thus far not produced very satisfactory results; presumably because the curative inoculations can be instituted only at a comparatively advanced stage of the disease.

So far as the *bubonic plague* is concerned, animals and human beings that are susceptible may be rendered immune by injections of sterilized cultures of the plague bacilli; and it appears, furthermore, that in the blood-serum of immunized animals (the horse, for example) there are present antitoxins which render it possible to utilize the serum both for immunization and for curative purposes.

Calmette claims that by means of inoculations of very small doses of *snake-poison*, continued throughout a considerable period of time, animals may be rendered immune from the injurious effects of this poison, and that when this has been accomplished the blood-serum of these animals will also be found to possess antitoxic virtues (as regards the same poison); from which latter circumstance it may rightly be inferred that the serum may also be employed for curative purposes. In Brazil, Mexico, Africa, and some other places, various methods are employed for the purpose of protecting persons from the injurious effects of a snake-bite, or for that of curing them after they have been bitten; and in all of these the snake-poison itself is used for the accomplishment of these purposes. Among these methods may be mentioned that of drinking some of the fluid secreted by the poison-glands, or that of rubbing some of the poison in a diluted state into small wounds made in the skin, etc. (Brenning).

According to the researches of Ehrlich, mice may be made immune against *ricin*, to which they are most susceptible, by mixing very small doses of it with their food, and then afterward injecting additional small doses beneath the skin. The appearance of the immunity first shows itself six days after the first dose, so that upon this day the animal can withstand a dose thirteen times as great as at the beginning. By means of continued systematic inoculations the animal is rendered insusceptible to a dose eight-hundredfold stronger. The immunity is produced by an antitoxic substance, antiricin, which suspends the action of the poison.

VII. The Internal Causes of Disease and the Inheritance of Pathological Conditions.

§ 31. Among the **internal causes of disease** must be mentioned, first, all those peculiarities which have their foundation in the organization of the individual and owe their origin to some **congenital local predisposition**, and which, furthermore, superinduce diseases independently of outside influences—i.e., without the aid of any other influences except such as our relations to the outside (more or less harmful) world necessarily bring with them. When morbid processes arise in this manner we speak of the special disease or of the special malformation thus arising as of spontaneous origin. In a broader sense we may also reckon among the internal causes of disease the individual peculiarities which have been described in the last part (VI.), and to which the names **predisposition** and **idiosyncrasy** have been applied; but we are justified in doing this only in so far as the diseases in question clearly owe their immediate development not merely to the action of some outside injurious influence, but also at the same time to the existence of a predisposition or of an idiosyncrasy.

Among the morbid conditions which arise from strictly internal causes—i.e., without the aid of specific external influences—and which either appear of themselves or are brought to development by some external influence, it is possible to distinguish different groups, namely, one in which the body as a whole—the constitution—is involved; another, in which only a portion of the body, or a system, shows itself to be functionally deranged or perhaps even pathologically altered in its structure; and, finally, a third, in which either a single organ or even, perhaps, only a part of an organ, manifests these functional or structural alterations. At the same time it should be stated that no sharp dividing-line exists between these groups, for local pathological alterations may be associated with constitutional conditions. Then, again, it should be remembered that very frequently it is not only difficult, but at times impossible, to determine what part internal conditions and what part external exciting causes are playing in the production of a pathological condition, since we cannot measure the force of the external influence which has called into activity the pathological processes.

Among the **constitutional diseases arising from internal causes** are to be mentioned, in the first place, the *development of dwarfs* and the *development of giants*—i.e., disturbances of growth, of which the first is marked by an abnormal deficiency in the growth of all the parts of the body, of the skeleton as well as of the soft parts; while the second is characterized by a growth exceeding that of the ordinary individual. It cannot be doubted that both the dwarf and the giant growths are dependent on a congenital tendency; but the same effects can be produced, at least so far as the inhibition of growth is concerned, by harmful influences during the period of gestation and during later development, so that it cannot be always told with certainty whether an abnormal bodily growth is dependent upon a congenital tendency or upon pathological influences which have occurred during the period of growth (see § 22)—as, for instance, upon disturbances of growth due to disease or to the loss of the thyroid gland.

The same difficulties are encountered when we attempt to explain the cases in which the body has perhaps attained a normal development of

height, but manifests a **general feebleness**—a constitution which has no power to withstand a great variety of external influences; for this condition may arise from an inherited weakly and defective body, or from harmful influences which have attacked it during intra- and extra-uterine development; and, again, a congenitally weak body and outside weakening influences may both have acted upon the growth of the individual in a similar manner.

Another constitutional peculiarity which may owe its origin to an inherited special predisposition is **corpulence** (*obesitas, adipositas, lipomatosis universalis*)—a condition in which fat is either deposited in excessive quantity only in tissues which normally should possess fat, or else is deposited also in regions which normally contain no fat, as, for instance, under the endocardium or between the muscles. In the ultimate analysis of this condition it must be recognized that this heaping up of fat in the body is always dependent upon a disproportion between fat-production (that is, the supply of fat to the parts) and fat-consumption; this disproportion showing itself at one time in the form of greatly increased fat-production, at another in that of an abnormal decrease in fat-consumption. As daily observation teaches, the energy with which metabolism goes on in the body is very different in different individuals, and changes also at different periods of life, so that the same amount of food tends at one time to fatten, while at another time it shows no such tendency.

In the pathological constitution termed obesity, which sometimes depends on a congenital predisposition, the energy of the protoplasmic forces of destructive metamorphosis is weakened, so that an abnormal amount of fat collects even when a moderate or perhaps only a slight amount of nutritive material is supplied to the tissues.

Gout, like obesity, is also a constitutional disease, which for the most part is dependent upon a constitutional inherited tendency, and consequently depends chiefly on internal causes. Exactly what is the essence of the disease we are unable as yet to state. One of its characteristic features is that a patient with this disease is subject to attacks in which deposits of uric acid are made in the tissues. According to Garrod and Ebstein, acute attacks of gout are dependent upon a stagnation of uric acid, which has its origin either in the kidney or in local conditions. Pfeiffer, on the other hand, is of the opinion that the essential feature of a gouty predisposition consists in the fact that the uric acid is produced in a form which is soluble only with difficulty. According to von Noorden, the production and deposit of uric acid are only secondary phenomena, which are induced by the presence of a particular ferment, which acts only locally and consequently is not dependent upon the amount and the behavior of the uric acid which is formed in another part of the body.

Pathological changes which arise in single systems and organs from internal causes may manifest themselves in all the tissues of the body, and they involve at one time an entire system or organ, at another only a part of one.

In the **skeleton,** in the first place, we may mention the following changes as illustrating what we have just stated: abnormal developments, as regards size, of single parts—e.g., abnormal smallness of the extremities (micromelia), or of the head also (microcephalus), in contrast with the trunk; or the abnormal size of one bone or of a group of bones (macrocephalus; the abnormal increase in the length of the fin-

gers; great growth of one finger, or of an entire foot, or of an extremity; the formation of ribs in the neck, etc.). Occasionally supernumerary bones are developed—for instance, bones in the wrist or phalanges, thus leading to the formation of supernumerary fingers. There can also be developed atypical formations, such as bony growths (exostoses, hyperostoses), which may extend over a larger or a smaller portion of the skeleton, and may originate either spontaneously or as a result of some traumatism.

In the **muscular system** are to be noted the production of pathological bony formations, which occur either singly or in multiple form (myositis ossificans), and occasionally, in the period of childhood, give rise to a progressive stiffening of the muscular apparatus, by the transformation of the muscles into osseous scales or plates.

In the **vascular system** the lesions which are found consist in part of gross anatomical alterations—such as an abnormal division of the arteries, or some pathological development of the heart—and in part of more delicate alterations, which reveal their existence only through some abnormal action on the part of the circulatory apparatus or through a tendency manifested by the patient to hemorrhages (*hæmophilia*) which take place spontaneously—i.e., without our being able to show that an injurious influence has been exerted upon the heart and blood-vessels.

Some of the *primary disturbances which the development of* **the central nervous system** *experiences* manifest themselves only by some *pathological disturbance of function* or by a special *predisposition to various forms of illness;* while others are distinguished by *gross*—i.e., by perceptible—*anatomical changes*, such as abnormal smallness of the cerebrum (micrencephalon) or of the spinal cord (micromyelia), defective or absent development of particular parts (compare the chapter on Malformations), misplacement of the gray substance (heterotopia of the gray substance), the abnormal formation of cavities (syringomyelia), abnormal formations of the neuroglia, etc. These disturbances may involve the functions of the organs of sensation and of the motor areas, as well as, and to an even greater extent, the psychical processes; and the pathological conditions termed idiocy, epilepsy, periodical and circular insanity, hysteria, and neurasthenia, as well as paralysis, mania, melancholia, and dementia, may have their origin in a congenital predisposition. Lately some persons have attempted to refer the tendency to crime to a congenital predisposition; and Lombroso in particular has sought to prove that the person who depends for his support upon crime and lives only for criminal purposes—the *homo delinquens*—is a congenital criminal—i.e., he is a man who suffers from bodily and mental abnormalities; possesses other physical and psychical characteristics than those which belong to the normal man, or even to one who is simply mentally diseased; in a word, he must be looked upon as presenting the symptoms of a special form of degeneration that tends in a well-defined direction. According to Lombroso, a subnormal development of the anterior half of the cranium, together with a corresponding lack of development of the anterior portion of the cerebrum, when associated with an increased development of the posterior portion of the brain, necessarily produces a feebler development of the intelligence and of the moral sense, and favors a strongly developed instinct-life. Benedikt even goes so far as to maintain that we can distinguish in criminals a peculiar configuration of the cerebral convolutions, which are similar in type, as he claims, to those of animals of prey.

The views of Lombroso and Benedikt have met with opposition from various quarters, and have been attacked as incorrect; and there can be no doubt that there does not exist a species of human beings who are characterized by definite anatomical peculiarities by means of which one can say that they belong to the class termed *homo delinquens* in contradistinction to that of the *homo sapiens;* for all the bodily peculiarities which have been mentioned as characteristic of the criminal type—as for instance, the beast-of-prey type of cerebral convolutions, the feebly developed frontal brain, the receding forehead, massiveness of the lower jaw, prognathia, asymmetry of the skull, marked prominence of the arcus superficialis and of the arcus frontalis, pathological conformations of the skull, etc.—are indeed frequent in criminals, but they are also far from infrequent in perfectly normal men. It is, however, not to be doubted that the tendency to criminality is very often dependent on a congenital predisposition, which is found in some special organization of the central nervous system; that, in this regard, the criminal has some resemblance to the insane person; and that also mental diseases —for instance, epilepsy and hysteria—are often observed in criminals.

The *pathological cerebral functions* in persons who are pathologically predisposed to this class of diseases may develop primarily—i.e., without external agencies having any influence on the disturbance; and under these circumstances the person concerned, even during the time of development and growth, or sometimes also later, manifests pathological changes in the functions of his cerebrum without having received any external injury that might explain such changes. In other cases, on the other hand, external influences—such as mental work, sorrow, care, psychical irritation, disease, etc.—are the causes which give rise to the particular illness—i.e., to the outbreak of pathological brain or spinal functions. In these cases the inherited predisposition consists merely in an abnormal weakness, a tendency to disease of the central nervous system, which expresses itself in the circumstance that transitory influences which would not act noticeably on a normal person are sufficient, in the case in question, to produce the morbid phenomena. Inasmuch as many influences—such as diseases, infections, psychical irritations—are adequate, under certain conditions, to produce mental disease in individuals whom one must look upon as normal, so it is clear that, in many instances, it is difficult, if not impossible, to distinguish what part the internal causes—the inherited predisposition—and what part the external causes have had in producing disease of the central nervous system.

As regards the **peripheral nerves**, it is especially their connective-tissue elements which often take on a pathological activity of growth under the influence of internal causes; and this activity manifests itself partly in the form of diffuse thickenings (fibromatosis of the nerves), partly in that of nodular thickenings (fibromata of the nerves), which either develop along the course of those nerves which are large enough to be dissected with the scalpel, or are scattered over the filaments of the finer nerves, often being present in large numbers throughout the areas of distribution of entire nerves, or even involving the entire territory supplied by the peripheral nerves, the skin being the part most often affected (multiple fibromata of the skin). In certain cases the fibromatosis of the nerves is associated with an increase in the number of nerve-fibres; and as a result of this change there will be found in a given territory of nerve-supply abnormally numerous bands of nerve-

fibres, thickened by a pathological increase of the endoneurium, mostly thrown into serpentine or twisted shapes, or interwoven (cirsoid neuroma, plexiform neuroma).

Among the **pathological conditions of the visual apparatus** which arise from internal causes we should mention particularly dyschromatopsia and achromatopsia, the congenital partial or total color-blindness, both of which conditions are frequently spoken of as daltonism, and are characterized by a want of perception for a portion of the colors (most frequently red and green), or even for all the colors. And, further, in this same category belongs the typical pigment-degeneration of the retina, in which a peculiar spotted-black pigmentation of the retina is seen, while simultaneously the acuteness of central vision and the perception of light are diminished and the visual field is narrowed. Finally, there should be added to this list certain forms of myopia, as well as albinism (the absence of pigment in the choroid), the latter of which conditions also involves some of the appendages of the skin.

The only affection of the **organ of hearing** which, at least in part, can be considered as a primary developmental disturbance is deaf-mutism. Then, in the next place, we may also place in this category the various malformations of the external ear.

In the **skin** and **subcutaneous connective tissue** new growths develop, which are the result of congenital predisposition. These growths are formed sometimes almost entirely of connective tissue, sometimes of epithelial tissues; they also often involve particular portions of the skin, as the cutaneous nerves, the blood-vessels, the lymphatics, or the adipose tissue. When they take on the form of extensive thickenings of the skin and the subcutaneous cellular tissues, they constitute the foundation of the conditions termed fibromatous, neuromatous, hæmangiomatous, lymphangiomatous, and lipomatous elephantiasis. When they occur as circumscribed formations, they are known as birth-marks, soft moles, lentigo, freckles, and also as tumors of the lymph- and blood-vessels. Epithelial hypertrophy produces those changes which are called fish-scale disease or ichthyosis, ichthyotic warts, and cutaneous horns.

In addition to the pathological conditions which have been enumerated there are many **malformations of the body** (compare the chapter on Malformations) **or also of the internal organs,** which must be considered as of primary origin—i.e., which are not produced by the action of external influences on the already developing fœtus. Finally, many forms of **tumors** (see the chapter relating to Tumors) belong in this class, especially those which are found to be already well developed at the time of birth, or which undergo development during childhood.

§ 32. Two explanations may be given of the **mode of origin of those diseases which we attribute to internal agencies**—diseases, therefore, in which external influences are either entirely absent during both intra- and extra-uterine life, or simply possess the significance of being a source of irritation sufficiently active to cause the development of a disease germ already present in the body. These two explanations are the following: *either the pathological peculiarities of the particular individual are inherited from the ancestors, or they are developed from the seed—i.e., from the sexual nuclei that have copulated or from the segmentation nucleus derived from such a combination.*

The **inheritance of pathological peculiarities** is a fact which we learn, in the first place, from clinical observations; for many of the instances cited in § 31 of diseases which result from internal causes are

also illustrations of inherited tendencies within the family. In a certain number these peculiarities are transmitted from parent to child, while in other instances the hereditary factor is shown by the fact that the grandchild manifests the peculiarities of the grandparents, the parents themselves remaining exempt; sometimes, again, it is shown by the fact that scattered members of the family (the collateral branches being included) manifest the pathological peculiarities which are under discussion. Dwarfishness and abnormal largeness of the body are peculiarities which frequently enough characterize certain families. Six fingers, harelip, right-sided position of the heart, birth-marks, multiple bony excrescences on the skeleton, fibromatous nerves, and multiple nerve-fibromata may appear in many generations of one family.

Congenital hæmophilia is also an inheritable pathological peculiarity, which in the descent is transmitted generally by the offspring to the male grandchild, whereby the daughters aid in the transmission, without themselves suffering from hæmophilia. There may be, however, a direct transmission of the hæmophilia to the children. Partial and total color-blindness is also sometimes an inherited family disease which attacks particularly the male members, and, like hæmophilia, is transmitted through the female line, which does not suffer, to the male descendants. Typical pigmentation of the retina is inheritable, as are also near-sightedness, deaf-mutism, and certain forms of progressive muscular atrophy and polyuria (Weyl).

Gairdner and Garrod state that in about ninety per cent of all persons suffering from gout the disease also existed in their forefathers.

Of the pathological conditions of the nervous system, many are transmissible; to these belong especially periodical and circular insanity, epilepsy, hysteria, and congenital madness (*originäre Verrücktheit*), and, to a somewhat less extent, melancholia, mania, frenzy, and alcoholism; while the progressive paralyses, the deliriums, and the conditions of mental exhaustion are but slightly influenced by heredity (Kraepelin). Hagen estimated the number of hereditary insane at 28.9 per cent, Leidesdorf at 25 per cent, Tigges at over 40 per cent of all cases, and Forel holds that from 69 to 85 per cent may be accounted for by heredity.

In the most severe forms of hereditary degeneration the pathological conditions themselves are inherited; but more frequently the hereditary influence only produces a predisposition to disease, and the actual morbid condition first shows itself only after the central nervous system has been acted upon by some external injurious influence. The form of the disease may remain the same in the descendants as in the ancestors (*identical heredity*). More frequently a change takes place in the form of the disease (*transformational heredity*), not infrequently in the sense that the severity of the disease increases from generation to generation, a condition which is termed *degenerative heredity*.

According to Morel, there may appear, for instance, in the first generation, nervous temperament, moral depravity, excesses; in the second, a tendency to apoplexy, severe neuroses, and alcoholism; in the third generation, psychical changes, suicide, intellectual incapacity; finally, in the fourth generation, congenital imbecility, malformations, arrests of development.

As already stated in § 29, the special *predispositions to this or that disease* which individual families or sometimes entire races show are hereditary peculiarities. Thus, for example, it cannot be doubted that

certain families have a stronger predisposition to certain infections (tuberculosis) than others. But, on the other hand, it often happens that *insusceptibility* to certain injurious influences is a valuable attribute of a family.

There is nothing at all strange in the fact that there are **inheritable diseases**, since it is a well-known fact that in a family not only the peculiarities of race, but also those of that particular family, may be inherited, and that the qualities characteristic of one or the other or of both parents often enough recur in the children. In order that hereditary transmission may take place, it is simply necessary that the peculiar quality under consideration should represent not merely a somatic change accidentally acquired in the course of the life of an ancestor, but rather an individual peculiarity of this ancestor which he in turn had inherited from his forefathers. Diseases which, in a normal individual, originate only when he is subjected to external harmful influences are never in the true sense inherited (see § 34); this expression can be employed only in regard to those *pathological conditions which already existed in the germ*. If, for example, a disease—such as a mental disease or nearsightedness—is the product of a special inherited predisposition plus the effect of harmful influences which have acted upon the body during life, only that part can be transmitted which was received by inheritance, but not that which was derived from external influences—i.e., the part which was acquired.

In *direct inheritance*—i.e., in that form of inheritance in which parental peculiarities are transmitted to the child—the transmission of both normal and pathological qualities can take place only when both sexual elements, in the condition in which they are at the moment of their union, contain, in a potential form, the characteristics of both parents, in so far as these characteristics are of a transmissible nature; and consequently the product of their union—the segmentation-cell—must then contain within itself both the paternal and the maternal qualities. Since the sexual cells do not represent a product of the body which is formed only after a certain stage in the course of life is reached, but should rather be looked upon as independent formations which, located in special organs, separate themselves at an early period from the rest of the body (that is, from the somatic cells) and then—continuing to derive their protection and nourishment from the body to which they belong—lead an independent life, there remains but one way in which we can explain the phenomenon of inheritance: we must assume that the separate sexual cells contain, from the time of their origin onward, essentially the same characteristics (in a potential form, of course) as belong to the body in which they dwell; in other words, that the sexual cells, as well as the body itself, have inherited in general the same qualities from the ancestors. Since in the act of fructification only the nuclei of the sexual cells—i.e., only parts of them—come to copulation, we are compelled further to assume that the bearers of these qualities are only the nuclei, and that the peculiarities belonging to the individual who grows out of this combination of the sexual nuclei reside in and are bound up with the organization of the nuclei.

If there appear in the descendants normal or pathological characteristics which are found collaterally (in an uncle, a great-aunt, or a cousin) but not in the parents, this is spoken of as *collateral hereditary transmission*; in this case the only supposition that will explain it is that the sexual nuclei, in their origin, received characteristics which the bodies

of the parents did not contain; or, at all events, we may assume that these characteristics did not undergo development and become manifest in these bodies, whereas in some of the relatives they did thus become manifest.

If there appear in an individual normal or pathological characteristics which were wanting in his parents, but were present in the grandparents or great-grandparents, this is spoken of as an *atavistic hereditary transmission;* and the appropriate explanation of this is to be found in the fact that the peculiarity of the grandparents or great-grandparents was transmitted to the sexual nuclei of the son—i.e., of the son and grandson—but did not develop in the body of the first, while this latent quality manifested itself again in the grandson and in the great-grandson.

The attempt has been made to give to the atavistic mode of transmission—which is of frequent occurrence and is confined to the nearest generations of the ancestors—a wider significance in pathology. Thus it has been proposed to explain many newly arising pathological manifestations, which seemed to resemble certain somatic peculiarities possessed by remote animal species in the ancestry of man, as a reversion to the type of those ancestors. Thus, for instance, microcephalia and micrencephalia have been explained as a reversion to the ape type, and Lombroso is also inclined to look on his *homo delinquens* as an atavistic appearance. Nevertheless there is no doubt but that they have gone too far in this respect, and have characterized, as atavistic formations, various acquired pathological formations and fresh variations of germs (compare § 33). Aside from the question of a reversion to the type of the nearest generations of ancestors, atavism plays only a minor part in pathology, and it can really be employed only in the explanation of pathological formations when their tissues show a certain fluctuating behavior, characterized by the fact that frequently formations arise which in phylogeny or ontogeny represent the primary stages of the then normal conditions. In this category belong, for instance, the occurrence of certain forms of the ear or of supernumerary ribs, the increase in number of the mammary glands and nipple, the development of certain muscles belonging to the Mammifera which come nearest to man in the scale of relationship.

It is accepted by many authors that *in isolated cases acquired diseases may, under certain circumstances, be transmitted to the descendants*, and some even go so far as to say that the possibility of hereditary transmission may be conceded to a deformity sustained through injury; indeed, they consider that this has actually been proved for some instances. In support of their opinion, they believe that they are warranted in pointing to the hereditary transmissibility of birthmarks, malformations of the fingers, myopia, mental diseases, predisposition to tuberculosis, and other conditions, in regard to which they assume that these conditions in the first instance showed themselves only as acquired maladies, and that they were then transmitted to the descendants. Further, they believe that they can point to observations on animals—full accounts of many such observations are on record—as evidence that injuries give rise to deformities which later on are bequeathed to their offspring.

An unprejudiced examination, however, of the collected material which is brought forward in support of this opinion shows that *observations which establish the existence of such a thing as the hereditary transmission of acquired pathological characteristics in an individual do not exist;* that in the observations in question the defectiveness of the proof consists at one time in an error of observation, at another in a false inference from a correctly made observation. Take, for instance, the fact that in a child a birth-mark appears in a region of the skin exactly corresponding to that in which the mother has a scar. The advocates of the doctrine under discussion would quote this as an example of the inheritance of a deformity; and yet they would be entirely wrong, for scars and

birth-marks represent two entirely different forms of tissue-change. When among the descendants of a man who suffered from any form whatever of mental disease, but revealed the existence of that disease by the perversity of his actions only after he had attained a certain age, there appears an inheritable affection of the central nervous system; or if we make a similar observation in regard to the appearance of myopia, we must not conclude from such observations that the disease first observed (in the ancestor) was strictly an acquired condition. The term *acquired*, in the sense in which it is employed in physical science, can be applied only to that which, in the course of the life of an individual, arises only through outward influences, but not to a peculiarity the first beginnings of which already existed in the germ, although the peculiarity itself may not have become recognizable until outside exciting causes had exerted their influence upon its development. Should there appear in a family hereditary mental disease or hereditary myopia, the first case may have already been due to a pathological condition of the germ, although no manifestations of the disease occurred until some of the outside influences of life called them into activity and so rendered the recognition of the pathological condition possible. Here, too, the particular pathological condition represents no true acquired disease.

There is still another thing that militates against the idea that an acquired pathological condition may be transmitted from parent to child; I refer to the simple consideration that the human race is exposed to so many injurious influences, and its individual members are so frequently sufferers from diseased conditions and mutilations, that, if this doctrine of the transmission of acquired pathological conditions was true, mankind would soon be in a condition of extreme suffering and misery, and would then perish. And this statement would still be true if only a portion of the acquired ailments was transmitted to the descendants; for, despite all their diseases and mutilations, human beings continue to bring descendants into the world.

The act of fructification—that is, the first step which leads to the production of a new individual—is accomplished by the copulation of the sexual nuclei—that is, of the ovum nucleus and that of the spermatozoön; and, according to the researches of the last decade, there is no longer any doubt that *these two nuclei are the bearers of the hereditary characteristics of the parents*, and that the individuality of the two copulating nuclei resides in their organization. It is impossible to imagine in what manner processes that take place in the body-cells can bring about in the sexual nuclei, which are lying inside of certain special cells in the sexual glands, such an alteration in their organization that from that moment onward they shall contain in potential form the acquired characteristics of the body, and shall transmit them, after copulation has taken place, to the descendants.

Darwin in his time defended the opinion that acquired characteristics could be transmitted to the succeeding generations, and sought to make these phenomena intelligible by assuming that molecules from all the cells of the body contribute to the formation of the embryonal cells, and that, as a result of this, any alterations which take place in the organism can be transmitted to the embryonal cells. Notwithstanding this expression of his opinion, Darwin makes statements in his writings which do not agree with this opinion; indeed, some of them directly contradict this view.

§ 33. As is shown in the explanations given in § 32, *inherited diseases are always such as arise in the first place from some internal predisposition—i.e., such as have developed from actual beginnings located in the germ or embryo—or at least they are diseases in which the element of predisposition is a congenital characteristic.* Conversely, the statement may be made that *all the normal or pathological qualities present in the embryo are transmissible.*

Consequently the question of the primary origin of inherited diseases coincides with the question concerning the nature of the causes of internal diseases—i.e., concerning the acquisition of those pathological characteristics which we regard, after they have made their appearance at some later date, as arising spontaneously, and as having their first traces in the germ or embryo.

The **first appearance of new pathological characteristics** which are hereditary may be connected with the fact that, as a result of **sexual procreation**—i.e., of the union of two sexual nuclei, of which the one is the bearer of the transmitted qualities of the paternal ancestor, the other of those of the maternal—**new variations** are constantly appear-

ing, so that the fruit—that is, the child—never entirely resembles one parent; more frequently, in addition to the qualities which the parents offer, it also possesses new qualities. Even if we assume that the sexual nuclei sometimes contain in potential form exactly the same characteristics as those belonging to the parent out of whom they originated, the product resulting from the copulation of these nuclei would nevertheless present a certain degree of variation from the type of either parent. It may be said, however, that in a case like this the differences between the children of such a couple would be only slight. As a matter of fact, the different products of the same parents may vary to an immeasurable extent by reason of the fact that the sexual nuclei themselves contain a mixture of the characteristics inherited from the paternal and maternal ancestors, and that this mixture is never the same in the separate sexual nuclei of the individual.

This statement is in harmony with the fact that the children in one family always present important differences in their bodily and mental characteristics, and with the further fact that a strong degree of resemblance is observed only in the case of twins that have been produced from one egg, or, in other words, only when the process of development has in both children started from the same act of copulation.

The **embryonal variations resulting from the mixture of two individually different hereditary tendencies** can find their expression in most varied qualities of the body and mind of the developing child. If these do not deviate in a marked degree from the characteristics which the different members of the same family are wont to show, the conditions are looked upon as normal, and generally receive no particular attention; but if, on the contrary, important differences in character are produced, the occurrence attracts greater attention, and, according to the value which it has for the individual, it is considered at one time as something favorable, at another as something unfavorable, something pathological. When small, weak parents beget children who grow to be big, strong men, or whose mental ability surpasses considerably that of the parents, it is regarded as a favorable occurrence. If a genius in any branch of human knowledge and skill should, as sometimes actually happens, develop suddenly in a family—i.e., without any hint of a particularly high mental development having been shown among the ancestors—the occurrence would attract universal attention and would be considered a fortunate event. But if, on the other hand, strong parents beget children that are weak or physically defective, or if their mental development remains considerably backward as compared with that of the parents, or if a complete arrest of development shows itself in some department of their mental faculties, *we call this newly appearing variation unnatural, pathological.*

If we take into account the experiences which the pathology of man and of animals furnishes, the assumption seems fully warranted that among the **transmissible pathological conditions and tendencies** very many, perhaps the majority, **are referable to a variation of the germ based upon the amphimixis.** This explanation is available, therefore, for the group of the hereditary diseased conditions and predispositions of the central nervous system, for hereditary myopia, for hæmophilia, for pigment-degeneration of the retina, and for polydactylism. If such abnormal characteristics repeatedly show themselves in the offspring of parents who are healthy and have healthy ancestors, one can conclude that the sexual nuclei of the parents, although individually normal, have

through their union produced a pathological variation. This conclusion is substantiated when one or both parents produce normal offspring through copulation with other individuals.

Besides the variations which are the result of normal sexual reproduction, it is highly probable that pathological variations of the germ, which lead to the production of transmissible pathological characteristics, also owe their origin to the circumstance that **harmful influences** may have been exerted **upon sexual nuclei or upon the segmentation nucleus**, or else that the **process of copulation**—i.e., the union of the sexual nuclei—may have been **disturbed** in some manner. The substance which acts prejudicially may be a product of the body, or it can come from without and at the same time also produce its harmful effect upon the body. Consequently in these cases one can speak of the *acquisition of a transmissible pathological peculiarity through some harmful influence emanating from the outer world.* But this expression is not intended to convey the idea, as many seem to believe, that the tissues of the body, under the influence of outside harmful agencies, first undergo certain alterations and then in some manner convey these alterations to the germ-cells. The proper explanation is, rather, that the injurious influence exerts its force directly upon the sexual nuclei or upon the segmentation nucleus, and here produces *some sort of a change*, which at a later date leads to a pathological transformation of the individual who is undergoing development from the impregnated egg. So far as the nature of the resulting pathological variation is concerned, it is a matter of no importance whether the somatic tissues are also subjected to alterations, and of what nature these are.

If a transmissible pathological characteristic has been produced, it may—provided it does not abridge life or prevent reproduction—actually be transmitted from parent to offspring, although this need not necessarily happen. The chances that this particular characteristic will be transmitted are greatest when the parents both possess it; when, for instance, both parents are affected with hereditary deaf-mutism or with near-sightedness. If the characteristic is wanting in one parent, there is a good prospect that a new germ-variation may be produced, in which the pathological characteristic fails entirely to manifest itself, and in later generations completely disappears. If there are several descendants, and if the tendency to this pathological defect has not entirely disappeared, it may show itself in only a few of the descendants, and then either in a modified or in an aggravated form. Finally, it sometimes happens that the characteristic remains latent in one generation—i.e., it does not extend beyond the sexual cells—and then reappears in the second.

There seems to me to be no doubt that, through the copulation of two sexual germs possessing different hereditary tendencies, variations may be produced, and that among these there may be certain ones which we should consider as pathological. It is a more difficult thing to answer the question whether, besides these, there are not transmissible variations of a pathological character which owe their origin to influences that affect the sexual nuclei or the segmentation nucleus; and with what frequency, if the question is answered in the affirmative, these influences are exerted effectively. Weismann, according to the statements made by him in his most recent publication, is of the opinion that the first beginnings of the hereditary variations are not to be located in the amphimixis, but rather in the direct action of external influences upon the sexual nuclei. Starting out with the assumption that the variable cells or groups of cells derived from the germ (by him called *hereditary pieces* or *determinates*) are represented in the germ-plasma by special particles, which are formed by the grouping together of a number of *life-trophoblasts*, or *biophores* (molecular groups which represent the smallest units of

living matter), and which he calls *determinants* or *determining pieces*, he believes that he is warranted in ascribing the transmissible variation primarily to the circumstance that external agencies alter these groups of determinants and determinates contained within the nuclear chromatin, in such a manner that afterward the hereditary pieces or determinates which are dependent upon them also undergo a change. He believes that such an influence might be exerted by excessive nourishment of a determinant, causing it to assume a more rapid growth. Thus, for example, he believes that many congenital malformations—as, for instance, an increase in the number of fingers and toes—can be attributed to the overfeeding and consequent reduplication of the groups of determinants. The amphimixis has, according to Weismann, only a secondary influence on the production of a lasting variation, and this influence he defines to be the following: that it constantly, in some new manner, mixes the variations which are necessitated by the alterations of the determinants, and yet does not itself produce any *new* variations. "The alterations in character which the determinants undergo, through unequal influences of nutrition, constitute the material out of which, by means of amphimixis in connection with selection, the visible individual variations are developed; and then, by an increase of these variations and by their combining one with another, entirely new varieties are created."

I agree with Weismann to this extent: I consider that the appearance of new variations of a pathological nature is partly to be considered as resulting from changes which have been effected in the determinants contained in the sexual nuclei through the direct action of outside influences. I do not, however, believe that there is sufficient ground for attributing, as does Weismann, the development of new separate parts to the greater nourishment of individual groups of determinants. Such a dependence of the germ-plasma upon the surrounding nutritive material appears to me to be scarcely conceivable, and is in opposition to all notions which we have hitherto held regarding the nutrition of cells. Accordingly, qualitative rather than quantitative alterations in the nutrient material would seem to be what is required in order to effect changes in the organization of the determinants; and, further, I believe that amphimixis holds not a secondary, but a primary position in the production of pathological variations, in the sense that it is itself competent to produce new variations. Finally, it seems to me that we cannot wholly set aside the hypothesis of Nägeli, according to which the idioplasma is capable of altering its own condition, from within outward, in certain fixed directions and according to certain fixed laws, and thus may produce new characteristics.

§ 34. In addition to the pathological conditions already enumerated, there are **a few infectious diseases** in which an **hereditary transmission** seems to occur. These are syphilis, small-pox, varicella, intermittent and recurrent fevers. At all events, in these diseases cases are sometimes observed in which a child, at the time of its birth or soon afterward, develops symptoms of the same disease from which the father or the mother had been suffering either at the time of procreation or during the period of gestation. This, however, is a phenomenon entirely different from that already spoken of as hereditary transmission.

Infectious diseases are caused by organisms which multiply in the body. The transmission of the disease to the child becomes possible only when the infecting organisms belonging to this particular disease either find their way into the sexual germ-cells and then also into the impregnated egg, or else pass from the maternal organism into the tissues of the child while developing in the uterus. The latter can occur so long as the child remains in the uterus, and it obliges us to assume that the infecting organisms pass through the decidual membranes and the outer coverings of the ovum—or, in the later periods of gestation, through the *placenta*—and thus are transported from the maternal to the child's organism. It is also possible that, when the parents keep up cohabitation for a certain length of time after impregnation has taken place, the micro-organisms which enter the vagina with the sperm may pass on into the uterus, and in this manner infect the already impregnated egg which is within that organ.

The transmission of bacterial infectious diseases to the embryo is beyond all doubt a possible thing. In the case of syphilis this may

take place at the instant of impregnation as well as later during intra-uterine development, and the syphilis may be communicated to the child as well by the father as by the mother. In the case of small-pox, endocardiitis, and scarlet fever, many instances of infection of the fœtus *in utero* have been reported; and, from recent observations and experimental investigations, there can no longer be any doubt that anthrax-bacilli, pus-cocci and pneumococci, and, under certain conditions, also typhoid-bacilli, can pass through the placenta to the fœtus. This can occur only when the bacteria gain an entrance into the maternal blood-channels of the placenta, and are capable of multiplying there, and then of penetrating into the fœtal vessels—a procedure which is rendered possible chiefly by the damage done by the multiplying bacteria to the placental tissue, thereby enabling them to penetrate into the latter and to multiply within it.

There are therefore both **conceptional** and **intra-uterine placental infections**, which constitute a **pseudo-form of hereditary transmission**, in which the peculiar characteristics of the individual are not transmitted to the embryo, but instead an organized poison finds its way into the germ or into the already partially developed fœtus, where it undergoes further development and then calls into activity the same disease as that with which the parent is infected.

Our knowledge concerning the frequency of these occurrences is, unfortunately, still deficient. In the case of the most frequent of all chronic infectious diseases, tuberculosis, the rôle played by the disease proper is still imperfectly understood. Such a form of hereditary transmission is believed to exist by many persons in lepra, but it is denied by others; and in syphilis, in which the frequency of its occurrence is not denied, our knowledge of the nature of the specific poison is still very meagre. In acute bacterial infections we know only of a transmission of the infection to the already developed embryo. How far the egg can be infected in the early stages of impregnation or at the actual moment of conception, without its further development being hindered thereby, is unknown.

If, during bacterial infections, infection occurs at the moment of conception, one must believe that the organisms belonging to the particular disease under consideration must have existed in the sexual glands at the time when the sexual cells were thrown off, then must have reached the egg at the moment when it became impregnated, or immediately afterward, and finally must have continued to live in it without hindering the further development of the egg. Then, besides, the assumption must be made that the schizomycetes push their way into certain regions of tissues during fœtal development, and yet do not give rise to pathological processes until a later date is reached.

In a manner similar to that by which infections are carried to the fœtus can an *acquired insusceptibility to some particular disease* be transmitted from the mother to the child—that is, the antibodies (Ehrlich) present in the maternal organism can be transmitted to the fœtus. On the other hand, a transmission of immunity through the sperm, at the moment of conception, does not take place, and likewise there is no such thing as a genuine hereditary transmission of an acquired immunity. The experiments of Charrin and Gley, which are quoted in support of this idea, admit of a different interpretation.

CHAPTER III.

Disturbances in the Circulation of the Blood and of the Lymph.

I. General Circulatory Disturbances Dependent upon Changes in the Function of the Heart, Changes in the General Vascular Resistance, and Changes in the Mass of the Blood.

§ 35. It is by the work of the heart, in the rhythmical contractions of its auricles and ventricles, that the mass of the blood is kept constantly in motion. The blood within the elastic walls of the aorta, as it is driven toward the periphery of the body, meets, in the friction which exists within the innumerable divisions and subdivisions of the arterial system, a considerable degree of resistance; and this occasions a relatively high pressure throughout the whole arterial system, a pressure which in the human arteria femoralis equals that of about 120 mm. of mercury. After passing through the capillaries the blood arrives in the veins with very little velocity, and stands in the veins under a very low pressure, which varies, however, according to the location of the vein, and is greatest where the vessel sustains a blood-column of considerable height. In the great venous trunks in the neighborhood of the thorax the pressure is generally negative, particularly during inspiration, as the thorax during this stage of respiration aspirates the blood from the veins lying without the chest. Only during forced expiration does the positive pressure within the veins rise somewhat higher.

At a given moment, the degree of pressure in the aorta, the mass of the blood remaining constant, is dependent upon the work of the heart and upon the resistance in the arterial system, and this in turn is dependent upon the combined cross-sections of the blood-vessels, an area which varies on account of the elasticity and contractility of the arteries. In the corporeal circulation the tension of the arteries is very considerable; in the pulmonary circulation it is but slight, the blood-pressure in the pulmonary artery being only from one-third to two-fifths that in the aorta. Both the heart and the arteries are under the influence of the nervous system which regulates their action.

The function of the heart consists in rhythmical contractions of the heart-muscle, and its normal efficiency presupposes that the heart-muscle as well as the heart-ganglia be sound. Every lesion of the heart, therefore, in just so much as it diminishes the contractility of the heart-muscle and disturbs the action of the cardiac ganglia, and in just so far as the diminution in the efficiency of certain parts of the heart-mechanism is not compensated by increased activity of other parts, will **impede the effective working of the heart.**

In many cases in which the efficiency of the heart-muscle has become impaired, certain anatomical changes, such as fatty degeneration and the disintegration of its cells, can be demonstrated; in others micro-

scopic examination fails to reveal any anatomical differences, particularly in cases in which the diminution of efficiency has resulted from the exhaustion consequent upon overexertion. This may occur either when —as, for instance, in cases of febrile temperature,—for a considerable length of time, the heart performs its function under unfavorable conditions, though at no time forced to work more than slightly beyond its normal rate; or when, for a brief period, the demands upon the heart become excessively severe. Moreover, either trophic disturbances, or the toxic condition accompanying the febrile infectious diseases, or sudden diminution of the blood-supply from obstruction of a coronary artery, may, under certain circumstances, bring about heart-failure within too short a time to allow anatomical lesions of the muscular tissue to become recognizable. A further obstacle to the working of the heart is occasionally caused by adhesions of the surface of the heart to the pericardium and to contiguous portions of the lung, inasmuch as the heart is thereby hindered in the amplitude of its contractions.

Through the serous collections in the pericardium which occur during the course of certain diseases, through pronounced degrees of thoracic deformity, through high convexity of the diaphragm, the ready enlargement of the heart during diastole may be impeded, and thereby the free afflux of blood from the venous system be interfered with to such an extent that ultimately the blood is but scantily furnished to the ventricles. Should rents or distortions of the flaps of the valves occur, or adhesions between them arise in consequence of pathological processes, or should the valve-flaps, on account of dilatation of the heart and spreading of its orifices, become relatively too short, then there will be developed at the orifices of the ventricles and of the auricles the conditions which are known as insufficiency and stenosis. The former of these is a condition in which a valve, during the dilatation of the auricle or ventricle next ahead of it, fails to completely close its proper orifice, the latter a condition in which, during the contraction of the auricle or ventricle behind it, the ostium fails to become sufficiently widely open. The effect of a stenosis is that of opposing additional obstacles to the passage of the blood during systole; in the case of insufficiency, aortic or pulmonary, the blood escapes during the ventricular diastole from the great vessels back into the ventricles; in the case of mitral or of tricuspid insufficiency the ventricular systole forces the blood back into the respective auricles.

Finally, clots are not infrequently formed in the heart, and these, under certain circumstances—particularly when they lie in proximity to the ostia—on the one hand interfere with the closure of the valves, and on the other hand cause a narrowing of the orifice.

The universal operation of all the above-mentioned pathological conditions of the heart is to produce the following results: **the efficiency of the heart's function becomes impaired,** too small a volume of blood is in a given time delivered to the arterial system, and consequently the blood-pressure in the aorta falls, the velocity of the blood-current is lessened, and the blood collects more and more in the venous system, while the pressure in the veins rises. There is consequently an inadequate *filling of the arteries* throughout the whole body, varying, indeed, according to the degree of contraction maintained in individual groups of arteries, while both veins and capillaries are, on the other hand, overfilled with blood. The condition becomes one of general **venous hyperæmia,** which may in some parts become so great that, on account of the

engorgement of the capillaries with venous blood, the tissues acquire a *livid, cyanotic appearance.* When the difference between the pressure in the arterial and that in the venous system reaches a certain minimum, the circulation is arrested, while the right auricle and ventricle become greatly distended with blood.

Should the contractions of the heart have become, from any cause, feeble and incomplete, then the pulse-wave also is small. Should the rate of the heart-beats become slower, the arterial system during the interval between two systoles tends to empty itself more than normally.

If the impairment of cardiac efficiency is essentially dependent upon imperfect function of the left side of the heart, as is the case, for instance, in valvular lesions of the left heart, then the disturbance of the circulation first becomes manifest in the arterial portion of the corporeal and in the pulmonary circulation.

With stenosis at the aortic orifice, the arteries, if the heart's action remains unchanged, fill but slowly and incompletely (pulsus tardus). With insufficiency of the aortic valves, a normal or even an increased volume of blood is indeed thrown into the arteries (pulsus celer), but a portion of this flows back into the ventricle during diastole. In both cases an overdistention of the left ventricle becomes more and more established, and eventually it leads to an interference with the emptying of the left auricle, and thereby to over-accumulation of blood in that chamber and subsequently in the pulmonary veins. Owing, however, to the low pressure in the pulmonary circulation, the blood is readily dammed back upon the right ventricle, and the tendency to blood-stasis, extending beyond this, reaches to the right auricle and finally to the venous system throughout the body.

A similar effect upon those portions of the circulatory apparatus which lie back of the left auricle is caused by valvular lesions at the mitral orifice, as in these cases also there are blood-stasis in the pulmonary circulation and a rise of pressure in the pulmonary veins and in the pulmonary arteries; while the left ventricle either receives too small a supply of blood (stenosis) or during its contraction drives back a portion of its contents (insufficiency) into the auricle.

In valvular lesions at the orifices of the right heart, the damming back of the blood is limited to the veins of the corporeal circulation, while in the pulmonary circulation both velocity and pressure are diminished. Ultimately the pressure falls in the aortic system also, as the left side of the heart receives a diminished supply of blood.

Damming back of the blood in the great veins of the body often gives rise to *venous pulsation* in the neighborhood of the thorax, as in these veins waves moving toward the capillaries arise, which overcome and pass the venous valves, and in particular the valve in the bulb at the junction of the internal jugular and subclavian veins. The cause of the venous pulsation is the failure of the valves in the veins to close. In case of imperfect function of the valve at the bulb this pulsation may be observed in a slight degree even during normal action of the heart; but when there is distention of the veins, and particularly when there is tricuspid insufficiency, the pulsation is far stronger and is traceable much farther toward the periphery. If the tricuspid still closes completely, the venous pulsation is then only the expression of the rhythmical recurrence of a hindrance to the outflow of the blood from the veins: if the tricuspid is incompetent, blood is driven back upon the veins during the contraction of the right ventricle.

When certain of the chambers of a heart affected with valvular lesions become distended with blood, the muscular walls of these chambers may, by an increased activity, **compensate, to a certain degree, for such valvular defects.** In course of time an increase in volume—a **hypertrophy of the heart-muscle**—follows, and enables the heart for an indefinite period to meet the increased demands upon it. Such compensation, however, frequently becomes inadequate, with the result that the pressure permanently remains abnormally low in the aorta and abnormally high in the veins. There is, at the same time, the danger that the heart-muscle may tire in time, or that a very slight illness may render the heart insufficient. Thus, for example, a prolonged quickening of the heart's action, in that it abbreviates the diastolic rest of the heart-muscle, may suffice to bring about fatigue and insufficiency of the heart. Cardiac arrest finally follows, with great accumulation of blood in the heart from sheer inability of the organ to drive onward the mass of blood flowing into it.

Increased heart action—that is, greater frequency of the contractions, each being strong and full—causes a rise in arterial blood-pressure and an increased velocity of the blood-current. When increased demands are repeatedly made upon the left side of the heart—as frequently happens in consequence of severe bodily labor, of high living, or of abnormal irritability of the cardiac nerves—the left ventricle may become hypertrophied and may act permanently with increased force. Inasmuch as from quickening of the blood-current the right cavities of the heart receive a larger amount of blood during diastole, the hypertrophy of the left side of the heart ordinarily becomes accompanied by a similar condition of the right ventricle.

Lessening of the mass of blood, or **general anæmia,** from hemorrhage, leads to a temporary lowering of pressure in the aorta; but if the loss of blood was not excessive, this pressure presently rises again as the blood-vessels adapt themselves to their new conditions, and, as a consequence of the stimulation of the vaso-motor centre through local anæmia, display a higher degree of contraction. Under normal conditions a speedy increase in the mass of the blood takes place through absorption of fluids, and later on through regeneration of the blood proper. Similarly, the arterial pressure is lowered and the blood-current slowed in **anhydræmia,**—i.e., in diminution of the fluid portion of the blood. After severe hemorrhage the arterial pressure remains low for a considerable period of time, the circulation being slowed, and the pulse, because of lessened stimulation of the vagus-centre (Cohnheim), being frequent and small.

In case of long-continued diminution of the mass of the blood—that condition which is known as **chronic anæmia,** and appears under many different circumstances—the vascular system is but imperfectly filled, the blood-pressure is lowered, and the blood-current is slowed. Both the heart and the blood-vessels adapt themselves to the new conditions and become diminished in volume. With great deficiency in hæmoglobin, degeneration of the heart-muscle—particularly fatty degeneration—frequently takes place.

In the lower animals **increase in the volume of the blood** through injection of blood or of salt-solution into the vessels is followed by only a temporary increase in the blood-pressure and in the velocity of the blood-current. A return to the normal follows, partly through the dilatation of a portion of the vascular system, particularly in the abdomen,

partly through the elimination of the surplus from the vessels. If the mass of the blood, as a result of some special diathesis or of high living, comes to stand in abnormally high proportion to the weight of the body, if there exists a **permanent condition of plethora**, the pressure in the aorta will then be permanently raised in consequence, the task of the heart will be permanently increased, and a corresponding degree of cardiac *hypertrophy* will ensue.

§ 36. **Increase of general vascular resistance** occurs as well in the corporeal as in the pulmonary circulation, and results in increased pressure behind the point of increased resistance, and diminished pressure ahead of it.

In the **corporeal circulation** the hindrance may lie either in the main vessel, the aorta, or else in the arterial branches, whose degree of contraction maintains and governs the pressure in the aorta. Vascular contraction involving areas supplied by a large number of arteries, and sufficiently well marked to increase the blood-pressure, is generally but a temporary phenomenon, passing off with the relaxation of the arterial excitement; nevertheless permanent increase in blood-pressure does occur, accompanied by hypertrophy of the left ventricle, and it cannot well be accounted for otherwise than as the result of a contraction of the lumen of the smaller arteries. Temporary arterial contraction and increase of pressure occur particularly through overcharging of the blood with carbonic acid; permanent increase of pressure in the aorta, on the contrary, is a result of chronic kidney-disease in which the secreting parenchyma of the kidney is cut off from the circulation. Inasmuch, however, as that portion of the vascular system which is in this case cut off is far too inconsiderable to cause, by itself, an increase of pressure throughout the whole aortic system,—since the blood-vessels leading in other directions might well become correspondingly relaxed,—we are compelled to assume that in the case of "contracted kidney" other obstacles to the circulation are developed throughout more considerable vascular areas, and these we most naturally seek in that apparatus which normally serves to maintain the aortic pressure at its proper level—namely, in the smaller arteries distributed throughout the body. Whether we have to do with reflex stimulation from the kidneys through the nerves, or whether with retained urinary ingredients working upon the vaso-motor centres or directly upon the walls of the vessels, or whether with the heart driven to more forcible action through stimulation of its nerves, we are not at present able to determine.

Increase of resistance in the aorta may result from stenosis of this vessel, as occurs in rare cases at the isthmus,[1] or from congenital narrowness of the whole aorta, or from large aortic thrombi, or from an advanced stage of disease of the vessel-wall, with the intima consequently rough and lumpy and the whole vessel rigid, inelastic, and unyielding, or, finally, from a general dilatation of the vessel, whereby counter-currents are formed in the passing blood-stream.

Diminution of the total resistance in the corporeal circulation is possible through relaxation of the tone of a large part of the arteries, an event which follows when the vaso-motor centre is paralyzed or when

[1] The "isthmus" is that part of the descending aorta which lies between the origin of the left subclavian artery and the attachment of the ligamentum arteriosum (the obliterated ductus arteriosus Botalli). Its calibre during fœtal life is commensurate with the relatively small amount of blood it carries from the left ventricle to the lower extremities (Luschka, "Die Anatomie des Menschen").—Translator's Note.

the cervical cord is divided or partly destroyed by any other process. As the blood, in this case, flows too quickly from the arteries over into the veins, an equalization of the pressure between arteries and veins follows, the blood-current is slackened, the heart receives during diastole an insufficiency of blood, and the circulation may finally come to a standstill.

Increase of the resistance in the pulmonary circulation arises most frequently in consequence of disease of the lungs and of the pleura. Simple adhesions of the pleura may be a cause of such increased resistance; and so also curvatures of the spine, in that they cause displacements of the lungs and hinder the respiratory movements of the chest-wall and thereby cause the withdrawal of an efficient aid to the circulation. Of great influence, moreover, are such pulmonary affections as hypertrophic emphysema, retractions and indurations of the lungs and the breaking down of portions of the lung-tissue,—all of which lead to impermeability of a portion of the pulmonary capillaries; and the same, furthermore, is true of compression of the lungs by pleural exudations, and of compression of the pulmonary arteries by aortic aneurism or by tumors.

If the obstacle is but inconsiderable, the blood can still make for itself a free passage to the left side of the heart without increase in the blood-pressure, provided the velocity of the flow is increased through the channels that still are open. Greater obstacles cause increase of pressure in the pulmonary artery and in the right side of the heart, and, if they continue for a long time, may cause hypertrophy of the right ventricle through increased exertion of the heart. This can come to pass, however, only when the nutrition of the heart-muscle is meantime maintained, and when the mass of the blood is not diminished to correspond with the diminution in the area of the pulmonary tract. If the right side of the heart does not succeed in overcoming the obstacles in the pulmonary circulation, the blood is then dammed back upon the right side of the heart and eventually upon the venous system.

Rise of the pressure in the right half of the thorax hinders the influx of the venous blood into the right auricle, and causes an accumulation of blood in the veins of the whole body. A sudden increase in the pressure may cause the blood to flow back into the neighboring veins.

The observation that cardiac hypertrophy results from various renal diseases has been differently explained by different authors. Some seek the cause of the phenomenon in an increase in the mass of the blood (Traube, Bamberger); others (Senator, Ewald) think it dependent upon a change in the composition of the blood; others, again (Gull and Sutton), ascribe it to a widespread alteration in the walls of the smaller arteries. Buhl attributes it to over-nourishment of the heart. The result of recent investigations places beyond doubt the dependence of the cardiac hypertrophy accompanying renal disease upon an increase of arterial pressure. This increase is very probably due to an increase in the degree of resistance offered by the small arteries generally throughout the body,—a resistance which owes its existence to the contraction of these small vessels. For an explanation of what causes the latter phenomenon we shall have to assume that it is due either to the direct stimulus supplied by the urinary elements that circulate in the blood, or to some reflex influence emanating from the kidney, or finally to some influence exerted upon the vaso-motor centre. It is possible also that in this matter some importance should attach to increased heart activity.

According to the observations of Löwit, compression of the trunk of the aorta sometimes does and sometimes does not cause an increase of blood-pressure in the pulmonary artery. Löwit considers this rise in pressure to be independent of the stasis in the left auricle. In his opinion, the rise does not result from a damming back of the blood from the left on to the right side of the heart, but much rather is caused by an increased afflux of blood to the right side of the heart, which is in its turn brought about

by a relaxation of the contracted arterioles due to cerebral anæmia. The correctness of Löwit's observations cannot be called in question, and his interpretation also is to be accepted, but it is by no means to be considered as showing that in cases of permanent obstructions in the corporeal circulation, or in the left side of the heart, which cause a setting back of the blood, such a damming back of the blood does not reach the pulmonary artery and by way of the lungs extend beyond it into the right side of the heart.

II. Local Hyperæmia and Local Anæmia.

§ 37. To the blood is assigned the function of carrying nourishment to all the organs and tissues of the body. The cells and cellular structures of which the various tissues are composed are able to maintain their existence but a short time without the advent of fresh supplies of nutritive material, and for this reason most of the tissues are provided with blood-vessels, and such tissues as lack them are placed in the most intimate connection with vascular structures.

The demands of the various tissues for blood are not always uniform, and there is consequently in the various tissues an alternating increase and decrease in the afflux of blood, and at the same time in the amount of blood contained within the organ or tissue at a given moment. An organ richly filled with blood is designated as **hyperæmic**; if containing but little blood it is said to be **anæmic.**

The regulation of the volume of blood which an organ receives under physiological conditions is brought about by a change of the resistance in the afferent arteries, and this change is effected exclusively by variations in the calibre of these vessels. Inasmuch as the mass of the blood in the body does not suffice to fill all the vessels at once, an extra supply for one organ becomes possible only by diverting the blood from other directions. The change in the calibre of an artery is determined, aside from the blood-pressure, by the elasticity of its walls and by the degree of contraction of its organic muscular fibres. These fibres are the regulating agents, and their action is dependent partly upon influences acting on them directly, partly upon nervous impulses from the intravascular plexuses and from the vaso-motor centres in the spinal cord and in the medulla oblongata; some stimulating and others inhibiting the muscular action.

When the variations from a mean in the blood-supply of a part overstep the physiological limits, or when these variations arise without their physiological causes, or when the condition is unduly protracted, we then call the state one of **pathological hyperæmia** or of **pathological anæmia.** These conditions are only in part caused by the same governing mechanism which determines the normal blood-supply of an organ.

§ 38. **Hyperæmia** of an organ is caused, under pathological conditions, either by an increase of the arterial supply or by an obstruction and hindrance to the venous outflow, and we distinguish, accordingly, an *active* or *congestive* (arterial) *hyperæmia* and a *passive* or *stagnation* (venous) *hyperæmia.* **Active hyperæmia** arises from an *increase of the afflux of blood* (*congestion*), and is either *idiopathic* or *collateral.* The first of these plays the more important rôle, and depends upon a relaxation of the muscular tunics, which is caused either by *paralysis of the vaso-constrictor nerves* (*neuroparalytic congestion*), or by *stimulation of the vaso-dilators* (*neurotic congestion*), or by direct *weakening* or *paralysis of the muscles* (as, for instance, through heat, bruising, the action of atro-

pine, brief interruptions of the blood-current), or, finally, by *diminution of the external pressure exerted upon the vessels. Collateral hyperæmia* is merely the result of a diminished flow of blood to other parts. It arises first in the immediate neighborhood of the parts whose blood-supply is lessened; afterward the blood may be driven also to such other more remote organs as may require it.

Active hyperæmia is accompanied by more or less *marked redness* and *swelling of the part*—changes which are quite striking in tissues that are rich in blood-vessels. The blood flows through its widened channels with increased velocity and lends to the tissue the color of arterial blood. Tissues situated superficially, and thus exposed to cooling, grow warmer in consequence of the more active passage of blood through them than through the surrounding parts less generously supplied.

Passive hyperæmia is a consequence of *retardation* or *obstruction of the flow of blood in the veins.* A *general tendency to blood-stasis throughout the corporeal circulation* follows directly whenever feebleness of the heart's action, insufficiency or stenosis of the cardiac valves, or obstructions in the pulmonary circulation impede the emptying of the large veins into the right side of the heart. In the pulmonary circulation it is more particularly aortic or mitral lesions, or weakness of the left side of the heart, less frequently obstacles in the arterial portion of the corporeal circulation, which, by obstructing the outflow of blood from the lungs, lead to a pulmonary stasis; and this may not infrequently reach a degree that will cause the damming back of the blood to become appreciable in the right side of the heart as well as in the veins of the corporeal circulation (cf. § 35 and § 36).

Local stasis may follow directly from the fact that the progress of the blood through the veins lacks the continued support of the action of the muscles and of the aspiration of the blood through the inspiratory enlargement of the thoracic cavity. The defection of the first of these auxiliary forces becomes most obvious in the area of distribution of the inferior vena cava; as, for instance, in subjects who live continuously sedentary lives, or who stand a great part of the time without active bodily movements, so that the task of emptying the deep-seated veins into the trunk of the vena cava falls almost exclusively upon the forces inherent in the walls of the veins—namely, their elasticity and contractility,—these forces being insufficient to drive onward the column of blood which distends the walls of the vessel. An inadequate aspiration through the respiratory movements makes itself felt when respiration is interfered with by inflammation or other disease processes in the lungs or the pleura.

A further cause of local passive hyperæmia consists in the narrowing or closing of particular veins, as occurs in compression, ligation, the formation of thrombi (§ 40), and the invasion of the veins by neoplasms. The pregnant uterus, for example, or a pelvic tumor may compress the veins of the pelvis, a thrombus may choke the cerebral sinuses or the femoral or the portal veins, or a sarcoma of the pelvis may grow into the great pelvic veins.

Should any single vein become occluded by any of the above processes, or be ligated during operation, the effect of such occlusion is often very inconsiderable, inasmuch as the vein in question may have free and manifold connection with other veins, so that no considerable obstacle is created to the progress of the blood. If, on the other hand, the occluded vein has no auxiliaries, or if these are insufficient for the

passage of the blood—as, for instance, is the case with the main divisions of the portal vein, with the sinuses of the dura mater, with the femoral or with the renal veins—then a greater or less degree of stasis occurs in the area of distribution of the vein affected.

The effect of the obstacle to the circulation shows itself first in the portion of the vein which lies between the obstruction and the periphery, the blood-current in this part becoming slowed or entirely checked, while at the same time, through continued afflux of blood from the capillaries, a progressive filling and stretching of the vein follows. If through the compensatory action of the elastic and contractile vessel-wall, in yielding more and more to the pressure, the obstruction can be overcome, circulation will persist, and, through such channels as it still finds open to it, the blood will flow on to the heart; oftentimes under these circumstances the small veins which have to perform this increased labor become gradually much dilated, and are eventually converted into veins of large size. If the obstruction cannot be overcome, and if no communicating vessels capable of dilatation are at hand, the circulation will be arrested, and a condition of complete stasis (§ 43) or of thrombosis (§ 40) will be brought about in the area of distribution of the obstructed vessel.

If the arrest of the blood-current in the area of distribution of a vein extends to the capillaries, so that these become distended with blood, this will impart a *reddish-blue, cyanotic hue* to the surrounding tissues, and a certain amount of *swelling* will take place in them.

Both active hyperæmia and passive hyperæmia, observed during life, may take on quite a different appearance after death, and may even, in not a few instances, entirely disappear. This is especially the case with active hyperæmia of the skin and sometimes with that of the mucous membranes, and it is dependent upon the fact that the tissues, put upon the stretch by the dilatation of the capillaries, contract down upon the latter after the ceasing of the circulation, and by their counter-pressure drive the contents of the capillaries on into the veins. Tissues which may have been reddened during life may accordingly appear pale after death. As converse to this, other tissues which during life were pale, or at least showed no particular redness, may take on, after death, a reddish-blue color. This occurs especially upon the sides and back of the trunk (unless these parts happen to be uppermost) and upon the back of the neck and the posterior aspect of the extremities of a cadaver lying face upward, and is to be explained by the fact that after death the blood sinks to the most dependent parts, and fills not only the veins, but finally also the capillaries. The phenomenon is known as *post-mortem hypostasis*, and the spots are known as **cadaveric petechiæ or lividity** (*livores*). They begin to appear at about the third hour after death, and their number and size are proportionate to the amount of blood contained in the skin and in the subcutaneous tissues at the moment of death.

In the internal organs post-mortem hypostasis is particularly apparent in the pia mater, whose dependent veins are generally more completely filled with blood than those lying above them. In the lungs we get, through the settling of the blood, engorgement not only of the veins, but also of the capillaries.

Whenever during life, on account of cardiac insufficiency, the general circulation is imperfect and partial stagnation of the blood follows, the blood often collects in a similar way in the dependent portions of the

body, partly because it is not driven out of them, and partly because it sinks into these parts from those situated on a higher level. This phenomenon, likewise designated as **hypostasis**, is particularly observed in the lungs (hypostatic congestion).

For observing the circulation during life, and its behavior under changes of velocity and pressure, we make use of either the tongue or the web of the foot of a curarized frog[1] properly spread on an object-holder. A very simple expedient, for instance, is to draw out the tongue and spread it over a cork cemented upon the object-holder, and fasten it there with pins. With a normal, as well as with a quickened circulation both the pulsating arterial current and the steady-flowing venous current exhibit a marginal zone of blood-plasma. If by ligation of the efferent veins we induce a partial stagnation the flow becomes slowed, the clear marginal zone of blood-plasma disappears from the veins, and both veins and capillaries become greatly distended with accumulated red blood-corpuscles. After a certain time the tongue begins to swell through infiltration with transuded fluid.

According to the investigations of Landerer,[2] the wall of a capillary vessel embedded in the tissues supports only from one-third to one-half the blood-pressure. The remainder is borne by the surrounding tissues, which afford an elastic resistance and so maintain the tension which is necessary to keep the blood in circulation. Hence in active hyperæmia as well as in passive hyperæmia, the tension of the tissues and the pressure upon them are increased; in anæmia both are diminished.

§ 39. **Localized anæmia** or **ischæmia** is a condition wherein certain tissues contain but a small amount of blood; it is always the result of a diminution in the afflux of blood. If the total bulk of the blood is normal, then the cause of the ischæmia is purely local; if there is an insufficient quantity of blood in the whole vascular system, the local insufficiency may partly depend upon that.

The **pathological diminution in the afflux of blood** to an organ is sometimes merely the result of an unusual *increase in the normal resistance* of the arteries—that is, of a contraction of the muscular tunics. In other cases *abnormal obstructions*—such as compression of the arteries, narrowing of the arterial lumen through pathological changes in the vessel-wall, deposits on the internal surface of the vessels, occlusion of the vessels by emboli (cf. § 17), etc.—act as hindrances to the blood-current.

The immediate consequence of the *narrowing of an artery* is always slowing and diminution of the stream beyond the point of constriction. *Complete occlusion* of an artery brings the circulation beyond the obstruction to an immediate standstill. If, back of the point of constriction or occlusion, the artery is provided with connecting branches of relatively considerable size—so-called *collateral arteries*—the disturbance of the circulation is abated by an increased flow through the collateral vessels; and the larger and the more distensible these are, the more complete the restoration of the circulation. If the constricted or occluded artery possesses no communicating branch in its area of distribution—if it is a so-called *terminal artery*—the slowing or the arrest of the circulation beyond the point of obstruction or of occlusion cannot be immediately done away with, and the area supplied by this vessel becomes presently partly or completely emptied of blood, as, through the contraction of the arteries, and through the pressure of the tissues upon the capillaries and veins, the blood is more or less completely forced out of the area of distribution of the artery in question. Frequently, however, after a time, an afflux of blood comes from neighboring capillaries.

When the current and the pressure beyond a *constricted point* have

[1] Cohnheim, *Virch. Arch.*, 40. Bd.
[2] "Die Gewebsspannung," Leipzig, 1884.

sunk below a certain minimum, little by little the driving force becomes less and less able to push along the mass of the blood. The red corpuscles, particularly, cease to move, and collect in the veins and capillaries, and as a consequence *the area supplied by the artery in question becomes filled with blood once more;* only not with circulating, but with stagnant blood. *The same thing occurs when, a terminal artery being completely occluded, the blood oozes into the affected area, under minimal pressure, through arteries incapable of adequate enlargement, or merely through communicating capillaries.* An accumulation of blood within the anæmic area may also occur by reflux from the veins. This occurs when the intravascular pressure within this area has sunk to nothing, whereas in the veins themselves a positive pressure exists. Arrest of the circulation in the veins will accordingly favor the reflux of the blood.

A further cause of anæmia in an organ may be the abnormal congestion of other organs, as in that case the total mass of the blood may not suffice to supply the remaining organs adequately. Anæmia from this cause is called *collateral anæmia.*

All *anæmic tissues* are characterized by *pallor.* They are at the same time flabby, not turgescent, and the color proper to each becomes distinctly appreciable.

The **significance of a condition of ischæmia** lies especially in the fact that, on account of the need of the tissues for a continuous supply of oxygen and other nutritive elements, the continuance, for a certain length of time, of the condition of imperfect blood-supply brings about *tissue-degeneration* (cf. § 3). Complete arrest of the blood-supply leads in a short time to *death* of the tissue involved. If blood comes to flow anew among the degenerated and dying tissues in the area of distribution of an obstructed vessel, and stagnates there, extravasation of blood into the tissues may follow, and a *hemorrhagic infarct* (cf. § 48) be formed.

The rapidity and completeness with which a *collateral circulation* may be developed after the occlusion of an artery depend upon the size and distensibility of those vessels which are in communication with the area which has become ischæmic. If these are numerous and distensible, the ischæmic area becomes very soon irrigated with an approximately normal volume of blood. If this is not the case the disturbance of the circulation corrects itself more slowly, and stasis and increased pressure are found to extend farther back from the point of obstruction toward the heart, so that a collateral hyperæmia occurs likewise in vessels situated farther back on the course of the blood, i.e., nearer the heart. In the further course of the process of reëstablishing the circulation, the increase in the volume and velocity of the blood-current remains confined to such vessels as communicate with the area deprived of its natural blood-supply—that is, confined to the capillary and arterial anastomoses; and here this increase of volume and velocity becomes permanent. This leads in turn to a permanent distention of the vessels of the part, and at the same time to a substantial increase in the vascular walls, not only in thickness, but, as becomes evident from the crooking and twisting of the vessels, in length also. According to Nothnagel, in rabbits the phenomenon of the increase in thickness of the walls of the anastomotic vessels may be demonstrated about six days after the ligation of an artery; and after the ligation in continuity of vessels of some size, the small arteries which carry on the collateral circulation become transformed, in the course of a few weeks, into quite capacious, thick-walled arteries.

III. Coagulation, Thrombosis, and Stasis.

§ 40. Upon the death of the individual, the blood lying in the heart and in the great vessels generally coagulates in part, sooner or later, and thence arise those formations known as **post-mortem clots.** If the clotting occurs at a time when the red blood-corpuscles are still evenly

distributed in the blood, and the whole mass of the blood becomes coagulated, the clots form dark-red masses—a condition in which the blood is termed *cruor*. If before coagulation, through the settling of the red corpuscles, the mass divides itself into a substratum rich in red blood-corpuscles and an upper fluid layer containing none and consisting exclusively of the plasma,—then, if the latter coagulate, there will be formed soft gelatinous lumps and stringy masses light yellow in color, elastic, with a smooth surface, and not adherent to the vessel-wall, which are designated as *lardaceous clots* or as *fibrinous deposits*. Through the inclusion of red blood-corpuscles in these formations, they may exhibit in parts a red or reddish-black color; when a large proportion of leucocytes are present, the color at such spots will border on white.

If blood is drawn from an artery or a vein and received into a vessel, within a short time *coagulation* will occur, as a result of the adhesion of

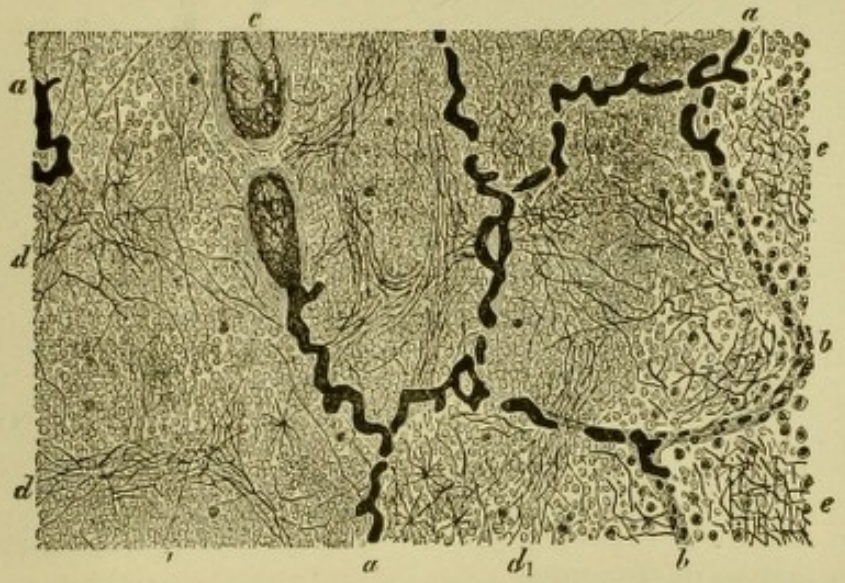


FIG. 12.—Coagulated blood in a recent hemorrhagic infarct of the lung. (Müller's fluid; hæmatoxylin; eosin.) *a*, Interalveolar septa without nuclei, containing capillaries filled with deep-violet thrombi of homogeneous appearance; *b*, septa showing nuclei; *c*, vein containing a red thrombus; *d*, alveoli distended by a firm blood-clot; *e*, alveoli filled with serous fluid, fibrin, and leucocytes. Magnified 100 diameters.

this fluid to the sides of the receptacle. When this change takes place the appearance presented by the coagulated blood will be that of a soft coherent mass. If freshly drawn blood be beaten with a solid body, in a short time stringy *fibrin* will be separated from the surface of the blood. *If within the body blood be extravasated in considerable quantity into the tissues*—for instance, into the pericardium or into the lungs—*coagulation* may occur here likewise, and among the red blood-corpuscles stringy masses are formed (Fig. 12, *d*, *e*), whose fibres run in the most varying directions, interlacing with one another continually, and frequently also proceeding radially from a central point.

The **coagulation of the blood** is a process difficult of chemical interpretation, and in spite of numerous investigations we have not succeeded in explaining this enigmatical phenomenon. We know, however, that for its occurrence the presence of a *fibrinogenic substance*, of a *ferment*, and of certain *salts*, especially *calcium salts*, is indispensable, and that the fibrinogenic substance is an albuminoid body, belonging to the class of the *globulins*, which is present in the blood, while the ferment is probably derived from the white (possibly also from the red) corpus-

cles of the blood, which either are dissolved in the blood-plasma (Schmidt), or yield to it certain constituents of their mass (Löwit). According to A. Schmidt, by means of the fibrin-ferment a very bulky albuminoid body is formed, in a way still obscure, out of the globulins preëxisting in the alkaline solution, which body is precipitated by the calcium salts present in the plasma; and in the process of coagulation we must recognize two stages—to wit, the stage of the production of the ferment and the stage of the fermentative action or coagulation proper. According to Pekelharing, on the other hand, the fibrin-ferment is itself a calcium compound (calcium-nucleo-albumin) which has the power of carrying lime over to the fibrinogen, whereby from the soluble fibrinogen an insoluble albuminous compound is formed, containing calcium, which body is **fibrin**. According to Freund, the substance which emanates from the cells and which excites coagulation, is phosphoric acid.

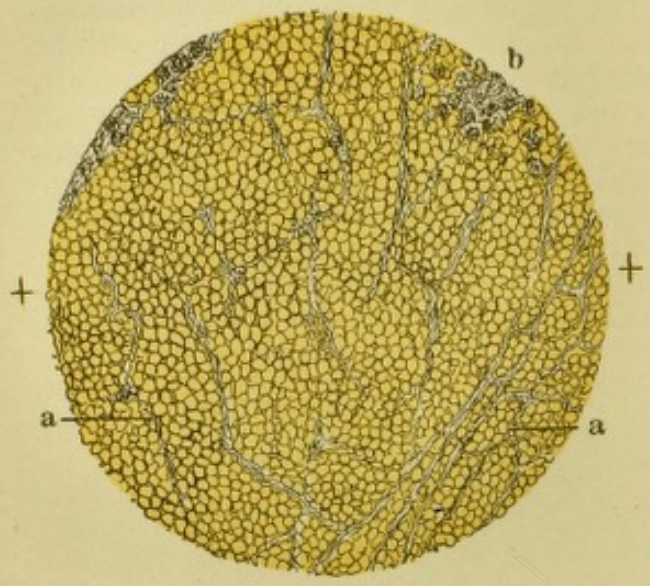


FIG. 13.—Section through a red thrombus formed in one of the muscular veins of the thigh after occlusion of the femoral vein. (Müller's fluid; hæmatoxylin.) *a*, Fibrin threads; *b*, leucocytes and granular bodies. Magnified 250 diameters.

If coagulation of the blood within the heart and the vessels takes place during life, or if a solidifying mass separates from the circulating blood, this process is called **thrombosis** and its product a **thrombus.**

If coagulation or **thrombosis occurs in a mass of blood deprived of motion,** there is formed a **dark-red thrombus** (Fig. 12, *c*, and Fig. 13), which, like the reddish-black post-mortem clots, or like the coagula of extravasated blood (Fig. 12, *d*), contains all of the red blood-corpuscles; the precipitated fibrin forming granules (Fig. 13, *b*) and fibres (Fig. 13, *a*). When we find a clot which has recently formed in some small blood-vessel, it is quite often possible to demonstrate after death, by the employment of suitable methods, the presence of bundles and star-shaped clusters of slender fibrin rods (Fig. 14) which radiate from centres of coagulation. In such cases, however, it is often impossible to determine with certainty to what extent the coagulation took place during the individual's

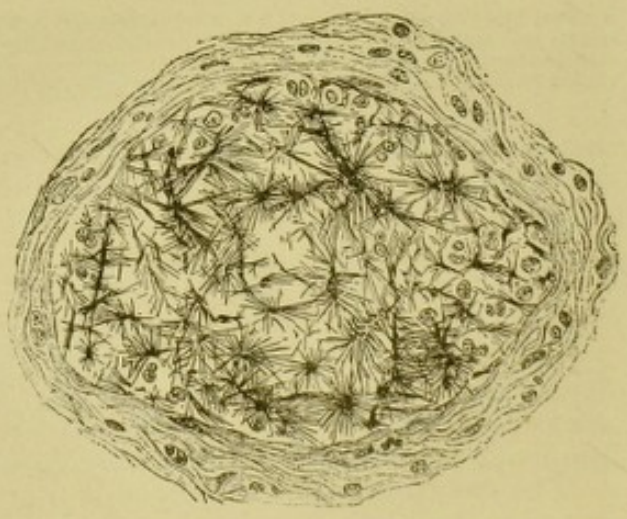


FIG. 14.—Bundles and star-shaped clusters of fibrin threads or rods within a blood-vessel. (Fibrin-stain.) Preparation taken from an inflamed tracheal mucous membrane. Magnified 500 diameters.

lifetime, and to what extent after death had occurred. In the majority of instances these coagulations are encountered in the midst of inflamed tissues, and we are therefore warranted in drawing the conclusion that it is the alterations in the blood which take place in such inflammatory foci which are the cause of the phenomena of coagulation.

Immediately after its formation the red thrombus is soft and rich in the fluids of the blood; later, it becomes tougher, denser, and drier as the fibrin contracts and presses out a portion of the fluid. At the same time it becomes paler, brownish-red or rust-colored, inasmuch as the blood-pigment undergoes changes similar to those which take place in extravasated blood.

The cause of the coagulation of blood inside a blood-vessel is to be found either in an increased production of fibrin-ferment and fibrinogenous substances (through the breaking down of cells), or in the with-

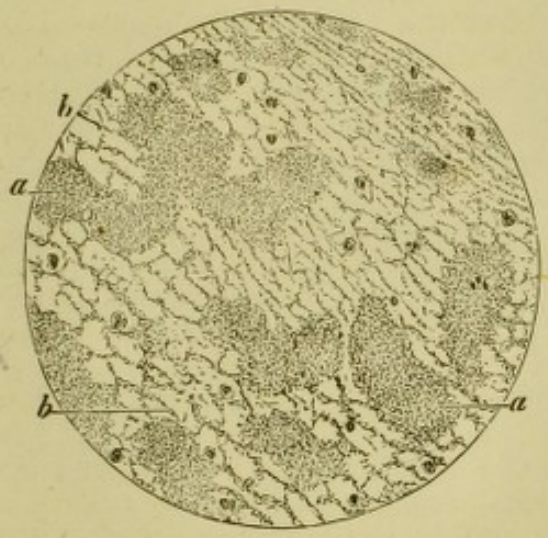


FIG. 15.—Section of a white thrombus containing but few cells. (Müller's fluid; hæmatoxylin.) *a*, Granular mass; *b*, granular and stringy fibrin in retiform arrangement; *c*, threads of fibrin in parallel arrangement. Magnified 200 diameters.

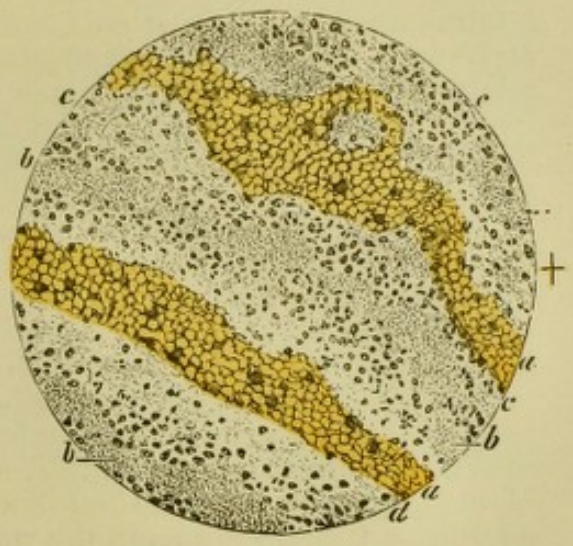


FIG. 16.—Section of a mixed thrombus rich in cells. (Müller's fluid; hæmatoxylin.) *a*, Red blood-corpuscles; *b*, granular mass; *c*, retiform disposition of fibrin with numerous leucocytes; *d*, threads of fibrin in parallel arrangement. Magnified 200 diameters.

drawal of the power—which the living walls of a blood-vessel possess—to prevent coagulation (Brücke). It is probable that the mere fact of the firmer adhesion of the blood to the wall of the vessel at a spot where it is somewhat degenerated is sufficient to induce coagulation. This occurs, consequently, in vessels which have been ligated, when the endothelium is destroyed at the point of ligation. It takes place, furthermore, when, through the breaking up of large numbers of white blood-corpuscles, fibrin-ferment is set free in large quantity in the blood-vessels—a condition which may be experimentally fulfilled by the injection of *blood whose serum is stained lake-red* through the partial breaking up of the blood-cells (*lackfarbenes Blut*).

The **fibrinous deposits from blood in circulation,** which not infrequently are formed on the internal surface of the heart or vessel-walls, are composed of masses either white, or of various shades of red, or with alternating red and white layers, and we may distinguish, accordingly, between **white, mixed,** and **laminated thrombi.** With the microscope we may discern that these thrombi are composed (Figs. 15 and 16) of granular and fibrous masses and of colorless and red corpus-

cles, which in varying proportions and arrangement make up their structure. The colorless thrombi may consist almost exclusively of granular masses (Fig. 15, *a*) and of fibro-granular fibrin, the latter displaying at one point (*b*) a retiform arrangement of its fibres, while at another point (*c*) they run more nearly in a parallel direction, both granular masses and fibrin-fibres enclosing only a scanty sprinkling of leucocytes. Other white thrombi contain more cells. In the mixed thrombi (Fig. 16), granular masses (*b*), more rarely hyaline masses, stringy fibrin (*c*), and red blood-corpuscles (*a*), in varying proportions and in diverse situations, compose the coagulated mass, and all of these component parts include more or less numerous—frequently very numerous—leucocytes (Fig. 16).

The fibro-granular masses which enter into the structure of the thrombi consist of **fibrin** which has been formed, just as takes place outside the vessels, by the action of a ferment. The granular and the hyaline masses, on the other hand, are at the present time regarded as structures formed from **blood-plates** which have become agglutinated together, although granular and hyaline masses may also be formed from leucocytes entangled in the meshes of the fibrin. The granular masses in the thrombi exhibit occasionally an arrangement similar to that of coral.

The formation of thrombi in circulating blood may be observed distinctly under the microscope, in suitable subjects, both in warm-blooded and in cold-blooded animals; and in this line it is more particularly the observations of Bizzozero, Eberth, Schimmelbusch, and Löwit which have led to very weighty conclusions.

When the blood flows through a vessel with its normal velocity, you may see under the microscope a broad, homogeneous, red stream in the axis of the blood-vessel (Fig. 17, *a*), while at the sides lies a clear zone of blood-plasma free from red blood-corpuscles. This may be observed as well in the arteries as in the veins and in the larger capillaries, but is best seen in the veins; in the smaller capillaries, just large enough to permit the passage of the blood-corpuscles, this differentiation into an axial and a peripheral stream does not hold.

In the axial stream the different constituents of the blood are not recognizable; in the peripheral stream, however, isolated white blood-corpuscles appear from time to time (Fig. 17, *d*), and these may be seen to roll slowly on along the vessel-wall.

If the blood-current becomes retarded to about the degree which allows the observer to make out indistinctly the blood-corpuscles of the axial stream (Fig. 18, *a*), the number of white blood-corpuscles floating slowly along in the peripheral zone, and adhering also at times to the vessel-wall, becomes increased (Fig. 18, *d*), and they finally come to occupy this zone in considerable numbers.

If the current is still further retarded so that the red blood-corpuscles become clearly recognizable (Fig. 19, *a*), then, in the peripheral zone, alongside of the white blood-corpuscles appear blood-plates (*d*), which increase more and more in number with the progressive retardation of the flow, while the number of the leucocytes becomes again diminished. When total arrest of the blood-current finally occurs, a distinct separation of the corpuscular elements in the lumen of the vessel follows.

When, in a vessel in which the circulation is retarded, the intima is injured at a certain point by compression or by crushing, or by chemi-

cal agents such as corrosive sublimate, nitrate of silver, or strong salt-solutions, and yet the lesion of the vessel-wall does not cause a complete arrest of the blood-current, we may observe *blood-plates adhering to the vessel-wall at the injured point*, and before long they cover the site of the injury in several layers (Fig. 19, d_1). Frequently more or less numerous *leucocytes*, or *colorless blood-corpuscles*, become lodged in this mass, and their number is proportionate to their abundance in the peripheral zone. Under some circumstances, indeed, the number of the leucocytes may be very considerable, and they may largely cover over the accumulation of blood-plates. In case of great irregularity of the circulation, or of extensive lesion of the vascular wall, *red blood-corpuscles* also may separate from the circulation, and *become adherent to the intima*, or to the colorless layers previously deposited upon it. Not infrequently portions of the segregated mass are swept away, in which case a new deposit of blood-plates is formed. Through a long-continued deposition of the elements of the blood the vessel may finally become completely closed.

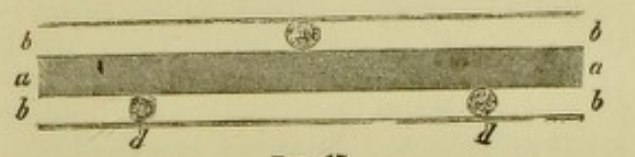


FIG. 17.

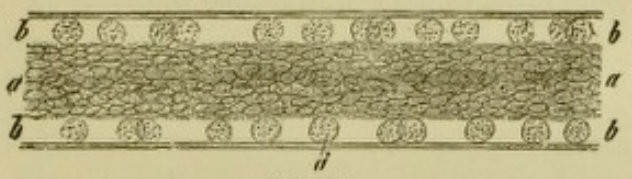


FIG. 18.

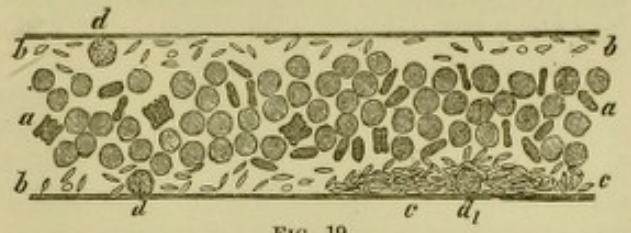


FIG. 19.

FIG. 17.—Quickly flowing blood-stream. *a*, Axial stream; *b*, peripheral stream with isolated leucocytes, *d*. (After Eberth and Schimmelbusch.)

FIG. 18.—Somewhat retarded blood-stream. *a*, Axial stream; *b*, peripheral zone with numerous leucocytes, *d*. (After Eberth and Schimmelbusch.)

FIG. 19.—Greatly retarded blood-stream. *a*, Axial stream; *b*, peripheral zone with blood-plates; *c*, a considerable collection of blood-plates; *d*, d_1, white blood-corpuscles. (After Eberth and Schimmelbusch.)

When at any point blood-plates have become adherent in considerable numbers, they become, after a time, coarsely granular at the centre, and finely granular or homogeneous at the periphery, and become fused together into one compact mass. The final result of the process is the formation of a colorless *blood-plate thrombus*, within which more or less numerous *white blood-corpuscles* may be imprisoned. Eberth designates the sticking together of the blood-plates by the term *conglutination;* their final fusion into a coherent thrombus he calls *viscous metamorphosis.*

If we compare the observations of Bizzozero, Eberth, and Schimmelbusch, as well as the recent observations of Löwit, on warm-blooded animals, with the histological findings in thrombi from the human subject, we are warranted in drawing the conclusion that the formation of thrombi in the circulating blood of man proceeds in a way similar to that observed in the lower animals, and we judge that their formation is directly dependent upon two causes: to wit, upon a **retardation of the blood-current** or other *disturbance of the circulation*—such as the *formation of eddies, which direct the blood-plates against the vascular wall* —and upon **local changes in the wall of the vessel.** Probably, too,

thrombosis is favored by **pathological changes in the blood.** From the variety of conditions under which thrombosis occurs in man we must assume, either that now one and again another of these causes plays the principal part in the formation of the thrombi, or that all three may concur in the process; and, on the other hand, that one of the factors, acting alone, is not under ordinary circumstances competent to cause thrombosis.

If a blood-plate thrombus or a conglutinate thrombus has formed at any point, *coagulation* may subsequently take place there, yielding threads of fibrin which imprison, in greater or less number—frequently in very great number—the cellular elements of the blood. *Conglutination and coagulation may accordingly occur together;* and the frequency with which this comes to pass, to judge from the composition of thrombi in man (Figs. 15 and 16), seems to denote that fibrin-ferment is set free in the formation of the blood-plate thrombus, and that hence, in the neighborhood of the conglutinated blood-plates, a process of coagulation occurs in the circumjacent peripheral zone of the blood-stream. If white blood-corpuscles alone are floating in the latter, the coagulating mass remains colorless (Fig. 15) and includes a greater or less number of leucocytes; while if red blood-corpuscles are circulating in the peripheral zone, or if the influence of the ferment extends as far as the axial stream, mixed thrombi will be formed (Fig. 16).

According to Eberth and Schimmelbusch, fibrin enters into the structure of artificially produced thrombi in those cases in which thrombosis has been provoked by the action of strong silver-solutions or by the introduction of foreign bodies.

Köhler and von Düring are of the opinion that if, as somewhat often happens, extensive thromboses form in individuals who are in a condition of marasmus, or in such as have been subjected to some traumatism, this pathological event must probably be dependent in some manner upon the toxic action of a ferment, and that local disturbances of the circulation merely determine the point of the coagulation. Vaquez is of the opinion that infection plays an important part in the formation of thrombi in cachectic subjects.

According to Naunyn, Franken, Köhler, Plosz, Gyorgyai, Hanau, and others, by the introduction of lake-red blood (*lackfarbenes Blut*), of solutions of hæmoglobin, of the salts of gallic acid, of ether, and of other substances into the circulation, more or less extensive coagulation may be produced; nevertheless the results of the experiments are not constant (Schiffer, Högyes, Landois, Eberth), and coagulation may not occur. The probability of effecting coagulation is proportionate to the degree of disturbance produced in the blood by the substance injected.

According to Arthus and Pagès, blood, as it flows from a blood-vessel, becomes incapable of spontaneous coagulation when sodium oxalate, or sodium fluoride, or soaps are added to it in such quantities that the mixture comes to contain from 0.07 to 0.1 per cent of the oxalate, or about 0.2 per cent of the fluoride, or 0.5 per cent of soap. These salts all operate by precipitating the calcium salts. If to blood, kept fluid by treatment with sodium oxalate, one-tenth of its volume of a one-per-cent solution of calcium chloride is added, coagulation takes place in from six to eight minutes, and the calcium salts enter into the constitution of the fibrin-molecule. The fibrin-ferment can act upon the fibrinogen only in the presence of calcium salts. Under the influence of the fibrin-ferment, and in the presence of calcium salts, the fibrinogen undergoes a chemical metamorphosis which results in the formation of a calcium-albumin compound —fibrin. For the occurrence of coagulation it is not necessary to invoke the aid of any peculiar fibrinoplastic, globulinoid substance, but there is need merely of the presence of calcium salts. The ferment which induces the coagulation is formed by the disintegration of cellular elements.

According to Freund, if blood is allowed to flow, beneath a layer of oil, into a vessel whose walls are coated with a film of vaseline, it will not coagulate; and from

this it is fair to conclude that the cause of the coagulation is to be sought for in the adhesion of the blood to a foreign body.

Bizzozero, in the year 1882, described as a new component of the blood certain minute, flat, homogeneous structures which he designated as blood-plates and regarded as identical with the hæmatoblasts described by Hayem. Relying upon profound experimental research, he concluded that it was these which, in breaking up, induced coagulation, while he declined to attribute this property to the white blood-corpuscles. Rauschenbach, Heyl, Weigert, Löwit, Eberth, Schimmelbusch, Hlava, Groth, and others have taken a stand against this doctrine of Bizzozero, as part of them deny any connection between the blood-plates and the coagulation of the blood, and part of them (Weigert, Hlava, Halla, and Löwit) do not regard the blood-plates as constant morphological elements of the blood, but rather as the débris of disintegrated white blood-corpuscles, or as the product of a precipitation of globulin (Löwit). From their contributions we may also gather that the destruction of white blood-corpuscles in a fluid containing fibrinogen may be followed by coagulation, thus showing that the blood-plates are not the only producers of fibrin. According to Groth, for example, the injection of large numbers of leucocytes into the circulation produces thrombosis. According to Rauschenbach, the dissolution of leucocytes is constantly occurring in the blood; but by an inhibitory action of the organism the supervention of coagulation is prevented, and the fibrin-ferment rendered inefficient.

Zahn, who in the year 1875 first undertook a strict differentiation of the red from the white and the mixed thrombi, held the view that the colorless substance of the white and of the mixed thrombi is a formation which is derived from the colorless blood-corpuscles which become separated from the blood-stream, then become adherent to rough points on the vessel-wall, and finally become fused together into a homogeneous or a granular mass. Up to a few years ago most authors coincided with this view, although since the investigations of Bizzozero, Lubnitzky, Eberth, Schimmelbusch, and Löwit there can be no doubt of the existence of the blood-plate thrombus also, into whose composition the white blood-corpuscles enter as but unimportant factors. It is equally well established that the thready fibrin observed in a thrombosis often contains very few leucocytes (Fig. 14).

According to Löwit, the blood-plates are not a constituent of normal blood, but rather make their appearance under definite conditions, and are nothing more than globulin precipitated in the form of plates. For their appearance very slight alterations in the circulation or in the composition of the blood suffice, and it is therefore difficult to make observations upon blood in circulation without causing them to appear; it is nevertheless possible, with proper precautions in investigating, to prove that the blood circulating through the mesentery of the mouse contains no morphological elements beyond the red and the white blood-corpuscles. Alterations of the vessel-wall and retardation of the blood-current lead to the separation of blood-plates and their adhesion to the walls of the vessel; and the blood-plates so separated then quickly undergo metamorphosis into a substance closely resembling ordinary fibrin, become comparatively insoluble, swell up, and take on a partly granular appearance. The fibrin derived from the blood-plates is very like ordinary fibrin in its capacity for taking dyes, and the formation of a blood-plate thrombus is also, indeed, a kind of coagulation. In cold-blooded animals no blood-plates appear under the conditions which would cause them to be formed in warm-blooded animals, but globulin is precipitated in a granular condition. Certain minute fusiform elements contained in the blood of birds and of cold-blooded animals, which Bizzozero, Eberth, and Schimmelbusch hold to be the equivalents of the blood-plates, are none other than young, colorless cells which develop, part into leucocytes and part into red blood-corpuscles. They accordingly are provided with a nucleus and may assume a spherical form, whereas the blood-plates are without a nucleus and are subject only to passive changes of form. Alterations of the vascular walls and retardation of the blood-current in cold-blooded animals lead to the formation of thrombi consisting essentially of leucocytes and capable of transformation into granular masses. At the beginning of cell-deposition we find the spindle-shaped leucocytes deposited with especial frequency.

I am unable to assent to the opinion expressed by Löwit in regard to the mode of origin of the blood-plates; I am much more disposed to believe that **the blood-plates are a product of the red blood-corpuscles**, and either are thrown off from the bodies of degenerating red blood-corpuscles, or are formed on the disintegration of the same. I base my opinion upon the investigations which Wlassow, at my suggestion, carried out in 1893 in my laboratory. He studied both the early stages of thrombus-formation and also the behavior of the blood-corpuscles when treated with various fluids, and his observations indicate, on the one hand, that at the beginning of a thrombosis, in circulating blood, red blood-corpuscles do become adherent to the vessel-wall and may subsequently become changed and transformed into a granular mass; and, on the other

hand, that a portion of the red blood-corpuscles—presumably those which are the oldest and are approaching their decadence—are extremely unstable cells, out of which are readily formed structures with properties corresponding to those of the blood-plates. As to whether such structures are developed under normal conditions, or whether, in the normal breaking down of the red blood-corpuscles, the colorless components of their structure enter immediately into solution, cannot be decided; this much only can be demonstrated: that the most diverse influences caused a plasmoschisis (a splitting up of the blood-plasma), accompanied by a formation of the so-called blood-plates. Arnold has quite recently published reports upon the products that result from the transformation of red blood-corpuscles (partly by a process of constriction, and partly by what might be termed excretion), and these confirm the observations made by Wlassow and myself.

A. Schmidt, in his work on the blood, published in 1892, wherein he collects the results of many years of study on coagulation, regards the fibrin-ferment or *thrombin* as a derivative of the life of the cells, which is developed from an inactive earlier state, *prothrombin*, under the influence of certain *zymoplastic substances*. In the same way he regards the *fibrinogenous substance*, or *metaglobulin*, as a product of the disintegration of cellular protoplasm. According to this view the generators of coagulation, as well as those of thrombosis, must all be regarded as cellular derivatives, and it would then be particularly *the red blood-corpuscles which would be the source of the materials of coagulation.* According to Corin, *coagulation occurs in the blood after death, only when the blood already contained ferment during life;* and the extent of the coagulation is directly proportional to the amount of ferment present at the time of death. A further production of ferment does not occur after death; on the contrary, the vessel-walls probably constitute a body inhibiting coagulation. Between the blood of those who have died suddenly (cases of strangulation) and that of those who have died more slowly, the difference is only relative, depending upon the amount of ferment present. No value can therefore be ascribed to the fluidity of the blood in the diagnosis of the mode of death.

§ 41. **Thrombosis** occurs most frequently in cases of degeneration and inflammation of the intima of the heart and of the vessels, as well as under certain circumstances which, like compression, stricture, or dilatation of the vessels, fatty infiltration and fatty degeneration of the heart, stenosis and insufficiency of the valvular orifices, etc., cause a retardation or an arrest of the circulation. If thrombi occur in cachectic individuals, they are called **marasmic thrombi** (thrombi marantici). When **perforating wounds of vessels** are not too large, they become closed by blood-plates and white blood-corpuscles which adhere to the edges of the opening and are also deposited all about it, so that in the wound there is formed a white thrombus projecting into the lumen of the vessel.

Different varieties of thrombi are distinguished according to their relations to the vessel containing them. Thus a **parietal thrombus** is one attached to the wall of the heart (Fig. 20, *c*) or of a vessel; a **valvular thrombus**, one which is situated upon a valve of the heart or of a vein (Fig. 21, *d*). Either kind may consist only of delicate, transparent, almost membranous, hyaline deposits; and then, again, they are often thicker and tougher, and project into the lumen of the heart or blood-vessel respectively. Their surface, in the latter case, often shows rib-like ridges of paler appearance than the other parts. If the lumen of a vessel becomes closed by a thrombus, the latter is spoken of as an **obturating thrombus** (Fig. 20, *a*, *b*). The coagula first formed are designated as **primary** or **autochthonous**; those subsequently deposited upon these, as **induced thrombi.** Through growth by accretion a parietal thrombus may become obturating. In such a case it not infrequently happens that a red thrombus is superadded to one originally white or mixed in color (Fig. 21, *c*), inasmuch as the thrombosis began in circulating blood, while later, after the closing off of the vessel, the blood became stagnant and the whole mass then coagulated.

The converse occurs when a red thrombus, obturating a vessel, contracts down to a smaller volume, and thus leaves a channel once more for the passage of the blood.

Thrombi may occur in all parts of the vascular system. **In the heart** it is particularly in the auricular appendages and in the recesses between the trabeculæ carneæ, as well as on any diseased spot of the heart-wall (Fig. 20, *b*), that they establish themselves. Their formation starts in the deep intertrabecular recesses; but through continual accretions more considerable coagulation-masses are formed, which project in the

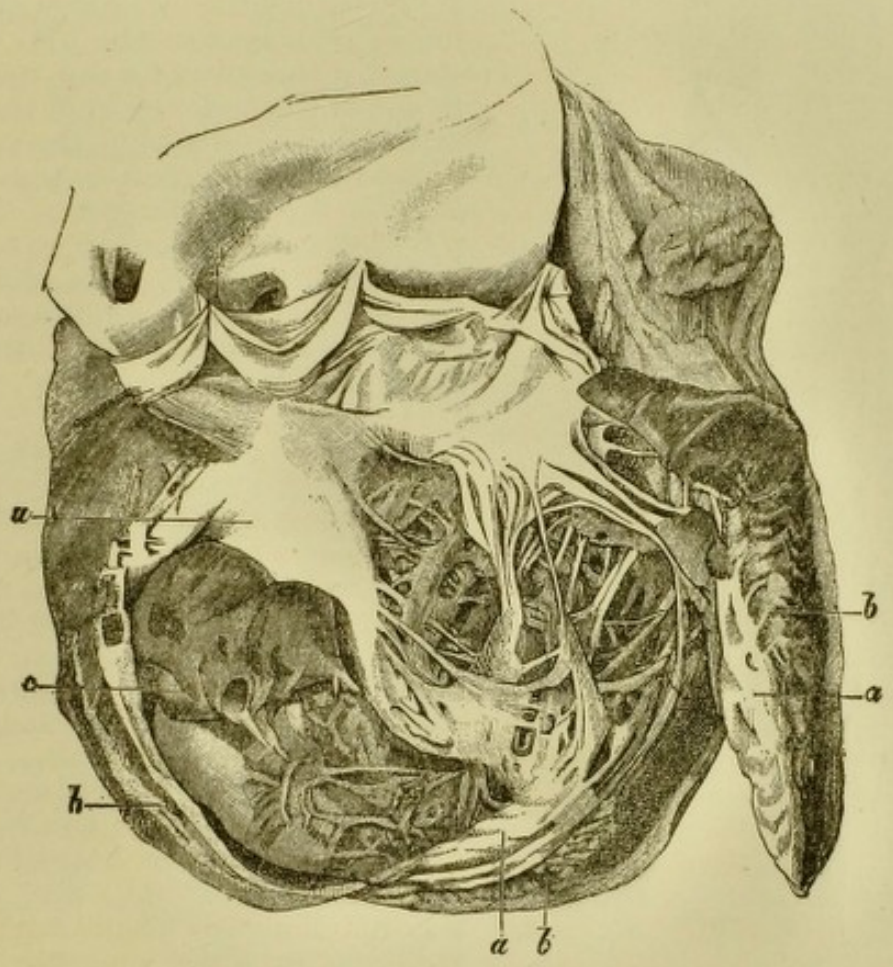


FIG. 20.—Thrombus-formation in the heart as a result of inflammatory degeneration and aneurismal dilatation of the heart-wall. *a*, Inflammatory thickening of the endocardium; *b*, inflammatory degeneration of the myocardium; *c*, thrombus. (Two-thirds natural size.)

form of polypi above the general surface (Fig. 20), and therefore are known as **heart-polypi.** They are sometimes more or less spherical in shape, with a broad base, and again they are more pear-shaped; their surface is often ribbed. As a rare occurrence, large globular or pear-shaped thrombi may become loosened, and then, in case they cannot pass the ostium, they lie free in the corresponding chamber of the heart. **Free globular thrombi** are sometimes seen in the auricles in cases of stenosis of the auriculo-ventricular orifices, although they are very rare. Very probably they become increased in size by the deposition of fresh layers of fibrin after they have been set loose. If coagulated masses attach themselves to an inflamed valve, they are designated as **valvular polypi.** Parietal and valvular polypi may become very bulky and may fill up a large part of one of the heart-chambers.

In the arterial trunks thrombi are found in a great variety of places, and are particularly apt to occur behind constrictions and in dilatations. Occasionally, in cachectic individuals with a much-degenerated intima, parietal thrombi, white or of a mixed color, and superficially adherent, are formed in the aorta.

In the veins thrombi occasionally are formed in the pockets of the valves (Fig. 21, *d*), from which they gradually protrude and develop into obturating thrombi. Frequently a thrombus grows out from a lesser vein in which it was formed into the lumen of a larger vein. So, for instance, a thrombus having its origin in one of the lesser veins of the lower extremity may grow up through the vena cava inferior until it reaches the heart. Specially important, by reason of the local disturbances to which they give rise, are the obturating thrombi of the femoral veins, the renal veins, the sinuses of the dura mater, the large venæ cavæ, and the portal veins.

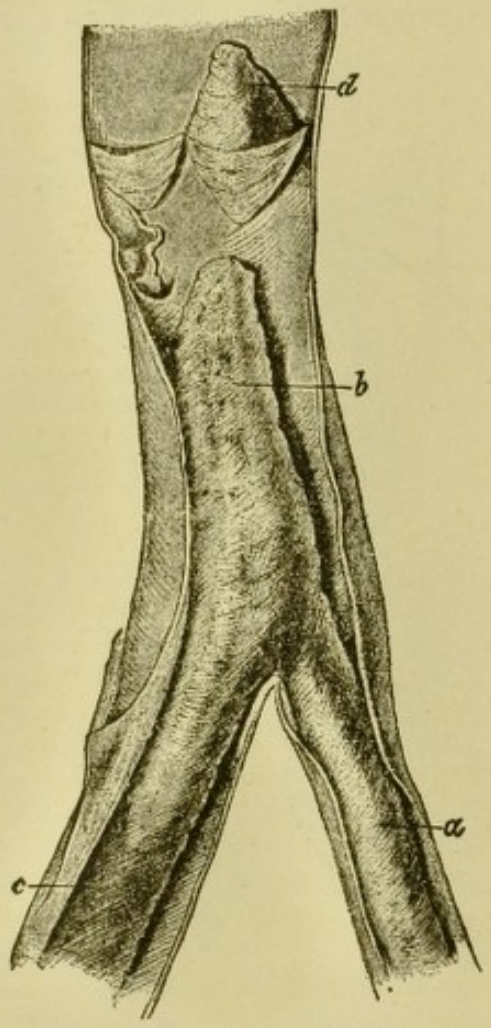


FIG. 21.—Thrombosis of the femoral and of the saphenous vein. *a*, *b*, An obturating thrombus, of mixed coloring and laminated; *c*, red thrombus with peripheral attachment; *d*, thrombus protruding from a valve. (Reduced one-fourth.)

Thrombi of the smallest vessels arise most frequently in consequence of disease of the surrounding tissues, and especially after infections and toxic inflammations and necrotic processes, and they have, for the most part, a hyaline composition. They are composed in large measure of the colorless elements of the red blood-corpuscles, which elements become fused into a homogeneous mass; and yet by a proper technique (Weigert's fibrin stain) it may sometimes be demonstrated that they also contain stringy fibrin. They are found, furthermore, after superficial burns (Klebs, Welti, Silbermann) and after poisoning—for instance, poisoning with corrosive sublimate (Kaufmann)—especially in the lungs. They frequently exist in hemorrhagic infarcts (Fig. 12, *c*). Thrombi, too, originating in the capillaries, may develop into the efferent veins, partly for the reason that through the obturation of a great number of capillaries the blood flows more slowly in the veins, and partly also for the reason that disintegrating blood-corpuscles and blood-plates find their way to the veins in great numbers.

The **first deposits** in the formation of a parietal thrombus are delicate, transparent, or whitish layers. The **fully formed thrombus** is a compact, dry mass, firmly attached to the inner surface of a vessel or of the heart, with the different qualities of color and structure described above. Thrombi, originally soft and succulent, undergo in time a process of **contraction**, and thereby become firmer and more dry. In this

way, in case of obturating thrombi, an obliterated channel may become open once more for the passage of the blood.

With long-continued contraction, the fibrin, the blood-plates, and the blood-corpuscles may become converted into a tough mass, which long remains in this condition, grows fast to the vessel-wall, and eventually becomes **calcified.** This occurs both in valvular thrombi of the heart and in thrombi located in the vessels. The chalky concretions in the veins, known as **phleboliths,** are formed in this way. Similar formations in the arteries, which occur, however, less frequently, may be called **arterioliths.**

Shrinking and calcification constitute a comparatively favorable issue of thrombosis. Far less favorable are the various kinds of disintegration which frequently follow and are known as simple and as puriform or septic yellow softening. In the **simple softening** the central portion of the thrombus becomes converted into a grayish-red, gray, or grayish-white grumous mass, consisting of broken-down and shrunken red blood-corpuscles, pigment granules, and colorless granular débris. If the softening extends to the superficial layers, and if there is, at the same time, a certain strength of blood-current in the region of the thrombus, the softening débris are swept along into the circulation. And if, under these conditions, somewhat large pieces become detached from their surroundings and are swept along with the blood-current, arterial emboli will be established (see Fig. 2, on page 41).

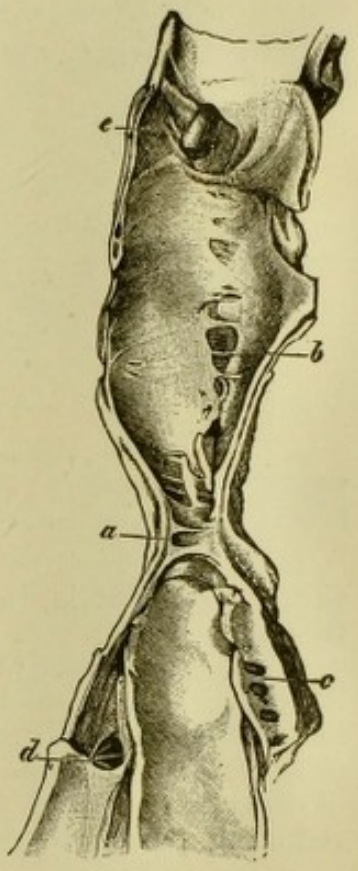


FIG. 22.—Remains of a thrombus of the right femoral vein, formed three years before death. *a*, Obliterated portion of the vein (the right common iliac vein was likewise obliterated); *b*, *c*, *d*, bridles of connective tissue in the interior of the vein and of its branches; *e*, recent thrombus. (Natural size.)

In the **yellow puriform** or **septic softening** the thrombus breaks down into a yellow or grayish-yellow or reddish-yellow mass similar to pus, grumous, creamy, and foul-smelling, which along with pus-corpuscles contains a great deal of a finely granular substance made up of fatty and albuminous detritus and micrococci. This mass acts as a destructive irritant, causing inflammation by its contact. As a result the intima becomes cloudy, and a suppurative inflammation arises in the media and adventitia, as well as in the parts about the vessel. After a short time all the vascular tunics become infiltrated and present a dirty-yellow or grayish-yellow appearance. Ulcerative destruction of the tissues eventually supervenes. If the puriform masses are carried along by the blood-current to other places, there too they lead to necrosis and septic disintegration of the tissues, and to suppurative inflammation, which affects not only the wall of the vessels, but also the circumjacent tissues.

The process of puriform softening of a venous or an arterial plug, coupled with the infiltration of the vascular wall, is denominated **thrombo-phlebitis purulenta** or **thrombo-arteritis purulenta.** The inflammation of the vessel-wall may start either in the softening thrombus or else in the parts adjacent to the vessel. In the latter case the

softening of the thrombus either goes on simultaneously with the inflammation of the vessel-wall or else succeeds it. These occurrences take place most frequently in the neighborhood of purulent foci.

The most favorable issue of thrombosis is in the **organization of the**

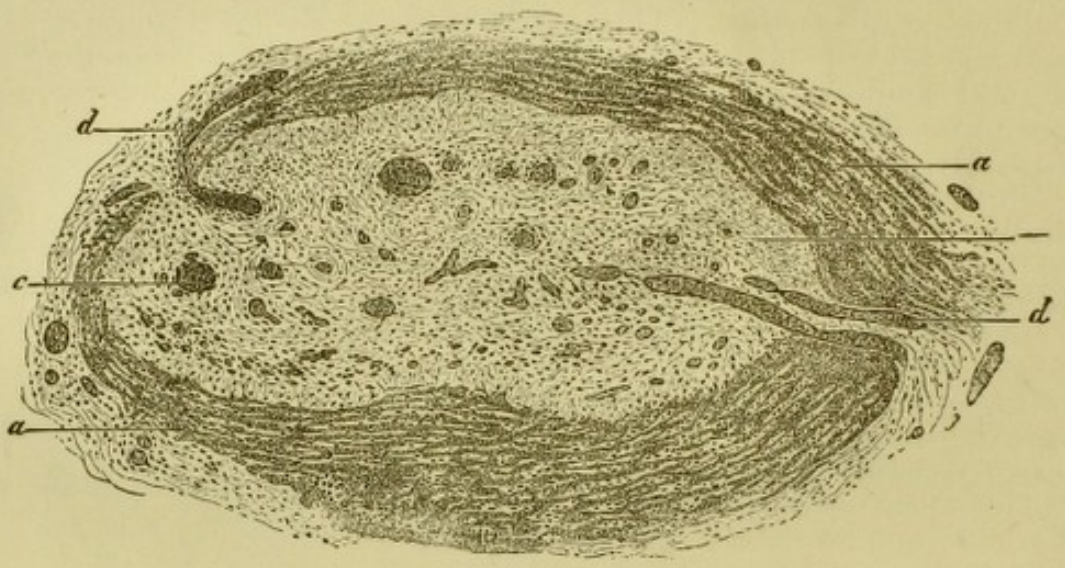


FIG. 23.—Closure of an artery of the lungs by a mass of connective tissue, which developed after the vessel had become plugged by an embolus. (Specimen preserved in Müller's fluid, and stained with hæmatoxylin and eosin.) *a*, Wall of the artery; *b*, connective tissue in the interior of the vessel; *c*, *d*, newly formed blood-vessels. Magnified 45 diameters.

thrombus—that is, in its being **replaced by vascularized connective tissue.**

The new connective tissue is developed from proliferating endothelial cells; but if these have been destroyed in the formation of the thrombus, then plastic migratory cells from the outer layers of the vessel-wall must take their place. The thrombus itself takes no part in the process of organization; it is a lifeless mass which excites inflammation in surrounding parts. In course of time the place of the lifeless thrombotic mass is taken by vascularized connective tissue (Fig. 23, *b*, *c*, *d*).

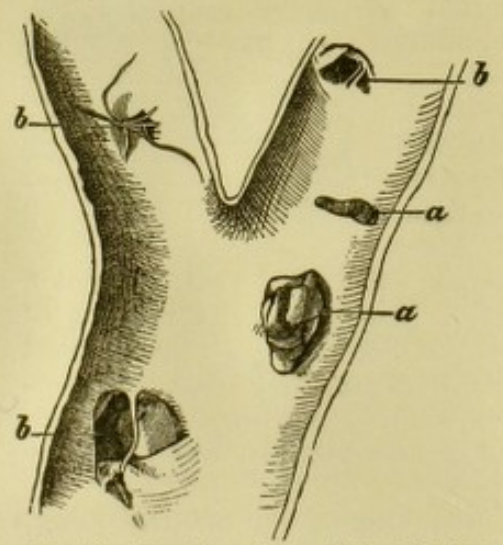


FIG. 24.—Remains of an embolic plug in a branch of the pulmonary artery. *a*, Shrunken embolus traversed by threads of connective tissue; *b*, bridles of connective tissue crossing over the orifices of branch vessels. (Natural size.)

The cicatricial tissue occupying the place of the thrombus shrinks more or less in course of time. Cicatrices after ligation become in this way very small. Such a cicatrix in the continuity of a vessel may later have the appearance of merely a thickening of the vessel-wall, or there may remain only threads and trabeculæ (Fig. 22, *b*, *c*, *d*), which cross the lumen of the thrombosed vessel, so that the blood-current can once more pass the affected spot. It not infrequently happens, nevertheless, that the connective-tissue bridles crossing the lumen of the vessel cause a marked lessening of its calibre; and this may proceed to a complete obliteration of

the vessel, so that the blood-vessels for a greater or less distance become converted entirely into solid fibrous cords.

Pieces broken off from a thrombus and carried into an artery and there wedged—so-called **emboli**—generally induce fresh deposits of fibrin upon their surface. Afterward they undergo the same changes as thrombi, and may either soften and break down or become shrunken (Fig. 24, *a*) and calcified. If the emboli are non-infectious they generally become replaced by vascular connective tissue (Fig. 23, *b*, *c*).

In many cases this new formation of connective tissue leads to the obliteration of the artery (Fig. 23). In other cases in the place of the embolus there becomes developed only a ridge of connective tissue or perhaps a knobbed or a flattened thickening of the intima. In still

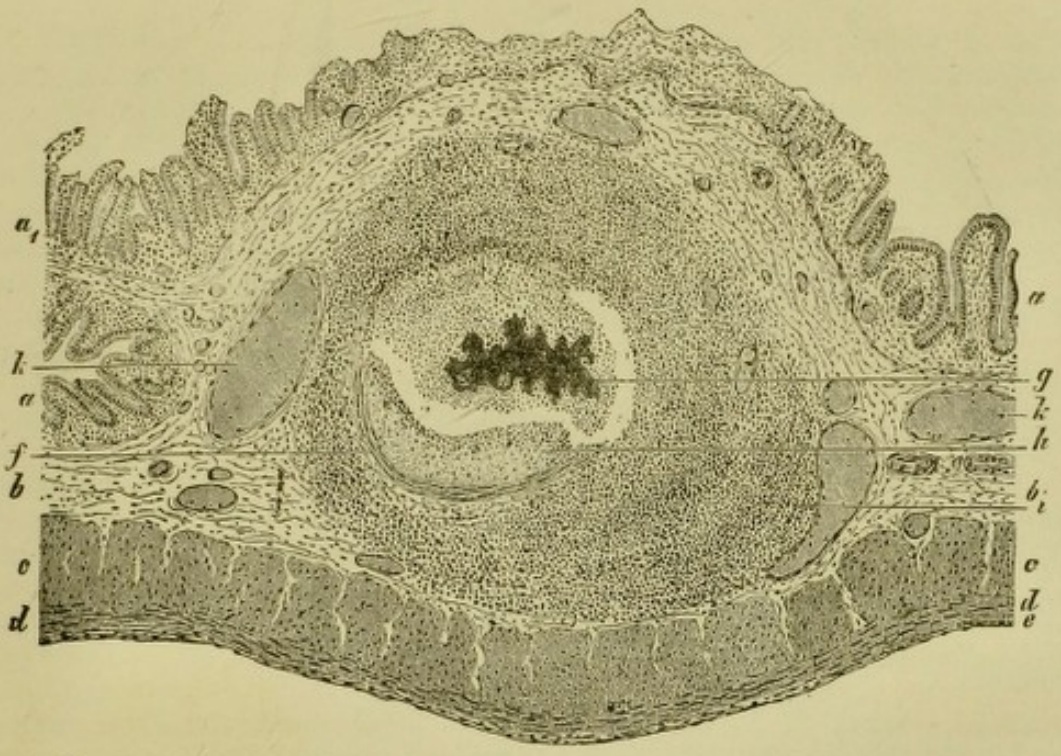


FIG. 25.—Embolus of an intestinal artery with suppurative arteritis, embolic aneurism, and periarteritic metastatic abscess. (Alcohol; fuchsin.) *a*, *b*, *c*, *d*, *e*, Layers of the intestinal wall; *f*, wall of the artery; *g*, the embolus, surrounded with pus-corpuscles, lying within the dilated and partially suppurating artery; *h*, parietal thrombus; *i*, periarterial purulent infiltration of the submucosa; *k*, veins gorged with blood. Magnified 30 diameters.

other cases the lumen of the vessel is traversed by bridles of connective tissue (Fig. 24, *b*), which either run separately, or, through mutual interlacings, form a wide- or a close-meshed network.

If the emboli contain pyogenic organisms, which is especially apt to be the case if the emboli come from a thrombus lying in a suppurating focus, suppuration then arises at the site of the embolus (Fig. 25, *g*), and occasionally ulceration also.

§ 42. In those conditions which have been described above as active and passive hyperæmia respectively, the blood during life is in circulation. In the active, congestive form the velocity of the blood-current is increased; in the passive form—venous hyperæmia—it is diminished. If *venous hyperæmia* becomes very marked, so that the blood entering a part cannot find exit, the circulation in the small veins and capillaries, and even in the smaller afferent arteries, may come to a complete standstill; and that condition then obtains which is known as **stasis** or **stag-**

nation of the blood (Fig. 26). Inasmuch as fresh masses of blood from the arteries strive with each pulse-beat to force their way into the area of stagnation, and thus distend the capillaries and the veins more and more, the pressure within these rises to be the same as that at the point of divergence of the nearest permeable artery, and by this means a great portion of the fluids of the blood is pressed out of the capillaries and the veins. The red blood-corpuscles consequently become so closely jammed together that their contours are no longer discernible, and the total contents of the vessels form a homogeneous, scarlet-red column

FIG. 26.—Stasis from venous hyperæmia in the vessels of the corium and of the papillæ of the plantar surface of the toes in a man succumbing to valvular disease, heart-failure, and arteriosclerosis. (Müller's fluid; alum-carmine.) Deep-violet coloring and commencing gangrene of the toes. Magnified 20 diameters.

(Fig. 26). At the same time, however, the blood-corpuscles are not fused together. As soon as the obstacle to the outflow is done away with and circulation is once more resumed, the individual blood-corpuscles become once more separated from one another.

Stasis is produced not only by damming back of the blood, but also by numerous influences affecting the vessel-walls and the blood itself. Thus *heat* and *cold*, *irritation with acids or with alkalies*, the *action of concentrated sugar- or common-salt solutions*, *of chloroform*, *alcohol*, etc., may cause not only contraction or relaxation of the vessels and disturbances of the circulation, but may, under certain circumstances, produce stasis. The immediate harm effected by these injurious agents lies in their action in abstracting water from the blood and from the vessel-walls;

in their further action, however, they induce essential changes in the composition of the blood-corpuscles, of the blood-plasma and of the vessel-walls, whereby the blood-corpuscles become less mobile, and the vessel-walls come to offer increased frictional resistance to the blood-current, while they, at the same time, permit the fluid portions to pass through them more readily. Stasis, accordingly, may also develop through the loss of water and the corresponding drying of the tissues,—an event which is likely to follow any injury which lays bare some structure (the intestine, for example) situated in the interior of the body.

IV. Œdema and Dropsy.

§ 43. The unconfined fluid which permeates the tissues is essentially a transudation from the blood, though, under some circumstances, a portion of the juice contained in the cells and fibres may also pass over into the unconfined fluid of the tissues (Heidenhain). The exudation of fluid from the vessels is not a process of simple filtration, but is rather to be regarded as a process of secretion, effected by means of the specific function of the capillary walls. The fluid secreted from the capillaries, which becomes mingled with the products of tissue-metabolism, is absorbed by the lymphatics from the interstices of the tissues, and is returned to the veins through the ductus thoracicus.

Every increase in the transudation of the blood-fluids occasions primarily an increase in the permeation of the tissues, which, for the most part, is again reduced by an increased absorption through the lymphatics. This equilibration, however, has its limits; with increased transudation from the blood-vessels we get a more or less permanent oversaturation of the tissues with the transuded fluid.

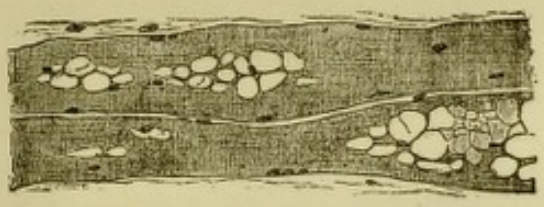


Fig. 27.—Longitudinal section through œdematous muscle-fibres of the gastrocnemius of a subject with chronic œdema of the legs. (Flemming's mixture; saffranin.) Magnified 45 diameters.

That condition which is produced by this collection of fluid in the tissues is known as **dropsy**, **œdema**, or **hydrops**, and we distinguish between a general and a localized dropsy according to the extent of the affection. Œdema extending over superficial portions of the body is known as **anasarca** or as **hyposarca**.

That transudate from the blood which constitutes the dropsical or œdematous fluid is always considerably less rich in albumin than the blood-plasma. The fluid collects first in the interstices of the tissues as free tissue-fluid, and may then soak into the tissues themselves and thus cause swelling of the cells and of the fibres, and, under some circumstances, the formation of vacuoles (Fig. 27), due to the accumulation of drops of fluid within the cells or their derivatives.

This may be most frequently demonstrated in tegumentary and in glandular epithelium, but becomes at times distinctly evident also in other tissue-elements, particularly in muscle-fibres (Fig. 27), whose fibrillæ become separated by drops of fluid. It may happen, moreover, that cells in œdematous tissues, particularly in the lungs and the serous membranes, become loosened from their attachment, and the fluid then comes to contain an admixture of epithelial cells in considerable numbers.

Tissues which are the seat of œdema appear swollen, though the degree of swelling is essentially dependent upon the structure of the tissue. The skin and the subcutaneous cellular tissue are able to take up into the interstices of their structure large quantities of liquid, and an extremity may accordingly become enormously swollen with œdema. Its appearance is then pale, it has a doughy feeling, and upon pressure with the finger an indentation remains behind. An incision sets free an abundance of clear liquid and reveals the tissues thoroughly saturated with fluid.

The lung behaves in a similar way. Owing to its limited room it is not especially distensible, but it contains multitudes of cavities filled with air, and these, upon the advent of œdema, become filled with liquid, which on pressure escapes from a cut surface, generally mingled with air-bubbles.

Far less capable of retaining fluids is the kidney; consequently but little fluid flows off on section of an œdematous kidney, though the cut surface is moist and glistening.

The amount of blood contained in œdematous tissues is variable, and their color is consequently so also.

Such cavities of the body as are the seat of dropsical effusion contain at one time a considerable, and at another a very small amount of clear, generally light-yellow, rarely quite colorless, alkaline fluid, which occasionally contains a few flakes of fibrin (cf. the chapter on Inflammation). Compressible organs are compressed by the exudation, and cavities are dilated.

A collection of fluid in the abdominal cavity goes by the name of **ascites.**

The proportion of albumin in pure transudates is not the same in all the tissues and cavities of the body, but differs within wide limits. According to Reuss, the proportion of albumin in transudations of the pleura is 22.5 *pro mille;* of the pericardium, 18.3; of the peritoneum, 11.1; of the subcutaneous cellular tissue, 5.8; of the cerebral and spinal cavities, 1.4. Therein lies a proof of the differing constitution of the vessel-wall in the several tissues of the body.

The water of the various organs and tissues, according to Heidenhain,[1] is made up of three parts—of the water present in the blood, of the lymph of the organ under consideration, and of the water contained in the cells and in the fibres—the tissue-fluid proper. This tissue-fluid may, under certain circumstances, undergo considerable variations, increasing at the expense of the watery part of the blood or of the lymph, or diminishing as the latter increases.

If the proportion of crystalloids in the blood (urea, sugar, salts) becomes greater, both blood and lymph come to contain a greater proportion of water, which is possible only in this way: that these substances, when thrown into the blood, pass over into the lymph-spaces, and, by their affinity for the tissue-fluids, excite a discharge of water from the tissue-elements. The prompt passage of the crystalloids from the blood and the lymph is accomplished with the aid of a force inherent in the capillary cells; that is, it is not a phenomenon of mere diffusion. The evidence of this lies in the fact that the proportion of salts or of sugar in the lymph is oftentimes greater than that in the blood.

§ 44. According to the etiology we distinguish **four varieties of œdema**—namely, œdema from stagnation of the blood in the blood-vessels, œdema caused by interference with the escape of the lymph, œdema due to some disturbance of the capillary secretion (the result of

[1] "Versuche und Fragen zur Lehre von der Lymphbildung" [Experiments and Queries Regarding the Theory of Lymph-formation], *Arch. f. d. ges. Physiologie*, 49. Bd., 1891, and *Verh. des X. internat. med. Cong.*, ii., Berlin, 1891.

alterations in the walls of the capillaries), and œdema ex vacuo. The third one of these varieties is designated by the practising physician by one or the other of the following terms: inflammatory œdema, hydræmic or cachectic œdema, and neuropathic œdema.

The **œdema of stagnation** owes its origin to the fact that when the escape of blood from the capillaries is seriously interfered with, the pressure in these small vessels increases, and the fluid portions of the blood then seek an outlet through their walls,—a state of affairs which gives rise to the escape of an abnormal amount of fluid from the vessels. The amount of the escaping fluids increases in proportion to the degree of discrepancy between the inflow and the outflow of the blood, and is therefore increased by an increase in the afflux of blood.

The escaping fluid never contains much albumin, though with increased pressure in the veins the proportion of albumin rises (Senator); the fluid, furthermore, may contain more or less numerous red blood-corpuscles, and their number increases with the degree of obstruction.

The immediate result of an increased transudation is an increased flow of lymph, and this may suffice to carry off all the fluid. If it does not so suffice, the fluid collects in the tissues and we have a condition of œdema or dropsy. According to Landerer, the occurrence of this condition is favored by the fact that the elasticity of the tissues becomes diminished in consequence of the long-continued increase of the pressure to which they are subjected.

Obstruction to the flow of the lymph, as experiments in this line have shown, is not ordinarily succeeded by œdema. In the first place, the lymph-vessels in the various parts of the body have elaborate anastomoses, so that an obstruction to the flow of lymph does not readily occur; and even when all the efferent lymphatics of an extremity are closed off, provided the lymph-formation remains normal, no dropsy generally ensues, inasmuch as the blood-vessels themselves are able to take up the lymph again. Only the *occlusion of the ductus thoracicus* is ordinarily followed by stasis of the lymph and by œdema, particularly by ascites; but we must still observe that even in this case collateral channels may open up, and may suffice to carry off the lymph.

Although lymphatic obstruction is not ordinarily sufficient to cause œdema of itself, yet it does increase an œdema already produced by excessive transudation from the blood-vessels.

Pathological alterations in the walls of the capillaries and veins of such a nature as to cause an increase in the vascular secretion[1] (*Heidenhain*), **and thus induce œdema,** may occur as the outcome merely of *long-continued passive congestion* and the resulting imperfect renewal of the blood. Such alterations occur, however, in the majority of cases, as the result of protracted *ischæmia*, of *imperfect oxygenation*, or of *chemical changes in the blood;* or they may be due to *the effect of high or low temperatures*, or to *active traumatism*. It is also probable that either *irritation or paralysis of the vaso-motor nerves* may lead to an increased vascular secretion.[1] Just what changes the vessels suffer under these circumstances we are not able to state precisely, but it is proper enough to suppose that some alteration of the endothelial cells and of the cementing substance between them is the most important part of the lesion. If through these influences œdema arises, then we may distinguish, according to the cause, **toxic, infectious, thermal, traumatic, ischæmic, neuropathic œdema,** etc., and such a division has

[1] *Vide supra*, § 43.

much to commend it. Hitherto the kinds of œdema here under consideration have generally been relegated to two groups, inflammatory œdema and cachectic œdema.

Inflammatory œdema is most undoubtedly to be referred to an *alteration in the wall of the vessel*, and is seen both as an independent affection, in the shape of circumscribed or more extensive swellings and dropsical effusions, and also as an epiphenomenon in the neighborhood of severe inflammatory processes. In the latter case it is frequently called *collateral œdema*. Inflammatory œdema is differentiated from the œdema of stagnation in that the transuded fluid holds far more albumin in solution and is much richer in white blood-corpuscles, and, furthermore, in that considerable coagula occur in it (cf. the chapter on Inflammation). Its origin is to be sought sometimes in infectious and toxic, sometimes in thermal or traumatic influences, and again in a temporary ischæmia.

As to **hydræmic** or **cachectic œdema**, it was long thought that hydræmia proper—i.e., diminution of the solids of the blood—as well as hydræmic plethora—i.e., retention of water in the blood—could be an immediate cause of increased transudation from the blood-vessels. It was supposed that the vessel-walls behaved as animal membranes and allowed a fluid poor in albumin to pass through more readily than one containing a larger amount of albumin. The vessel-walls are not, however, lifeless animal membranes, but are to be regarded as a living organ. Hydræmia, experimentally produced, is not, according to Cohnheim, followed by œdema; and even when we succeed, through the production of hydræmic plethora—i.e., through overfilling the vascular system with watered blood—in obtaining an increased transudation from the vessels, and eventually œdema, this œdema supervenes only after the proportion of water in the blood has become very large, and, moreover, it does not develop in the same localities where the so-called hydræmic œdema in man develops. We are driven, then, to assume that the œdema of cachectic individuals, as well as that of "nephritics"—i.e., of individuals whose renal function is imperfect—is due essentially to an *alteration of the vessel-walls*, an alteration caused either by the hydrated condition of the blood or by a poison circulating in that fluid. Probably other lesions of the tissues should be considered in this connection (Landerer)—lesions which diminish the elasticity of the tissues. Under these conditions the *hydræmia indeed favors the appearance of œdema*, but is not the sole cause thereof, nor does it determine the site of the same.

Hydræmic œdema is distinguished from inflammatory œdema by the facts that the transudate is less rich in albumin, and that it contains corpuscular elements in smaller proportion.

Œdema ex vacuo occurs principally in the cranial cavity and in the spinal canal, and arises in all cases in which a portion of the brain or of the spinal cord is lost and its place is not taken by some other tissue. In atrophy of the brain and of the cord the subarachnoidal spaces in particular become enlarged; occasionally the ventricles also. Local defects either become filled by dilatation of the nearest subarachnoidal spaces or of the adjacent portions of the ventricles, or fluid collects directly at the site of the defect.

According to Cohnheim and Lichtheim, injections of aqueous solutions of salt into the vascular system of dogs[1] show that hydration of the blood does not produce œdema.

[1] *Virch. Arch.*, 69. Bd.

If the mass of the blood is increased, an increase is observed in almost all the secretions (saliva, intestinal juices, bile, urine, etc.) and also in the flow of lymph; the last, however, not universally—for instance, not in the extremities. In an advanced state of hydræmic plethora the abdominal organs become œdematous, but never the extremities. Control-experiments recently made by Francotte confirm the observation that hydræmic plethora artificially induced in the lower animals results directly in dropsy of the abdominal organs; but Francotte obtained œdema also of the skin and of the subcutaneous cellular tissue.

The view that the so-called hydræmic œdema is merely the result of an increase of the absolute amount of water in the blood is championed especially by von Recklinghausen and by Pisenti. The distribution of the dropsy is, according to von Recklinghausen, essentially dependent upon bodily position, external pressure, impeded circulation, difference in innervation of the several vascular areas, and upon the consequent difference in the fulness of their vessels.

I can subscribe to these opinions only in so far as they apply to the modifying factors named, not, however, as regards their general drift. Opposed to this are not only the experiments of Cohnheim and Lichtheim above referred to, but also the fact that in nephritic as well as in cachectic subjects œdema not infrequently appears at a time when no hydræmic plethora is present, and that, conversely, with hydræmic plethora present, œdema may be wanting. I therefore look upon the increase in the amount of water as only one factor which is favorable to the occurrence of œdema.

According to Löwit, for the development of an œdema of stagnation in the lungs, an obstruction to the outflow of the blood from the lungs is not alone sufficient; there must at the same time be an increased afflux of blood to the lungs, which, moreover, must persist for a certain length of time.

According to Heidenhain, the specific function of the capillary walls plays a controlling part in the formation of lymph, and consequently the formation of this material can be influenced by various substances present in the blood. The fact that crystalloid substances are quickly eliminated from the capillaries and cause a discharge of tissue-fluids into the lymph has already been mentioned in § 43. Heidenhain has, however, found substances which, when injected, increase the transudation of water from the blood-vessels into the lymph. This may be accomplished, for instance, with decoctions of the muscles of crabs and of fresh-water mussels, or of the heads and bodies of leeches or with injections of peptone and of egg-albumen; and by these means the quantity of lymph flowing from the ductus thoracicus may be increased from five to six or even fifteen fold. There is also a concomitant increase in the proportion of organic matter in the lymph. The exciting substance must then stimulate the specific function of those cells in the capillary walls which secrete the lymph. If we reason from these observations, it seems very probable that many skin-affections described as neuropathic, and characterized by cutaneous hyperæmia accompanied by œdematous swelling—as, for example, urticaria, erythema nodosum, and herpes zoster—are to be regarded as intoxications coupled with nervous affections and with disturbances of the secretory activity of the capillaries. Possibly the secretion of the capillaries may be affected also by direct innervation.

V. Hemorrhage and the Formation of Infarcts.

§ 45. By **hemorrhage** we understand the escape of all the ingredients of the blood from the vessels (*extravasation*) into the tissues or upon a free surface. It is either *arterial* or *venous* or *capillary*, or else occurs from all the vessels at once. The blood which has escaped from the capillaries is termed an **extravasate**; at the same time, for the different forms of hemorrhage there are a great variety of names in use. If the hemorrhagic foci are small and form more or less sharply defined, punctate, red or reddish-black spots, we designate them as *petechiæ* or *ecchymoses;* if they are larger and less clearly defined, as *suggillations* and as *bloody suffusions*. If the affected tissue is solidly infiltrated with the escaped blood, but yet not rent nor broken up, we call it a *hemorrhagic infarct*. If the blood forms a tumor we speak of it as a *hæmatoma*, or a *blood-tumor*.

The blood which escapes from the vessels into the neighboring tissues collects at first in the interstices (Fig. 28). If a large quantity of blood is poured out, the structure of the tissue may be completely con-

cealed. The more delicate structures, like those of the brain and spinal cord, may be destroyed by a somewhat copious hemorrhage.

If the hemorrhage occurs at the free surface of an organ the blood either escapes externally or is poured out into the cavity surrounding the organ.

Hemorrhage from the mucous membrane of the nose is called *epistaxis;* vomiting of blood, *hæmatemesis;* bleeding from the lungs, *hæmoptoë* or *hæmoptysis;* from the uterus, *metrorrhagia* or *menorrhagia* (during menstruation); from the urinary organs, *hæmaturia;* and from the sweat-glands, *hæmathidrosis.*

A collection of blood in the uterus is designated as *hæmatometra*, in the pleural cavity as *hæmothorax*, in the tunica vaginalis testis as *hæmatocele*, in the pericardium as *hæmopericardium.*

Those hemorrhages in the skin which are not the result of violence are generally designated as *purpura* (Fig. 28). What are called *hemorrhagic blebs*—accumulations of blood and serum beneath the epidermis—form at spots where disintegration has taken place in the deeper layers of the epithelium.

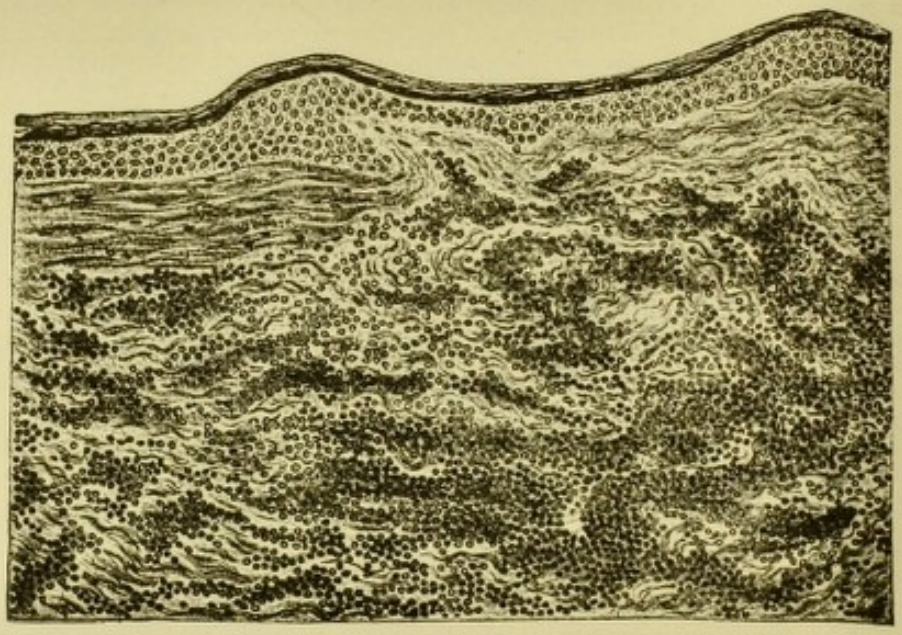


FIG. 28.—Hemorrhage in the skin near the knee; from a man eighty-one years of age. (Formalin; hæmatoxylin; eosin.) Magnified 80 diameters.

Recent extravasations of blood have the color characteristic of arterial or of venous blood. Later, the extravasate undergoes various alterations, which are particularly characterized by color-changes. Subcutaneous suggillations become first brown, then blue and green, and finally yellow. In course of time extravasates become absorbed again (compare Chapter IV.), and while this is in progress a certain amount of proliferation of the tissues often takes place. Connective tissue may push out bourgeons into large collections of blood, growing through them in every direction, or may encapsulate them entirely (compare Chapter VI.).

Hemorrhages may occur, on the one hand, from **interruption in the continuity of the vessel-wall,** and are then called **hemorrhages per rhexin** or **per diabrosin.** This is the only form of arterial hemorrhage. From the capillaries and the veins hemorrhage may occur, on the other

hand, in still another manner—to wit, **per diapedesin**; that is, by a process in which red blood-corpuscles pass through the vessel-wall without any previous rent in the same. Such hemorrhages are often quite small and of inconsiderable extent; in other cases the process continues for a longer time, and the infiltration of the tissues with red blood-corpuscles becomes very extensive. Hemorrhages by diapedesis are accordingly not always small, and hemorrhages by rhexis not always great. Rupture of a capillary or of a small vein does not cause profuse bleeding; on the other hand, the escape of blood by diapedesis may attain to very great proportions. In a given case it is by no means always easy—indeed, it is often impossible—to make out whether hemorrhage has taken place by rhexis or by diapedesis.

The phenomenon of diapedesis may be observed under the microscope in the frog's mesentery or in the web of the frog's foot. If before the examination we ligate the efferent veins, we see that the capillaries and the veins become gorged with blood. After a certain time the red blood-corpuscles begin to escape from the capillaries and the veins.[1] Hering[2] regards the process as one of filtration. As a result of obstruction to the outflow, the blood seeks to escape laterally and is forced through the vessel-wall by pressure.

Exhaustive investigations in regard to diapedesis of the red blood-corpuscles, as well as in regard to the escape of other anatomical elements within the blood-vessels, have been carried on by Arnold.[3] He thought first that we must admit the presence of gaps in the endothelial tube at the points of exit of the corpuscular elements, and he designated these gaps as stigmata and stomata. He subsequently recognized the supposed openings to be but accumulations of the intercellular cement-substance between the endothelial cells. Under pathological conditions this cement-substance becomes softened and permits the passage of the red blood-corpuscles.

§ 46. The causes of **interruptions of continuity in the vessel-walls** are partly *mechanical injury*, partly *increase in the intravascular pressure*, partly *disease of the blood-vessels*. Increase in the blood-pressure in the capillaries and smallest veins is sufficient of itself to cause rupture without the aid of vascular changes, especially in cases of marked obstruction. Sound arteries and sound veins of larger size, on the other hand, cannot be dilated to the point of rupture by the mere rise of blood-pressure; diseased or abnormally thin-walled arteries, however, may burst. New-formed vessels are very fragile.

Diapedesis follows upon *rise of pressure in the capillaries and veins*, as well as upon *increased permeability of the vessel-walls*. If the outflow of venous blood in a given vascular area is totally interrupted, diapedesis of the red blood-corpuscles from the involved capillaries and veins starts up then and there; this is to be regarded as the result of the local increase in intravascular pressure. The exodus of blood-corpuscles through vascular degeneration occurs particularly after mechanical, chemical, and thermal lesions of the vessel-walls, and we may suppose that certain *poisons* affect the vessel-walls with especial virulence. An abnormal permeability of the vessel-walls may, furthermore, be observed when, for a long period, the vessels have not been traversed by the blood-stream, and have suffered in their nutrition in consequence.

When an individual manifests a tendency to hemorrhage, the condition is called one of **hemorrhagic diathesis**, of which we recognize a congenital and an acquired form.

The **congenital hemorrhagic diathesis or congenital hæmophilia**,

[1] Cf. Cohnheim, "Allgemeine Pathologie," I. Th., and *Virchow's Arch.*, 41. Bd.
[2] *Sitzungsber. d. Wiener Akademie*, 1868, 57. Bd.
[3] *Virchow's Arch.*, 58., 62., and 64. Bd.

which, as stated in §§ 31 and 32, belongs to the hereditary diseases, probably has its cause in an abnormal constitution of the vascular walls, though the constitution of the blood, withal, may not be normal, and, in consequence of this condition, it may not be possible to arrest, through a process of coagulation, a bleeding after it has once begun.

An **acquired hemorrhagic diathesis** attends those diseases known as scurvy, morbus maculosus Werlholfii, purpura simplex, purpura (peliosis) rheumatica, purpura hæmorrhagica, hæmophilia, and melæna neonatorum, and Moeller's or Barlow's disease (infantile scurvy), and furthermore plays a part in many infectious diseases and intoxications—e.g., septicæmia, endocarditis, malignant pustule, spotted typhus, cholera, small-pox, the plague, acute yellow atrophy of the liver, yellow fever, nephritis, phosphorus-poisoning, snake-bite, etc.—and also, finally, in pernicious anæmia, leucocythæmia, and pseudo-leucocythæmia. The cause of the diseases named in the first group—in all of which the occurrence of hemorrhages in the skin, as well as in the mucous membranes, and in the parenchyma of other organs and tissues,[1] constitutes a prominent symptom—is ordinarily supposed to lie in a *general disturbance of nutrition and circulation*, although observations of the last few years make it probable that at least a great proportion of them belong to the class of *infectious diseases*. W. Koch is of the opinion that scurvy is an infectious disease, and that purpura in its many forms, and erythema nodosum, and the hemorrhages occurring in the new-born, are varieties of the same infection. In the last few years bacteria have frequently been found in these latter affections also—that is, in purpura hæmorrhagica and also in hæmophilia neonatorum. In this connection we must refer particularly to the investigations of Kolb, Babes, Gärtner, Tizzoni, and Giovannini, who have found in those suffering from these diseases bacilli which were also pathogenic for the lower animals, and when injected produced an affection characterized by hemorrhages. With these diseases those other infections which are characterized by hemorrhages are probably connected, and it is to be supposed that the bleeding is produced partly by *local changes in the walls of the vessels*, caused by *localized growths of bacteria*, partly by the *injurious influence of toxic substances produced by the bacteria themselves*. In this case they should in part be reckoned among the hemorrhages of intoxication.

The hemorrhages occurring in conditions of anæmia are to be regarded as a consequence of anæmic degeneration of the vessels, though partly also as a result of disturbances of the circulation.

A whole list, finally, of apparently spontaneous hemorrhages is connected with *irritation or paralysis of the vaso-motor nerves*, arising either from the central nervous system, or by reflex action, or through lesion of the conducting nerve-fibres. Here belong the hemorrhage of menstruation, many forms of nasal, intestinal, and bladder hemorrhage; furthermore, bleeding from the conjunctiva, from the skin (stigmatization), from healthy kidneys, from the breasts, from hemorrhoids, from wounds, etc. Here also are to be reckoned a portion of those pulmonary hemorrhages which follow upon severe cerebral lesions, though in a particular case a trustworthy judgment often cannot be given, because disturbances of respiration, as also the aspiration of irritating substances into the lungs, may likewise lead to hyperæmia and to the escape of

[1] In Barlow's disease, which in children of from one and a half to two years of age often develops in connection with rachitis, the hemorrhages are found to have taken place between the periosteum and the bone.

blood in the lungs. Lastly, there occur in brain disease—particularly in disease of the crura cerebri—gastric and intestinal hemorrhages which are dependent upon the cerebral lesion. According to von Preuschen, the gastric and intestinal hemorrhages occurring during the first days of life, and known as melæna neonatorum, belong to this category, inasmuch as during labor hemorrhages and ecchymoses are not infrequently produced in the brain, in consequence of which the intestinal hemorrhages follow. By others, on the contrary (Gärtner), melæna neonatorum is classed among the infectious diseases.

Hemorrhages per rhexin cease as soon as the pressure upon the outside of the bleeding vessel becomes as great as the intravascular pressure, or as soon as the narrowing of the vessel and the processes of coag-

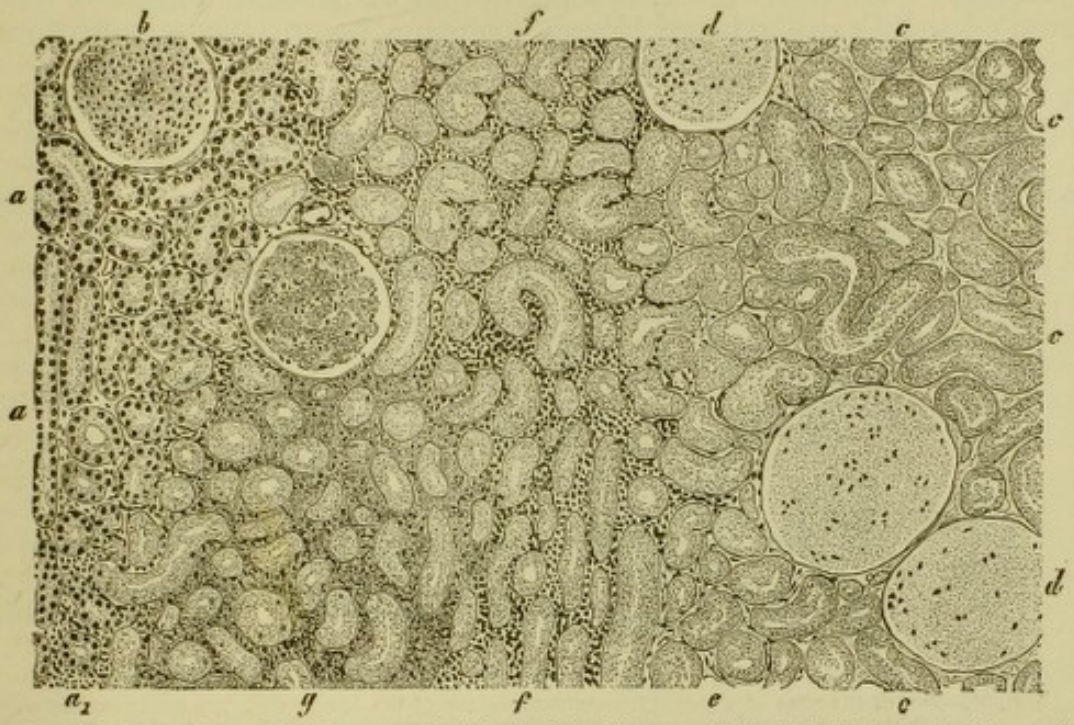


FIG. 29.—Part of the edge of an anæmic infarct of the kidney. (Müller's fluid; hæmatoxylin; eosin.) *a*, Normal uriniferous tubules in a normal stroma; a_1 normal uriniferous tubules in a stroma infiltrated with cells; *b*, normal glomerulus; *c*, necrotic tissue without nuclei, with granular coagula in the tubules; *d*, necrotic glomerulus, swollen and with few nuclei; *e*, uriniferous tubules without nuclei, in a stroma with nuclei still persisting; *f*, necrotic tissue with cellular, and, *g*, with hemorrhagic infiltration. Magnified 50 diameters.

ulation and of thrombus-formation effect a closure of the rupture. In the case of *hemorrhage by diapedesis* the bleeding will cease when blood is no longer supplied to the vessel which bleeds, when the abnormal intravascular blood-pressure is withdrawn, and when the vessel-wall is restored to a normal state.

§ 47. When an **artery is suddenly closed** by thrombosis, or by embolism, or by ligation, or by any other means, there occurs beyond the obstructed point, as has already been stated in § 39, an arrest of the circulation, after the vessel has more or less emptied itself by the contraction of its walls; while from the point of obstruction back to the point of divergence of the nearest arterial branch the blood-pressure increases. If the branches of the artery beyond the point of obstruction have free arterial communication with some other unobstructed artery, this latter by becoming dilated is able to carry a supply of blood suffi-

cient for the area of distribution of the obstructed vessel, and the arrested circulation is thus restored.

If the obstructed area has no vascular connections through which it can draw its blood-supply, that portion of tissue which is thus deprived of its nutrition remains empty of blood and dies; thus there is formed an **anæmic infarct.** Parenchymatous organs, such as the spleen and the kidneys, in those portions which are deprived of blood, appear cloudy, opaque, yellowish-white, often clay-colored, and the microscope shows that the tissues are dead, and that therefore the nuclei of the cells (Fig. 29, *c*, *d*, *e*, *f*, *g*) no longer take the stain.

If the area of distribution of the obstructed vessel has no arterial anastomosis, if the obstructed vessel is a **terminal artery**, but if there remains, on the other hand, the possibility of a scanty afflux of blood from adjacent capillaries or from the veins, a **hemorrhagic infarct** may

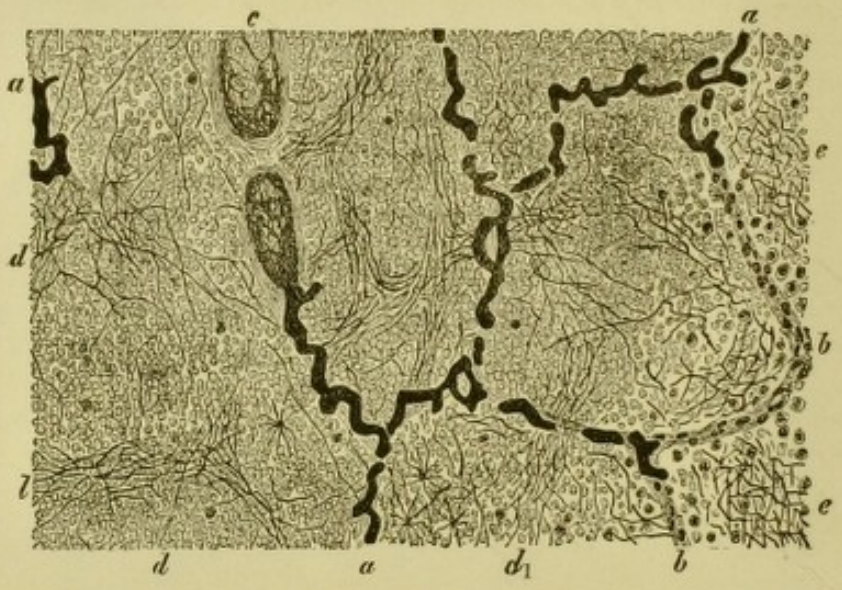


FIG. 30.—Part of the edge of a recent hemorrhagic infarct of the lung. (Müller's fluid; hæmatoxylin; eosin.) *a*, Interalveolar septa without nuclei, containing capillaries gorged with thrombotic masses, homogeneous in appearance and deep-bluish violet in color; *b*, septa containing nuclei; *c*, a vein with a red thrombus; *d*, alveoli completely filled with clotted blood; *e*, alveoli filled with serous fluid, fibrin, and leucocytes. Magnified 100 diameters.

be formed. The capillaries of the region rendered anæmic by the obstruction become slowly filled once more with blood, which comes in part from capillaries belonging to the domain of adjacent vessels, in part from the veins, from whence the blood flows in a retrograde direction. The blood flowing in from the adjacent capillaries is under very low pressure, which does not suffice to drive the blood promptly through the obstructed area into the veins. When the relative pressures become such that a retrograde current sets in from the veins into the capillaries, a restoration of the normal circulation becomes, at once, entirely out of the question.

Unless, by a speedy adjustment of the conditions of pressure throughout the vascular system, a normal flow of blood is promptly reëstablished through the obstructed area, the imperfect circulation (which by the progress of coagulation in the veins [Fig. 30, *c*] and capillaries [*a*] will eventuate in complete arrest of the blood-current) leads sooner or later to degeneration, and even to necrosis of the vessel walls, and thus to their *exaggerated permeability*. As a result of this, if

the afflux of blood is continued, *diapedesis of the red blood-corpuscles* begins in the obstructed area, and goes on to infiltration of the tissue with extravasated blood-corpuscles, whereby the affected area takes on a dark-red color and acquires a firmer consistency,—in short, there is formed a hemorrhagic infarct.

Embolic hemorrhagic infarcts are to be found *in the lungs* (Fig. 30), but they are formed, after the embolic obstruction of an artery, *only when there is a tendency to stagnation of the pulmonary circulation;* while with a normal pulmonary circulation such circulatory disturbances as follow upon embolism are generally promptly allayed. In the corporeal circulation extensive hemorrhages from embolism are confined, almost exclusively, to the territory of the superior mesenteric artery, whose branches, although they are not terminal vessels, yet possess but few anastomoses. *Anæmic infarcts* occur particularly *in the spleen, in the heart, in the kidneys, and in the retina*, though hemorrhage is found in these also, along the *borders* of the obstructed region, so that the bloodless foci have a *hemorrhagic border* surrounding them, or at least present *hemorrhagic spots* (Fig. 29, *g*). The necrotic tissue, furthermore, becomes saturated with fluid, and may then swell (Fig. 29, *d*) and present granular or fibrous coagula in its interstices (Fig. 29, *c*). In case of the obstruction of arteries of the brain, or of those of the extremities, or of the central artery of the retina, hemorrhages may also occur in spots. In the interior of the infarct the tissues are generally wholly or in greater part dead, and it is especially the specific elements of the affected organ (Fig. 29, *c*, *d*) which are the first to die. After a time exudative inflammation arises in the neighborhood of ischæmic and of hemorrhagic infarcts, with the formation of a cellular (Fig. 29, *f*) or fibro-cellular exudate (Fig. 30, *e*); and this is followed by tissue-proliferation, by means of which the dead tissue, with its hemorrhagic infiltration, becomes absorbed, and its place is taken by connective tissue. (Compare Part II. of Chapter VI.)

In his published works Virchow, who was the first to institute any profound experimental researches into the matter of thrombosis and embolism, left the question of the origin of the hemorrhagic infarct still open, but he expresses the opinion that in the area of distribution of the obstructed artery the vascular walls suffer certain alterations which render them more fragile and permeable. If a collateral circulation afterward becomes established, this secondary hyperæmia causes exudation and extravasation. Cohnheim, who observed directly under the microscope the results of embolism in the frog's tongue, demonstrated the retrograde flow of the blood in the veins, the refilling of the capillaries, and the escape of the blood by diapedesis. The cause of the diapedesis he thought was essentially the disorganization of the vascular wall due to the anæmia. Litten considers the reflux of the blood from the veins to be but an unessential part of the phenomenon, and ascribes the refilling of the exsanguinated area to the pouring in of blood from the neighboring vascular fields. The disorganization of the vessel-walls he thinks also unnecessary for the production of infarction, inasmuch as the stagnation suffices of itself, just as in venous obstruction, to explain the diapedesis. The diapedesis is therefore increased whenever in such foci the blood coagulates in the efferent veins.

Von Recklinghausen considers the principal cause of the formation of a hemorrhagic infarct to be the hyaline thrombosis of the capillary vessels of the region involved by the embolism. If subsequently blood from neighboring vessels enters the still pervious portions of the implicated territory, it encounters resistance, becomes stagnant, and then escapes from the vessels. According to Klebs,[1] emboli thrown into the circulation of the lower animals cause infarction only when blood rich in ferment is thrown in after the embolus, or else when substances provoking coagulation become disseminated through the obstructing plug.

Grawitz is of the opinion that hemorrhagic infarcts of the lungs are never to be ascribed to vascular obstruction by embolism, but rather that stagnation and pulmonary

[1] *Schweizer Arch. f. Thierheilk.*, Bd. 28, 1886.

inflammation are to be regarded as the cause of the hemorrhages. There is no room, however, to doubt the existence of embolic pulmonary infarcts. They can occur, it is true, only when there is a tendency to stagnation in the lungs, and therefore, in animals with unimpaired pulmonary circulation, they are not to be provoked by the introduction of obstructing particles into the pulmonary arteries. The essential causes of the escape of the blood are to be found in the stagnation of the blood within the obstructed area, and in the necrosis of the tissues as well as of the vessels themselves. This last may be positively recognized in the disappearance of the nuclei (Fig. 30, *a*). Secondary thromboses in the vessels within the area of obstruction (Fig. 30, *c*) are frequent, and increase the extent of stagnation and of extravasation; they are not, however, invariably present at the time of the extravasation, and are therefore not essential to the occurrence of the hemorrhage. When conditions of stagnation and inflammation exist in the lungs copious hemorrhages often occur, and these—if limited to distinctly circumscribed areas—would present a very close resemblance to embolic infarcts. They are generally, however, less sharply defined and less firm, so that they are for the most part easily distinguishable from embolic infarcts.

VI. Lymphorrhagia.

§ 48. **Lymphorrhagia** occurs when the continuity of a lymphatic vessel becomes interrupted at a certain point and the lymph is poured out into the surrounding parts. As the pressure in the lymphatics is very low—that is, is not greater than in the surrounding tissues—it follows that lymph can be poured out from a lymphatic only when the affected vessel lies on the external surface, or when a natural cavity is at hand into which the lymph can flow, or when, by the same cause which effected the breach in the lymph-vessel, an open space was formed in the tissues. So, for example, in wounds we may see lymph escaping along with the blood, but the outflow is checked upon the least counterpressure. If after the wounding of a lymphatic vessel the aperture persists, so that there is a permanent flow of lymph escaping externally (as in ulcers) or into one of the cavities of the body, we have a so-called **lymph-fistula**, through which considerable quantities of lymph may become lost. Most important and also most dangerous is a *division of the ductus thoracicus*, observed sometimes after traumatism, and occasionally also as the result of obstruction to the lymph-flow at some point through compression of the duct (after inflammation, or in the course of the development of tumors). The lymph is poured out into the thoracic or the abdominal cavity, and a *chylous hydrothorax*, or a *chylous ascites*, or, in very rare cases, a *chylopericardium* ensues.

In very rare cases it happens that the urine, as it comes from the bladder, has the appearance of a milk-white, or a yellowish, or, through the admixture of blood, a reddish emulsion, and contains, along with albumin, large quantities of fat subdivided into very minute globules. The phenomenon is consequently known as **chyluria.** It occurs endemically in certain tropical regions (Brazil, India, the Antilles, Zanzibar, Egypt), where it is caused by a parasite, the *Filaria Bancroftii*, which inhabits the abdominal lymph-vessels and there produces its embryos (*Filaria sanguinis*); these, during the repose of the patient in the horizontal posture, swarm in great numbers in the blood and are also contained in the chylous urine. The connection between the chyluria and the invasion of the lymph-vessels by the filaria has not yet been satisfactorily demonstrated by anatomical investigations; it is nevertheless probable that, on account of the obstruction which occurs in the lymph-circulation, chyle escapes from the ruptured lymphatics of the bladder and mingles with the urine, so that the chyle-like fluid does not come from the blood and through the kidneys (Scheube, Grimm); and in corroboration of this view we may mention the facts, first, that upon autopsy the abdominal lymphatics exhibit marked dilatation (Havelburg), while the kidneys are but slightly altered, and second, that, according to an observation of Havelburg's, the urine coming directly from the ureter showed no admixture of chyle, although chyluria was present at the time.

CHAPTER IV.

Retrograde Disturbances of Nutrition and Infiltrations of the Tissues.

I. On Retrograde Disturbances of Nutrition and Infiltrations of the Tissues in General.

§ 49. **Retrograde disturbances** are characterized in general by *degeneration of the affected tissue*, often with *diminution in its size* as a whole and *disappearance of its elements*. Accompanying this there is *disturbance of the function of the tissue*.

Infiltrations of the tissues are characterized, on the other hand, by *a deposit in them of pathological substances* which are either formed in the body itself or have been introduced into it from without. In this case, also, the *function of the tissue is usually interfered with*. The *infiltration is often only a result of preceding degenerative changes*, or, on the other hand, *it may itself represent the principal manifestation of this degeneration*.

Retrograde disturbances of nutrition may affect the body in its completely developed form or during its period of development and growth, and in either case they lead to an abnormal smallness of the affected organ or portion of the body. In the former case this diminution in size depends upon disappearance of the fundamental elements of the affected tissue, and is designated **atrophy**. In the latter case, on the other hand, it depends upon an imperfect development of the affected organ, shown by a more or less rudimentary condition of its elements. If in this way an organ or portion of an organ entirely fails of development, so that it is either completely absent or at most only a mere rudiment of it is present, the condition is spoken of as **agenesia** or **aplasia**. But if the affected portion of the body is only moderately below the norm in its development, the condition is spoken of as **hypoplasia**.

The **causes of agenesia and of hypoplasia** may be either intrinsic or extrinsic—that is to say, the diminished size and imperfect formation of the organ may depend on pathological conditions within itself, or they may be the result of the action of injurious external influences. The maldevelopment may further affect either the entire body, in which case a *dwarf* results, or it may affect a portion of it only, giving rise then to *imperfect formation of single parts or organs*.

The **causes of degeneration of tissue and of the resulting atrophy** are for the most part injurious extrinsic influences to which the tissue is exposed during life, and yet at times they may also be traced to intrinsic conditions. This latter is notably the case with the tissues during old age, when they are reaching their physiological limit and are gradually becoming incapable of properly nourishing and preserving themselves. In many tissues a similar retrograde change, dependent upon intrinsic causes, occurs earlier in life, as, for example, physiologically in the ovary and in the thymus gland.

Among the extrinsic harmful influences which may lead to degenerations, nearly all those should be mentioned which have been discussed in Chapter II. Thus an important part is played by disturbances of the circulation, with imperfect transport of oxygen and nutriment to the tissues, and by poisons. Usually *degenerations are of limited extent*, so that one speaks of **degenerations of special tissues or of particular organs**; but, on the other hand, **disturbances of nutrition may be more general** and the entire organism may suffer. Thus the picture of a general disease may be produced by a degenerative or atrophic condition of the blood, which may show itself by a diminution either of the red blood-corpuscles or of their hæmoglobin content, whereby a permanent condition of **general anæmia** or **insufficient blood-supply** is induced, the nutrition of the tissue being correspondingly impaired.

Again, as the result of an insufficient ingestion of food or of disordered assimilation on the one hand, and of excessive waste of proteids and fats of the body on the other, there may result a condition of weakness and malnutrition, often associated with anæmia, leading to atrophy of the body as a whole. This is spoken of as **cachexia** or **marasmus.** If, under these circumstances, it appears likely that certain substances are undergoing formation in the body which, when taken into the blood and various fluids, act as impurities and alter the constitution of those fluids, the condition is spoken of as one of **dyscrasia.**

II. Death.

§ 50. All life comes sooner or later to an end—to death. When this occurs at an advanced age, without preceding well-defined symptoms of disease, it may be regarded as the normal termination of life, and is to be attributed, at least in part, to the cessation of function of certain of the organs necessary to the continuance of life. This occurs usually as the result of intrinsic causes, although in most cases it is impossible to exclude the influence of extrinsic conditions in bringing about the cessation of function of the organs in question.

When death occurs early in life—that is to say, at an age earlier than the average age of death in man—and when it is preceded by symptoms of disease, it must be considered abnormal. Its occurrence under these circumstances is for the most part referable to extrinsic influences, though it may occasionally be due to intrinsic inherited conditions. It is obviously impossible to draw any sharp line of separation between what may be called physiological and pathological death.

The causes of pathological death are those which have been discussed in Chapter II. as the causes of disease.

A body is said to be dead when all of its functions have forever ceased. Death is, however, inevitable at that instant when one or more of the functions imperatively necessary to life have ceased, although it is not necessary that at that moment *all* functions shall have ceased. Indeed, after life is irrevocably lost, many organs are still capable of performing their function, and it is only after a little time that all the organs die. Thus the life of the organism passes gradually, by the progressive cessation of the functions of its various organs, into the state which we term death.

The discontinuance of the functions of the heart, of the lungs, and of the nervous system results in an immediate death of the entire

organism. Discontinuance of the functions of the intestine, of the liver, and of the kidneys renders life impossible after a certain length of time, often measured by days. Destruction of the organs of reproduction in no wise endangers either the health or the life of the affected individual, and, similarly, one or more of the organs of special sense may be spared.

Death is usually inevitable after cessation of respiration, and certain after cessation of the heart-beat. With discontinuance of breathing it is impossible for any organ to continue alive longer than a very short time. The stoppage of the heart similarly makes impossible any further nourishment of the tissues, and the central nervous system quickly becomes unable to continue the performance of its functions.

After death the body may present considerable diversity of appearance. The distribution of the blood at the time of death has much to do with the aspect of its visible portions. Thus an abundant supply of blood in the skin causes it to have a bluish-red color, while if anæmic it is pale. Furthermore, disease may materially alter the appearance of the exterior of the body.

Sooner or later after death certain changes occur in the tissues of the body which may be regarded as **unquestionable signs of death**. In the first place, *the temperature of the body falls*, so that after a variable interval it reaches the temperature of the surrounding air. It should, however, be borne in mind that the temperature at times does not begin to sink immediately after death, but first rises somewhat. The rapidity of the cooling of the body depends partly upon the character of the body itself and partly upon the nature of its surroundings. The time required may vary from one to twenty-four hours.

The *coldness of the dead* is spoken of as *algor mortis*.

At the time of death the skin is usually pale, but after a variable period—from six to twelve hours, or even less—bluish-red blotches appear on the dependent portions of the body. These are designated *livores mortis* or *blotches of cadaveric lividity*, and depend upon the accumulation of the blood in the capillaries and veins of the more dependent portions of the skin. They are not observed in those parts of the body which are subjected to pressure. Their number and size depend upon the amount of blood in the skin at the time of death. Parts which have been cyanotic in life may retain this appearance after death; this is particularly the case with the head, the fingers, and the toes. The color of these blotches of cadaveric lividity is for the most part bluish-red, and there may be considerable difference in the intensity of their coloring. In cases of poisoning by carbon monoxide it is bright red.

The weight of the body causes flattening of those muscular parts of the body upon which it rests.

Sooner or later there occurs *a cadaveric stiffening of the muscles*, to which the term *rigor mortis* is applied. This is characterized by contraction of the muscles, which, according to Bruecke and Kuehne, is dependent upon the coagulation of their contractile substance. It makes its appearance usually in from four to twelve hours after death, though it may occur almost immediately thereafter, or may not appear until twenty-four hours have elapsed. It usually is first noticed in the muscles of the jaw, throat, and neck, and extends from them to the trunk and extremities. After from twenty-four to forty-eight hours it usually disappears, but may occasionally persist for several days.

This rigor mortis affects the smooth muscle-fibres as well as the

striated. The contraction of these elements in the skin is the cause of the so-called goose-flesh of the cadaver.

Putrefaction begins somewhat before the disappearance of rigor mortis. It is evinced by its peculiar odor, by change in color of the skin and of the mucous membranes, and by change in the consistence of the tissues. Much influence upon the commencement and progress of putrefaction is exerted by the condition of nutrition of the body, by the nature of the disease which has preceded death, and by the nature of the surrounding medium, especially the temperature. Occasionally putrefactive changes occur in portions of the body which are dead even before the death of the entire body; and in cases in which putrefactive bacteria are present in the body at the time of death putrefaction may begin immediately thereafter.

As an early sign of putrefaction there is usually greenish discoloration of the skin, commonly appearing first over the abdomen. With the progress of putrefaction the unpleasant odor and discoloration increase, and gases are formed in the intestine, in the blood, and in the tissues, which at the same time become soft and friable.

Shortly after death *the cornea becomes lustreless and clouded, the eyeball loses its prominence,* and *dark spots* after a time *develop in the sclera.* These changes in the eye are due to evaporation and putrefaction. When the eyelids are not closed the *results of drying are very evident in the uncovered portions of the eyeball.* Wherever the skin has lost its epidermis the exposed tissues become dried.

Under certain circumstances the evidence of life may be reduced to a minimum, and a condition of **apparent death** may result which may be mistaken for death. Post-mortem lividity, rigor mortis, and evidences of putrefaction are unmistakable signs of death; but, since these changes do not appear until some time after death, an interval is left during which it may occasionally be doubtful whether death has actually taken place or not. To ascertain the truth with certainty under these circumstances it must be determined by an appropriate examination whether the heart still beats, whether respiration is going on, whether the blood still circulates, and whether the nerves and muscles still remain irritable.

This condition of apparent death may occur under a variety of circumstances, as, for example, in the course of cholera, in catalepsy, in hysteria, after great bodily exertion, after violent concussion of the nervous system, after profuse hemorrhage, when respiration is suspended as the result of strangulation, hanging or drowning, in certain cases of poisoning, in lightning-stroke, after prolonged exposure to cold, etc. The duration of this condition is usually short, but it may occasionally persist for hours or even days.

III. Necrosis.

§ 51. By **necrosis** is understood a condition of *local death*, or death of single cells and groups of cells. As the result of necrosis there is always a permanent cessation of the functions peculiar to the affected tissue.

It is only occasionally that the necrosis of a cell-group or of an entire organ makes itself at once evident in recognizable changes of structure; that is to say, the slight histological changes which the cells undergo as the result of their death do not permit us always to determine with certainty the moment of the cessation of their life, nor does the macroscopic appearance of the visible portions of the body inform us when a portion thereof becomes necrotic.

Necrosis of a tissue is therefore evident upon anatomical examination only when certain changes in its structure have occurred either

coincidently with its death or subsequently thereto. The immediate occurrence of such changes is met with occasionally in the case of traumatism, while the changes which develop later always make their appearance after the lapse of a certain length of time. It is customary to distinguish several forms of necrosis, according to the nature of the changes which take place.

Histologically **necrosis of a cell** is very often indicated by the *disintegration and disappearance of its nucleus* (*karyorrhexis* and *karyolysis*). In this process the chromatin of the latter—the substance which is stained by the nuclear dyes—forms small masses and granules which occasionally leave the nucleus and get into the cell-body, where they dissolve and disappear. In some cases the nucleus, before disappearing, shows *evidences of shrinking;* and when this is the case it will receive from nuclear stains a deeper shade of color than it would under normal conditions. In other cases *the nucleus, while still retaining its form, first loses its power of staining,* and then gradually dissolves and disappears (Fig. 31, *c*, *d*), so that even in well hardened and stained preparations there may be no trace whatever of the nucleus. Thus, for example, in those portions of the spleen or kidney which have been rendered ischæmic by the cutting off of the blood-supply in embolism of the arteries of these two organs, the nuclei of the cells of the spleen and of the kidney epithelium (Fig. 29, *c*, *d*, *f*, *g*) are very soon lost, and at the same time the affected tissues assume a distinctly pale, cloudy, yellowish-white appearance, which makes it possible to recognize the onset of necrosis even with the naked eye.

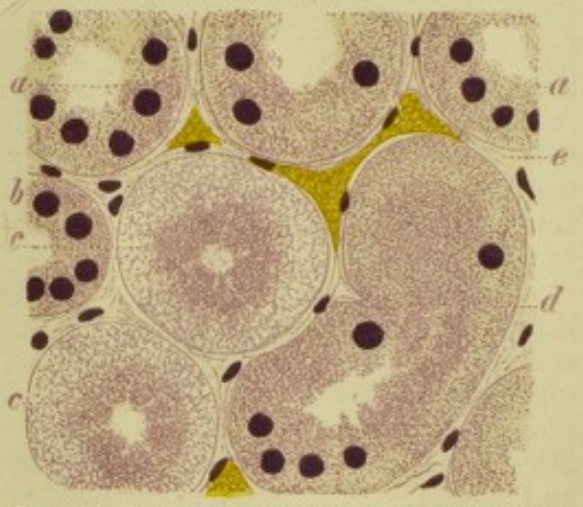


FIG. 31.—Necrosis of the epithelium of the uriniferous tubes in a case of icterus gravis. *a*, Normal convoluted tubule; *b*, ascending looped tubule; *c*, convoluted tubule with necrotic epithelium; *d*, convoluted tubule with only a part of its epithelium necrotic; *e*, stroma and blood-vessels, as yet unaltered. (Preparation hardened in Müller's fluid, and stained with gentian violet.) Magnified 300 diameters.

Sooner or later changes take place also in the *protoplasm* of the dying cells, and these, according to the mode of death, begin before the cells are actually dead, or they may occur only in the dead cells. The kind of change depends upon three factors: the nature of the cells themselves, the particular kind of destructive influence, and the number and condition of the surrounding cells and fluid. Amœboid cells usually take on a *globular form* after death. Delicate and only slightly modified cell-bodies, rich in protoplasm, often become, either before or after death has taken place, markedly granular—less frequently, homogeneous or flaky—through the access of fluid; the protoplasm and sometimes also the nucleus swell up and show in their interior drops of fluid—*vacuoles;* and, as a result of this swelling, breaks occur in the continuity of the protoplasm (*plasmoschisis*). When this latter change occurs, portions of cell-bodies may be cut off entirely from the parent cell through *a process of constriction*, or they may simply be extruded. The ultimate issue of all these changes is *the reduction of the protoplasm and nucleus to a granular mass*, and fat is often formed at the same time.

Cells which, under natural conditions, have undergone a decided transformation—as is the case with cells which have become horny—show comparatively few striking changes; yet even they may swell up and finally disintegrate. The least pronounced morphological changes are those which occur in cells which, when dying, simply grow more dense and dry up (*inspissation*). Under these conditions the cells become smaller, and yet at times they also may lose their nuclei and may be converted into a shapeless scaly mass.

The injuries which lead to death of limited portions of the body may be classed in five groups. The first two include those which destroy the tissue directly through **mechanical violence** or through the **action of chemicals.** Thus, for example, a finger may be crushed by violence, and sulphuric acid may destroy a portion of the skin. A third group of **injurious influences are of a thermal character.** Elevation of the temperature of a tissue for any length of time to from 54° to 68° C. results in its death. Higher temperatures act more quickly. Similarly, excessive cold can be borne for only a short time (cf. § 5). A fourth group is composed of diseases which owe their origin to **infections** with vegetable or with animal parasites. A fifth form of necrosis, characterized as **anæmic necrosis** or as **local asphyxia,** is the result of **discontinuance of the supply of nourishment and oxygen to the tissues.**

In addition to these, many authors distinguish as a special group those forms of necrosis which result from lesions of the central nervous system or of the peripheral nerves, and which may be designated as **neuropathic necroses.** By some this form of necrosis is believed to be the direct result of lesion of the trophic nerves, while by others it is attributed to changes in the circulation and to the effects of pressure and mechanical injury of anæsthetic and paralyzed portions of the body. The observations thus far made upon man, and experiments upon animals, indicate that, at all events, an important part in the production of this form of necrosis is always played by external injuries and by disturbances of the circulation.

Again, all those conditions seriously affecting the circulation and leading to stoppage of the blood-supply—such as thrombosis, embolism, closure of a vessel as the result of lasting abnormal contraction, disease of its wall, or ligation, pressure on the tissue, inflammation, hemorrhage, etc.—may result in necrosis of the affected part; nor is it necessary that the disturbance of the circulation should be permanent, since a comparatively transient interference with the blood-supply may be followed by death of tissue. Whether or not hemorrhage occurs in such cases, as was stated in § 47, would appear to be immaterial to the result, influencing only the appearance of the diseased tissue. *Hemorrhagic infarction* has therefore precisely the same significance as an *anæmic necrosis combined with hemorrhage.*

When death of a tissue supervenes quickly upon the infliction of an injury, it is called **direct necrosis**; when it occurs slowly, and is preceded by degenerative changes in the tissue, it is termed **indirect necrosis** or **necrobiosis.**

Mechanical, chemical, thermal, and infectious sources of injury, as well as anæmia, may exert their effect coincidently in the production of necrosis, or they may act separately, one after the other. When the tissue is damaged by either of the three injuries first named, the blood itself also frequently undergoes a change, which terminates in stasis and

coagulation of this fluid in the capillaries, as well as in the veins and arteries; and as a result of this the circulation is arrested.

Whether or not any given injury will cause necrosis does not depend wholly upon its nature and severity, but is influenced to a considerable degree by the condition of the affected tissue at the time of the occurrence. Thus, if a tissue has been subjected for a long time to the depressing influence of an impaired circulation, or if its vitality has been lowered by marasmus or hydræmia or a diseased condition of the blood, it dies much more easily than if it had been previously healthy. As an example of this may be cited the frequency of necrosis after comparatively slight injuries, more particularly of the extremities, in the aged and in those who suffer from uncompensated valvular lesions of the heart. Furthermore, disturbances of the nerves of the vessels, in so far as they lead to impairment of the circulation, may afford a predisposition to necrosis. In the prostration incident to typhoid fever, comparatively slight pressure on the hip, elbow, sacrum, or heel may be sufficient to bring about gangrenous destruction of the skin and of the subcutaneous tissue. These forms are known as **senile** and **marasmic necrosis**, or as **marasmic gangrene** and as **decubitus**.

The structure of the tissue, its position, the manner of its death, and the causes of the necrosis, all exert a determining influence upon the **course of the necrosis**, that is to say, upon the changes in the tissue which will result therefrom. An important influence is also exerted by the amount of blood and lymph in the tissue, and by the opportunity for access of the air and of the ferments of putrefaction. Not without influence, also, are alterations in the tissue which may have antedated the onset of necrosis—as, for example, fatty degeneration, inflammation, hemorrhage, etc.

As the **result of necrosis** there is always *inflammation of more or less intensity in the surrounding tissue* (cf. Figs. 29, *f*, and 30, *e*), and it is most intense when processes of decomposition set up in the necrotic tissues. Through the formation of a zone of inflammation the necrotic area is shut off from the surrounding tissue—is isolated and sequestered; and the *inflammation is accordingly spoken of as limiting or sequestering*, and the dead tissue thus shut off is termed a *sequestrum*. A detailed description of these inflammatory processes will be found in Chapter VI.

If we exclude from consideration for the present the more special complications of necrosis—as, for example, the development of specific irritating materials—five **sequelæ** are to be distinguished: 1. The dead tissue may be completely *absorbed*, or may be *cast off* from a surface, and *its place taken by newly formed normal tissue*. This is spoken of as *regeneration*. 2. The dead tissue is similarly removed, but, instead of the normal tissue of the part being reproduced, simple connective tissue, the so-called *cicatricial tissue*, more or less completely supplies the defect. 3. The necrotic tissue is either cast off entirely or becomes dissolved (as in the formation of gastric ulcers through the digestion of portions of tissue which have died), but the lost tissues are not again replaced; an *ulcer* remains. 4. The dead tissue is only partially absorbed or cast off, and *a sequestrum of necrotic tissue remains*, which may later become calcified, and which is in time surrounded by a dense connective-tissue capsule. 5. There is *cyst-formation* at the site of the necrosis, resulting from *encapsulation of the dead tissue by connective tissue*, absorption of the necrotic mass, and substitution for it of a

liquid, which fills the space within the capsule and thus forms a cyst. This result of necrosis is most often met with in the brain.

The time required for the induction of necrosis after stoppage of the circulation varies with the different tissues. Ganglion-cells, renal epithelium, and the epithelium of the intestine die in so short a time as two hours, while skin, bone, and connective tissue may remain alive for twelve hours or more. In general it may be stated that all tissues performing special functions die much sooner than those, such as connective tissue, which have only themselves to sustain.

The cause of the above-described changes in, and final disappearance of, the nuclei in necrotic areas is found in the infiltration of the necrotic tissue with lymph from the surrounding tissue; and these changes are consequently absent when, for any reason, the circulation of the lymph in the diseased organ is stopped. Putrefaction is also a potent influence in inducing a rapid disintegration and disappearance of the nuclei; but Fr. Kraus has shown that portions of tissue preserved aseptically and out of all contact with bacteria, in moist chambers at the body-temperature, lose their nuclei after a time. The tissue of the liver most quickly shows this change (Goldmann), while it may not appear in the spleen and kidney until much later, and all nuclei may not have disappeared even after the lapse of from eight to fourteen days. It has been found by Goldmann that the disappearance of the nuclei occurs only in the presence of a considerable degree of moisture, and may be prevented by desiccation of the tissue.

§ 52. According to the various conditions in which the tissues are found after they have died, it is customary to distinguish **four principal forms of necrosis,** viz., *coagulation necrosis*, *cheesy degeneration*, *liquefactive necrosis*, and *gangrene*.

Coagulation necrosis (Weigert, Cohnheim) is characterized by the previous occurrence of coagulation, which may take place outside the cells, in the surrounding fluid, or within the cells; and when the latter event happens, the alterations which occur in the cells are of a peculiar character.

When the process of coagulation takes place outside the cells and leads to necrosis, there should be reckoned, as one of its phenomena, the *coagulation of blood* both within the blood-vessels (Figs. 13–16) and on their outside (Fig. 12, *d*); for in this phenomenon there are seen an actual death of the blood and a destruction of the cells. Among the other phenomena may be mentioned the coagulations which take place, in the progress of an inflammation, in the fluids (more or less rich in cells) which exude from the blood-vessels (compare Chapter VI.). These exudations, which occur partly on the surface and partly in the interior of the tissues, present, when coagulated, either a fibrillated (Fig. 32, *a*), or a somewhat granular, or a hyaline appearance.

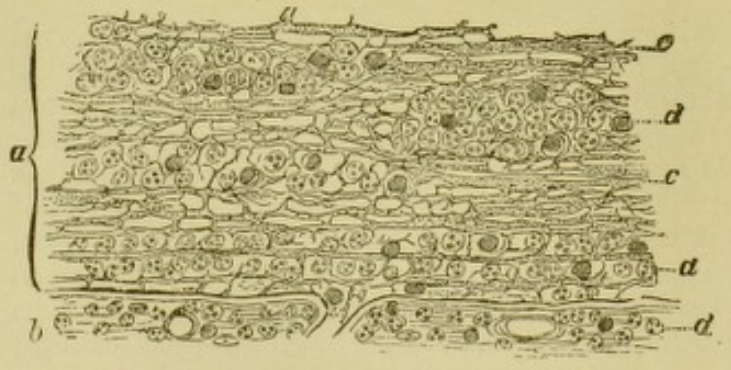


FIG. 32.—Croupous membrane from the trachea. *a*, Transverse section of the membrane; *b*, uppermost layer of the mucous membrane, with pus-cells, d_1, scattered throughout its substance; *c*, fibrin threads and granules; *d*, pus-cells. (Magnified 250 diameters.)

Intracellular coagulation takes place when the dead cells or cell-products are thoroughly permeated by fibrin-containing tissue-lymph. When this occurs the cells lose their nuclei, and present either a granular (Fig. 29, *c*, *d*, and Fig. 31, *c*), or a hyaline (Fig. 33, *b*) or a scaly appearance. They remain in this condition for a certain length of time, and then break down into granules and finally disappear.

Coagulation necrosis is most often observed in anæmic, toxic, and thermal tissue-necroses; as, for instance, in ischæmic infarcts of the kidney (Fig. 29) and spleen, in necroses of muscular tissue, which occur in the course of certain infectious diseases, such as typhoid fever (Fig. 33), and in many inflammatory processes in which there is marked infiltration of the tissues, the result of exudation from the blood-vessels.

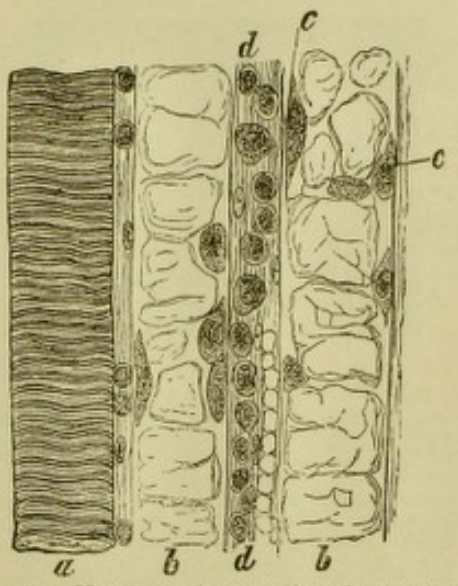


FIG. 33.—Waxy degeneration of muscular fibres, from a case of typhoid fever. *a*, Normal muscular fibre; *b*, *b*, degenerated fibres, which have broken down into separate masses; *c*, *c*, cells lying inside of the sarcolemma; *d*, connective tissue infiltrated with cells. Magnified 250 diameters.

In the case of anæmic infarcts, the necrotic tissue looks pale, yellowish-white, often clay-colored. Muscles in which there are many dead muscular fibres in a condition of hyaline coagulation are pale red, faintly glistening, and not unlike the flesh of fish. Tissues which have first been inflamed and then have undergone coagulation necrosis are opaque and grayish-white; but decided changes in color may result from the admixture of blood or bile (for example, in the intestine).

A tissue which is the seat of coagulation necrosis may—if only the more delicate parts have been destroyed—still be clearly recognized in its structure. If, however, all the parts have been altered, the whole tissue may be changed into a structureless, hyaline, or granular mass, containing few or no nuclei; and this result occurs very often in the necrosis of tissues which have been inflamed and which are filled with fluid exudation. If the specimen has been properly treated, there may frequently be seen, in these necrotic areas, a fibrillated condition of the intercellular coagulation. The same thing may be seen even in ischæmic infarcts, although it will be found more often in the necrosis of inflammatory tissue (Fig. 34).

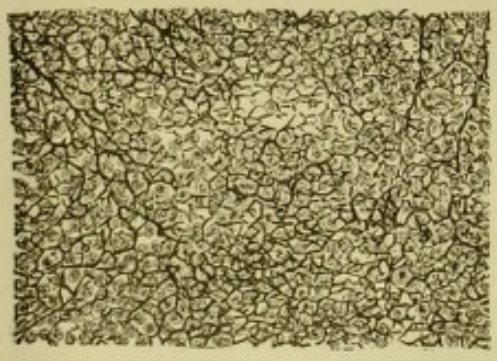


FIG. 34.—Coagulation-necrosis in the interior of an enormously swollen mesenteric lymph-gland, from a patient who died of typhoid fever. (Alcohol; fibrin stain.) Network of fibrin separating the necrotic cells. Magnified 300 diameters.

Cheesy degeneration is regarded as a form of coagulation necrosis in which the necrotic tissue presents the appearance either of hard or of cream cheese. In the first instance the necrotic tissue is firm, yellowish-white in color, and like hard cheese or raw potato; in the second, it is soft, white, sometimes dry, at other times moist, and frequently it looks like a mass of thick cream.

Cheesy degeneration occurs in a typical form most often in tuberculous new-formations, and represents, under these circumstances, the characteristic ending of the retrogressive changes. It also occurs in syphilitic granulations and in tumors rich in cells; and inflammatory exudations may also undergo cheesy degeneration.

The process of cheesy degeneration of cellular tissues, which is a

striking characteristic of tuberculous granulations, takes place gradually, and is accordingly regarded as one of the phenomena of **necrobiosis.** The cells are changed, one after another, into non-nucleated, homogeneous, scaly masses, which later split and break up into a granular mass (Fig. 35, a_1, a). While these changes are taking place there often appears between the cells a material which presents different appearances at different times. Thus, at one time, it forms a hyaline framework around the cells; at another, it constitutes a somewhat granular "*fibrinoid mass*"; and at still another, it has all the characteristics of *typical fibrillated fibrin* (Fig. 36, a), and assumes a deep blue color when treated with Weigert's fibrin-staining material. It is therefore fair to assume that these substances are the result of the coagulation of fluid which has exuded from the blood-vessels.

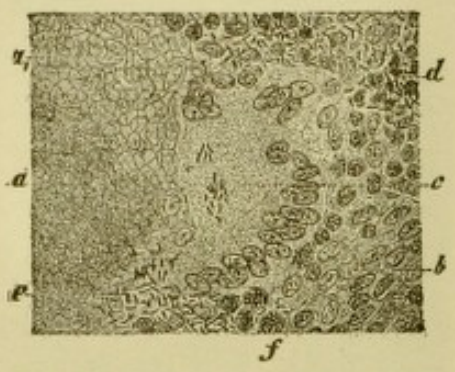


FIG. 35.—Tissue from a focus of tuberculous disease, showing bacilli and a limited area of cheesy degeneration. (Alcohol; fuchsin; aniline blue.) *a*, Granular cheesy material; a_1, cheesy material in the form of small separate aggregations; *b*, fibrocellular tissue; *c*, partly necrotic giant cell, with bacilli; *d*, cellular tissue invaded by bacilli; *e*, a similar invasion in tissue that is necrotic; *f*, bacilli enclosed in cells. Magnified 200 diameters.

Through the progressive breaking up and disintegration of the necrotic cells, the fibrinoid substance, and the fibrin, the dead tissue is ultimately changed into a finely granular mass, in which it is no longer possible to recognize the original structure.

The cheesy metamorphosis of the cellular and fibrinous exudations which are found, for instance, in the alveoli of the lungs, in the neighborhood of tubercles, is accomplished by the loss of the nuclei and by the breaking up of the cells and fibrin, until nothing remains but a granular mass in which there are no nuclei.

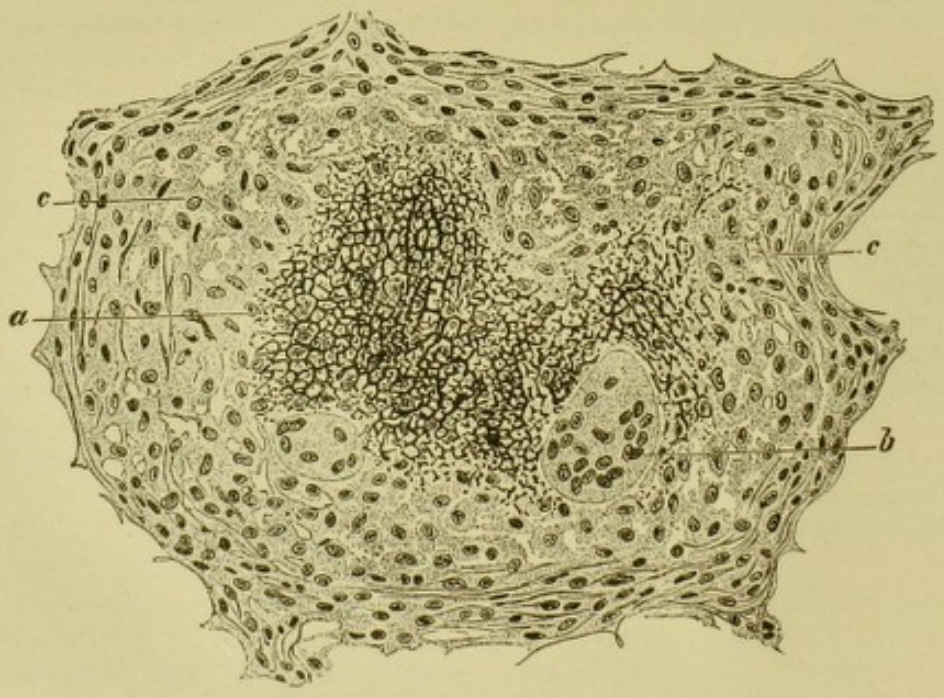


FIG. 36.—Deposit of fibrin in a tubercle of the lung. (Alcohol; hæmatoxylin; fibrin-staining mixture.) *a*, Fibrin; *b*, giant cells; *c*, cellular portion of the tubercle. Magnified 300 diameters.

The granules of the soft cheesy masses in tuberculous and non-tuberculous foci are in part albumin granules, in part fat drops. The further fate of this mass may be either a *liquefaction and conversion into a pap-like material*, or *a removal through absorption*, or finally *a solidification and conversion into calcareous material.*

Liquefaction necrosis is chiefly characterized by the fact that *the necrotic* parts are dissolved in the fluid present in the tissue. This dissolution may be accomplished by swelling and liquefaction as well as by breaking up of the tissue, or through a combination of both processes. Thus, for instance, in burns of moderate severity, those cells of the skin (exclusive of the horny layers) which have been killed by the heat, are dissolved in the fluid which exudes from the papillary bodies

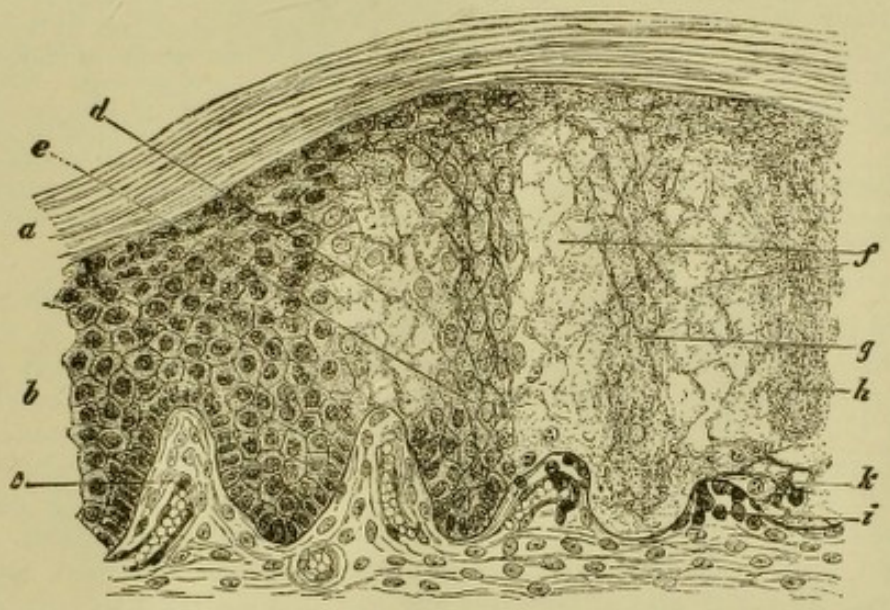


FIG. 37.—Section through the epidermal and papillary portions of a cat's paw, a short time after it had been burned with fluid sealing-wax. (Alcohol; carmine.) *a*, Horny layer of the epidermis; *b*, rete Malpighii; *c*, normal papilla of the skin; *d*, swollen epithelial cells, the nuclei of which are still visible at a few points, while at others they have entirely disappeared; *e*, epithelial cells lying between the papillæ, the upper ones being swollen and elongated, while the lower still remain in a normal condition; *f*, fibrinous network composed of epithelial cells (broken down so as to be no longer recognizable as such) and exudate; *g*, an interpapillary mass of cells which have become swollen and have lost their nuclei; *h*, a part of a similar mass in which the cells have been entirely destroyed; *i*, a papilla that has been flattened by pressure and that is infiltrated with cells; *k*, solidified subepithelial exudate. Magnified 150 diameters.

(Fig. 37, *d*, *f*). In ischæmic brain necrosis the brain substance undergoes softening, and, in the course of this process, drops and granules are formed. As the process advances the brain tissue will be reduced to a milky, pap-like mass, in which the products of the destruction of the brain tissue are represented by smaller and smaller particles, which are sometimes free, sometimes are contained in the cells. Eventually these particles are dissolved, or they are entirely removed by absorption. In the process known as tissue-suppuration, which occurs very often in purulent inflammations, the so-called pus corpuscles are destroyed, some of them first swelling up and bursting, while the others become disintegrated without any preliminary imbibition of fluid. The ground-substances—as, for example, the fibres of the connective tissue—gradually dissolve and disappear, in the course of tissue-suppuration.

Necrotic tissue of the stomach-wall is dissolved by the action of the stomach secretion.

Coagulation necrosis may give rise to liquefaction, and, *vice versa, liquefaction may induce coagulation*. Thus, for example, in an inflammatory exudation the dissolution of the leucocytes may produce coagulation; and later, the coagulation products may in their turn be dissolved. In gangrenous blebs produced by the dissolution of epithelial cells, there may occur a coagulation, the products of which are later dissolved. As already stated, fibrinous deposits which were originally produced in the course of some inflammation or in connection with the development of granulation tissue, and which have become necrotic or have undergone cheesy degeneration, very often at a later stage become liquefied.

The changes described above as occurring in necrotic or dying tissues are not the only ones which may occur during the course of their destruction; attention has been paid only to the principal types which occur in the course of a comparatively rapid death. Many of the forms of tissue-degeneration which are described in the following paragraphs also lead, not infrequently, to ultimate death of the tissue; and consequently they must be reckoned as belonging under the heading *tissue-necrobiosis*. Granular degeneration, fatty degeneration, mucous degeneration, and dropsical degeneration often end in the destruction of cells; and the same result may be produced in connective tissue by hyaline degeneration and by amyloid degeneration, for these processes are not only capable of producing a permanent change in the basis substance of the tissue, but they may also cause it to undergo disintegration, and they may even produce the death of the cellular elements of the tissue.

§ 53. Under the name of **gangrene** may be classed those forms of necrosis in which the tissue—partly through the influence of exposure to air and partly through the agency of bacteria—undergoes changes that give to it the appearance and also the physical characteristics of burned tissue. If the portion of tissue which has died becomes dry through exposure to the air, and through the resulting evaporation of the water which it contains, it is customary to apply to this condition the terms **dry gangrene** (*gangræna sicca*) and **mummification.** But if the dead part continues to remain moist, the terms **moist gangrene** (*gangræna humida*) and **sphacelus** are the proper ones to employ. If, through the agency of bacteria, decomposition sets in, there will be established a *foul-smelling gangrene*—a **putrid gangrene** (*gangræna fœtida*). The formation of gas bubbles as a result of the putrefactive changes warrants the employment of the term **emphysematous gangrene** (*gangræna emphysematosa*).

Moist gangrene and putrid gangrene are in general identical, since bacteria develop only in very moist tissues. Nevertheless, a dry gangrene may also be a putrid gangrene—a fact which may be explained by the assumption that bacteria multiplied in the tissues before the process of drying took place. Dry gangrene may therefore develop from the moist form, and, on the other hand, it may also, through the absorption of water, develop into moist gangrene.

If the necrotic, putrid, or mummified tissue contains a great deal of blood, it looks black, dark-brown, or dark-green in color, and is then called **black gangrene.** Gangrenous parts which are poor in blood are sometimes spoken of as being affected with **white gangrene.** This expression, however, is often inappropriate, for the dead parts are generally more or less discolored.

In the case of parts which are situated at the surface of the body, it is not unusual to distinguish, according to the temperature of the tissues which have died, a *cold gangrene* and a *warm or hot gangrene;* the last of these terms being used when the dead parts are kept warm by the flow of blood through the tissues of the neighborhood.

Gangrene may be caused by external injuries, by heat, by cold, by cauterization, by crushing, by pressure, by infections, etc.; it may also be caused by disturbances of the circulation.

Gangrene from disturbance of the circulation or from its entire arrest occurs most frequently in old people (*senile gangrene*), in the extremities, and particularly in the toes, the foot, and the leg. It is of the dry variety, and is caused by general disturbance of the circulation as well as by narrowing of the arteries of the extremities through thickening of their walls (Fig. 38). The dying parts look bluish-black from venous congestion. General circulatory disturbances, such as accompany heart disease and embolism of the arteries, may cause similar changes.

Gangrene from cold affects especially the terminal parts of the extremities, the nose, and the external ear, and it is characterized by the same pathological alterations as those which have already been described.

Gangrene from heat is confined to the area directly influenced by the hot material.

Gangrene from pressure, or **bedsore** (*decubitus*), is most frequently observed in marasmic individuals. The parts most often affected are

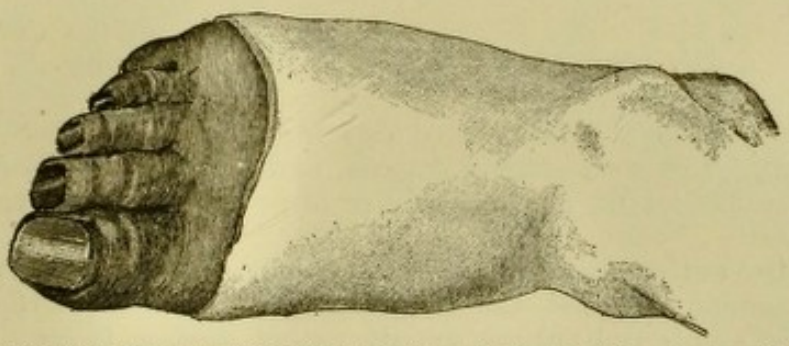


FIG. 38.—Dry gangrene of the toes, caused by narrowing and closure of the arteries which supply these parts—arteriosclerosis.

the region over the sacrum and the heels, both of which regions are exposed to pressure when the patient lies on the back. At first bluish-red spots appear, and within this area the tissues die, then undergo decomposition through the aid of bacteria, and finally break down into detritus. The putrid decomposition may involve an area of large extent when the part affected is the region of the sacrum. It is in this locality that the bony structures may be extensively laid bare through the disintegration of the overlying soft parts.

Toxic gangrene is observed at the very ends of the extremities, especially in ergot poisoning, which causes closure of the smallest blood-vessels through contraction of their walls and the formation of thrombi.

Infectious gangrene occurs particularly in various infections of the skin and subcutaneous tissue, and the process may be accompanied by gas-formation.

Infections which are associated with foul-smelling disintegration of the tissues may occur in various internal organs, but more especially in the lungs and intestines.

Neuropathic gangrene takes place when a part which is affected with either a sensory or a motor paralysis is wounded or is subjected to continued pressure. The cause is therefore to be sought for partly in an infection and partly in some disturbance of the circulation. As

already stated in § 51, it has not yet been demonstrated that the withdrawal of the trophic influence of nerves is competent to produce gangrene. *Symmetrical gangrene*, which affects corresponding parts of the extremities, and is looked upon by many as a neuropathic affection, should rather be considered as the outcome of some circulatory disease.

In moist gangrene the tissues break down and become dissolved with a varying degree of rapidity, the fasciæ resisting for the longest time. Among the crystalline products of the chemical changes which occur in the course of this disintegration, the following may be mentioned: needles both of fat and of tyrosin, globules of leucin, coffin-lid crystals of triple phosphate, and hæmatoidin crystals. When the gangrenous process comes to a standstill, a demarcation-line of inflammation will surround the necrotic tissue—that is to say, the dead will be separated from the living tissue, and will ultimately be removed from the organism. In the case of necrotic osseous tissue a very long time will be required before this separation can be effected. A continued extension of the gangrenous process—through infection, or through the continuance of a defective circulation—leads sooner or later to death, especially if toxic material from the gangrenous area or even bacteria are taken up into the blood and the lymph.

IV. Hypoplasia, Agenesia, and Atrophy.

§ 54. **Hypoplasia** or defective development, may affect the entire body or only organs or parts of organs, and may occur either during the period of intra-uterine development or after birth, during the period of growth.

When the entire skeleton or a very considerable part of it undergoes maldevelopment, so that the bones are much shorter than normal, abnormally small individuals result, called *dwarfs* (Figs. 39 and 40), whose parts may be either fairly well proportioned (Fig. 39) or else unsymmetrically developed (Fig. 40). In the latter figure may be seen an example of a dwarf whose trunk was of nearly the normal size, while the extremities were abnormally small. Again, the body and extremities may be abnormally small, while the head develops to about the normal size, being then out of all proportion to the body. When the maldevelopment is confined to a single part of the skeleton, or is here much more marked than elsewhere, a rudimentary condition of that part results. Thus, as the result of maldevelopment of the cranium, conditions of *microcephalus* (Fig. 41) and *micrencephalus* (Fig. 42) are induced; as the result of maldevelopment of the humerus or of the bones of the hand we may have shortening of the upper arm or of the hand respectively; and, similarly, imperfect development of the lateral masses of the sacrum may lead to transverse narrowing of the pelvis.

Among the separate organs the central nervous system (Figs. 42 and 43) and the genito-urinary system suffer perhaps most frequently from maldevelopment, although the intestine, heart, lungs, and liver by no means escape. In Fig. 42 is presented an example of abnormal smallness and retarded development of the whole brain; but there are also cases in which one hemisphere alone suffers (Fig. 43, *c*, *d*), either wholly or in part. A part of the intestine may be so imperfectly developed as to form only a thin and quite useless canal (Fig. 45, *d*) or to be merely a small solid cord (Fig. 45, *e*). The uterus not infrequently

remains in an undeveloped state (Fig. 44), and occasionally the entire group of female generative organs, both internal and external, may remain at the time of puberty in the undeveloped condition of a young child. Among the organs of the urinary system a more or less complete maldevelopment of the kidney is not uncommon. In the development

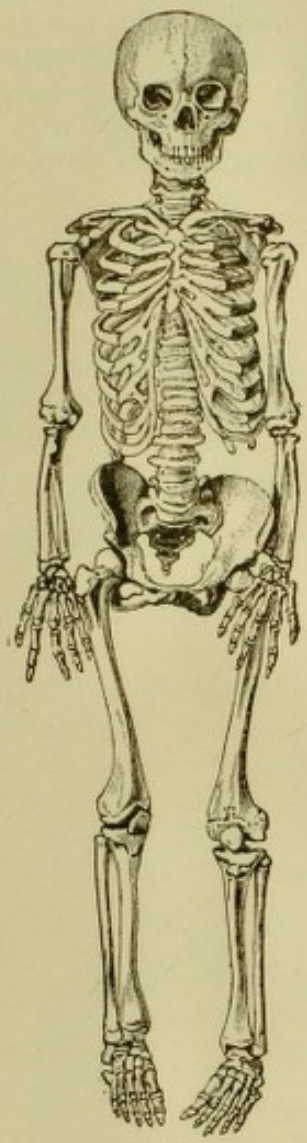


FIG. 39.

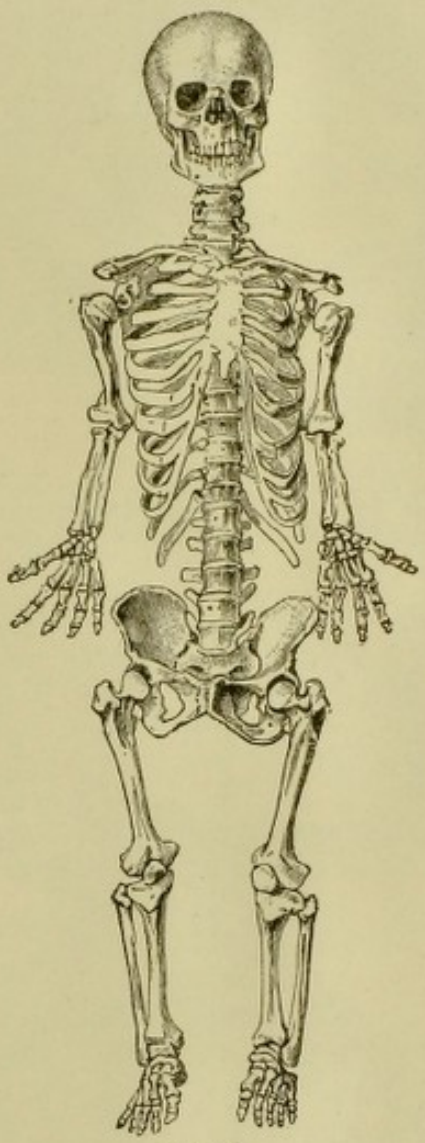


FIG. 40.

FIG. 39.—Skeleton of a female dwarf, thirty-one years of age, 118 cm. in height, an idiot, and possessing a klinocephalic skull. All the discs of cartilage at the diaphyses of the long bones and pelvic bones are still present; so also is the frontal suture. The individual parts of the skeleton are, in the main, correctly related to one another, the upper extremities alone being relatively somewhat short.

FIG. 40.—Skeleton of a female dwarf, fifty-eight years of age, 117 cm. in height, and with a long trunk and very short arm- and leg-bones. The discs of cartilage are still present; the articular ends of the bones are thick.

of the respiratory tract the alveoli of one portion of the lungs may fail to develop, as the result of which a whole lobe or a part of a lobe may be made up entirely of connective tissue and dilated bronchi (Fig. 46).

The above-mentioned examples of hypoplasia, to which many others might be added, are all due either to causes operating within the developing fœtal organism itself, in which case they may be said to be inherited, or to external deleterious influences working upon normal

tissues during their developmental period. Thus, as causes of maldevelopment of the bones we may mention disease of the thyroid gland (cf. § 23), insufficient nutrition (rachitis), disuse (Fig. 43), and inflammation. When portions of the body or single organs fail of all development, the condition is spoken of as **agenesia.** This depends upon an entire failure of development of the part in question from the very start, or

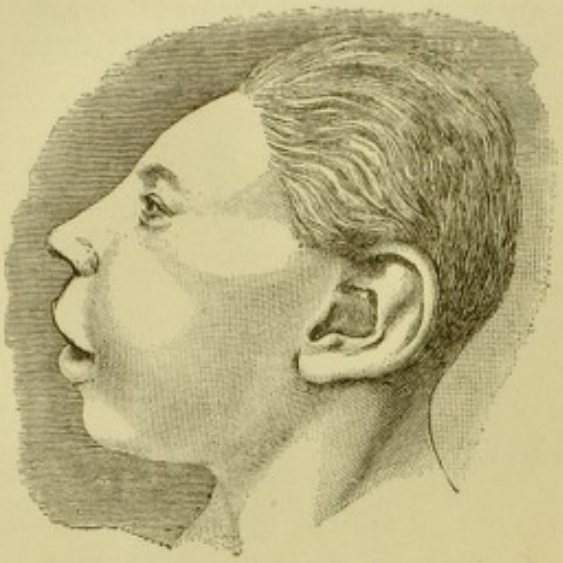


FIG. 41.—Head of Helene Becker (microcephalic), at the age of five years. (From a photograph taken by A. Ecker in 1868.)

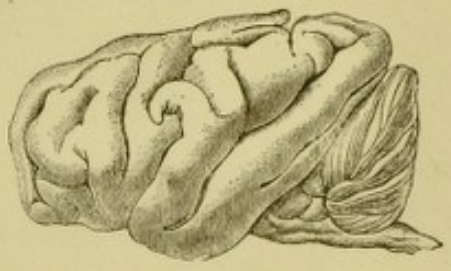


FIG. 42.—Brain of Helene Becker (microcephalic), who died at the age of eight years. (From von Bischoff.) This brain weighed 219 gm. (instead of 1,377 gm., as Vierordt claims that it should).

upon a total destruction of the part after it has begun to develop (cf. the chapter on Malformations).

The tissue composing hypoplastic organs or parts of organs is at

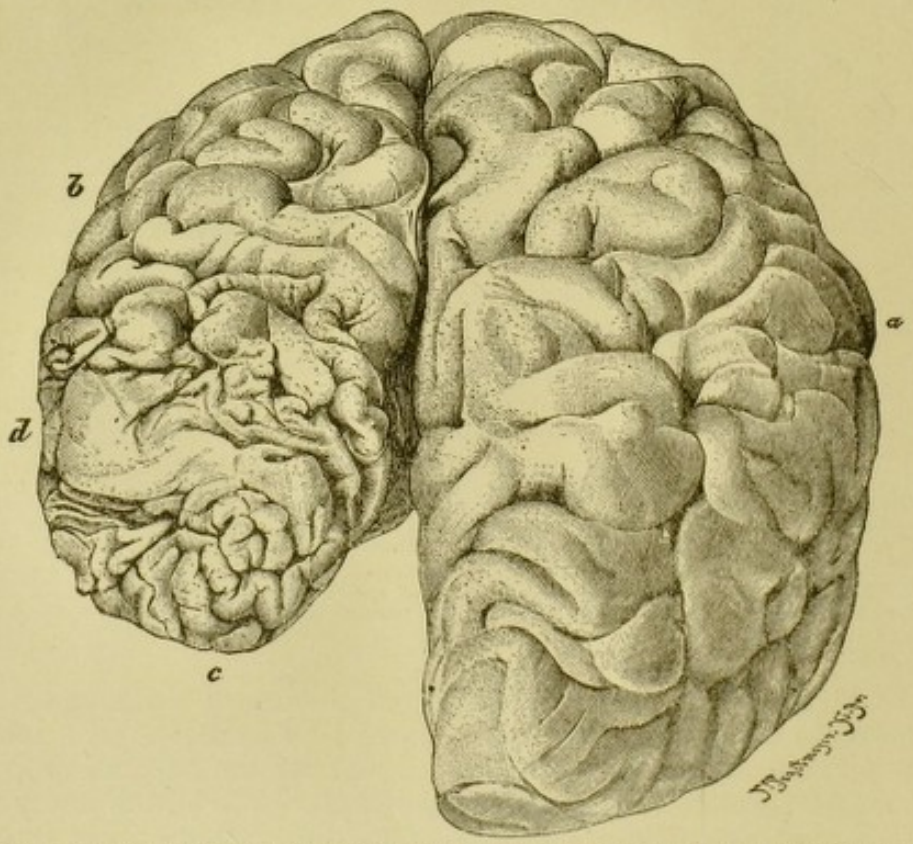


FIG. 43.—Hypoplasia and microgyria of the left cerebral hemisphere: case of a deaf-mute. *a*, Right hemisphere; *b*, left hemisphere; *c*, occipital lobe, diminished in size and in a state of microgyria; *d*, membranous cyst in the region of the parietal lobe. (Seen from above, after removal of the cerebellum. Two-thirds natural size.)

times normal in structure; but there is often associated with the abnormal smallness of the organ an **imperfect organization of its integral parts,** with failure of development of some of its more highly

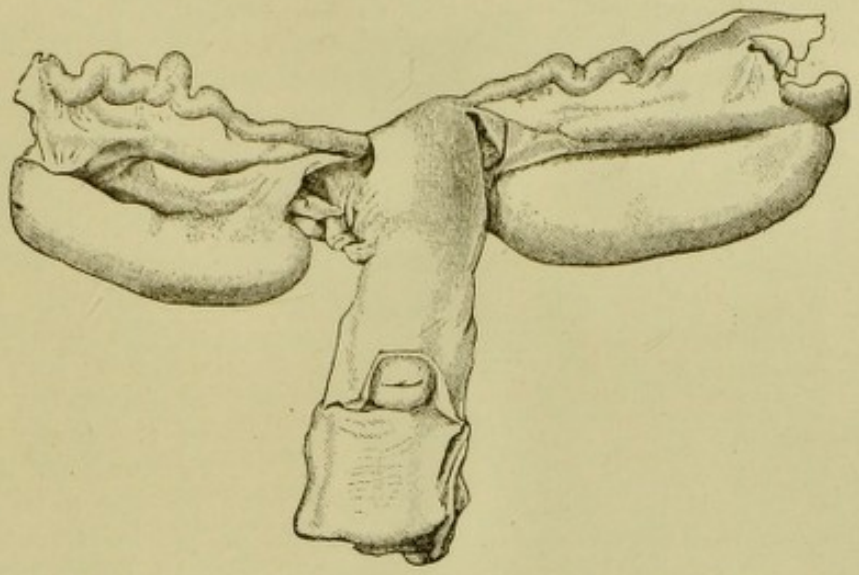


FIG. 44.—Hypoplasia of the uterus, with well-developed ovaries. (From an idiotic girl, eighteen years of age.)

specialized elements, so that associated with a hypoplasia of the entire organ there may be *agenesia* of some of its elements. Thus in hypoplasia of the ovary the formation of ova may fail in part; in hypoplasia of the brain there may at the same time be a faulty development of the ganglion-cells and nerve-fibres, and at times portions of the brain may be represented by merely membranous masses (Fig. 43, *d*), in which ganglion-cells are entirely absent; and in hypoplasia of the lung (Fig. 46) there may occasionally be complete failure of development of the alveoli, the lung-tissue then consisting chiefly of rather vascular connective tissue in which bronchi, usually dilated, lie.

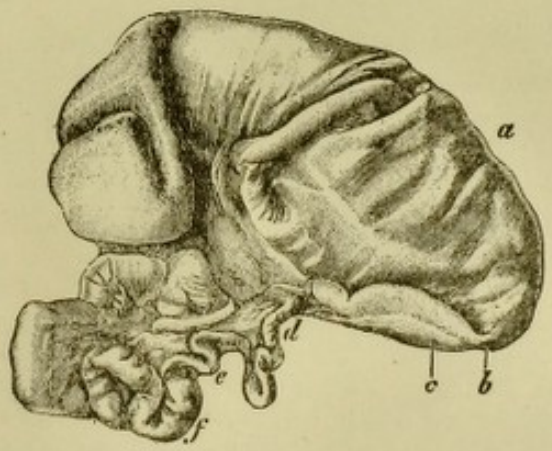


FIG. 45.—Hypoplasia of the small intestine of a newborn child. *a*, A much-dilated portion; *b*, *c*, *d*, *e*, portions that are much narrowed and wasted; *f*, normally developed small intestine. (Five-sevenths natural size.)

§ 55. **Atrophy** is diminution in size of an organ as the result of diminution in size and disappearance of its elements. It may occur at any period of life, and is, in fact, a very frequent result of many different pathological processes. Within certain limits it may be regarded as a *physiological process*, since in advanced age a retrograde change in all the organs is of constant occurrence and is always associated with more or less diminution in their size. A few of the organs suffer a similar change even before old age—as, for example, the thymus, which becomes completely atrophied even before the completion of the period of adolescence, and the ovary, a part only of whose ova are discharged during the period of sexual activity, the remainder undergoing atrophy.

In the atrophy of old age the lymphadenoid tissues, the muscles, and the bones suffer most as a rule, though there is much difference in this regard in different individuals, the brain or the glands of some of them undergoing the earliest and most rapid change.

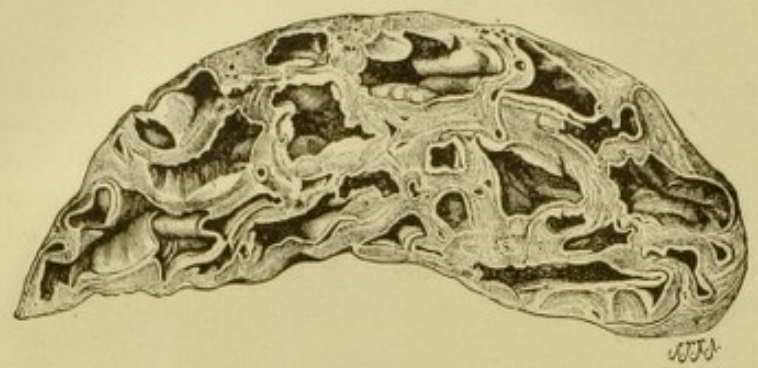


FIG. 46.—Agenesia of the respiratory parenchyma of the left lung. The lung consists of dense connective tissue in the midst of which dilated bronchi are found. (Horizontal section through the apex of the upper lobe. Natural size.)

The most striking evidence of atrophy of an organ is its diminution in size. When the muscles atrophy (Fig. 47) the affected portions of the body become smaller; and in cases of extensive atrophy of the muscles of the extremities the impression is given as if nothing intervened between the skin and the bones. When the atrophy of an organ goes on symmetrically in all its parts its normal shape may be preserved. But it often progresses more rapidly in one part than in another, in which case great asymmetry of the organ may result, there being often deep pits upon its surface (Fig. 49) and cicatricial contractions (Fig. 52), so that the affected organ—for example, liver or kidney—may present a knobbed or granular surface. In cases in which the tissues undergoing atrophy are in any way prevented from contracting, as is the case in bones and in the lung, the outward form of the organ is preserved. In the case of bone, however, the Haversian canals and the medullary cavity become enlarged, and a condition results which is designated *excentric atrophy* or *osteoporosis* (Fig. 48). In the lungs the alveoli become united into large air-spaces as the result of disappearance of the intervening alveolar walls.

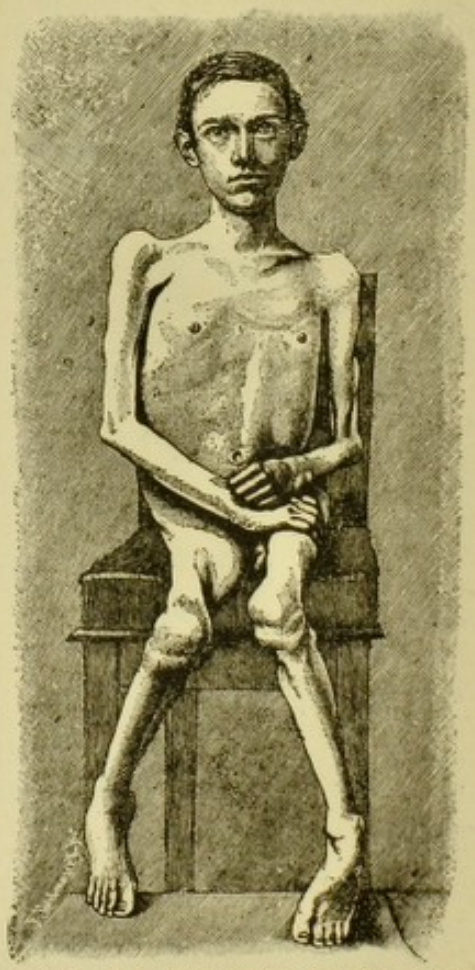


FIG. 47.—Juvenile muscular atrophy. (Case observed by de Souza.)

When atrophy affects glands and muscles there is often a change in their color, though this is of but secondary importance, depending either upon an *unusual distinctness of the pigment* of the affected organ because of the disappearance of parts ordinarily overshadowing it, or upon *the deposit of pigment in the atrophied tissue*, or, finally, upon a changed blood-content of the atrophied tissue.

The diminution in size of atrophic organs is the result of diminution in size and disappearance of the structural

elements of the tissues composing them. In the majority of the organs—more particularly glandular organs, muscle, and bone—the more highly specialized portions suffer, in undergoing atrophy, to a much greater extent than the connective-tissue framework which supports them. Indeed, it is not uncommon to find this latter tissue quite intact, or even increased in amount, in an organ from which all the more highly differentiated parenchyma has disappeared. Thus in atrophic muscle-tissue (Fig. 50) the contractile substance within the sarcolemma frequently disappears entirely without the occurrence of any noticeable atrophy in the connective tissue between the muscle-bundles, the nuclei of which may be actually increased in number (Fig. 50, c_1).

In atrophy of the kidney the epithelial cells of the urinary tubules (Fig. 51, *f*) become smaller and smaller, and ultimately disappear, the tubules then undergoing complete collapse. A similar change occurs in the epithelium of the glomeruli, the capillaries of which disappear.

The same thing occurs in simple atrophy of the liver, in which the entire parenchyma of a lobe may disappear without any considerable diminution in the amount of its connective-tissue stroma. Similarly the ganglion-cells of the brain and of the spinal cord may atrophy without any diminution in the neuroglia, which is often actually increased in amount.

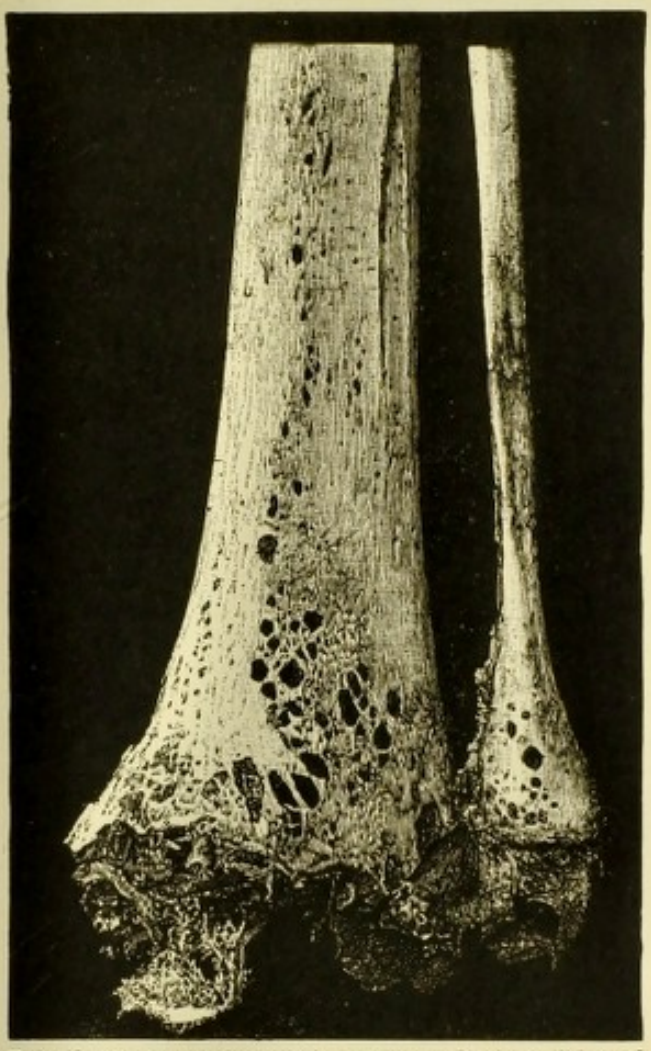


FIG. 48.—Excentric atrophy of the lower ends of the tibia and fibula, with osteoporosis. (Natural size.)

In atrophy of bone it is the true bone-tissue which becomes diminished in amount, and in excentric bone-atrophy and osteoporosis the marrow is materially increased. In some cases, however, the fat of the marrow may also disappear, leaving spaces which then become filled with liquid.

In atrophy of lymphatic tissue and of the spleen it is more particularly the free cells which undergo diminution and in parts completely disappear.

The change in an organ resulting in its atrophy may occur without any appreciable change in the structure of its component parts (Fig. 50), the atrophy being the result of a simple diminution in size of the various tissue-elements. This form of atrophy, called **simple atrophy,** is to be carefully distinguished from the **degenerative atrophies,** in which changes in the structure of the various tissue-elements occur from

the beginning and are frequently associated with deposits of pathological substances in them. Thus a cell may become granular and undergo fragmentation, or may swell up and liquefy, or droplets of fat or mucus may form in it, all of these changes being indicative of degenerative processes in the protoplasm of the cell. The special *varieties of degenerative changes* which occur in tissues will be treated of in the succeeding paragraphs of this chapter. Coincidently with changes in the protoplasm of the cell-body there may be similar degenerative changes in the nucleus, such as fragmentation, change of shape, irregular distribution of the chromatin, discharge of the chromatin into the cell-body, and swelling and disappearance of the nucleus, all of which ultimately lead to destruction of the nucleus, and secondarily of the cell itself.

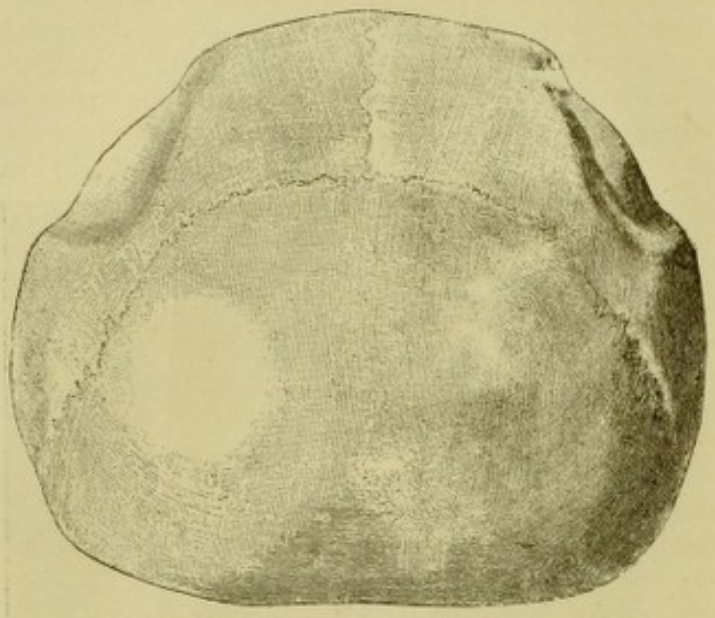


FIG. 49.—Senile atrophy of the calvarium, with defect of the external table and of the spongy portion throughout the central parts of the parietal bones.

Degenerations thus ultimately leading to atrophy of the affected organ are of very frequent occurrence, particularly in glandular organs. Frequently inflammation is also a complicating factor in the production of these conditions.

§ 56. The various **atrophies** may be separated according to their origin into **active** and **passive**. The cause of the first lies in the inabil-

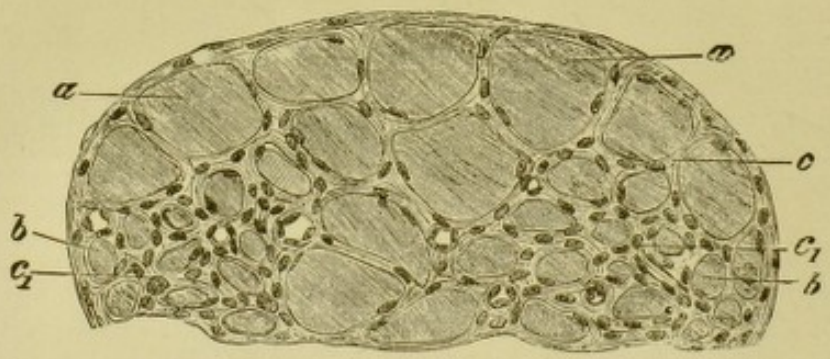


FIG. 50.—Section of an atrophied muscle, from a case of progressive muscular atrophy. (Müller's fluid; Bismarck brown.) *a*, *a*, Normal muscular fibres; *b*, atrophic muscular fibres; *c*, perimysium internum, the nuclei of which, at c_1, seem to be increased in number. Magnified 200 diameters.

ity of the cell to assimilate as it should the food which is brought to it. In the passive form insufficient food is brought to the cell, or such as is brought is of an improper kind, or harmful substances are contained in it which impair the nutritive function of the cell. Active atrophy is more particularly observed as a part of *senile degeneration*, but it occurs

also under pathological conditions, especially in nerves, glands, and muscles (Fig. 47) whose function is interfered with.

Clinicians are apt to prefer to the above another classification of the atrophies, distinguishing senile atrophy, atrophy dependent upon impaired nutrition, pressure atrophy, atrophy of disuse, and neuropathic atrophy.

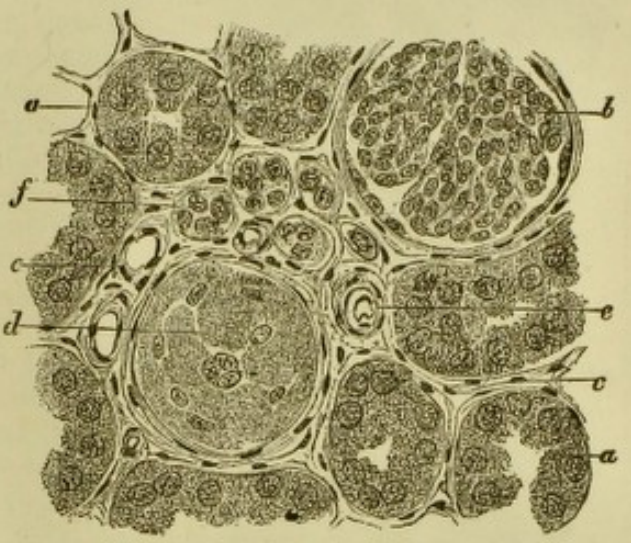


FIG. 51.—Senile atrophy of the kidney. (Alcohol; alum-carmine.) *a*, *a*, Normal uriniferous tubules; *b*, normal glomerulus; *c*, stroma, with blood-vessels; *d*, atrophic glomerulus; *e*, small artery, with somewhat thickened intima; *f*, atrophied and collapsed uriniferous tubules. Magnified 200 diameters.

Senile atrophy (Fig. 49) is partly active, partly passive, since it is not simply the result of gradually diminishing energy on the part of the cell, but depends also in part upon narrowing and obliteration of the vessels conveying nourishment to it. It may occur in all the organs, and is often more pronounced in one organ than in another. The bones, the kidneys, the liver, the brain, and the heart may all thus suffer a decided diminution in their volume.

The **atrophy dependent upon impaired nutrition** may result from an insufficient supply of food to the body as a whole or from extensive loss of the fluids of the body, and then affects the whole body, although even then the fat, the blood, the muscles, and the abdominal glands suffer most. *Local atrophies* may result from interference with the blood-supply of limited regions (Fig. 52), and are a frequent result of *diseases of the blood-vessels*. Furthermore, they are of frequent occurrence as a result of or as a part of *inflammatory processes*, though in this connection it should be stated that the disappearance of the tissue-elements is not, as a rule, the result of simple atrophy, but of a variety

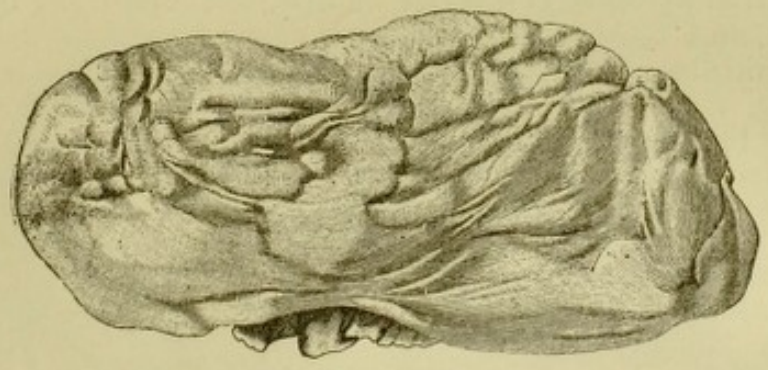


FIG. 52.—Arteriosclerotic atrophy of the kidney. (Natural size.)

of *degenerative changes* which lead to the destruction of the cells and of the tissues.

Occasionally atrophy of a tissue may result from the presence of deleterious substances in the blood. Thus iodine causes in time a diminution in size of the thyroid gland, and in chronic lead-poisoning the extensor muscles of the forearm are apt to undergo atrophy.

Pressure atrophy results from continued and moderate pressure upon a tissue (Fig. 53). It would appear to depend both upon direct injury to the tissue and upon interference with its circulation. Typical examples are: the atrophy of the liver which results from tight lacing and consequent pressure of the ribs upon the liver; and the disappearance of bone as the result of pressure of an aneurism (Fig. 53) or of an accumulation of liquid in the ventricles of the brain.

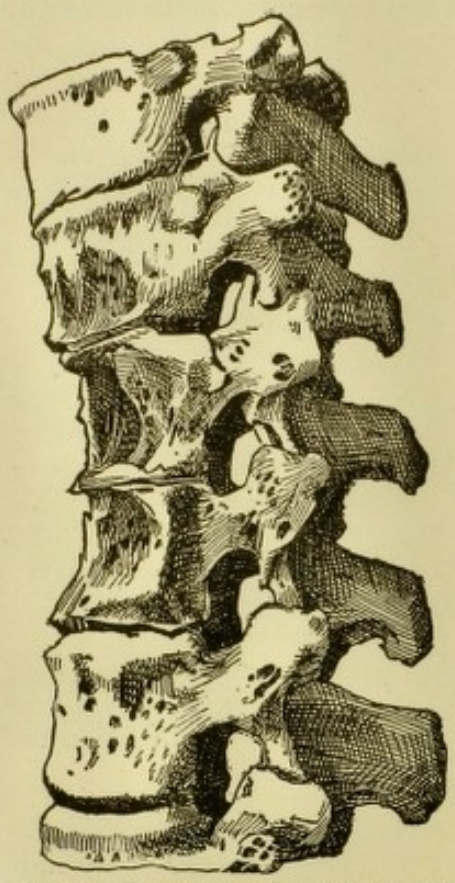


FIG. 53.—Pressure atrophy of the spinal column, caused by the encroachment of an aneurism of the aorta.

Disuse atrophy occurs in muscles and glands, as well as in bones, skin, and other tissues, and is due to non-use of the tissues in question. In the case of muscles and glands the atrophy is essentially active, but as the result of their functional inactivity there is at the same time a considerable diminution in their nutritive activity and in the activity of the circulation in them. In the other tissues the atrophy is chiefly due to a lowering of the nutrition of the unused parts, though it is impossible to quite eliminate from consideration a change in the power of assimilation of the cells. When the disuse is operative during the developmental period, and the tissue is on that account poorly nourished and undergoes but an imperfect development, the resulting condition is properly regarded as one of hypoplasia; and yet it is impossible sharply to separate this condition from one of atrophy, since in hypoplasia there may be also a disappearance of structures which had undergone a certain degree of development.

Neuropathic atrophy is a result of diseased conditions of the nervous system, and is apparent most often in a rapid atrophy of the nerves and muscles, though it may also affect any of the other tissues.

Thus disease of the anterior horns of the spinal cord or of the motor roots is followed by atrophy of the corresponding nerves and muscles. Injury of the peripheral nerves is commonly followed by atrophy of the skin. Numerous authors maintain that after the nerve-trunks of one side of the face have become diseased, a *neuropathic atrophy of the corresponding side of the face* (Fig. 54) may take place, and yet there are many other authorities (e.g., Möbius) who deny

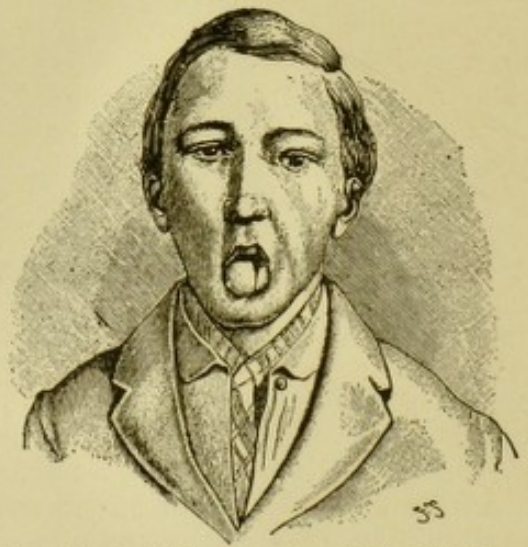


FIG. 54.—Facial hemiatrophy. (After Lichtheim and Borel.)

that this atrophy is of a neuropathic nature. Unilateral affections of the brain during fœtal life or during childhood may lead to atrophy of the opposite half of the body (*congenital and infantile hemiatrophy*).

In all these pathological alterations of neuropathic origin we very often have to deal not with true atrophies, but with various degenerative processes; and the term atrophy as applied to them is justifiable only to this extent, namely, that the ultimate result of the process is an atrophic condition of the affected parts. The causes of the degenerative processes are found in part in vaso-motor disturbances, in part in loss of function, and in part in severance of the affected tissues, the nerves, from their centres in the spinal cord or brain.

V. Cloudy Swelling and Hydropic Degeneration of Cells.

§ 57. The term **cloudy swelling**, or *parenchymatous degeneration*, or *granular degeneration*, was proposed by Virchow to indicate a condition of swelling and enlargement of cells resulting from absorption of various extraneous substances. He characterized it as a kind of hypertrophy with tendency to degeneration. At all events, the greatest weight is to be laid upon the degenerative character of the change. Histologically the process is characterized by the formation of fine granules within the bodies of the swollen cells—for example, in kidney epithelium, liver-cells (Fig. 55), or heart-muscle. Their microchemical reactions (solubility in acetic acid, insolubility in alkalies and ether) would indicate the albuminous nature of these granules. Their presence gives to the cell a cloudy, granular appearance, and at the same time, as the result of swelling, the normal structure and form of the cell are lost. Thus in cloudy swelling of the tubular epithelium of the kidney the rod-like markings of its protoplasm (Fig. 56, *a*) and the cell-processes extending into the lumen of the tubule disappear, the cell becomes larger (*b*, *c*, *d*), and dark granules make their appearance throughout its substance. This change is to be regarded as a *disorganization of the cell-protoplasm* following the absorption of liquid into its substance, and leading to a partial separation of its solid and liquid constituents. *The nucleus not infrequently participates in these changes, undergoing a similar disorganization.*

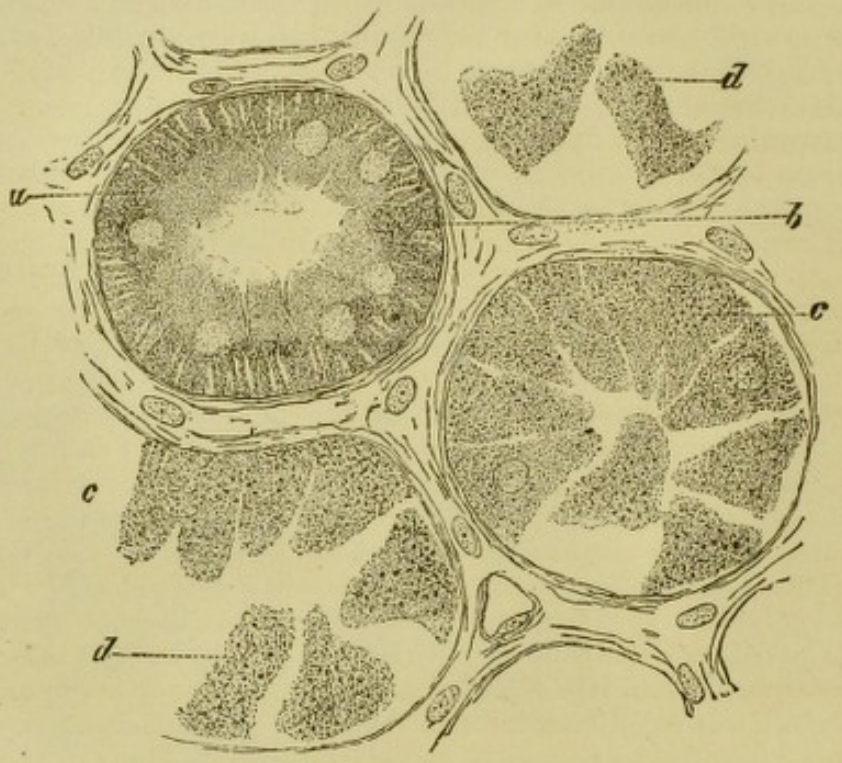
FIG. 55.—Cloudy swelling of liver-cells. (Scraped from the cut surface of the liver of a man who had died of septicæmia; examined in salt solution.) Magnified 350 diameters.

Recovery from a moderate degree of this degeneration is quite possible, in which case the cell is restored to its normal condition; but often there is a complete destruction of the cell, which then ultimately breaks up into finely granular fragments. Fatty degeneration is frequently associated with the degeneration under discussion.

Cloudy swelling occurs in the cells of nearly all the parenchymatous organs in the course of the majority of the infectious diseases, particularly in scarlatina, typhoid fever, variola, erysipelas, diphtheria, septicæmia, etc. Organs thus affected present a cloudy, less shining appearance than normal, and often appear gray. When the lesion is very marked the tissue has the appearance of having been boiled, its blood-content is generally very small, its consistence is doughy, and the finer details of its structure are lost.

§ 58. The term **hydropic degeneration** is very properly applied to a

change frequently observed, in cells of different kinds, whereby they become swollen as the result of imbibition of liquid. When epithelial



56.—Cloudy swelling of kidney epithelium. (Ammonium chromate; glycerin.) *a*, Normal epithelium; *b*, epithelium beginning to be cloudy; *c*, advanced degeneration; *d*, cast-off degenerated epithelial cells. Magnified 600 diameters.

cells undergo this degeneration the cell-contents appear clear, the protoplasm granules being pressed apart by the imbibed liquid, and often being present only as a granular ring at the periphery of the cell; the cells thus coming in a measure to resemble plant-cells (Fig. 57, *b*). Occasionally distinct vacuoles (*b*) are formed—i.e., globular drops of clear liquid in the cell-protoplasm. The nucleus (*c*) also becomes swollen, and may be indicated merely by a large globule with liquid contents. When muscle is the affected tissue, clear droplets of liquid appear between the fibrils, pressing them apart (Fig. 58; Fig. 59, *a*, *b*; and Fig. 66, *c*), so that, when the disease is extensive, the formation of the clear round spaces may give to the muscle a distinctly bubbly appearance (Fig. 58). For a time the muscle-fibrils between these drops may remain unchanged, but with a continuance of the process they degenerate and undergo *liquefaction*.

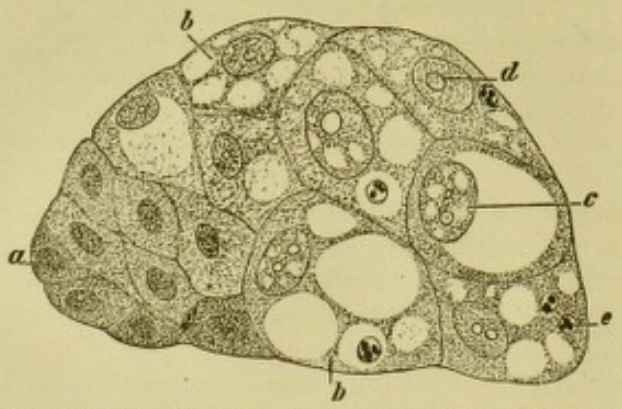


FIG. 57.—Hydropic degeneration of epithelial cells, from a carcinoma of the breast. (Müller's fluid; aniline brown.) *a*, Ordinary epithelial cell; *b*, hydropic cells, with bladder-like drops of fluid (physalides) in their interior; *c*, hydropic nuclei; *d*, enlarged nucleoli; *e*, wandering cells. Magnified 300 diameters.

Hydropic degeneration may be the result of œdema (Figs. 58 and

59), or it may occur in inflammatory conditions or in tumors (Fig. 57). When it results from inflammation its degenerative character is usually much more pronounced than when it occurs merely as an accompaniment of œdema, and it may then lead to complete disintegration of both the cells and the nuclei. In œdematous conditions the cells often remain alive for a very considerable time, notwithstanding their hydropic condition.

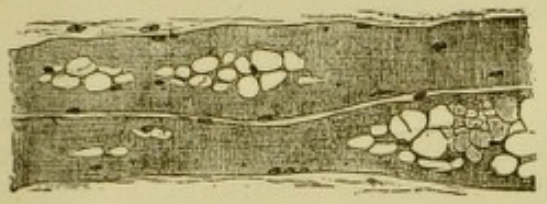


FIG. 58. — Hydropically degenerated muscular fibres, from the gastrocnemius of a patient suffering from chronic œdema of the legs. (Flemming's mixture; safranin.) Magnified 45 diameters.

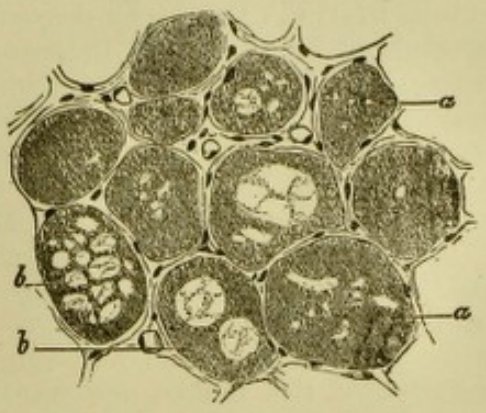


FIG. 59.—Transverse section of a bundle of muscular fibres in a state of hydropic degeneration. (Müller's fluid; hæmatoxylin.) *a*, Muscular fibres with small drops of fluid; *b*, fibres with large drops. Magnified 66 diameters.

VI. Lipomatosis, Atrophy of Adipose Tissue, and Fatty Degeneration of the Tissues.

§ 59. Certain of the tissues contain, under normal conditions, a considerable amount of fat, which is present in their cells in such amount as to be readily recognizable by the naked eye. This fat has its origin in the fat ingested with the food, or has been formed in the body from albumin and carbohydrates, and has then been deposited in the tissues in which it is found.

When the ingestion of fat or of fat-forming substances is abnormally great, or the body is unable to make proper use of the fat consumed or elaborated in it, a disturbance of the balance between fat-production and fat-consumption results, leading to an increase of the storing of fat in the body, and in time interfering with the performance of its functions, and thereby assuming pathological importance. This inordinate accumulation of fat leads to the condition termed **obesity**, or *adiposity*, or *lipomatosis*.

The tissues in which fat is normally present are the first to be affected in this process, and consequently the subcutaneous fat-tissue, the fat underlying the serous membranes, the marrow of the bones, and the liver suffer first (Fig. 60, *b*). Subsequently fat appears in tissues of which it is not a normal constituent, as, for example, in the connective tissue between the muscle-fibres of the heart, in the endocardium of the ventricles and auricles, in the intermuscular connective tissue of the skeletal muscles (Fig. 61), etc.

In connective-tissue cells and in the hepatic cells the fat is deposited in the form of small drops (Fig. 62, *a*, *b*), which soon coalesce to form larger drops, ultimately replacing the entire cell-body and converting it into a spheroidal mass of fat.

The causes of the **pathological deposition of fat** (*lipomatosis*) are to be found in a congenital predisposition on the part of the tissues, and

in certain disorders of the vital processes. *That variety of lipomatosis which is due to the existence of a congenital predisposition* manifests itself in two forms, viz., as a general obesity and as one that is confined to certain limited areas. In *general obesity* the adipose tissue everywhere throughout the body is increased in volume. In the *limited form of obesity*,—the tumor-like accumulations of fat are here left out of the consideration,—the excessive development of fat is most often confined to the muscles of the lower extremities (Fig. 61). These muscles increase in volume, but at the same time they lose a part of their fibres (atrophia musculorum lipomatosa pseudohypertrophica).

Among the *disordered vital processes which lead to a pathological accumulation of fat* must be mentioned: first, *a luxurious mode of living;* second, *overtaxing of one's physical strength;* and third, *marasmus*, such as is observed especially in connection with chronic tuberculosis. In the first of the conditions named the fat will be distributed generally throughout the body; whereas in the last the accumulation of fat is generally restricted to the liver (Fig. 60), where it lends to the tissues—at least those in which the fat is deposited—a light yellowish-brown or a straw-yellow color. The cause of the fat-accumulation in the first-named condition is the excess of nutritive material taken into the system, whereas in the last-named it is the inability of the organism to decompose, in sufficient quantity, the fat received into the body or already stored there.

If, through a diminution in the amount of nourishment taken into the body, or through a deficient formation of fat in the body, or, finally, through an increased activity in the metabolic processes, the quantity of fat which belongs normally to the body is lost, then an **atrophy of the fat tissue** will be established. In this condition, while the processes of absorption and decomposition of the fat are going on, that

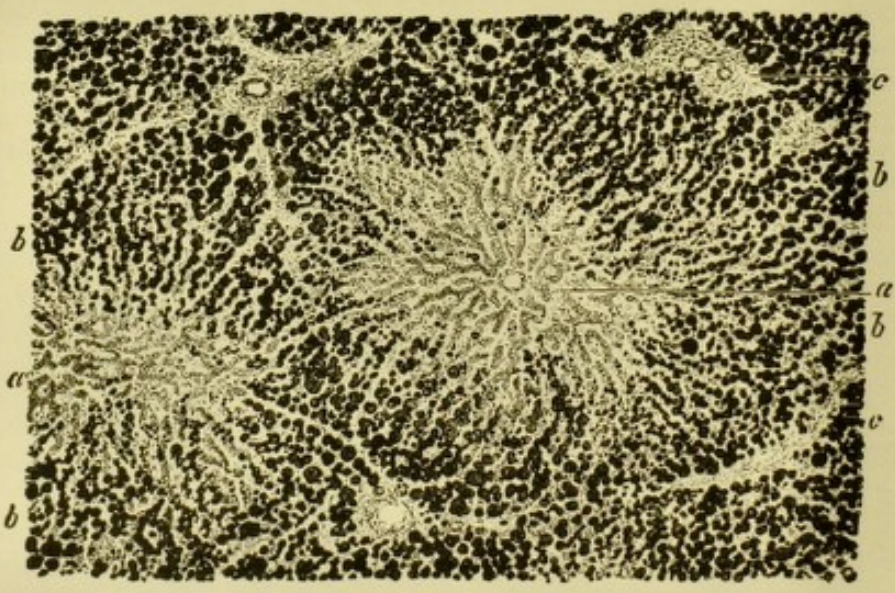


FIG. 60.—Fatty liver from a man who died of pulmonary tuberculosis. (Flemming's preparation; safranin.) *a*, Central portion of a lobule; *b*, peripheral zone, characterized by the presence of fat; *c*, periportal connective tissue. Magnified 30 diameters.

which remains in the cells again breaks up into small globules, and the connective-tissue cells are again converted into small connective-tissue cells. If, after the fat has largely disappeared from the spaces between

the shrinking fat-cells, a serous fluid finds its way into the tissues, the fat-tissue—as can be seen with special frequency in the panniculus adiposus of the heart—assumes a translucent appearance, not unlike that

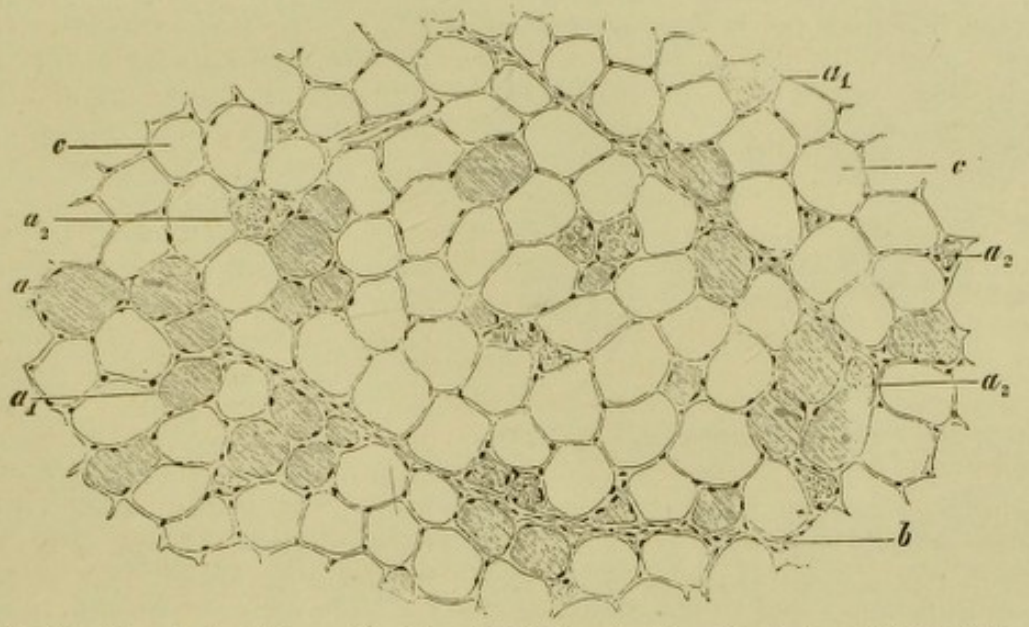


FIG. 61.—Lipomatosis of the muscles of the calf of the leg, together with atrophy. (Müller's fluid; carmine.) Transverse sections of a normal (a) and an atrophied (a_1) muscular fibre; a_2, transverse section of a tubular sarcolemma containing contractile substance in a condition of disintegration; b, bands of connective tissue; c, fat-tissue. Magnified 60 diameters.

of mucous tissue. Hence the name, which is often applied to this condition, of *serous atrophy of fat-tissue*. If, while these fat-cells are undergoing atrophy, pigment is deposited in them, the tissue in which they lie will assume a yellowish or yellowish-brown color,—a condition to which the term *pigment-atrophy of fat-tissue* has been applied.

According to Voit, the body may store up fat directly from the fat contained in the ingested food, or it may elaborate it from absorbed fatty acids by a process of synthesis with glycerin, or from albumin and carbohydrates. The important factor in the metabolism of nutrition is not the oxygen of the blood, but the cell itself, whose protoplasm possesses the power to convert complex chemical compounds into simpler ones. The substances most readily lending themselves to this change are the albumin brought to the cell in soluble form and the carbohydrates. Fat is, on the other hand, resistant, both that directly absorbed from the food and that formed in the body. Now, when fat is supplied to the cell in excess, or when the metabolic potential of the cell is lowered so that it is unable to further decomposé the fat which it elaborates from the albumin brought to it, fat of necessity remains in its protoplasm. When these two influences act in combination, the effect is of course greater. Improved nutritive conditions, exercise, and elevation of the body-temperature increase the metabolic activity of the cells, while it is diminished by alcohol, morphine, and quinine. Obesity depends on assimilation of food in excess of the ability of the body to make use of it. In its production the metabolic power of the cells of the body as a whole may be normal, or it may be diminished as the result of weakness or diminution in number of the cells. The accumulation of fat which is often noticed in anæmia is explained on the ground of diminution in the cell-mass of the body, resulting in diminished metabolic power. The deposit of fat in the intermuscular connective tissue of atrophied muscles would appear to be a direct result of the diminished metabolic changes in the paralyzed muscle-tissue.

According to Gautier the metabolism of proteids in the cell occurs in two stages. In the first, the stage of ferment-action without oxidation, or of hydrolytic separation, uric acid or analogous substances (urates and creatin derivates) are formed from the protoplasm, the carbohydrates at the same time being converted into fats. In the second stage, that of oxidation, the sugars and fats disappear, both those originally derived from the food and those resulting from the metabolism of proteids. The carbohydrates are in part oxidized, but the greater part of them, particularly during muscular inac-

tivity, are converted into fat by a simple fermentative process in the course of which a large amount of carbonic acid is liberated. Ultimately the fats also undergo oxidation and disappear.

§ 60. The term **fatty degeneration** is applied to a form of cell-degeneration in which fat is formed from the albumin of the cell-body—that is, from organic albumin; the fat thus formed manifesting itself in the shape of granules and drops of different sizes within the cell-body.

FIG. 62.

FIG. 63.

FIG. 62.—Fat-containing liver-cells. *a*, *b*, Fat-infiltration; *c*, *d*, *e*, *f*, fatty degeneration. Magnified 400 diameters.

FIG. 63.—Fatty degeneration of the muscular tissue of the heart. Magnified 350 diameters.

Cells which are in the condition of fatty degeneration always contain easily recognizable *drops of irregular size*, colorless, highly refracting (Fig. 62, *c*, *d*, *e*, *f*, and Fig. 63), insoluble in acetic acid, soluble in alcohol and in ether. Perosmic acid stains these droplets black (Fig. 64, *b*, and Fig. 65, A, B, C); this coloration being due to the fact that the fat reduces the osmium tetraoxide to a black osmium hydrate. Their number and size vary greatly, though the largest rarely attain great size. Thus heart-muscle in a condition of fatty degeneration (Fig. 63; Fig. 64, *b*; and Fig. 66, *b*) shows minute fat-droplets scattered through its substance, varying in number with the intensity of the process, but which seldom become conglomerated together to form large drops.

A similar appearance is presented by liver-cells (Fig. 62, *c*, *d*) and by the tubular epithelium of the kidney (Fig. 65, A, B) when undergoing fatty degeneration, though it should be said that here the fat-droplets are frequently of greater irregularity in size, and when the process is far advanced in these organs many of the cells may become broken up into a *fatty detritus* composed of fine granules and minute fat-droplets (Fig. 62, *f*).

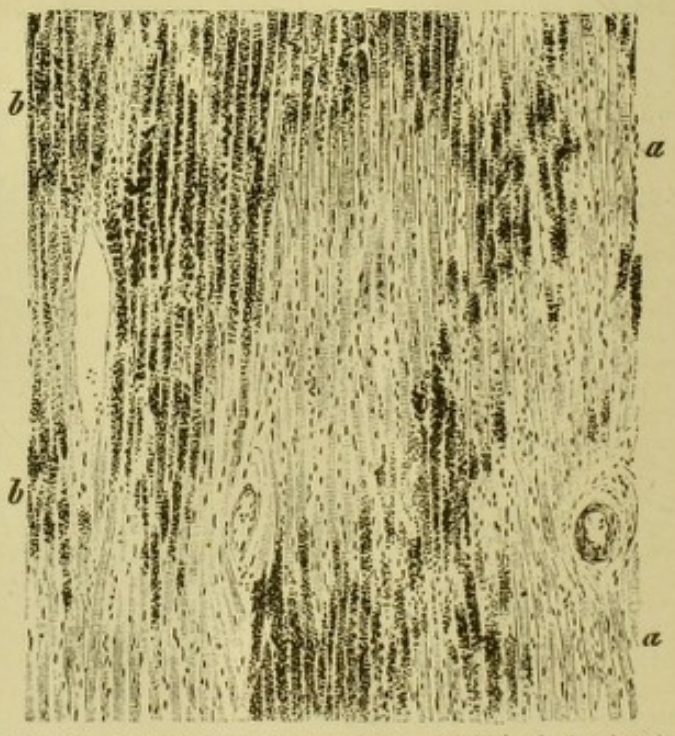


FIG. 64.—Marked fatty degeneration (chronic) of the heart. (Flemming's mixture; safranin.) *a*, Healthy muscular tissue; *b*, places where the muscle has undergone fatty degeneration. Magnified 80 diameters.

Fatty degeneration affects connective-tissue cells (Fig. 65, B, C, *d*) and muscles, as well as epithelium. When many cells closely associated are affected, the condition is usually readily recognizable with the

naked eye; the more readily, of course, the more intense the process, the less striking the color of the tissue involved, and the smaller its blood-content. Colorless, transparent tissues, like the intima of the heart and of the vessels, assume an opaque, whitish appearance; the cortical substance of the kidney becomes grayish, and when the process is intense, even yellowish-white and opaque; the heart-muscle presents a yellowish and sometimes also a spotted appearance (this latter condition being due to the existence of localized areas of fatty degeneration [Fig. 64]), and even the skeletal muscles may come to have a pale yellowish-brown color.

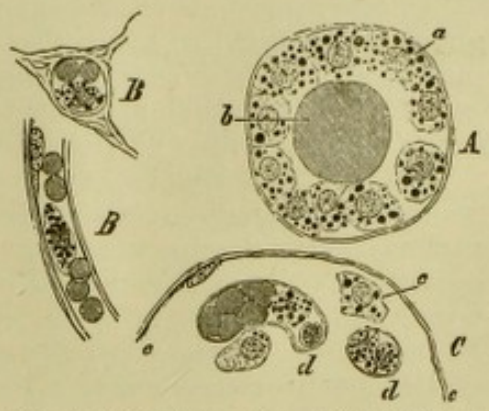


FIG. 65.—Fatty degeneration of the renal epithelial cells, the capillary endothelia, and the leucocytes, in diphtheria. (Flemming's mixture; safranin.) *A*, Uriniferous tubule, lined with epithelium (*a*) in a state of fatty degeneration, and containing a hyaline cast (*b*), both shown in transverse section; *B*, intertubular capillaries; *C*, border of a glomerulus containing fatty epithelial cells (*c*) and capillaries (*d*) in the interior of which are fatty cells; *e*, Bowman's capsule. Magnified 300 diameters.

The cells contained in liquids—as, for example, those in pus—frequently undergo extensive fatty degeneration, ending usually in the disintegration of the cell. The same is true of the cells of coagulated exudates.

Fatty degeneration would appear to depend in part upon a change both in the supply and in the composition of the blood, consequently in the nutritive substance brought to the cells,—and in part upon *a lowered vitality of the cells themselves.* An important part in its production is undoubtedly played by *persistent diminution in the supply of oxygen* to the cells, as a result of which an increase takes place in the breaking down of albumin; and this latter change in turn is accompanied by the production of fat and by the excretion, by way of the urine, of the nitrogenous products of the breaking-down process. Accordingly, fatty degeneration may be observed in a variety of diseases, as, for example, in acute anæmia following any considerable loss of blood (fatty degeneration of heart and optic nerve); in chronic anæmia and leukæmia (organs affected: heart, liver, intima of the blood-vessels); in narrowing and occlusion of arteries (part affected: the area supplied by the narrowed vessel); in persistent venous congestions; in various poisonings, as by camphor, arsenic, chloroform, and certain vegetable fungi (parts affected: heart, liver, kidneys, and blood-vessels—especially the capillaries); in several

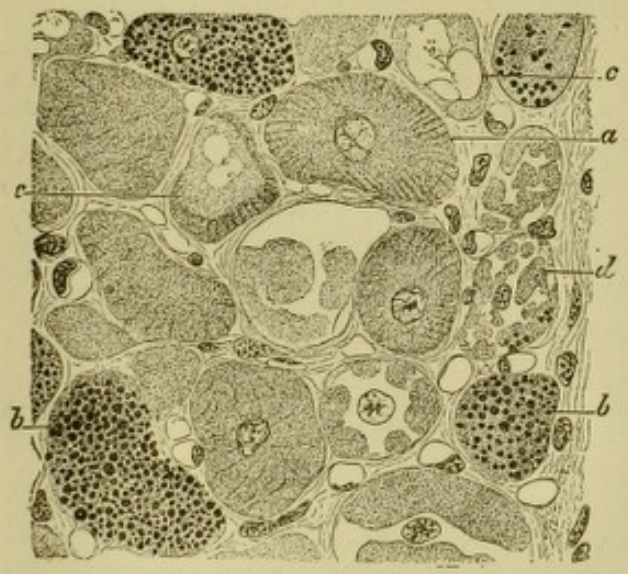


FIG. 66.—Fatty degeneration, the formation of vacuoles, and the disorganization of the muscular tissue of the heart, in a patient who died from pneumonia and nephritis. (Flemming's mixture; safranin.) *a*, Transverse section of a normal muscle cell; *b*, muscle cell in a state of fatty degeneration; *c*, muscle cell containing vacuoles; *d*, disorganized cell. Magnified 400 diameters.

of the infectious diseases, such as diphtheria (kidneys, leucocytes, and heart), pneumonia (kidneys, heart [Fig. 66, *b*]); and in chronic ulcerous pulmonary tuberculosis (kidneys).

In the infectious diseases the fatty degeneration which takes place in glandular organs, in leucocytes, and in the heart, may be attributed primarily to the effect of the poisons of these diseases. It must be remembered, however, that an elevated body-temperature, if continued for a long time, may also produce fatty degeneration of the organs.

Cells which become detached from their natural positions and are transferred to some new situation among the tissues, are also very apt to undergo fatty degeneration; and the same is true in regard to cast-off epithelial cells and connective-tissue cells, and in regard to leucocytes which, in the course of an inflammation, have left the blood-vessels. Furthermore, a large part of the cells which are produced in the course of the proliferative activity incident to inflammatory and regenerative processes, and of those which are developed in tumors, die after passing through the stage of fatty degeneration; and the chief reason why this happens is, that the nutrition which they receive is insufficient.

This fatty degeneration of the cells is usually the only histological change which we are able to demonstrate. Nevertheless, fatty degeneration may be combined with other degenerative alterations. *The most frequent combination is that of cloudy swelling and granular degeneration with fatty degeneration;* and we may also encounter *fatty degeneration in combination with hydropic degeneration and the formation of vacuoles* (Fig. 66, *c*). Both of these combinations are observed in cases of poisoning and in inflammations of the tissues. As a general rule, fatty degeneration of the cells is associated with a variety of degenerations of the ground substance or framework (e.g., with amyloid degeneration of the connective tissue [compare § 66, Fig. 81]).

The question whether the fat which is found in the cells of an organ is the product of a degenerative process or merely represents an accumulation, is one which is easily determined in most cases. It is only in a few instances that the problem is a difficult one to solve. It is generally assumed that in degenerative atrophy the fat occurs in the form of small drops, which show no disposition to run together, whereas in a simple accumulation of fat the tendency is to form large drops. This assumption is true as regards the majority of tissues, but not as regards all of them. It applies, for example, to transversely striated muscles, to those of the heart, to non-striated muscles, to glia cells, etc. On the other hand, drops of fairly large size are found in fatty degeneration of the renal epithelium, and when the liver is the seat of this pathological change, both small and large drops will be found (e.g., in phosphorus poisoning and in acute yellow atrophy of the liver).

In addition to these facts it must not be forgotten that, even in simple accumulation of fat, this material is deposited first in the form of very small drops, and that at a later period, when the accumulated fat begins to be absorbed, the large drops break up into small globules.

If from a mere histological examination we are unable to make a correct diagnosis, the locality in which the fat is found ought, as a rule, to throw some light upon the question. Thus, for example, if fat drops are found in cells which normally contain no fat, and if the circumstances are such that we can exclude an increased supply of this material, it may safely be concluded that it comes from cell-albumin, or, in other words, that the cells of the part are undergoing disintegration. It is only when we are dealing with tissues which, on the one hand, normally serve as places of deposit for fat, and, on the other, are prone to undergo fatty degeneration (the tissues of the liver, for example), that any serious difficulty is experienced. It is often hard to determine, in the case of the organ mentioned, just how much of the fat observed has originated at the spot, and how much of it has been brought there as a mere deposit. The difficulties are still further enhanced by the fact that fat which has been produced by a process of degeneration may be transported and lodged in certain spots as distinct deposits or in the form of an infiltration.

It is not an exceptional thing to find, in a disintegrating tissue, and particularly in disintegrating brain or spinal-cord tissue, cells which are entirely filled with fat globules and at the same time are more or less enlarged. Owing to the appearance which these cells present, they have been designated as **fat-granule cells** (Fig. 67, *a*) or *fat-granule globules*. Many authorities have considered these large fat-granule globules to be tissue cells which have undergone fatty degeneration—or, in the case of the brain, to be ganglion cells and glia cells which have undergone fatty degeneration. This, however, is not the correct view. The genuine fat-granule globules or cells are not the permanent tissue-cells which have undergone fatty degeneration, but rather amœboid leucocytes and the offspring of proliferating permanent tissue-cells, which have, in their phagocytic activity, taken up into themselves either the fatty products of the disintegration of a tissue (the spinal cord, more particularly) or else fat in a dissolved state (which afterward, within the leucocyte or newly produced cell, reassumed the form of drops).

A cell which presents appearances of fatty degeneration in its protoplasm should, as a rule, be considered in the light of a cell which has to a certain extent begun to degenerate; and, as a matter of fact, this degeneration very often terminates in the destruction of the cells which are thus affected. And yet, on the other hand, one may often note the fact that *cells which possess a protoplasm that is in a fatty state, display karyokinetic figures*—an evidence, therefore, that in these cells formative vital processes are still at work. In other words, these cells, so long as their nuclei remain intact, may be restored again to an integral condition.

According to the investigations of Starke, osmium tetraoxide is reduced only by olein or by oleic acid, whereas palmitin and stearin are not capable of directly producing this reduction; they simply bind or fix the osmic acid. However, a reduction of the osmium tetraoxide which is thus bound to the palmitin and stearin fats, will take place when the material is transferred to alcohol.

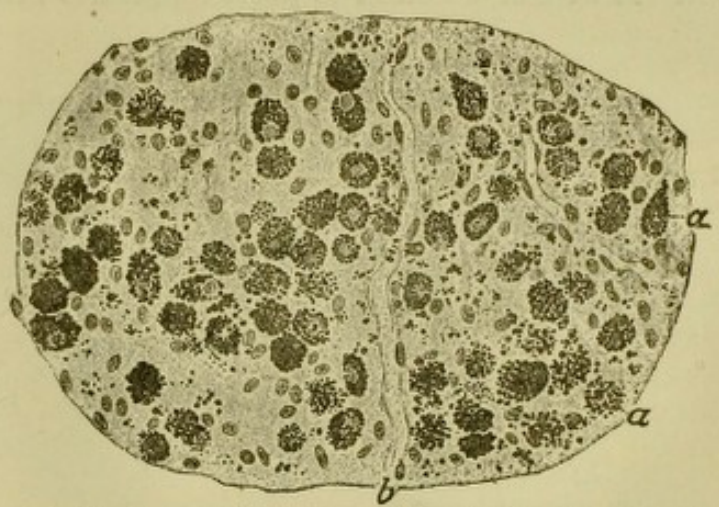


FIG. 67.—Fat-granule cells from an ischæmic centre of softening in the brain. (Marchi's fluid.) *a*, Fat-granule cells; *b*, blood-vessel. Magnified 280 diameters.

§ 61. The **fats** which occur in the human body are mixtures of *olein*, *palmitin*, and *stearin*. The first of these is liquid at the ordinary temperature, the second melts at 46° C., stearin at 53° C. Since the fatty portions of various regions of the body contain these fats in different proportions, there is considerable variety as regards their firmness and melting-point. As fat is insoluble in water and aqueous liquids, that contained in the cells of the body or lying free among the tissues is not dissolved by their juices. At most, only traces of it can be dissolved in the blood, lymph, chyle, and bile, which contain small quantities of soaps. When the body is cooled after death to a point below the melting-point of the contained fats, the palmitin and stearin separate in the form of fine star-shaped or feathery needles (Fig. 68, *b*, *c*, *d*), which are commonly called **margarin crystals**, and which are often found both in fat-cells and free in the tissue-liquids.

Cholesterin in the form of thin rhombic plates, often with irregular corners and edges (Fig. 68, *a*), is frequently deposited in areas of fat-containing detritus which may have originated from extravasated blood or from degenerated masses of cells. This may occur, for example, in the tunica vaginalis testis, in a dilated sebaceous duct or gland, or in a softened area of the intima of a diseased aorta. When the substance in

which these cholesterin plates form is liquid, they may often be visible to the naked eye as little glistening scales.

Cholesterin is a constant ingredient of the bile, which is furnished by the mucous membrane of the gall-bladder and gall-ducts, and in which the cholesterin is held in solution by the bile salts and soaps. It occurs also in the medullary sheath of nerve-fibres, and in small amount in the blood, where it is similarly held in solution by the fats and soaps. Burchard believes it to be present in small amount in all the organs.

Water, dilute acids, caustic alkalies, and cold alcohol fail to dissolve cholesterin, which is, however, soluble in boiling alcohol, ether, chloroform, and benzol.

When treated with a mixture of 5 parts concentrated sulphuric acid and 1 part water, cholesterin crystals assume a deep carmine-red color, beginning at their borders, and this color then slowly changes into violet. A weaker solution (3 parts sulphuric acid, 1 part water) causes a

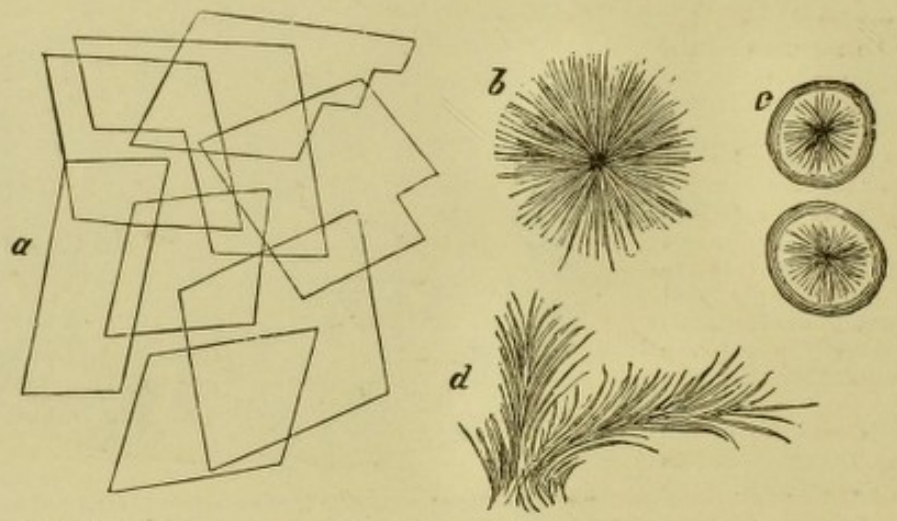


FIG. 68.—*a*, Cholesterin plates; *b*, a free cluster of margarin needles; *c*, needles inclosed in fat-cells; *d*, grass-like bundle of margarin needles. Magnified 300 diameters.

violet coloration of the edges of the crystals. Sulphuric acid containing a trace of iodine colors the crystals violet, blue, green, and red.

The source of cholesterin is not clearly understood. It is, however, in all probability an intermediate product in the metabolism of proteids. Accordingly it is encountered, under pathological conditions, in tissues and exudates which are in process of fatty degeneration.

VII. The Formation and Deposit of Glycogen in the Tissues.

§ 62. **Glycogen** is a carbohydrate, readily convertible into sugar, which is obtained chiefly from the carbohydrates of the food, but which may also be formed from albumin and from gelatin.

Glycogen is found in the tissues as a *hyaline substance*, which is more often situated in the cell-bodies than elsewhere, but may also at times lie in the intercellular spaces of the tissue. It is generally found in the form of spherules of different sizes, and in the cells these spherules usually lie rather near the nucleus.

Although glycogen is soluble in water, there would appear to be, according to Langhans, some difference in the degree of its solubility

when obtained from different tissues; that contained in the liver, kidney, muscles, pus-corpuscles, etc., being distinctly more easily soluble than that from cartilage-cells and pavement epithelium. Hardening of tissues in alcohol makes the contained glycogen distinctly less soluble. The glycogen contained in the liver at the time of death is quickly converted into sugar by the diastatic ferment of the liver.

Iodine causes glycogen to assume a brownish-red color. To avoid the solution in water of the glycogen contained in fresh preparations, it is advisable to immerse the portions of tissue for examination in a syrupy mixture of gum and iodine (Ehrlich), or in glycerin to which a little iodine has been added (Barfurth). Sections of tissues which have been hardened in alcohol may be best studied after treatment with a dilute iodine tincture (1 part tincture of iodine, 4 parts absolute alcohol) and clearing in oil of origanum. The reaction after such treatment is of considerable duration.

Glycogen occurs normally in the liver, in the muscles (including the heart-muscle), in the leucocytes, in the blood-serum (Gabritschewski), in cartilage-cells, and in almost all embryonic tissues, as well as in the fœtal membranes of young embryos. During starvation the glycogen of the liver undergoes diminution, and under pathological conditions it may disappear entirely.

In diabetes there is a deposit of glycogen in the epithelium of the kidney, particularly in that lining Henle's loops, in the isthmus of which the cells are commonly almost filled with it, leaving, after solution in water, clear spaces in the cell-bodies. In the blood of diabetic patients both the intracellular and the extracellular glycogen is increased.

In fresh inflammatory exudates glycogen may be present in the pus-cells. The leucocytes of the blood contain glycogen in excess, more particularly in conditions of cachexia. Glycogen has also been observed in tumors of various kinds, as, for example, in the epithelial cells of condylomata, in carcinomata and adenomata of the testicle, in endotheliomata, in myxosarcomata, enchondromata, and sarcomata of bone, and more rarely, also, in these same varieties of tumors when they are located in other tissues. It is almost never found in tumors of the breast (Langhans), and it is very unusual to meet with it in carcinomata of the stomach or intestine, and in tumors of the ovary, of the kidney, and of lymph-nodes. It is also absent from fibromata, lipomata, myxomata, osteomata, angiomata, and leiomyomata, and from the tissue of the infectious granulomata.

According to Langhans, glycogen is met with in the epithelium of the body and portio vaginalis of the uterus, but is absent from the tubes and is very scanty in the cervix. It is also present in the epithelium of the vagina and in those tumors of the portio vaginalis and of the vagina which contain stratified epithelium. Carcinomata of the uterus rarely contain more than minute traces of glycogen.

VIII. Mucous Degeneration.

§ 63. **Mucous degeneration** has its physiological prototype in the production of mucus by the mucous membranes and mucous glands, and in the formation of mucus in the connective tissue of the umbilical cord, of tendons, of bursæ, and of synovial membranes. In the umbilical cord the mucus occurs as a jelly-like matrix; in the joints, bursæ, and tendon-sheaths it forms a stringy, clear liquid.

The formation of mucus in mucous membranes takes place in *epithelial cells*, called beaker- or goblet-cells (Fig. 69, *a*), whose cell-bodies are in great part occupied by clear substance, which may be stained with hæmatoxylin. In mucus-formation in mucous glands the epithelial cells swell, their centres become transparent, and the protoplasm granules become reduced to small groups or strings. The so-called mucus-corpuscles of the salivary secretion, characterized by glassy transparent contents in which vibrating protoplasm granules are often present, are spheroidal cells which have undergone mucous degeneration.

The mucus thus formed from the protoplasm of the cells may be discharged, and the cell may either retain its integrity or it may be completely destroyed.

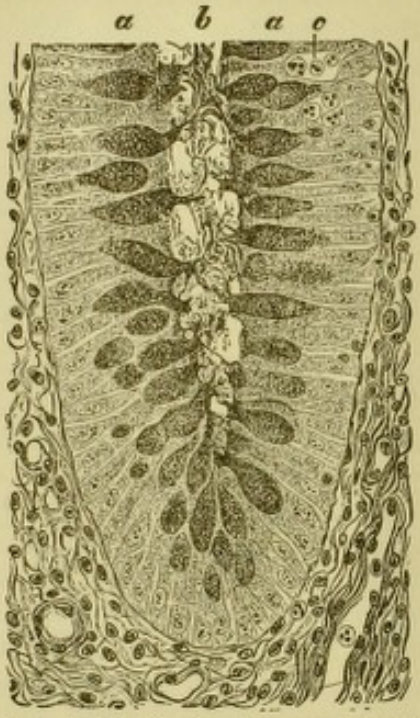


FIG. 69.—Production of mucus inside the epithelial cells of an adenomatous polypus of the small intestine. (Alcohol; hæmatoxylin.) *a*, Epithelium with dark-bordered (hæmatoxylin) drops of mucus within the cells; *b*, free mucus; *c*, leucocytes in the epithelium. Magnified 300 diameters.

The formation of mucus occurs under pathological conditions (Fig. 69, *a*) in the same manner as normally. In catarrh of the mucous membranes the stringy excretion which forms is chiefly the result of excessive mucus-production by the cells of the mucous membrane and of its glands. Pus-corpuscles may also undergo mucous degeneration, in the course of which mucin would appear to be formed from the nuclein of their nuclei (Kossel). In mucous membranes containing cylindrical epithelium the number of beaker-cells is greatly increased as the result of catarrhal inflammation, and the exudate often contains cells which have undergone complete mucous degeneration, and which appear as glassy masses often containing a few fine granules. Again, the cells may contain mucus in the shape of irregular drops of various sizes.

Just as in normal tissues, so also in pathological, the epithelial cells may undergo mucous degeneration. Thus the epithelial lining of cysts of the ovary and of tumors of the intestine may often contain many beaker-cells (Fig. 70, *a*) and cells in which the entire cell-bodies have changed into mucus (*b*). In the so-called gelatinous carcinomata a large part of the epithelial cells undergo a mucous metamorphosis.

A number of the *connective-tissue group of tissues* may also undergo a form of mucous degeneration, and in consequence acquire a gelatinous, transparent appearance. Besides connective tissue itself, cartilage, bone, fat, bone-marrow, and the tissue of sarcomata may be mentioned as belonging to this class. It is here more particularly the intercellular matrix (Fig. 71, *b*) which undergoes the mucous change, becoming converted into a homogeneous, structureless mass. The cells themselves may remain unchanged, may become fatty, or may also undergo mucous degeneration, in which case the whole tissue becomes a clear translucent mass, with scarcely anything left to suggest the original tissue, except here and there connective-tissue bands and single cells or groups of cells less degenerated.

The stringy, gelatinous material which results from mucous degeneration is no single chemical substance, since in it several different varieties of mucin and pseudomucin may be detected.

The **mucins**—of which several kinds may be distinguished, according to their source, as submaxillary mucin, intestinal mucin, tendon mucin—are nitrogenous substances, which dissolve or swell up in water, forming a stringy, mucous liquid. From such solution they are precipitated, by alcohol or acetic acid, in the form of stringy masses which fail to redissolve in excess of the acid, thus differing from the true albuminoids. They dissolve in neutral salt-solutions and in caustic alkalies and alkaline carbonates, gradually forming alkali albuminates in the latter.

All mucins contain both nitrogen and sulphur, the percentage of carbon, oxygen, nitrogen, and sulphur varying somewhat in the different varieties. By proper treatment a carbohydrate, called animal gum (Landwehr, Hammarsten), may be separated from the mucins; and

FIG. 70.

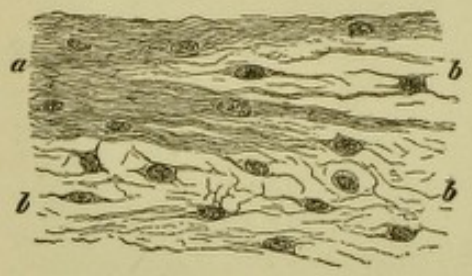


FIG. 71.

FIG. 70.—Epithelial cells which have undergone mucous degeneration, from a cystadenoma of the ovary. *a*, Cells which are only slightly affected; *b*, cells which show a high degree of mucous degeneration. Magnified 400 diameters.

FIG. 71.—Mucous degeneration of the connective tissue of the aortic valves. (Osmic acid; glycerin.) *a*, Fibrous tissue; *b*, tissue that has undergone mucous degeneration. Magnified 350 diameters.

mucin may therefore appropriately be called a glycoproteid (Pfannenstiel).

Pseudomucin is also soluble in water, appearing then as a mucous liquid, from which alcohol throws it down in the form of stringy flakes, which are again soluble in water. Acetic acid does not precipitate it. On boiling with dilute mineral acids a carbohydrate is formed (as happens in the case of mucin) which reduces copper sulphate in alkaline solution (Pfannenstiel).

According to Pfannenstiel, pseudomucin occurs especially in the ovarian cystadenomata, and the peculiar gelatinous and mucous consistence of the contents of these cysts is due to its presence. It is produced by the epithelium of these tumors (Fig. 70), and in forming this material these cells undergo changes analogous to those described in discussing the formation of mucin by epithelial cells. In all probability the gelatinous substance found in gelatinous carcinomata is a substance closely related to pseudomucin or metalbumin—i.e., there are, according to Pfannenstiel, several varieties of pseudomucin, of which the two mentioned are examples.

The mucin-like substance contained in the *synovial secretion*, which is coagulated by acetic acid, differs, according to Salkowski, from nucleo-albumin in that it contains no phosphorus, and from ordinary mucin in its different behavior when treated with the mineral acids, since it is not converted by them, on boiling, into a reducing substance.

Mitjukoff has obtained from the jelly-like contents of an ovarian cyst a substance

which resembles mucin, and to which he has given the name of *paramucin*. It differs from pseudomucin in one respect, viz., it is able, without being previously boiled in a diluted acid, to reduce the oxide of copper from an alkaline solution.

IX. The Formation of Colloid in Epithelium, and Epithelial Hyaline Concretions.

§ 64. The **production of colloid by epithelial cells** is a process closely related to the production of mucus by the same cells. The colloid is partly secreted by gland cells, and in part it represents a transformation of entire cells into this material. Under physiological conditions colloid occurs in the thyroid gland (Fig. 72), where it appears in the form of *hyaline, somewhat firm, colorless or slightly colored, jelly-like*

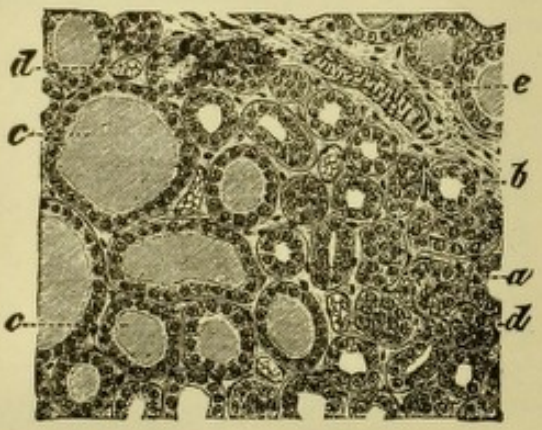


FIG. 72.

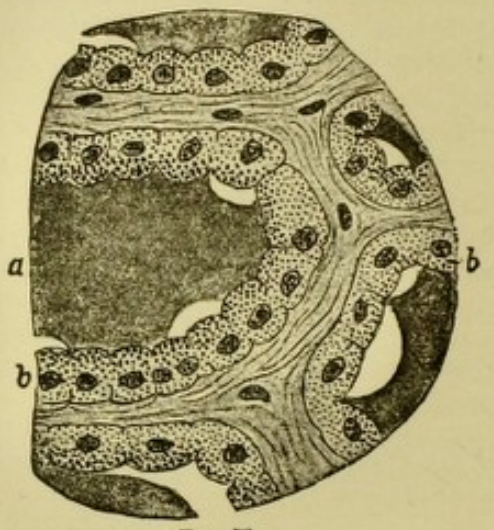


FIG. 73.

FIG. 72.—Colloid in a specimen taken from an enlarged thyroid gland. (Alcohol; hæmatoxylin.) *a*, Follicle filled with cells; *b*, follicle with a lumen; *c*, *c*, masses of colloid; *d*, capillaries; *e*, connective-tissue septum, with artery. Magnified 60 diameters.

FIG. 73.—Secretion of colloid in the thyroid gland. (From Bozzi.) *a*, Colloid; *b*, secreting cells containing granules.

masses, which first fill the follicles (*c*), but may also extend into the lymph-vessels of the thyroid gland. The pathological accumulation of colloid occurs both in normal gland-tissue and in that which represents a pathological new-growth. This accumulation causes a more or less marked distention of the follicles, and also at the same time a corresponding degree of enlargement of the affected glands. The term colloid goitre or bronchocele is applied to this condition.

The typical secretion of colloid is characterized by the formation of small lumps and globules of an homogeneous material within the epithelial cells (Fig. 73), and a few of these cells may be entirely filled with the material. When the tendency to develop this material is unusually strong and of an atypical character, cast-off cells may undergo a transformation into the hyaline colloid substance.

The colloid substance of the thyroid gland is found to be *homogeneous* even when it is subjected to a microscopic examination, and from its appearance it seems proper to call it *epithelial hyalin*. As a rule it contains no cellular elements, but occasionally cells in various stages of degeneration may be present. Neither hardening in alcohol nor the employment of acetic acid produces a clouding of this substance or a

precipitation in the form of threads, as happens when mucus is thus treated. By means of Van Gieson's staining method colloid is given an orange-red color, whereas the connective tissue, under this method, receives a fuchsin-red stain. At the same time it should be borne in mind that the substance which is contained in the follicles of the thyroid gland, and to which the name colloid is given, does not always present the same physical characteristics. Thus, for example, it is firm at one time, and quite soft at another—in some cases being even fluid or at least readily soluble in water. Instead of remaining homogeneous when soaked in alcohol, it may assume a granular appearance or may develop cracks, through shrinking of its substance. Finally, staining mixtures do not always affect it in the same way.

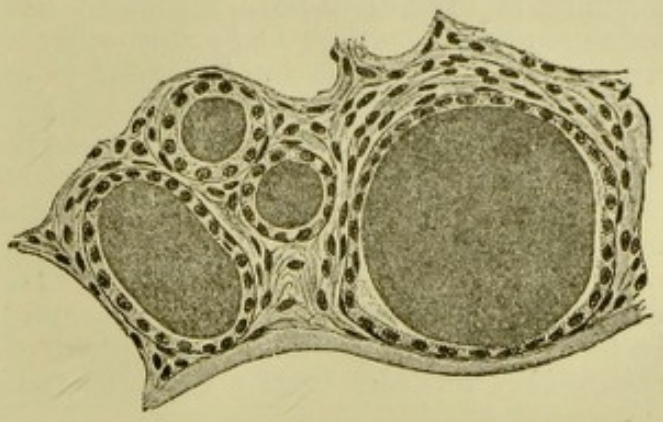


FIG. 74.—Uriniferous tubules which are dilated and filled with colloid. (Müller's fluid; hæmatoxylin; eosin.) Magnified 250 diameters.

Our knowledge of the chemical composition of colloid of the thyroid gland is very imperfect, and it is highly probable that the material contained in the follicles is not always of the same nature. It is likely that it is an albuminous body, and that it is united with the active substance of the thyroid gland—the iodothyrin.

After the thyroid gland the regions in which epithelial colloid is most often observed are the following: the glands of the hypophysis cerebri, the uriniferous tubules of diseased kidneys (Fig. 74, *f*), the prostate gland (Fig. 76, *d*), cysts of the parovarium (Fig. 75, *d*), and, more rarely, other glands. Even in the last-named organs the colloid may occur in the form of a smooth, homogeneous mass, completely filling the affected portion of the gland. Then, again, the colloid may be observed in the shape of **hyaline** and in part **laminated concretions** (Fig. 75, *d*, and Fig. 76, *d*), of more or less firm consistence.

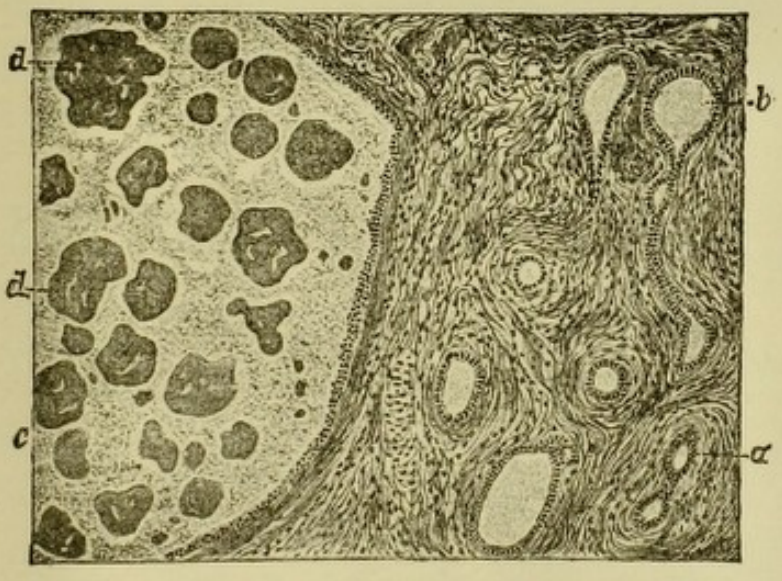


FIG. 75.—Colloid concretions in cyst-like dilated tubules of the parovarium. (Formalin; Van Gieson's staining mixture.) *a*, *b*, Glandular tubules of the parovarium; *c*, cysts containing colloid concretions (*d*). Magnified 80 diameters.

It must not be assumed that these last-named formations are iden-

tical, as regards their chemical composition, with the colloid material found in the thyroid gland. The only thing which they possess in common is this: they both represent *transformed protoplasm of gland cells*—a material which is *hyaline*, which possesses a certain degree of firmness, *and which does not respond to certain chemical reagents in the same manner as does mucin.* These concretions, accordingly, may also undergo changes which necessitate, on their part, a different behavior in the presence of certain micro-chemical reactions. This is particularly the case with the prostatic concretions, which often give, in the presence of iodine, a reaction that has led some to speak of them as being composed of amyloid material (compare § 67). The proof that they consist of cell-material which has been converted into hyaline substance may be furnished not only from the mode of development of these prostatic concretions but also from a study of renal colloid. Unfortunately, in

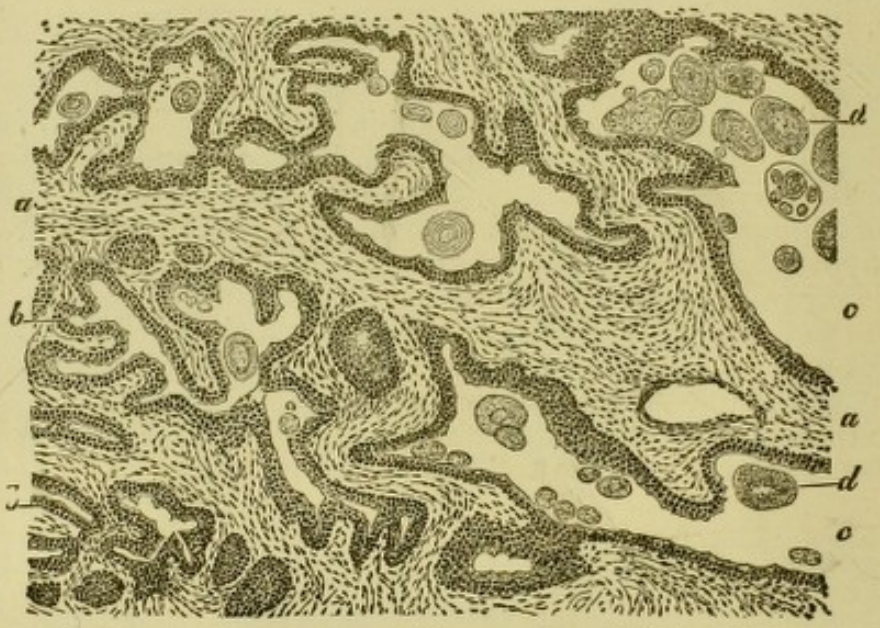


FIG. 76.—Section of an hypertrophied prostate containing concretions. (Müller's fluid; hæmatoxylin; eosin.) *a*, Stroma; *b*, glands; *c*, dilated glands; *d*, concretions. Magnified 45 diameters.

the case of the latter, it is only under certain special conditions that we are able to exclude the participation (in the formation of this material) of the albumin which is derived from the glomeruli.

The name **colloid** is a **collective term** which is applied to a great variety of formations that possess only certain physical attributes in common. There is also a great divergence of opinions among authors in regard to the use of the term. Von Recklinghausen, for example, includes, under the conception colloid degeneration, the mucous, amyloid, and hyaline forms of degeneration, and he also places in the same category the formation of epithelial colloid, hyaline degeneration of connective tissue, the hyaline coagulation-necroses, and the hyaline thrombi. Marchand, on the other hand, gives to the term a more limited scope. Nevertheless, he includes under the idea of colloid, the production, by epithelium, of certain varieties of mucus (particularly in tumors), and various hyaline formations in connective tissue. Inasmuch as colloid is not a well-defined chemical substance, and inasmuch as the different stains do not permit us to draw a sharp dividing-line between it and other substances which present a hyaline appearance, I believe that our best course is to apply the term only to those products of epithelium which present a hyaline appearance and yet at the same time do not possess the characteristics of mucin. In accordance with this belief I have also classified as belonging to the colloid formations the epithelial concretions which have hitherto, at least in part, been included—by reason of their behavior in the presence of iodine (brownish or bluish coloring produced by weak iodine solutions)—among the

amyloid products. If any opposition is made to the suggestion that these concretions be classified among the colloid formations, they may also be placed under the heading of formations of **epithelial hyalin.** I believe, however, that in the interest of clearness it is better to restrict the use of the term hyalin to conjunctival products (§ 69).

It is also customary to reckon as epithelial hyalin (keratohyalin?) the *hyaline granules and globules* which have been described by Russel, Klein, and others, which are found more particularly in cancer cells, and which receive a very deep stain from fuchsin and may also be colored by Gram's method or by Weigert's fibrin-staining mixture. Through some strange misconception these granules have been held to be parasites.

X. The Pathological Cornification of Epithelium.

§ 65. The **cornification of the surface epithelium,** over the entire surface of the body, is a physiological process, the most prominent feature of which consists in the fact that the cells in the most superficial portions of the prickle layer of the stratum germinativum assume a horn-like consistence. This cornification takes place first at the periphery of the cells and in the prickle-like processes which bind the cells together, while at the same time the interior portions and the nucleus shrink to such an extent that the cells as a whole become mere thin, flattened, horn-like scales. This horny substance, or *keratin*, is a very resistant, modified type of albumin, which possesses an homogeneous composition, and is capable of resisting digestion by the juices of the stomach or of the pancreas.

As a concomitant phenomenon of cornification may be mentioned the fact that peculiar small bodies and globules, which have a hyaline appearance and look as if they might be composed of colloid, and which assume an intense coloring when nuclear staining fluids are employed, make their appearance among the cells of the prickle layer. The material of which these bodies are composed has been called by Waldeyer *keratohyalin*. At those places in the skin where the horny layer is thicker than elsewhere, there will be found a sharply limited layer of cells containing this keratohyalin, and to this layer the name of *stratum granulosum* has been given. At those spots where the horny layer is somewhat thinner than it is in most places this stratum granulosum is imperfectly developed and presents breaks in its continuity.

Pathological processes of cornification occur in a variety of different forms. In the first place, there may be an increase in the production of horny material throughout areas of small or of large extent, and as a result we shall have conditions of *hypertrophy of the horny layer of the epidermis* (compare Chapter V., § 80)—or *hyperkeratosis*, if that term is preferred. This pathological phenomenon may be of a primary nature, —i.e., it may be due to some internal cause, such as a predisposition located in the skin itself (ichthyosis, lichen piliaris),—or it may also owe its origin to external influences, such as mechanical injuries, infections, inflammations (callosities, corns). Then, in the next place, the process of cornification, as it occurs in the skin, may be subjected to disturbing influences, and, in consequence of these, certain pathological manifestations, sufficiently marked to be recognized even by the naked eye (e.g., desquamation of the skin in the form of scales), make their appearance. To these manifestations the name *parakeratoses* has been given. They occur especially as sequelæ or as concomitant phenomena of infections of the epidermis and of inflammations of the corium and the papillary body. They may also sometimes occur without any

recognizable cause, and when this happens neither the process of cornification nor the formation of keratohyalin seems to be disturbed.

Finally, *pathological cornification often occurs at places in the body where under normal conditions it either does not occur at all, or manifests itself only in a feeble manner.* Thus, for example, in the skin itself the horny change may extend to the outlet channels of the sebaceous glands and to the hair follicles (ichthyosis). Then, in the next place, pathological cornifications occur not infrequently in the mucous membrane of the mouth, in which locality they take the form of white thickenings of the epithelium or even sometimes of hair-like formations (hairy tongue). This horny change is observed, furthermore, in the mucous membrane of the middle ear, in the mastoid cells, and in the descending urinary channels (*formation of cholesteatomata*), and in these places it may lead to the production of scales of a glistening white color.

It is also not an unusual thing to encounter *the products of this horny change in cancers*, especially in cancers of the skin, in which the horny scales are generally found in the form of balls which resemble onions or pearls. The same horny products are also encountered in *cholesteatomata of the pia and of the brain.*

The pathological horny change in mucous membranes and in tumors is either limited to the hardening of the cell-envelope and the shrinking of the cell as a whole, or else it is combined, as it is in typical cornification, with the production of keratohyalin. This latter process and the cornification of epithelial cells, especially in cancers, often occur without any regularity in their distribution.

According to Mertsching and Ernst the keratohyalin granules are derived from the nucleus, and represent chromatin which has escaped from the nucleus. In favor of this view may be mentioned the fact that the nuclei lose their chromatin simultaneously with the appearance of the keratohyalin.

XI. Amyloid Degeneration and Amyloid Concretions.

§ 66. The term **amyloid degeneration** is applied to a **peculiar degeneration of the connective-tissue elements of blood-vessels,** in the course of which an *albuminous body* (called *amyloid substance*) is deposited in the parts affected. As a result of this alteration the tissues increase in size and assume a *peculiar waxy appearance.* The degeneration may occur in almost all the organs of the body, but is more frequently met with in the spleen, liver, kidneys, intestine, stomach, suprarenal bodies, pancreas, and in the lymph-glands. It is encountered less often in fat-tissue, in the thyroid gland, in the aorta, in the heart, in the muscles, in the ovaries, in the uterus, and in the urinary passages.

When extensive it is readily recognizable by the naked eye, as the affected parts present a translucent waxy appearance (*lardaceous degeneration*).

In the *spleen* the change occurs most frequently in the region of the glomeruli, which may become completely changed into homogeneous, transparent bodies (Fig. 77, *b*) resembling grains of boiled sago, whence this form of amyloid spleen has come to be called the *sago-spleen.* When the amyloid degeneration is present also in the spleen-pulp, more or less distinctly recognizable waxy lines and streaks appear on its cut surface. At times almost the entire substance of the spleen may be thus

affected. The spleen is then enlarged and feels hard, and may look as if composed entirely of wax (*lardaceous spleen*).

The *liver*, when the amyloid degeneration is well marked, increases in size and becomes more resistant. When a section is made through the organ it will be seen that the tissues present a translucent appearance, somewhat like that of pork. The liver-tissue lying between the masses of amyloid substance is in some places of a brownish color, in others rather yellow, from the presence of an abundant quantity of fat.

The *kidney*, when in a condition of marked amyloid degeneration, may also be enlarged and hardened, and when cut open it may show, upon the cut surface, hyaline lardaceous spots and streaks that have a firm consistence. More frequently it presents the picture of a white, fatty, swollen, or normal-sized kidney, in which only here and there

FIG. 77.—Amyloid degeneration of the follicles of the spleen and of the neighboring tissues. (Müller's fluid; hæmatoxylin; eosin.) *a*, Transverse sections of splenic arteries; *b*, amyloid deposits; *c*, pulp; *d*, trabeculæ. Magnified 30 diameters.

small, hyaline masses or streaks can be seen, or in which the spots which have undergone amyloid degeneration can be distinguished only after the tissues have been treated with iodine.

In the intestine and in the lymph-glands the amyloid degeneration is not, as a rule, distinguishable without the aid of the microscope and chemical reagents; and the same thing is true in regard to the other, less frequently affected, organs—the adipose tissue, the heart, the large trunks of the blood-vessels, the thyroid gland, etc.

The substance which is deposited in amyloid degeneration forms for the most part **shining, homogeneous masses** which develop a *peculiar reaction with iodine and with some of the aniline dyes*. Iodine in water, or, better, in a solution of potassium iodide, when poured over amyloid tissue causes the amyloid substance to assume a dark mahogany-red color. In thin sections, under the microscope, this reaction differentiates the amyloid substance very clearly from the pale-yellow surrounding tissue (Fig. 78, *b*).

In very well-marked amyloid degeneration, when the tissues are of an almost wooden hardness, this reaction sometimes results in the production of a violet or bluish or green color; and specimens which have been changed to a mahogany color by the action of iodine, when treated with dilute sulphuric acid or with solution of chloride of zinc, may similarly turn red, violet, blue, or green, or, on the other hand, the original mahogany color may simply be intensified. This reaction is, however, often unsatisfactory.

The aniline dye known as *methyl violet* colors amyloid substance ruby red (Fig. 79, *a*, *b*), while the healthy tissue is at the same time stained blue or deep violet.

Virchow, on account of this peculiar reaction with iodine, was led to look upon the amyloid substance as a body devoid of nitrogen and closely related to cellulose or to starch. In reaching this conclusion he was influenced by the fact that cellulose, when treated with iodine and concentrated sulphuric acid, assumes an intense blue color, and similarly starch becomes of an ultramarine blue when treated with iodine alone. Virchow accordingly gave the name amyloid to the newly discovered substance. It was not until several years later that Friedreich and Kekulé demonstrated that the so-called amyloid is in reality a nitrogenous substance of an albuminous nature. According to Tschermak it is a coagulated albuminous substance.

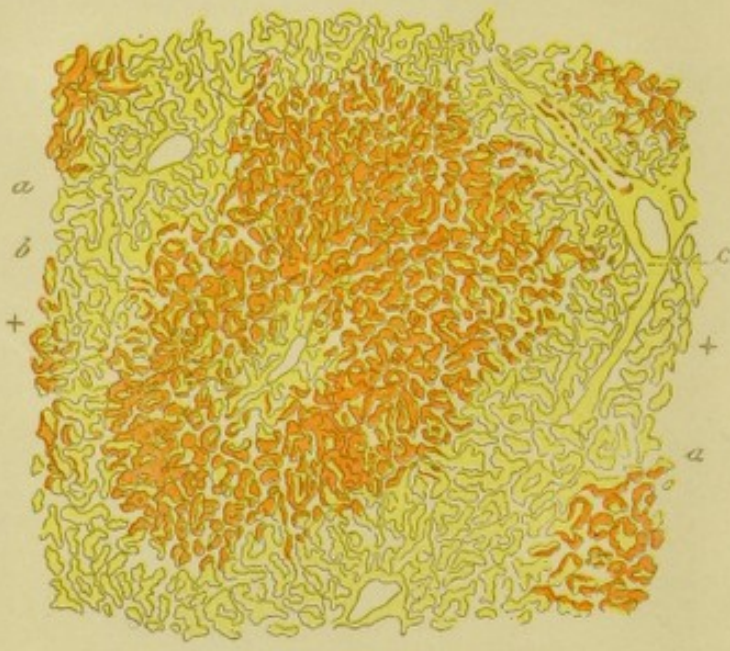


FIG. 78.—Section of an amyloid liver, showing the effects of staining it with a solution of iodine. *a*, Normal liver tissue; *b*, tissue that has undergone amyloid degeneration; *c*, Glisson's capsule. Magnified 35 diameters.

The peculiar reaction of amyloid substance makes it possible to detect its presence in the tissues in cases in which it is present in such small amount as to be quite invisible without the aid of iodine. In applying the test to fresh tissues, care should be taken to wash out the blood as perfectly as possible, since the color resulting from the combination of the red hæmoglobin and the yellowish-brown iodine rather closely resembles the mahogany red of the amyloid.

Amyloid is very resistant to acids and alkalies. It is not changed by alcohol and chromic acid, and it is only slowly affected by the changes of putrefaction.

Amyloid material is deposited *in the framework composed of blood-vessels and connective tissue, and more particularly in the walls themselves of the smaller blood-vessels.* Living cells are not affected by it. In connective tissue the amyloid material would appear to be first deposited between the connective-tissue fibres.

In the acini of the liver the amyloid material is found in close proximity to the capillary tubes. The endothelium (Fig. 80, *c*) is covered on its outer side by a more or less thick layer of homogeneous, glassy substance composed wholly of amyloid material. The liver-cells between the amyloid masses are either still preserved (Fig. 80, *a*) or they may be compressed and already undergoing atrophy, or, finally, they may have disappeared altogether. They often contain fat. The larger blood-vessels of the liver also at times show amyloid changes, more particularly in the media of the arteries.

In the kidney (Fig. 81) the amyloid is found most abundantly in the walls of the vessels, the vessels of the glomeruli (*b*) being moderately swollen and homogeneous, and similar homogeneous deposits occurring also in the arteries (*i*), veins, and capillaries (*k*) of other parts

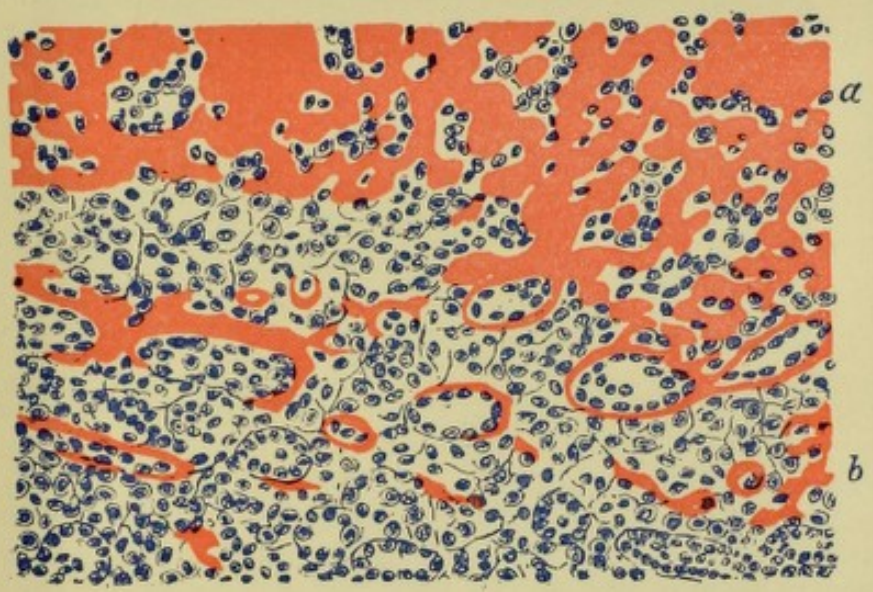


FIG. 79.—Amyloid degeneration of the follicles and pulp of the spleen. (Alcohol; methyl violet; hydrochloric acid.) *a*, Follicular tissue in a marked state of amyloid degeneration; *b*, pulp tissue in which the degeneration has begun. Magnified 300 diameters.

of the kidney. In the mucous membrane of the intestine the amyloid deposit also occurs in the walls of the blood-vessels more particularly.

In fat-tissue, which is often extensively affected with amyloid disease, the waxy material is found both in the walls of the blood-vessels and in the connective-tissue stroma, so that at times the thin connective-tissue sheath of the fat-cells may be converted into a clear hyaline substance. In the spleen it is the connective-tissue framework and the walls of the blood-vessels which are more especially affected and which often become much thickened (Fig. 79, *a*, *b*). In striated muscle it is the perimysium internum and the sarcolemma which are involved. In glandular organs possessing a tunica propria—as, for example, the mucous glands and the kidney—this membrane may also be affected and swell to a very considerable extent.

The **results** of amyloid degeneration which make themselves apparent to the eye, and which in a measure account for the perversions of function observed in cases of amyloid disease, are *the pronounced change in structure* of the affected tissue, and *the degenerative changes which take place in the cells of the affected organ and eventually cause them to disappear entirely*. Amyloid disease, consequently, has a distinctly

degenerative quality. The connective tissue itself is permanently changed, as the insoluble amyloid substance appears never to be removed from it.

The deposit of amyloid material in the blood-vessels leads to very considerable thickening of their walls, and at the same time to narrow-

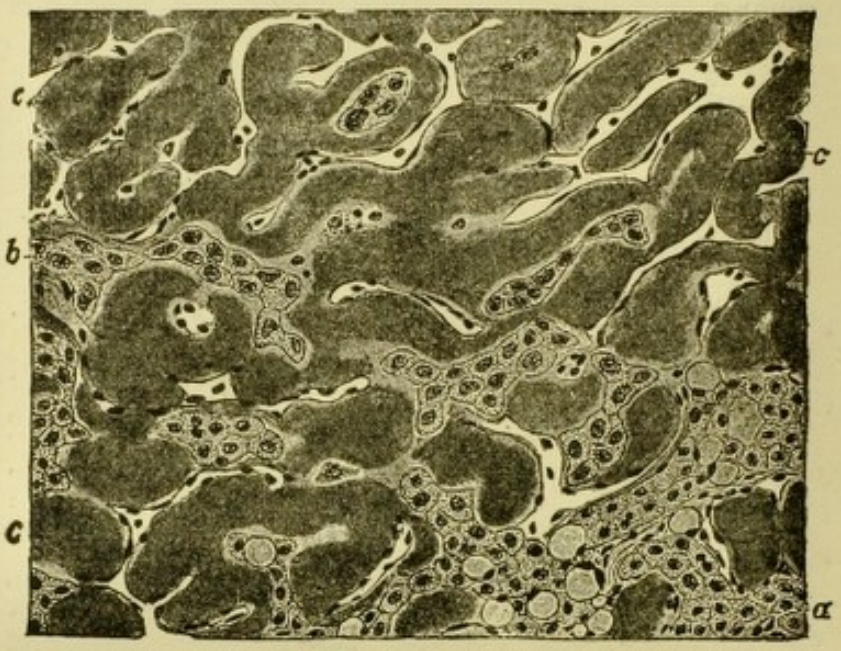


FIG. 80.—Amyloid degeneration of the liver. (Alcohol; Van Gieson's mixture.) *a*, Liver cells, to some extent fatty; *b*, compressed liver cells; *c*, amyloid substance. Magnified 240 diameters.

ing or even obliteration of their lumina (Fig. 81, *b*), both of which conditions entail permanent interference with the circulation. The amyloid masses compress the surrounding epithelial structures (Fig. 80) and cause them to atrophy. At the same time there is often a fatty degeneration of the epithelial cells (Fig. 81, *e*, *f*), especially in the kidneys; and yet this change cannot be attributed wholly to the disturbances in the circulation which result from the amyloid disease. It is more likely that this fatty degeneration is in some measure an independent pathological process, running parallel with the amyloid disease. In consequence of this, one may sometimes find very marked fatty degeneration associated with very slight amyloid changes.

In the spleen and lymph-glands, also, the cells lying in the meshes of the swollen trabeculæ disappear as the result of atrophy and fatty degeneration (Fig. 79), and in muscles the contractile substance diminishes *pari passu* with the increase of the amyloid material.

Regarding the **causes** and **nature of amyloid degeneration** but little can be stated with certainty. We know that it is of most frequent occurrence in the *various cachectic states*, but we are wholly in the dark as to the precise perversions of nutrition which bring it about. The diseases with which it is most frequently associated are tuberculosis of the lungs and of the bones, syphilis, chronic dysentery, and leukæmia, and often in these diseases the most extensive amyloid degeneration will be found, while in the cachexia resulting from carcinoma it is but rarely observed. Occasionally it occurs without any discoverable pre-existent disease, and observations by Cohnheim would make it appear that it may become well developed in from two to three months.

Amyloid change which is widely distributed throughout the body must result from general causes. *The amyloid substance itself does not exist in the blood, but the material from which it is formed is undoubtedly derived from the blood,* and it would appear that the lowered vitality of the tissues resulting from general cachexia favors its formation. Perhaps in the conditions mentioned this peculiar amyloid substance results from the union of an albuminous material derived from the blood (serum albumin) with some constituents of the tissues; or, as the result of impaired nutrition, *a peculiarly modified albuminous body may be separated from the albumin in the circulation.*

According to the published reports of Czerny and Krawkow, it is possible in chickens and rabbits, by means of injections of turpentine and also of staphylococci, which produce foci of suppuration, to call amyloid degenerations into existence in from three to sixty days. The experiments made in my laboratory by Dr. Grandry satisfy me that the statements of the above-named authors in regard to this matter are erroneous.

§ 67. The form of amyloid degeneration which we have thus far considered is a disease which usually affects a number of organs of the body, or, if confined to one of them, is more or less uniformly distributed throughout its entire substance. There is, however, a form of amyloid change in which localized deposits of amyloid material occur

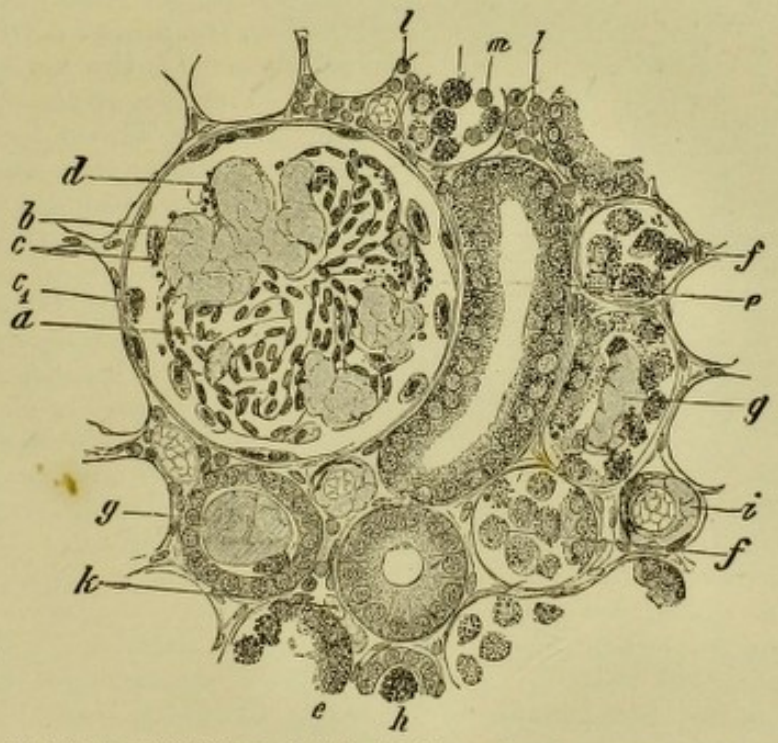


FIG. 81.—Section of an amyloid kidney. (Müller's fluid; osmic acid; methyl violet.) *a*, Normal vascular loops; *b*, loops affected with amyloid disease; *c*, fatty glomerulus epithileum; c_1, fatty capsule epithelium; *d*, fat-drops lying against the outer surface of the capillaries; *e*, fatty epithelium *in situ*; *f*, desquamated and fatty epithelium; *g*, hyaline coagulations (urinary casts); *h*, transverse section of a cast composed of fat-drops; *i*, amyloid artery; *k*, amyloid capillary; *l*, cellular infiltration of the connective tissue; *m*, round cells within the uriniferous tubules. Magnified 300 diameters.

either in the form of *localized amyloid infiltrations of the tissues* or as *free concretions.*

Local amyloid infiltrations are met with in granulations which are rich in cells, in chronically inflamed tissues, in cicatrices, and in hyperplastic connective-tissue growths. They occur also in tumors in which other degenerative processes are in progress. In some cases only small

particles of amyloid material are formed, and then frequently in the walls of the vessels; but in other cases large masses are met with, composed almost entirely of amyloid substance and often almost as hard as wood.

The *amyloid substance is here also deposited in the basement substance of the tissue*, though it is held by some authors (Rählmann) that the cells of the tissue may also acquire a hyaline appearance and give the reactions characteristic of amyloid.

Such local amyloid deposits have been found in the inflamed conjunctiva, in syphilitic scars in the liver, tongue, and larynx, in inflamed lymph-glands, in ulcers of bone, and in tumors of the larynx and stomach. Tumor-like amyloid masses are also occasionally met with in the conjunctiva, tongue, larynx, and trachea under conditions in which it is impossible to establish any relationship between them and some inflammatory process, and where, besides, there is but little normal connective tissue in the vicinity of the amyloid masses.

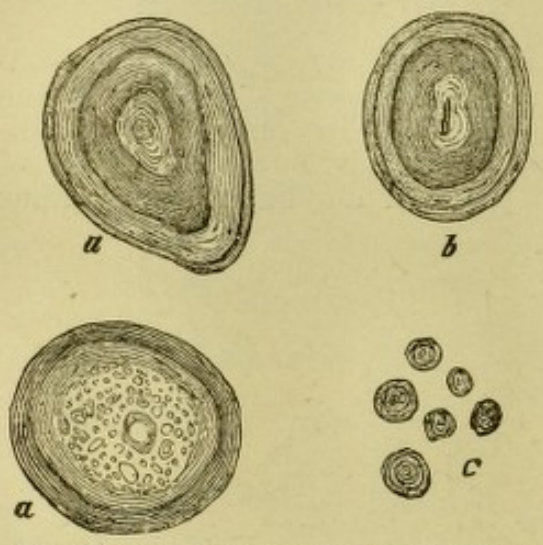


FIG. 82.—Corpora amylacea. *a*, Laminated concretions from the prostate. Magnified 200 diameters. *b*, Corpus amylaceum from an old hemorrhagic infarction of the lungs, with hæmatoidin crystals in the nucleus. Magnified 200 diameters. *c*, Corpora amylacea from the spinal cord. Magnified 400 diameters.

Freely lying amyloid concretions, or **corpora amylacea**, are most often found in the tissues of the central nervous system, especially in the spinal cord and in the ependyma of the cerebral ventricles. They occur also in the prostate gland. Those found in the nervous system are for the most part small, homogeneous, and somewhat shining particles (Redlich), usually devoid of any definite nucleus (Fig. 82, *c*). In the prostate they are larger and usually show distinct stratification (Fig. 82, *a*). Wagner and Langhans have observed corpora amylacea in carcinomata, and they have also been found in the lung (Friedreich, Zahn, Ziegler), in inflammatory areas, in bloody extravasations (*b*), and in emphysema.

These local deposits of amyloid material and the amyloid concretions should not be considered as altogether similar to the progressive amyloid degeneration of connective tissue. Some of them, it is true, give the characteristic amyloid reaction, and the corpora amylacea of the nervous system, in particular, assume the characteristic blue color when treated with iodine and sulphuric acid. But, in the case of these bodies, we have to do with formations which are dependent essentially upon local conditions for their origin, and which are derived in part from epithelial cells and in part from the cells of connective tissue. Accordingly they may be considered partly as a modified epithelial hyaline substance (§ 65), and partly as a modified conjunctival hyaline substance (§ 69). The concretions of the prostate are made up of degenerating epithelium or of fragments of the same matted together in layers (epithelial colloid; compare § 65), and it is probable that the similar bodies in the lung and in tumors are composed chiefly of fragments of degenerated cells, though in part, also, of albumin from the blood. Redlich considers the corpora

amylacea of the nervous system, which stain similarly to nuclei with hæmatoxylin, to be made up of the nuclei of neuroglia-cells and to be a senile retrograde development of the tissue. Stroebe, however, believes them to be composed of fragments of swollen axis-cylinders, while Siegert believes them to have originated from cells.

XII. Hyaline Degeneration of Connective Tissue and the Hyaline Products of Connective-Tissue Cells.

§ 68. Under the head of **hyaline degeneration of connective tissue** may be classed a group of changes in which *the fibrous basic substance of the connective-tissue layer of the blood-vessels assumes the peculiarities of hyalin without giving the characteristic reaction of amyloid* (Fig. 83). The change may involve normal connective tissue (Fig. 83), or that which has been altered by inflammation, or finally newly formed connective tissue—both that which is produced in inflammatory new-growths and that which develops in tumors. The pathological process is dependent upon local or general nutritive disturbances. The favorite seats of this degeneration are the following: the connective tissue of the thyroid gland (Fig. 83, *b*); the valvular endocardium; the intima of the arteries; the entire wall of the small blood-vessels, particularly of the brain and spinal cord; the lymph-glands (Fig. 85, *a*, *b*); the glomeruli of the kidney; the connective tissue and the blood-vessels of connective-tissue tumors of the dura mater (psammomata) and of the parotid and submaxillary glands (angiosarcomata); the connective tissue of the peripheral portions of tuberculous nodules; and the connective tissue of tuberculously affected sheaths of tendons and bursæ mucosæ (Fig. 84, *b*).

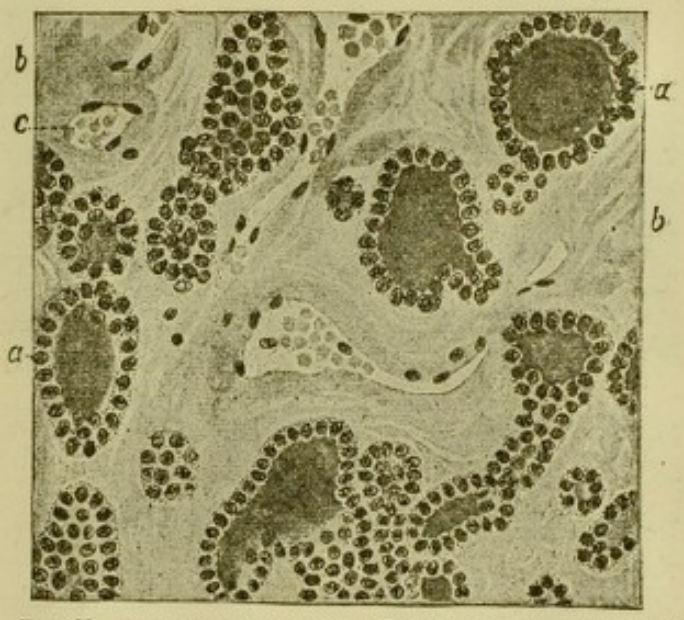


FIG. 83.—Hyaline degeneration of the connective tissue of a goitre which contained colloid substance. (Alcohol; Van Gieson's mixture.) *a*, Gland-follicles containing colloid; *b*, connective tissue in a state of hyaline degeneration; *c*, blood-vessels. Magnified 300 diameters.

There are no specially characteristic reactions for connective tissue when affected with hyaline degeneration, such as exist for the amyloid degeneration of this tissue. Van Gieson's method of staining this tissue (fuchsin and picric acid) gives to it—although not always—a deep fuchsin-red color. There is no doubt, furthermore, that much of what is designated as hyaline degeneration of connective tissue is in reality one or the other of a variety of degenerative conditions.

In many cases (those, for example, of thickened valves of the heart, and of thickening of the intima of arteries) the tissue, when examined under the microscope, shows itself to be very thick and dense, and from

this fact some have felt themselves justified in naming the condition **sclerosis.** It is not clear to what immediate causes the thickening and the homogeneous character of the tissue are due. The gradual wasting of the nuclei, the subsequent calcification (compare § 70) or softening—up to the point of complete disintegration (for example, in sclerosed portions of the intima),—the sequestration of the altered tissue from that which is healthy (for example, in those portions of bursæ mucosæ where the walls have undergone degeneration),—all these circumstances, it seems to me, point to the fact that the process under consideration is distinctively degenerative in its character.

In other cases the appearance of a tissue which has undergone hyaline degeneration approaches closely to that produced by amyloid degeneration, and it is also at the same time associated with a decided increase in bulk (as, for instance, in hyaline degeneration of the small blood-vessels of the central nervous system and the lymph-glands [Fig. 85, *a*, *b*], and, more rarely, in the various forms of hyaline degeneration of the connective tissue). On the other hand, one sometimes encounters —although very rarely —forms of hyaline degeneration which involve, one after the other, a number of organs (such as the heart [Fig. 86, *b*, *c*], the serous membranes, the intestinal wall, etc.), which are accompanied by the production of vitreous scales, and some of which give the typical amyloid reaction; and, furthermore, a number of authors have described the presence, in proliferative outgrowths of the conjunctiva, of hyaline degenerations which involved the reticular framework, which were characterized by nodular thickenings of this framework, and only some of which gave the amyloid reaction. From all these facts we are warranted in drawing the conclusion that there is a form of hyaline degeneration of the connective tissue which seems to be closely related to amyloid degeneration and which may in fact gradually become such in reality; and, as a further conclusion, it may be stated that this form of degeneration is ushered in by the deposit, in the tissues, of a hyaline, insoluble, albuminous body which probably originates in the blood.

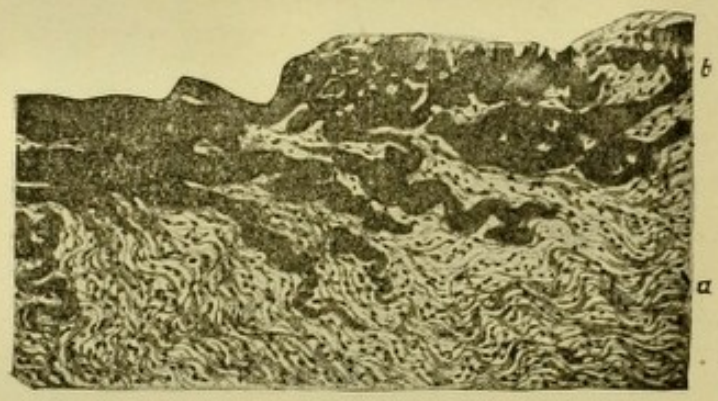


FIG. 84.—Hyaline degeneration of the connective tissue which formed a part of the wall of a tuberculously affected bursa mucosa. (Müller's fluid; hæmatoxylin; eosin.) *a*, Fibrillated connective tissue; *b*, hyaline connective tissue. Magnified 40 diameters.

The preparation pictured on the next page (Fig. 86) was obtained from the heart of a woman about fifty-five years of age, the greater part of which had undergone hyaline degeneration. Numerous hyaline plates and masses were found in the endocardium and pericardium. The muscle-tissue was in parts degenerated as shown in the figure. Associated with this condition in the heart there was extensive degeneration of the blood-vessels, particularly of the intestine, tongue, lungs, heart, and bladder. The peritoneum was also thickly bestrewn with hyaline masses. The fact that the smaller hyaline areas and the periphery of the larger areas gave no iodine reaction, while the central portions of the larger areas did so, appears to me to make the close relationship between hyaline and amyloid substance unquestionable. And this is further supported by the fact that amyloid organs occasionally contain areas of hyaline degeneration which give no iodine reaction.

§ 69. **Hyaline products of connective-tissue cells** may originate in a variety of ways. In the first place, *flat connective-tissue cells* may arrange themselves, in concentric fashion, in the form of balls (as happens in the case of cornified epithelial cells), and then may undergo a change into *a hyaline substance which contains no nuclei.* Formations like these are found most frequently in the membranes of the brain, in the plexuses, in the pineal gland, and in the new-growths which spring from them, and ultimately they lead, by the aid of calcification, to the formation of laminated chalky concretions (compare § 70, Fig. 91).

Another kind of hyaline formation is that which probably owes its origin to a sort of secretory activity on the part of the connective-tissue cells. The product resulting from this activity may be termed *secretory conjunctival hyalin*, and yet it is important to call attention here to the fact that under this term are often included a variety of formations, and that, as happens in the formation of colloid, *hyaline products may result from a degeneration of cells in their entirety.* In this category may be placed, first, the so-called *granules* (granula), *i.e.*, small masses of matter

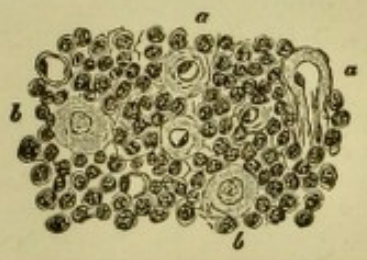


FIG. 85.

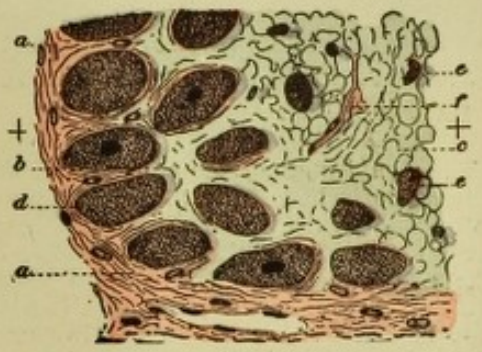


FIG. 86.

FIG. 85.—Hyaline degeneration of the blood-vessels of an atrophic lymph-gland from the axilla. (Alcohol; carmine.) *a*, Vessels which have undergone hyaline degeneration, but still possess an open lumen; *b*, obliterated vessels. Magnified 200 diameters.

FIG. 86.—Hyaline degeneration of connective tissue of the myocardium. (Alcohol, hæmatoxylin; carmine.) *a*, Normal connective tissue; *b*, connective tissue that has undergone hyaline degeneration; *c*, hyaline masses; *d*, transverse sections of normal muscle-cells; *e*, transverse sections of muscle-cells which are atrophic. Magnified 250 diameters.

which are contained within colorless blood-corpuscles, and also in many connective-tissue cells which are found in normal tissues or in those which are inflamed or otherwise disordered, or finally in tissues which have undergone proliferation. Some of these granules are greedy for oxygen (oxyphile) and are readily stained by eosin; in consequence of which the cells which contain them are called *eosinophile cells.* Among these granule cells there are others which are commonly termed *feeding cells* (*Mastzellen*) (Ehrlich), and which possess the property of being deeply stained, especially by basic coloring materials. In both of these forms of cells the granules may be crowded together in such numbers as to convert the cells into granule-globules.

Then, as a third variety, may be mentioned certain globules and balls which present a hyaline appearance; which take a very deep fuchsin stain, while responding also to other staining procedures, such as those with methyl violet, with gentian violet, etc.; and which may be grouped together under the name of *fuchsinophile* bodies. These formations are often also termed Russel's bodies, from the fact that Russel (who considered them to be parasitic fission-fungi) described them somewhat thoroughly.

The fuchsin bodies are encountered both in normal or only slightly altered tissues (suprarenal capsules, various mucous membranes—that of the stomach, for example,—the brain, the spleen, and the lymph-adenoid tissue), and also in inflamed tissues (particularly mucous membranes), in inflammatory new-growths, and in connective-tissue tumors. At one time they will be found—sometimes in large numbers—lying within the cells, while at another they lie upon the outside. When found in this position they are probably to be looked upon as a product of the cells—either as something that has, as it were, been secreted by them, or as a product of their disintegration. More accurate information in regard to their mode of origin or their composition is not obtainable. It is possible that they have a near relationship to the so-called feeding cells. Those which are found in the brain and spinal cord are generally classed as corpora amylacea (§ 67), even although they do not give the specific iodine reaction.

Finally, it is right to place in this same category those larger *hyaline balls and casts of tubes* (altered blood-vessels) which present some resemblance to epithelial colloid and which are often observed in sarcomata (see under Endothelioma and Angiosarcoma); for these formations are also products either of a secretory or of a degenerative process on the part of cells.

The *significance of the granules* of the eosinophile cells and the feeding cells—to which may also be added the neutrophile granules of the leucocytes (which are susceptible of being stained by a neutral coloring material, such as may be obtained by a mixture of acid fuchsin and basic methyl green)—cannot be positively stated at the present time. Altmann, who by the aid of special methods has demonstrated the existence of these granules in a great variety of cells, believed that in them (the granules) he had discovered the morphological unit of living matter; and accordingly he gave them the name of *bioblasts*. To those bioblasts which possess the power to live independently (as do the micro-organisms), he gave the name of autoblasts; and those which are congregated together within cells received from him the name of cytoblasts. These latter were again divided by him, according to the position which they occupied inside the cell, into karyoblasts and somatoblasts. Unfortunately, Altmann's scheme can scarcely be accepted as harmonizing with the facts. The hypothesis which was put forward by Ehrlich in explanation of the granular leucocytes, and which has been accepted by Heidenhain and Löwit, seems to me to be the more correct of the two. Ehrlich holds that these granules are secretory products of a specific metabolism which takes place in the cells in which they are found,—a view which justifies one in looking upon these particular cells as unicellular glands. So far as the so-called feeding cells are concerned, the views of authors are very much divided; some (for instance, Browicz and Raudnitz) looking upon them as degenerating cells; others, like Neumann, considering them to represent a stage in the development of proliferating cells; and, finally, still others maintaining—as do Ehrlich, Rosenheim, and Korybutt-Daszkiewicz—that they are simply cells which have received an excess of nutriment.

The conditions which are described in § 68 and § 69 as *conjunctival hyalin* are, beyond all doubt, pathological products which, so far as their mode of origin and their chemical composition are concerned, differ widely. As we do not yet know, however, what is the nature of the processes which lead to the formation of these hyaline products, the only course which remains open for us is to arrange them in different groups according to the fixed points of view adopted by different authors.

Von Recklinghausen employs the term hyalin in a much more comprehensive manner than I do. Accordingly, he places under the head of hyaline degeneration a number of pathological changes which I have placed under other heads. He defines hyalin as an albuminous body which takes a strong stain when treated with eosin, carmine, picrocarmine, and acid fuchsin; which at the same time is homogeneous and refracts the light strongly; which is altered very little by treatment with acids; and which, in its capacity to resist alcohol, water, ammonia, and acids, resembles amyloid, and yet does not respond to the iodine test. Among the hyaline substances he reckons not only epithelial colloid and the hyaline products of connective-tissue cells, but also the hyaline degeneration of the framework of connective tissue, the hyaline thrombi, the inflammatory exudations which undergo coagulation into a hyaline material, and

the tissue-necroses which present a hyaline appearance. According to this author these products owe their formation to a soldering together of the component parts of neighboring cells.

From their external appearance, all the products which I have enumerated may properly receive the designation of *hyalin*. At the same time the following subdivisions should be recognized: *epithelial hyalin* (colloid; keratohyalin); *conjunctival hyalin* (hyaline degeneration of the framework of connective tissue; hyaline cell-products; cells which have become hyaline); *blood hyalin* (hyaline thrombi); *exudation hyalin* (exudations which have been poured out upon the surface of a mucous membrane or a serous membrane, or into inflamed connective tissue, or into uriniferous tubules, or into tubercles, etc., and have there become converted, by a sort of coagulation, into hyaline material); and, finally, *hyaline tissue-necrosis*. Furthermore, in conjunctival hyalin a distinction must be made between a secretory hyalin which is the product of cells (closely related, in its mode of origin, to epithelial colloid), and a hyaline degeneration of the connective-tissue framework.

XIII. Calcification and the Formation of Concretions and Calculi.

§ 70. It is, on the whole, a rather frequent occurrence for crystals, or amorphous and granular masses, to be precipitated here and there in the body; and when such deposits are in sufficient amount to cause hardening of the affected tissue, the resultant condition is spoken of as **petrifaction** or, when the deposited material consists of lime-salts, as **calcification.**

Such deposits may occur in a tissue which forms an integral part of an organ and which bears its normal relation to the surrounding tissues. In other cases it may form an incrustation around tissues which have been separated in some manner from their surroundings, or around foreign bodies which have found their way into the body from without, and have then become the centres of a process of incrustation.

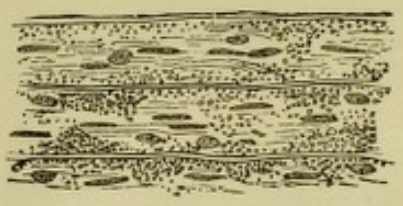


FIG. 87.—Calcification of the media of the aorta. Magnified 350 diameters.

In the first case **calcification of the tissue** results; in the second, **free concretions and calculi** are formed. It is to be remembered, however, that concretions which may have been at first free may occasionally become firmly attached to the tissues of the organ in which they lie by growth into them of some of the surrounding tissue; and, on the other hand, a portion of calcified tissue may gradually undergo separation from the surrounding tissue and ultimately form a free concretion.

The *cause of calcification is for the most part to be found in local changes in the tissues*, since the deposit of lime-salts usually occurs in localities in which the tissue has already died or is in process of degeneration and necrobiosis. It looks as if dying tissue, which has undergone more or less modification, possesses a kind of attraction for the lime-salts in solution in the body, and enters into intimate combination with them. Among the degenerating or dead tissues which are particularly prone to undergo calcification we may mention in particular connective tissue (§ 68) which has undergone hyaline degeneration, is in a sclerosed condition, and either contains no nuclei or is very scantily provided with them; such connective tissue being quite often encountered in the walls of the blood-vessels, in the endocardium, in an enlarged and degenerated thyroid, or in thickenings of the pleura or pericardium. It is common, also, in degenerative areas in the walls of

blood-vessels, or in tumors, or in any other portion of the body in which hyaline and fatty degeneration are in progress; in degenerating cartilage; in degenerating or already dead cell-bodies, as, for example, in ganglion-cells [Fig. 88] or kidney epithelium (especially in corrosive-sublimate, aloin-, or bismuth-poisoning [Fig. 89]); or in circumscribed, cheesy areas of considerable size.

Calcification occurs, also, at times in tissues which have undergone much less degeneration and in which there are still living

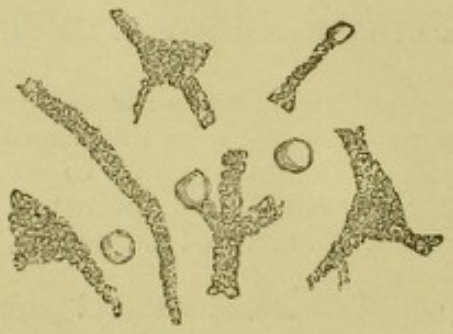


FIG. 88.

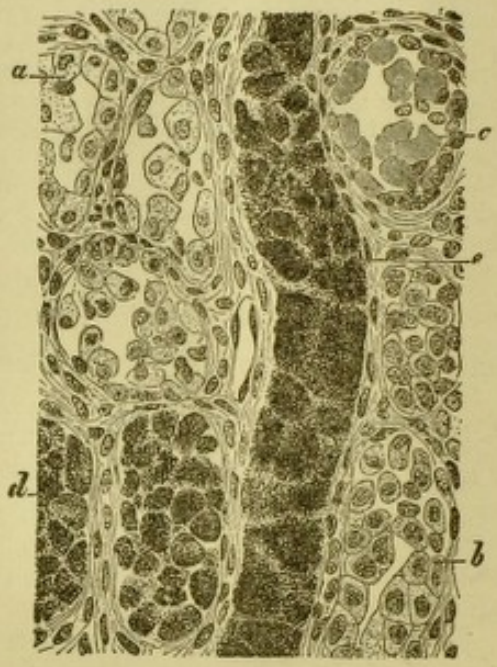


FIG. 89.

FIG. 88.—Calcified ganglion-cells from the brain of a demented person affected with hemiplegia and with a dropsical effusion in the ventricle of one side. Magnified 500 diameters.

FIG. 89.—Calcification of the epithelial cells of the uriniferous tubules. Patient died seven days after he had been poisoned with corrosive sublimate. (Alcohol; hæmatoxylin.) *a*, Normal uriniferous tubule; *b*, uriniferous tubule with desquamated epithelium; *c*, uriniferous tubule with desquamated, necrotic, and non-nucleated epithelium; *d*, *e*, tubules with degenerated and calcareous epithelial cells. Magnified 300 diameters.

cells; and under very exceptional conditions it may take place in tissues which show no recognizable change. This occurs more particularly in advanced age, when the lime-salts of the skeleton are undergoing more rapid absorption, in which case they may be deposited in the lungs as well as in the kidneys and in the mucous membrane of the stomach.

The lime-salts are deposited in the form of small granules (Figs. 87 and 88), and preparations are occasionally met with in which the separate calcareous granules are still visible.

As the result of conglomeration of these granules, larger masses and spherules may be developed (Fig. 88). More frequently, however, a more homogeneous deposit forms, in which it is impossible to distinguish the individual granules.

Both cells (Fig. 88) and intercellular substance (Fig. 87) may undergo calcification, and when calcification is in progress the degenerated tissue comports itself somewhat differently toward certain stains than normal, unchanged cell-protoplasm or intercellular substance does. Thus hæmatoxylin imparts a dirty bluish-violet color to it, and it usually stains red with picrocarmine (Fig. 89, *d*, *e*). This applies, however, only to deposits of carbonates and phosphates of lime, not to those of oxalate of lime.

Calcification may affect small or large areas of tissue, causing, in the latter instance, distinct hardening of the tissue and a whitish coloration. At times such calcified areas are sharply separated from the sur-

rounding tissue in the shape of spheroidal, spindle-shaped, or cactus-like masses (Fig. 90 and Fig. 91, *a*, *b*, *c*), being in reality **concretions lying in the tissue.** Not infrequently these are of sufficient size to be readily visible to the naked eye. Such concretions occur physiologically in the form of stratified calcific spherules in the pineal gland and in the choroid plexus, and are then known as *brain-sand* (*acervulus cerebri*). Pathologically they are met with in various localities in the pia and dura mater, in tumors of these membranes (psammomata—Fig. 91), in cheesy areas (Fig. 90, *b*), and in nodular growths of connective tissue (Fig. 90, *a*). The formation of these bodies may perhaps be best described as it occurs in the psammomata. Some of the cells of the tissue (Fig. 91, *a*, *b*, *c*) or certain portions of fibrillated connective tissue (*d*) undergo hyaline degeneration, the nuclei being at first preserved, but later lost. In this way small hyaline spherical areas are formed, and in these the deposit of lime-salts takes place. The more spheroidal concretions would appear to be formed from masses of degenerated cells, while the longer, spindle-shaped concretions seem to have their origin in the connective tissue, though it would appear that the spheroidal masses may also be formed in it. The variety of connective tissue which first undergoes degeneration and then calcification is the ordinary connective tissue, but concretions may also occasionally form in the degenerated walls of the blood-vessels.

§ 71. The ordinary petrifaction or calcification of the tissues results from a deposit of carbonate and phosphate of lime, to which occasionally magnesium-salts are added. In certain states of the body, however, a **deposit of uric-acid salts** takes place. This is notably the case in **gout,** in which an excess of uric acid accumulates in the body as the result of chronic disturbance of nutrition.

Gout is usually inherited, though it may occasionally be acquired.

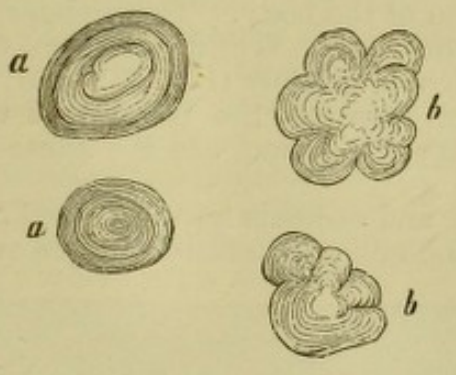


FIG. 90.

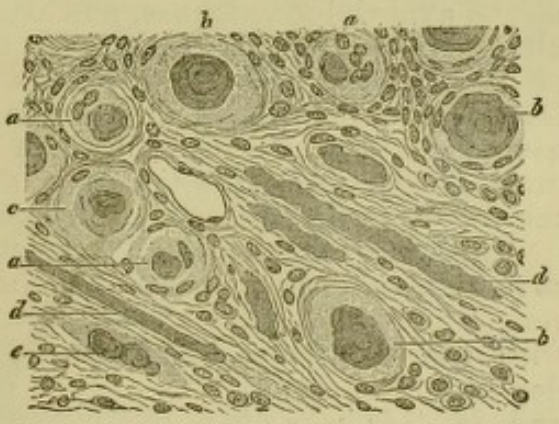


FIG. 91.

FIG. 90.—Calcareous concretions. *a*, Concretions from an inflame omentum *b*, Calcareous glands from a tuberculous lymph-gland that has undergone cheesy degeneration. Magnified 200 diameters.

FIG. 91.—Section of a psammoma of the dura mater, with calcareous formations. (Alcohol; picric acid; hæmatoxylin; eosin.) *a*, Hyaline nucleated balls with an inclosed grain of calcareous material; *b*, calcareous formations surrounded by a non-nucleated hyaline substance encapsulated in an envelope of fibrous connective tissue; *c*, calcareous nodule surrounded by hyaline connective tissue; *d*, calcareous spiculæ in the connective tissue; *e*, a calcareous spicule, with three separate concretions, embedded in the connective tissue. Magnified 200 diameters.

It is of very frequent occurrence in England and in northern Germany, but is rare in other localities, as, for example, in southern Germany. As to its ultimate cause we know practically nothing. It is character-

ized chiefly by the deposit in the body of urates (Fig. 92, *b*), particularly of sodium urate, with which small quantities of carbonates and

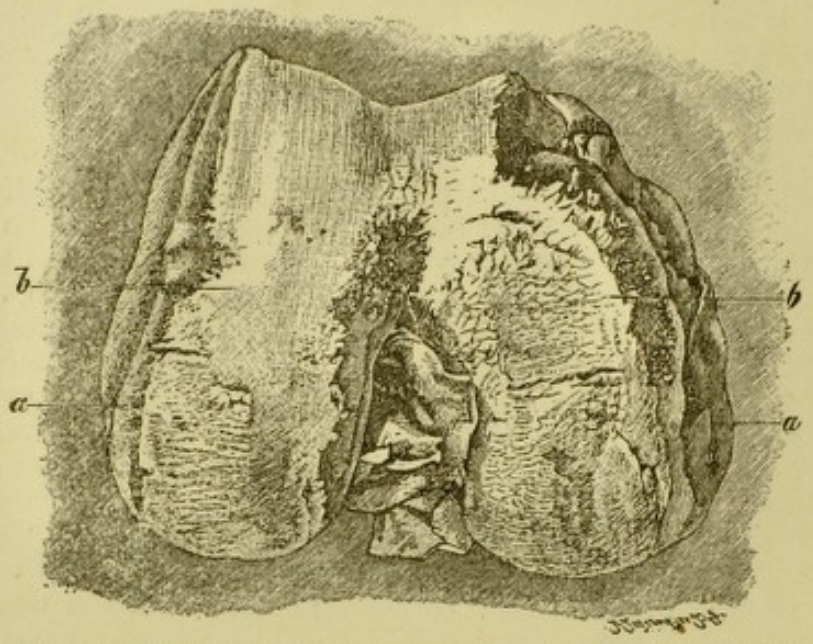


FIG. 92.—Deposits of urates in the knee-joint, in a case of gout. *a*, Condyles of the femur; *b*, deposits of urates upon the cartilaginous surface. (Two-thirds natural size.)

phosphates are sometimes associated. The deposit of these salts is usually accompanied by symptoms of a very acute nature—pain and inflammation; though at times, when the deposit takes place very slowly, there may be no characteristic acute attack. The kidneys and the skin and subcutaneous tissue are perhaps most often affected, though deposits may also take place in the tendon-sheaths, the tendons, ligaments, synovial membranes, and articular cartilages (Fig. 92), and may ultimately be found in nearly every organ of the body. The metatarsophalangeal joint of the great toe is a favorite site. The deposits consist for the most part of bunches of fine acicular crystals (Fig. 93), and lie usually in necrotic tissue; which fact warrants the belief that the urates, which enter the tissues in a state of solution, are the cause of the necrosis which takes place in them.

The areas in which this incrustation and necrosis have occurred are at first small, but soon cause inflammation and proliferation in the surrounding tissue. These areas, with the occurrence of fresh deposits, may increase in size, and in this way often attain, after a time, considerable dimensions. These larger deposits are called *tophi*. They consist of white, plaster-like substance, and at times form large rounded masses, more especially in the joints and tendons (Fig. 94).

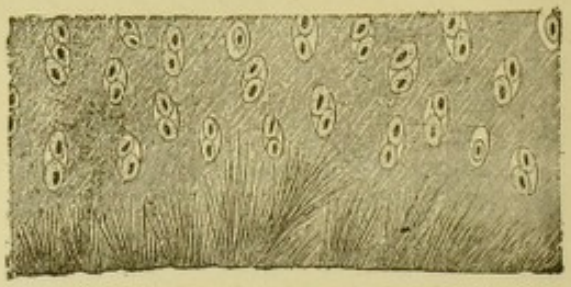


FIG. 93.—Deposit of needle-shaped crystals of urate of soda in the articular cartilage. (After Lancereaux.) Magnified 200 diameters.

In the joints the articular cartilage looks at first as if it had been sprinkled over with plaster of Paris (Fig. 92, *b*), but with the lapse of time the white substance pene-

trates deeper and deeper into it, until finally it may permeate the whole cartilage. In the kidney the necrosis of tissue and inflammatory condition consequent upon a deposit of urates may lead to induration and contraction of the organ. The deposit is more abundant in the medullary substance of the kidney, but is also met with in the cortex.

According to Garrod and Ebstein, the acute exacerbation in gout depends upon excessive accumulation of uric acid, either as the result of deficient excretion by the kidneys (Garrod) or on account of local changes in the affected tissue (Ebstein). Pfeiffer explains it by supposing that the deposits of salts depend simply upon the presence in excess, in the body-liquids, of a substance which is soluble with difficulty in them, and which therefore may very readily be deposited in various parts of the body, sometimes accumulating there in such quantity as to induce a localized necrosis. The symptoms of the attack are supposed to depend upon a temporary increase in alkalinity of the liquids of the body, enabling them to dissolve and absorb a portion of the deposited salts, in the course of which procedure pain and inflammation are induced. Von Noorden, on the other hand, considers uric-acid formation and deposit to be a secondary phenomenon, caused by the presence of a localized ferment of some sort, and quite independent of the amount and condition of the uric acid formed in other parts of the body.

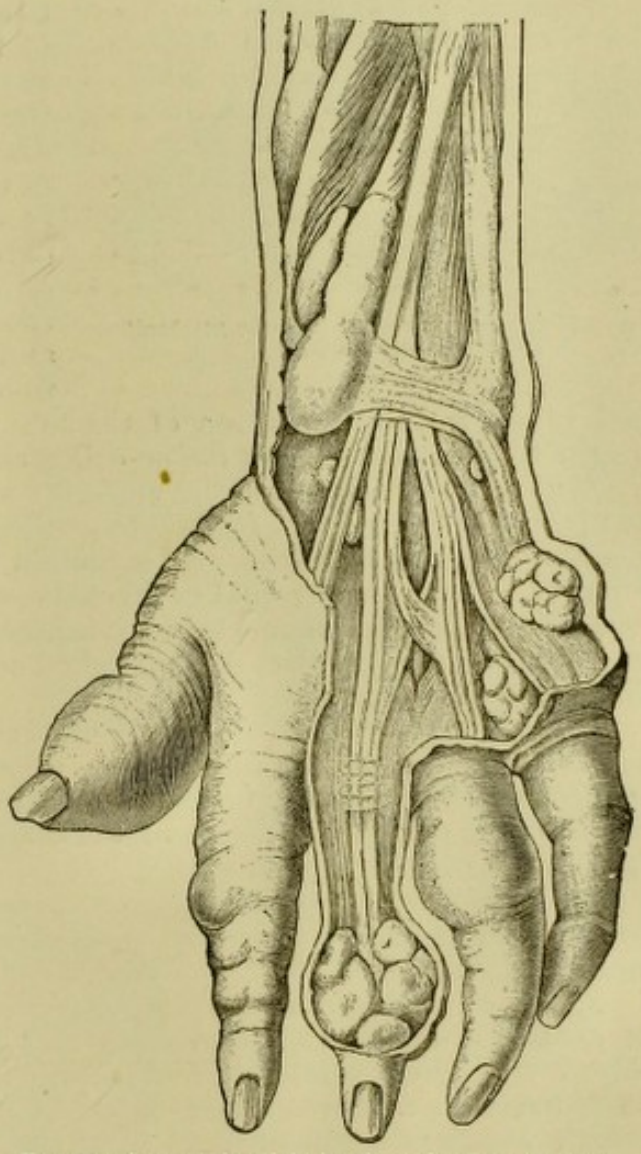


FIG. 94.—Gouty nodes of the hand. (After Lancereaux.)

§ 72. **Free concretions** occur most often in ducts and in cavities of the body which are lined by epithelium, as in the intestine, in the ducts of the glands pouring their secretions into the intestine, in the gall-bladder, in the urinary passages, and in the respiratory passages. The concretions occasionally met with in the lumina of vessels and in serous cavities might also be included in this group, although they are for the most part closely bound to the surrounding tissue.

All free concretions have an organic basis or nucleus. Thus *enteroliths* which form in the intestine have a basis of inspissated fæces, or hairs

(bezoar-stones, ægagropilæ), or indigestible vegetable material, or something of the sort, in which phosphates of ammonia, magnesia, and lime, and carbonates are deposited in varying proportions, according to the nature of the food taken. The *tartar* of the teeth is formed by the deposit of lime-salts in particles of food, mucus, or masses of bacteria, which collect upon the teeth; and it is probable that the calculi which form in the ducts of the salivary glands and in the ducts of the pancreas originate primarily from a substance derived from the epithelium.

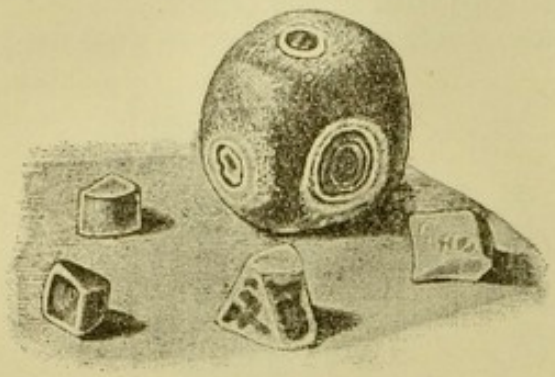


FIG. 95.—Faceted concretions from the gall-bladder. (Natural size.)

Bronchial calculi result from the deposit of lime-salts in dried and thickened bronchial secretion, and those found in arteries and veins, from calcification of thrombi. *Prostatic calculi* owe their origin to a calcification of the so-called amyloid concretions.

Gall-stones often seem to be made up entirely of crystalline material; but by the employment of suitable methods of examination it is always possible to show that they also contain a nitrogenous basis. They are for the most part spheroidal or faceted concretions of various sizes (Fig. 95), whose cleavage suggests a crystalline structure. Several varieties of gall-stones are, in fact, distinguished according to the substance deposited in them.

Thus there are gall-stones composed of cholesterin alone, or cholesterin and bile-pigment, others of bilirubin, others of biliverdin and lime, and still others of carbonate of lime alone. The most frequent are the first two, and the calculi composed of them have a ray-like, crystalline, and sometimes stratified cleavage, and are white or colored in proportion to their content of bile-pigment.

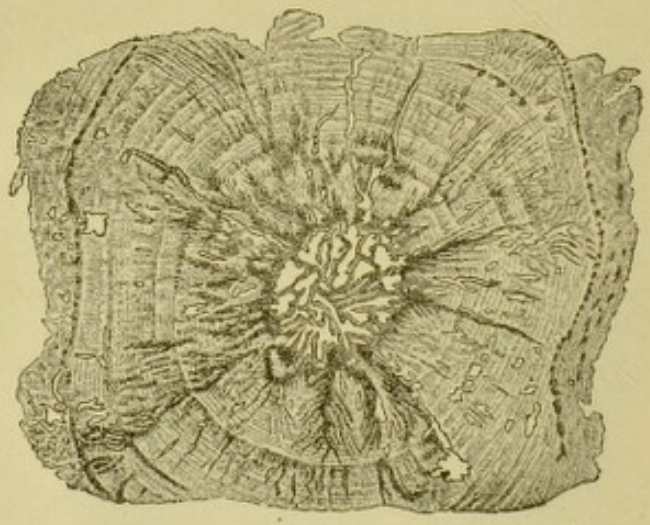


FIG. 96.—Transverse section of a small so-called cholesterin calculus after the removal of all the cholesterin. Magnified 15 diameters.

If the cholesterin of one of these gall-stones is dissolved out by ether, it will be found that a rather yellowish substance remains, which preserves the shape of the original stone, and which, when embedded and cut for microscopic examination, will be found to consist of a delicate homogeneous material (Fig. 96) in which there are usually radiating spaces formerly occupied by the crystals, and which frequently shows concentric stratification. It is possible to demonstrate a similar ground-substance in other calculi after solution of their contained salts.

There can, then, be no doubt that gall-stones also are the result of

incrustation of an organic substratum in all probability derived from the mucous membrane of the bile-ducts and gall-bladder. Gall-stones are more apt to form in advanced life; stagnation of the bile in the biliary passages favors their formation. Diseases of the mucous membrane of the gall-ducts lead to desquamation and degeneration of the epithelium, and in the products resulting from these pathological changes cholesterin and bile coloring-matters are deposited. In conformity with this view is the fact demonstrated by Steinmann that albuminous substances are capable of precipitating lime from solutions in which it is present as chloride or sulphate, in the form of carbonate; and he has shown that the shells of mollusks are produced by calcification, in this way, of mucous material elaborated by the mantle epithelium. When a concretion has once started, its growth continues as the result of fresh deposits of degenerated material which is encrusted with cholesterin and bile-pigment as before, and so on. At the same time the original softer nucleus of the concretion undergoes a change in that its solid ingredients seem to be attracted to the denser periphery of the stone, while its organic ingredients may liquefy. This accounts for the occasional presence of a cavity filled with liquid in the centre of gall-stones. In time cholesterin fills this cavity and in great part replaces the bile-pigment in the remainder of the stone. Carbonate of lime may also be deposited.

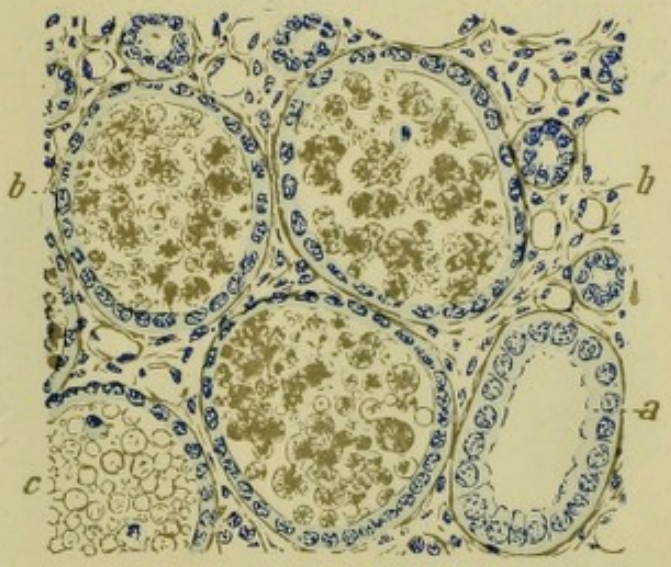


FIG. 97.—Uric-acid infarction from a new-born child. Transverse section of a pyramid of the kidney. (Alcohol; hæmatoxylin; the drawing made from a specimen which had been allowed to soak for some time in water.) *a*, Collecting-tube of the papillary zone of the medullary portion, seen in transverse section and as yet in a normal condition; *b*, dilated collecting-tubes filled with uric-acid concretions; *c* shows what remains in one of these tubes after the concretions have been extracted by the aid of water. Magnified 200 diameters.

Gall-stones consequently occur where epithelium of the mucous membrane is degenerating, and it is probable that much of the cholesterin which composes these masses is derived from its protoplasm. The chalky deposits stained with bilirubin have their origin in the lime-salts secreted by the mucous membrane, and their precipitation would appear to be aided by the presence, in the secreted mucus, of the degenerating albuminous material. Of course the cause of the epithelial degeneration is inflammation of the bile-passages, which may be brought about by stagnation of the bile, or perhaps, also, by penetration of bacteria into the common duct.

Finally, Ebstein has shown that the *concretions and calculi found in the urinary passages* are also composed of an albuminous stroma in which various ingredients of the urine have been deposited. These concretions are described, according to their situation, as occurring in the kidney or in the urinary passages leading from it. In the kidney they are, as a rule, small deposits which, as already alluded to in §§ 70 and 71, may form in the tissue of the kidney or in the lumina of the urinary

tubules, in which latter case they are interspersed with débris of the tubular epithelium. This is true, for the most part, of the calcifications which are observed in cases of poisoning by corrosive sublimate, bismuth, and aloin, and, more rarely, in poisoning by phosphorus, potassium chromate, and oxalic acid. It is also true of at least some of the gouty deposits. Furthermore, concretions of uric acid are frequently met with in the uriniferous tubules of children who have died during the first two weeks or so of life. The epithelium lining the tubules in which these concretions are found is for the most part well preserved, but in places slight desquamation and degeneration of the desquamated cells will be found. In the lumina of the tubules are many small spherules (Fig. 97, *b*), radially striated, colorless, or slightly brownish, and composed chiefly of urates or of uric acid. On solution of the uric acid a fine, delicate stroma remains (*c*). If, as the result of the presence of these concretions, further desquamation and degeneration of the epithe-

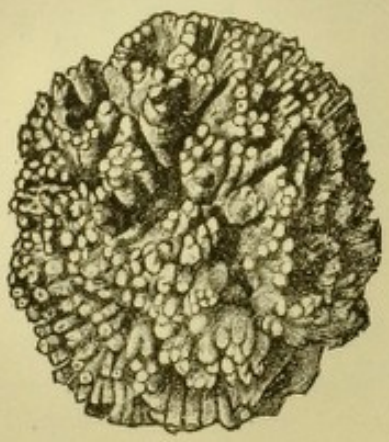


FIG. 98.

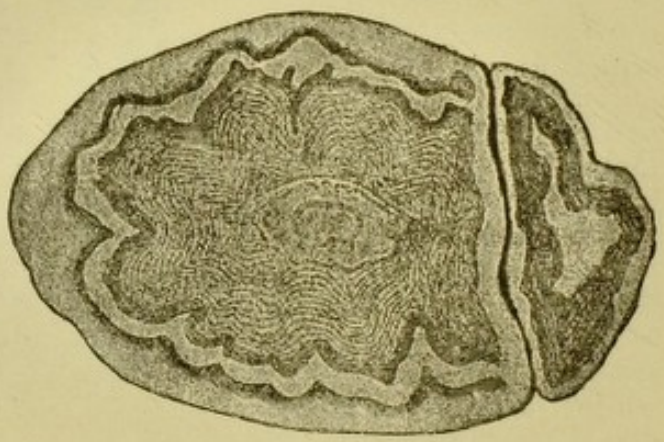


FIG. 99.

FIG. 98.—Coral-shaped stone from the bladder, composed of oxalate and phosphate of lime. (Natural size.)

FIG. 99.—Transverse section of two stones from the bladder, closely fitted together, and composed of urate of soda and ammonio-magnesium phosphate. (Natural size.)

lium take place, leading to the formation of considerable albuminous degenerated material in the tubules, some of the smaller concretions may gradually grow, as the result of accretion, to stones of considerable size; but this is unusual.

Concretions may also form in the pelvis of the kidney, in the ureters, in the bladder, in the urethra, or even under the prepuce, in the form of sand, gravel, or calculi. The last-mentioned are spheroidal or oval in shape, as a rule, and may be smooth upon the surface, or rough, mulberry-like or coral-like (Figs. 98 and 99). When several stones lie together, their adjacent surfaces usually become faceted, as shown in Fig. 99. When they occupy the pelvis of the kidney, their shape not infrequently represents quite accurately the shape of the pelvis.

Seen in section, urinary calculi are sometimes homogeneous, at other times distinctly stratified (Fig. 99) or radially streaked, and often show a nucleus and several distinct zones of different appearance. Ebstein has shown that in these calculi, also, an organic substance, albuminous in nature, is left after solution of the various salts. In stratified calculi this stroma also shows stratification, often with radially disposed slits. When stratification is absent, the stroma is composed of a network of

irregular construction, or, more rarely, of a homogeneous mass. There would seem to be little doubt that the crystalline bodies are deposited in this stroma, partly in the spaces and partly in its substance; and it is also most probable that the stroma itself is a product of the mucous membrane of the urinary passages, whose formation is assisted by the accumulation of débris and mucus consequent upon catarrhal inflammation or upon toxic degeneration of the epithelium.

What particular substances are deposited in any given case of stone-formation depends upon a variety of circumstances. When the uric-acid diathesis is present coincidently with the condition of epithelial degeneration necessary to the formation of a calculus, urates are usually deposited. Decomposition of the urine, with formation of ammonio-magnesium phosphate, gives the condition necessary for the formation of a phosphatic calculus. Cystin calculi may form when cystin is excreted by the kidneys as the result of peculiar metamorphoses of albuminous material in the intestine, brought about by bacteria (Baumann, von Udransky, Brieger). When a calculus has once begun to form, the irritation of the mucous membrane which it produces, and the decomposition which results from stagnation of the urine, cause its further growth by fresh accretion, and in the same way *foreign bodies* which have in any manner found their way into the bladder *may act as a nucleus for a calculus*.

Urinary calculi are classified according to the substances of which they are composed, as follows:

1. *Calculi composed chiefly of uric acid or urates.*

Pure uric-acid calculi are for the most part small, hard. They are yellowish, reddish, or brownish in color.

Calculi of urates are rarely pure. They are usually covered on the surface by coatings of oxalate of lime and ammonio-magnesium phosphate.

2. *Calculi composed chiefly of phosphates and carbonates.*

To this group belong *calculi composed of calcium phosphate, ammonio-magnesium phosphate, and calcium carbonate.* The last mentioned are rare. All these calculi are white or grayish. Those composed of the triple phosphate are soft and friable; the others are hard.

3. *Calculi composed of calcium oxalate.* They are hard and rough. Their color is brown.

4. *Calculi composed of cystin.* These are soft, waxy, and brownish-yellow.

5. *Calculi composed of xanthin.* These are cinnabar red in color, smooth, and their fracture is earthy.

Ebstein and Nicolaier succeeded in producing urinary calculi artificially by feeding animals with oxamide, an ammonium derivate of oxalic acid, as the result of which concretions of a greenish-yellow color formed in the urinary passages of dogs and rabbits. These were found to be composed of oxamide and to have a concentrically stratified structure with radial striations. They possessed an albuminous stroma, which resulted from desquamation and necrosis of the tubular epithelium induced in the excretion of the oxamide.

XIV. The Pathological Formation of Pigment.

§ 73. **Pigment** is normally present in connective and epithelial tissues in several parts of the body (**autochthonous pigment**). It lies within the cell-bodies and consists of yellow, brown, and black granules, or is diffuse, imparting its color to the cell-protoplasm. These pigment granules are known by the various names of **melanin, lipochrome,** and **hæmofuscin.** Among the epithelial structures containing pigment may be mentioned the deepest layers of the rete Malpighii which in all the colored parts of the skin contain pigment, the hairs, the pigment epithelium of the retina, and many ganglion-cells. In the skin the pigment

granules are for the most part yellow and brown; in the retina, black. When the skin is unusually dark, other layers of the rete Malpighii contain pigment also. Among the connective-tissue structures which may contain yellow or brown pigment granules are the cells of the pia, of the choroid, of the sclerotic, of the cutis vera, of the heart-muscle, and of the non-striated muscular fibres of the intestine.

Under various physiological and pathological conditions this normal **pigment**, of autochthonous origin, may increase in amount. Thus *during pregnancy the pigment of the skin usually increases more or less* (*chloasma uterinum*), particularly in brunettes. In *Addison's disease*, which would appear to depend upon changes in the suprarenal capsules (compare § 24), decided pigmentation of the skin occurs as the result of increase of the normal pigment. In atrophic conditions of the heart-muscle there is usually increase of its pigment, and atrophy of the voluntary muscles is often accompanied by an accumulation of yellow pigment in the fibres. In old persons the smooth muscle-fibres of the intestine always contain more or less pigment, and when this is the case the external surface of the intestine may present a yellowish or a yellowish-brown coloration.

FIG. 100.—Large hairy pigmented mole over the lower part of the back and on the posterior aspect of the hip, with scattered spots of discoloration over the trunk and shoulders. (From Röhring.)

The most intense grades of pathological pigmentation are met with in *freckles*, in *pigmented moles* (Fig. 100), and in various pigmented tumors (*melanotic tumors*). The amount of pigment may be so great as to impart a perfectly black color to the tissue.

The pigment is for the most part contained in the cell-bodies (chromatophores), though it is occasionally in the intracellular substance also, and is composed of yellow, brown, or black granules. Occasionally cells are diffusely colored. In Addison's disease the pigment granules are situated partly in the epithelial cells—especially in those which lie directly upon the connective tissue (Fig. 101, A, *a*, *b*, and B, *a*)—and partly in branched connective-tissue cells, some of the pigmented branches of which, as a rule, extend up between the epithelial cells (B, c).

In pigmented spots in the skin and in melanotic sarcomata the pigment is to a great extent contained in large, specially differentiated connective-tissue cells, in part also in ordinary connective-tissue cells in the neighborhood of blood-vessels and in their walls.

So far as may be inferred from histological examination, *the pigments which we have been describing are the result of a special kind of cell activity*, and we must suppose that many connective-tissue cells, ganglion-cells, and muscle-cells are able to form pigment out of the material brought to

them. The pigment would appear to be formed for the most part where it is found, though it has been shown that it may at times be transported, and that the pigment of the skin in particular, as well as that of the hair, is, in part at least, formed in connective-tissue cells lying close under the rete Malpighii, and sending branching processes (Fig. 101, *c*, *d*) between its epithelial cells, from which the pigment is taken into the epithelial cells.

The frequent proximity of the pigment to blood-vessels seems to indicate that its antecedents are derived from the blood, and many accept the theory without question that the pigment is derived from the coloring-matter of the blood. It is distinctly against this view, however, that when pigment is found in the neighborhood of blood-vessels, there is usually an entire absence of any evidence in the blood itself, or in the neighborhood of the vessels, suggestive of an escape of the blood-corpuscles or of a breaking down and solution of the same. From this circumstance it seems probable that the pigment is formed either from the circulating albumin or from the albumin of the cells.

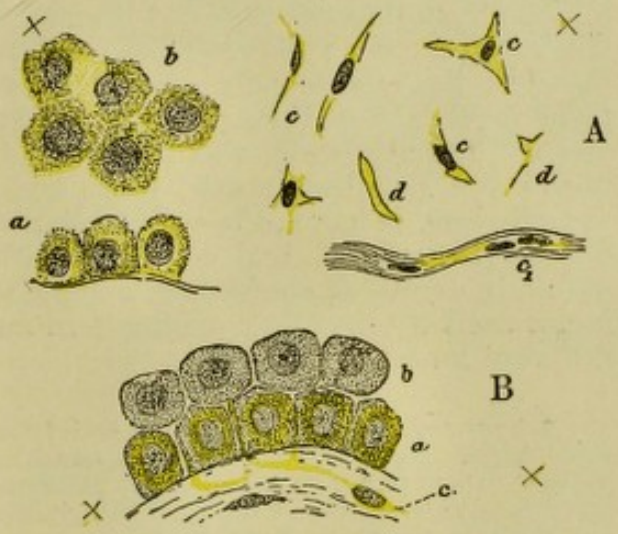


FIG. 101. A and B.—Pigmented cells of the skin, from a case of Addison's disease with cheesy tuberculosis of both suprarenal capsules. (Alcohol: carmine.) *a*, Pigmented epithelial cells from the deepest layer in a section made at right angles to the surface; A, *b*, pigmented epithelial cells from a section made in a plane parallel with the surface; B, *b*, epithelial cells containing no pigment; c_1, *c*, nucleated pigmented connective-tissue cells, the terminal processes of which push their way, in B, between the epithelial cells; *d*, pigmented terminal processes of cells. Magnified 350 diameters.

The attempt has been made to solve this question by chemical means, with the result that several facts have been discovered tending to show that the pigments are products of cell-activity and are formed from albuminous bodies. The different forms of **melanin**, among which the pigments of the skin and of the choroid membrane are usually classed, are bodies all of which—according to the investigations of von Nencki, Sieber, Abel, Davids, and Schmiedeberg—are rich in sulphur and contain nitrogen. Nevertheless, they differ in their chemical composition. According to Schmiedeberg, this varying composition is due to the differences in their mode of origin; for these different forms of coloring matter represent *the final product of a long series of metamorphoses that occur in the products of albuminous bodies*. In this respect we may compare the gradual development of this final product with that of humus (the ordinary dark-brown soil). The genuine albuminous bodies or substances do not, according to Schmiedeberg, furnish the material for the building up of this final product. It is contributed, rather, by the sulphur-containing products which result from the splitting up of these albuminous substances, and which, furthermore, have already experienced the loss resulting from the separation of certain carbon-containing groups. Ultimately, therefore, the combinations from which the different forms of melanin are derived are richer in sulphur than are the carbon-containing products.

The majority of authors maintain that the various forms of melanin contain no iron. On the other hand, Brandl, Pfeiffer, Mörner, and others have found small quantities of iron in melanosarcomata.

The mere fact that the pigment of melanotic tumors contains iron is no proof that it is derived from the hæmoglobin, since tumors often contain, in addition to melanin granules, other products of the disintegration of the blood—products which are distinctly colored and which contain iron. It is not possible to demonstrate, even microchemically, the presence of iron in most of the pigment granules.

Very little is known in regard to the origin of the different forms of **lipochrome,** which supplies the coloring matter for fatty tissue, for the corpora lutea, for the ganglion cells (Rosin), and for those green-colored tumors which are termed chloromata (Krukenberg).

The term **hæmofuscin** has been applied by von Recklinghausen and Goebel to certain yellowish bodies which contain no iron and which are found in the muscle-cells of the heart-muscle, in the smooth and the transversely striated muscular fibres, in the cells of the gastric, intestinal, and lachrymal glands, and in the mucous and sweat glands. According to von Recklinghausen, these bodies are derived from the blood; nevertheless, it has not been established as a fact that hæmoglobin produces this material, and consequently these bodies cannot be classed, with any degree of confidence, among the hæmochromatoses (§ 74). It is not unlikely that they originate in much the same manner as do the different forms of melanin.

Aeby was the first to express the belief that the epithelial cells themselves do not form pigment, but derive that which is found in them from wandering cells laden with pigment, which penetrate between the individual epithelial cells and then degenerate, the pigment and débris of the cells being taken up by the epithelium. According to von Kölliker, "the pigment of the hair and of the skin is derived from pigmented connective-tissue cells which send processes between the epithelial cells of the deepest layers of the hair-bulbs and of the rete Malpighii, which processes divide and subdivide, penetrating deeper and deeper between the cells, and in some instances even passing into the bodies of the cells themselves and depositing their pigment there. These pigmented connective-tissue cells are always confined to the deepest layers of the rete." The pigment of the ganglion-cells and of the cells of the retina is formed in these cells themselves. Riehl and Ehrmann concur with von Kölliker in this opinion. Karg has arrived at much the same conclusion, as the result of the study of the effect of grafting white skin on the floor of an ulcer of the leg in a negro. In the course of from twelve to fourteen weeks the grafted skin became quite black, like the skin of the rest of the negro's body. Examination showed fine pigmented processes, believed to be offshoots of connective-tissue cells, lying between the epithelial cells at a time when the epithelial cells themselves had not as yet become pigmented. Von Wild has also shown that in melanosarcomata of the skin the pigmented connective-tissue cells penetrate between the epithelial cells. The pigmented skin of persons affected with Addison's disease shows similar pigmented connective-tissue cells, though these are not always to be found everywhere in such cases.

Histological studies of the mode of formation of pigments in animals, which have been carried on chiefly on fishes, amphibia, and reptiles, have led to various conclusions. Thus Jarisch is of the opinion that the pigment of the skin and teeth of tadpoles is not derived from the blood, but is a product of the protoplasm of the cells, while List thinks that he can trace the pigment of the skin of fishes and amphibia to disintegrated red corpuscles. According to Kromayer, the pigment of the skin of mammals is derived from protoplasmic processes of the epithelial cells and represents a product of their degeneration.

A curious **melanosis of the internal organs** is met with in some domesticated animals, occasionally associated with melanosis of the subcutaneous tissue, in which the heart, lungs, intestine, etc., contain grayish or black spots, looking like ink-spots, in varying numbers, and which are produced by the presence of pigment in connective-tissue cells otherwise apparently healthy.

Virchow has described, under the term **ochronosis of cartilage,** a peculiar pig-

mentation of cartilaginous structures, tendon-sheaths, and synovial membranes by an iron-free pigment, whose imbibition into the matrix of the cartilage imparts to it a brownish or black color. He explains this on the supposition that blood-pigment has soaked into the stroma of the cartilage, and compares this form of pigmentation with that which occurs in freckles. It is probable that this condition is only a more pronounced form of the diffuse *brownish pigmentation* especially noticeable *in the costal cartilages* of old persons. Occasionally this pigment is also deposited in granular form.

§ 74. **Hæmatogenous pigment**—that is to say, *pigment whose origin from the blood-coloring matter is certain*—is derived usually from blood which has escaped from the vessels or has undergone coagulation in the vessels, and consequently *depends upon local changes*. Occasionally, also, it may be traced to the absorption of hæmoglobin by the blood, or to changes in the blood as the result of which granular pigment or hæmoglobin gets into the plasma and when deposited gives rise to pigmentation of the tissue. Such deposits of blood-pigment have been called *hæmochromatoses* by von Recklinghausen.

Extravasations of blood quickly undergo changes which are visible, even to the naked eye. In the skin they are at first brownish, then blue-green, and yellow. When small hemorrhages have occurred in the substance of a tissue, as in the peritoneum, pleura, or lung, reddish-brown or blackish spots will be visible long afterward. In bodies which are rapidly putrefying these areas may be slate-colored. Larger hemorrhages into the tissues—for example, in the brain or in the lung—come to have a rusty color after a time, and still later the affected spot shows ochre-yellow, yellowish-brown, or brown pigmentation. Corresponding with all these changes in color are physical and chemical changes in the hæmoglobin and in the iron contained in it.

FIG. 102.—A, Cells containing amorphous blood pigment: *a*, those in which there are only a few larger fragments of red blood-corpuscles; *b*, *c*, those in which these fragments are numerous, but quite small; B, rhombic plates and needles of hæmatoidin. Magnified 500 diameters.

When **hemorrhages** occur in the tissues or in any of the cavities of the body, a considerable quantity of the blood-plasma and of the corpuscles is taken up unchanged by the lymph-vessels in the neighborhood. Other red corpuscles seem to have the hæmoglobin dissolved out of them, leaving the colorless stroma. This dissolved *hæmoglobin* diffuses itself into the surrounding tissues and gives rise to the changes in color of the tissues in the neighborhood of the extravasation. Part of this dissolved coloring-matter may be eliminated in the urine in the form of *urobilin* (*urobilinuria*), but some of it is precipitated in the tissue in the form of granules and crystals. These latter are *yellowish-red or ruby-red rhombic plates and needles of hæmatoidin* (Fig. 102, B), and are a frequent residuum of hemorrhages. Part of the dissolved blood-pigment may be taken up by cells and be converted by them into yellow and brown pigment granules.

A third portion of the blood-corpuscles in breaking down form *yellow and brown pigment granules and scales*. This occurs particularly in

the larger extravasations—in the so-called *hæmatomata*. Pigment derived in any of these ways from the blood is very frequently taken up by cells, and in this manner are formed the so-called *blood-corpuscle cells and pigment-carrying cells* (Fig. 102, A, and Fig. 103, *a*, *b*).

When red blood-corpuscles are just beginning to disintegrate, the coloring-matter found is hæmoglobin; but this is quickly changed, and the yellow and brown masses and granules found both in the cells and lying free in the tissue are, as a rule, **derivatives of hæmoglobin** and not hæmoglobin itself. These derivatives of hæmoglobin are divided into two groups according as they contain iron or not, the former being called *hæmosiderin*, the latter *hæmatoidin*.

Hæmatoidin, identical chemically with *bilirubin*, is a ruby-red (Fig. 102, B) or reddish-yellow (Fig. 103, *b*) pigment, which occurs either in crystalline form or as irregular granules, which may be quite amorphous or may be rather angular in shape, suggesting a rudimentary and imperfect crystalline form. It is soluble in chloroform, carbon disulphide,

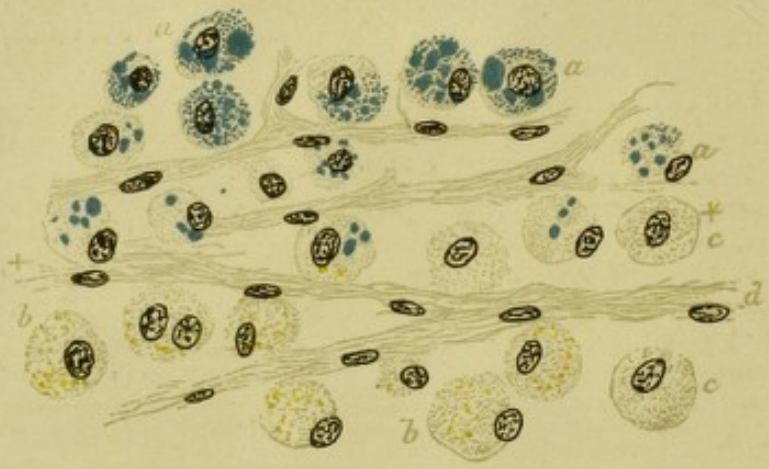


FIG. 103.—Cells containing hæmosiderin and hæmatoidin, from an old hemorrhagic focus in the brain. (Alcohol; Berlin blue reaction.) *a*, Cells containing hæmosiderin; *b*, cells containing hæmatoidin; *c*, fat-granule cells which have become clear; *d*, newly formed connective tissue. Magnified 300 diameters.

and absolute ether, but insoluble in water and alcohol. It would appear to be more abundant when the blood-pigment is not much exposed to the action of living cells, as in the centre of large extravasations and in hemorrhages into preformed cavities of the body, as, for example, into the pelvis of the kidney or into the subdural space. It may be produced artificially by introducing blood in glass cells under the skin or into the peritoneal cavity in such a way that the body-fluids may have access to it.

The granules and crystals of hæmatoidin are found both in the cells (Fig. 103, *b*) and loose in the tissues (Fig. 102, B). When it is contained in cells it has usually got there as the result of phagocytosis, though occasionally, particularly in cartilage- and fat-cells, the hæmatoidin will have been absorbed while in solution, and have been deposited afterward in the solid form.

Hæmosiderin, the derivative of hæmoglobin containing *iron*, is met with in the tissues for the most part in the form of yellow, orange, or brown masses and granules, which deepen in color with time, and are usually contained in cells, sometimes in the very red corpuscles from which the hæmoglobin has been absorbed. When treated with potassium ferrocyanide and dilute hydrochloric acid, hæmosiderin becomes blue as the result of the formation of Prussian blue (Fig. 103, *a*); it

becomes black when acted upon by sulphide of ammonium, iron sulphide being formed.

Hæmosiderin is formed, according to Neumann, more particularly when the extravasated blood, or that composing a thrombus in a vessel, is subjected to the action of the cells, and it is consequently more abundant in small extravasations and in the neighborhood of larger ones. The formation of hæmosiderin may take place in the cells or in the intercellular spaces. That which is found in the cells may have been formed from fragments of disintegrated blood-corpuscles which have been taken up by the cells, or from dissolved hæmoglobin which has infiltrated them, as is indicated by the occasional finding of both wandering and fixed cells whose bodies are stained diffusely yellow and which are stained blue by the Prussian-blue reaction. Furthermore, when hæmoglobin is excreted by the kidneys, iron-containing pigment frequently forms in the tubular epithelium; and cartilage-cells, which could hardly be supposed to act as phagocytes and take up solid fragments of blood-corpuscles, often contain granules of similar pigment, even when lying at some distance from a hemorrhagic area.

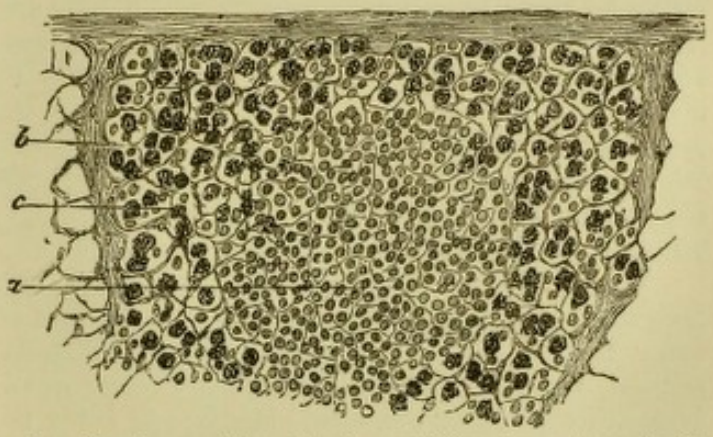


FIG. 104.—Accumulation of cells containing pigment granules in the lymph-glands after the absorption of an extravasation of blood. (Müller's fluid; carmine.) *a*, Peripheral nodule; *b*, lymph-sinus; *c*, cells containing pigment granules. Magnified 100 diameters.

The free pigment and the pigmented cells, then, cause distinct and early pigmentation of the tissue in the neighborhood of an area of extravasated blood. But soon the pigmented cells find their way into the lymph-channels and form *metastases* along the course of the lymphatics and in the adjoining lymph-nodes (Fig. 104), in which at first the pigment is lodged in the bodies of the free lymphoid cells, but later may come to lie in the tissue-cells also. After a time hæmosiderin is either destroyed and disappears, or it changes into a pigment which no longer gives the reaction for iron.

If hæmosiderin comes in contact after death with hydrogen sulphide it becomes black, and then causes the black and gray spots or diffuse patches spoken of as **pseudomelanosis**. This is observed most often in the intestine, in the peritoneum, and in suppurating wounds, since in these localities hydrogen sulphide is more apt to be formed in the course of putrefaction.

The question whether hæmosiderin granules may be converted into a pigment devoid of iron is differentlly answered by different authors. M. Schmidt and Neumann are of the opinion that the iron reaction of hæmosiderin is by no means constant, that it is quickly lost, and that it may even be absent from the first. The fact is that not infrequently the iron reaction is not obtained when the conditions are all such as to lead one to infer the presence of hæmosiderin. From this circumstance we are warranted in drawing the conclusion that the iron may disappear from the hæmosiderin, or else it may undergo a modification which it is impossible to demonstrate by microchemical methods; either one of these changes may take place without the occurrence of any loss of color in the affected granule. This phenomenon is observed oftenest in hæmosiderin in the lungs, and under these circumstances it assumes a dark-brown color.

The black pigment characteristic of *pseudomelanosis* has been believed by most

authorities to be due to the formation of sulphide of iron as the result of the action of hydrogen sulphide upon the iron of the hæmoglobin. According to the investigations of E. Neumann, pseudomelanin owes its origin to a simple cadaveric process of decomposition. It depends to a large extent upon local conditions, one of which is that iron-containing products of the decomposition of hæmoglobin should be formed during life, whereupon the hæmosiderin, through the action of hydrogen sulphide, assumes after death a black coloring. According to the investigations of Zeller, Arnold, and Ernst (*Centralbl. f. allg. Path.*, vii., p. 858), black pigment may also be formed during life through the agency of bacteria which produce hydrogen sulphide.

§ 75. **When large numbers of red blood-corpuscles break down in the blood,** hæmoglobin or methæmoglobin may come to be dissolved in the plasma, or portions of broken-down corpuscles may be swept about in the circulation. This condition is most pronounced in poisoning by arsenic, toluylendiamin, potassium chlorate, and mushroom, though it is observed also in many infectious diseases, in malaria, and in pernicious anæmia. Dissolved hæmoglobin or methæmoglobin imparts a red color to the blood-plasma (compare § 10), and this condition is termed *hæmoglobinæmia.* When much dissolved hæmoglobin is contained in the blood a portion of it may be excreted by the kidneys, giving rise to *hæmoglobinuria* and *methæmoglobinuria*, in which case the urine is of a reddish color that varies from a light brownish-red to a decidedly dark red. This is especially the case in arsenic-poisoning, but occurs occasionally as the result of other influences, as, for example, after exposure to cold (periodical hæmoglobinuria).

When the disintegration of the red corpuscles is not so complete, and fragments of them remain in the blood, as is the case not infrequently after burns, the fragments accumulate in the capillaries of the liver, spleen, lymph-nodes, and bone-marrow, and to a much less extent in some of the other organs. Sooner or later they are taken up by cells.

In the liver, as the result of this increased supply of hæmoglobin, there is considerable increase of functional activity, which is shown by the presence of an increased amount of bile-pigment in the bile, and occasionally oxyhæmoglobin also may be present in it (Stern). At times, when the amount of hæmoglobin brought to the liver is too great to be wholly disposed of in this way, one or other of the **derivatives of hæmoglobin may be deposited in the cells of the liver itself** or in other organs, or may be **eliminated by the kidneys.** When organs are colored yellow, orange, or brown as the result of such deposits, the condition has been aptly named by von Recklinghausen **hæmochromatosis.**

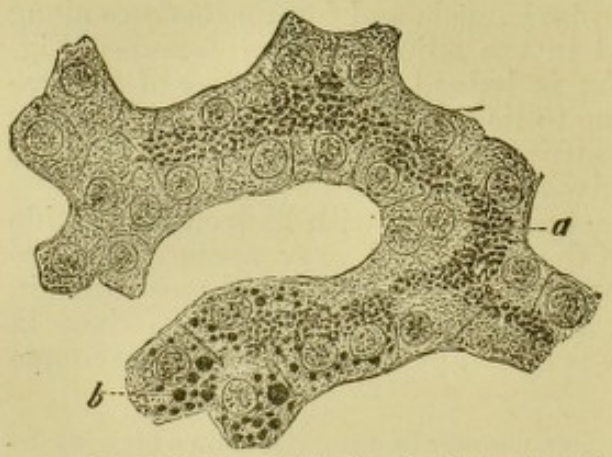


FIG. 105.—Infiltration of the trabeculæ of liver-cells with yellow hæmosiderin granules (as at *a*), from a case of pernicious anæmia. (Osmic acid.) *b*, Cells in a condition of fatty degeneration. Magnified 250 diameters.

The derivatives of hæmoglobin deposited in this way are the same as those met with in other extravasations of blood, and consist partly of pigments free from iron and partly of hæmosiderin. The latter is a frequent cause of pigmentation of the tissues, and it is therefore permissible to speak of a **pigmentation by hæmatogenous siderosis.**

These **deposits of iron-containing pigment** are most often met with in the liver, where they occur as yellow granules or masses in leucocytes and endothelial cells, in the plasma of the capillaries, in the liver-cells (Fig. 105, *a*), and in the star-cells of Kupffer. In pernicious

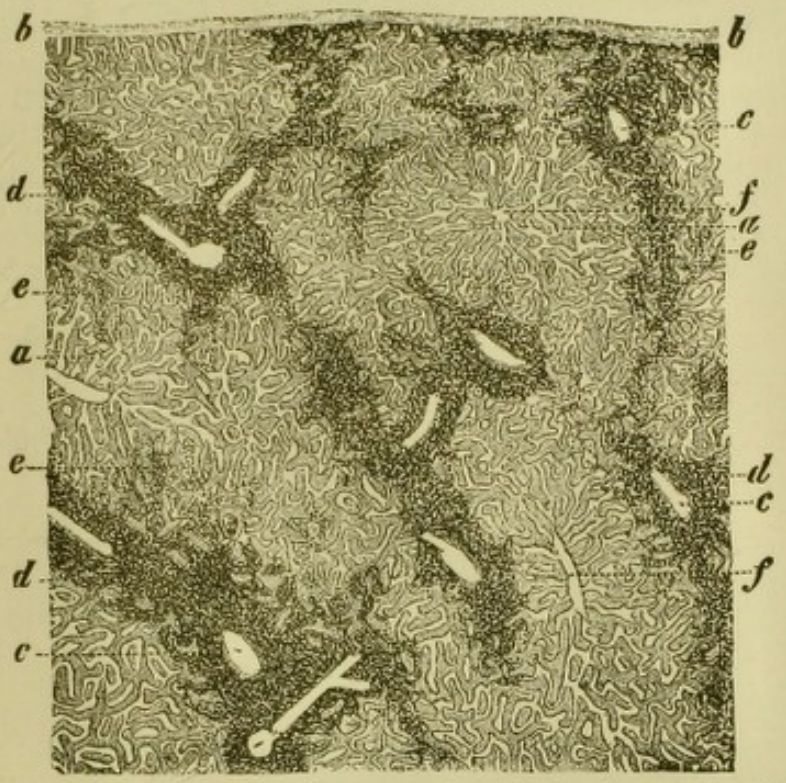


FIG. 106.—Hæmochromatosis of the liver, from a man who died of morbus maculosus Werlhofii. (Alcohol; carmine.) *a*, Acini; *b*, peritoneum; *c*, *c*, branches of the portal vein; *d*, infiltrated periportal connective tissue; *e*, pigment deposited inside of the capillaries of the hepatic lobules; *f*, venulæ centrales. Magnified 20 diameters.

malaria and pernicious anæmia the majority of the liver-cells may contain such pigment, as the result of which the whole liver may have a brownish color.

When large quantities of broken-down corpuscles or of hæmoglobin derivatives are brought to the liver, they accumulate more especially at the periphery of the acini (Fig. 106, *d*, *e*), and in the periportal connective tissue, lying, as before stated, partly free in the capillaries, or in the tissues themselves, and partly inside of leucocytes, liver-cells, connective-tissue cells, and the endothelial cells of the capillaries. The tissues thus infiltrated present a reddish-brown coloration distinctly visible to the naked eye.

The pigment which is carried to the *spleen* is found for the most part in cells lying loosely in the pulp, at times also in the fixed cells of the tissues. In the *lymph-glands* the iron granules lie chiefly in cells within the lymph-channels. In the *bone-marrow* retained hæmosiderin is found imprisoned partly in free cells lying within the blood-vessels, partly in the endothelial cells which line them, and partly in the cells of the pulp. The number of such iron-containing cells may be quite large. Hæmosiderin is found in cells in the capillaries, in the capillary endothelium, and in the pulp-cells.

In the *kidneys* the hæmosiderin granules are most abundant in the epithelium lining the convoluted tubes (Fig. 107, *a*), but they are also met with in the lumina of the tubules (*b*), in the capsular epithelium (*e*),

and in the endothelium of the capillaries. When scales of hæmosiderin are present in the circulation they are almost certain to be found in the capillaries of the kidney. When hæmoglobin is being eliminated by the kidney it is usually to be found in the lumina of some of the tubules. When pigmentation of the kidney is extensive, it may often be detected with the naked eye.

A large part of the hæmosiderin which is found in the various organs has been brought to them in the forms of granules or small flakes, and is then, as a rule, contained in leucocytes in the capillaries. But, in addition to this, solid particles of pigment would also appear to be formed in the cells themselves from material brought to them in solution. This view is sustained by the fact that, in applying the Prussian-blue reaction for the detection of iron, many of the cells which contain no definite granules nevertheless stain diffusely blue, indicating the presence of iron diffused through their substance. The iron-containing pigment which thus infiltrates the cells would appear to be later excreted by them in the form of solid masses of pigment, though it is, of course, possible that some of this diffuse coloration may have resulted from the solution of the iron within the cells. It is also suggested by the observations of a number of investigators that colorless iron-containing material—albuminates, perhaps—may at times be present in cells in the body, since the iron reaction develops oftentimes many more iron-containing granules than were otherwise visible in the tissue.

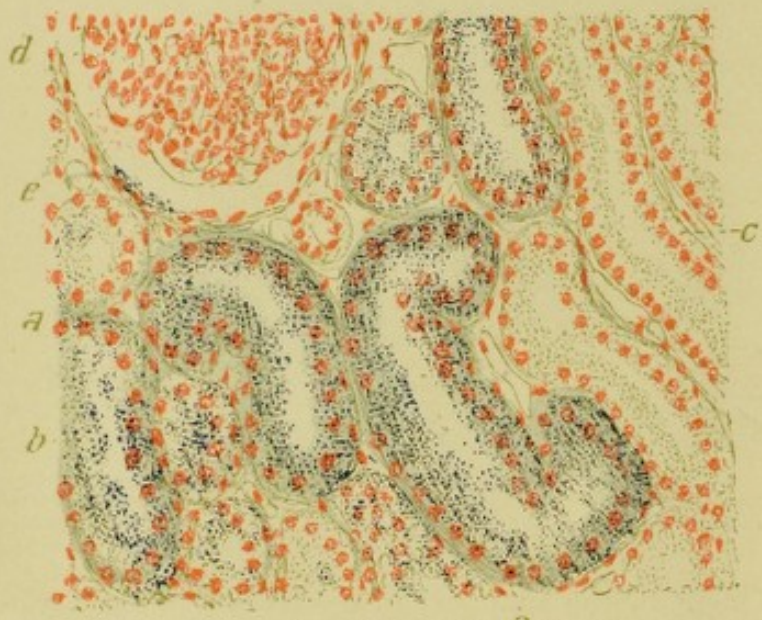


FIG. 107.—Hæmatogenous deposit of iron in the kidney, from a patient who died of pernicious malaria (contracted in Bagamayo). (Alcohol; carmine.) *a*, Convoluted uriniferous tubules, the lining epithelial cells of which contain granules of iron and are stained a pale-blue color; *b*, iron granules in the lumen of the tubule; *c*, straight uriniferous tubules; *d*, glomerulus; *e*, capsule epithelium, also containing iron granules. Magnified 150 diameters.

The **deposit of iron-free pigments,** *hæmatoidin* or *bilirubin*, is usually very scanty in cases of hæmatogenous pigmentation. Occasionally, however, there are also found, in the organs which I have enumerated, yellow bodies which do not give the reaction for iron, and which, it is reasonable to suppose, have not contained iron at any time, though it should be remembered that after a time hæmosiderin fails to respond to this reaction.

The organism supplies itself with what iron it may need by the **assimilation of the iron compounds** which exist in the iron-containing articles of food. The iron contained in the iron preparations commonly prescribed is absorbed into the system from the duodenum. When an excess of iron is absorbed, a portion of it, like the hæmosiderin, is stored in the spleen, in the bone-marrow, in the lymph-glands, and, for a brief length of time, also in the liver, while the rest of it is excreted by way of the kidneys, the liver, and the large intestine.

In **malaria** *two pigments* result from the destruction of the red corpuscles by the micro-organisms of that disease. The one is formed by the plasmodia themselves. It is black, gives no iron reaction, and lies in the bodies of the plasmodia. Nothing is known as to its nature. The other is hæmosiderin, which passes into the plasma of the blood as the result of the destruction of the corpuscles, and is later deposited in the liver, spleen, and marrow of the bones. When excessive destruction of the blood occurs, it may also lead to a condition of siderosis of the kidneys (Fig. 107) and to elimination of iron in the urine.

The *greenish coloration which is observed, in decomposing cadavers, in the neighborhood of blood-vessels filled with blood*, is dependent upon the formation of sulphide of methæmoglobin through the action of the hydrogen sulphide upon the blood.

§ 76. A pathological pigmentation of the tissues by bile-pigment is designated **jaundice** or **icterus**. Icterus is a symptom which is frequently present in the course of a number of diseases of the liver, and is a frequent occurrence during the first few days of life (*icterus neonatorum*).

During life the pigmentation known as jaundice is apparent chiefly in the skin, conjunctivæ, and urine, but after death it may be detected also in the internal organs, in the serous membranes, in the lungs, in the kidneys, in the liver, in the subcutaneous and intermuscular connective tissue, in the blood-plasma, in clots in the vessels, etc. Fresh icteric colorations are yellow, but after a time the skin may assume an olive-green or dirty grayish-green color; and similar colorations are also met with in the internal organs, particularly in the liver and occasionally also in the kidneys.

Jaundice results from the entrance of bile or of bile-pigment (bilirubin) into the blood and liquids of the body. During its continuance the urine contains bile-pigment also. These biliary pigments have their origin in the liver, and jaundice is consequently a hepatogenous disease. It commonly depends upon some diseased condition of the biliary passages or of the liver itself, as the result of which the outflow of bile from the liver is impeded. The bile is then taken up by the lymphatics and blood-vessels of the liver. Such a damming up of the bile may be brought about by catarrh of the bile-ducts; by narrowing or obliteration of the bile-ducts by cicatrices, by gall-stones, or by tumors which may have originated in the gall-ducts themselves or in the tissue in their neighborhood, and which compress them; by inflammatory conditions, abscesses, connective-tissue growths, tumors; or, finally, by congestion of the blood-vessels of the liver itself, which causes pressure upon or obliteration of the gall-ducts within the liver, and so prevents the outflow of bile through the gall-capillaries and smaller gall-ducts.

When for any reason the bile is congested in the small gall-ducts of the liver, the first thing which occurs, in all probability, is an absorption of a certain amount of the bile by the lymphatics of the liver. But as the process continues the bile accumulates more and more in the intra-acinous gall-capillaries (Fig. 108, *a*) and in the liver-cells themselves (*c*); and, as a result of this state of affairs, the stagnating mass of bile-pigment (*g*) may finally force its way—through a small rupture which can sometimes be demonstrated under the microscope—into the capillary blood-vessels.

According to the more recent investigations regarding the structure of the liver, the intracellular bile-capillaries extend into intracellular *vacuoles* which are filled with secretion, and from which are given off (still inside the cell) extremely delicate canaliculi (Nauwerck, Stroebe, and Browicz) that surround the nucleus like a network and are also des-

tined to convey secretion. Then at other points the liver-cells also stand in the closest relationship to blood-capillaries. Under normal conditions, therefore, a double secretion must take place in the liver—an

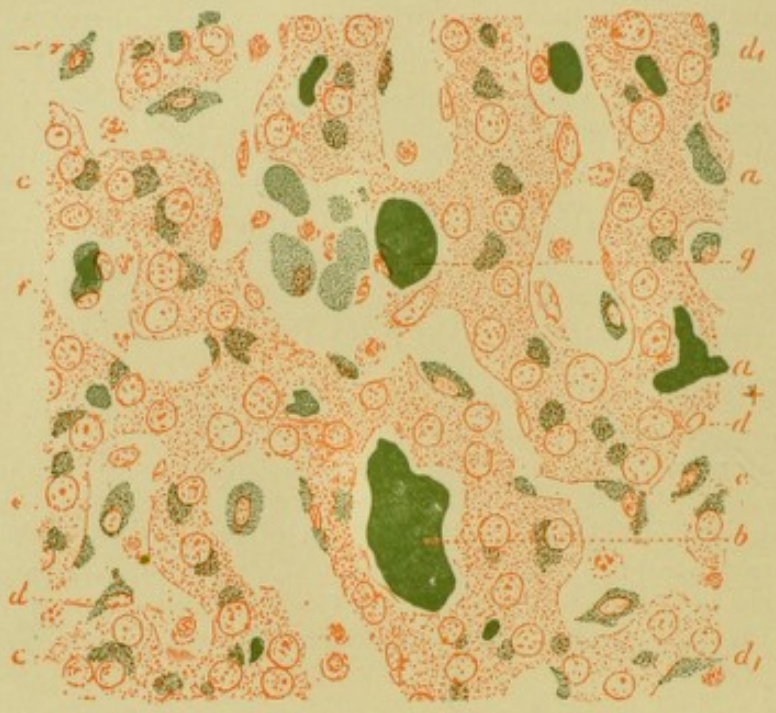


FIG. 108.—Icterus of the liver, from a case of cancer of the gall-bladder, in which there was compression of the ductus choledochus. (Corrosive sublimate; alum carmine.) *a*, Moderately dilated intravenous bile-ducts filled with bile; *b*, a large mass of bile pigment in a widely dilated intravenous bile-duct; *c*, bile-pigment in the liver-cells; *d*, d_1, still firmly attached endothelial and Kupffer's cells, stained by granules of bile-pigment; *e*, desquamated endothelial cells stained with bile; *f*, portions of pigment surrounded by cells; *g*, escape of pigment contained in the bile-ducts into a capillary. Magnified 365 diameters.

external one, of biliary acids and biliary coloring matter, in the direction of the gall-ducts; and an internal one, of sugar and urea, in the direction of the blood-vessels (Minkowski). Furthermore, Nauwerck believes that this latter secretion is also carried on through a network of the most delicate intracellular canaliculi. It is easy to understand, therefore, that disturbances of the secretion are of rather frequent occurrence, and that an escape of bile into the blood may occur, not only through a stasis in the flow of bile, but also through diseased conditions of the liver-cells, such as occur in the course of *certain infections and intoxications*. Accordingly, it is permissible to distinguish two kinds of jaundice or icterus: an *icterus due to a stasis in the flow of bile*—or a *stasis-parapedesis* (Minkowski); and an *icterus due to a toxic and infectious parapedesis of the bile* (Pick's paracholia). It is probable that the interpretation here given applies correctly to many forms of icterus which were formerly attributed to catarrh of the gall-ducts.

It is possible that disturbances in the innervation and circulation of the liver may also suffice to bring about an escape of bile into the intra-acinous lymph-channels or into the blood; a condition of things which would justify the employment of the term *nervous paracholia*.

In paracholia of long standing and of a pronounced character—such, for example, as is established when the gall-ducts are closed for a long period—not only do the liver-cells become stained, but also Kupffer's cells and the endothelial cells of the blood-vessels (Fig. 108, *d*, d_1); and in consequence of this impregnation the latter cells often become detached

from the walls of the vessel and lie free in its lumen. At a later stage other degenerative changes often develop as a consequence of the biliary stasis. Such are the following: cell-necroses, and inflammation and proliferation of the connective tissue.

When bile-pigment, either still in solution or in the form of granules or small masses, finds its way into the blood in the manner above described, *the tissues of the body, being bathed constantly by bile-stained lymph, gradually absorb some of the coloring-matter* and are colored by it. Solid particles which may be circulating in the blood, for the most part in cells, slowly accumulate in the spleen and in the bone-marrow. After a time the bile-pigment in solution in the various liquids of the body becomes deposited as fine granules, or more rarely as rhombic or acicular crystals, which have already been described as hæmatoidin (Fig. 102). This crystalline deposit rarely occurs except in new-born infants, where the crystals form in fixed and wandering connective-tissue cells, in the liver-cells, and in the tubular epithelium of the kidneys. In intense icteric conditions very many of the cells of the body come to contain bile-pigment. This is often accumulated in large amount in the lymph-glands (Fig. 109, *c*), to which it is, as a rule, carried by cells, and whose lymph-channels may be so filled with the yellow granules as to give to the whole gland a yellowish-brown color.

In the kidneys, which are active in eliminating the biliary pigment from the body in jaundice, there is also much pigmentation, particularly of the secreting epithelium of the tubules, which often desquamates

FIG. 109.—Icterus of the lymph-glands, following an attack of jaundice due to obstructed outflow of bile. (Corrosive sublimate; carmine.) *a*, Lymph-follicles with distended blood-vessels; *b*, capsule; *c*, lymph-channels with cells which contain yellowish-green pigment granules (entirely free from iron). Magnified 45 diameters.

in consequence (Fig. 110, *d*). When casts of the urinary tubules are formed as the result of the degeneration of the tubular epithelium, these casts are usually colored by the bile-pigment (Fig. 110, *b*, *c*).

Associated with the deposits of bilirubin in jaundice, there is always

more or less deposit of *hæmosiderin*, chiefly noticeable in the bone-marrow, in the spleen, and in the lymph-glands, occasionally also in the liver, so that the pigmentation of the tissues depends in part upon the presence of an iron-containing pigment in this condition also.

When *unusual disintegration of red blood-corpuscles* occurs within the blood, hæmatoidin or bilirubin is formed in association with hæmosid-

FIG. 110.—Icterus of the kidney, following an attack of jaundice due to obstructed outflow of bile. (Corrosive sublimate; carmine.) *a*, Tubular epithelium containing yellowish-green granules; *b*, large yellowish-green urinary cast; *c*, cast with pigment-cells entangled in its substance; *d*, desquamated epithelium containing bile-pigment granules. Magnified 200 diameters.

erin, as was explained in § 75, and is deposited in various parts of the body. Such extrahepatic bilirubin-formation is, however, very slight, and is never sufficient alone to cause jaundice, so that *a purely hæmatogenous icterus does not occur*. The liver is the great elaborator of bilirubin, and the production of this substance is at times increased in the liver as the result of disintegration of red corpuscles. *Jaundice, then, which follows breaking down of the blood, can occur only when associated with changes in the liver which result in the passage of bile into the blood.*

The question as to whether jaundice may be of hæmatogenous as well as hepatogenous origin has been under discussion and is still unsettled, notwithstanding numerous experimental investigations directed to its solution. Since, as a matter of fact, bilirubin may be formed in the tissues as the result of extravasation of blood, the likelihood of the occurrence of hæmatogenous icterus would *a priori* seem quite plausible. Experiments made with arsenious acid, toluylendiamin, and potassium chlorate, to determine the result of the disintegration of red blood-corpuscles in the blood, have, however, shown that the derivative of the blood which forms and is deposited in the various tissues is hæmosiderin, and that the formation of bilirubin under these circumstances is confined to the liver, which for the time being excretes an increased amount of intensely pigmented bile.

According to Minkowski and Naunyn, the urine of geese and ducks contains no bile-pigment after extirpation of the liver—a fact which would indicate that the transformation of blood-pigment into bile-pigment is ordinarily limited to the liver. The inhalation of vapor of arsenic for a very few minutes is sufficient to produce in geese intense polycholia and hæmaturia, the urine containing hæmoglobin in solution, fragments of red corpuscles, and biliverdin. If, now, the liver of such a goose be extirpated, biliverdin quickly ceases to be present in the urine, and there is, at the same time, no biliverdin in the blood. It is thus evident that in arsenic-poisoning the formation of the bile-pigment which appears in the urine must occur in the liver, in which broken-down blood-corpuscles are found in large numbers.

So far as may be inferred from the results of experiments which have been made up to the present time, it would seem that a purely hæmatogenous jaundice does not occur. The mere fact of the occurrence of jaundice in intoxications, after ether and chloroform inhalations, transfusion, and snake-bite, and in septicæmia, typhoid fever, yellow fever, paroxysmal hæmoglobinuria, etc., is in no wise proof that the jaundice in these cases is of hæmatogenous origin. There is, indeed, in these conditions an increased destruction of red blood-corpuscles; but bilirubin is essentially a product of the liver, and its presence in the blood may readily be accounted for on the supposition that a part of the bile produced in excess in these conditions finds its way into the blood. In fact, Stadelmann has shown that change in the density of the bile may bring about its absorption by the blood.

§ 77. **Pigmentation of the tissues by foreign substances introduced into the body from without** occurs when substances possessed of color in themselves, and incapable of resisting the action of the body-fluids, gain access in any manner to the tissues and remain there. The substances which may act in this way are naturally numerous, as are also the modes of their entrance into the body. *The lungs are their most frequent channel of entrance*, but they may also be taken in through the intestine or from wounds. *Tattooing of the skin* affords a familiar example of the introduction of pigment through wounds. This staining is effected by rubbing insoluble granular pigments, such as lampblack or cinnabar, into slight wounds of the skin. The pigments penetrate into the wounds and infiltrate the tissue in their immediate neighborhood, part of the pigment remaining permanently in the corium (Fig. 111, *c*), while some of it is carried to neighboring lymph-glands, which then participate in the pigmentation.

The lungs and their lymph-glands are often intensely pigmented as the result of inhalation of particles of dust, more particularly coal-dust, soot, iron-dust, etc. They may become actually black in consequence of inhalation of coal-dust. A part of the dust inhaled is carried to the

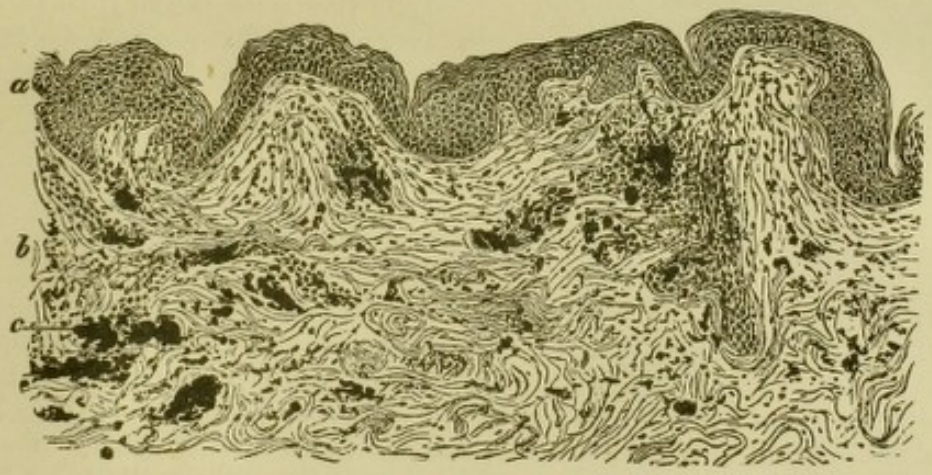


FIG. 111.—The deposit of cinnabar in a tattooed skin. (Alcohol; alum carmine.) *a*, Epithelium; *b*, corium; *c*, cinnabar. Magnified 80 diameters.

bronchial lymph-glands, which often become quite black, and may undergo more or less softening when the pigmentation is excessive. When these glands are situated near blood-vessels, the latter may be secondarily involved in the pigmentation, and sometimes also in the softening, and in this way particles of the pigment may gain access to the circulation and may be carried to remote organs, such as the liver, spleen, and bone-marrow, where they may be deposited (cf. § 18).

Among the pigmentations which may result from absorption through the intestine we may mention the condition known as *argyria*, which is dependent upon the long-continued use of preparations of silver. The skin under these circumstances may assume an intense grayish-brown coloration, and in a similar way the internal organs may undergo pigmentation to a greater or less degree. The silver is deposited in the form of fine grains in the stroma of the tissues, more especially in the glomeruli and in the connective tissue of the medullary portion of the kidneys (Fig. 112, *b*), in the intima of the larger vessels, in the adventitia of the smaller arteries, in the neighborhood of mucous glands, in the papillæ of the skin, in the connective tissue of the intestinal villi, and in the choroid plexus of the lateral ventricles. Deposits may also occur in the serous membranes, but epithelial tissues, the brain, and the cerebral vessels escape. Extensive deposits in the medullary portion of the kidney may lead to growth of dense connective tissue, which then not infrequently undergoes calcification.

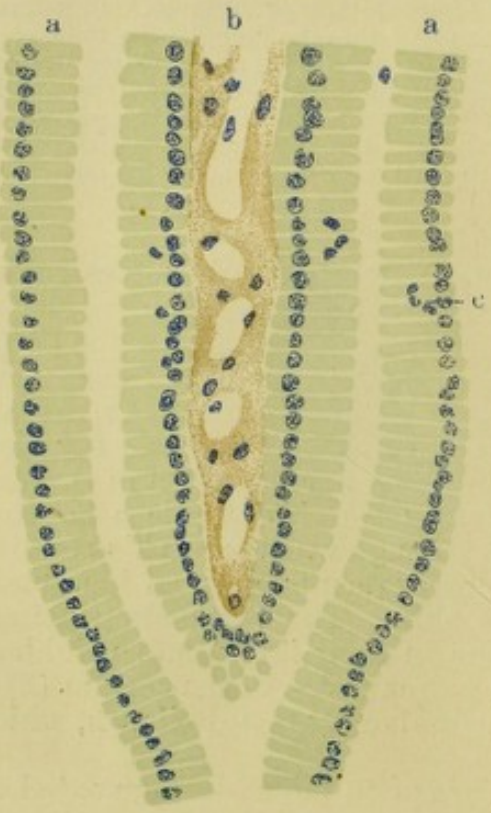


FIG. 112.—Deposits of silver in the pyramidal portion of a rabbit's kidney, after the animal had regularly received fixed doses of a silver-preparation for a period of seven months (experiment of von Kahlden). (Alcohol; hæmatoxylin.) *a*, Epithelium of the collecting-tubes; *b*, connective tissue filled with brown granules of silver. Magnified 500 diameters.

Iron particles taken into the body in large amount may also lead to pigmentation of the bone-marrow, spleen, and lymph-glands, though rarely to such an extent as to be visible to the unaided eye.

XV. The Pathological Absence of Pigment.

§ 78. **The absence of pigment** occurs, in the first place, as a congenital, inherited affection, and is then termed **albinism** or **leukopathia congenita.** In some of the cases the absence of pigment extends over the entire body (*universal albinism; Kakerlaken; albinos*), while in others it is confined to a few portions of the skin (*partial albinism*). In those parts of the skin where the pigment is absent the hairs will also be found to lack pigment; they are white, or yellowish-white (*poliosis seu leukotrichia congenita universalis et circumscripta*). In universal albinism the pigment is absent even from the retina, the choroid, and the iris; and consequently the choroid, from the amount of blood which it contains, appears red, while the iris, according to the angle at which it is viewed and also according to the character of the illumination, may appear either bluish-white or red. Under the microscope the only thing that can be discovered is the absence of pigmented cells.

A second form of absence of pigment is that which is known as

vitiligo or **leukopathia acquisita.** This affection, which develops only in the later years of life, occurs partly as a concomitant of certain well-known diseases (scarlet fever, typhoid fever, and relapsing fever), partly as a symptom of an epidemic disease (vitiligo endemica) the etiology of which is unknown, and partly without any recognizable cause. The formation of white patches within the area of which the hairs also lose their color (leukotrichia acquisita circumscripta), takes place as a rule in a symmetrical manner, and it may spread throughout the greater part of the body (Fig. 113). The white patches are surrounded by a border of skin somewhat more darkly pigmented than usual; and this condition suggests the idea that when the pigment disappears from one part it merely undergoes a displacement to an adjacent part. The loss of color in the hairs always begins—as it does in the process of growing-gray in the later years of life—in the root; and the reason for this loss is to be found in the fact that the hair papilla no longer furnishes any pigment to the bulb of the hair. Eventually, even the pigment cells of the hair papilla disappear altogether.

A third form of loss of pigment is observed in connection with traumatic or infectious *inflammations* of the skin, and especially with syphilitic exanthemata and with lepra. The term **leukoderma** may be employed to cover all the cases which belong in this category.

In cicatrices of the skin which remain white, the tissue that replaces that which has been destroyed does not receive the power of again producing pigment, and consequently it presents itself in the simple form of a colorless cicatrix covered with epithelium. A scar of this kind is often bordered by pigmented tissue. In the milder forms of inflammation, in which (as in syphilis) the tissue of the skin is not destroyed, the process of decoloration sets in either immediately after the subsidence of the inflammation or else at some later date,—sometimes only after the skin has passed through a stage in which there is an actual increase in the pigmentation. According to Ehrmann, the cause of this lack of pigment is to be sought for either in the fact that, at the boundary where it is separated from the epithelium, the corium possesses no pigment-cells which are capable of furnishing pigment to the epithelial cells, or else in the fact that the epithelial cells, in their altered condition, are not able to appropriate the pigment. The pigment which still remains in the cutis may be absorbed.

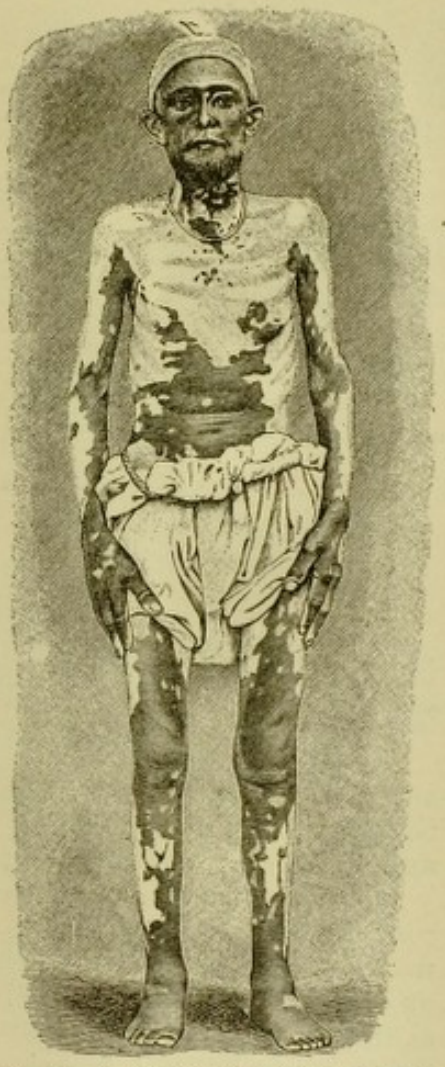


FIG. 113.—Vitiligo endemica (from a photograph sent to me by Professor Münch).

According to Münch vitiligo is quite common throughout Turkestan, and is considered by the natives (Sarts) to be contagious. In consequence of this belief they are

in the habit of isolating those who have the disease and of confining them in enclosed courts along with persons suffering from leprosy. It is probable that in medical literature endemic vitiligo and lepra maculosa have been mistaken, the one for the other, by many writers, and that the first of these two has been described under the designation "white leprosy of the Jews."

XVI. Cyst-formation.

§ 79. A **cyst** is a circumscribed cavity which is shut off from the surrounding tissues by a connective-tissue membrane or by tissue of complex structure, and which possesses contents the nature of which is different from that of this capsule. When a cyst comprises only a single such cavity it is called a *simple cyst;* when it is divided into a number of compartments it is said to be *multilocular*.

The most frequent form of cyst is the so-called **retention cyst,** *which results from the accumulation of secretion in preëxisting spaces that are lined with epithelium or with endothelium.*

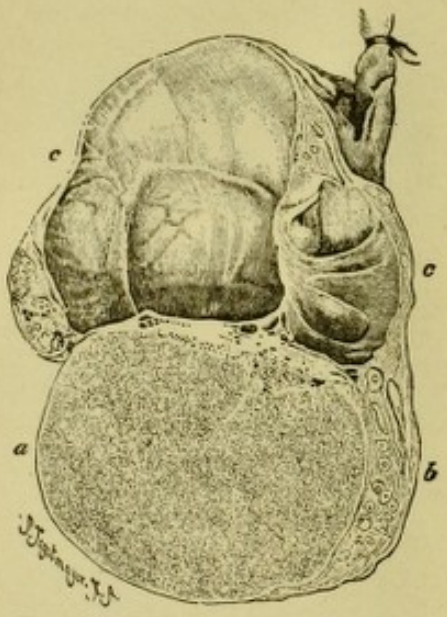


FIG. 114.—Section of the testicle and epididymis, showing multiple cysts in the head of the epididymis. *a*, Testicle; *b*, epididymis; *c*, cyst broken up into compartments. (Nearly natural size.)

These cysts form in **glands provided with an open duct,** when obliteration of this outlet occurs in any part of its course, provided that actively secreting parenchyma still exists beyond the point of obliteration. They are accordingly met with in the sebaceous glands of the skin, in the hair-follicles, in the uterine glands, in the mucous glands of the alimentary tract, in the epididymis (Fig. 114, *c*), in the urinary tubules (Fig. 74), and less frequently in the gall-ducts and their glands, in the breast, in the pancreas (Fig. 115, *b*), in the glands of the mouth, etc. Larger canals may also become cystic—as, for example, the ureters, the vermiform appendix, and the Fallopian tubes (Fig. 116, *c*).

The obstruction of the duct necessary to cause a retention cyst may be brought about by accumulation of the secretion of the gland, or by cicatricial or neoplastic compression and consequent obliteration.

Closed glandular cavities and tubes such as the follicles of the thyroid gland and of the ovary, or the glandular tubes of the parovarium, undergo cystic degeneration when their walls pour out an inordinate amount of secretion. Similarly, **remains of fœtal canals or clefts**—for example, those of the branchial clefts, of the urachus, or of Müller's ducts—may become cystic.

Small cysts, such as are met with in mucous glands, vary in size up to that of a pea. Larger cysts, like those occurring in the liver and in the ovary, may attain the size of the fist or be even larger.

The **contents of cysts** depend upon the nature of the tissue in which they are formed. Thus cysts of the hair-follicles and of the sebaceous glands (*atheromata*) contain a semi-solid material, whitish, grayish, or brownish in color, composed chiefly of squamous epithelial cells, fat-

globules, and cholesterin; cysts formed in mucous glands contain clear, or, when cellular elements are also present, milky, mucous liquid.

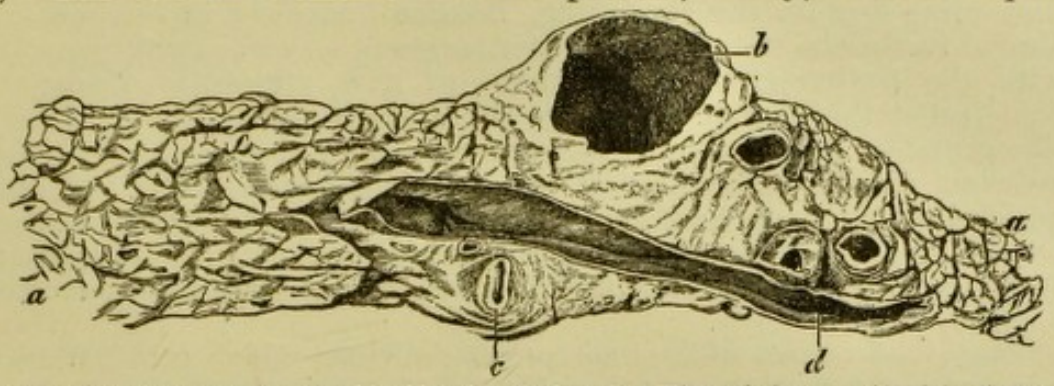


FIG. 115.—Cyst of the pancreas, caused by dilatation of a branch of Wirsung's duct. *a*, Glandular tissue; *b*, cyst; *c*, transverse section of an artery; *d*, longitudinal section of a vein. (Natural size.)

When hemorrhages take place into cystic cavities the blood imparts its color to the cyst-contents, making them red or brownish. Cystic Graafian follicles usually contain clear, more or less colored liquid; cysts of the thyroid gland and of the kidney contain colloid material, or clear, though occasionally cloudy, liquid.

Retention cysts lined with endothelium may arise from blood-vessels, lymphatics, lymph-spaces, synovial membranes, or tendon-sheaths. Here also the nature of the cyst-contents depends upon its place of origin. Not infrequently the condition resulting in cyst-formation is caused by the shutting off of a portion of one of the cavities already named by a constriction.

As enlargement of a retention cyst goes on it is quite necessary that the tissue composing its wall should also develop, for otherwise defects

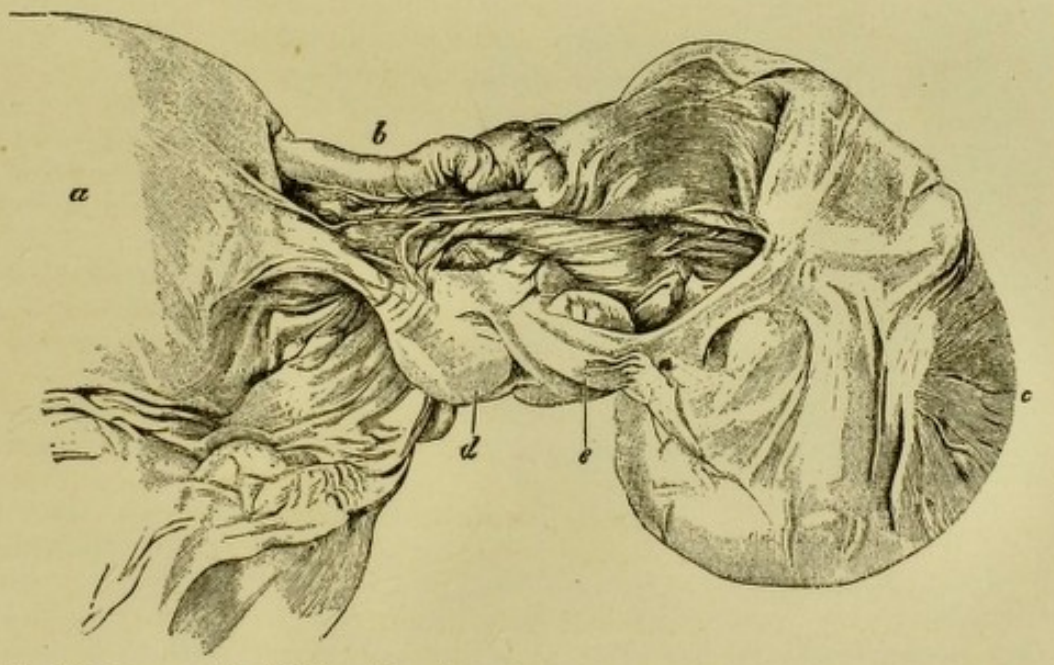


FIG. 116.—Dropsy of the Fallopian tube, with perisalpingitic and periovarian adhesions. *a*, Uterus; *b*, uterine portion of the tube; *c*, abdominal end of the tube, in a condition of cystic degeneration and adhering to the neighboring parts; *d*, ovary; *e*, membranous adhesion. (Two-thirds natural size.)

in its wall would result. **Cyst-formation** is, therefore, not an exclusively degenerative process. The epithelial or endothelial cells lining

the cyst-wall are the first to show this development, but the connective tissue upon which these cells rest participates in it also, as a rule, and may even, despite the stretching, become increased in thickness. It should further be stated that cyst-formation is very frequently associated with the **pathological development of new glandular tissue**, and constitutes, therefore, a secondary alteration in hypertrophic or tumor-like growths. Consequently it is sometimes impossible to distinguish between simple retention cysts of preëxistent gland-ducts and gland-vesicles, on the one hand, and those tumors, on the other, which are characterized by the presence of cyst-formations (the **cystomata**). Similarly, *cysts lined with endothelium may originate from newly developed lymph spaces and ducts.*

A second variety of cyst comprises the **cysts which result from degeneration, softening, and liquefaction of a portion of tissue.** Cysts are formed in this manner in the brain, in enlarged thyroid glands, and even in tumors. They are usually filled with either a clear or a more or less cloudy liquid.

A third kind of cyst results from the formation of a dense **capsule of connective tissue about any foreign substance** which may have found entrance into the body—as, for example, around a parasite.

A fourth variety of cyst is formed by **parasites** which pass through a cystic stage in the course of their development in the body.

CHAPTER V.

Hypertrophy and Regeneration of the Tissues and Organs.

I. General Considerations Concerning the Processes called Hypertrophy, Regeneration, and Heteroplasia, and the Cellular Changes that Accompany Them. Transplantation of Tissues.

§ 80. By **hypertrophy** is meant an increase in the substance of a tissue or organ, brought about by an increase in, or multiplication of its elements in such a way that the structure of the hypertrophied tissue is similar to, or at least does not materially differ from, that of the normal.

By **regeneration** is meant the process by which a loss of substance in a tissue is restored by a new tissue that is exactly like that which was lost, or at least that contains the same elements which it had.

Hypertrophy may result from a morbid impulse existing in the germ-plasm itself, or from an impulse originating during the life of the individual. Regeneration, on the contrary, is always secondary to a tissue-lesion, which, however, may occur during either intra-uterine or extra-uterine life. And yet the degree of the completeness of the restoration depends here also upon the individual powers possessed by the different tissues.

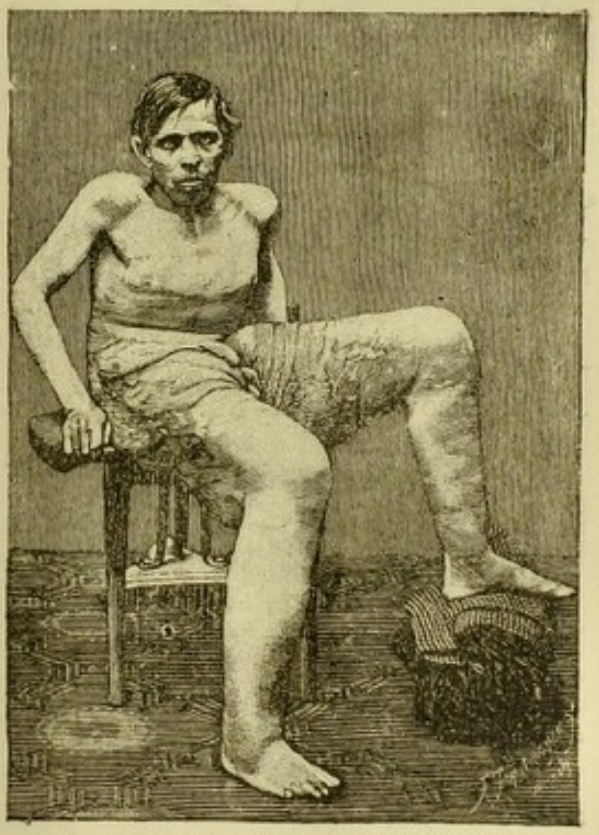


FIG. 117.—Elephantiasis femorum neuromatosa.

If an abnormal tissue-increase takes place during the period of embryonic development or of extra-uterine growth, and if there are no influences discoverable which would seem to account for the tissue-growth, then we are disposed to regard it as the result of **embryonic impulses**, and so we call it **hypertrophy of congenital origin.** If the enlargement affects the entire body—for example, if a newly born child weighs 5 or 6 kgm., or if an individual reaches the height of 180 or 200 cm.—this is called **general giant growth.** If the growth affects only certain parts of the body—for example, the entire head or one-

half of it, or one extremity, as a finger, or the labia majora or minora—it is called a **partial giant growth.** Hypertrophic growths of the skin that lead to changes suggesting the skin-formation of the pachydermata are called **elephantiasis** (Figs. 117 and 118).

FIG. 118.—Elephantiasis cruris lymphangiectatica.

In hypertrophy of a limb or of a finger all the elements of the part are uniformly enlarged. In elephantiasis of the extremities the connective tissue of the skin and of the subcutaneous structures especially is apt to increase, though the development and structure of these growths show considerable variations in that the pathological new formation sometimes affects all the connective-tissue elements uniformly, sometimes single elements only—as, for example, the connective tissue of the nerves or the blood- or lymph-vessels—or at least takes its start from these. For this reason it has been customary to distinguish different varieties of elephantiasis, named, according to the structure of the hypertrophic tissue, elephantiasis neuromatosa (Fig. 117), angiomatosa, lymphangiectatica (Fig. 118), lipomatosa, fibrosa, etc.

If, as a result of some peculiarity in the condition of the skin, an hypertrophy of the horny layer of the epidermis takes place (Fig. 119, *c*), and as a result of this process the skin becomes covered with hornlike plates and scales, or even with spur-like

FIG. 119.—Ichthyosis congenita. Section through the skin of the trunk of the body. (Alkaline picrocarmine preparation.) *a*, Corium, with glands; *b*, papillary body, with rete Malpighii; *c*, hypertrophied horny layer of the epidermis; *d*, dilated hair follicles, lined with horny epithelium; *e*, hairs. Magnified 40 diameters.

formations, the condition thus presented will be that to which the name **ichthyosis** is commonly given.

This peculiar alteration of the skin is even met with at birth (*ichthyosis congenita*), and the newly born child (Fig. 120) may be completely covered with hard, horny plates, which have split open at different points through the upward growth of the subjacent tissues. This pathological horny alteration first affects only the superficial parts of the skin (Fig. 119, *c*), but it may also extend into the hair follicles (Fig. 119, *d*).

FIG. 120.—Ichthyosis congenita.

In other cases, at a later period—for instance, during the first year of life—circumscribed areas of thickening of the epidermis develop, which form firm scales and plates, sometimes smaller, sometimes larger, giving the skin a rough or checkered appearance. The corium and the papillary layer generally are not involved in the ichthyosis. Nevertheless there are cases in which, in the areas of ichthyosis, the papillary layer is hypertrophied, and in these cases the roughness of the surface is intensified (*ichthyosis hystrix*). If the change is confined to small, limited spots, then circumscribed warts with rough epithelial covering are formed, and these may be called *ichthyotic warts*. In rare cases there are developed still more extensive layers of epithelium over the hypertrophied papillæ, whose scales are arranged perpendicularly to the layers of the skin; and these sometimes reach such dimensions that they are called *epidermal horns* (Figs. 121 and 122.)

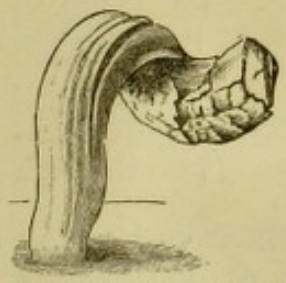


FIG. 121.—Cornu cutaneum, removed from back of hand. (Natural size.)

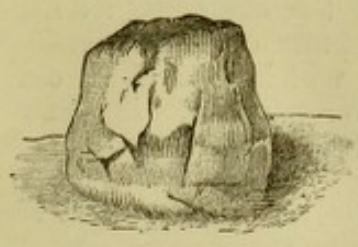


FIG. 122.—Cornu cutaneum, removed from arm. (Natural size.)

By the hypertrophic development of hair in situations where only woolly hair, or even no permanent hair at all, should occur, there is brought about an abnormal hairiness over a larger or smaller area of the body, which is known as **hypertrichosis**, and this is explained either as a persistence or abnormal development of the primary or down-like hairs (Fig. 123. Hypertrichosis lanuginosa fœtalis), or as a pathological development of the secondary hairs.

Excessive growth of the nails leads to their pathological overgrowth, to *hyperonychia*, which is often followed by *onychogryphosis*, or claw-like deformities of the nails. It must, however, be noted that pathological increase of the nails is generally an acquired disease.

The **bony structures** of the body undergo different forms of hypertrophy. In the first place, they are apt to become enlarged during the progress of the disease known as giant growth—either general or partial. Then, in the next place, they may become the seat of a form of hypertrophy which corresponds to inherited elephantiasis of the skin; the disease showing itself most often in some part of the head, and occasionally producing an extraordinary increase in the size of the bones (Fig. 124). The disfiguration which is thus produced, and which gives to the patient's head a certain resemblance to that of a lion, has for this reason led to the adoption of the name **leontiasis ossea** for this condition. Then, in addition to the above, circumscribed tumors

FIG. 123.—Head of a hairy individual, a woman. (From Hebra.)

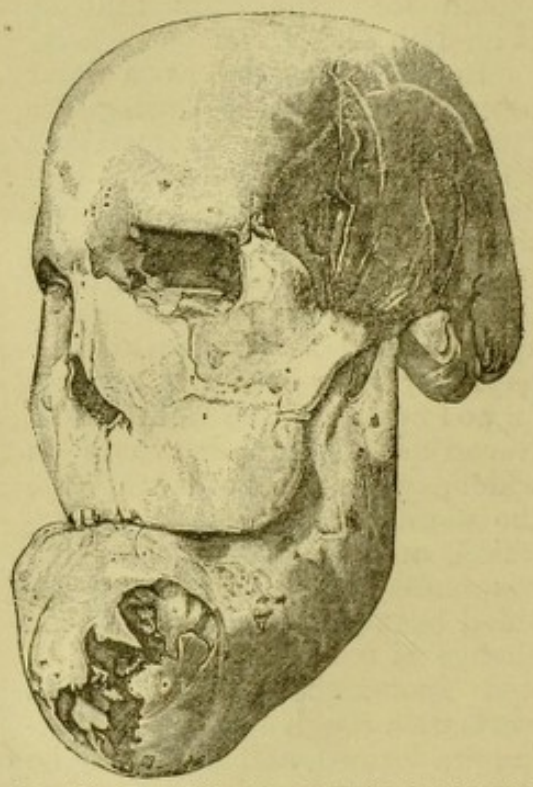


FIG. 124.—Leontiasis ossea, occurring in a boy the subject of general giant growth. (Observed by von Buhl.)

of bone, commonly termed **exostoses**, often develop upon the skull, as they may in other parts of the skeleton, as hereditary pathological growths, quite independent of any outside influences.

Hypertrophic processes, which owe their origin to an excessive impulse of growth, and not to any outside influences, rarely occur in **internal organs**; and yet the brain may attain an abnormal size through mere hypertrophy.

It cannot be stated definitely to what extent the different forms of hypertrophy of the tissues, like those described above, are to be attributed to congenital predisposition; for all sorts of external influences are competent to bring into existence similar products of tissue-proliferation, and even internal causes may produce them. Thus, for example, the horny growths of the skin and the thickenings which characterize elephantiasis of the skin may develop as a result of simple inflammation.

As a general rule, the early appearance of hypertrophic growth, as

well as the hereditary nature of the pathological peculiarity and the absence of any external cause for the trouble, favors the idea of a congenital predisposition. And yet the fact that there were later influences which evidently gave rise to the growth does not preclude the existence of a congenital predisposition. Thus, for example, the bony growths of the head referred to above may in one sense be attributed to some external injury or to an acute inflammation. These latter were doubtless the exciting causes, but they alone could not have called these growths into existence; for we know by experience that causes like these can give rise to such pathological products only when the tissues already possess a special predisposition.

The size of the entire body as well as of its separate parts and organs is subject to considerable variations within the normal physiological limits, according to race, family, and individual idiosyncrasy. The variation in the relation of the size of the separate parts and organs to that of the entire body is less great.

The average height of well-built individuals is, according to Vierordt,[1] as follows: men 172 cm., women 160 cm.; of the newly born, males 47.4, females 46.75 cm. The average body-weight in Europe is for men 65 kgm., for women 55 kgm., for the newly born 3,250 gm.

The average weight of organs is as follows, the figures in parentheses being for the newly born: brain, 1,397 (385) gm.; heart, 304 (24); lungs, 1,172 (58); liver, 1,612 (118); spleen, 201 (11.1); right kidney, 131; left kidney, 150; both kidneys, 299 (23.6); testicles, 48 (0.8); muscles, 29,880 (625); skeleton, 11,560 (445) gm. Expressed in percentages of the body-weight we have the following figures, those in parentheses being for the newly born: heart, 0.52 (0.89); kidneys, 0.48 (0.88); lungs, 2.01 (2.16); stomach and intestinal canal, 2.34 (2.53); spleen, 0.346 (0.41); liver, 2.77 (4.39); brain, 2.37 (14.34); suprarenal bodies, 0.014 (0.31); thymus, 0.0086 (0.54); skeleton, 15.35 (16.7); muscles, 43.09 (23.4).

§ 81. The **hypertrophies of the tissues which owe their origin wholly to outside influences, without the co-operation of the force which predisposition furnishes,** are the following: hypertrophy due to an increase in the activity of a tissue, hypertrophy dependent upon diminished use, hypertrophy due to defective retrograde changes, and finally hypertrophy due to prolonged or frequently repeated mechanical, chemical, and infectious irritations of the tissues. Under certain circumstances the simple removal of a pressure which weighs heavily upon a limited area of the tissues is sufficient to effect a localized hypertrophy.

Hypertrophy from overwork is oftenest met with *in muscles* and *in glands*, but may occur in other structures. If the heart is called upon to do an extra amount of work, by reason of special valvular, or aortic, or even renal conditions, and if these conditions exist for a considerable length of time, then that part of the heart-muscle upon which this extra work falls suffers a more or less marked hypertrophy (Fig. 125), and in this way the total bulk of the organ may reach double the normal, or even more.

Similarly, striated muscle, also the muscular layers of the bladder, the ureters, the uterus, the intestine, and the blood-vessels, may become hypertrophied from a persistent increase in their activity.

Of the glands, it is *the kidneys* and *the liver* especially that are capable of changing their size to suit functional needs, and correspondingly it is these glands that are most liable to undergo hypertrophy. If one kidney becomes destroyed, the other is capable of undergoing such an enlargement that it may reach approximately the same weight that the

[1] Vierordt: "Anatomische, physiologische und physikalische Daten und Tabellen zum Gebrauche für Mediciner," Jena, 1893.

two kidneys together originally had. In the same way, the liver, after destruction of part of its parenchyma by disease, is capable of compensating for its loss by a hypertrophy of the remainder. This advantageous increase is called **compensatory hypertrophy**, because by it the normal function of the organ is restored. One may apply the same term also to muscle-hypertrophy, if by means of it lost function is restored. In the case of some other glands, as the salivary glands, ovaries, testicles, and mammæ, compensatory hypertrophy either does not occur at all or takes place only during the period of development. For example, the loss of one ovary or testicle in adult life can hardly result in an increased activity or hypertrophy of the remaining one. In the case of the thyroid gland, extirpation of the larger part of it is generally not followed by any material hypertrophy of the piece remaining. On the other hand, the hypophysis suffers an enlargement which must be re-

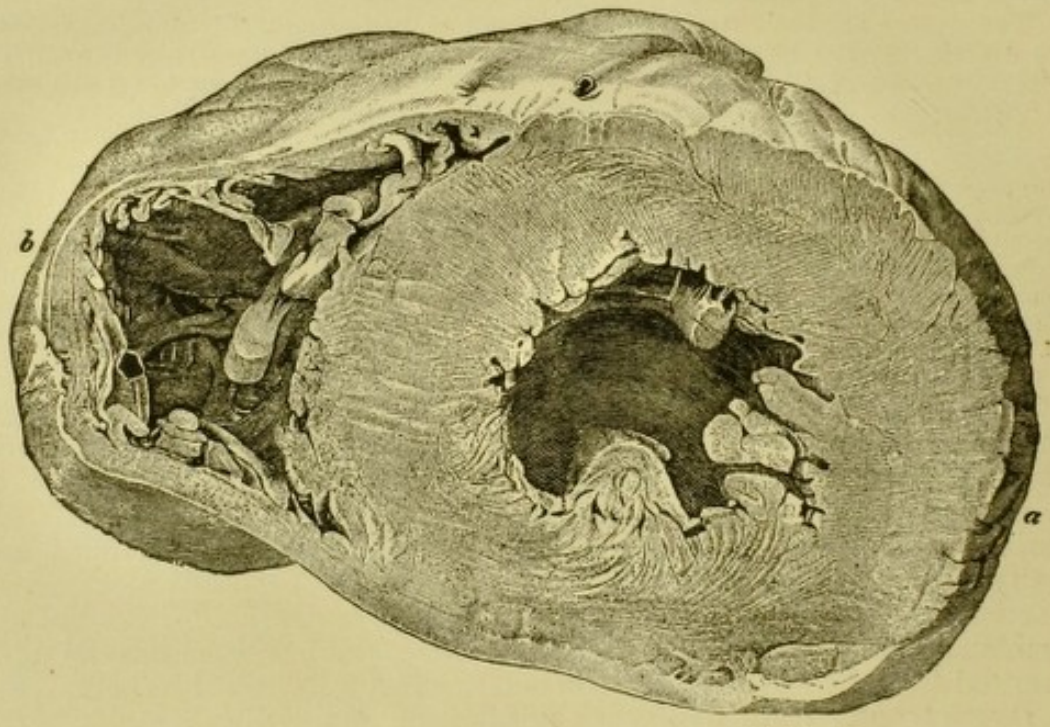


FIG. 125.—Transverse section of a heart, with hypertrophy of the left ventricle, in insufficiency and stenosis of the aortic valves. *a*, Left ventricle; *b*, right ventricle. (Natural size.)

garded as compensatory. In the case of the lungs, an increase in the activity of one portion, after loss or destruction of other parts, is generally followed only by a permanent distention, which, indeed, may even go on to atrophy. On the contrary, if during embryo life a faulty development of one lung takes place, the other may become the seat of a compensatory growth; and in the case of total failure of one lung to develop, this enlargement of the other may reach a very marked extent. Other tissues also behave in a similar way (the testicles, for example, according to Ribbert), and it may be stated as a general rule that compensatory development of a tissue is more nearly complete the younger the individual is. In the same way, compensatory development of the kidneys is more marked in young than in old persons. In the case of the brain, a compensatory growth of one part, after loss of another, is possible only during the earlier stages of the developmental period.

In tissues that are in constant use a **lessening wear** may lead to

hypertrophy. For instance, a diminished desquamation of the epidermal layer of the skin leads to a pathological thickening of it. If the incisor teeth of rodents are no longer normally worn down, by reason of the destruction of an opposing tooth or the oblique position of the teeth, they may grow to be very long and curved (Fig. 126). In the same way, finger- or toe-nails may reach an abnormal size, by reason either of absence of wear or of their being left uncut. Organs which, after the lapse of a certain fixed period of physiological growth, usually undergo a diminution in size, may become hypertrophied from a **failure to undergo retrograde changes.** For example, the uterus, after pregnancy, may remain abnormally large, from involution failing to take place. The thymus gland, which, after the tenth year of life, should begin to wither away and disappear, may persist for a considerable length of time beyond this period. The **removal of a pressure which weighs heavily upon a tissue** may—especially in the case of bone-tissue—lead to a certain degree of hypertrophy of the tissue, but as a rule the increase is apt to be insignificant.

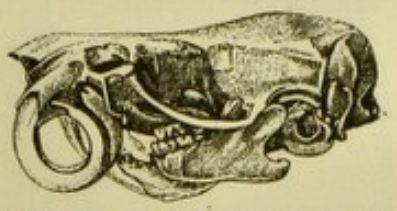


FIG. 126.—Hypertrophy of incisor tooth of a white rat, occurring by reason of oblique position of the jaw. (Natural size.)

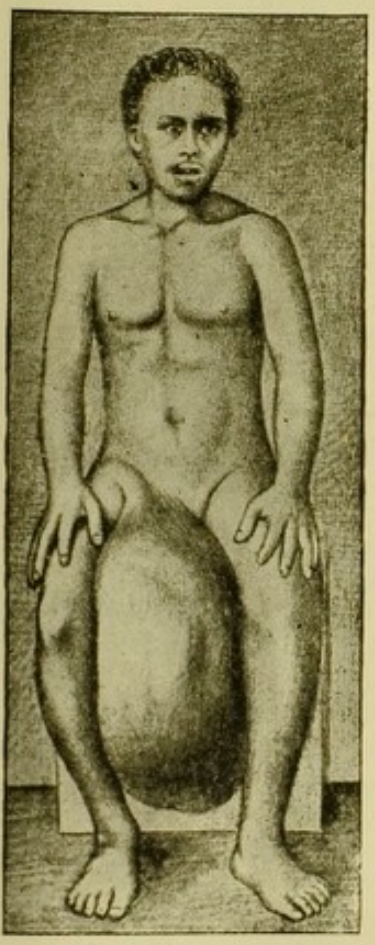


FIG. 127.—Elephantiasis scroti in a native of Samoa nineteen years old. (After Uthemann, Deutsche med. Wochenschr., 1895.)

Frequently repeated or long-protracted mechanical, thermal, chemical, or infectious irritation occasions proliferative processes leading to tissue-hypertrophy, which, from their origin and course, may be ascribed to the category of chronic inflammations, so that we may regard these new tissue-formations as an **inflammatory tissue hypertrophy.**

If the skin is subjected to frequent mechanical irritation and pressure, as the toes, for instance, are irritated by an ill-fitting boot, thickenings of the horny layer of the epidermis will follow, known under the name *callus* or *corn* (clavus). Prolonged irritation of the skin, in the neighborhood of the genital apertures, by gonorrhœal secretion, may cause a very considerable elongation and branching of the skin-papillæ with an attendant thickening of the epithelium, leading to those wartlike, cauliflower-growths known as *condylomata acuminata* or *venereal warts.* Chronic inflammations of the corium, caused by infection, not infrequently give rise to enormous fibrous tissue-hypertrophies known as *elephantiasis* (Fig. 127), and such elephantiasic tissue-hypertrophies may attain extraordinarily large proportions. In a similar manner very extensive hypertrophies, characterized by increase of the substance of the bone, may occur in the bony system as the result of chronic infections (e.g., syphilis).

In most cases of such tissue-hypertrophies as appear to be acquired

during life through the operation of external agencies, the efficient cause may be recognized with more or less certainty, but there are also many cases in which this is, at the present time, either quite impossible, or possible only to a very limited extent. So, for instance, we have *enlargements of the spleen, and of the lymph-adenoid tissue* of the lymph-glands, and of the lymph-nodes of the mucous membranes, which are of the character of hypertrophies, whose causes we are nevertheless unable to recognize. Very uncertain, too, is our knowledge concerning the etiology of those *enlargements of the distal portions of the extremities* (Fig. 128) resembling partial giant-growth, described as **acromegaly** (Marie), **pachyakria** (v. Recklinghausen), and *ostéoarthropathie hypertrophiante* (Marie), which are connected, in a certain proportion of cases, with enlargement of the facial portion of the skull and with deformities of the spinal column. These enlargements arise generally in youth or middle age, less frequently in later life, and proceed to a gradual further development.

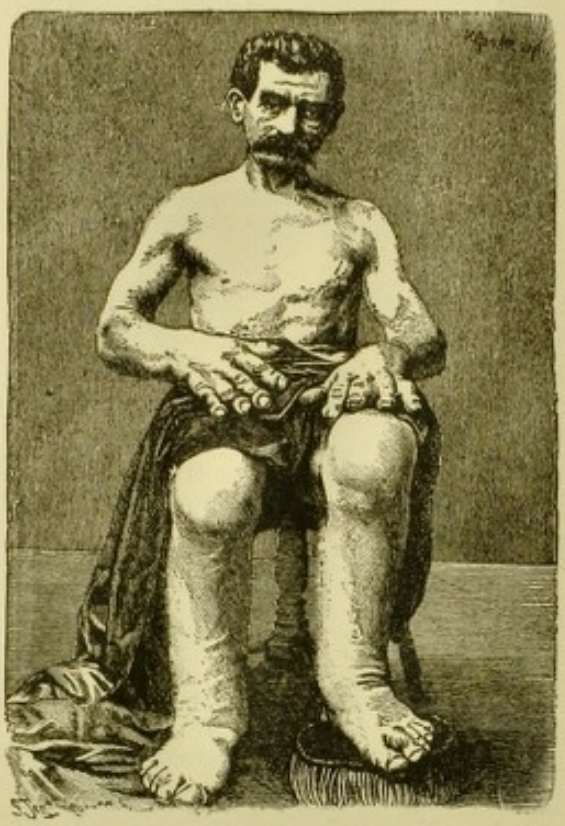


FIG. 128.—Acromegaly, according to Erb and Arnold. (Ostéoarthropathie, according to Marie and Souza-Leite.)

So far as anatomical investigation (by Arnold, Marie, Marinesco, Thomson, and Holsti) has been able to make out, the change consists in an increase in all the tissues that go to make up the extremities and the face. In this increase the bones also take part, in that they grow thicker (Fig. 129) and at the same time may be the seat of rounded or pointed exostoses. On the other hand, up to the present, an increase in the length of the bones has not been demonstrated in this disease (von Recklinghausen, Arnold), and so the term pachyakria, of von Recklinghausen, is fittingly chosen.

The cause and nature of these morbid phenomena are still obscure, and the terms mentioned above are not used by all authors with the same significance. In Germany the term acromegaly is applied to all forms of enlargements of the ends of the limbs which lead to a paw-like appearance of the hands and a gigantesque appearance of the feet, while Marie, who first described these pathological manifestations, tries to draw a marked distinction between acromegaly and ostéoarthropathie hypertrophiante. He holds that in acromegaly the hands and feet are not deformed, but symmetrically enlarged, and, indeed, that the thickening and broadening diminish at the ends, so that the terminal phalanges are only slightly thickened. On the other hand, he holds that in ostéoarthropathie hypertrophiante the terminal phalanges are swollen so as to resemble drumsticks, and the articular ends of the bones are irregularly thickened. In the former case, moreover, the lower jaw is lengthened, while in the latter case it is thickened. Marie believes that

in many cases ostéoarthropathie hypertrophiante is a sequela of an inflammatory affection of the lungs and pleuræ. Accordingly he calls it ostéoarthropathie hypertrophiante pneumique, and he believes that the cause is to be found in a taking up of the toxic products of the body-fluids from the foci of inflammation in the lungs, so that the disease of the bones may be regarded as an infectious, toxic, hypertrophic inflammation.

Some other authors regard acromegaly and ostéoarthropathie hypertrophiante as the result of a congenital predisposition (Virchow); others, as the result of disturbances of the sexual organs (Freund); others, again, as due to hypertrophy of the hypophysis (Henrot, Klebs), or to a persistence of the thymus gland (Erb, Klebs); and, finally, still others believe them to be due to nervous influences (von Recklinghausen). Nevertheless, none of these hypotheses is supported by anatomical and clinical observations. Finally, as a result of the investigations that have been made, it seems fair to assume that in the disease under consideration we have to do, not with excessive growth that can be compared with the partial giant growths, but with *acquired morbid conditions*, which develop either as independent diseases (acromegaly, pachyakria) or as secondary phenomena in the course of other diseases (ostéoarthropathie hypertrophiante pneumique).

§ 82. When a new-formation of tissue occurs in any organ, leading to **regeneration**, that is, to the restoration of lost tissue, or to **hypertrophy**, that is, to the formation of an excess of tissue, it very frequently comes about that the new-formed tissue conforms only partially to the type of the old; in short, that **regeneration is but incomplete**, and that

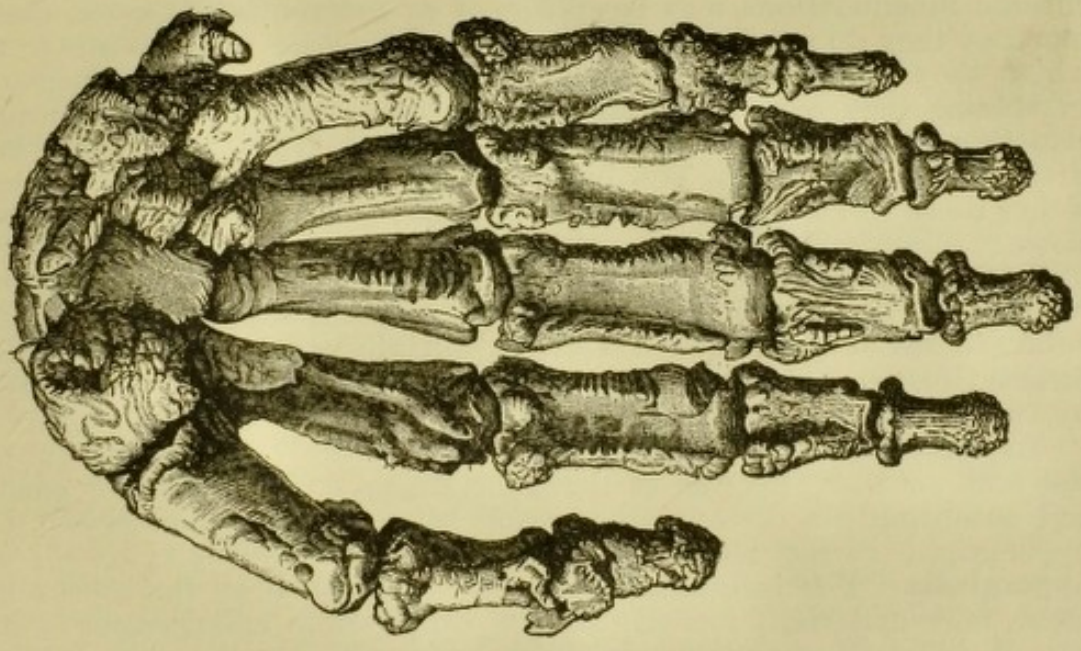


FIG. 129.—Skeleton of the hand with hypertrophied bones, from the case of acromegaly pictured in Fig. 128. (After Arnold.)

the **hypertrophy is but partial**, and is limited to a portion of the constituents of the organ.

In the restoration of lost tissues by regeneration very often only the connective tissue, and eventually the limiting epithelium and the nerves, are reproduced; whereas other elements of the injured tissues, gland-

acini, gland-ducts, ganglion-cells, muscle-fibres, etc., either are not reformed at all, or are but very imperfectly reproduced. A less valuable tissue, then, takes the place of the old, this formation consisting principally of connective tissue; if the loss occurs on a free surface of the body, the defect is closed over with epithelium and is ordinarily known as a **scar.**

This phenomenon depends upon the circumstance that the several tissue-elements have not an equal capacity of reproduction, so that, under a given set of conditions not all the parts are able to reproduce their kind, but rather it is often only the connective tissue and the limiting epithelium which produce new tissue, while the other organic elements either produce no new tissue at all, or produce it in very limited and functionally unimportant quantity.

Similar conditions are also met with in the new-formation of tissue leading to the hypertrophy of an organ, inasmuch as we often have to do in this case with a **connective-tissue hypertrophy** in which the specific tissue-elements, especially the glands, do not participate, or may even become atrophied. This condition holds particularly in those tissue-proliferations which are the result of the prolonged influence of mechanical and infectious agencies and are ordinarily described and treated of as chronic inflammations.

It occurs, finally, with great frequency, that proliferations which lead to the enlargement of an organ, or produce more or less circumscribed new-formations within an organ, are made up of a tissue which does not normally appear in that place; so that, as opposed to a hypertrophy which may be regarded as a homoplastic formation, we have to consider also a **heteroplastic new-formation of tissue.** In a certain sense, indeed, even scar-tissue and the fibrous product of acute and chronic inflammations may be spoken of as heteroplastic tissues, inasmuch as they do not wholly correspond in structure to the tissue from which they have sprung, whose place they occupy, or whose increase in volume they cause; nevertheless, the departures from the normal structure of the local connective tissue are not so considerable as to entirely justify the term. The heteroplastic new-formations proper are rather those which we designate as "*growths*," or **tumors** in the stricter sense.

§ 83. **Changes in the cells themselves are always the initial phenomenon of hypertrophy and regeneration,** changes which lead first to **enlargement of the cells** and then to **multiplication** of them. In the further development of the new growth **the basement substance formed by the cells may be increased.**

In **hypertrophy** the increase may be due entirely to enlargement of the cells, or there may be at the same time a multiplication of them; and accordingly a distinction is made between *simple hypertrophy*, or hypertrophy in the narrower sense, and a *numerical hypertrophy*, or **hyperplasia.** For instance, a muscular organ, such as the uterus or heart, may materially increase in size simply from enlargement of its muscle-cells. Moreover, in glandular hypertrophy an increase in size may occur in the same way from enlargement of the cells; though in these cases, if the hypertrophy is of considerable extent, there always occurs in addition a new cell-formation, so that the process has to be called a hyperplasia in the histological sense.

Under special circumstances **regeneration** also may consist of *simple enlargement of preëxisting cells*, or of *restitution of parts of cells that have been lost* (regeneration of axis-cylinder processes of ganglion-cells). In

the case of a loss of considerable portions of a tissue there always occurs a *multiplication of the cells by division*, in addition to enlargement of them.

Cell-division leading to a formation of new tissue is always *characterized by peculiar preliminary changes in the nuclei and protoplasm;* that is, peculiar changes take place in the nuclei which enable us to predict the coming division of nucleus and cell, even in its preliminary stages.

A **nucleus at rest** consists of an outer shell, or *membrane*, and the *nuclear contents*. These latter seem to consist of two parts: the nuclear substance, and the colorless nuclear fluid. To the *nuclear substance* belong, in the first place, the *nuclear corpuscles;* in the second place, scattered *granules* and *threads*, which often form a *lattice-work* which is clearly visible after proper treatment, and may be stained by the agents which color nuclei.

The **nuclear lattice-work** is that part of the nucleus which undergoes a **series of typical changes of form** in the **subdivision of the nucleus** —changes which result in the separation of the nucleus into two masses of equal size.

The process of nuclear division is often called **karyokinesis** (*κάρυον*,

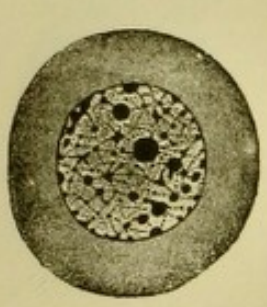


FIG. 130.

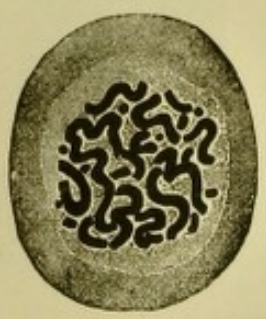


FIG. 131.

FIG. 132.

FIG. 130.—Nucleus magnified; increase in the chromatin.

FIG. 131.—Thick, open skein, with segmentation of the threads into chromosomes; nucleus and nuclear membrane have disappeared.

FIG. 132.—Grouping of the completed chromosomes in the form of a star or wreath.

kernel of a nut; *κίνησις*, movement), referring to these changes of form. Flemming, having in mind the skein-like structure of the nucleus when in process of division, has given to it the name **mitosis** or **karyomitosis** (*μίτος*, thread). Arnold terms the process **indirect segmentation.** The solid substance of the nucleus, which is colored by nuclear-staining dyes, is called **nuclein** or **chromatin** (Flemming).

When a nucleus is to undergo **division,** there is ordinarily found, at first, an *increase of the chromatin*, and the *lattice-work* of the chromatin becomes more distinct (Fig. 130). The nuclear substance then forms a close skein, which coincidently with the disappearance of the nucleolus and of the nuclear membrane, subsequently changes (Fig. 131) to *an open skein with thick threads*, whose several components divide themselves (Fig. 131 and Fig. 132) into *nuclear segments* (Hertwig), or *chromosomes* (Waldeyer).

In that these last group themselves in the equatorial portion of the nucleus, with their angles directed toward the centre, they come to form, when viewed from the polar aspect, a wreath-like figure (Fig. 132), and later a star-like figure, lying in the equatorial plane, known as the *mother-star* (Fig. 133 and Fig. 134), or also (Flemming) as the equatorial plate.

Sometimes earlier, sometimes later, *two poles* become visible in the interior of the cell—that is, two extremely small spheres known as *polar*

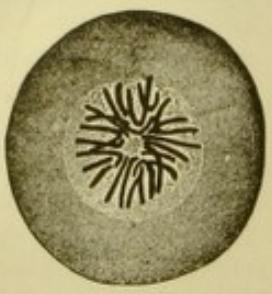


FIG. 133.

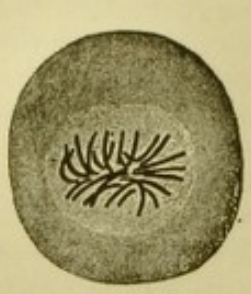


FIG. 134.

FIG. 135.

FIG. 136.

FIG. 137.

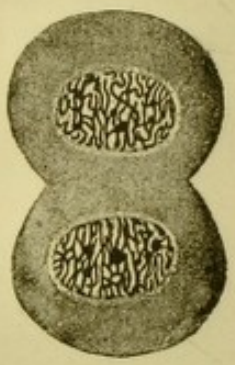


FIG. 138.

FIG. 133.—Completely developed mother-star; polar view.

FIG. 134.—Mother-star; equatorial view.

FIG. 135.—Stage of metakinesis; single loops visible, whose angles are pointed to the pole; delicate spindle-figure in interior of nucleus.

FIG. 136.—Daughter-star; side view (nucleus barrel-shaped); spindle-figure in nucleus, and radial arrangement of protoplasm.

FIG. 137.—Daughter-star separated; above, polar view; below, side view.

FIG. 138.—Daughter-skein with fine threads (above), and lattice-work form of the daughter-nucleus (below); division of cell-protoplasm completed.

corpuscles or *central corpuscles*, or *centrosomes*. They lie at first close together, then later on separate from each other and act as centres, about which the nuclear elements group themselves. Between them is developed the *nuclear spindle* (Figs. 135 and 136), which consists of fine fibres which do not stain with nuclear dyes and which converge at the polar corpuscles. In the neighborhood of the polar corpuscles themselves the granules of protoplasm show a radial arrangement, so that figures are produced (Fig. 136) which are called *rays* or *stars* or *attraction-spheres*. In the next following stage of division of the nucleus, called *metakinesis*, a movement takes place among the chromosomes leading to the formation of V-shaped figures with their angles pointed toward the pole. Next, two star-shaped figures called *daughter-stars* are formed by the movement of the V's toward the poles following the arrangement of the spindle-fibres (Figs. 136 and 137). From the star-like figure of the daughter-nucleus there is developed, later on, a skein, first with coarse filaments, then with fine (Fig. 138, upper part), which then changes to a lattice-work figure (Fig. 138, lower part). In the last stages of the phenomena of subdivision a new nuclear membrane is formed.

The **division of the cell-protoplasm** ordinarily takes place at the

time of the return of the star-form of the daughter nucleus to the ordinary condition of the nuclear structures, and it consists in a sundering of the same by progressive constriction (Fig. 138). We must look upon the radiating figures (Fig. 136) about the centrosomes, as evidences of movements within the protoplasm. There is probably a complicated interrelationship between the nucleus and the cell-protoplasm, but the *nucleus is to be regarded as the more highly organized substance, as the centre of cellular potentialities.* Moreover, *the nuclei are the bearers of the hereditarily transmissible properties of the cells,* while the protoplasm regulates their relation with their environment.

According to Rabl, whose studies were directed to the large-nucleated cells of cold-blooded animals, the closely wound mother-skein consists of several pieces, all of which turn at one end of the nucleus,—the end that is called the polar field,—leaving the pole itself free (Fig. 139, *a*). On the other hand, at the opposite end they pass across the pole (*b*). The transition from the closer to the more open skein (Fig. 140) is brought about by the threads becoming thicker and shorter. At the same time, some of them divide, so that the number of loops becomes greater.

The stage of the *segmented skein* (Fig. 141) which follows next, is characterized, as Flemming has already stated, chiefly by *longitudinal fission of some of the loops*, so that the chromatic material is divided into two equal portions. The further course of karyokinesis is an effort toward the uniting of each of these halves of the chromatin threads into a new group.

During the stage of the coarse open skein a *spindle-shaped figure* has already come into view (Fig. 140, *c*), composed of delicate threads and terminating in small shining granules, the *centrosomes*. Later on, this spindle pushes deeper into the nuclear substance (Fig. 141) and exerts an influence upon the threads of chromatin. In the plane of its equator, later on, the division of the nucleus takes place.

To initiate the process of division the loops of threads group themselves about the equator of the spindle in such a way that the angle points toward the centre, the arms

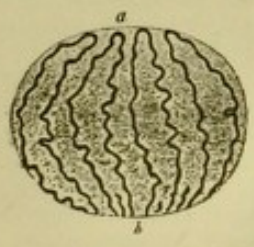


FIG. 139.

FIG. 140.

FIG. 141.

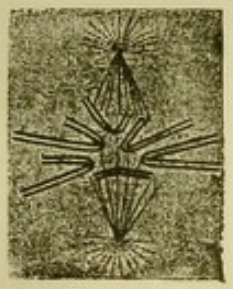


FIG. 142.

FIG. 143.

FIG. 144.

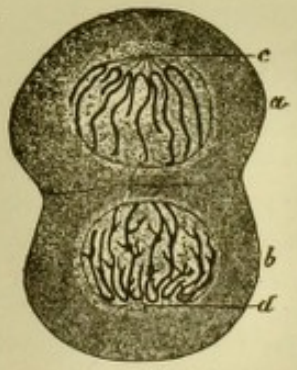


FIG. 145.

FIG. 139.—Close skein, viewed from the side.

FIG. 140.—Open skein, viewed from the side.

FIG. 141.—Final stage of the skein, with split threads.

FIG. 142.—Mother-star.

FIG. 143.—Metakinesis.

FIG. 144.—Daughter-stars.

FIG. 145.—Daughter-skein, *a*, and daughter lattice-work, *b*; *c*, polar area, with the remains of the spindle; *d*, polar area.

toward the periphery (Fig. 142); the mother-star is then completed. At the same time the nuclear membrane disappears, while radially arranged fibrils (Figs. 142, 143, and 144) extend out from the poles of the spindle into the cell-protoplasm (*cytaster; attraction-spheres*).

The *metakinesis* is characterized by a separation of the daughter-threads, which have resulted from the preliminary longitudinal division, and which up to this time had remained parallel with one another; and it is completed sometimes by a movement of part of the threads toward the opposite pole of the spindle (Fig. 143). The new loops resulting in this way have their angles toward the pole.

The *daughter-stars* (Fig. 144) are formed by the chromatic loops that have moved toward the pole of the spindle.

The *daughter-skeins* (*Dispirem* of Flemming), which proceed from the daughter-stars, consist of loops of fibrils which bend around at the point where the poles of the spindle are situated (Fig. 145, *a*) and leave a polar field (*c*, *d*) free from loops.

The transition from the skein to the lattice-work stage of the resting nucleus (Fig. 145, *b*) follows upon the division of the cell-protoplasm, and is initiated by the chromatic fibrils sending out processes. Flemming, Strasburger, Heuser, and Retzius believe that the chromatic fibrils are directly united one with another.

The significance of the *nuclear granules* is still a matter of dispute. Flemming and Pfitzner believe that they are different from the nuclear lattice-work, while others regard them as much-thickened nodal points of the lattice-work fibrils. What becomes of them after division of the nucleus is not known.

The *elements of the nuclear lattice-work* form at the periphery a denser, basket-like layer, next to which on the outer side lies a membrane which does not stain.

Flemming and Hertwig believe that the *spindle-figure*, whose fibres are only imperfectly stained by nucleus-staining dyes, originates from the above-mentioned achromatic material of the nuclear lattice-work, while Strasburger thinks that it comes from the cell-protoplasm.

The *centrosomes* or *polar corpuscles*, which always exist in nuclear segmentation, are present also in cells that are at rest. Nevertheless, up to the present time, they have been demonstrated only in a part of the cells, in largest numbers in lymph-corpuscles and in giant cells of the spinal cord. According to the investigations of von Kölliker, Flemming, M. Heidenhain, and others, it seems likely that the centrosomes belong to all cells, and lie sometimes in the protoplasm, sometimes in the interior of the nucleus, where they are difficult to demonstrate. This is because they do not stain with the ordinary nuclear dyes, but with acid aniline colors such as acid fuchsin and safranin. Whether they belong to the nucleus or to the protoplasm has not yet been made out. According to van Beneden, Beveri, and Rabl, the mitosis of the nuclear substances is to be explained on the ground of a direct drawing apart, starting from the divided centrosomes, and brought about by the agency of the achromatic fibres. According to Heidenhain, the central corpuscles are sharply circumscribed granules which possess the power of assimilation, of growth, and of multiplication by budding, by which means they are in the habit of forming groups. They may form the central point of insertion of a system of contractile fibrils (spindle-figure, microsome rays), whether alone or united into groups, and they consist of a specific substance, in a chemical sense, which is not present in other parts of the cell.

Flemming describes the cell as a circumscribed mass of living matter, and in the cell-body he distinguishes two different elements, of which one, the protoplasm (*filar mass, mitome, lattice-work*) is somewhat more highly refractile and is arranged in the form of threads, while the other, the paraplasm (*interfilar mass, paramitome*), occupies the remaining space. The more exact structure of the filar mass cannot be made out. The products of metabolism, granules, vacuoles, and other inclusions which the cells at times contain, do not belong to the cell-substance proper.

§ 84. In the multiplication of tissue-cells, **processes varying from typical karyomitosis** are met with, both in normal and in pathological tissues, and they often give rise to nuclear forms of very peculiar appearance.

In the first place karyomitosis may itself show variations, in the sense that instead of normal bipolar division, a *pluripolar division* takes place, so that there are formed from two to six or more nuclear spindles and a correspondingly increased number of equatorial plates (Fig. 146, *a*); or further, in the place of a simple mother-star, a figure of complicated structure is formed out of chromatin loops, and from this several daughter-stars are presently evolved. Not infrequently do we

observe also an *asymmetrical division of the nucleus* (Fig. 146, *b*, *c*), especially in tumors, but occasionally also in the new-formation of tissue accompanying regenerative or inflammatory processes.

A further variation consists in simple division by progressive constriction, without any increase of the chromatin or characteristic grouping and change in its disposition by thread-formation, a method of division which has been called *holoschisis* (Flemming) or *direct segmentation* (Arnold).

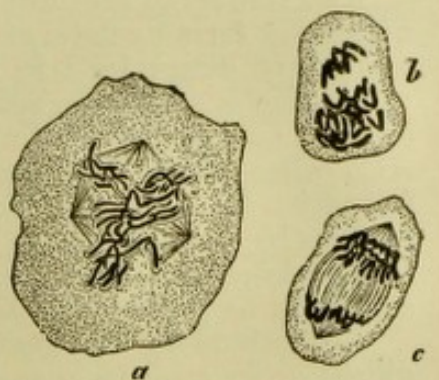


FIG. 146.—*a*, Pluripolar nuclear-division figure; *b*, *c*, asymmetrical nuclear-division figures.

Then we meet, and that too not infrequently, with instances of nucleus-division characterized by *abnormal size* of the nucleus, by its *abnormal richness in chromatin*, and by *manifold variations in its shape*. Types of nuclei dividing in this manner are those that are large, oval, or bean-shaped (Fig. 147), or knobbed in appearance, those lying in convoluted, ribbon-like masses, or lobulated and branching (Fig. 148), or wreath-shaped, or basket-shaped (Fig. 149), or of still other forms. Finally, there are occasionally found in the cells more or less extensive, indistinctly delimited accumulations of granular, flaky chromatin (Fig. 150).

Such nuclear forms, aside from the polynuclear leucocytes, are met with especially in the cells of the bone-marrow, of the spleen, and of the lymph-glands, as also in tumors arising from the bone-marrow or from the periosteum; but they have also been observed in other situations, particularly in sarcomata. In certain of these forms we have evidently to do only with evidences of contraction having no relation to cell-division. In other cases these changes of size and arrangement are the precursors of a division of the nucleus by the progressive constriction of certain portions, the division taking place now with, or again without, an increase of the chromatin. The first of these methods of division

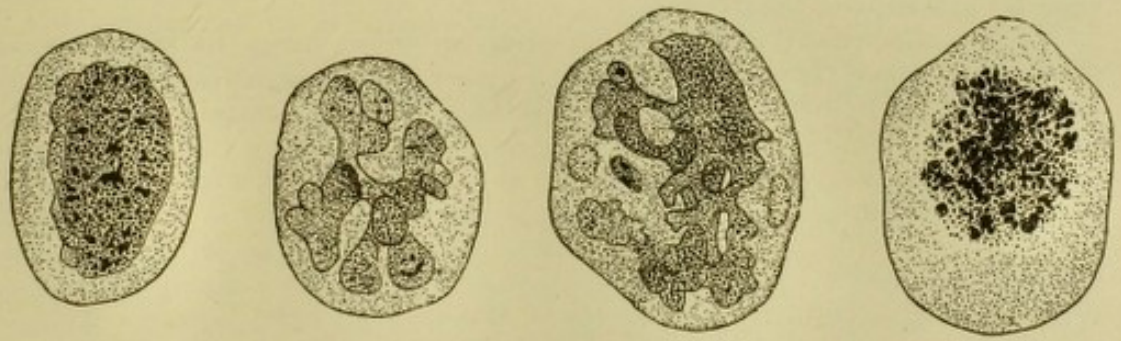


FIG. 147. FIG. 148. FIG. 149. FIG. 150.

FIG. 147.—Cell with oval, slightly knobbed giant-nucleus, rich in chromatin.

FIG. 148.—Cell with lobulated giant-nucleus. FIG. 149.—Cell with basket-shaped giant nucleus.

FIG. 150.—Cell with large masses of chromatin. All cells from an osteosarcoma. (Stroebe, "Beiträge von Ziegler," VII.)

(i.e., division of the nucleus with an increase of the chromatin) Arnold has denominated *indirect fragmentation;* the second (i.e., that without increase of chromatin) he calls *direct fragmentation*. Indirect fragmentation is distinguished from mitosis, or indirect segmentation, by the lack of an orderly arrangement of the chromatin in threads and by the

irregularity with which the severance of the chromatin particles results in new nuclei.

The import of all these methods of division, which are also included under the term *amitotic nuclear division*, cannot at the present time be accurately determined in all cases. It is established that leucocytes whose nuclei are in the act of fragmentation are approaching their decadence and no longer form new cells. It is probable also that other cells whose nuclei undergo amitotic division are incapable of tissue-formation; yet it may occur that along with the division of cell and nucleus by holoschisis, or direct segmentation, there may be joined (as in muscle-cells) amitotic nucleus-division as well, and that the resulting cells may have the capability of further tissue-formation.

Variations in the method of the division of the cellular protoplasm occur most frequently in this sense, that the *division of the protoplasm* either *follows tardily* upon the division of the nucleus, or *fails entirely to come to pass*. Both phenomena are observed to follow upon mitotic as well as upon amitotic division of the nucleus, and to lead to the formation of binuclear cells. By progressive dichotomous division, or by simultaneous multiple division of the nucleus, **multinucleated giant-cells** may also be formed which either persist as such or undergo further division later on. Cells of the spleen and of the bone-marrow, and those of tumors originating in the bone-marrow, manifest this phenomenon with special frequency. This phenomenon is also met with very often when proliferating cells lie applied to the surface of a foreign body, and likewise in the cellular new-formations which are caused by the multiplication of tubercle bacilli, where the formation of multinuclear giant-cells is a typical occurrence. The adhesion of the cellular protoplasm to a solid body, and also the degeneration of the protoplasm from bacterial activity, seem here to be factors hindering division.

Occasionally, in the process of dividing, the protoplasm of the cells puts forth **buds** or **offshoots**, and this may be observed to occur as well before as after the division of the nucleus. Into these buds, or offshoots, an immigration of nuclear substance (*cf.* new-formation of blood-vessels) afterwards takes place.

§ 85. **Cells newly developed** through division form the **material** or the **germinative tissue**, both in the process of regeneration and in that of hypertrophy, **out of which new tissue can be evolved.** The characteristics of this germinative tissue are determined by the characteristics of the mother-tissue from which it arose. The law of the **specific character of the cells** finds an application, therefore, in this sense, that *in every case cellular germinative tissue is capable of evolving only such tissue-structures as correspond to the mother-tissue, or are closely akin to it.* When once the primitive elements of the embryo have become divided into germinal layers, and when within these germinal layers the several tissue-formations have once become differentiated, the proliferative capacity of the cells becomes limited to the production of certain, definite species of tissue, whether in the increase attending physiological multiplication, or in the re-awakening of arrested proliferative processes.

Epithelium can produce only epithelium and never connective tissue. The gland-cells, the derivatives of epithelium, can produce only gland-cells of a particular kind, or functionless, abortive variants of the same, but never a new kind of gland-tissue having the functions of some other gland.

With the starting up of proliferation, the cells of the connective tissue produce connective tissue directly, and under some circumstances, i.e., if some particular species of connective tissue is involved (periosteum, perichondrium, bone-marrow), even bone and cartilage also; but we never find a transmutation of connective-tissue cells into epithelial cells or gland-cells. So too, cartilage cells produce only cartilage, or some other connective-tissue derivative belonging to the mesoblast.

The cells of the several tissue-formations, ganglion-cells, glia-cells, and muscle-cells, form only such tissues as conform in structure and characteristics to the type of the mother-tissue.

The conditions of new tissue-formation reside immediately in the **proliferative faculty of the cells**, which remains an attribute of many cells throughout life, and abides even in cells which do not multiply under normal conditions. There are also, however, *cells which are not capable of proliferation*, and these are particularly those which, like the non-nucleated red blood-corpuscles, the horny cells of the epidermis, and the bone-cells, have undergone extensive metamorphosis and involution. Among potentially proliferative cells it is particularly the epithelial cells, and so also many gland-cells, the connective-tissue cells, and those of the vessel-walls, which are distinguished by a capacity for rapid and extensive multiplication, while cartilage-cells, glia-cells, and ganglion-cells multiply only under particular circumstances, and for the most part produce but limited quantities of tissue.

The causes of the pathological new formation of cells and of tissues, as they underlie the development of hypertrophy and regeneration, can be traced both to an inherited proclivity of a tissue to pathological growth, and also to external influences acting upon normally disposed tissue.

We must assume that there is present **a hereditary tendency originating in the germ**, in all those cases in which general or partial giant-growth, or local tissue new-formation of the nature of elephantiasis, or tumor-growths arise without external causes, either entirely of themselves or after very slight incitation, entirely incommensurate with the subsequent tissue-proliferation. Whether in such cases the pathological growth is started up by an abnormally strong proliferative tendency of the tissues, or by an abnormally limited inhibitory faculty residing in the tissues, and due to their mutual interrelationship, is a question which does not admit of a positive answer; we must, however, assume that the formative capabilities of the cells are the controlling factor in the potential reproductivity of the tissues.

The external influences, which induce pathological new-formation of the cells and the tissues, consist either in **the abolition of the restraints upon growth**, which under normal circumstances inhibit the unlimited growth of a tissue, or in **the increase of the capacity and the tendency of the cells to multiply**, or, again, in **the combined influence** of both agencies.

Where the formation of the several tissues and organs has been completed, their cells are firmly engaged in the organized whole by means of cement-substances or strongly elaborated ground-substance, and it is beyond doubt that the transformation, which the originally cellular constitution of the tissues has thereby undergone, eventually confines the multiplication of the cells to well-defined limits, or brings it to a complete standstill. If vacant spaces are formed in a tissue by the destruction of individual cells, or if, through traumatisms or inflamma-

tions, greater defects, or more extensive disorganization of the firmer framework of the tissues, is brought about, then the mutual interaction of the several neighboring tissue elements also becomes modified, and the observed fact that under such circumstances cell-division starts up, supports the idea that in this way *a portion of those influences which inhibit the uninterrupted multiplication of the cells has been done away with.*

The proposition, that *an increased tendency to proliferation*, leading up to an actual inauguration of nucleus- and cell-division, may be due to the action of external influences, involves the proviso that *cells may be stimulated not only to functional, but also to nutritive and formative activity.* The first of these provisions enjoys universal recognition, but the latter has been widely disputed. It cannot, however, be denied that external influences act, not only to bring into play the specific functions of cells, such as contraction and secretion, but act also to increase their nutritive and reproductive capacity, or to excite them once more into action when in abeyance. These **formative stimuli**, so far as we are acquainted with them, are identical with functional stimuli; the hypertrophy following on increased action in muscles and glands indicates that the irritations which provoke muscular contraction and glandular secretion cause at the same time an increase in the nutritive processes in the cells, and that, in case they increase beyond a certain measure, they lead to the formation of new cells of like functional capability. It is not possible to state with positiveness whether outside these physiological stimuli there exist also other pathological stimuli capable of inaugurating a proliferation of cells.

Inasmuch as in glands (liver and kidney) the presence of certain definite substances increases both functional and formative activity, the assumption is justified that other substances also, not present in the organism during health, may act in the same manner. It is also possible that a certain increase in the temperature of the tissues may have such an effect, and we may adduce, in support of this, the fact that heat promotes proliferation within damaged and inflamed tissues which are superficially located. Here, however, we have to do with tissues in which proliferation is already under way, and in which the removal of influences inhibitory to tissue-growth is already operative in starting the proliferation.

Heightened nutrition from increased blood-supply has often been brought forward as a cause of proliferation. But *increase in blood-supply does not induce tissue-proliferation in normal tissue.* The cell is not fed, but rather it feeds itself, and a superfluity of nutritive material is not sufficient to increase the nutritive function. It is a more reasonable possibility that a qualitative change in the nutritive material should operate to this end, at least on occasions when the conditions for an increase in the nutritive and formative activity of the cells are present.

Most recently, Grawitz[1] has advanced the view that *cells may also arise from intercellular substance*, and he claims that, in the formation of connective tissue, cells are transformed into fibres, and pass over into a *resting stage*, in which nuclei are no longer visible under the microscope. From these invisible *resting cells* (*Schlummerzellen*) new cells are formed again in inflammation and tissue-growth. By means of this rest theory, Grawitz has brought again into discussion, as a new teaching, views which years before

[1] Grawitz: "Ueber die schlummernden Zellen des Bindegewebes und ihr Verhalten bei progressiven Ernährungsstörungen," *Virchow's Archiv*, 127. Bd., 1892; "Atlas der pathologischen Gewebelehre," Berlin, 1893.

Stricker and Heitzmann had offered; but the work done by himself and his pupils in his institute contains nothing which substantiates his view. The well-known phenomena of growing and inflamed tissue are described, and no observations are communicated which can be regarded as proving that cells may spring from intercellular substance—that is, from invisible resting cells.

The fertilized ovum is capable of forming, by its progeny, all the various tissues of the body, and we have to assume that this capability is situated in the nucleus, which is the seat of the inherited characteristics. With the advancing differentiation of the tissues there comes a simplification of the structure of the nucleus; that is, a special protoplasmic impulse obtains control, so that now the cell is capable of producing only a special kind of tissue. The statements therefore are in error which say that from epithelium connective tissue may be formed, or from connective-tissue cells, gland-tissue or nerves. According to Hansemann, the specific quality of the cells is indicated not only by the special structure of the complete cell, but also by the course of the karyokinesis, since individual differences in this process occur in the different kinds of tissue, by which one can recognize the separate tissues by the form of their mitosis (size, number, and shape of the chromosomes).

The views of different authors in regard to the causes of tissue-proliferation vary very widely. This is dependent upon the fact that these causes are not open to exact recognition, so that we are obliged to have recourse to hypotheses. It is not practicable at this place to enter into a thorough discussion of the different opinions. I have collected them in my treatise concerning the causes of tissue-proliferation,[1] and have there more exactly defined and substantiated my views. That over-nourishment is not able, of itself alone, to bring about new-formation of tissue is made evident, to a certain degree, by the fact that an increase in the fleshy parts of the domestic animals cannot be brought about by forced feeding, but only an increase in the accumulation of fat. According to Penzo, growth of the tissues in young animals is very greatly promoted by temperatures of from 37° to 40° C. (98.5° to 104° F.), while by temperatures of from 10° to 12° C. (50° to 55.6° F.) growth and cell regeneration are retarded. Roemer believes that injection into the blood of fluid containing protein causes a multiplication of leucocytes by division.

§ 86. If portions of tissue are removed from the body, they do not immediately die, but continue to live for a certain period of time; and, in the case of some of the tissues, it is a possible thing to transplant a certain portion from one part of the body to another, and to secure its continued living in the new position. **Transplantation** and **implantation** may, accordingly, be practised, with the result that, under special conditions, a maintenance of the tissue-grafts, and even a continued growth will follow.

Attempts at transplantation are very old, and have been made upon various tissues; for instance, periosteum and marrow have been transplanted to soft parts or into blood-vessels, and made to grow there (Ollier, Bruns, Barkow, Cohnheim, Maas, and others). Further, the spurs of young cocks have been transplanted to the combs of other cocks, and rats' tails have been successfully brought under the skin of the back of other rats (Dohamel, Hunter, P. Bert). Attempts have also been made to effect a successful implantation of the tissues of the thyroid gland (von Eiselsberg, Christiani, and others), the pancreas (Minkowski, Hédon) and the ovary (Knauer).

The most numerous transplantations of tissue have been made with skin. The investigations of Reverdin and Thiersch gave the impulse to the utilization therapeutically of *skin-transplantation* for the healing over of broad, open wounds. The same procedure is made use of when completely separated pieces of skin are to be made to unite again, by healing, with the underlying tissues from which they had been separated.

For successful transplantation—that is, transplantation followed by multiplication of the cells and formation of new tissue—the best struc-

[1] Ziegler: "Die Ursachen der pathol. Gewebsneubildungen," Intern. Beitr., Festsch. f. Virchow, Berlin, 1891.

tures are those whose cells are capable of rapid growth—for example, epithelium and periosteum. Cartilage of adult animals, for example, does not continue to grow if transplanted, while embryonic cartilage does grow (Leopold and Zahn). When living embryos are buried in the abdominal cavity or in the tissues of an animal, the softer tissues are quickly absorbed, while the firmer ones may manifest a certain growth, though later these too likewise vanish. Periosteal tissue, ovarian, pancreatic, thyroid, and splenic tissues, implanted into animals of the same species, may heal up within the body, and later even functionate; they generally, however, after a time undergo involution and eventually become disintegrated, and their place is taken by cicatricial tissue. Christiani, however, in the case of the implantation of thyroid tissue in rats, was able to demonstrate a regenerative new-formation of portions of tissue which at first had begun to degenerate, and these regenerated portions of the implanted thyroid-tissue maintained themselves as long as the animals lived (two years).

Skin-grafting can be undertaken as well in fresh as in granulating wounds—that is, wounds where the tissues infiltrated and inflamed are in a state of active growth. In these cases, one cuts with a sharp knife thin strips of skin which contain not only the epithelium, but also the tips of the papillæ, and in part also the uppermost layers of the corium. These are laid upon the fresh wound—that is, upon the subcutaneous tissue, fascia, muscle, periosteum—or upon the shaved-off granulations, and pressed firmly in place by moistened gauze. The fastening of the strip upon the wound-surface takes place by coagulated lymph or coagulated blood. In successful cases, in eight days they are firmly united.

The nourishment of the transplanted pieces takes place, first, by the taking up of material from the exuded tissue-fluids. Later on, there rises up from the subjacent surfaces embryonic tissue, with vessels, which makes its way through the superjacent coagulum into the transplanted structure, so that its connective tissue contains new vessels. The upper horny layers of the epithelium are desquamated. The deeper layers begin to grow from the second day on, and form new epithelium, on the surface of which, later on, a horny layer appears. If connective tissue is transplanted with the epithelium, then its cells may also go on to grow and produce connective tissue. According to the observations of Goldmann, however, the elastic fibres which are to be seen later in the grafted portion come from the surrounding tissue. Later on—that is to say, after the lapse of several weeks—there not infrequently occurs a shedding of the epidermis. Nevertheless, when the transplanted skin has once healed and begun to grow, it is generally permanent.

If, as a result of violence, some of the epithelial structures of the skin are transferred to some deeper locality in the body, *epithelial cysts* may develop from these cells.

II. The Processes of Hyperplasia and Regeneration in the Various Tissues.

§ 87. The morphological changes in the **regeneration and hyperplasia of epithelium** are comparatively simple. The karyomitoses (Fig. 151, *a–d*) correspond in the main to those described in § 83. The division of the protoplasm ensues either in the later stages of the process of nucleus-division or follows after it. Sometimes processes are formed

first from the proliferating epithelia, and into them, later, nuclei migrate. These processes become independent by separation from the mother-cell.

Epithelium springs only from epithelium, and, moreover, the various forms of epithelium do not pass over into one another. It is, however, to be noted that under certain conditions—for example, in cases of inflammatory irritation of long standing—epithelium which is regenerating may change its character; so that pavement epithelium may be developed on surfaces which originally possessed ciliated cylindrical epithelium. This may happen, for example, in the case of cicatrices in the bronchi. Lesions of ciliated epithelium are in the first place repaired by flat cells, which later on are transformed into high or cylindrical cells.

Slight losses of substance in the superficial epithelium are generally quickly replaced by regenerative growth in the neighborhood. In the intestine a lesion of the epithelium is very rapidly healed by a growth of the epithelial cells situated in the deep parts of Lieberkühn's follicles. In the same way, glandular epithelium—for example, in the liver or the kidneys—is quickly replaced after loss, provided the structure of the tissue—that is to say, the substratum upon which it rests—is not changed or destroyed. After destruction of liver-tissue the liver-cells, as well as the epithelium of the bile-ducts (Fig. 151), are developed, and when the liver is injured the division of the nuclei of the liver-cells may occur at a comparatively great distance from the wound. Wounds made purposely in the liver heal through the intervention of new-formed connective tissue, into which, however, only offshoots from the small bile-ducts penetrate. A local reproduction of liver tissue does not take place. Only under special conditions does a transformation of proliferated bile-ducts into liver-trabeculæ eventually occur. So also in the kidneys, the testicles, the thyroid gland, and the ovary, the local production of gland-tissue in the connective-tissue cicatrix is very limited or entirely absent, and does not proceed to the formation of functionating tissue. In the salivary and mucous glands, on the contrary, there occurs a lively reproduction of the glandular canaliculi and a new-formation of alveoli.

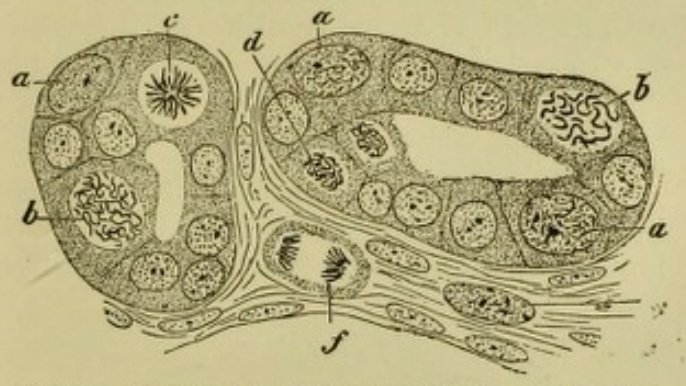


FIG. 151.—Regeneration of the epithelium of the biliary passages in the neighborhood of a wound five days old. (Flemming's mixture; safranin.) *a*, Enlarged nucleus of epithelial cell, with increased chromatin; *b*, epithelial cell with mother-skein; *c*, epithelial cell with mother-star; *d*, epithelial cell with daughter-skein; *f*, connective-tissue cell with daughter-star. Magnified 400 diameters.

If portions of the intestinal mucosa and submucosa are destroyed by ulceration, there takes place during the healing process a proliferation of gland-tissue also, which, according to the nature of the defect, produces now typical, and again more atypical new-formed glands (Fig. 152, *i*), which grow into the submucosa. The new gland-formation starts from the old glands, whose epithelium spreads itself out over the edge and the base of the ulcer (Fig. 151, *g*, *h*), and likewise overspreads any

hollows (*k*) which happen to be present. In similar fashion, ulcerative defects in the stomach are restored, and even extensive ulcers may become covered over again with glandiferous mucous membrane, although, indeed, the glands do not, for the most part, reach a typical development.

The epithelial portions of the uterine mucous membrane, which are physiologically shed in part during menstruation and parturition, and reproduce themselves thereafter, are restored also in the healing of pathological defects in the mucous membrane. The new-formation of epithelium proceeds from the glandular remains.

If **compensatory hypertrophy** takes place in a kidney or liver, as a consequence of loss of kidney- or liver-tissue, it is brought about by the *formation of new gland-cells and enlargement of existing gland-tubes and stroma*. After extirpation of a kidney the commencement of compensatory hypertrophy may, under some circumstances, occur on the third day with the appearance of nuclear-division figures in the epithelium of the urinary canals, and then there takes place a further permanent growth of the epithelium of the tubules and the glomeruli, as well as of the cells of the vessel-walls. As a result of these changes all these parts undergo enlargement. In the liver, for example, the lobules of gland-tissue become enlarged, but no actual new-formation of these tissues take place.

§ 88. The **new formation of blood-vessels** plays an important part in the hyperplasia of the most varied tissues. If connective tissue, bone, or gland is to be reproduced in any considerable amount, the new

FIG. 152.—Healing of an ulcer of the small intestine, with formation of new gland-tubes in the submucosa. (Müller's fluid; hæmatoxylin.) *a*, Mucosa; *b*, submucosa; *c*, *d*, muscularis; *e*, serosa; *f*, rest of the base of ulcer not yet covered with epithelium; *g*, overhanging edge of ulcer; *h*, base of ulcer covered with epithelium; *i*, new-formed glands situated in the submucosa; *k*, deep crypt covered with epithelium. Magnified 20 diameters.

formation of blood-vessels is essential, since only by means of these can sufficient nutriment be brought to the growing tissue.

The development of new blood-vessels takes place by the **formation of offshoots** from the wall of preëxisting vessels (Fig. 153). Shortly after, or at the same time with, the formation of the offshoot, or even earlier, a **growth of the cells of the vessel-wall** takes place—that is, of

the **endothelium** (Fig. 154)—in which nuclear division occurs by **karyomitosis.**

As the first indication of a new vessel, one notices on the outer side of some capillary loop a tent-shaped elevation, which terminates in a fine protoplasmic thread (Fig. 153, *a*), standing out from the vessel, and which becomes longer and longer, while at the same time, also, the granular mass grows. In this way there is then formed a *solid granular arch of protoplasm*, which ends in a *thread of protoplasm* (*a*), and after a certain time contains nuclei. It may penetrate into another vessel or unite with some other arch which it meets, or finally return again to the same vessel from which it started.

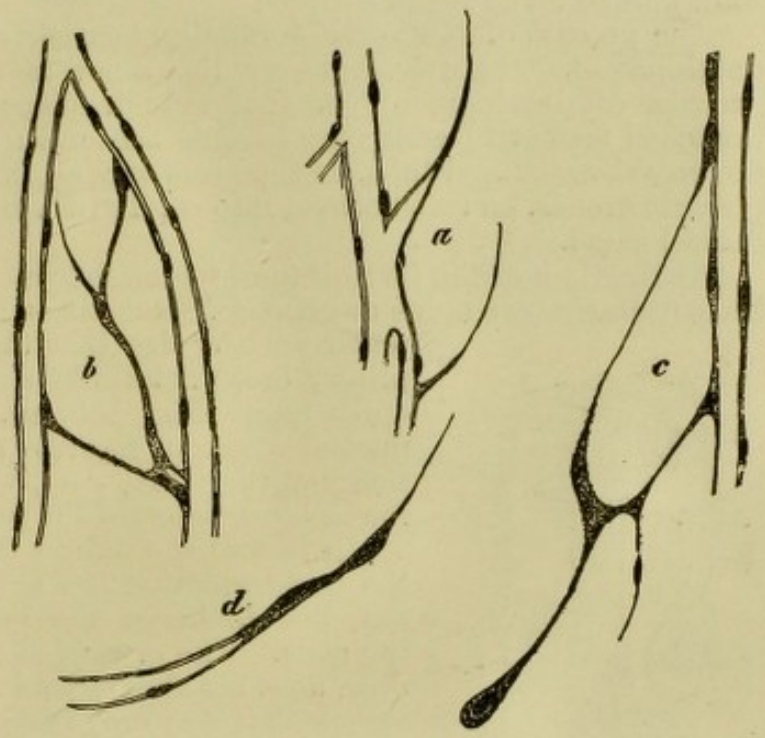


FIG. 153.—Development of a blood-vessel by formation of offshoots, from preparations which were taken from a formation of inflammatory granulations. *a*, *b*, *c*, *d*, Different forms of offshoots—some solid (*b*, *c*), some becoming hollow (*a*, *b*, *d*), some simple (*a*, *d*), some branching (*b*, *c*), some without nuclei (*a*, *d*), some with nuclei (*b*, *c*). Formative cells have applied themselves to the outside of the offshoots.

Furthermore, from the arch itself new arches may spring (Fig. 153, *b*, *c*), or it may end in a club-shaped process.

The arch, which in the first place was solid, after a certain time becomes hollow (*b*, *a*) by the liquefaction of its central part, and this space either at once or very soon comes to communicate with the lumen of the blood-vessel (*a*), or else there is developed a protrusion of the lumen of the vessel at the seat of the arch. The blood of the parent-vessel makes its way at once into the cavity of the daughter-vessel and widens it out. By reason of the fact that the hollowing out advances and extends to the point of entry of the protoplasm-arch into another blood-vessel, there is formed a new capillary loop permeable for blood.

The arch of protoplasm which raises itself from the wall of a blood-vessel is to be regarded as a process of a cell of the vessel-wall, and later on, after it has acquired a nucleus, it comes to be an independent cell. Accordingly, *the blood-vessels arise from the hollowing out of a filiform cell.*

Immediately after the opening of the way for blood, the capillary is a tube with a homogeneous wall. After a certain length of time the protoplasm gathers itself about the nuclei, which have in the mean time divided and multiplied so that eventually the capillary is made up of pavement epithelium. As Arnold has shown, the line of division between the separate flat cells may be demonstrated by injecting a solution of silver into the vessel (endothelial cells). At this time the wall ap-

pears already materially thickened, partly from growth of the cells themselves of the vessel-walls, but partly also because a considerable number of the formative cells of the neighborhood heap themselves upon the surface of the young vessel (Fig. 153, *d*), apply themselves to the wall, and so make it thicker.

The process of new vessel-formation consists mainly of the phases of development. It seems, however, that a new feature may appear in the process of development, in that spindle-shaped or club-shaped or branched formative cells may become associated with the processes of the vessel-walls, and then, in the same way as in the case of the protoplasmic arches, be transformed into capillaries, by the development of a central canal.

At the time of the formation of the offshoots, the endothelial cells of the capillaries are much swollen, and sometimes in growing tissues they reach such a size that the cross-section of a capillary looks not unlike a gland-duct lined with epithelium (Fig. 155, *d*). At the same time, nuclear-division figures appear in the endothelium (Fig. 154, *a–c*), which later on are followed by division of the nucleus and cell.

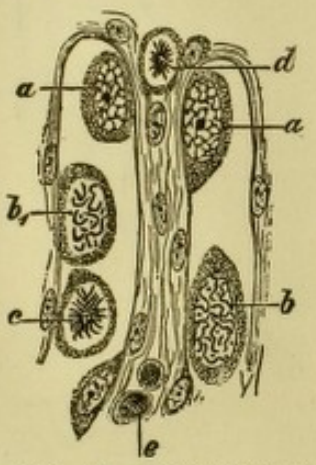


FIG. 154. — Two vessels of the papillary layer, whose endothelial cells are in process of growth; five days after painting the skin of the back of the foot with iodine. (Flemming's mixture; safranin; picric acid.) *a*, Nucleus with chromatin framework; *b*, b_1, skein forms; *c*, mother-star; *d*, connective-tissue cell with nuclear-division figure; *e*, uninuclear leucocytes. Magnified 350 diameters.

In just what relation these growths stand to the bud-formation has not yet been clearly made out, but doubtless the buds spring from growing cells. The growth of the endothelium, however, does not always lead to the formation of new vessels, but may only bring about a thickening of the wall, and finally an obliteration of the lumen.

If the new-formed capillaries are to become arteries and veins—a change which in the case of extensive new growths must always occur in a part of the capillaries—this takes place by a growth of the cells of the vessel-wall. The different parts of the arteries and veins are developed from this formative material by special processes of differentiation.

In the handbooks of pathological anatomy and surgery, three forms of new formation of vessels are generally described, and distinguished as primary, secondary, and tertiary.

In the primary form the cells of the germ-tissue are directly transformed into red blood-cells and the elements of the vessel-walls, and this takes place as follows: the germ-cells unite together to form strings, whose axial portions become red blood-cells, while the peripheral parts become the structure of the wall. This form of vessel-development which occurs in the embryo, does not take place pathologically.

In the secondary form, according to Billroth, O. Weber, and Rindfleisch, spindle-cells unite to form cords in such a way that they inclose between them a canal.

So far as I can see, these observations are based upon errors; because, very early, spindle-cells heap themselves upon the vessel-buds—for example, in granulations—cover over the buds, and form strings of cells about them.

The so-called tertiary formation is that which has been described in the main text.

§ 89. The **connective-tissue structures** are almost all capable not only of a hyperplastic, but also of a regenerative growth. This especially holds good of unformed and formed connective tissue, the periosteum, and the marrow, while cartilage possesses only a feeble power of regeneration, and the completely developed bone takes no share in the new formation of bone-tissue. In case of destruction of connective tis-

sue the substitution tissue newly formed by regenerative growth is very often not the same as the original tissue. More often another form of connective tissue comes in its place. Thus defects in cartilage are for the most part replaced by connective tissue or by bone, and in the place of destroyed fat, lymph-glands, tendons, etc., there is developed thick, fibrillated connective tissue—so-called *scar-tissue*.

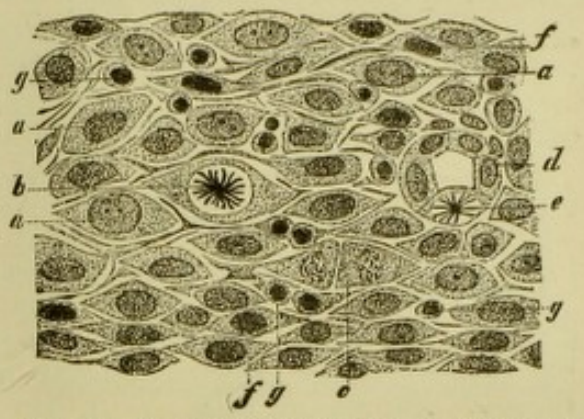


FIG. 155.—Proliferating periosteum, four days after fracture of a bone. (Flemming's mixture; hæmatoxylin.) *a*, Pale formative cells with large nuclei; *b*, osteoblast with nuclear-division figures; *c*, two cells soon after division, showing thread-skein in nucleus; *d*, blood-vessel with proliferating endothelium; *e*, endothelial cell with nuclear figure; *f*, small dark-colored formative cells; *g*, leucocytes. Magnified 400 diameters.

Hyperplastic and regenerative growth of connective tissues is ushered in by *cell-multiplication*, in the course of which the above-described karyomitoses occur (Fig. 151, *f*; Fig. 154, *d*; Fig. 155, *b*, *c*).

In injuries to the tissues, the cell-proliferation begins very early, so that, for example, in fractures of bones, already on the second day single cells of the periosteum have enlarged and show nuclear-division figures. In regeneration and hyperplasia after slight injuries, here and there karyokinetic figures occur, and lead soon to the formation of new cells (Fig. 154, *d*).

If only a few cells are destroyed by an injury to a tissue, new-formed cells are developed in the place of those lost, without any considerable change in the structure of the tissue taking place. If, on the contrary, under pathological conditions, a considerable amount of new structure is formed in a short time, the proliferating cells form an **embryonic tissue** consisting for the most part of cells and blood-vessels (Fig. 155). The extent of this, naturally, may vary considerably, and depends partly

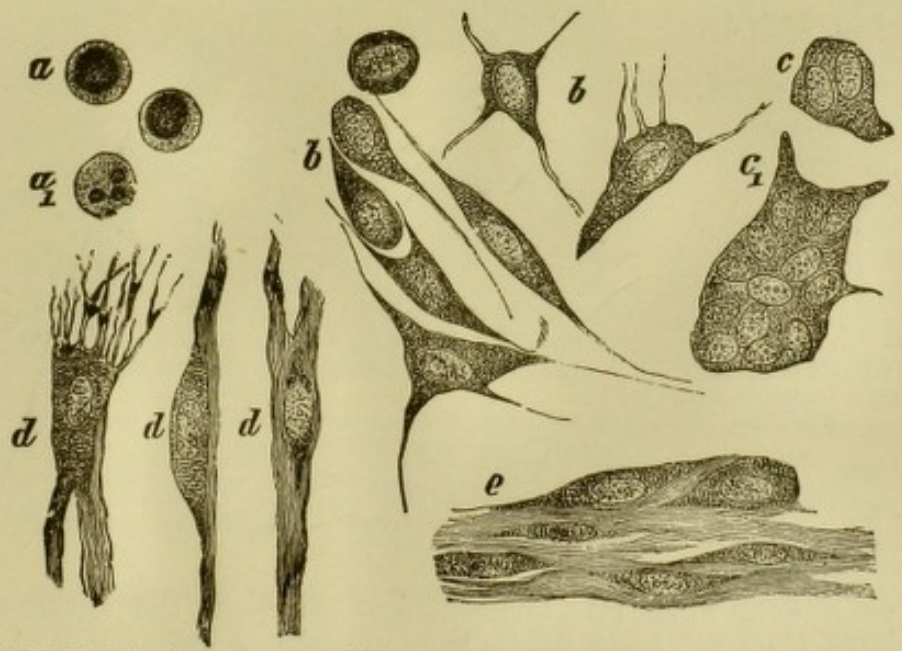


FIG. 156.—Isolated cells from a granulating wound. (Picrocarmine.) *a*, Uninuclear leucocytes; a_1, multinuclear leucocyte; *b*, different shapes of uninuclear formative cells; *c*, double-nucleated formative cells; c_1, multinucleated formative cells; *d*, formative cells in the process of tissue-formation; *e*, completed connective tissue. Magnified 500 diameters.

upon the capacity of the tissue for proliferation, partly upon the nature of the lesion which leads to the proliferation. For example, the periosteum, proliferating after fracture of a bone, forms a continuous layer of developing embryonic tissue (Fig. 155), while proliferating cartilage generally produces only small foci consisting of a limited number of cells.

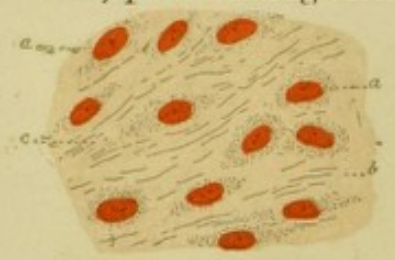


FIG. 157.—Development of connective tissue from fibroblasts. (Müllers fluid; picrocarmine.) *a*, Fibroblast; *b*, hyaline basement substance with separated fibrils; *c*, fibrils around fibroblasts. Magnified 400 diameters.

The proliferating cells are always larger than those of fully developed and quiescent connective tissue, and contain large bladder-like nuclei with nucleoli. They have for the most part one or two nuclei (Figs. 155 and 156), though multinuclear cells also occur (Fig. 156, c_1) —the so-called *giant cells*.

Since all of these cells are the antecedents of the future tissues, they are called **formative cells.** If connective tissue is to develop later from the embryonic tissue, then these cells are called **fibroblasts** (Fig. 156, *b*, *c*, *d*, *e*, and Fig. 157, *a*). The antecedents of cartilage and bone are called **chondroblasts** (Fig. 158, *a*, *c*) and **osteoblasts** (Fig. 155, *a*, *b*, *c*).

The shape of the formative cells may vary (Fig. 156, *b*, *c*, *d*, *e*), and depends in part upon internal causes—that is, upon changes in shape spontaneously developed,—in part upon the influence of the environment, which under certain circumstances compels the cells to take certain definite shapes. The most varied shapes occur in the cells which produce connective tissue.

If **connective tissue** is to be developed from an embryonic tissue, either fine *fibrillæ* (Fig. 156, *d*, *e*) appear at once in certain parts of the cell-protoplasm, or else there appears first a *homogeneous intercellular substance* (Fig. 157, *b*), in which, subsequently, the fibrillæ become differentiated. The formative cells meanwhile diminish in size, and come to lie, for the most part, in small clefts (Fig. 156, *e*) which are situated in the basement substance.

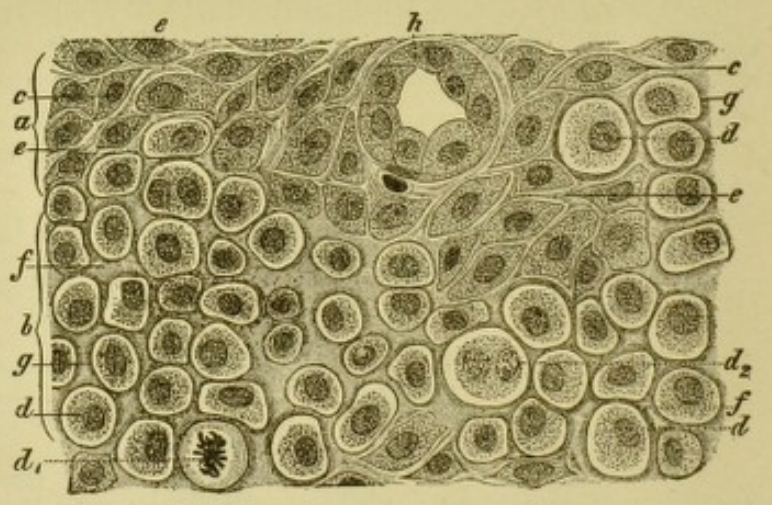


FIG. 158.—Periosteal cartilage-formation in a fracture five days old. (Flemming's mixture; hæmatoxylin; glycerin.) *a*, Cellular embryonic tissue; *b*, cartilage-tissue; *c*, proliferating periosteal formative cells; *d*, cartilage-cells; d_1, d_2, nuclear-division figures in cartilage-cells; *e*, basement substance of the embryonic tissue; *f*, basement substance of the cartilage; *g*, cartilage-cell capsules; *h*, proliferated endothelium of a blood-vessel. Magnified 250 diameters.

Elastic fibres first make their appearance in newly formed connective tissue at a somewhat late stage. According to the investigations which have thus far been made, they are also a product of the cells. At first they present the appearance of very delicate fibrils, but they may also unite to form fibres of some degree of thickness.

In the development of **hyaline cartilage** there appears between the cells a hyaline basement substance (Fig. 158, *f*), while the chondroblasts (*c*) at the same time take on a more rounded form (*d*). As time goes on the basement substance increases, and the chondroblasts shrink, and come to lie in rounded cavities whose walls are denser than the rest of the basement substance, and later on form the part of the ground-substance which is called cartilage-capsule.

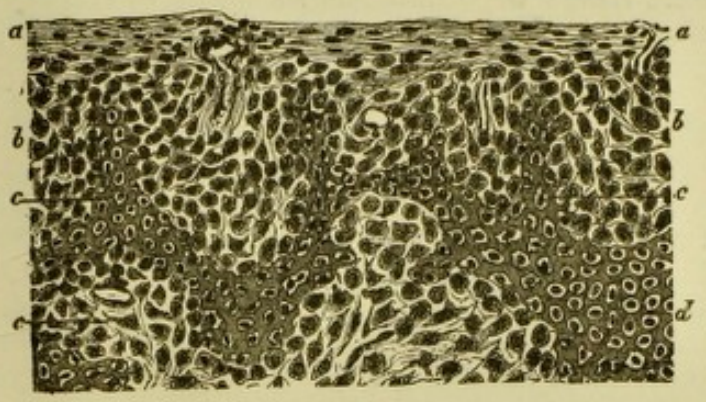


FIG. 159.—Formation of osteoid trabeculæ from the proliferating periosteum. Preparation from a fracture fourteen days old. (Müller's fluid; picric acid; hæmatoxylin; carmine.) *a*, Fibre-layer belonging to the outer periosteum; *b*, embryonic tissue; *c*, osteoid tissue; *d*, cartilage-tissue; *e*, marrow. Magnified 50 diameters.

If **bone** is to develop from cellular embryonic tissue there appears between the formative cells a homogeneous or fibrillated dense basement substance (Fig. 159, *c*), which later on becomes impregnated with calcareous salts. The osteoblasts come to lie in irregular spaces with processes (Fig. 159, *c*, and Fig. 160, *b*) which are generally called bone-corpuscles. In extensive development of cellular embryonic tissue, its transformation into bone always is limited to a part of the tissue, so that within the embryonic tissue trabeculæ (Fig. 159, *c*) are formed, which are called **osteoid trabeculæ** as long as they remain incomplete and do not contain lime-salts. The tissue between (*b*) is transformed into **marrow** by the cells becoming united to one another by processes, while there appears between them a fluid basement substance, in which, later on, round cells become embedded. If only a little bone is to be formed and old bony trabeculæ are to be coated over, then osteoblasts form a layer on its surface (Fig. 160, *c*) and these, later on, produce bone in the above-described way.

Mucous tissue develops from embryonic tissue by the formation of a homogeneous, gelatinous matrix containing mucin and lying between the cells, while the latter, at least in part, form a network by means of processes.

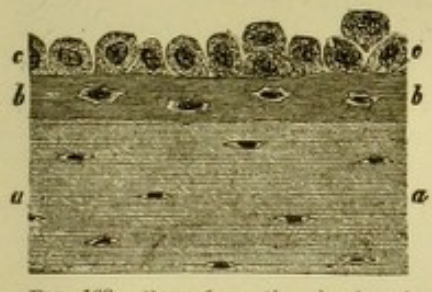


FIG. 160.—Bone-formation by heaping up of osteoblasts upon old bone. (Müller's fluid: picric acid; hæmatoxylin; carmine.) *a*, Old bone; *b*, new-formed bone; *c*, osteoblasts. Magnified 300 diameters.

Lymphadenoid tissue develops from embryonic tissue by the formation of a part of the cells into a supporting reticulum, while lymphatic round cells gather in the meshes of this network, which contains fluid. In injured lymph-glands the cells of the framework first take on a proliferative activity and then produce ordinary fibrillated connective tissue. It is only to a very limited extent that the latter disposes itself in the form of a reticulum, and so presents the characteristics of lymph-adenoid connective tissue.

Spleen tissue proper is not reproduced when this organ receives an injury; the wound heals through the growth of ordinary cicatricial tis-

sue. It is also a fact that compensatory hypertrophy does not take place after the removal of a considerable portion of the organ.

Fatty tissue arises by the taking up of fat into the cells of embryonic tissue or of mucous tissue or of connective tissue, while the cells change to fat-cells by the running together of the fat-drops which they contain.

The **basement substance** of the tissues described is **a product of the protoplasm of the formative cells.** Whether in the process parts of the protoplasm are directly changed into basement substance, or whether they secrete the basement substance or manufacture it from the intercellular fluid, are questions difficult to decide; yet it is probable that only the two first-mentioned methods of formation occur (*cf.* Fig. 156, *d*, and Fig. 157). In suitable specimens one may often notice that the *fibrillæ*, not only of the ordinary connective tissue and the osteoid tissue, but also of the newly formed cartilage tissue, *are connected with cells;* that is to say, they represent simple or branching processes of such cells, or they may even in some places enter into the granular protoplasmic substance (Fig. 155, *d*), thus forming an integral part of the cell-body.

With the advancing development of the fibrillated ground-substance the fibrillæ, to a great extent, become separated from the protoplasm.

Fibrillated connective tissue can develop from any of the connective substances which may take on proliferative activity; but in the course of this process there must be an intermediate stage of embryonic tissue.

Bone arises most often from periosteum, perichondrium, and marrow, but can take origin at times also from other connective-tissue structures, as, for example, intermuscular connective tissue.

Cartilage arises most often from proliferating perichondrium, periosteum, marrow, and cartilage itself, but occurs also in other connective-tissue structures—for example, in the connective tissue of the testis and the parotid. The cartilage-cells near a lesion may, under certain circumstances, by proliferation produce a large-celled embryonic tissue, but this does not reach any considerable size. In enchondroma, the cell-multiplication and the new formation of cartilage take place in the same way as in physiological cartilage-growth. Very often the cartilage formed under pathological conditions is only a transitional tissue and changes very soon again into bone and marrow or into connective tissue.

New lymphadenoid tissue may, under pathological conditions, develop as well from lymphadenoid tissue as from adipose tissue (Bayer) and fibrillated connected tissue, and it is formed from the latter most often in the connective tissue of the mucosa and submucosa of the intestinal tract, as well as in the glandular organs; rarely in intermuscular connective tissue.

Mucous tissue may develop from all proliferating connective tissue, but appears only rarely in large masses, and is also for the most part a transitional form, which changes into adipose or connective tissue.

Adipose tissue develops in those situations which already normally contain fat, but occurs also at times in other places—for example, in the reticulated framework of atrophic lymph-glands, in the perimysium internum of atrophied muscles, etc.

The near relationship of the different forms of connective tissue to one another enables the various forms to pass from one to another without the need of an intermediate stage of embryonic tissue. Further details in regard to this matter are contained in the next part.

§ 90. The **new formation of the white blood-cells** occurs, in the first place, within the lymphadenoid tissue of the lymph-glands, spleen, and intestinal tract, and the lymph-nodes contain areas distinctly separated off from their surroundings, in which there are always a large number of nuclear-division figures which belong for the most part to free cells. These areas are called *germ-centres* (Flemming). It is also probable that leucocytes are produced in the bone-marrow and that they gain an entrance into the blood-vessels of the part (Neumann). Moreover, proliferation of leucocytes by division occurs also in the lymph-channels of the lymph-glands and the tissues, and now there is no doubt that the leucocytes also undergo division in the circulating blood and in the tissue-spaces.

The division occurs first of all by mitosis; but amitotic division also takes place, and upon this phenomenon depends the fact that a large part of the leucocytes contain broken-up portions of nuclei, of peculiar lobulated or wreath-like shapes.

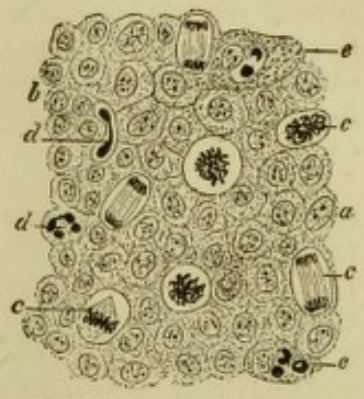


FIG. 161.—Section from the centre of development of a mesenteric gland (from Flemming). *a*, Large leucocytes; *b*, small leucocytes; *c*, karyomitoses; *d*, direct division of the nucleus, or nuclear fragmentation, the significance of which is still unknown; *e*, cells which contain, about the nucleus, large bodies that stain and smaller yellow pigment granules whose meaning is unknown. Preparation treated with Flemming's acid-mixture and stained with safranin and gentian violet. Magnified 400 diameters.

Mitotic division is the one which leads to the formation of viable cells. In how far amitotic division (fragmentation of the nuclei) is followed by cell-division is hard to tell, but there is no doubt that the leucocytes with broken-up nuclei represent for the most part elements undergoing retrograde metamorphosis. Consequently the transformation of uninuclear into multinuclear leucocytes would have to be regarded as an evidence of their death.

Not infrequently in pathological conditions an *increase in leucocyte-formation* takes place, and this may occur not only in the germ-centres, but also in other situations. This increase may lead to a temporary increase of the leucocytes of the blood—to a *leucocytosis*,—as, for example, in the course of many infectious diseases, as pyæmia, erysipelas, pneumonia, pleurisy, peritonitis, in which especially the polynuclear cells are increased in number. It must, however, be noted that an increase of the leucocytes of the blood is no proof of an increased production, for the cells may be transferred from the lymphadenoid tissue into the blood in larger numbers. In the chronic disease called *leukæmia*, the mononuclear leucocytes in the blood are increased. Since in leukæmia sometimes the spleen, sometimes the lymph-glands, sometimes the marrow, and in some cases all these organs together, show a condition of hypertrophy with increased cell-production, it is likely that the leucocytes present in the blood come also, for the most part, from these organs. In harmony with this view stands the fact that, in lymphatic leukæmia, it is particularly the small mononuclear cell-forms that make their appearance in the blood, and these correspond with the cells of the lymphadenoid tissue; in myelogenetic and mixed forms of leukæmia, rather the large mononucleated cells, such as correspond to the bone-marrow-cells and are not a component of normal blood. In leukæmia, furthermore, a multiplication of leucocytes may occur also in the vessels and in a variety of organs.

The **new formation of the red blood-cells** occurs (Bizzozero, Neumann, Flemming) by mitotic division of nucleated young forms of red blood-cells—the **erythroblasts.** In the human adult the seat of this growth is limited to the bone-marrow, and this also holds good (Bizzozero) in the case of mammals, birds, reptiles, and tailless amphibia, while in tailed amphibia and in fishes the spleen also has a share in it. In embryos the development and multiplication of red blood-cells take place in the entire vascular system; later this productive activity is confined to the spleen, the liver, and the marrow, and finally to the latter alone.

Neumann claims that the multiplication of the young forms of the red blood-cells takes place in the lymphoid marrow. According to Bizzozero and Denys, it takes place only within the vessels of the marrow, and the complete development of the red cells is carried out in the same situation. Timofejewsky states that under pathological conditions it may also take place in the circulating blood. The transformation of the nucleated into non-nucleated cells takes place, according to most observers, by disappearance of the nucleus. Rindfleisch and Howell hold that the nucleus passes out of the cell. According to Malassez the cell separates off from the nucleus.

The origin of the nucleated red cells has not yet been satisfactorily explained. According to Bizzozero, the young red corpuscles are cells of a peculiar kind which always contain hæmoglobin and have no colorless periphery. Denys, Löwit, and Howell, on the contrary, assume that they arise from nucleated colorless cells without hæmoglobin, which, according to Denys, proliferate within the vessels of the marrow, while Löwit believes that the colorless antecedents of the red cells, dividing by mitosis, and which he calls erythroblasts, occur as well in the lymph-glands and spleen as in the marrow, and as well in the vessels as in the meshes of the reticulated tissue.

Flemming, who agrees with Bizzozero regarding the hæmoglobin of the nucleated young red blood-cells, is inclined to assume that the young forms which are present in later life are direct descendants of those of the embryo period, while Neumann believes that this hypothesis is not sufficient to explain all the phenomena of later life, as, for example, the replacing of the fatty marrow containing no nucleated red cells by blood-forming lymphoid marrow, and the formation of blood in newly produced marrow. He finds himself driven to the assumption either that a development of the nucleated blood-cells takes place from the leucocytes of the blood which are carried to the marrow after birth by the arteries, or that the cells arise from the tissue-elements of the marrow.

In the increased blood-formation which takes place after loss of blood, as well, also, as in severe chronic anæmias and in leukæmia, nucleated red blood-cells occur also in the circulating blood outside the marrow, while under normal conditions they are not found there. The fatty marrow acquires in this way once more, in part, the character of lymphoid marrow, and this transformation is completed by disappearance of the fat, by a widening of the blood-vessels with an increase in their contents, and by an increase in the number of the colorless corpuscles of the marrow.

Ehrlich[1] and Einhorn[2] distinguish among the leucocytes of the normal blood: (1)

[1] *Zeitschrift für klin. Med.*, i.; *Charité-Annalen*, 1884; *Verhandl. der Phys. Gesellschaft zu Berlin*, 1878–79; and *Deutsche med. Wochenschr.*, 1883.

[2] "Ueber das Verhalten der Lymphocyten zu den weissen Blutkörperchen," I.-D., Berlin, 1884; *ref. Fortschritte der Med.*, iii.

small lymphocytes with relatively large nuclei that stain deeply, and with little protoplasm; (2) *large lymphocytes* with large nuclei that stain faintly, and with more protoplasm; (3) *mononuclear transition forms* with irregular nuclei; (4) *polynuclear neutrophile leucocytes* with polymorphous nuclei, or with several nuclei and neutrophile granules (granules which stain with a neutral dye, obtained by mixing acid fuchsin with basic methyl green), these forming about seventy per cent. of all the white cells of the blood, and migrating in purulent inflammations; and (5) *eosinophile cells*, whose protoplasm contains numerous granules which stain with acid dyes (eosin).

According to Quincke, the life of a red blood-cell is probably about two or three weeks; but this estimate seems too small in view of some other observations, which indicate that a dog manufactures about 20 gm. of blood a day. As soon as the red cells are incapable of performing their function they are taken up by white blood-cells and eliminated from the blood-current, and this takes place by preference in the spleen and liver as well as in the marrow and lymph-glands. The red cells inclosed in the colorless cells (pulp-cells, marrow-cells), or their degeneration-products, are changed to colored or colorless iron compounds, which may be demonstrated microchemically sometimes in soluble, sometimes in granular form. A part of these iron compounds is later on taken up into the blood in the spleen and marrow, and probably also in the liver, and is used again in the formation of new red blood-cells. Another part of the iron, on the contrary, is excreted through the liver-cells.

Löwit distinguishes two separate forms of colorless blood-corpuscles, leucoblasts and erythroblasts, which, he thinks, have an entirely different meaning and do not pass from one form into the other. The leucoblasts are the lymphoid cells with chromatin arranged in lumps, and which do not suffer division by mitosis, but are changed to multinuclear leucocytes by fragmentation of the nucleus. The erythroblasts are the colorless youthful forms of the red blood-cells, which undergo mitotic division and differ from the lymphoid cells by the homogeneous character and slight contractility of the protoplasm. He claims that the transformation into cells containing hæmoglobin takes place partly in the blood, partly in the marrow.

Flemming considers Löwit in error, and claims that a transformation of colorless erythroblasts into red cells does not follow from Löwit's observations; he calls attention to the fact that leucocytes that do not go on to form red cells suffer mitotic division. Neumann also is unable to agree with Löwit.

Howell claims that the marrow contains numerous colorless erythroblasts, which change in the marrow first into nucleated red cells, and, later on, into the non-nucleated form by extrusion of the nucleus.

Hayem is of the opinion that the red blood-cells arise from biconcave, non-nucleated discs, the blood-plates, which he accordingly calls hæmatoblasts. He considers that the blood-plates develop into colorless lymph-corpuscles, which are set free from the lymph before they come into the blood. Cadet and Pouchet hold opinions like the above, but the latter thinks that the nucleated red cells are formed by direct transformation of leucocytes. Malassez thinks they come from buds from nucleated cells of the marrow. According to Denys, with whom also E. H. Ziegler agrees, the red corpuscles have a peculiar origin. In birds they are formed from the wall of the venous capillaries of the bone-marrow, which have a germinal area for red cells, in the shape of a cellular coating of many layers, which gives up into the blood-stream cells which then come to contain hæmoglobin.

Foà and Salvioli advance the hypothesis that the large cells of the marrow, with central lobulated nucleus, produce red cells by the development of a bud from the nucleus, which comes to be surrounded by hyaline substance, then is constricted off, and finally comes to contain hæmoglobin.

§ 91. The **new formation of transversely striated muscle-fibres** starts from portions of old muscle-fibre; and if, after injury to a muscle, the intermuscular connective tissue goes on to active growth, it forms, later on, only connective tissue, or probably also the sarcolemma of the new fibres, but never new contractile muscle-fibres.

After injury of a muscle, the first signs of formative activity appear in the muscle-nuclei. These stretch out lengthwise and then (Steudel, Nauwerck) divide into a varying number of pieces. Already on the second day mitotic division of the nuclei may begin (Fig. 162, *a*, *b*), which seems to be the only way in which the tissue multiplies; and under favorable conditions this takes place quite actively after the second day.

The behavior of the contractile substance of the muscle differs very materially according to the nature and extent of the injury. In the case of traumatic, as well as of toxic and ischæmic injuries, it suffers fragmentation into larger and smaller portions, so that the muscle-cells come to lie in spaces of various sizes in the midst of the débris of the muscle-fibres. Crushing and tearing can bring about a wide separation of the parts of contractile substance. The ends of the pieces of fibre then become sometimes pointed, sometimes oblique, transverse, or with irregular edges. Not infrequently, also, after a short time, the ends become split into several pointed filaments (Fig. 162, *a*).

The mitotic division of the muscle-nucleus takes place not only in the case of nuclei that rest upon living fibres (*a*), but also in the muscle-cells (*b*) lying free in the spaces between the fibres that have separated from one another, and is followed in both cases by the development of

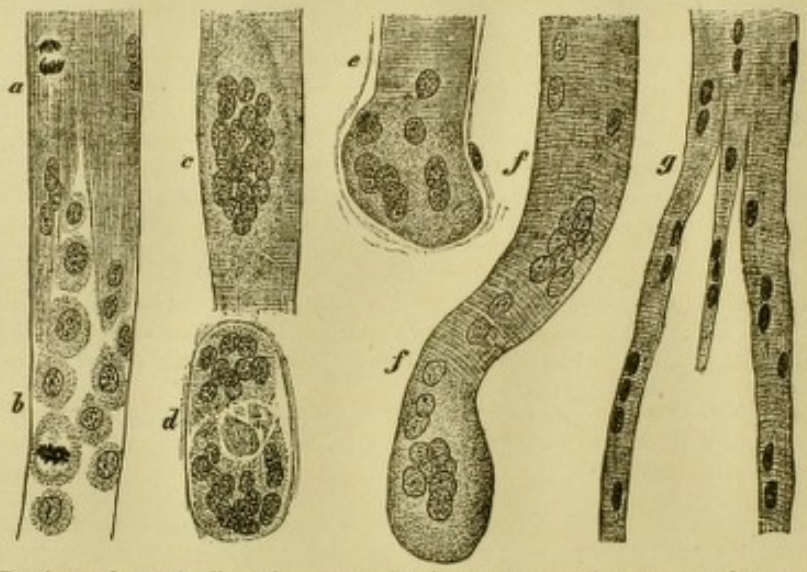


FIG. 162.—Portions of muscle-fibre, from wounds of muscle at various stages of regenerative growth. (Flemming's mixture; safranin.) *a*, Pointed ends of a muscle-fibre with nuclear-division figures, three days after being torn across; *b*, proliferated muscle-nuclei transformed into cells rich in protoplasm, of which one is in process of mitotic division; *c*, piece of muscle-fibre eight days after tying across a muscle; *d*, giant cells which inclose a necrotic piece of muscle, from a muscle-cicatrix twenty-six days old; *e*, *f*, muscle-fibres ending in masses of protoplasm (muscle-buds)—*e* from a ten-days-old, *f* from a twenty-one-days-old cicatrix; *g*, muscle-fibre dividing, from a forty-three-days-old cicatrix. Magnified 350 diameters.

large multinuclear cells, which lead to the formation of multinuclear protoplasmic masses on the ends of the muscle-fibres (*e*, *f*), as well as in the body of the fibres (*c*). Between these and the transversely striated muscle-substance there is no sharp line of demarcation. There occurs, therefore, *with multiplication of the nuclei, a growth of the sarcoplasm of the muscle-fibres, and this becomes clearly visible;* and it is probable that the muscle-fibrillæ also may suffer a transformation again into sarcoplasm.

The muscle-cells that are not connected with living contractile substance become transformed into *large epithelioid cells with a large nucleus* (*b*), which again is changed, by continued nuclear division, into *multinuclear masses of protoplasm* (*d*); and a cicatrix of from eight to thirty days, consisting of growing connective tissue, may possess such giant cells in large number, which often contain (*d*) débris of the old fibres.

The *new muscle-fibres are developed from the sarcoplasm rich in nuclei* which appears in the continuity and at the ends of the muscle-fibres, and is associated with the formation of numerous large nuclei; and by

its increase in bulk it forms a growth in the muscle, which has been called *bud-formation* by Neumann. With the transition of the sarcoplasm into muscle-fibrillæ there appears gradually a longitudinal and, later on, also a transverse striation, an indication that the organic structure of the plasma has completed its development in the way characteristic of muscle.

The greater part of the *muscle-cells growing without connection with living muscle-fibres* die. Yet it must be noted that they last a long time, so that in many muscle-cicatrices of from eight to forty days one can often find large numbers of masses of protoplasm rich in nuclei, which, under some circumstances, may form long continuous bands or whole rows of separate pieces of protoplasm. There is also no doubt that a part of these cells are, under favorable circumstances, transformed into transversely striated muscle-substance; and this occurs either by the formation of independent new muscle-fibres, or by union with old muscle-fibres or muscle-buds. The non-continuous growth of muscle from proliferating muscle-cells may be observed with special frequency at points where the contractile substance perishes while the enveloping sarcolemma remains intact (as, for example, in typhoid fever). On the other hand, the budding process can be seen best at the ends of divided muscular fibres.

The buds springing from their ends or from their sides may form a simple prolongation of the muscle-fibre, frequently deviating from its original direction (*f*). Often there occur fibres split up into two or three parts (*g*), so that the old fibres branch as they pass into the muscle-scar. As far as we know, this splitting up occurs very early—often, indeed (*a*), before the proliferating muscle-nuclei have formed much sarcoplasm—so that the proliferation appears first in the products of the division of the fibres. As a result of this fission, cicatrices in muscle often contain a larger number of muscle-fibres than were originally present in the area in question.

Hypertrophy of striated muscle takes place by enlargement of the separate muscle-fibres, and yet a proliferation of the fibres may also be associated with this.

A **new development of cardiac muscle** seems to occur only to a very limited extent. To be sure, after injuries to the heart, nuclear-division figures may appear in the muscle-cells. Nevertheless, even after a few days, these can no longer be demonstrated, and the wound heals with ordinary scar-tissue. Foci of degeneration of the cardiac muscle heal in the same way by cicatricial connective tissue. If the **heart-muscle** is for any reason **hypertrophied,** this increase in size takes place by enlargement of the muscle-cells; whether or not a proliferation of the cells also is present is not yet positively known.

A **new formation of smooth muscle** occurs, as does regeneration, after traumatic or toxic and ischæmic degeneration. It occurs also in hypertrophic new formation of muscle-tissue—for example, in tumors—and is initiated by a mitotic division of the nuclei of the muscle-cells, which is followed by cell-division. According to both experimental work and observations upon the muscle-tissues of man, the reproduction of the fibres is slight, while after injuries and focal degeneration it ceases again after a short period. Thus, for example, defects in the muscularis of the stomach and intestine or of the bladder are repaired, for the most part, only by connective tissue. New muscle-tissue probably arises only from old muscle-tissue.

Hypertrophy of the smooth muscle-fibres is a phenomenon which, within certain limits, very often occurs. In the gravid uterus the size of the muscle-cells reaches from five to ten times the ordinary. Of the other organs, the bladder most often shows a considerable hypertrophy of its smooth muscle.

§ 92. **Regenerative new formation of the nerve-elements of the central nervous system by new formation of ganglion-cells,** as far as is known, does not occur in man and mammals in post-embryonic life. According to the investigations of Stroebe, on the contrary, *divided nerve-fibres* (in mammals) *may grow somewhat lengthwise by sprouting of the axis-cylinder;* and this holds good for the fibres of the pyramidal tract and of the posterior roots, both of which, after being cut through, grow out into the cicatricial tissue which develops at this point, the former in a downward, the latter in an upward direction. But a complete restoration of the nerve-tissue does not occur, and a traumatic defect in the spinal cord is really replaced by connective tissue, partly by neuroglia. It is not yet known whether the loss of separate nerve-fibres of the brain and spinal cord may, under favorable circumstances, be entirely restored by the growing out of the axis-cylinders—for instance, if the supporting tissue be left intact.

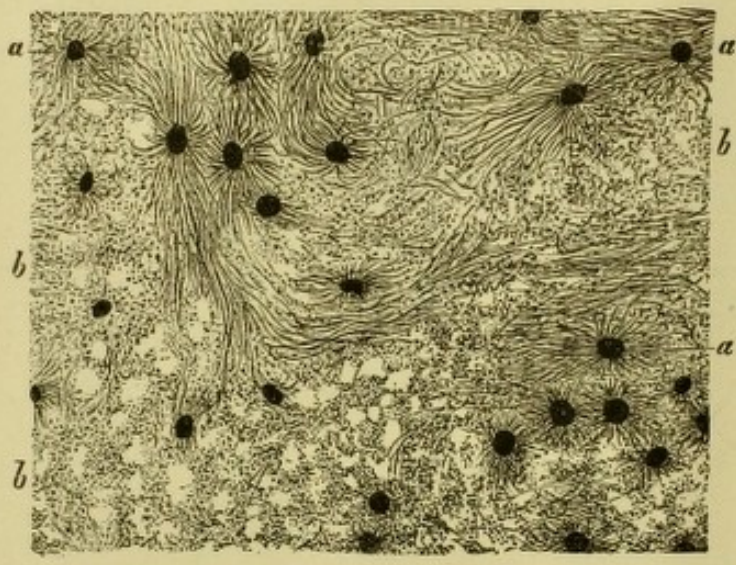


FIG. 163.—Sclerotic tissue from the posterior columns in a case of multiple sclerosis. (Müller's fluid; staining by Mallory's method.) *a*, Glia cells with numerous processes seen in longitudinal section; *b*, sclerosed tissue with the glia fibres cut transversely. Magnified 500 diameters.

Regenerative and hypertrophic growths of the neuroglia are phenomena which frequently occur in morbid affections of the nervous system and either follow close upon degenerative changes in the nervous elements or upon destruction of the neuroglia itself, or they appear without such antecedents, and then take their origin partly in the period of development.

The new formation is introduced by a mitotic division of the nuclei and bodies of the glia-cells, eventually also of the ependyma-cells.

The new-formed glia-cells produce later a great profusion of delicate fibrillary processes (Fig. 163, *a*) and, just as in normal tissues of the central nervous system, so among these cells, known as *astrocytes* (or Deiter's cells), we may distinguish two varieties, the so-called "*mossy cells*" (Kurzstrahler), with short branching processes, and the so-called "*spider cells*" (Langstrahler), (*a*) with long, rigid, less freely branching processes. These cell-processes form here a looser and there a denser felt-work of fine fibrils (*a*, *b*), between which are wedged the cells, scantily provided with protoplasm. After full development of the tissue a separation of these processes from the cell-bodies may occur. The compaction of the tissue caused by the proliferation is designated *sclerosis*.

Regenerative new formation of the nerve-fibres of the peripheral nervous system occurs very often, and is present in all those cases in which the continuity of a nerve-fibre is interrupted or partly destroyed by any influences whatsoever. For its accomplishment, however, it is necessary that the ganglion-cell whose process forms the nerve-fibre in question be preserved.

If a nerve has been divided by cutting, the axis-cylinders, as well as the medullary sheaths, in the distal portion, undergo degeneration, in the course of which the sheaths break up into granular débris, which is later on absorbed. During the destruction of the nerve-fibres the nuclei situated beneath the sheath of Schwann continue to grow with the formation of mitoses, and form cells rich in protoplasm, which may take up into themselves the products of the destruction of the nerve-fibres.

Of the central portion of the nerve only the peripheral extremity degenerates, up to the next Ranvier's node, or the next but one.

The regeneration of the nerve begins a few days after the operation, in the proximal portion, and, indeed, according to Ranvier and Stroebe, in the very neighborhood of the incision; according to Vanlair, on the contrary, at a distance of from 1.5 to 2 cm. from it.

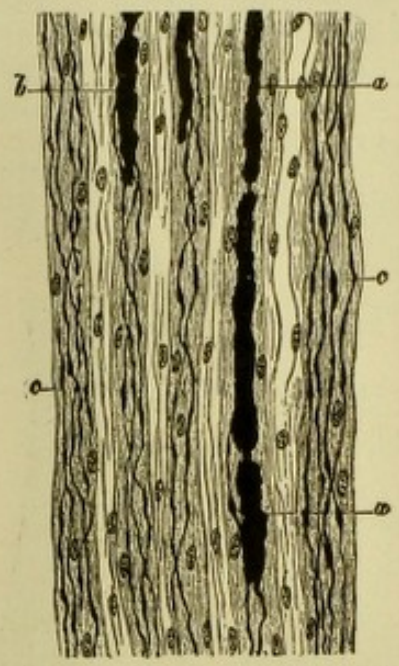


FIG. 164.—Old and newly formed nerve-fibres, from an amputation stump, in longitudinal section. (Müllers' fluid; staining by Weigert's method.) *a*, *b*, Old nerve-fibres, from which several young nerve-fibres have grown; *c*, neurilemma, with young nerve-fibres. Magnified 200 diameters.

The first change consists in a swelling of separate axis-cylinders in the peripheral parts of the nerve-bundles of the central portion, which is later on followed by a splitting off of from two to five or more new axis-cylinders. The new axis-cylinders arising from the splitting up of the old ones grow in a longitudinal direction (Fig. 164, *a*, *b*), and form, within the sheath of Schwann, whole bundles (Fig. 164, *c*, and Fig. 165, *e*) of new nerve-fibres, which for the most part fill the entire lumen of the old nerve-tubes, and, indeed, stretch it, and, more rarely, also inclose remains of the old fibres (Fig. 165, *f*). According to Vanlair, they may even break through the old sheath of Schwann, and then either go on further in the endoneurium, or push through the perineurium of the nerve-bundles into the epineurium.

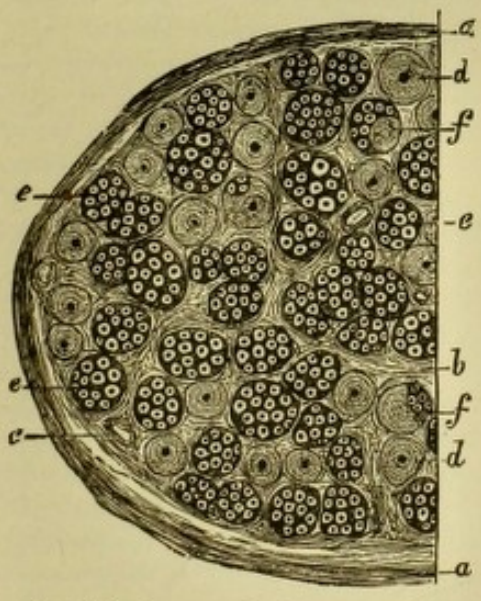


FIG. 165.—Cross-section of a nerve-bundle of the median nerve, just above a wound made four months previously. (Müller's fluid; carmine.) *a*, Perineurium; *b*, endoneurium; *c*, cross-section of a vessel; *d*, old unchanged nerve-fibre; *e*, bundle of newly formed nerve-fibres; *f*, newly formed nerves, with remains of the old fibres inside the same sheath. Magnified 200 diameters.

In this way there are formed, on the lower end of the proximal portion of the nerve, a large number of new

nerve-fibres, which originally consist only of the newly formed axis-cylinders, but immediately surround themselves with a medullary sheath which, by reason of the irregularity of its development, gives to the nerve-fibres a varicose appearance (Fig. 164, *c*). Later, the fibres acquire a neurilemma sheath—that is to say, a connective-tissue shell, which probably is formed from the nerve-corpuscles concerned in the growth.

If a nerve is entirely severed and there is no possibility of a union of its cut ends—as, for example, occurs in all amputations of extremities—then there is developed in the region of the cut end a germ-tissue springing from the connective tissue of the nerve, which later on changes into connective tissue. Originally free from nerves, this connective tissue becomes traversed by young nerves which grow out from the nerve-stump, and which, arranged in small bundles, or scattered, grow into the cicatricial tissue and pierce it in every direction (Fig. 166). Often the growth of nerves is so extensive that knob-like or clubbed swellings —known as *amputation neuromata*—arise on the ends of the nerves (Fig. 166, *b*).

FIG. 166.—Amputation neuroma of sciatic nerve in longitudinal section (amputation of the nerve nine years before). (Müller's fluid.) *a*, Nerve; *b*, neuroma. Magnified 3 diameters.

If a nerve is divided, but, after the division, has been again united, or if the division has been incomplete, the nerve-fibres which grow out from the proximal portion, piercing through the connective tissue which is formed in the neighborhood of the wound, may in part, or all, find their way into the peripheral portion, where, in the mean while, the nerve-fibres have perished. Their penetration into this peripheral portion *gives back to it, at least in some measure, its supply of nerves.*

According to the investigations of Vanlair, the growth of a nerve in process of regeneration amounts to 0.2–1.0 mm. per day, according to the nature of the tissue in which it lies. Single young nerve-fibres may burrow into the old empty sheaths of Schwann, but the majority of them press into the epineurium and perineurium, and in this situation grow toward the end-organs. Separate fibres also pass by the ends of the nerves, and grow toward the periphery either along the old nerves, or by an independent route of their own. Finally, many fibres which have left the old route are lost in the tissues. In the lower half of the intermediate portion the nerve-strands have already begun to separate into bundles again, and, with the formation of a perineurium about the latter, the regenerated nerve may take on more and more the structure of a normal nerve.

The above-described process of regeneration requires for its accom-

plishment weeks or even months, and sometimes is not complete even after several months.

The question of the **regeneration of the nervous elements of the central nervous system** is still under discussion. We may accept, as generally conceded, that in cold-blooded animals, reptiles, and tailed amphibia, a regenerative new formation of portions of the central nervous system can take place. In warm-blooded animals, especially in mammals, most experiments have failed to demonstrate a new formation of ganglion-cells. Very recently Tedeschi, Vitzon, and others have asserted that they have observed, after a variety of injuries, along with new formation of glia-cells, a simultaneous new formation of ganglion-cells and of nerve-fibres. Relying upon investigations which Tschistowitsch has pursued in my laboratory, I regard these assertions as erroneous.

In the ganglion-cells of the sympathetic, Monti and Fieschi could demonstrate no traces of regeneration after injuries. Tirelli found nothing but retrogressive changes in the ganglion-cells, after injuries of the intervertebral ganglia.

The **new formation of peripheral nerve-fibres** is a fact coming under extremely frequent observation, and the steps of the new formation, described above, have, for the most part, been very precisely ascertained. Authors, nevertheless, make very varied assertions in this regard.

Waller, Schiff, Rindfleisch, Cornil, Ranvier, Eichhorst, Vanlair, Stroebe, and others believe that it occurs through a longitudinal fission of, and an outgrowth from the old axis-cylinders of the central portion. According to Philippeaux, Vulpian, Remak, Dobbert, Daszkiewicz, and others, the new fibres originate in the peripheral end, and, indeed, according to Leegard, from the nuclei of the neurilemma; according to Remak, by longitudinal division of the old axis-cylinders that have remained intact; according to Daszkiewicz, from the remains of the old axis-cylinders broken up transversely; according to Neumann and Dobbert, from a protoplasmic mass which has developed in advance by a chemical metamorphosis of the medulla and the axis-cylinder. According to Cattani, new axis-cylinders develop in degenerated nerves in the interior of a nucleated protoplasmic mass which, in the degenerated fibres, fills the sheath of Schwann. Nassee, Günther, Schön, and Steinbrück claim that the axis-cylinders originate from the old fibres of both ends; Leut, Einsiedel, Weir Mitchell, Beneke, Gluck, and von Büngner, that they come from the nuclei of the sheaths of Schwann of both portions; while, according to Laveran and Herz, they spring from white blood-corpuscles; finally, Hjelt and Wolberg think they arise from the cells of the perineurium.

The regenerative new formation of the tissues of the organs of special sense has been only partially and inadequately investigated. According to Baquis, in the injured retina of rabbits, both ganglion-cells and neuro-epithelial cells undergo division. According to Wolff and Müller, in salamanders, the crystalline lens, after extirpation, is regenerated from the epithelium of the iris. According to Gonin, after its partial extirpation in rabbits, it is regenerated from the epithelial lenticular fibres of the residue (stump), but never reaches its original size. After total extirpation, no regeneration occurs.

III. Metaplasia of the Tissues.

§ 93. By **metaplasia** of a tissue is understood a process by which *an already completely formed tissue is transformed into another* without a cellular intermediate stage—that is, an embryonic tissue or formative tissue. Such a transformation occurs only in structures that are closely related to one another, especially, therefore, in the connective tissues. In this group, under pathological conditions, all the forms may be transformed one into another without the appearance of any intermediate growth—a phenomenon which is not startling, for, indeed, it occurs normally. If mucous tissue is changed to adipose, then the star-shaped tissue-cells change to round adipose cells by taking up fat, while the mucous basement substance disappears. In the same way, lymph-adenoid tissue, after disappearance of the lymphatic elements, may change to adipose tissue by the taking up of fat in the cells of the reticulum. The cellular and gelatinous bone-marrow also behaves in the same way.

By disappearance of the fat, adipose tissue may take on the appearance of mucous tissue, and at times, also, may contain nuclei. If the basement substance of hyaline cartilage becomes fluid, so as to form a mucilaginous jelly, or if it becomes completely dissolved, then the cartilage-cells (Fig. 167, *a*) set free in this way change to stellate cells anastomosing with one another (*c*, *b*), so that a tissue is formed which corresponds in its structure to mucoid tissue or to the reticular tissue of bone-marrow. By taking up of fat the latter may become adipose tissue; by storing up of round cells in its meshes it becomes cellular marrow-tissue. If the basement substance of hyaline cartilage becomes fibrous, and if it changes at once to a glue-producing material, then connective-tissue cartilage is produced. If the cartilage-cells lose their characteristic nature, and if they become flat connective-tissue cells, then the cartilage changes into ordinary connective tissue.

If portions of the cartilage change to medullary tissue, then other parts of it may at the same time be transformed into bone, in which case the basement substance is changed into a gelatinous material and impregnated with lime-salts, while the cartilage-cells are transformed into bone-cells, in the neighborhood of which the basement substance of the bone forms the bone-corpuscles. If connective tissue changes directly into bone (Fig. 168), then in the first place a condensation of the basement substance (*b*) takes place, and later on a storing up of lime (*c*), in the course of which the connective-tissue cells (*d*) come to lie in indented spaces or bone-corpuscles and become bone-cells (d_1).

If connective tissue is to be transformed into mucous tissue, then the fibrillæ disappear, and there appears in their place a gelatinous

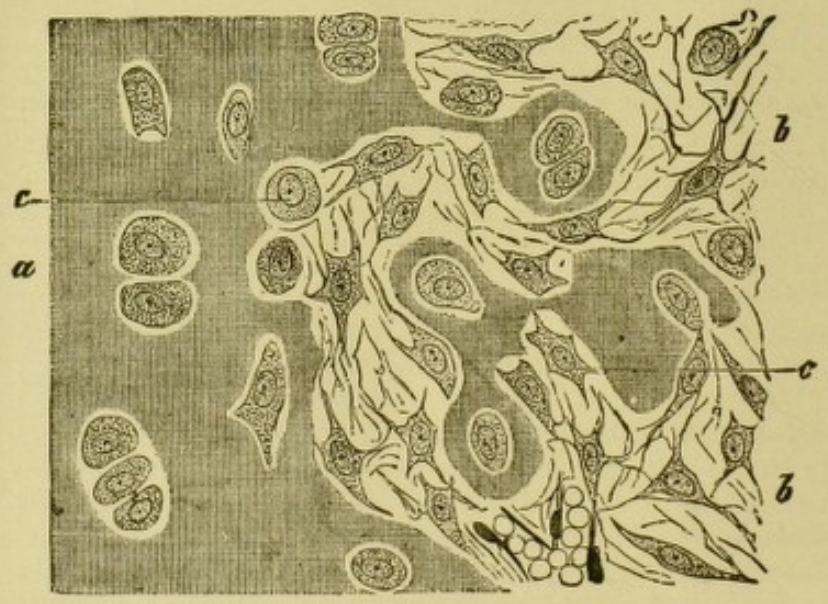


FIG. 167.—Metaplasia of cartilage into reticular tissue, in arthritis fungosa. (Alcohol; hæmatoxylin.) *a*, Hyaline cartilage; *b*, tissue consisting of branching cells; *c*, cartilage-cells set free by solution of the cartilage basement substance and passing over into mucous-tissue cells. Magnified 400 diameters.

mucus. If numerous lymphatic round cells establish themselves in a fibrillated connective tissue, and if at the same time a breaking up or a disappearance of the connective-tissue fibres takes place, while the connective-tissue cells persist, and unite to form a recticular tissue by the development of processes, then in this case a lymphadenoid tissue may be developed from it.

Metaplasia of connective tissue is to be distinguished not only from simple degeneration, but also from the processes of growth. From the former no new tissue arises, but the old tissue perishes. In the latter it is a question of a new tissue, rich in cells, and taking its origin in cell-division. Metaplasia stands, in a certain sense, midway between the two. A new tissue, to be sure, is formed, but cell-growth is not present, or at least is a minor matter.

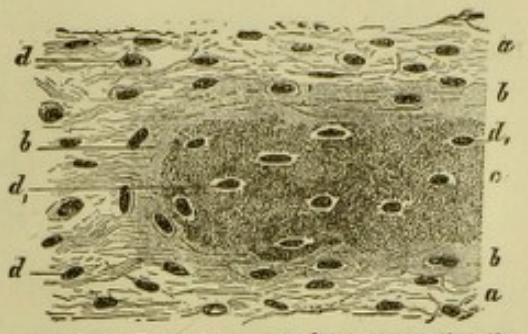


FIG. 168.—Bone-formation from connective tissue. Cross-section through a bone-trabecula in process of formation from an ossifying fibroma of the periosteum of the upper jaw. (Alcohol; hæmatoxylin.) *a*, Connective tissue; *b*, thickened tissue, forming the groundwork of the new bone; *c*, lime-deposit; *d*, connective-tissue cells; d_1, bone-corpuscles. Magnified 200 diameters.

In many ways the process is allied to the retrogressive changes; for example, the change into mucous tissue is a process very similar to mucous degeneration. Moreover, the new tissue is not infrequently a perishable one. On the other hand, one often enough observes developmental processes following upon metaplasia. Sometimes the condition of the blood-vessels has the greatest influence upon the subsequent course of events, since a good vascular supply for the tissue suffering metaplasia favors a further development of it, while its absence, on the contrary, encourages retrograde metamorphosis.

In mucous membranes the seat of chronic inflammation—for example, of the uterus and the respiratory tract—it not rarely happens that the cylindrical epithelium in places changes to pavement epithelium, a phenomenon which is known as *epithelial metaplasia*. The transformation takes place in this way: the regenerating epithelium changes its character after repeated loss of the original epithelium. In the stratified pavement epithelium of a mucous membrane, moreover, a *horny degeneration* of the upper layer of cells may take place, and, indeed, not only in situations which normally possess pavement epithelium—for example, in the urinary passages—but also in those in which it has developed pathologically, as in the nose and uterus.

CHAPTER VI.

Inflammation and the Associated Processes of Repair.

I. Acute Inflammation and its Various Forms.

§ 94. **Inflammation** is essentially a **local tissue-degeneration combined with pathological exudations from the blood-vessels,** caused by some injurious agency, and with these pathological changes are associated, sometimes earlier, sometimes later, **tissue-proliferations** leading to regeneration or to hypertrophy.

In acute inflammation the exudation is generally associated with a pronounced hyperæmia, which begins even before the exudation, and introduces it. As a result of the combination of hyperæmia and exudation, the inflamed tissue is reddened and swollen. If it is situated on the surface of the body, where the tissues are cool, the increased supply of warm blood from the deeper parts produces local increase of temperature. If the tissue contains sensory nerves, the sensation of pain sets in at the same time with the changed conditions in the inflamed area.

Redness, swelling, increased heat, and **painfulness of the inflamed tissue** are phenomena which even in antiquity the physicians regarded as signs of inflammation; and **rubor, tumor, calor,** and **dolor** were designated by Celsus, at the beginning of our era, as the **cardinal symptoms of inflammation.** To the four was then added a still further symptom—**functio læsa, altered function** of the inflamed tissue.

The **causes of inflammation** may be attributed to *mechanical, thermal, electrical, or chemical actions,* and also to the *influence of parasites.* It is a common characteristic of all these injurious agencies to produce at first a *local tissue-degeneration, which in a certain degree of extent and of intensity is associated with disturbances of the circulation and of the vascular secretion.* The causes of inflammation are not specific injurious agencies; but, rather, every injurious agency may produce inflammation, if, on the one hand, its action is sufficiently intense to induce certain disturbances of circulation with tissue-degeneration, while at the same time it does not act strongly enough to destroy the tissue and stop the circulation.

Most causes of inflammation reach the human organism from the outside, but excitants of inflammation may also be formed in the interior of the body. Bacteria which have penetrated into the tissues very often produce at first—either within their own protoplasm or from substances which are present in the body—products whose action induces inflammation. Then, moreover, substances that excite inflammation can develop in the organism even without the aid of parasites; for example, if tissues die in large masses from any cause—*e.g.*, as a result of ischæmia—or if, in consequence of disturbances of the processes of

assimilation (gout), abnormal products of metabolism are deposited in the tissues.

The exciters of inflammation can act upon the tissues both from the external parts of the body and from the lymphatics and the blood, and one can accordingly distinguish **ectogenous, lymphogenous,** and **hæmatogenous inflammations.** Through the extension of inflammations to the neighboring regions there arise **inflammations by continuity**; the transfer of the producer of inflammation from a focus of inflammation through the lymph- or blood-stream leads to **metastatic inflammations.** If noxious substances are discharged by the excretory organs, *excretory inflammations* may arise.

When a local injury to tissues has reached such a degree as to produce the exudation characteristic of inflammation, there is usually present a **congestive hyperæmia,** on account of which the blood flows with increased quickness through the dilated channel. After a short time there occurs, however, on the other hand, a lessening of the speed of the circulation, which ends in a **slowing of the blood-current.**

The first disturbances of the circulation, which find their expression in the congestive hyperæmia, can be due either to an irritation or a paralysis of the vaso-motor nervous system, or to a direct action on the walls of the vessels, particularly those of the arteries, which has as a result a dilatation of the channel. Although these very often precede the inflammatory exudations, they still form no essential characteristic of inflammation, but occur very often when an inflammatory exudate does not follow them. The circulatory disturbance characteristic of inflammation is shown only when the **slowing of the blood-current** and the **pathological exudation** from the vessels set in. The slowing of the blood-stream in the widened channel and the pathological exudation are caused by a *modification of structure*, **an alteration of the vascular walls,** evidences of which are shown in the lasting dilatation of the vessels, in an increase of the adhesion of the blood to their walls, in *an increase of resistance from friction*, and lastly in *an increased permeability of the vascular walls.* In the capillaries the lasting dilatation is chiefly the result of *relaxation of the connective tissue surrounding them*, while the thinness of the capillary walls makes this tissue bear a great part of the pressure upon them.

The **tissue-lesion** which leads to the phenomena of inflammatory disturbance of circulation and exudation affects generally all parts of the tissue, but may, under certain conditions, be confined to the vascular walls, particularly when it is a case of hæmatogenous inflammation, in which the injurious agency acts from the blood. However, the tissue in the region adjoining the capillaries must soon become involved in associated suffering. The tissue-changes which are established by the excitants of inflammation are sometimes only transient, and not easily, or not at all, recognizable even by microscopical examination; at other times they are serious, so that they can be easily recognized even by macroscopic inspection. The latter is particularly the case when a considerable time has passed since the occurrence of the damage. In the subsequent progress there are often added to the lesions established by the causes of inflammation, other tissue-changes, which are produced by the inflammatory disturbances of circulation and by the collection of exudate in the tissues.

If in any tissue the cause of inflammation has led to that alteration of the vessels which is the requisite antecedent of the inflammatory dis-

turbance of secretion—*i.e.*, the formation of inflammatory exudate,—and if as a result of this there is already evident a slowing of the blood-current, the circulation in the capillaries is performed in an irregular way, and there is here and there stagnation, or transient or permanent cessation of flow. Since, in this event, the colorless blood-cells often remain attached to the walls, while the red blood-corpuscles are carried on, there occurs **in the capillaries** a more or less marked **increase of the colorless blood-corpuscles** as compared to the red. **In the veins,** in which one can distinguish in the normal circulation an axial red stream and a cell-less plasmatic peripheral zone, more or less numerous **leucocytes pass over into the peripheral plasmatic zone** when there is a certain degree of slowing of the circulation. Still greater slowing of the circulation results in the passing over of blood-plates and of red blood-corpuscles into the peripheral plasmatic zone, and finally the difference between the axial stream and peripheral zone may be entirely lost.

When leucocytes have passed over into the peripheral zone they either roll along further or attach themselves to the vein-wall, either to roll on again further after a time or to remain permanently attached. If this occurrence leads to a marked accumulation of leucocytes along the walls of the veins, the appearance is called **marginal disposition of the colorless corpuscles** (Fig. 169, *d*).

Related to the accumulation of leucocytes in the capillaries and to the marginal disposition in the veins is the *emigration of the leucocytes from the vessels* involved (Fig. 169, *d*, *e*), and there occurs simultaneously a *pouring out of fluid from the vessels.*

The **emigration of the colorless blood-corpuscles** is an active process, which is accomplished by the amœboid movement of the cells, and it also occurs independently under normal conditions. The cause of the enormous outpouring, as it is observed in inflammations, is doubtless a change in the vessel-walls, which is favored by the circumstance that the leucocytes attach themselves to these walls and also pass through them. According to the researches of Arnold, Thoma, and others, the places where the wandering out occurs are the cement lines between the endothelial cells, and in the inflammatory vascular alteration a partial widening of these spots occurs. The emigration is accomplished in such a manner that the leucocyte first sends a process through the vessel-wall and then follows after the process with the rest of the cell-body, until finally the whole mass lies outside of the vessel. Arrived here, the leucocytes may remain stationary at first, but generally they wander further, when the direction of the excursion is generally settled by *chemotaxis*—*i.e.*, the attraction or repulsion due to chemical substances present in solution in the tissue-juices. Possibly chemotactic influences sometimes exert an influence both on the leucocytes situated at the periphery and on those which are at a standstill in the capillaries. The leucocytes that have migrated from the vessels are chiefly polynuclear forms that make up about seventy per cent. of the colorless corpuscles in the blood. Their number varies greatly.

The **pouring out of the fluid exudate,** whose composition always varies more or less from that of the normal tissue-lymph and is distinguished by a relatively *high proportion of albumin*, is a process which is also to be referred to an *alteration of the vessel-walls*, in consequence of which *the secretory function of the latter suffers a disturbance.* It takes place simultaneously with the migration of leucocytes; it may also, how-

ever, begin even before this occurrence, or it may take place in cases in which emigration of leucocytes is lacking or remains within very narrow limits. The *composition of the exudate* is dependent in every case partly on the peculiar property of the vessels affected—which always varies according to the formation of the tissue to which they belong,—partly on the degree of vascular alteration; and it is to be assumed that the quantity of albumin is larger the more the vascular wall is injured. If the extravasated fluid contains fibrinogenous substances and fibrin-ferment, and if, on the other side, no influences opposed to such a change are acting, **coagulation**—*i.e.*, a **separation of the fibrin**—may occur in the exudate.

If the alteration of the vessels is of a very high degree, or if at the same time the stasis is pronounced, **red blood-corpuscles may emerge**

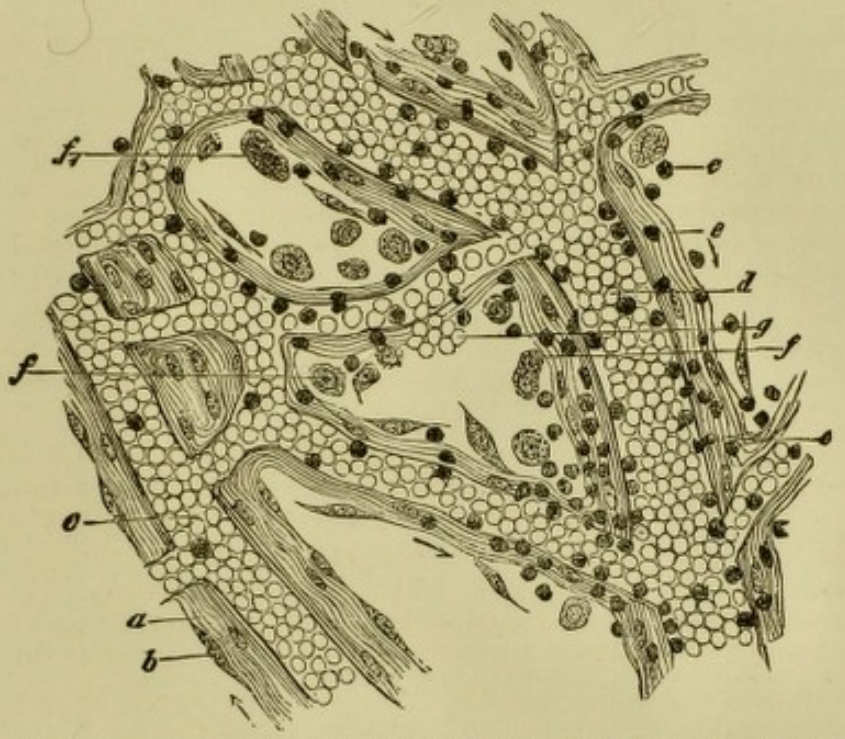


FIG. 169.—Inflamed human mesentery. (Osmic-acid preparation.) *a*, Normal trabecula of mesentery; *b*, normal epithelium; *c*, small artery; *d*, vein with peripheral colorless blood-corpuscles; *e*, colorless blood-corpuscles, emigrated or emigrating; *f*, desquamated epithelium; f_1, polynuclear cell; *g*, extravasated red blood-corpuscles. Magnified 180 diameters.

from the vessels along with the fluid, either by diapedesis or by rhexis. The diapedesis takes place, according to Thoma and Engelmann, especially at the places where leucocytes have previously passed through the wall of the vessel, and the escape of red blood-corpuscles by the same route may follow very quickly. Since the red blood-corpuscles are not motile, their escape must be regarded as a passive process which is performed under the influence of pressure within the capillaries.

The **escape of blood-plates** into the exudate can occur both in exudates which are rich and in those which are poor in cells, but occurs principally in exudates that are distinguished by their rich proportion of fibrin and red blood-corpuscles.

The clinical significance of the term *inflammation* (*phlogosis*) has, on the whole, changed little in the course of time, since the cardinal symptoms of inflammation brought forward by Celsus, and accepted by Galen, are recognized as such at the present day. Just so much the more do the views differ about the differentiation of the essential

from the accidental in the symptom-complex of inflammation, and about the accurate determination of its real nature. A comparison of the expressions concerning these points on the part of recent authors (Virchow, von Recklinghausen, Cohnheim, Samuel, Thoma, Neumann, Stricker, Heitzmann, Grawitz, Leber, Metschnikoff, and others) shows that no single one defines inflammation in the same way as any other, or judges in exactly the same way the individual phenomena of inflammation. The definition which I have given above can accordingly not lay claim to universal recognition; yet since it was first advanced[1] it has received the approval of a number of highly esteemed pathologists.

Formerly it was believed that one should discern in hyperæmia the most essential symptom of inflammation. Rokitansky maintained that every inflammation was characterized by a dilatation of the capillary vessels, slowing of the blood-stream, and stasis, which was caused by a thickening of the blood through the effusion of serum, and by an adhesion of the red blood-corpuscles one to another. Henle, Stilling, and Rokitansky attributed the dilatation of the vessels and the slowing of the blood-stream to a paralysis of the vessel-nerves, the cause of which, according to Henle and Rokitansky, is an increased excitement of the sensory nerves; while according to Stilling, the cause is a paralysis of these nerves induced by the inflammatory irritant. Eisenmann, Heine, and Brücke sought to attribute the disturbances of the circulation to a primary spasm of the vessels, which is brought about by irritation of sensory nerves, and which produces, behind the contracted places, slowing of the current, irregular circulation, and finally even stasis. Vogel, Emmert, Paget, and others, on the other hand, attributed the dilatation of the vessels and the stasis to an abnormal attraction of the tissues for the blood. In opposition to these opinions, however, one must maintain that all the changes of circulation produced by contractions and paralysis of the vessels certainly precede or accompany the inflammatory—*i.e.*, the circulatory—disturbances which lead to the formation of exudate, and may have a modifying influence on the course of the inflammation, but that they do not belong to the essence of inflammation, and therefore may either be lacking or be present in it, without the accompaniment of inflammatory exudate.

Rokitansky sought to explain the pouring out of fluid from the vessels in inflammation by the assumption that with the dilatation of the vessels there occurred also a thinning and an increased permeability of the vascular wall. Vogel, C. Emmert, and Paget, on the other hand, made this phenomenon also dependent on an increased attraction between the blood and tissue parenchyma or juices. Virchow, however, believed (1854) that a part of the exudate—that which collects in the tissue-crevices and is poured out on the free surfaces of the body—is the result of mechanical pressure in the vessels—*i.e.*, is pressed-out blood-serum; while a part, which is chiefly derived from the "irritated" cells, is to be considered as the product of an increased attraction on the part of the tissues for the blood-constituents. Of the cells that collect in the inflamed region, he believed that all originate from a proliferation of the tissue-cells occurring in consequence of the action of the inflammatory irritant.

The recognition that the formation of exudate is to be referred to an injury to the vessel-walls we owe chiefly to Cohnheim, whose researches in various directions were completed by Samuel, Arnold, Thoma, Binz, and others. Cohnheim also showed that in inflammation the colorless corpuscles emigrate and form an essential constituent of the inflammatory exudate.

Dutrochet[2] and Waller[3] already in the years 1842 and 1846 had described the escape of colorless corpuscles from the circulating blood. The observation, however, fell into complete oblivion till Cohnheim rediscovered the occurrence in 1867.

As follows from the researches of Schklarewsky,[4] the peripheral disposition of the colorless blood-corpuscles in the veins is a purely physical phenomenon. If one makes liquid, in which finely pulverized substances of varying specific gravity are suspended, flow in tubes, at a certain degree of retardation of the current the specifically lighter bodies pass over to the peripheral zone; and when the rate becomes still slower, the heavier bodies also enter this zone.

For the emigration of the colorless corpuscles to occur, it is necessary, according to the researches of Binz, Thoma, and Lavdowsky, that they be capable of motion and of adhering to the vessel-wall. According to these authorities, therefore, the emigration of the colorless blood-cells is not a purely passive, but at least in part an active

[1] Cf. Ziegler, "Historisches und Kritisches über die Lehre von der Entzündung," *Beitr. v. Ziegler*, xii., 1892.

[2] "Rech. anatomiques et physiologiques sur la structure interne des animaux et des végétaux et sur leur motilité," Paris, 1842, p. 214.

[3] *Philosoph. Magaz.*, xxix., 1846, pp. 271, 398.

[4] *Pflüger's Arch.*, 1. Bd.

process. If one reduces the motility of the colorless corpuscles by irrigation of the mesentery with a 1.5 per cent. solution of salt (Thoma), or if one lowers their vital activity with quinine or iodoform (Binz, Appert, Kerner), the emigration is also inhibited. Pekelharing, on the other hand, believes that one should accept the view that quinine, oil of eucalyptus, and salicylic acid produce a narrowing of the veins, restrict the increase of permeability of their walls, and thus reduce the extravasation of colorless corpuscles; a view which is rejected, however, by Disselhorst, who observed a dilatation of the veins after irrigation of the tissues with quinine, carbolic acid, salicylic acid, and sublimate. As there occurs in this case a retardation of the current after a transient acceleration, without the emigration of the leucocytes that pass out into the peripheral zone; and as, on the other hand, leucocytes from blood-vessels that have been irrigated for an hour with quinine are still of complete vitality (Eberth). Disselhorst is of the opinion that the drugs mentioned so change the inflamed vessel-wall that an accumulation of the moving leucocytes either cannot occur at all, or can do so only with difficulty.

Very probably a lesion of the vascular wall is not absolutely necessary for the emigration of leucocytes (Thoma). Since vaso-motor disturbances of the circulation can produce migration (von Recklinghausen, Thoma), a slowing of the blood-stream, the ability of the colorless corpuscles to perform amœboid movements and to adhere to the wall of the vessel, and their disposition to remain in the peripheral zone of the stream, probably furnish all the conditions necessary for this migration. Possibly differences in the watery contents of the tissues (Thoma) also exert some influence, since an increased amount of water increases amœboid movement. It is also possible that the presence, in the tissue-fluids, of substances having chemotactic action may lead to migration of leucocytes which remain attached to the inner wall of the vessel (*vide* §103).

According to the researches of Arnold, Thoma, and Engelmann, a soft cement substance lies between the borders of the endothelial cells, and this substance suffers a change in the circulatory disturbances associated with cell-migration—a change which may sometimes (although not always, according to Löwit) be recognized in the histological examination in the form of numerous circumscribed widenings of these intercellular areas (Engelmann). If leucocytes pass through these parts of the vessel in large quantities, the cement substance becomes still more permeable, and soon permits red blood-corpuscles also to pass through in quick succession (Thoma).

Under normal conditions, wandering cells are found in many tissues (von Recklinghausen), and wander from there partly into the lymph-vessels (Hering, Thoma), sometimes also into the blood-vessels (Bubnoff, Schulin, Ranvier, Senftleben) or to the surfaces of mucous membranes, to which they penetrate between the epithelial cells. About collections of lymphadenoid tissue in the mucous membrane they may constantly be found in abundance, and wander from there to the surface through the epithelial layer. According to observations of Kunkel and Siebel, a few of them may also reach the free surface of the alveoli of the lungs.

The inflammatory disturbances of the circulation and the formation of exudate may be most easily followed on the transparent membranes of the cold-blooded animals, especially on the mesentery or the extended tongue or the spread-out web-membrane of the frog. On the frog's mesentery, which has been spread out on a suitable object-stand, circulatory disturbances and inflammation develop from simple contact with the air and the drying that results; the tongue and the web-membrane must be cauterized in order to become inflamed. By the employment of suitable apparatus, the circulation of the blood and the formation of inflammatory exudate can be observed with the microscope on the thin membranes of mammals also (mesentery of rabbits, wing-membrane of bats), and observations made in this manner show that the phenomena which occur agree completely with those observed in the frog.

§ 95. The *cellular and fluid exudates* secreted by the vessels collect first in their neighborhood (Fig. 169), but soon spread out in the vicinity, mass themselves in the *lymph-spaces of the tissues*, and thus form a **tissue-infiltrate** (Fig. 170, *e;* Fig. 172, *b;* and Fig. 174, *p*). When the exudate is abundant, it can spread out and infiltrate also the neighboring sound tissue that has not been injured by the cause of the inflammation. This **infiltration** may be so considerable as to produce new disturbances of circulation and nutrition, and thus increase *the area of tissue-degeneration and inflammatory exudation.*

When *exudate* is present in a tissue, it *may be absorbed in part by the tissue-elements themselves*, so that they swell up, become separated

from their surroundings (Fig. 170, *c*, *d*), and not rarely contain *drops of fluid* (*d*), which are ordinarily called *vacuoles*. There often occurs,

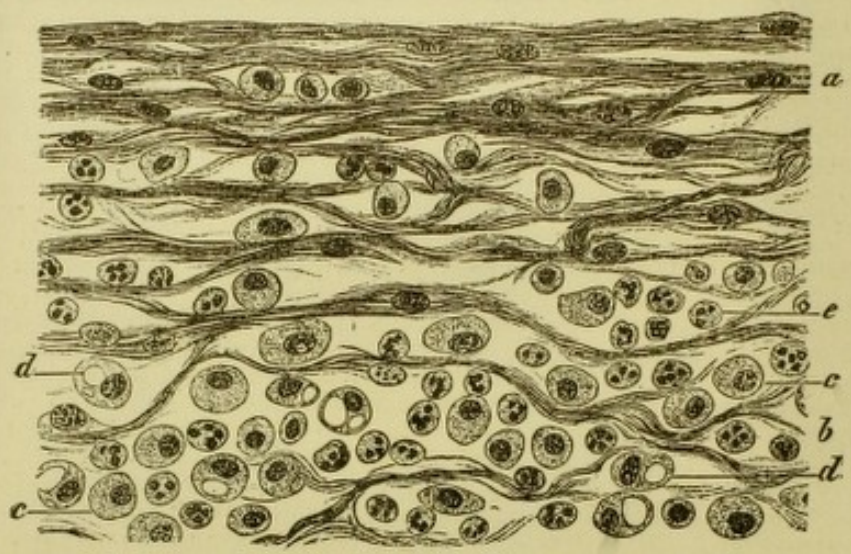


FIG. 170.—Recent purulent meningitis. (Müller's fluid; hæmatoxylin.) *a*, The arachnoid; *b*, the subarachnoid tissue; *c*, *d*, desquamated endothelium; *e*, pus-corpuscles. Magnified 300 diameters.

also, a complete **dissolution of the tissue-elements** in the exudate, especially of the connective-tissue cells (Fig. 171, *d*, *f*), and not seldom, also, of the intercellular substance. In this way both brain- and muscle-tissue, as well as ordinary connective tissue, may be completely liquefied in the course of an inflammation.

If dead cells become saturated with lymph containing fibrinogen,

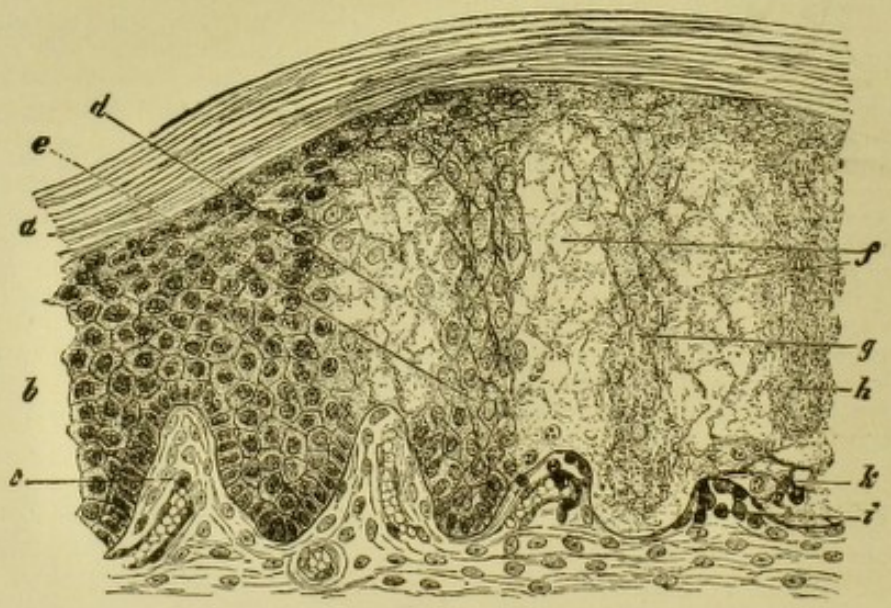


FIG. 171.—Section through the border of a blister. (Alcohol; carmine.) *a*, Horny layer of the epidermis; *b*, rete Malpighii; *c*, normal papillæ; *d*, swollen cells, some of the nuclei of which are still visible, but pale, while others have been entirely destroyed; *e*, interpapillary epithelial cells, the deep ones intact, while in the upper layers they are drawn out lengthwise and are somewhat swollen, without nuclei; *f*, total liquefaction of the cells; *g*, interpapillary cells without nuclei, swollen, and raised from the cutis; *h*, total degeneration of the interpapillary cells which are separated from the cutis; *i*, flattened papillæ infiltrated with cells; *k*, coagulated exudate (fibrin) lying under the lifted epithelium. Magnified 150 diameters.

and fibrin-ferment is formed, a **coagulation** may precede the liquefaction of the infiltrated tissue; in which case the cells are transformed

partly into homogeneous masses without nuclei, and partly into granules and filaments (Fig. 173, *c*, *d*).

If the exudate within an organ—e.g., a gland—is chiefly in the supporting tissue, while the specific parenchyma appears little altered, the form of the inflammation is designated as an **interstitial inflammation** (Fig. 172, *b*). On the other hand, if the degeneration of the specific tissue—e.g., of the epithelium of the uriniferous tubules (Fig. 173, *c*, *d*) of the kidney, of the liver-cells in the liver, of the contractile substance in the muscles—is prominent, and these parts appear saturated with exudate, one calls the condition **parenchymatous inflammation.**

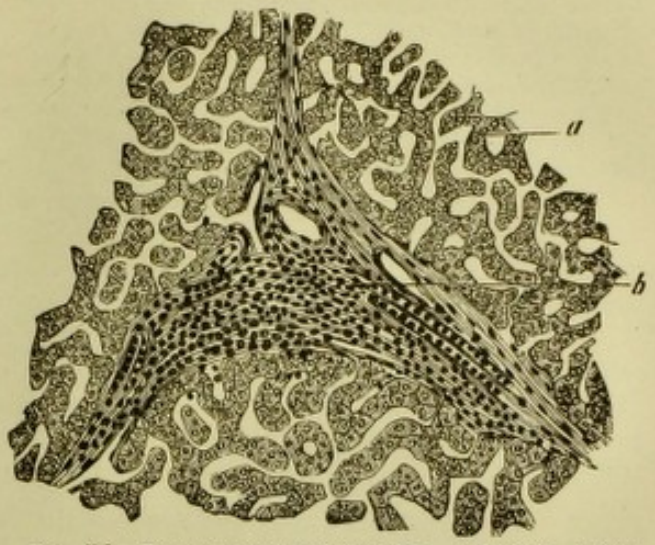


FIG. 172.—Recent interstitial hepatitis. (Alcohol; hæmatoxylin.) *a*, Normal liver-tissue; *b*, small-celled infiltration of the periportal connective tissue. Magnified 80 diameters.

If the seat of an inflammation is the surface of an organ, one calls it a **superficial inflammation** (Fig. 174). If the exudate can gain free access to the surface, and flows from it mixed with particles of cast-off tissue (Fig. 174, *d*, *e*, *f*, *f*$_1$, *h*), the inflammation is called a **catarrh.** If the pouring out of a liquid exudate on the surface of the skin or of a mucous membrane is impeded by coherent, horny epithelium (Fig. 171, *a*), and there form under this cover circumscribed collections of fluid, in which the deep soft layers of epithelium dissolve (Fig. 171, *d*, *f*, *g*), the lesions thus formed are called **vesicles** and **blisters.** When the exudate from serous surfaces collects in the cavities of the body, there are formed in them **inflammatory effusions,** which not rarely reach a considerable bulk, distend the affected cavity, and compress the organs contained therein.

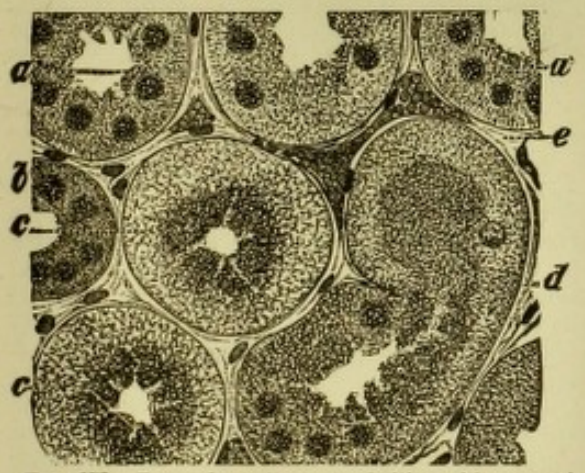


FIG. 173.—Parenchymatous nephritis, with necrosis of the epithelium of the uriniferous tubules, in icterus gravis. (Müller's fluid; gentian violet.) *a*, Normal convoluted tubule; *b*, ascending loop; *c*, convoluted tubule with necrotic epithelium; *d*, convoluted tubule with epithelium partly intact, partly necrotic; *e*, stroma with blood-vessels. Magnified 300 diameters.

If an organ is in a condition of inflammation, it is customary to express it by adding the termination "itis" to the Greek name of the organ. In this way are formed, for example, the terms endocarditis, myocarditis, pericarditis, pleuritis, peritonitis, encephalitis, pharyngitis, keratitis, orchitis, oöphoritis, colpitis, metritis, hepatitis, nephritis, amygdalitis, glossitis, gastritis. The ending "itis" is sometimes fixed to the Latin names. One says, e.g., conjunctivitis, tonsillitis, and vaginitis. If one wishes to denote that the serous covering or the neighborhood of an organ is inflamed, one

places before the Greek name with the termination "itis" a "peri" or "para." Thus are formed the words perimetritis, parametritis, periproctitis, perityphlitis, paranephritis, perihepatitis.

For isolated forms of inflammation there are also in use special

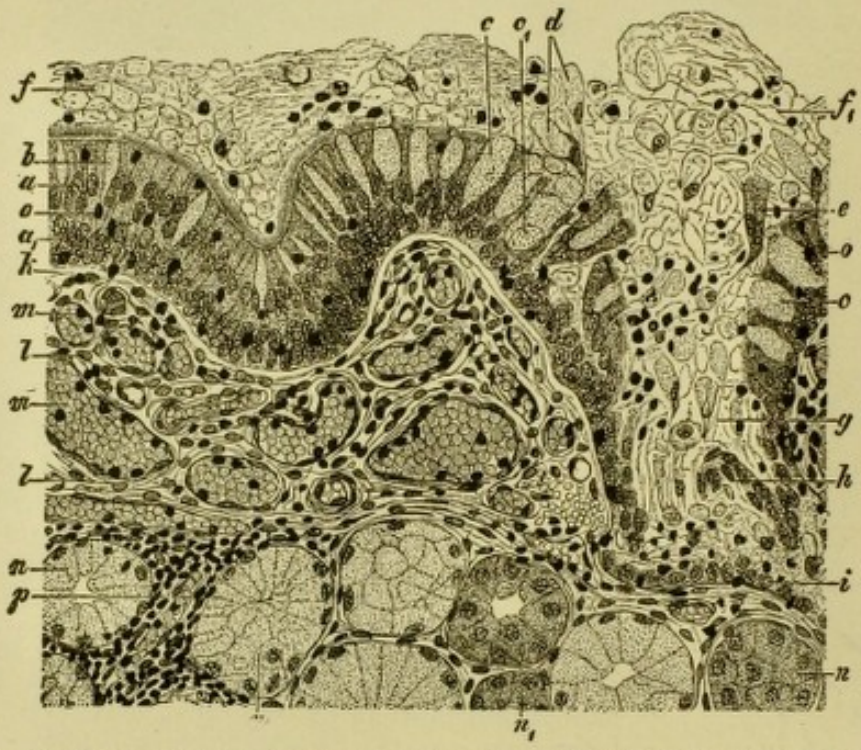


FIG. 174.—Superficial catarrhal inflammation of a bronchus. (Müller's fluid; aniline brown.) *a*, Ciliated cells; a_1, deep cell-layers; *b*, goblet-cells; *c*, markedly mucoid cells; c_1, mucoid cells with mucoid nucleus; *d*, desquamated mucoid cells; *e*, desquamated ciliated cells; *f*, layer of drops of mucus; f_1, layer of stringy mucus and pus-corpuscles; *g*, excretory duct of a mucous gland filled with mucus and cells; *h*, desquamated epithelium of the excretory duct; *i*, intact epithelium of the excretory duct; *k*, swollen hyaline basement membrane; *l*, connective tissue of the mucosa, partly infiltrated with cells; *m*, dilated blood-vessel; *n*, mucous gland filled with mucus; n_1, lobule of a mucous gland without mucus; *o*, migrating cell in the epithelium; *p*, cellular infiltration of the connective tissue of the mucous glands. Magnified 120 diameters.

names; thus one calls inflammation of the lungs, pneumonia; inflammation of the arch of the palate and tonsils, angina.

Since Cohnheim taught us to recognize the migration of colorless blood-corpuscles *en masse* as an important part of inflammation, and showed that they might serve as a new source of origin for the cells present in the exudate, the question of the origin of the cells present in the exudate of fresh inflammations has been many times the subject of discussion. While some regarded all cells present in the exudate as extravasated leucocytes, others believed that the leucocytes coming from the blood formed only an accidental component of the exudate, and that the cells contained in it for the most part have originated on the spot from the tissue "irritated" by the cause of the inflammation.

Stricker is of the opinion that the swelling and hardening of the tissue in inflammation are not caused by the collection of exudate, but by a swelling of the cell-reticulum which traverses the tissues, and that it is a phenomenon of growth of the cells and their prolongations characterized by swelling. The cellular exudate—i.e., the pus—he accounts for partly by a segmentation and division of the cellular reticulum swollen from the inflammation, partly by a transformation of the connective-tissue fibrils into pus-corpuscles. Heitzmann considers the inflammatory tissue-changes as a reversion of the tissues to the embryonal condition, and believes that the living material is not contained in the cells only, but infiltrates the entire ground substance, and increases, in the progress of an inflammation, with the liquefaction of the ground substance. Connective tissue, cartilage, and bone become resolved in inflammation into those elements from which they are formed—i.e., into cells—which then immediately reproduce their like. Grawitz believes that both the cellular infiltrate and the pus occur without any participation of the leucocytes worth mentioning. Everywhere in the tissue, cells which he calls slumber-cells lie latent in large quantities, not affected by our nuclei-staining dyes

and therefore not recognizable (only from five to ten per cent. of the tissue-cells, according to him, are known to us), but which in inflammation awake, increase in size, respond to nuclei-staining dyes, and therefore again become recognizable.

After what an unprejudiced careful examination of inflamed tissue exhibits, there can be no doubt that the description of the origin of the inflammatory infiltrate given by Stricker, Heitzmann, Grawitz, and their pupils, does not correspond to the conditions as they actually exist. The cells which are found lying in the midst of recently inflamed tissues consist in part of leucocytes which have escaped from the blood-vessels, (Fig. 170, *e*), and in part of tissue-cells which are in a more or less degenerate condition, and have, at least in many instances, become separated from the underlying tissues (Fig. 170, *c*, *d*). Farther on, in the course of the inflammation, there will be added, to the preceding, cells which are the recent product, through a process of subdivision, of pre-existing cells.

§ 96. Both the local tissue-degeneration and the exudation may appear very differently in different cases, and one can distinguish conformably different **forms of inflammation.**

If the exudate consists principally of fluid, while the cellular components are comparatively insignificant, it is called a **serous exudate.** If this is within a tissue—for example, the cutaneous and subcutaneous tissues or the kidneys (Fig. 175, *a*)—it leads to **inflammatory œdema.**

Escape of fluid on the surface of a mucous or serous membrane gives the picture of a **serous catarrh**; a localized collection of fluid beneath the horny layer of the epidermis, with the liquefaction of the soft layers of epithelium, leads to the formation of **vesicles** and **blisters** with clear contents (Fig. 171, *d*, *f*).

If the fluid exuded on the surface of a mucous membrane is associated with marked mucoid change of the superficial epithelium (Fig. 174,

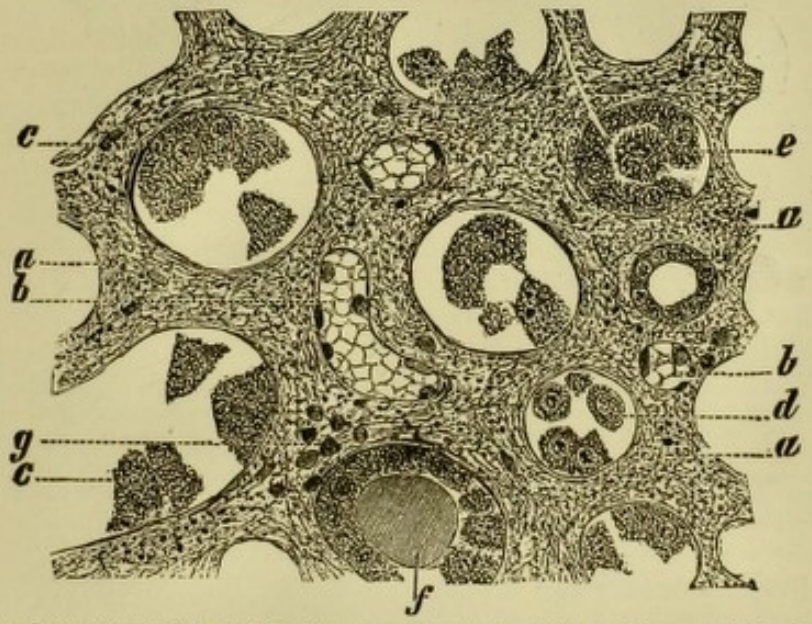


FIG. 175.—Inflammatory œdema of the kidney, with catarrh of the uriniferous tubules (from a man who died of suppurative mediastinitis and pleuritis with nephritis on the tenth day after the beginning of the illness). (Osmic acid; glycerin.) *a*, Stroma distended by fluid, and infiltrated with granules and filaments of fibrin and separate fat-droplets; *b*, capillaries; *c*, epithelia of the convoluted tubules, in parts slightly fatty and desquamating; *d*, desquamated epithelial cells in a looped tubule; *e*, granular and fatty detritus in a looped tubule, whose epithelium remains, but is cloudy; *f*, hyaline cylinder (cast) in a convoluted tubule; *g*, round cells. Magnified 350 diameters.

b, *c*, *c*$_1$) and of the mucous glands (*n*), there is a **mucous catarrh** (Fig. 174, *d*, *f*, *f*$_1$). If a marked desquamation of the epithelium of the mucous membrane, with or without mucoid change, occurs, there is a **desquamative catarrh,** and it may occur not only in mucous membranes,

but also in the respiratory parenchyma of the lungs, on serous surfaces (Fig. 169, *f*), in the kidney-tubules (Fig. 175, *c*, *d*), etc.

In desquamative catarrh, if the secretion is mixed with much epithelium, it is cloudy and contains a large number of cells, which consist, according to the source of the catarrh, sometimes of mucoid cylindrical and ciliated cells (Fig. 176, *3*, *5*, *6*), sometimes of squamous epithelium (*11*, *12*, *18*, *19*). At the same time there generally are found also round cells (Fig. 176, *1*, *2*, *7*, *9*, *10*, *13*, *20*), and often also bacteria (*4*, *14*, *15*, *16*, *17*, *21*).

If the deposition of fibrin, or coagulation, occurs in a liquid exudate, there are formed **fibrinous and sero-fibrinous exudates**, which are often

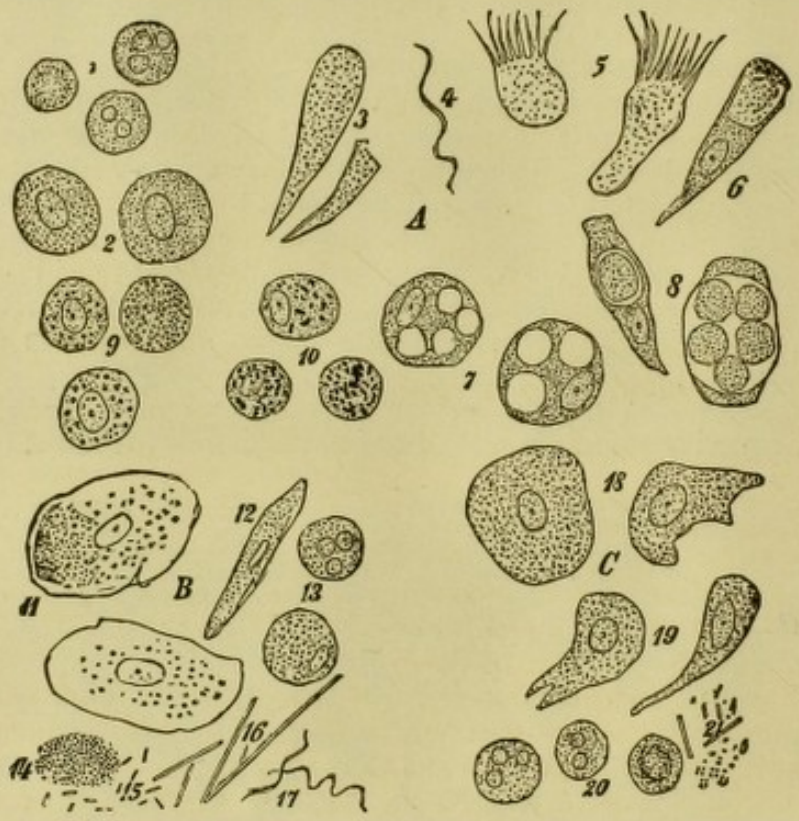


FIG. 176.—Catarrhal secretion of various mucous membranes. A, Secretion from mucous membranes with cylindrical epithelium; B, from the mouth; C, from the uninary bladder. 1, Round cells (pus-corpuscles); 2, large round cells with bright nuclei from the nose; 3, mucoid cylindrical cells from the nose; 4, spirillum from the nose; 5, mucoid cells with cilia from the nose; 6, goblet-cell from the trachea; 7, round cells with mucoid masses from the nose; 8, epithelial cells containing pus-corpuscles from the nose; 9, fatty cells in chronic catarrh of the larynx and pharynx; 10, cells from sputum containing coal-pigment; 11 and 12, squamous epithelium from the mouth; 13, mucous corpuscles; 14, micrococci; 15, bacteria; 16, *leptothrix buccalis*; 17, *spirochaete denticola*; 18, superficial, 19, middle layer of bladder epithelium; 20, pus-corpuscles; 21, schizomycetes. Magnified 400 diameters.

also called *croupous*. They occur chiefly on the surface of serous or mucous membranes and in the lungs, but masses of fibrin can also be deposited within tissues infiltrated with exudate as well as in lymphatic vessels.

Fibrinous exudates on *mucous surfaces* form whitish patches and coherent membranes, which sometimes lie upon them only loosely, sometimes are firmly attached to the under surface. In the serous cavities the deposits of fibrin float in the form of flakes in the fluid exudate, or attach themselves firmly to the surface of the membranes. These deposits consist at times only of small, attached granules and flakes, which give to the affected surface a cloudy, dull, rough, or even

granular appearance; at other times they consist of larger yellowish or yellowish-red tough membranes, which often give the surface a felted or villous appearance (cor villosum, pericarditis villosa). In the lung, croupous inflammation leads to the filling of the alveoli with a coagulated mass, as a result of which the lung acquires a firm consistence.

The formation of croupous membrane on mucous surfaces occurs only if the epithelium is already desquamated and the connective tissue, in part at least, exposed; but tissue covered with epithelium may be coated over with coagulated fibrin extending from spots free from epithelium. The desquamation of epithelium follows, in such a case, sometimes gradually, sometimes quickly, through the lifting up of whole layers of epithelium (Fig. 177, *b*), which are either still well preserved or already degenerated or necrotic and infiltrated with exudate (Fig. 179, *a*).

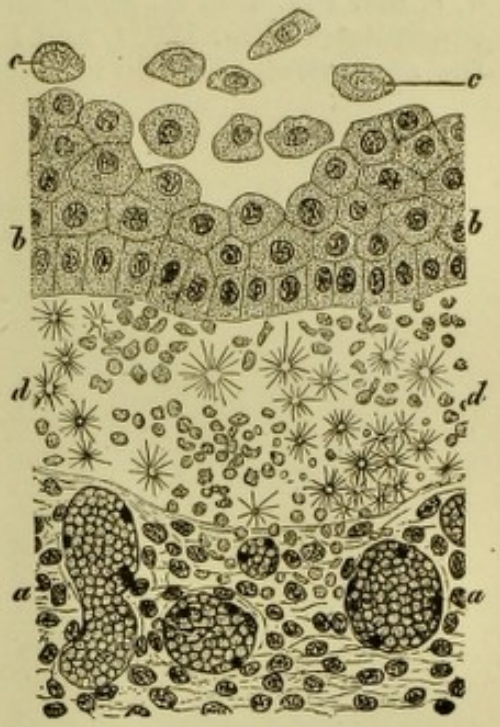


FIG. 177.—Acute hemorrhagic fibrinous inflammation of the trachea, caused by the vapor of ammonia. (Müller's fluid; hæmatoxylin, eosin.) *a*, Superficial connective-tissue layer of the mucosa, with escaped red blood-corpuscles and widely dilated vessels filled with blood; *b*, deep layer of epithelium raised up in its entirety; *c*, desquamated epithelial cells; *d*, hemorrhagic fibrinous exudate with radiating, crystal-like deposit of fibrin partly consisting of small colorless masses. Magnified 300 diameters.

The deposit of fibrin may begin under the raised-up epithelium, with the formation of slender forms like acicular crystals (Fig. 177, *d*), which are arranged radially about a centre, in which there often lies a small corpuscle, probably a product of disintegration of a red blood-corpuscle, or a blood-plate. There form, however, very soon, thicker or thinner threads (Fig. 178, *c*, and Fig. 179, *b*, *c*) which inclose a larger or smaller number of leucocytes and red blood-corpuscles. The arrangement of the threads is generally reticular, but the thickness of the meshwork and the width of the meshes vary greatly. When there is unequal development of the threads and strands of fibrin, the principal strands have a direction sometimes parallel to the mucous membrane (Fig. 178, *a*), sometimes perpendicular to it (Fig. 179, *c*). Thick fibrin membranes often show a real stratification (Fig. 179, *a*, *b*, *c*), a hint that their formation occurs in batches.

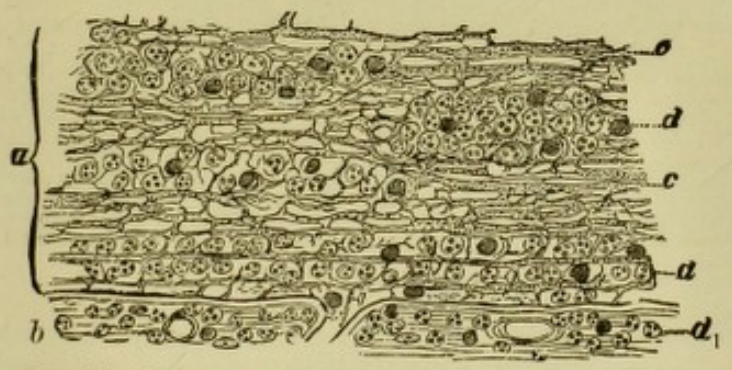


FIG. 178.—Croupous membrane from the trachea. *a*, Section through the membrane; *b*, upper layer of the mucous membrane, infiltrated with pus-corpuscles, *d*; *c*, threads and granules of fibrin; *d*, pus-corpuscles. Magnified 250 diameters.

When a mucous membrane becomes the seat of a deposition of fibrin,

the underlying connective tissue is always more or less hyperæmic (Fig. 179, *g*), swollen with œdema, infiltrated with leucocytes (Fig. 179, *d*, *e*, and Fig. 180, *e*), and contains generally here and there also fibrin-precipitates (Fig. 179, *l*, and Fig. 180, *f*). Very often the tendency to the separation of fibrin is manifest even within the blood-vessels (Fig.

FIG. 179.—Section of a uvula inflamed and covered with a stratified fibrin membrane, from a case of diphtheritic croup of the pharyngeal organs. (Müller's fluid; hæmatoxylin; eosin.) *a*, Superficial layer of coagulation, consisting of epithelial plates and fibrin and dotted with numerous balls of cocci; *b*, second layer of coagulation, which consists of a close-meshed reticulum of fibrin enclosing leucocytes; *c*, third layer of coagulation, lying on the connective tissue, and consisting of a wide-meshed reticulum of fibrin enclosing leucocytes; *d*, connective tissue infiltrated with cells; *e*, infiltrated boundary-layer of the connective tissue of the mucous membrane; *f*, mass of red blood-corpuscles; *g*, congested blood-vessels; *h*, lymphatic vessel distended with fluid, fibrin, and leucocytes; *i*, excretory duct of a mucous gland distended with secretion; *k*, transverse section of a gland; *l*, reticulum of fibrin in the superficial layers of connective tissue. Magnified 50 diameters.

180), inasmuch as these contain, now threads and rods of fibrin, lying in tangled groups (*b*), and again needle-shaped fibrin-particles, grouped in clusters and star-forms (*a*, *c*, *d*), which, according to Zenker, often proceed from degenerated endothelial cells or leucocytes, or from blood-plates, or originate in spots bare of endothelium. In like manner, we also find, in the dilated lymph-spaces, fibrin-fibres along with fluid and cellular exudate (Fig. 179, *h*).

Upon *serous membranes*, fibrin deposits appear partly in the form of

granular (Fig. 182, *d*) and thready (Fig. 181, *d*, *e*) masses, partly rather in dense and homogeneous masses (Fig. 182, *c*, and Fig. 183, *d*), or also

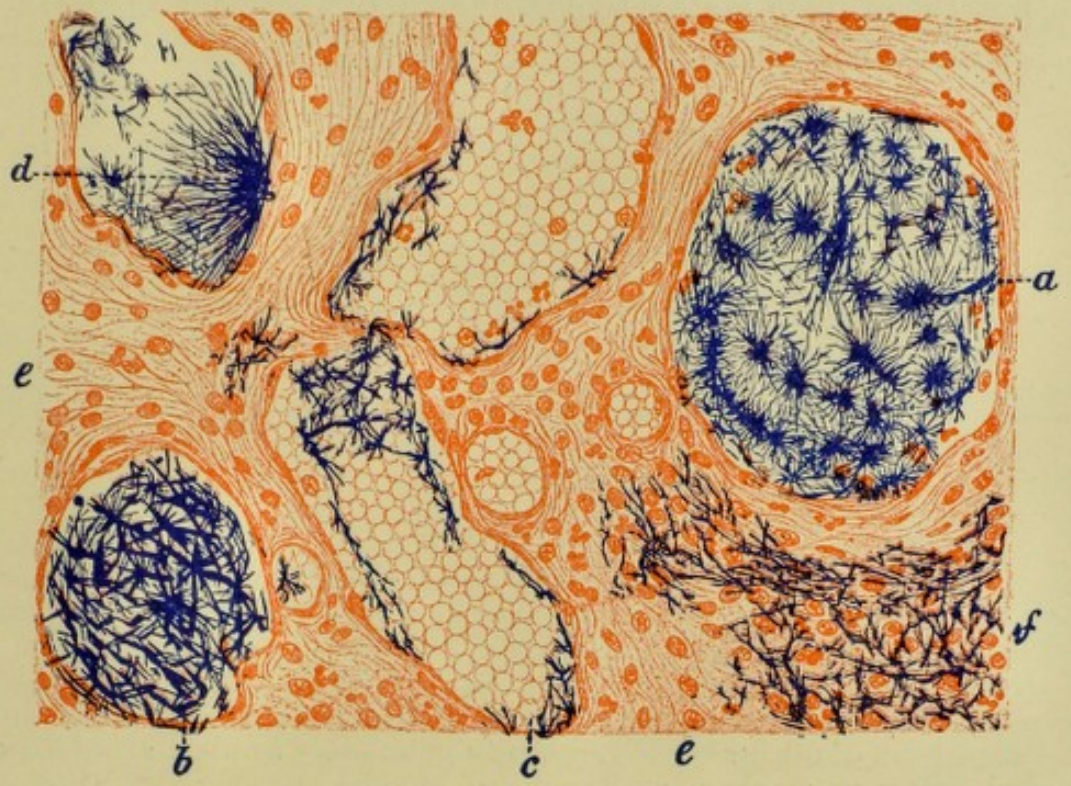


FIG. 180.—Croupous tracheitis. Section through the connective tissue of the mucosa. (Carmine and fibrin-stain). *a*, *b*, *c*, *d*, Blood-vessels, containing fibrin precipitates; *e*, œdematous and swollen connective tissue with leucocytes; *f*, connective tissue with fibrin-threads. Magnified 500 diameters.

in the form of ribbon-like bands (Fig. 183, *e*). Here, too, the epithelium is exfoliated at the point of deposition (Fig. 181, *d*, *e*, and Fig. 182), but may remain attached in spots (Fig. 181, *c*, and Fig. 183, *c*) and the fibrin be deposited upon it. The connective tissue of the serous membranes is sometimes more, and sometimes less infiltrated in croupous inflammation, and may contain leucocytes and fibrin, both in the engorged blood-vessels themselves (Fig. 183, *g*) and in the interstices of the connective tissue (*a*, *b*) as well.

Fibrinous exudates in the lungs are characterized by the formation of

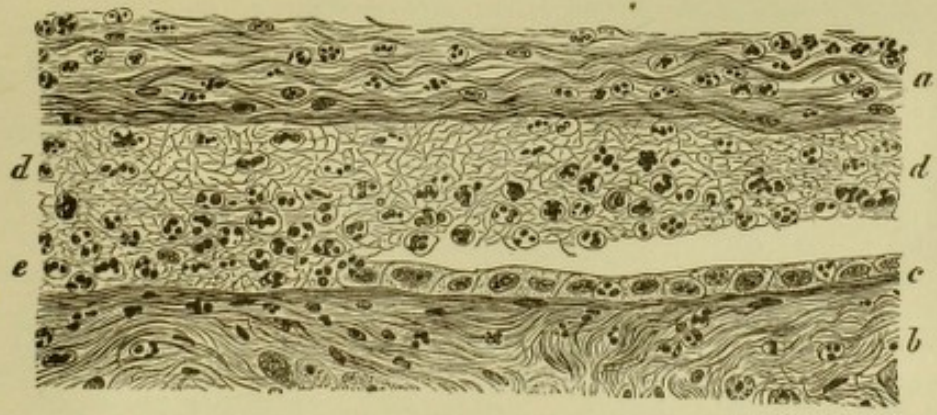


FIG. 181.—Traumatic fibrino-purulent peritonitis. (Alcohol; Van Gieson's mixture.) *a*, Peritoneum of the abdominal wall; *b*, serosa of a knuckle of gut which had been sutured to the abdominal wall; *c*, persisting epithelium; *d*, *e*, deposit of fibrin. Magnified 200 diameters.

a network of fibrin-threads, more or less close, in the meshes and in the general neighborhood of which lie leucocytes and usually also red blood-corpuscles (*c*), interspersed with desquamated epithelium. In the first stages there are occasionally found also globular and wreath-

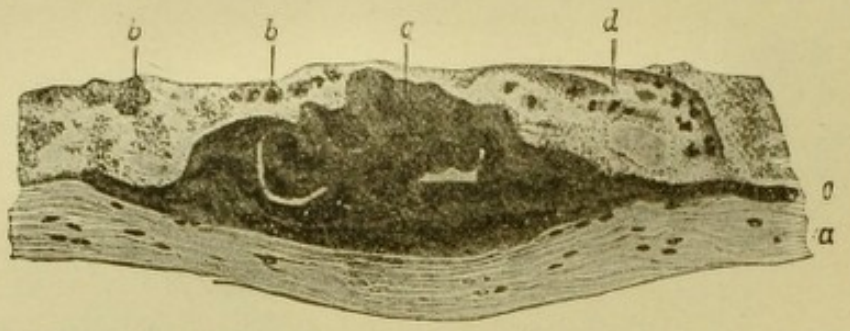


FIG. 182.—Fibrinous pleuritis. (Alcohol; Van Gieson's mixture.) *a*, Connective tissue; *b*, exfoliated epithelium; *c*, homogeneous, dense,—and *d*, granular fibrin-deposit with leucocytes. Magnified 100 diameters.

shaped precipitates of fibrin. Fibrin threads, too, may develop in and upon lifeless epithelial scales (Hauser).

In the *kidneys* deposits of fibrin may occur in the form of fine filaments or fibrinous masses in the uriniferous tubules and in the glomerular capsule. In the *lymphatic glands* fibrin filaments form principally within the lymph-passages.

Hemorrhagic exudate—i.e., exudate which contains red blood-corpuscles in large quantities—occurs particularly in connection with the deposition of fibrin. Thus croupous pulmonary exudate always contains a larger or smaller number of red blood-corpuscles (Fig. 184, *c*), and in the same way, in fibrinous pericarditis and pleuritis, large quantities of red blood-corpuscles quite often escape. Hemorrhagic inflammations occur also not rarely in the central nervous system, in the lymphatic glands, in the skin, and in the kidneys.

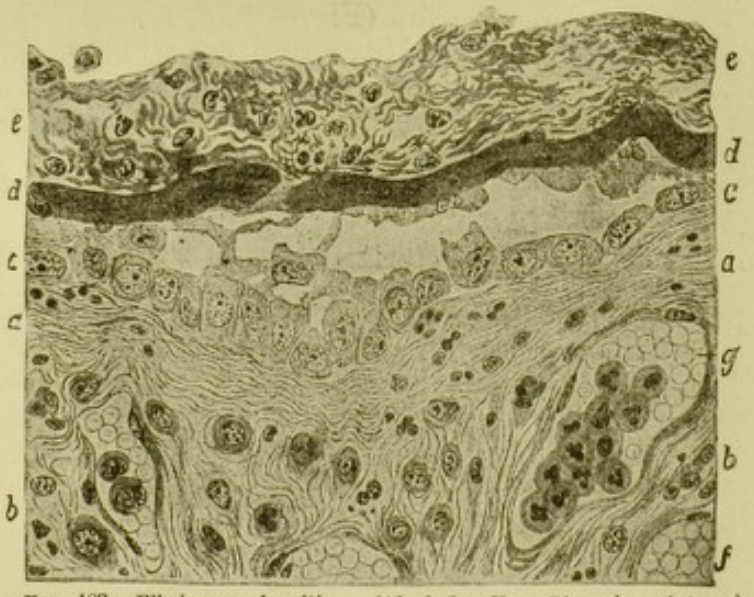


FIG. 183.—Fibrinous pleuritis. (Alcohol; Van Gieson's mixture.) *a*, *b*, Inflamed pleura-tissue; *c*, epithelium; *d*, *e*, fibrinous exudate; *f*, *g*, blood-vessels. Magnified 300 diameters.

The serous, fibrinous, and sero-fibrinous inflammations may be caused both by thermal and chemical influences and by bacteria, but are most often the result of infection, especially of infection with the *Diplococcus pneumoniæ* and the *Bacillus diphtheriæ*. The former causes particularly croupous inflammations of the lungs and the pleuræ, the latter fibrinous inflammations of the pharynx, palate, and respiratory passages.

Neumann is of the opinion that, in recent fibrinous inflammation of the serous membranes, the hyaline bands and flakes on the surface of the membranes are not exudative

fibrin, but represent layers of the connective tissue which have undergone a fibrinoid degeneration. This opinion I cannot endorse, but I agree rather with the majority of authors who have expressed opinions on the subject, that they are deposits of exudative fibrin. Moreover, the illustrations which Neumann has presented in his work are in no sense confirmatory of his opinion, but enable us rather to affirm that Neumann had exudative fibrin before him in his specimens. In severe inflammations, fibrin may indeed separate out, even within the connective tissue of the serous membranes, and be the

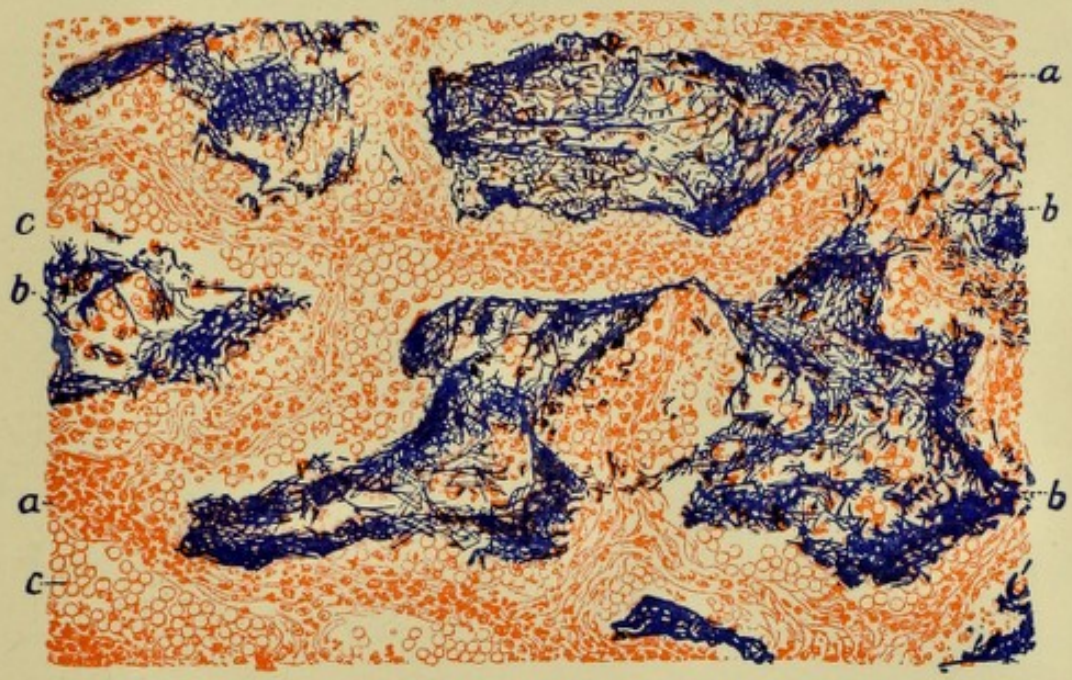


FIG. 184.—Croupous pneumonia. Red hepatization of the lungs. (Alcohol; carmine; fibrin stain.) *a*, Infiltrated alveolar septa; *b*, fibrinous exudate; *c*, red blood corpuscles. Magnified 200 diameters.

cause of their peculiar coloration when treated with stains—only we are dealing, not with a fibrinoid degeneration of the connective-tissue fibres, but with a deposition of exudative fibrin.

§ 97. When the inflammatory exudate consists principally of leucocytes, there is an **infiltration of the tissues with small cells** (Fig. 185, *d*, *e*, *f*), which may at times be so crowded as to obscure the structure of the tissue. If leucocytes with fluid exudate appear in large quantities on the surface of a mucous membrane or an external wound, a white fluid is seen on the affected part, which is called **pus**, and has given occasion to name the inflammation a **purulent catarrh** (Fig. 185, *a*). When an abundant secretion persists, the phenomenon is called a *blennorrhœa*. If such pus collects within body-cavities—e.g., in the pericardium or in the pleura or in joint-cavities—it forms confined *purulent effusions* or **empyemata**. If an abundant collection of lymphocytes takes place within a blister produced by the liquefaction of epithelium under the horny layer, the fluid becomes more and more turbid, white, purulent, and the vesicle changes to a **pustule** (Fig. 186, f_1).

The cells that emigrate, especially in purulent inflammations, and which are therefore called **pus-corpuscles**, are polynuclear leucocytes. They may reach the surface of a mucous membrane both after the desquamation of the epithelium and while the epithelium is still preserved, and they accomplish this by passing between the epithelial cells (Fig. 185, *c*, c_1, c_2); and the epithelium of the external skin may be penetrated by them in the same way (Fig. 186, *g*).

When very numerous pus-corpuscles collect in a tissue, so that the tissue acquires a white or grayish-white or yellowish-white color, the

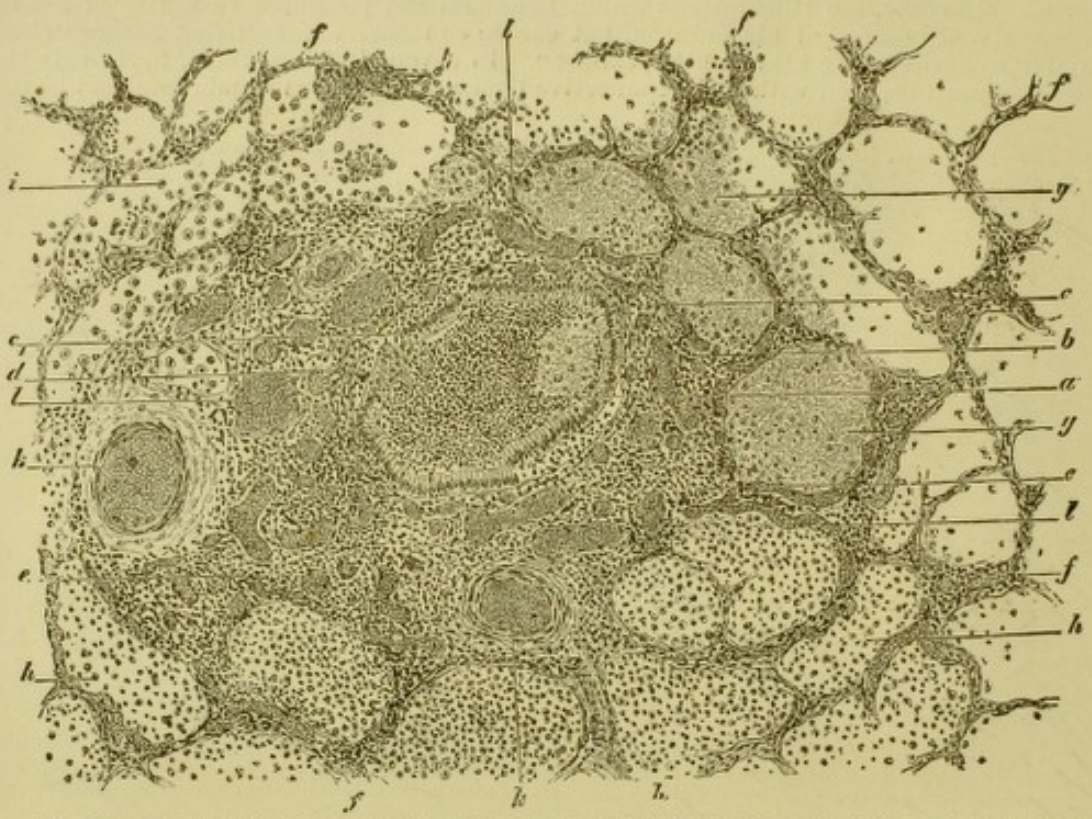


FIG. 185.—Purulent bronchitis, peribronchitis, and peribronchial broncho-pneumonia (from a child aged fifteen months). (Müller's fluid; hæmatoxylin; eosin.) *a*, Purulent bronchial contents; *b*, mucoid bronchial contents; *c*, c_1, bronchial epithelium infiltrated with round cells and partly raised up (c_2); *d*, bronchial wall infiltrated with cells and its blood-vessels markedly distended with blood; *e*, peribronchial and periarterial connective tissue infiltrated with cells; *f*, septa between the pulmonary alveoli, partly infiltrated with cells; *g*, fibrinous exudate in the alveoli; *h*, alveoli filled with exudate containing many cells; *i*, alveoli filled with exudate containing few cells; *k*, transverse section of pulmonary artery; *l*, congested bronchial, peribronchial, and interlobular vessels. Magnified 45 diameters.

process takes on the character of a **purulent infiltration.** If finally liquefaction and dissolution of the tissues take place, we may speak of these changes as **suppuration of tissue** and **abscess-formation** (Fig. 187, *i*)—i.e., the formation of a cavity filled with pus.

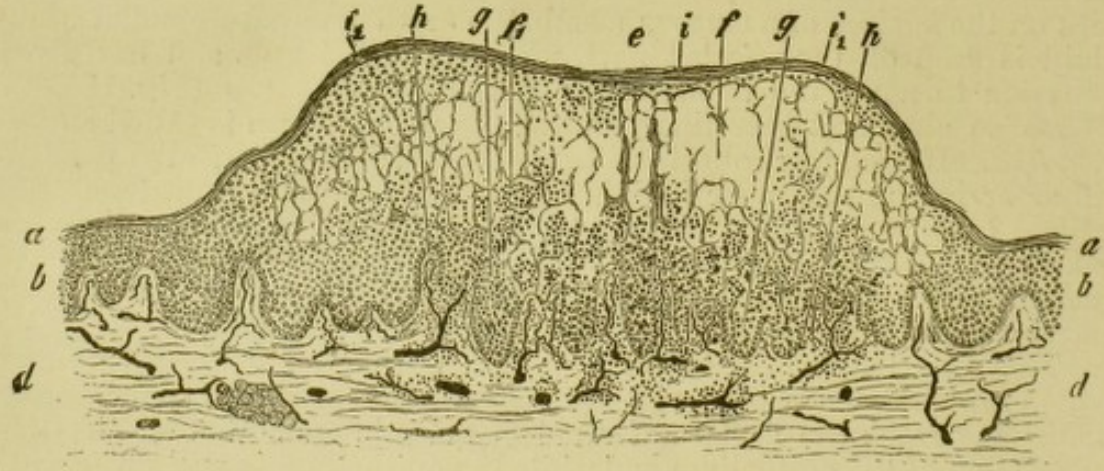


FIG. 186.—Section of a smallpox pustule. (Injected hæmatoxylin preparation.) *a*, Horny layer; *b*, mucous layer of epidermis; *d*, cutis; *e*, smallpox pustule; *f*, cavity of the pock, containing at f_1 pus-corpuscles; *g*, remains of epithelium between the papillæ, infiltrated with pus-corpuscles; *h*, papillæ infiltrated with cells; *i*, umbilication with thin pock cover; i_1, border of the pock, whose roof is here formed of the horny and transition layers. Magnified 25 diameters.

When the suppurative infiltration and tissue-solution occur on the surface of an organ—for example, of a mucous membrane (Fig. 188, *d*,

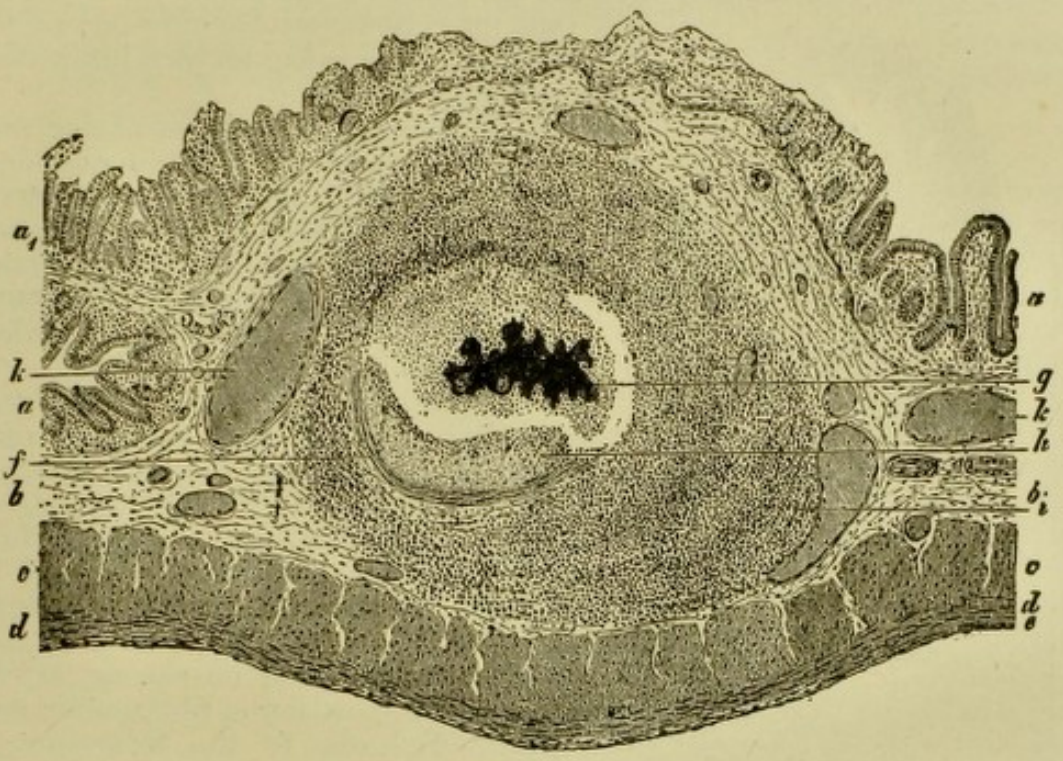


FIG. 187.—Embolic abscess of the intestinal wall, with embolic suppurative arteritis and embolic aneurism, in cross-section. (Alcohol; fuchsin.) *a*, *b*, *c*, *d*, *e*, Layers of intestinal wall; *f*, remains of the arterial wall, in transverse section; *g*, embolus, surrounded by pus-corpuscles within the dilated and partly suppurating artery; *h*, parietal thrombus; *i*, periarterial purulent inflammation of the submucosa; *k*, vein filled with blood. Magnified 30 diameters.

f, *g*)—the process leads to the formation of a superficial loss of substance—an **ulcer.** If there form, through suppuration, pervious cavities, they are called **fistulous tracts.**

The dissolution of the tissues, which is designated as suppuration,

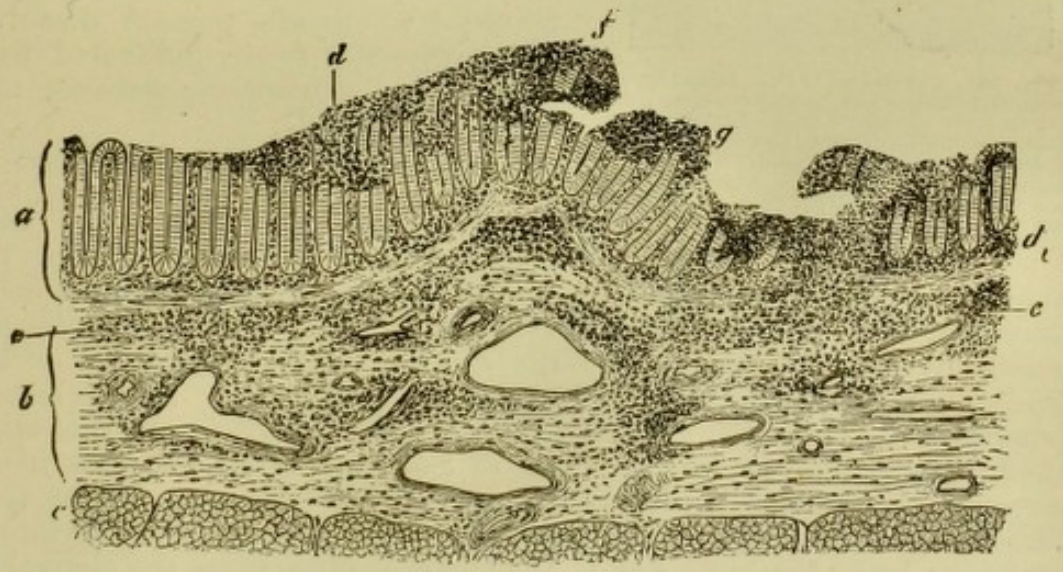


FIG. 188.—Suppuration and necrosis of the mucous membrane of the large intestine in dysentery. (Müller's fluid; hæmatoxylin; eosin.) Section of the mucosa, *a*, and submucosa, *b*, of the colon; *c*, muscularis; *d*, interglandular, d_1, subglandular infiltration of the mucosa; *e*, infiltrated area in the submucosa; *f*, infiltrated upper glandular layer, desquamating; *g*, ulcer whose base is infiltrated with cells. Magnified 25 diameters.

is possible only on condition that they die. This tissue-necrosis is generally present even before the occurrence of suppuration, and is caused by the specific action of the producer of inflammation. The tissue may, however, die only during the course of the inflammatory infiltration and then liquefy.

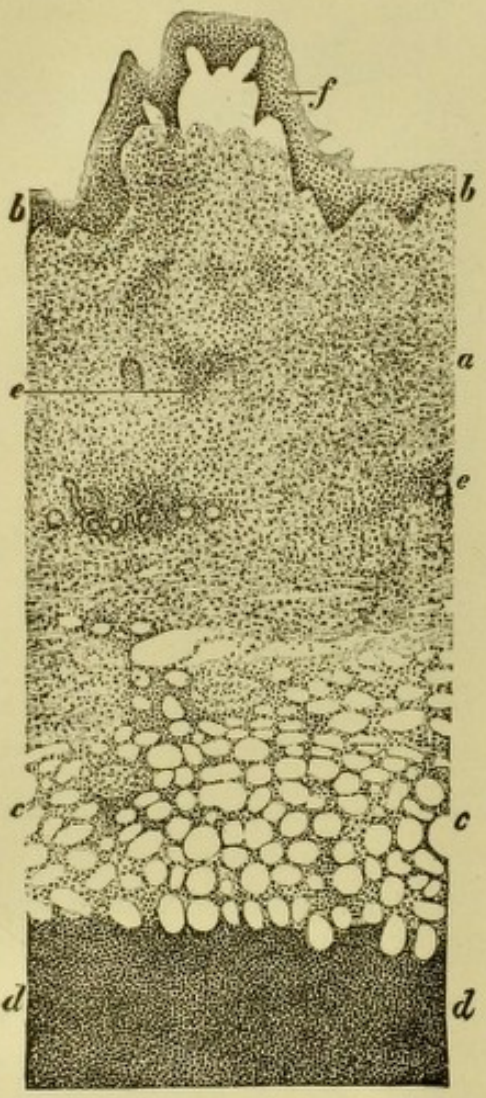


FIG. 189.—Phlegmon of the subcutaneous connective tissue, with formation of an œdematous bleb. (Müller's fluid; hæmatoxylin; eosin.) *a*, Corium; *b*, epidermis; *c*, adipose tissue infiltrated with the products of inflammation; *d*, focus of pus; *e*, aggregation of cells in the corium; *f*, subepithelial œdematous blebs. Magnified 30 diameters.

If an accumulation of pus-corpuscles is associated with an abundant collection of fluid, there occur **sero-purulent exudates,** which, infiltrating the tissues, give rise to a condition which is often called **purulent œdema.** When a purulent or a sero-purulent inflammation spreads rapidly over wide areas—for example, over a large portion of the subcutaneous or any submucous tissue—the process is called **phlegmon** (Fig. 189, *c*, *d*, *e*). It leads often to the formation of extensive pus-cavities, in which there lie shreds of breaking-down tissue infiltrated with pus.

The association of serous exudation and deposition of fibrin with suppuration leads to the formation of **fibrino-purulent exudates** (Fig. 181, *d*, *e*); and both effusions into the body-cavities and meningeal exudates, as well as croupous exudates on mucous membranes and in the lungs, and also phlegmons may bear this character; yet it is to be noted that with increase of suppuration the formation of fibrin decreases and the masses of coagulated material which are present dissolve. The masses of fibrin infiltrated with pus present a white appearance and are readily friable.

The suppurations and the associated formations of abscesses and ulcers are generally caused by **bacteria,** and most frequently by the *Staphylococcus pyogenes aureus*, the *Streptococcus pyogenes*, and the *gonococcus* (gonorrhœal virus). Yet suppurations are not rare which are caused by *actinomycetes*, or by the *Bacillus typhi abdominalis*, or the *Diplococcus pneumoniæ*, or the *Bacterium coli commune*. Staphylococci generally cause localized inflammations; streptococci, on the other hand, phlegmonous. The presence of certain bacteria (*Bacillus phlegmones emphysematosæ*, Fränkel) may cause the formation of **gas** (*gas-phlegmon*). Suppuration is sometimes ectogenous, sometimes lymphogenous or hæmatogenous, and in the last case often bears the characters of a metastatic process (Fig. 187).

Among the **chemical substances** which may lead to suppuration when introduced into the tissues are mercury, oil of turpentine, petro-

leum, five to ten per cent. solutions of nitrate of silver, creolin, digitoxin, dilute croton-oil, sterilized cultures of a variety of bacteria, in which latter the bacterial proteins are the active agents. The suppurations produced by chemical substances differ from the infections by healing more readily, by not spreading in the tissues, nor forming metastases, and by their products lacking virulence when inoculated.

§ 98. As was explained in § 97, suppurative inflammation always leads to tissue-necrosis; but this necrosis is again immediately lost sight of in the presence of the liquefaction and dissolution of the tissues, which form the characteristic feature of suppuration. When the action on the tissues is of a different sort, it may lead to a tissue-necrosis of larger extent, visible to the eye, which is not followed by suppuration, but which rather is characterized by the fact that the necrotic pieces of tissue remain unchanged for a time, and only relatively late are separated by sequestration and desquamation, or are gotten rid of by absorption. As the tissue-necrosis here forms the chief feature, one may fittingly call the disease a **necrotic inflammation.**

The tissue-necrosis associated with inflammation may be caused by caustic **chemicals,** by **high or low temperatures,** and by **ischæmia,** as well as by **infection** (typhoid, diphtheria, and dysentery).

Caustic chemicals produce necrosis chiefly on those tissues with which they first come in contact; but many substances (sublimate, the salts of chromic acid, cantharidin) may exert a necrotic effect only after their diffusion throughout the body by the blood and tissue-juices; this effect showing itself especially in the kidneys, the ducts leading from them, and the intestine, where they are excreted. Bacteria produce necrosis at the spots where they multiply and where the poisonous substances formed by them are collected in a concentrated condition.

The necrosis of the tissue may appear immediately, as the first effect of the injurious action, while the inflammatory exudation takes place

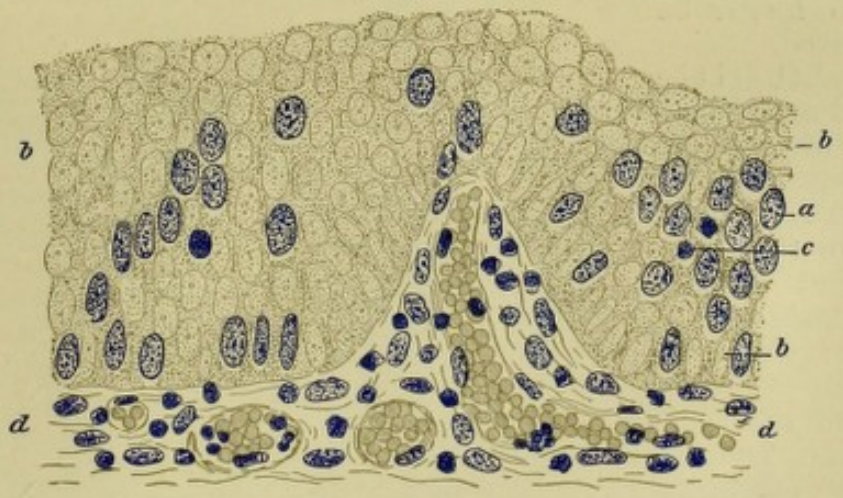


FIG. 190.—Necrosis of the epithelium of the epiglottis. Müller's fluid; hæmatoxylin.) *a*, Living epithelium with well-stained nuclei; *b*, necrotic epithelium with unstained nuclei; *c*, leucocytes situated in the epithelium; *d*, hyperæmic, inflamed, and infiltrated connective tissue. Magnified 300 diameters.

only later, and is confined to the region adjoining the necrosis; and this occurs especially after the action of caustic substances, after exposure to a high temperature, and in ischæmia. In other cases, which

belong chiefly to the infections, an inflammation is first established, and then afterward necrosis affects the inflamed and infiltrated tissue. In tuberculous infections the necrosis appears only after the tissue-proliferation has developed and has existed for some time.

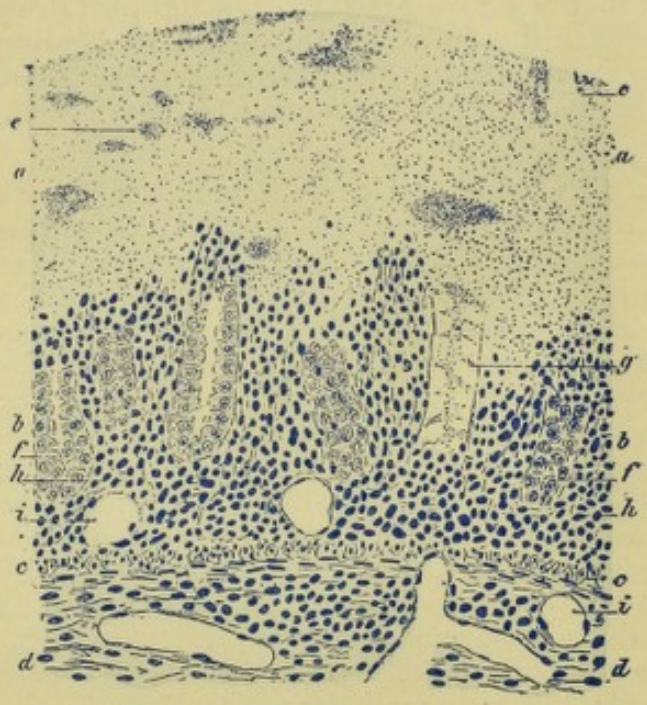


FIG. 191.—Bacillary diphtheritis of the large intestine (dysentery). (Alcohol; gentian violet.) *a*, Necrotic portion of the glandular layer of the mucosa, infiltrated with bacilli; *b*, remaining inflamed mucosa; *c*, muscularis mucosæ; *d*, submucosa; *e*, swarms of bacilli; *f*, glands with epithelium still preserved; *g*, gland with necrotic epithelium and bacilli; *h*, connective tissue infiltrated with cells; *i*, blood-vessels. Magnified 80 diameters.

Necrotic inflammations are most often observed on the mucous membranes, and are here generally called **diphtheritic,** particularly those which are caused by infection. The necrosis may here affect at first the epithelium only, which, as a result, loses its nuclei (Fig. 190, *b*), and later acquires a flaky appearance. If white opaque patches form on the mucous membrane, as in the pharynx in diphtheria, one may speak of *epithelial or superficial diphtheritis.* Ordinarily the term *diphtheritis* is applied, however, only to tissue-necrosis in which *the inflamed and infiltrated tissue undergoes necrosis* (Fig. 191, *a*) and changes into a lumpy or granular mass without nuclei, or a rather homogeneous mass containing fibrin, in which the structure of the tissue can no longer be recognized.

Diphtheritic sloughing of the tissues of a mucous membrane is observed particularly often in the intestine, but is also not lacking in other mucous membranes, as in those of the vagina, the efferent urinary passages, the region of the throat, where the tonsils are oftenest affected, etc. The necrotic tissue forms a slough that is white or

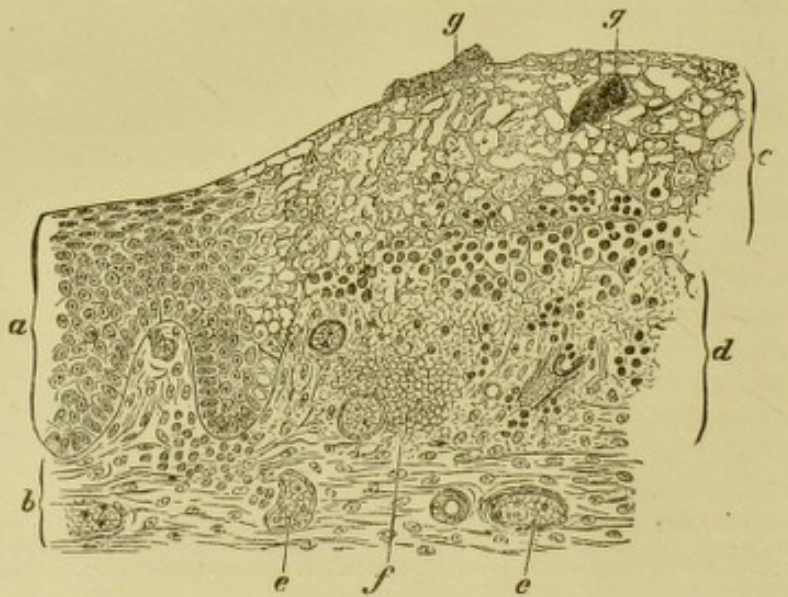


FIG. 192.—Section of the uvula in pharyngeal diphtheria with croupous deposits. (Alcohol; aniline brown.) *a*, Normal epithelium; *b*, connective tissue of the mucous membrane; *c*, reticulated fibrin; *d*, connective tissue of the mucosa, infiltrated with coagulated fibrin and round cells, and partly necrotic; *e*, blood-vessels; *f*, hemorrhage; *g*, masses of micrococci. Magnified 75 diameters.

grayish-white, or, from admixture of blood or bile, or other impurities, is stained dark green, yellow, or brown, or any other color. If a long time has elapsed since its formation, and if there has occurred a tissue-liquefaction on the border separating the dead from the living tissues, the necrosed parts form loosely attached or quite free deposits on the surface of the mucous membrane; these deposits consisting sometimes only of small particles or granules, sometimes of quite large membranes.

Diphtheritis of mucous membranes may also be associated with croupous deposits (Fig. 192, *c*, *d*), so that the tissue-necrosis (*d*) may be covered with fibrin excretion (*c*).

Wound-granulations may also necrose in the same way as do inflamed mucous membranes, so that one may also speak of *wound-diphtheria*.

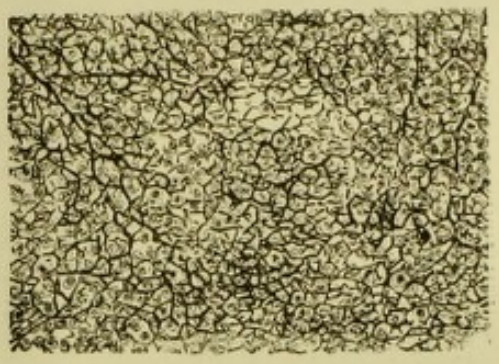


FIG. 193.—An area of diphtheritic necrosis in the interior of a swollen mesenteric gland taken from a typhoid-fever patient. (Alcohol; fibrin stain.) Network of fibrin between the necrotic cells. Magnified 300 diameters.

Acute tissue-necroses caused by infection are observed in the internal organs — chiefly in the lymphatic glands (Fig. 193), the spleen, and the bone-marrow—and are characterized by the formation of partly opaque grayish-white or yellowish-white or dirty-gray sloughs. It is not an unusual thing to find fibrinous exudations (Fig. 192, *d*, and Fig. 193) in the interior of a mass of necrotic tissue.

In the necrosis caused by tuberculosis the destruction of the tissue occurs only gradually and bears the character of a **caseation.**

When an inflammatory focus contains bacteria, which excite a putrid decomposition of the albuminoid bodies, the inflammation may also bear a **gangrenous, foul-smelling character,** the tissue then decomposing into a dirty-gray or black tinder-like mass, which gradually dissolves and exhales an extremely disagreeable odor. Gas-bubbles are also sometimes developed in the focus.

II. The Processes of Repair and the Proliferation of the Tissues.—Formation of Granulation and Cicatricial Tissues.—Absorption of Exudates and Tissue-Necroses, and Substitution of Connective Tissue for Them.

§ 99. When an inflammation—that is, a tissue-degeneration associated with formation of exudate—exists in any tissue, there always arise, earlier or later, processes whose object is to remove the changes established and to restore the degenerated tissue, and which must therefore be regarded as **processes of repair.** If the cause which has excited the inflammation is no longer present, these processes consist really in this: that the pathological exudation ceases and is replaced by a normal vascular secretion; that the exudate present and the necrosed tissue are absorbed or cast out; and that the tissue destroyed is restored. If the excitant of the inflammation is still present and active in the tissue, this must also be excreted or rendered inert.

The **cessation of the alteration of the vascular walls** is attained by supplying normal blood to the injured vessels, so that their nutrition

again becomes normal. If the alteration was slight, and if the excitant of inflammation acted only for a short time—if it is the case, for example, only of the brief action of a trauma or high temperature or a chemical substance that was quickly removed—restoration of the vessels may also result in a short time—i.e., in a time that may be measured in minutes and hours.

When the excitant of inflammation acts for a considerable length of time, as in the case of bacteria which remain and multiply in the tissues for some time, or if changes are established by the inflammation itself which act in such a manner as to alter the vessels—if there has been, for example, a tissue-necrosis—the vessels continue for quite a long time to experience an injury which hinders the complete restoration of their functions.

The **absorption of the exudate** occurs in many cases easily and quickly, because it is taken up by the lymphatic circulation. It occurs most quickly in serous exudates; yet in many places fibrinous exudates also may be quite rapidly removed, but only when the coagula soon liquefy. Firm fibrinous exudates, as they occur especially on serous surfaces, and also large collections of pus, generally offer considerable resistance to absorption, and are the cause of the prolonged duration of the inflammation, although the character of this may change from what it was at first. In very many cases absorption is accomplished by the simultaneous substitution, for the exudate, of embryonic tissue, which is converted later into connective tissue.

The **sequestration and absorption of necrosed tissue,** with the exception of the casting loose of dead epithelium, which may be very quickly accomplished, always requires a long time, which, however, varies very considerably with the nature, situation, and extent of the dead tissue. The inflammation generally lasts as long as necrotic tissue is still present. *Superficial necrosed tissues may be cast off after the separation of the dead from the living*—i.e., *after sequestration.* In deep-seated tissue-necroses, in which the tissue does not soon undergo total liquefaction, absorption is generally slow, and is performed by a gradual substitution of living tissue for the dead.

The **regeneration of degenerated tissue** is dependent, for its occurrence, partly on the degree and extent of the degeneration, partly on the nature of the tissue, partly on the mode of action of the excitant of the inflammation.

When the tissue-cells in the neighborhood of the inflammation are only slightly degenerated, they can soon be restored when the nutrition is normal. When single cells have been destroyed, but the organization of the whole is not damaged, in most tissues a rapid renewal of cells by regenerative growth of the remaining cells may occur. This is the case particularly in the various connective-tissue formations, the superficial epithelium, the liver, and the kidneys; while ganglion-cells, bone-cells, cartilage-cells, and heart-muscle cells possess either no power, or at most a very slight power, of regeneration (*cf.* Chapter V.). Extensive tissue-destructions with solutions of continuity, wounds, fractures, suppurations, necrosing inflammations, etc., lead to tissue-developments which are indeed competent to repair the defect, but which lead generally not to a restoration of the normal tissue, but to the formation of a deteriorated tissue, that is called in its young condition **granulation tissue,** in its complete development **cicatricial tissue.** Of the same character is also the tissue which is substituted in the course of time

for the exudates that are not readily absorbed, and for the tissue-necroses.

With the occurrence of regenerative growth and granulation, a new phenomenon appears in the course of inflammation, and gives to the inflammation, later on, a special character, so that one calls it a **proliferating inflammation.**

The **phenomena of proliferation** begin in inflamed tissues, at the earliest, after eight hours, but are generally first clearly recognizable after twenty-four or forty-eight hours have elapsed.

They occur in general the more quickly the milder the inflammation is and the faster the pathological exudation is subdued or diminished. Suppuration, necrosis, and gangrene of the tissue hinder its proliferation, and retard the beginning of repair proportionately, or at least confine the reparative processes to the neighboring tissues.

Every tissue capable of growth furnishes formative cells only for a tissue like or closely allied to it. Pus-corpuscles are not formed from the tissue-cells, but *cells newly developed from the tissue-cells by proliferation may become mixed with the exudate, degenerate in it, and die.* Thus not all cells newly developed by proliferation can fulfil their function of producing new tissue.

The **removal of the excitant of inflammation** takes place very differently in different cases, and depends in the first place on the nature of the excitant. Many traumatisms and thermal influences act for only a very short time, and have no further influence on the later course of the inflammation. Many substances which act chemically may be quickly taken up by the tissue-juices and made inert or excreted, while others remain locally active a longer time. Of the bacteria which produce inflammation, many die soon, while others remain and constantly form new generations, which also continually renew inflammation; generally, it is true, in such a way that in the first diseased focus the inflammation subsides and healing begins, while in the neighborhood, or even in distant regions, *metastatic inflammations* develop.

On account of the great variation which exists both in the nature and in the qualities of the excitants of inflammation, as well as in the course of the inflammatory tissue-degenerations and of the exudate, and in the course of the processes of repair, it is easy to comprehend that the whole progress of an inflammation to the final healing may be of a very different character in different cases, so that all the different possibilities of its course can hardly be reviewed. At the same time it is not difficult to comprehend the decline of the various forms of inflammation, because ultimately the entire process is always made up of similar processes—i.e., of tissue-degenerations and pathological exudates that form the essence of inflammation, and of processes of repair that are appropriate for the removal of the disturbances established by the inflammation.

Many authors consider the tissue-proliferations which arise during the course of inflammation as also constituting an essential part of inflammation. For example, Neumann groups under the term inflammation all those phenomena which develop locally after a primary tissue-lesion and are directed to the healing of this lesion. If this be so, regeneration forms the most important part of the inflammatory process, for it is preëminently fitted to restore the defect of tissue caused by the primary tissue-lesion, or, as Neumann says, the uninterrupted continuity of the tissues. Such an identification of inflammation with tissue-regeneration I hold as inadmissible, in the first place because tissue-regenerations occur which clinically and anatomically in no way bear the characters of an inflammatory process. Then also the inflammatory pathological exu-

dates cannot be regarded as a phenomenon that can be compared to regeneration, and that, like it, has for an end the healing of a primary tissue-lesion. Even if they may act benignly in individual cases, yet this is not always the case. They cause much more often serious damages, which increase those established by the primary tissue-lesion, and often enough they form hindrances to the early beginning of healing.

In my opinion, all processes of healing, including also tissue-proliferation, are the very common results of an inflammatory disturbance in the tissues, but they do not constitute the essential feature of an inflammation. At the same time one may properly speak of *inflammatory tissue-growth* or of *proliferating inflammation*, for by these terms are understood tissue-growths which are connected with inflammation and run their course simultaneously with progressing inflammatory exudation; in other words, they are inflammations during whose course regenerative tissue-growths have already developed.

§ 100. The **granulation tissue** which forms in the course of numerous inflammatory processes exhibits nothing else than an **embryonic tissue formed by cell-proliferation and infiltrated with leucocytes.** Primarily the tissue consists actually of *cells and newly formed vessels*, which at first depend for their support upon the ground substance of the tissue from which they develop, but soon form for themselves a new ground substance.

The **cells of granulation tissue** are partly **hypertrophied tissue-cells** (Fig. 194, *b*, *c*, *d*), partly **mono-** and **polynuclear leucocytes** (*a*, a_1). In most cases the hypertrophied cells are connective-tissue cells, which later on produce connective tissue (Fig. 194, *d*, *e*), and may therefore be termed **fibroblasts.** Granulation tissue, however, may contain the offspring of other tissues, e.g., of periosteal tissue, medullary tissue, muscle-tissue—or *osteoblasts*, *chondroblasts*, and *sarcoblasts*—which are

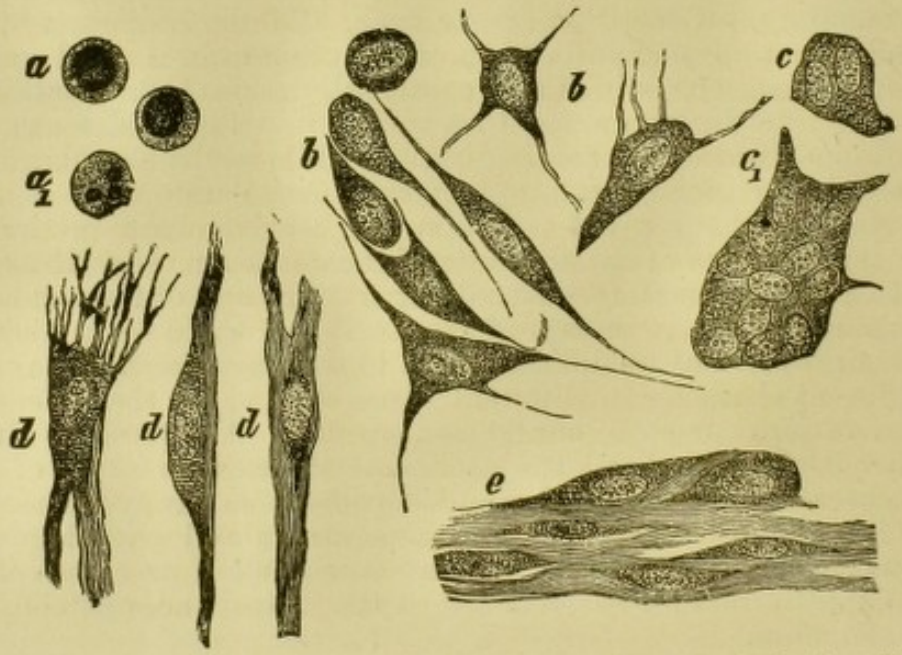


FIG. 194.—Isolated cells from a wound-granulation. (Müller's fluid; picrocarmine.) *a*, Mononuclear leucocytes; a_1, polynuclear leucocytes; *b*, various forms of mononuclear formative cells; *c*, binuclear formative cells; c_1, polynuclear formative cells; *d*, formative cells in the stage of connective-tissue formation; *e*, completed connective tissue. Magnified 500 diameters.

able to form bone-, cartilage-, and muscle-tissue. There may also be found: in or upon the granulation tissue, within newly formed glands, *glandular epithelial cells;* in mucous membranes and the integument, *covering epithelial cells;* and these are able forthwith to form *epithelial-tissue structures.* The *formative cells* of granulation tissue may move

away from the places of their origin, and are thus in a certain sense *wandering cells*. In the formation of connective tissue they take on the most varied shapes (Fig. 194, *c*, *d*, *e*). Sometimes polynuclear cells also form (c_1). They are distinguished by their large, bright, oval nuclei, which, being less deeply stained by nuclei-staining dyes, are thus distinguished from the nuclei of leucocytes, which are very deeply stained. The formative cells of connective tissue are often termed *epithelioid cells* on account of their resemblance to epithelial cells.

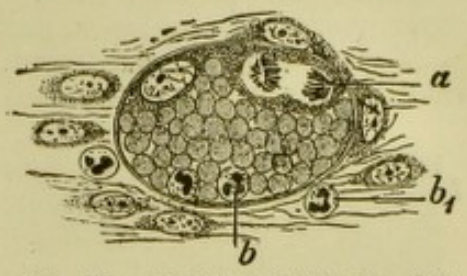


FIG. 195. — Blood-vessel from the deep layer of the skin cut transversely, forty hours after painting the skin of a rabbit with tincture of iodine. (Flemming's mixture; safranin.) *a*, Endothelial cells with mitoses; *b*, b_1, leucocytes. Magnified 350 diameters.

The **leucocytes of granulation tissue** are cells that have migrated from the blood-vessels, and from their presence it may be concluded that the inflammatory exudation from the vessels still continues. Their number may also be regarded in general as an index of the degree of the still existing inflammation, which complicates the recovery.

The **blood-vessels of granluation tissue** develop by sprouting from old vessels (cf. Fig. 153), and permit one very soon—indeed, at the time when an emigration of leucocytes occurs (Fig. 195, *b*)—to recognize processes of proliferation (*a*); and in the formation of granulation tissue they take on a very lively growth. The young embryonic tissue is in consequence supplied with unusually abundant vessels, which make it appear red. At the time of the change of the granulation tissue into connective tissue or **cicatricial tissue** an *obliteration of the vessels* occurs, and with it a blanching of the cicatrix.

§ 101. If an **open wound** occurs on any part of the surface of the body, and if it is not infected by bacteria or seriously injured in any other way, its walls and base after twenty-four hours appear deeply reddened and somewhat swollen. One can still clearly recognize the individual components of the tissue, only the tissue appears somewhat infiltrated, and here and there one sees small shreds of necrotic tissue. On the second day the gelatinous condition of the tissues is more apparent. The limits of the individual tissue-elements are confused, the color is grayish-red. On the wound lies a reddish-yellow fluid. After the second day there appear over the whole wound small red papules, which rapidly increase in number and size, become confluent, and after two or three days form a granular red surface—a **granulation surface.** This is covered with more or less abundant wound-secretion, that forms a gray, gelatinous layer, later a more yellow, creamy one. The latter consists of a *coagulable exudate* rich in albumin; and numerous round cells, that usually have two or three round nuclei, are termed *pus-corpuscles*, and, being incapable of further development, undergo destruction.

The changes which the surface of the wound shows are caused, in the first two days, by local hyperæmia and infiltration of the tissue with cellular and fluid exudate, and by the imbibition and liquefaction of the tissue. After that there is joined thereto a tissue-growth and new formation of vessels, which lead to the formation of **wound-granulations.** After a few days there will be found to have developed in the

wound an *embryonic tissue* (*a*), *abounding with wide vessels* (Fig. 196, *c*), *and consisting of fibroblasts and leucocytes, while a fibrillary ground substance also appears very soon.* The leucocytes which generally belong to the polynuclear form are found in all layers of fresh granulations, but are massed especially in the superficial strata, and, *embedded in fibrin*, cover over the granulation surface (*b*).

The freshly formed fibroblasts are round cells; but later there develop cells partly club-shaped, partly spindle-shaped, partly with many branches, which are combined together in various ways (Fig. 194, *b*, *c*, *d*). At the same time the number of large formative cells increases, so that they finally surpass the small round cells in number, and in places lie close together. When their number has reached a certain point, the development of connective tissue begins—i.e., the formation of the fibrillary intercellular substance (Fig. 194, *d*, *e*, and Fig. 196, *a*)—which is perfected in the manner described in § 89. When there is a certain abundance of fibrillæ the formation of bundles of fibres arrests the process; the remainder of the formative cells, with their nuclei, remain as fixed connective-tissue cells (Fig. 194, *e*), and attach themselves to the surface of the bundles of fibrillæ. The process has then reached its conclusion—*the granulation tissue has become* **cicatricial tissue.**

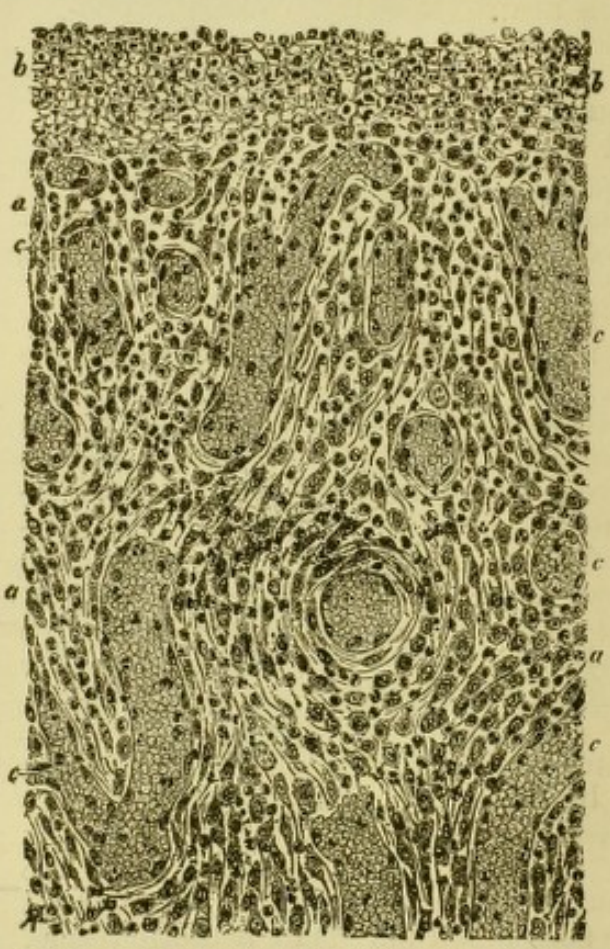


FIG. 196.—Wound-granulations from an open wound, with fibrino-purulent surface deposit. (Müller's fluid; hæmatoxylin.) *a*, Granulation tissue; *b*, fibrino-purulent layer; *c*, blood-vessels. Magnified 150 diameters.

In **open wounds of the integument,** when infections do not disturb the course of the healing, the formation of granulations usually lasts until the wound is again covered over with epithelium. The regeneration of the latter proceeds from the edges; the epithelium gradually pushing itself over the granulations (Figs. 169 and 170). With the formation of connective tissue the reproductive processes in reality terminate, but in the cicatricial tissue processes of transformation continue for a considerable period longer. Shortly after its formation the cicatrix is still rich in blood, and therefore looks red; later it loses a part of its blood-vessels by obliteration, becomes pale, and at the same time contracts to a volume smaller than the original. Large cicatrices of the integument exhibit for a long time a smooth surface, for the papillæ are not reformed, or only incompletely (Fig. 170, *c*). The scar-tissue itself remains for several months abnormally rich in cells (Fig. 170, *d*), but approaches in its structure more and more to the connective tissue from which it originated.

When the repair of a wound takes place in such a manner that the defect is closed by the formation of a granulating tissue visible to the unaided eye, it is termed *repair by second intention.*

The **repair of incised wounds of the skin,** *whose edges, united by sutures, grow together by the way known as healing by first intention,* occurs in essentially the same way as repair of an open wound by second intention; but the processes of inflammation, proliferation, and formation of new tissue are less apparent, partly because they occur below the skin, partly because their extent and intensity are less.

The result of such a cut is always a more or less abundant exudation

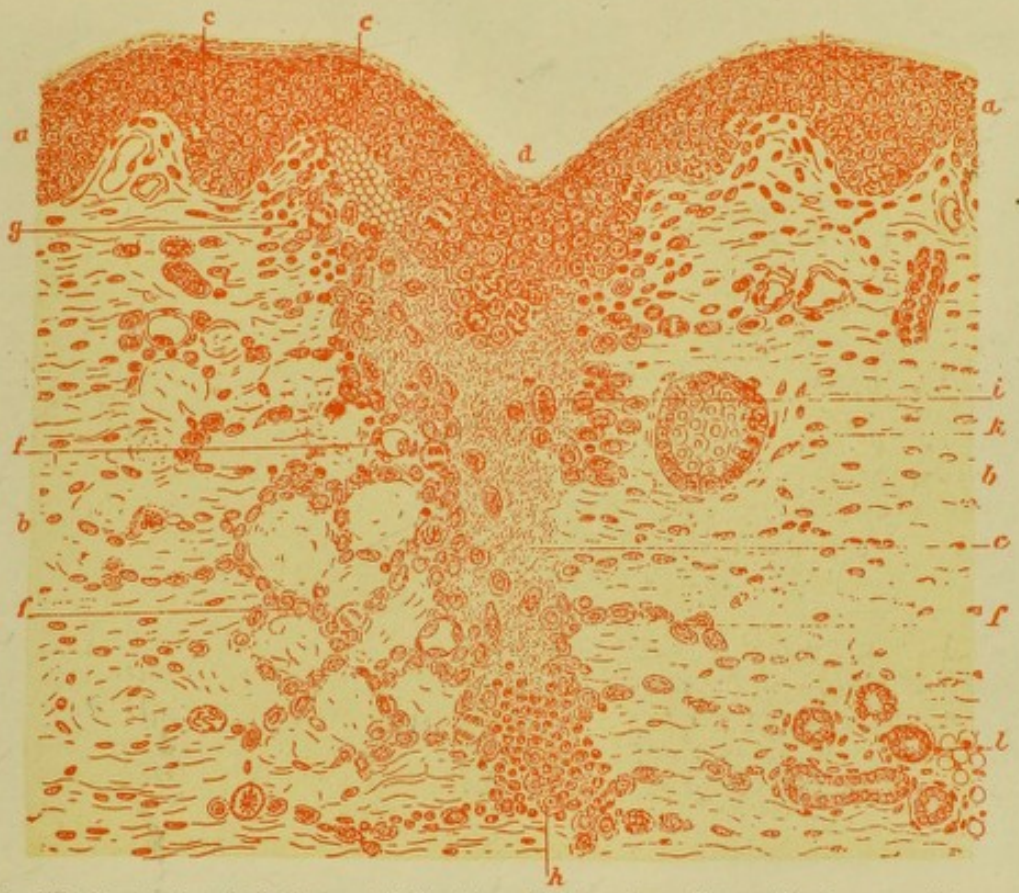


FIG. 197.—Repair of an incised wound of the skin united by suture. Preparation shows condition on the sixth day. (Flemming's mixture; safranin.) *a*, Epidermis; *b*, corium; *c*, fibrinous exudate; c_1, bloody exudate; *d*, newly formed epidermis, which contains numerous figures of dividing nuclei and has plugs of epithelium driven into the subjacent exudate; *e*, karyokinetic figures in epithelium remote from the incision; *f*, growing embryonic tissue, which develops from the connective-tissue spaces and contains cells with karyokinetic figures and some vessels with proliferating walls; *g*, proliferating embryonic tissue with leucocytes; *h*, collection of leucocytes in the deepest angle of the wound; *i*, fibroblasts lying within the exudate, one with a karyokinetic figure; *k*, sebaceous gland; *l*, sweat-gland. Magnified 80 diameters.

on the surfaces of the wound, this exudation producing a coagulated material, often containing blood (Fig. 197, *c*, c_1), that holds together the opposing surfaces of the wound. There also occurs very often an inflammatory infiltration of the edges of the wound, which varies in degree in different cases, and when the course of repair is aseptic, it is never very extensive (*g*, *h*), being greatest about the second, third, or fourth day, growing less from the fifth to the seventh, and completely disappearing at or soon after the end of the second week. The inflammatory infiltration is generally greater in the neighborhood of the wound-sutures than elsewhere.

As early as on the second day, regenerative proliferative processes begin in the connective tissue and vessels, and lead, in the course of several days, to the formation of an embryonal tissue, which is situated partly in the spaces of the connective tissue at the edges of the wound (Fig. 197, *f*), partly in the open space of the wound itself (*i*); and here the new tissue gradually grows into the coagulation-mass which is present, and replaces it. In different parts of the wound this tissue is usually present in very different quantity (Fig. 197), and may be entirely absent in places. After several days, whose number varies considerably according to the size of the wound, the thickness of the exudate between the edges of the wound, and the intensity of the proliferation, a

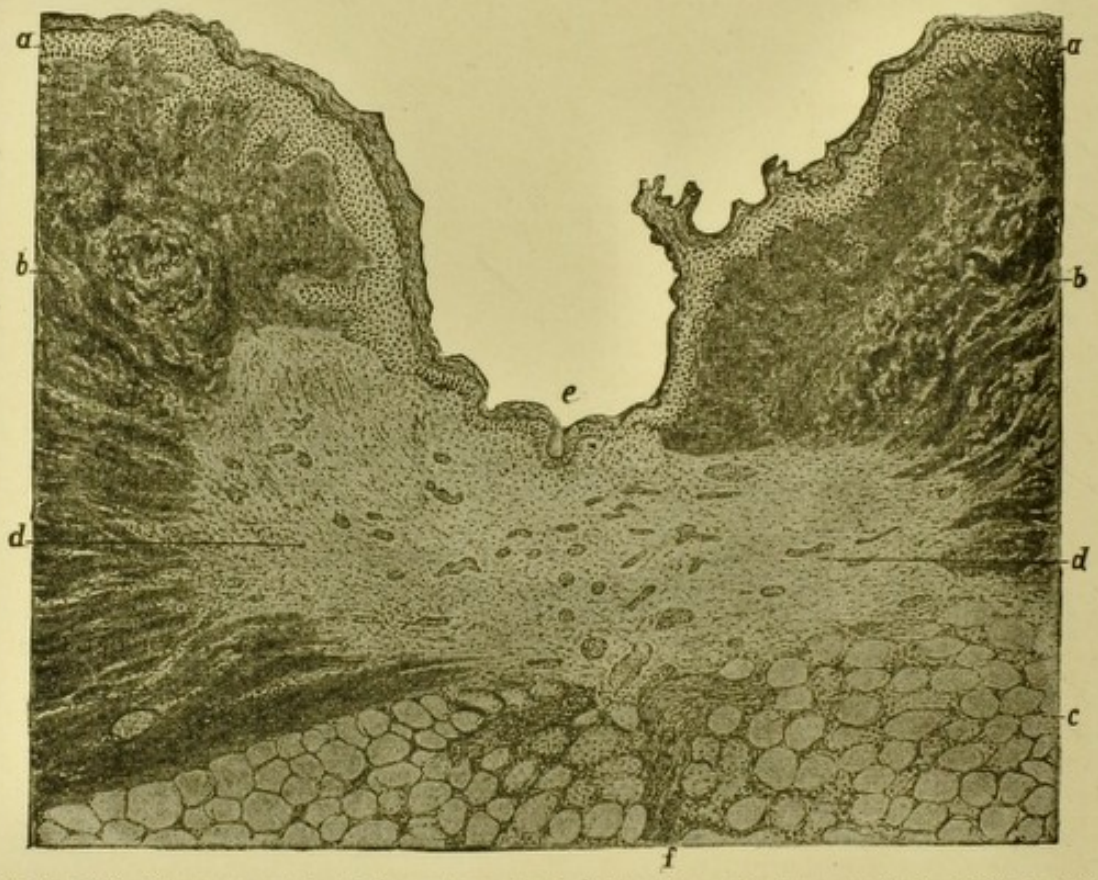


FIG. 198.—Cutaneous portion of a laparotomy cicatrix (sixteen days after the operation). (Müller's fluid; Van Gieson's mixture.) *a*, Epithelium; *b*, corium; *c*, subcutaneous adipose tissue; *d*, cicatrix in the corium; *e*, new epithelial covering; *f*, cicatrix in the adipose tissue. Magnified 40 diameters.

blending takes place between the masses of embryonal tissue that have developed from the edges of the wound, and later this is followed by a formation of young connective tissue, which joins the edges of the wound together, and at the same time extends into the old tissue, so that the limits between old and new grow more and more dim.

While connective tissue is being newly formed in the depth, the epithelial covering on the surface is also regenerated (Fig. 197, *d*) by the occurrence here and there in the epithelial covering of the edges of the wound, of a division of the epithelial cells (*d*, *e*). As a result of this the epithelium gradually pushes across the exudate in the wound-opening, covers over the young embryonal tissue, and after a time again forms a horny layer.

The young connective tissue of the cicatrix that unites the edges of

the wound is distinguishable for a long time, by its richness in cells (Fig. 198, *d*) as well as by the finer fibrillation of its ground substance, from the surrounding old cutaneous tissue. In large incised wounds of the skin (Fig. 198) one can find here and there, after the lapse of weeks or even months, slight appearances of proliferation and inflammation (*e*). In general, however, transformation processes develop gradually in the blanching scar, and as a result this new tissue approaches closer and closer to the normal, until finally the place of the incision can no longer be easily recognized. When, however, the wound heals by the interposition of abundant embryonal tissue, a lack of the papillæ may persist (Fig. 198, *e*), so that the region of the wound remains smooth.

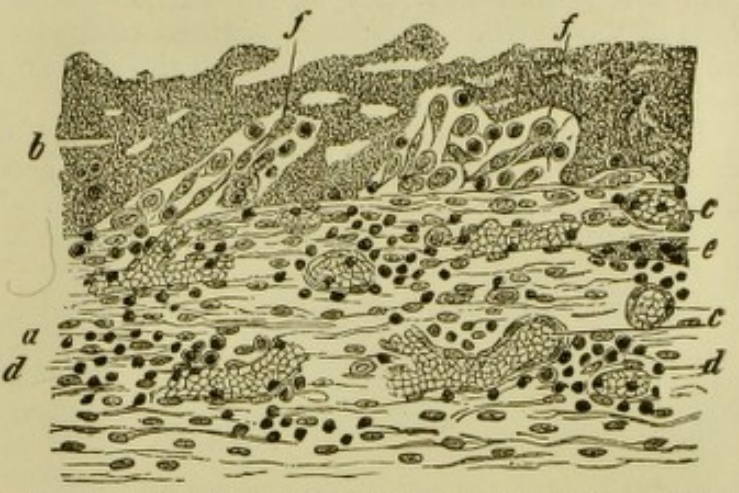


FIG. 199.—Fibrin-deposit and beginning formation of granulations in a fibrinous pericarditis five days old. (Müller's fluid; hæmatoxylin.) *a*, Epicardium; *b*, fibrinous membrane; *c*, dilated, congested blood-vessel; *d*, round cells infiltrating the tissue; *e*, lymphatic vessel filled with cells and coagula; *f*, formative cells within the deposit. Magnified 150 diameters.

§ 102. When an **adherent layer of fibrin** (*b*) occurs on the surface of an inflamed serous membrane (Fig. 199, *a*), **granulation formations** generally develop very quickly underneath it. Their first beginnings can be observed as early as on the fourth day after the formation of the fibrinous deposit, and they consist at first of the appearance of *fibroblasts* (*f*) in the deepest layers of the fibrin membrane. The fibroblasts result from a proliferation of the tissue-cells of the affected membrane, these cells having wandered, later on, to the surface and penetrated into the crevices of the fibrin. Upon this phenomenon follows presently a new formation of vessels, and in the course of days and weeks there is developed, on the surface, a vascular embryonal tissue or granulation tissue, which, in case of a compact structure of the fibrin-

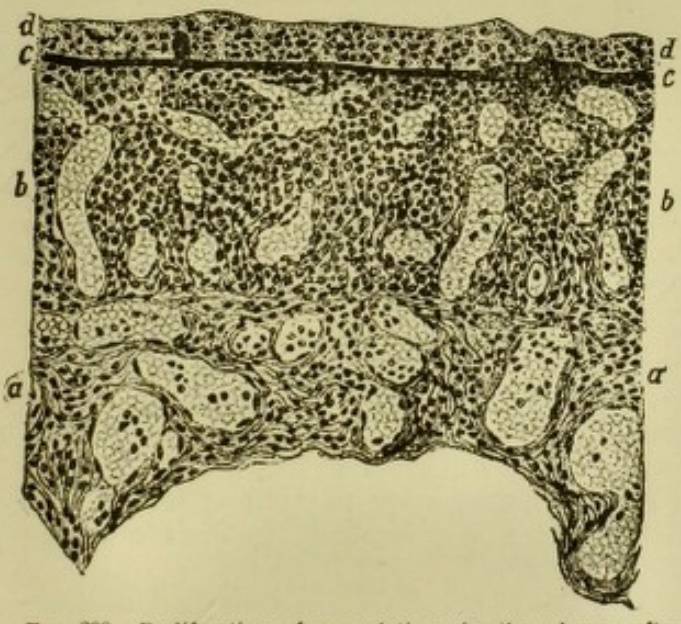


FIG. 200.—Proliferation of granulations in the pleura, after bronchopneumonia and pleuritis, lasting fourteen days. (Alcohol; Van Gieson's mixture.) *a*, Hyperæmic and infiltrated pleura; *b*, vascular granulation tissue; *c*, fibrin; *d*, pus-cells and granules of precipitated albumen. Magnified 200 diameters.

deposit, lifts up this layer *in toto* (Fig. 200, *b*, *c*), in case of a more open structure of the fibrin-membrane, insinuates itself into its interstices (Fig. 199, *f*, and Fig. 201, *b*, *d*), and in course of time occupies the place of the fibrin. Residual portions of fibrin (Fig. 201, *c*), nevertheless, remain within the granulation tissue for a long time, even for weeks and months.

In the formation of the granulation tissue, and in the structure of the cicatricial tissue, the epithelium of the serous membranes has no share, inasmuch as it produces no fibroblasts. On the other hand, the products of inflammatory proliferation acquire a covering of epithelium later on.

The final result of the process is the formation of **connective tissue,** which causes either only a *thickening* of the fibrin-covered serosa, or an *adhesion of opposing surfaces of the serous membrane*, so that the *inflammation is termed adhesive.*

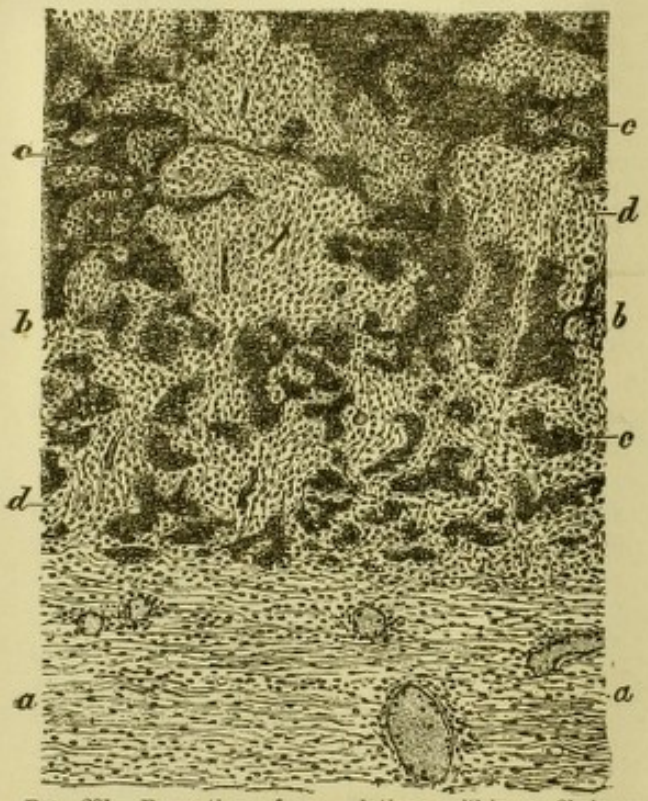


FIG. 201.—Formation of granulations within a fibrinous deposit in pericarditis several weeks old. (Müller's fluid; hæmatoxylin; eosin.) *a*, Epicardium; *b*, deposit on the epicardium, consisting of granulation tissue, *d*, and fibrin, *c*. Magnified 45 diameters.

The result in individual cases depends partly on the abundance of the fibrinous deposit, partly on the situation of the affected organ and its condition during the process of recovery.

Small deposits of fibrin, limited to one surface of the serous membrane, lead only to thickening of the membrane, which, growing pale with the disappearance of the vessels, presents a white thickening that is very often called a *milk-patch* or a **tendinous spot.** Firm gluing together of two serous laminæ by an abundant deposit of fibrin may also lead to their becoming united by abundantly developed connective tissue. With a smaller quantity of fibrin, and repeated rubbing past one another of the membranes, there are generally formed only loose *membranous or filamentous adhesions*, which still permit the serous surfaces to glide over one another. Very large quantities of *fibrin* may also at times partly resist absorption, so that they persist in the newly formed connective tissue and then generally become *calcified.*

Coagulated exudates in the lung are generally soon liquefied and *absorbed;* yet their removal in this manner may be associated with *connective-tissue proliferation*, which terminates in *induration of the lung.*

Masses of coagula within the vessels, which are termed thrombi, give rise, when no infection intervenes, to an inflammatory proliferation of the vessel-walls, a *proliferating vasculitis*—i.e., a process which is associated with cell-migration, and which exactly corresponds to the in-

flammatory proliferation of the serous membranes. It is entirely immaterial whether the thrombus has been caused by a preceding inflammatory process or by any other conditions; for the presence of the coagulated mass is itself sufficient to produce inflammation and tissue-proliferation.

The first change which is introduced, in the **replacement of a thrombus by connective tissue,** is here also the appearance of fibroblasts (Fig. 202, *h*), which arise from the vessel-wall, and later, with the aid of vessels that grow in from the vessel-wall and its neighborhood, form an embryonal tissue that is finally converted into connective tissue. The complete replacement of an obstructing thrombus or embolus results in the obliteration of the lumen of the vessel by vascular connective tissue (Fig. 204, *g*). Replacement of a peripheral thrombus, on the other hand, results in fibrous thickening of the wall. Owing to incomplete replacement and liquefaction of the part not replaced, there

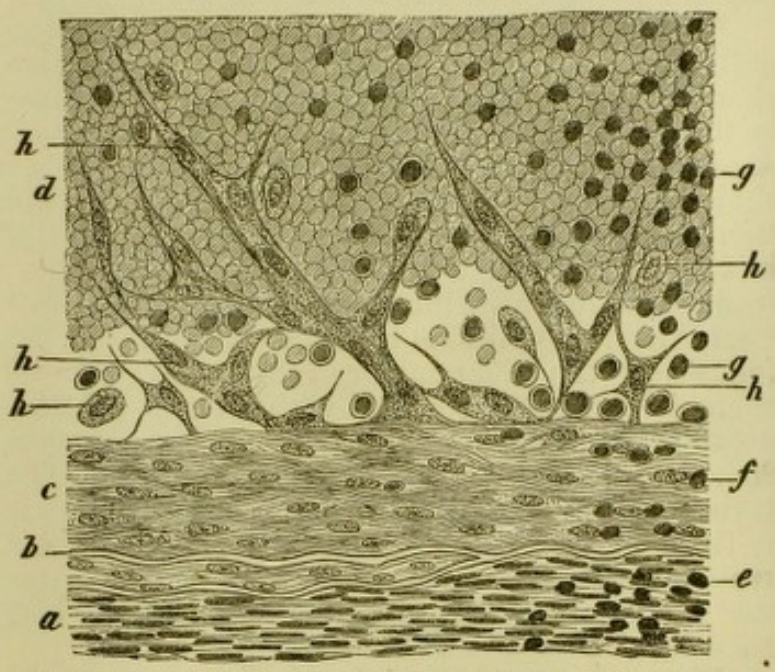


FIG. 202.—Development of embryonal tissue in a thrombosed femoral artery of an old man, three weeks after ligation. (Alcohol; hæmatoxylin.) *a*, Media; *b*, elastic boundary layer; *c*, intima thickened by old chronic inflammatory processes; *d*, coagulated blood; *e*, cellular infiltration of the media; *f*, the same of the intima; *g*, round cells partly within the thrombus, partly between the latter and the intima; *h*, different forms of formative cells. Magnified 300 diameters.

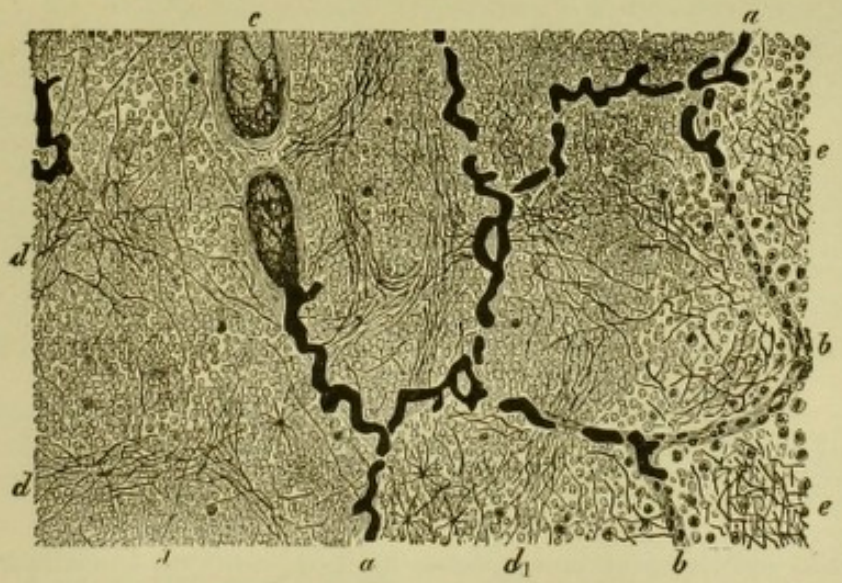


FIG. 203.—Border of a recent hemorrhagic infarct of the lung. (Müller's fluid; hæmatoxylin; eosin.) *a*, Non-nucleated alveolar septa, whose capillaries are filled with hyaline thrombi; *b*, nucleated septa; *c*, vessels filled with red thrombi; *d*, d_1, alveoli filled with coagulated blood; *e*, fibrino-cellular exudate in the alveoli. Magnified 100 diameters.

arise strings and threads of connective tissue, which cross the lumen of the vessel. Calcification of the parts of thrombi which are not replaced by connective tissue leads to the formation of vascular calculi.

Necrotic tissues, which cannot be sequestrated and discharged externally, are also **replaced by vascular connective tissue** that becomes changed into **cicatricial tissue**; and this replacement is accomplished in the same way as in the case of the fibrinous exudates and thrombi. A preliminary condition for this replacement is that the necrotic tissue shall contain no substances (bacteria) which hinder a tissue-proliferation and produce severe inflammation. For the rest, it is immaterial how the necrosis has occurred, and whether the necrotic tissue is free from exudate or is infiltrated with exudate or blood (Fig. 203, *d*, d_1). Under these conditions the first phenomenon leading to healing is the following: the inflammatory infiltration (*e*) in the neighborhood of the necrosis becomes associated with a tissue-proliferation, which produces **granulation tissue**, and this in turn grows toward the necrosis (Fig. 204, *d*, *e*), pushes it aside, and replaces it. If this process is not disturbed by any influence, even extensive tissue-necroses may disappear in the course of weeks or months, and be replaced by connective tissue. It may also happen, however, that certain tissues resist absorption, or that the development of granulations stops so early that *some remains of the necrosis persist and then become calcified.*

When, owing to an inflammation or an ischæmia within an organ, only the more sensitive elements die—for example, the epithelia or the

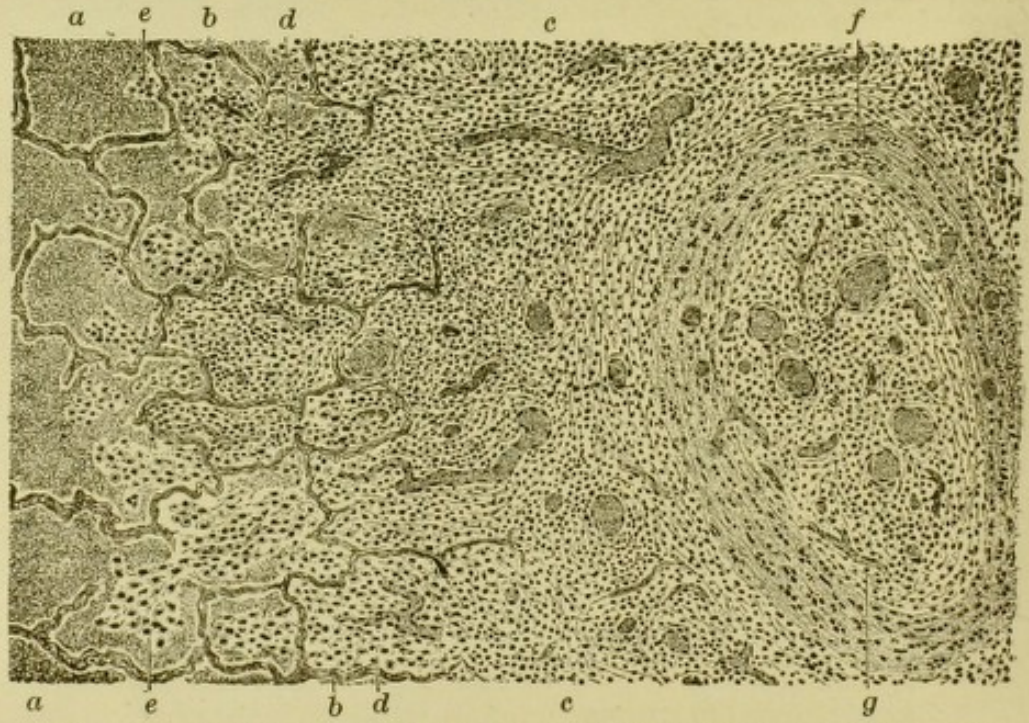


FIG. 204.—Peripheral portion of a healing infarction of the lung. (Müller's fluid; hæmatoxylin; eosin.) *a*, Blood-extravasation changed into a granular, yellowish mass; *b*, necrotic alveolar septa without nuclei; *c*, newly formed connective tissue; *d*, vascular granulation tissue within the alveoli; *e*, fibroblasts within alveoli containing the residue of the hemorrhage; *f*, artery; *g*, vascular connective tissue formed within the artery at the place of the embolus. Magnified 45 diameters.

muscle-cells—while the connective tissue is preserved, the absorption of the necrosis is performed quickly, and in a short time there develops a *scar or callus of connective tissue* (Fig. 205, *e*), in which the specific tissue-elements are lacking.

Pus is quickly *absorbed* from small abscesses, and *the defect is closed by granulation and scar tissue.* Large amounts of pus may also be absorbed from the cavities of the body and from the lungs.

Abscesses cause a **development of granulations** in their neighborhood, and this leads to the formation of an **abscess membrane.** The cavity may be obliterated by the absorption of the pus and by the growing together of the granulating abscess membrane; and so the abscess may heal, leaving a **scar** behind. Incomplete absorption may lead to thickening of the pus, and later to *calcification of the residue.* If the thickening of the pus, however, does not occur, the abscess remains, and may increase in size in the course of time by secretion from its wall.

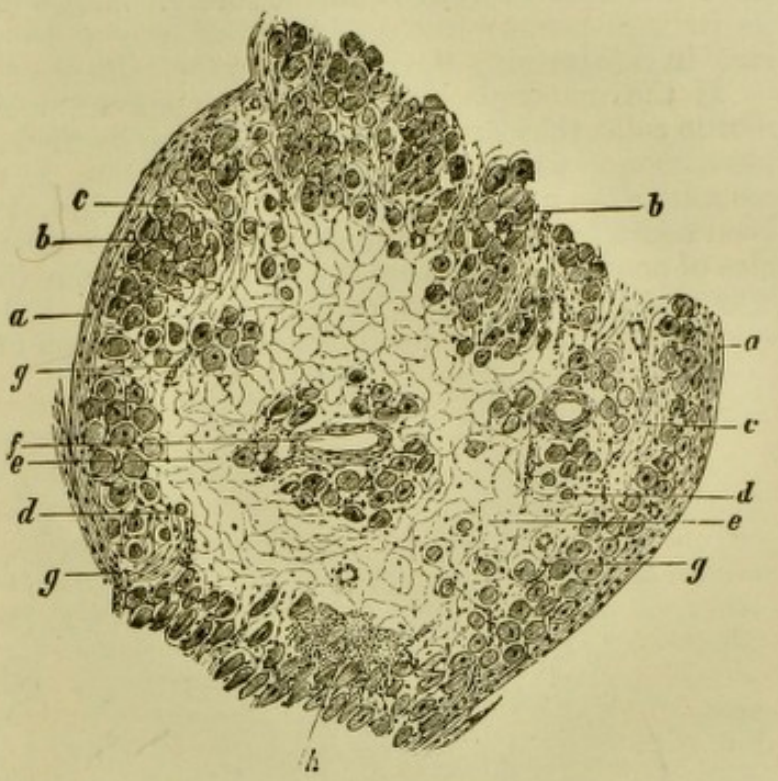


FIG. 205.—Callosity of heart. Section through a muscle trabecula that has undergone fibroid degeneration. (Müller's fluid; hæmatoxylin.) *a*, Endocardium; *b*, transverse section of normal muscle-cells; *c*, connective-tissue hyperplasia rich in cells; *d*, atrophic muscle-cells in hyperplastic connective tissue; *e*, dense connective tissue without nuclei or muscle-cells; *f*, veins, in whose neighborhood a few muscle-cells still remain; *g*, small blood-vessels; *h*, small-celled infiltration. Magnified 40 diameters.

Like abscesses, **empyemata** may heal by the absorption of the pus. At the time of absorption the tissues inclosing the pus produce **granulation and cicatricial tissues,** which may attain considerable size when the absorption takes a long time. When incompletely absorbed, *inspissated pus may calcify.*

Foreign bodies, so far as they are capable of absorption and exert no specific influence on their environment, are dissolved and replaced by connective tissue in the same way as are tissue-necroses or masses of fibrin.

III. Phagocytosis Occurring in the Course of Inflammations, and the Formation of Giant Cells.—Chemotaxis.

§ 103. When **small foreign bodies,** or **portions or particles of devitalized tissue,** are found in the human body, there is very often a marked *assembling of cells* at their place of deposition. These are, first, *leucocytes* which have migrated from the vessels, but later also *tissue-cells that have become motile, or that are proliferating,* wander into the neighborhood of the foreign body or of the remains of devitalized tissue.

According to the researches of Leber, Buchner, Massart, Bordet,

Gabritschewsky, and others, it is certain that this assembling of cells is partly brought about by **chemotaxis**—i.e., by an attraction exerted by fluid materials derived from the foreign bodies or from the particles of devitalized tissue; but doubtless other conditions also exert an influence in determining the spot where the cells are to assemble.

If the materials, while still undissolved, reach the sphere of the motile cells, they are very often taken up by them, and there occurs that phenomenon which is termed **phagocytosis.** If one observes the process under the microscope—which is easy to do, if tissue-lymph that has been taken from the frog and that is rich in cells, is mixed with granules of soot—one sees that the motile cells pour their protoplasm, if one may use the expression, around the foreign bodies, and absorb them completely into their protoplasm by the union of the pseudopodia ex-

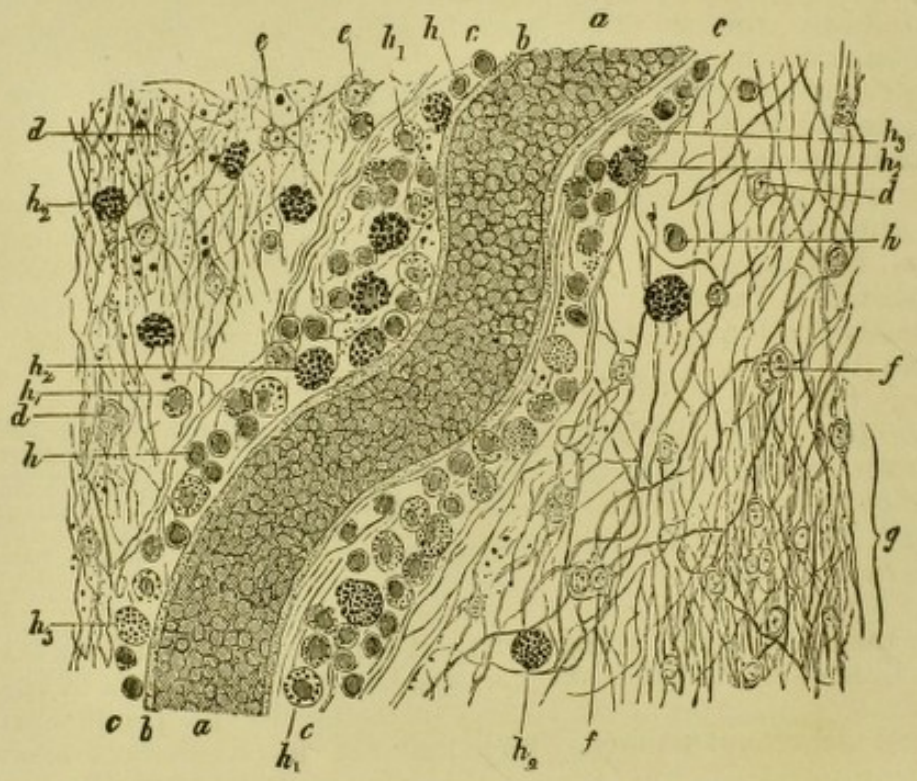


FIG. 206.—Granular cells in a focus of degeneration of the brain. (Teased preparation treated with osmic acid.) *a*, Blood-vessel with blood; *b*, media; *c*, adventitia with lymphatic sheath; *d*, unchanged glia-cells; *e*, fatty glia-cells; *f*, binuclear glia-cells; *g*, sclerosed tissue; *h*, round cells; h_1, round cells with single droplets of fat; h_2, fatty-granule spheres; h_3, pigmented-granule spheres. Magnified 300 diameters.

tended over the bodies. Among the foreign bodies that have penetrated from the outside, which are particularly often taken up by the leucocytes or tissue-cells, are chiefly the *various forms of dust* (especially soot), which are taken into the lungs with the respired air, and *bacteria.* It is to be noted, however, that phagocytosis does not occur in all infections caused by bacteria, but is rather confined to special infections, and even in these does not appear in all stages of the local disease.

Among the débris of tissues one finds most often fat-droplets (Fig. 206, h_1, h_2) and products of the destruction of the red blood-corpuscles (Fig. 206, h_2, Fig. 208, *c*, and Fig. 102). These products of destruction may be taken up by the cells until they are stuffed with them and converted into large granular forms that are termed *fatty-granule spheres* and *pigmented-granule spheres.* Besides fat and blood-pigment, other fragments of tissue also—as, for example, particles of the contractile sub-

stance of muscle-cells or of elastic tissue-fibres or even of fibrin—may be taken up by the cells. The cells which take up all these substances are principally tissue-cells in luxuriant proliferation—fibroblasts, osteoblasts, sarcoblasts, etc. If an inflammatory exudation runs its course at the same time as the proliferation, and if the proliferating tissue contains *leucocytes*, these *may also be taken up by the phagocytes* (Fig. 207, *a*, *b*, *c*).

FIG. 207.—Phagocytes from granulating tissue with included leucocytes and their fragments. (Corrosive sublimate; Biondi's staining mixture.) *a*, Round fibroblast with two leucocytes; *b*, swollen spindle-shaped connective-tissue cell with one leucocyte; *c*, *d*, *e*, fibroblasts with fragments of leucocytes. Magnified 500 diameters.

The substances taken up by the phagocytes may be partly dissolved and destroyed within the cells; and this is true particularly for the leucocytes, which gradually disappear inside of the cell-protoplasm of the phagocytes (Fig. 207, *c*, *d*, *e*), but it also holds equally for various fragments of tissue, except blood-pigment (Fig. 208, *c*), which may remain a long time within the cells. The insoluble substances (soot) behave in the same way, while the bacteria taken up by the cells, in each case according to their vital properties and the condition in which they entered the cells, are sometimes dissolved and destroyed, but sometimes, on the other hand, remain and multiply even in the cells.

The cells loaded with foreign bodies are situated at first at the place where the phagocytosis occurred, but they may also migrate farther and enter the lymphatic circulation (Fig. 206, *c*) and the lymph-glands (Fig. 208), and later also the blood, from which they are deposited principally in the spleen, marrow of bone, and liver (cf. §§ 17 and 18).

If the **foreign bodies** which have penetrated into the body from the exterior, or the **dying** or already **necrotic fragments of tissue**, are too numerous to be taken up by leucocytes or proliferated tissue-cells, there form very often, in the granulation tissue that develops in their neighborhood, **polynuclear giant cells**, which arrange themselves on the surface of the foreign body or the superfluous mass of tissue, exactly as this occurs on the part of osteoclasts under physiological conditions (Fig. 209, *d*). If the bodies are not too large they may be still taken up by these polynuclear cells; in the other case the cells remain attached to the surface and produce the gradual dissolution of soluble substances (e.g., strands of catgut, fragments of dead muscle-fibres). It sometimes happens that mononuclear cells take up small foreign bodies into their interior, and after this, by division, their nuclei become polynuclear. This is observed most often after the inclusion of bacteria (lepra, tuberculosis), which still multiply within the cells.

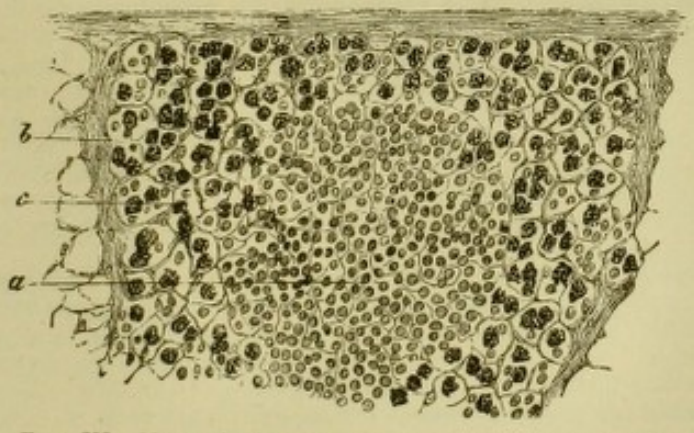


FIG. 208.—Mass of pigmented-granule spheres in a lymphatic gland. (Alcohol; carmine.) *a*, Lymph-node; *b*, trabeculæ of the lymphatic gland; *c*, lymph-passage with pigmented-granule spheres. Magnified 80 diameters.

When a foreign body in the tissues cannot be absorbed it is surrounded by granulation tissue that changes later into connective tissue (Fig. 209, *b*, *c*), and in this way becomes encapsulated. The proliferation may be very slight, however, in the immediate vicinity of smooth, completely insoluble substances (glass beads).

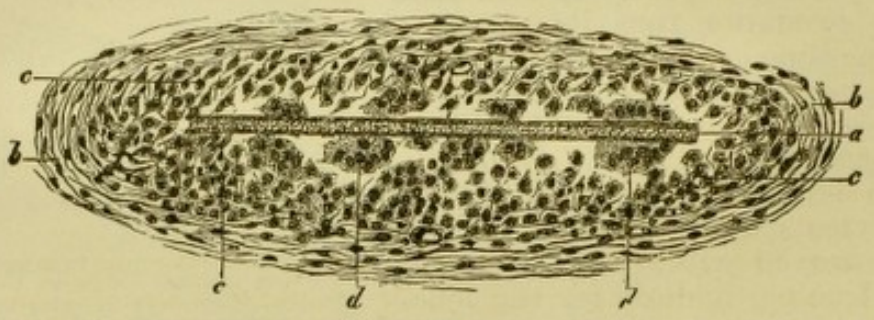


FIG. 209.—Dog's hair encapsulated in subcutaneous tissue. (Alcohol; Bismarck brown.) *a*, Hair; *b*, fibrous tissue; *c*, proliferating granulation tissue; *d*, giant cells. Magnified 66 diameters.

The phenomena of **chemotropism** or **chemotaxis**—i.e., the attraction or repulsion of freely motile cells by substances soluble in water—were first observed by Strahl and Pfeffer, who made researches particularly on myxomycetes, infusoria, bacteria, seminal filaments, and swarming spores. Researches of Leber, Buchner, Massart, Bordet, Gabritschewsky, and others have shown that the leucocytes may also be attracted (*positive chemotropism* or *chemotaxis*) or repelled (*negative chemotropism*) by chemical substances. There are particular products of the vital activity of fission-fungi (Leber, Massart, Bordet, Gabritschewsky) or bacterial proteins—i.e., the albuminoid bodies of dead bacterial cells (Buchner)—which even after great dilution (according to Buchner, the protein of pyocyaneus is still active in a dilution of 1 : 3,000) are positively chemotactic. According to Buchner, this property belongs also to gluten-casein from wheat-paste and legumin, to glue from bones, and to alkali albuminate from peas, while ammonium butyrate, trimethylamin, ammonia, leucin, tyrosin, urea, and skatol exhibit negative chemotaxis.

Phagocytosis is a vital phenomenon that has been long known and has many times been made the subject of investigation. Von Recklinghausen, Ponfick, Hoffmann, Langerhans, Slavjansky, von Ins, Ruppert, Langhans, Rindfleisch, and others conducted such experiments in the sixties and seventies, and described particularly the relations of cells to granules of dust and the disintegration products of the blood. In the year 1874 I made the observation that the fibroblasts of the granulation tissue take up and destroy leucocytes. It is to be assumed that one has in this phenomenon *an act of nutrition*—that the phagocytes digest and assimilate the leucocytes taken up. This is indicated by the fact that phagocytosis is a vital function of cells, which in the first place is directed to the taking up of nutriment. But since a phagocytosis is also observed in cells which give off substances to the excreta (e.g., in the renal epithelia); since, also, wandering cells loaded with dust appear at the surface of mucous membranes and in glands, and may thus cleanse the tissues of the substances mentioned, one may regard phagocytosis as a process which is directed also partly to the excretion of certain substances.

Since the year 1883 Metschnikoff has occupied himself in a particularly thorough fashion with phagocytosis (he has also introduced this name), and has demonstrated that it is one of the most widely spread phenomena in the whole animal world, and is most often observed in mesodermal cells. He is of the opinion that phagocytosis represents the essential and characteristic token of inflammation, and that *the inflammatory process is a combat waged by the cells against intruders or disease producers.* This view is, however, completely erroneous and finds no support in the actual conditions. Metschnikoff, in putting forward his definition of inflammation as a battle of phagocytes against disease producers, pays no attention to those phenomena which have been termed inflammation from antiquity onward, and names inflammation only a single chosen vital process to which he has given his interest. If one starts from processes that are recognized on all sides as inflammation, it is apparent that legitimate inflammations occur in which no phagocytosis is present; so that phagocytosis does not even form an inseparable concomitant of inflammation. For the rest, it is to be remarked that phagocytosis is a phenomenon that often occurs in the course of even non-inflammatory processes (e.g., within tumors). Finally, one cannot see in phagocytosis any appearance

of a struggle, since in the taking up of cinnabar or soot or fragments of red blood-corpuscles or pus-corpuscles every possibility of resistance on the part of that which is devoured is excluded. And even when bacteria are taken up, no struggle can be observed, at least in those cases in which (as actually often happens) the bacteria are only taken up when they are dead or at least dying.

IV. Chronic Inflammations.

§ 104. Inflammation is naturally an acute process, but various conditions may cause the phenomena of tissue-degeneration and exudation to last longer, and the inflammation to become chronic.

The **cause of an inflammation becoming chronic** may be found, in the first place, in the fact that *in the course of an acute inflammation changes occur which prevent a rapid healing.* As may be deduced from the foregoing, all large defects of tissue and tissue-necroses, as well as large masses of exudate that are difficult to absorb, act in this way. When necrotic masses of tissue are not completely absorbable, as in the case of large pieces of bone, they may indeed be sequestrated, but they then persist as sequestra for years (Fig. 210, *a*), and maintain a constant inflammation. When a large superficial defect of the integument is produced by a burn, granulations develop, but it may be months before the wounded surface is skinned over from the edges and the process thus completed.

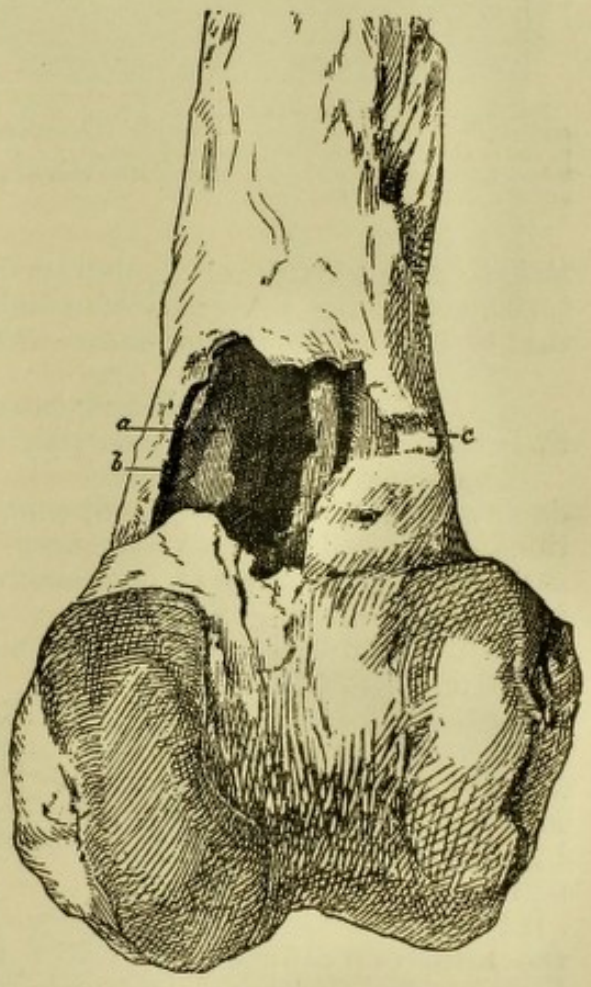


FIG. 210.—Necrosis of fifteen years' duration in the lower part of the diaphysis of the femur. *a*, Sequestrum; *b*, *c*, edges of the opening in the thickened bone. (Alcohol preparation. Reduced to two-thirds natural size.)

A further cause of chronic inflammations is always found in *repeated injury by external influences.* Thus, for example, repeated inhalation of dust may cause chronic inflammation of the lung; repeated friction of the skin may perpetuate a chronic inflammation of the part; and repeated pathological alterations of the stomach-contents may promote inflammation of the stomach. In the canals of the body in which *concretions* form, these latter may also be a cause of lasting tissue-lesions.

When *unfavorable nutritive conditions* exist in a tissue—e.g., great congestion—these may also enable even slight external influences, that under normal conditions produce no inflammation or one that soon stops, to set up ulceration without any tendency to heal. In this way, for example, chronic ulcers of the leg may occur.

Infections are also a frequent cause of chronic inflammations, especially those by *bacteria and moulds*, which multiply in the body and so constantly produce new inflammatory irritation. The inflammations which they cause are distinguished from others chiefly by the fact that they often have a *progressive character*, and by the further fact that they cause metastases by way of the lymphatic vessels and the blood.

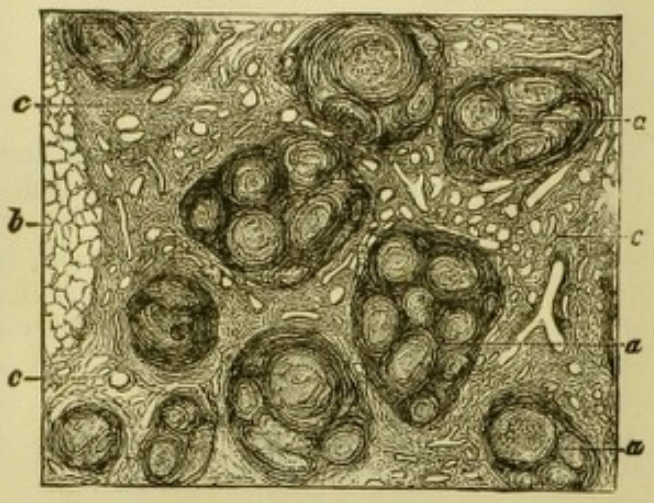


FIG. 211.—Section of a stone-cutter's lung with bronchopneumonic fibrous nodules. (Alcohol: picrocarmine.) *a*, Group of fibrous nodules; *b*, normal lung-tissue; *c*, pulmonary tissue, thickened, but still containing bronchi, vessels, and a few alveoli. Magnified 9 diameters.

Finally, *chronic intoxications* form a last cause. They act particularly on the kidneys and liver, and may be attributed either to the introduction into the organism, through the intestinal canal or the lungs or even the integument, of substances that are injurious to the organs affected or to others; or to the production in the body itself, by disturbances of the processes of metabolism, of injurious substances, so that there is a *chronic auto-intoxication*.

§ 105. The **forms of chronic inflammation** are determined partly by their fundamental causes, partly by the nature of the tissue affected.

The remains of acute processes, as they are seen in fibrinous exudates and tissue-necroses, lead, when not complicated by specific infections, to an **inflammatory tissue-proliferation**. For the rest, **inflammatory hypertrophies of connective tissue** result from various chronic irritations of the tissues. So, for example, chronic irritation of the lung by *the deposition of stone-dust may lead to a connective-tissue hypertrophy in the lung*, which is essentially characterized by the formation of circumscribed nodules (Fig. 211, *a*), but occurs also partly in the form of a diffuse hypertrophy (*c*). Continued irritating conditions in the neighborhood of the orifices of the urogenital apparatus, where they are maintained by the discharge of irritating secretions, often lead to the formation of *acuminate condylomata*—i.e., to hypertrophy of the papillæ, in which the inflamed and infiltrated papillæ, with their vessels, enlarge (Fig. 212, *a*, *b*) and often also divide into branches.

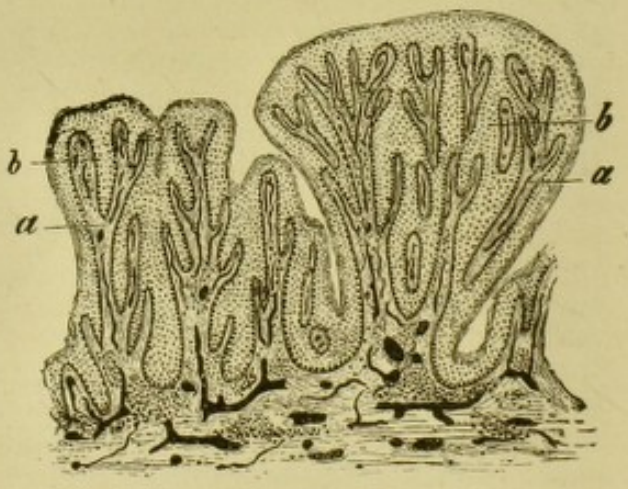


FIG. 212.—Condyloma acuminatum. *a*, Enlarged and branching papillæ; *b*, epidermis. (Injected preparation.) Magnified 20 diameters.

Frequently repeated and rather persistent mild inflammations of the skin and subcutaneous tissue, which are caused by mechanical lesions, by parasites, or by any other continued irritation, may also often, when they acquire a considerable extent, lead to diffuse connective-tissue hypertrophy, which is known as *elephantiasis*.

Inflammatory growths of the periosteum and medulla of bone, which lead to *pathological new formation of bone*, or a *hyperostosis* (Fig. 213), may be caused both by non-specific irritations—e.g., by inflammations which run their course in the neighborhood of chronic ulcers—and by specific infections, as the syphilitic and tuberculous.

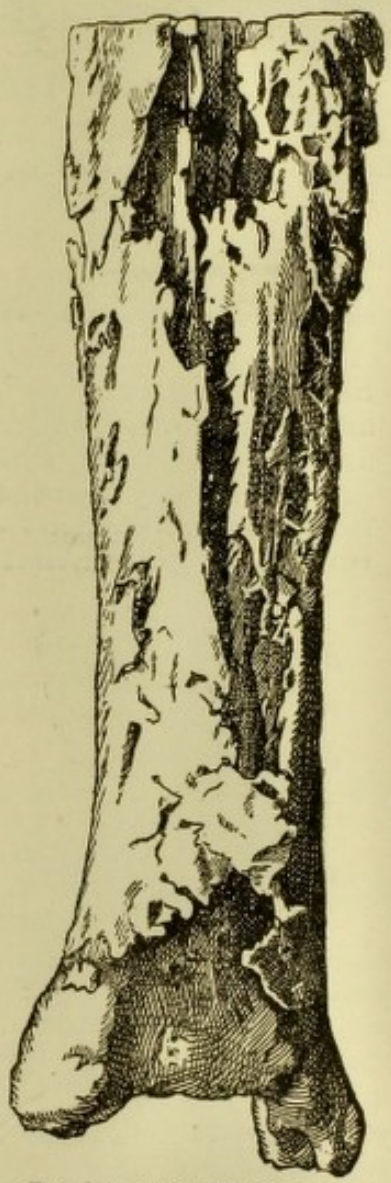


FIG. 213.—Periosteal hyperostosis of the tibia, at the base of a chronic ulcer of the leg. (Reduced to three-fifths natural size.)

Chronic catarrhs of mucous membranes are sometimes caused by specific infections (gonorrhœa, tuberculosis), sometimes by a non-specific injury (concretions, pathological changes in the contents of stomach and intestine), sometimes by continued disturbances of the circulation (congestions).

Chronic abscesses generally result from acute abscesses, and have the same etiology, but may also develop more gradually, and are then caused by special infections, generally tuberculosis or actinomycosis. They are usually limited externally by a connective-tissue membrane covered with granulations, and may increase in size partly by the secretion of pus from the abscess-wall, partly by the destruction of the wall and its neighborhood. Progressive enlargement toward the deep-lying parts leads to the formation of **burrowing or congestive abscesses.** Their increase in size is really always to be ascribed to the persistence of the infection. Perforation into neighboring tissues leads accordingly, also, to new infectious inflammations.

The tuberculous and actinomycotic forms of chronic abscess are distinguished from others partly by the peculiar quality of the pus, partly by a special construction of the abscess membrane (see Tuberculosis and Actinomycosis in Chapter IX.).

Chronic ulcers are generally caused by specific infections (tuberculosis, syphilis, glanders), but non-specific harmful factors also lead to chronic ulceration in tissue which is specially susceptible to such ulceration. Thus chronic congestions in the vascular system of the leg may interfere with the healing of ulcers caused by any mechanical influence that may have been exerted under the ordinary conditions of the leg. In the same way the peculiar qualities of the stomach-contents may prevent the healing of an ulcer of the stomach. When healing begins at the border of an ulcer, while the ulceration advances at other parts, the ulcer is termed *serpiginous*. Active growth of granulation tissue in

an ulcer leads to the formation of an *ulcus elevatum hypertrophicum;* dense, callous, gristly induration of the edge and base leads to the formation of an *ulcus callosum*, or *indolens*, or *atonicum*.

Chronic granulation growths (granulations) which persist as such a longer or shorter time, without undergoing conversion into connective

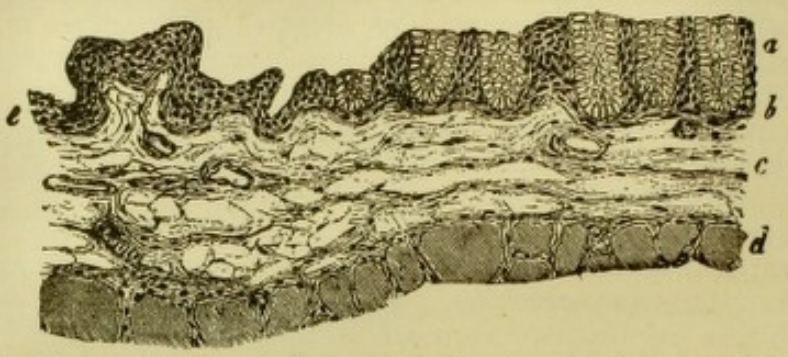


FIG. 214.—Transverse section through the mucosa and submucosa of an atrophic large intestine. (Alcohol; alum carmine.) *a*, Glandular layer reduced to one-half its height; *b*, muscularis mucosæ; c, submucosa; *d*, muscularis; *e*, mucous membrane entirely atrophied. Magnified 30 diameters.

tissue, reach, under various **specific infections,** conditions in which they are best known as *tuberculosis*, *syphilis*, *leprosy*, *glanders*, *rhinoscleroma*, and *actinomycosis*. Since the granulations, in these infections, often produce spongy growths and tumor-like formations, they are also called **fungous granulations** or **caro luxurians,** and **infectious granulation tumors** or **granulomata.** They show all the special peculiarities that

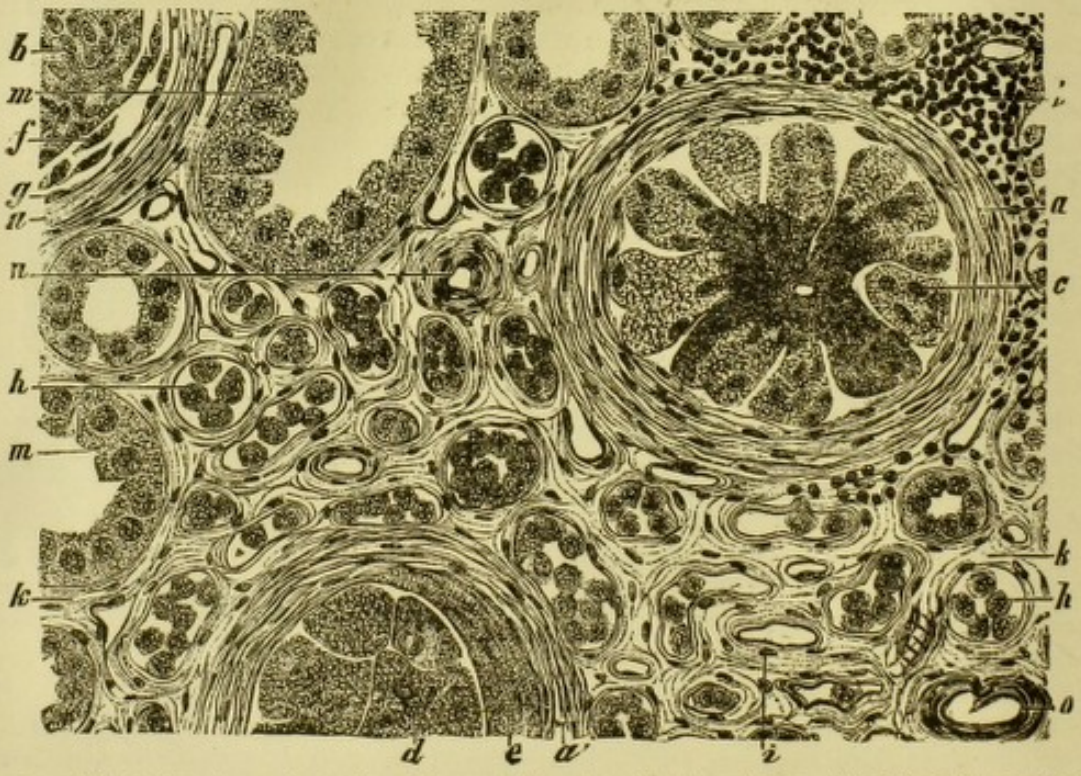


FIG. 215.—Induration and atrophy of the renal tissue in chronic nephritis. (Alcohol; alum carmine.) *a*, Thickened and fibrous Bowman's capsule; *b*, normal glomerular vessels; *c*, glomerulus whose vascular loops are partly impermeable and homogeneous, and its epithelium mostly lost; *d*, completely ruined glomerulus; *e*, homogeneous mass of coagulation studded with nuclei, and consisting of exudate and epithelium; *f*, desquamated glomerular epithelium; *g*, epithelium from the capsule; *h*, collapsed urinary tubule with atrophic epithelium; *i*, collapsed tubule without epithelium; *k*, hyperplastic connective-tissue stroma; *l*, collection of small cells; *m*, normal, somewhat dilated urinary tubule; *n*, afferent vessel; *o*, vein. Magnified 250 diameters.

enable one to recognize, from the structure, the development and life-history of the granulation formations, as well as their special etiology (cf. Chapter IX.). It should, however, be mentioned that the etiology of some granulomata that develop in the skin is still unknown.

Chronic inflammations, in which **atrophy of the specific tissue** is associated with **hypertrophy of the connective tissue,** are observed principally in the mucous membrane of the intestinal canal, and in the kidneys and liver.

In the **intestinal canal** the cause may reside both in specific causes (dysentery) and in non-specific irritations, which are set up by any abnormal property of the contents of the intestinal canal. The epithelial constituents either die, under manifestations of persistent desquamation, while the connective tissue remains, or they decay at the same time as the connective tissue on which they are situated undergoes necrosis and

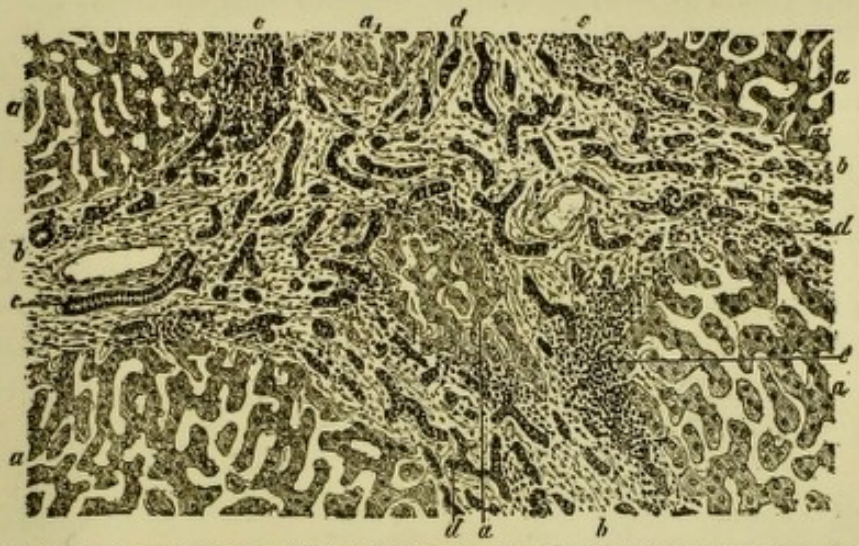


FIG. 216.—Connective-tissue hyperplasia and development of bile-ducts in chronic hepatitis. (Alcohol; hæmatoxylin.) *a*, a_1, Lobules of the liver; *b*, hyperplastic periportal connective tissue; *c*, old bile-ducts; *d*, newly formed bile-ducts; *e*, collection of small cells. Magnified 60 diameters.

destruction. The final result is a mucous membrane (Fig. 214) which contains either no glands (*e*) or only rudimentary ones (*a*).

In the **liver** and **kidneys** the chronic inflammations that lead to atrophy and induration, and whose results are called **cirrhosis of the liver** and **indurated contracted kidneys,** are hæmatogenous diseases, so far as they do not depend on disturbances in the domain of the excretory ducts (obstruction, formation of concretions), and are caused partly by *infections*, partly by *intoxications*. They begin either acutely or more insidiously, and are characterized by atrophy and degeneration of the glandular tissue (Fig. 215, *h*, *i*), by hypertrophy of the connective tissue (Fig. 215, *a*, *k*, and Fig. 216, *b*), by cellular infiltration, by the formation of granulations (Fig. 215, *l*, and Fig. 216, *e*), by obliteration of old vessels (Fig. 215, *c*, *d*,) and by the formation of new vessels. In the liver there is often also the formation of new bile-ducts (Fig. 216, *d*), which, however, for the greater part do not perform their function.

CHAPTER VII.

Tumors.

I. General Considerations.

§ 106. **A neoplasm,** or **spontaneous new growth,** or **tumor** in the narrower sense, is a new formation of tissue, not produced by infection, which has an atypical structure, serves no useful purpose in the organism, and to whose growth there is no definite characteristic termination. The outward appearance of a tumor is atypical no less than its internal structure, for a true tumor differs more or less in its make-up from that of a normal organ. If this difference is slight, the tumor closely resembles an hypertrophy of tissue. In certain instances this resemblance may be so close that one cannot say with certainty whether the new growth of tissue should be called a tumor or an hypertrophy.

Tumors may develop in every tissue of the body which is capable of growth. They arise from a **proliferation of the fixed cells of the part,** and with the process is associated the **formation of new blood-vessels.** Frequently also there is a *migration of leucocytes* into the tumor tissue,

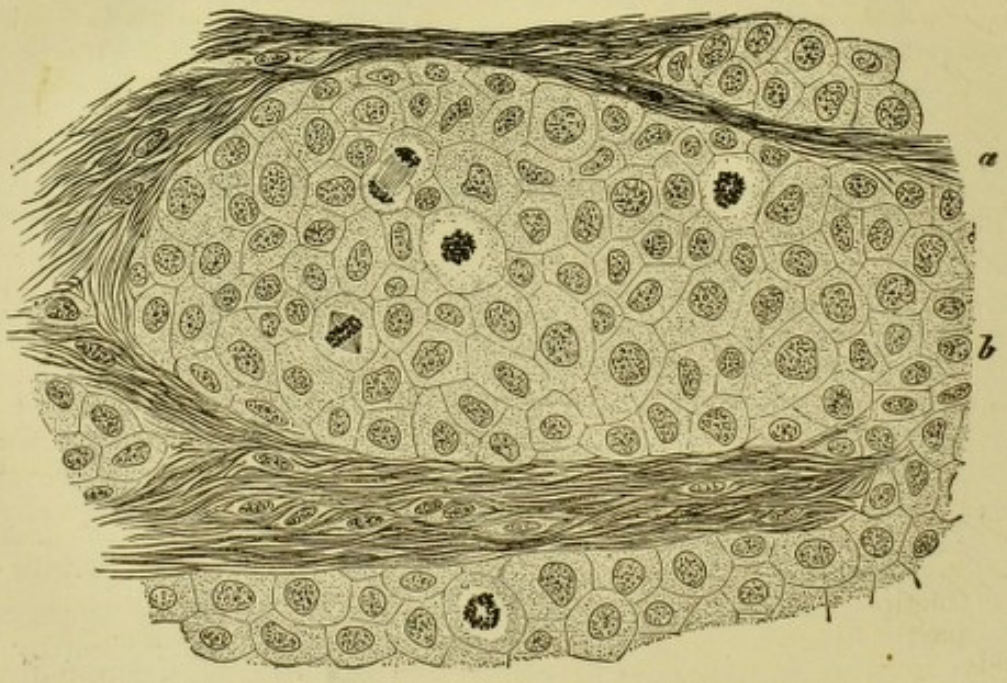


FIG. 217.—Tissue taken from a mammary carcinoma, with numerous figures which show nuclear subdivision in the different phases of the mitosis. (Staining with Flemming's safranin.) *a*, Stroma; *b*, epithelial plugs. Magnified 500 diameters.

but this is not an essential part of the process. The steps of cell-division and formation of new blood-vessels are the same as those described in § 83 and § 88—i.e., the cells divide by karyomitosis, and the new vessels are formed from sprouts which shoot out from the growing cells of the existing vessels. The mitotic forms are usually typical (Fig. 217, *b*), but there are also many atypical forms, asymmetrical divisions,

nuclear figures with abnormally large chromatin masses (the so-called giant mitoses), pluripolar mitoses, and finally examples of nuclear fragmentation (cf. § 84, Figs. 146 to 150) and of direct segmentation.

When developed a tumor is for the most part *sharply defined from the surrounding tissue*, but the opposite may be true. Moreover, *several organs in their entirety may be changed into a single tumor*, or *considerable portions of tissue which are not sharply marked off from their surrounding tissues may take on the character of a tumor*. By the degeneration of masses of tumor tissue, *ulcers* frequently arise.

The difference in structure between tumors and physiological tissue is usually evident to the naked eye; but there are also tumors which so resemble the part from which they spring that the difference is to be made out only by the most exact examination.

Tumors that have well-defined boundaries are generally nodular (Fig. 218, *d*; Fig. 219, *d*, *e*; Fig. 220, *a*); and the size of the nodules varies, according to the character of the tumor and the stage of development at the time of examination, from the smallest visible speck to a mass of from twenty to sixty pounds or more. If nodular tumors grow on the surface of an organ they often take on the form of a sponge (Fig. 218, *d*) or of a polyp, and are named accordingly *fungous or polypoid tumors*. If a new growth develops on the surface of the mucous membrane or the skin, and the papillæ there present divide or new papillæ are developed, we have *warty, verrucose, or papillary tumors, or papillomata*. A further development of the papillary structure gives a *dendritic or cauliflower mass*.

Tumors usually develop from small beginnings. It is a comparatively rare thing for one to develop from a number of centres scattered diffusely throughout an entire organ. At one time their growth may be quite rapid, while at another it advances slowly and with occasional periods of quiescence. In some instances a tumor may remain perfectly quiet and unchanged for a period of several years, and then suddenly it may take on an active growth.

The **structure of a tumor** *is determined by the tissue from which it grows*; and although true tumors always show an *atypical character*, yet they also possess certain of the features of their parent-tissues.

Tumors may be divided into three groups according to their structure and their genesis. The three are, *a connective-tissue group, an epithelial group*, and finally a group containing *teratoid tumors* and *cysts*. It should be remembered, however, that many forms of tumor may be classified as belonging at the same time to two or even to three groups, according to the point of view which is adopted.

The **connective-tissue tumors**, which are often called *histoid tumors*, are made up of tissues which sometimes resemble, in their structure, the connective tissue of an adult, and sometimes that of the mesoderm; and, as a matter of fact, they may take their origin from mesodermal connective tissue. Usually the tumors which spring from the component parts of the nervous system—from the cells of the glia, as well as from those of the ganglia—are classed in this group; since in their structure they come much closer to the connective-tissue than they do to the epithelial tumors.

The differences in the types of connective-tissue tumors are due to differences in their framework, in part also to differences in the cells. If a tumor is rich in cells while its framework is poorly developed, it is soft and is reckoned among the *sarcomata*. Very soft forms are spoken

of as *medullary* or *fungous*. *Mixed tumors* contain several different kinds of connective tissue.

Epithelial tumors are composed of cells which are the progeny of epithelial cells or of gland-cells, and also of connective tissue which is provided with blood-vessels; and the two are arranged in such a manner that the connective-tissue forms a support or network, in the meshes of which the cells resulting from the proliferation of the epithelial cells or the gland-cells are grouped in a special manner. Inasmuch as this arrangement of the tissues gives to these tumors a structure which reminds one of that of a gland, they are often spoken of as *organoid tumors*—a designation which places them in contrast with the histoid connective-tissue tumors. Attention should be called, however, to the fact that certain tumors which are reckoned among the connective-tissue tumors (viz., the sarcomata), possess an organoid structure.

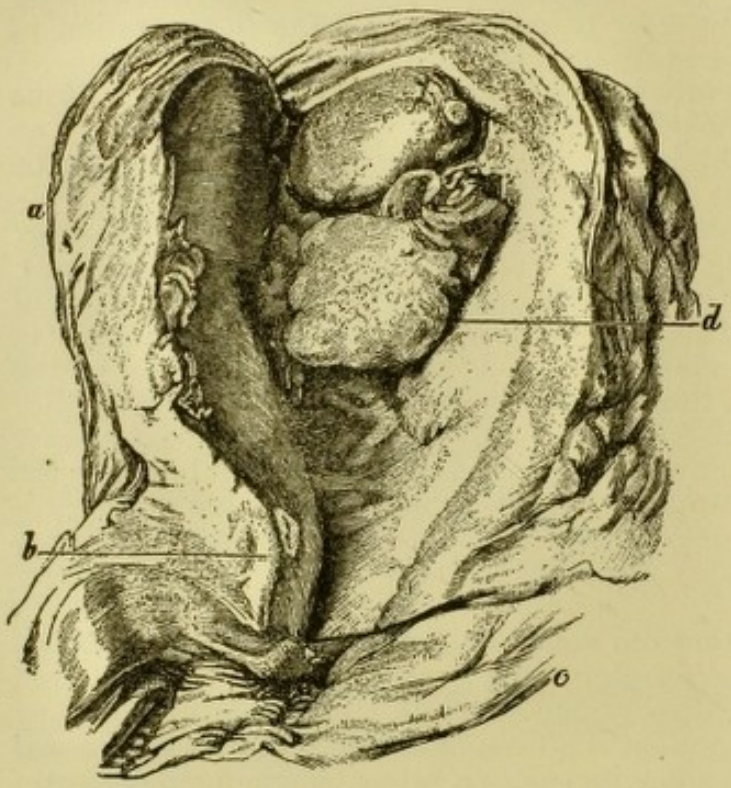


FIG. 218.—Spongy carcinoma of the mucous membrane of the posterior wall of the cavity of the uterus. *a*, Body of the uterus; *b*, cervix; *c*, vagina; *d*, tumor. (Two-thirds life size.)

The cells which give the epithelial tumors their especial character spring from either the ectoderm or the entoderm, or from the glands derived from them; or it may be from the mesodermal epithelial layer of the pericardial or pleuro-peritoneal cavities, or from the glands which are developed from this layer—namely, the kidneys, suprarenal capsules, and genital glands. Such tumors often show more or less distinctly the especial characteristics of the parent tissue from which they are derived.

Soft epithelial tumors which are rich in cells are also called *medullary cancers*.

Teratoid tumors and cysts form a group whose especial characteristic is the fact that they may contain the most varying kinds of tissue, derived from all three layers of the embryo; and also the fact that the tumors come in places where the tissue which they contain is not normally found. Tumors, therefore, which according to their structure might be counted in one of the other groups, may be considered as teratomata on account of their situation. The class is also made to include formations which, according to their structure, origin, and physiological relations, ought not to be considered as tumors at all.

Tumors usually **develop singly**; but it also happens that in a certain system of tissue, simultaneously or one after the other, there will appear a **great number of tumors** of the same sort, so that we must

assume that the conditions requisite for the development of these tumors are present in the different parts of the system where they appear. Sometimes it happens that, at the same time, there appear in different parts of the body *two entirely different varieties of tumor*, which stand in no relation to each other, and whose simultaneous appearance is purely accidental.

The exact determination of what should be included under the term tumor is scarcely a possible thing, and consequently the word is used by different authors differently. I hold it advisable, and warranted by the characteristics of the life of the new growths which we are about to consider, to exclude from tumors all hyperplastic swellings and all retention cysts which are purely retention cysts and show no independent tissue-development. And furthermore, according to my view, all increase of tissue dependent upon the presence of parasites or upon infection is to be excluded from the domain of tumors; and so also should the infectious granulation growths which occur in connection with tuberculosis, syphilis, leprosy, etc., be excluded. If it should be proved—which so far has not yet been done—that some of the new growths now reckoned among epithelial tumors are caused by infection, then we must exclude these also from the category of true tumors.

All authors do not give the same prominence to the atypical structure of tumors as is here insisted upon. This is especially the case with those tumors which are similar to the tissue from which they spring, and which may therefore be called homoöplastic tumors. But, even in these tumors (chondromata, osteomata, fibromata, etc.), there are variations from the normal in microscopical and in coarse structure, as well as in outward appearance; and, besides, the proliferations due to infective inflammation may greatly resemble tumors in their structure. It is therefore not always easy to determine whether a new growth is a tumor or not.

Tumors are in no sense useful to the organism, as hypertrophies may be, and a tumor does not have the special function of the tissue from which it originates. Hence they can in no way be looked upon as serviceable new formations of tissue. In certain tumors the **processes of secretion** may go on. Thus epithelial tumors may manufacture mucus or horny or colloid material (thyroid tumors), or biliary pigments (hepatic tumors), and indeed these processes may take place in metastatic nodules; but from these facts we merely conclude that cells in tumors which do not differ too decidedly from the parent tissue may retain their functional activities in a certain degree from generation to generation. The inference that the organism has been enriched by new serviceable tissue, similar to the tissue produced by hypertrophy from work, is wholly without foundation; for the products are generally of no use to the body, or if it is conceivable that they may be used, as in the case of colloid material or bile, yet their value is certainly far below that of the normal material.

The tumors which spring from the mesodermal epithelium of the serous membranes or of the glands which originate from this epithelium, are also reckoned as epithelial tumors. This is justified by the fact that the tumors which originate from this epithelium are in structure and in clinical characteristics very like those which spring from the ectoderm and entoderm. I have considered the question whether it would not be advisable (as Hansemann has proposed) to reckon among the epithelial tumors (i.e., among the adenomata and carcinomata) such tumors as have a network of connective tissue whose meshes are filled with proliferated endothelial cells from blood- or lymph-vessels. In favor of this plan may be mentioned the similarity of structure, and also the fact that the endothelium of the vessels is frequently referred to as mesodermal epithelium. The following facts, on the other hand, militate against the plan: first, that the term endothelioma has been generally accepted; second, that the behavior of the proliferated endothelium of the blood- and lymph-vessels is quite different from that of epithelium; and, finally, that in many tumors it is impossible to tell the products of the growth of the cells of the blood- or lymph-vessels, from those of the connective-tissue cells.

When the tumors of the central nervous system (gliomata and ganglionic neurogliomata) are reckoned as connective-tissue tumors, a mistake is committed, inasmuch as these ganglion and glia cells do not spring from the mesoderm but from the ectoderm, and they represent modified ectodermal epithelium. Nevertheless, the character of the central nervous system, and of the tumors which arise from it, is such that it is far better to classify them with the connective-tissue tumors than with the epithelial ones.

§ 107. The **etiology of tumors** is by no means uniform, and often cannot be determined with certainty. But in most cases the conditions under

which the new growth appeared can be given, and we may therefore, according to their origin, establish several groups of tumors.

One group of tumors arises from some localized predisposition of the tissues of a distinctly congenital nature, and we may therefore speak of them as *local malformations of tissue*. They either develop during intra-uterine life, and are therefore present at birth, or they develop during

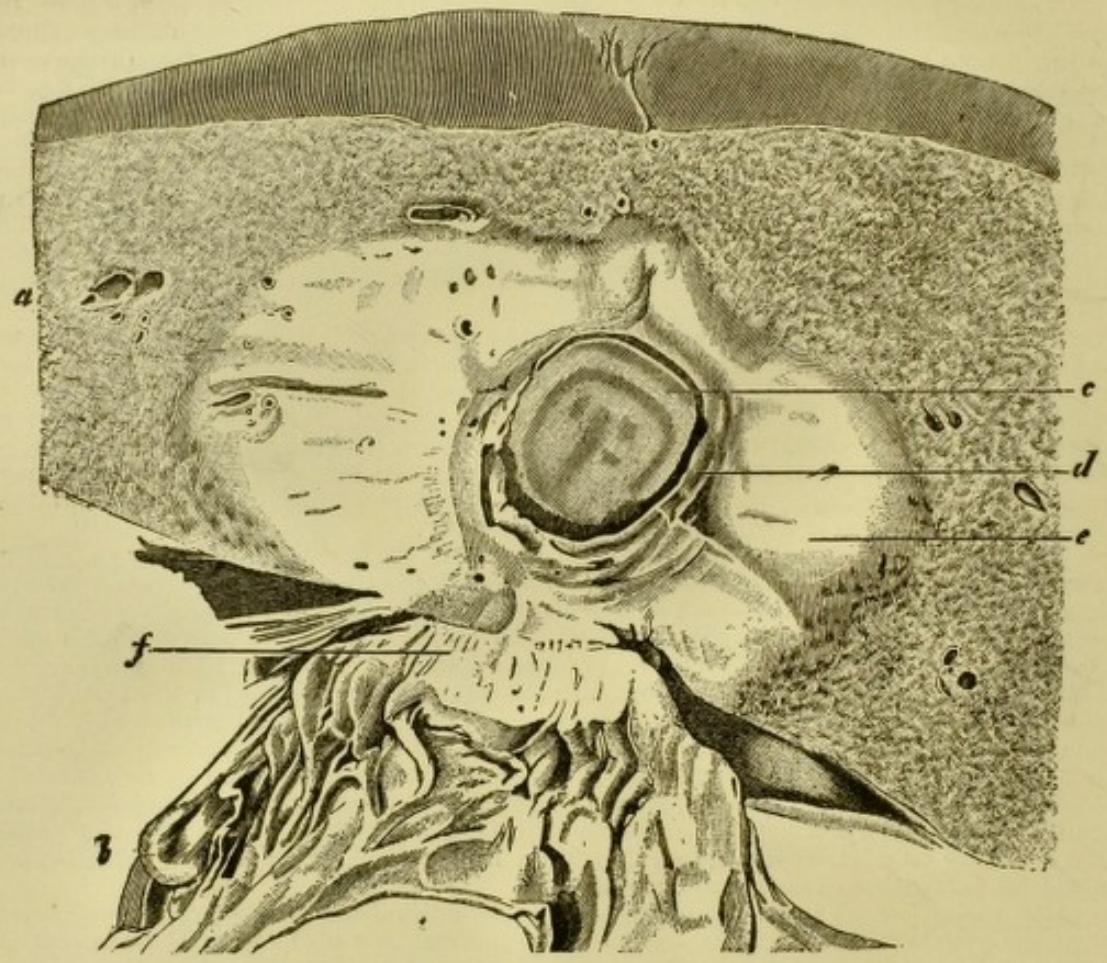


FIG. 219.—Primary cancer of the gall-bladder with an impacted stone in this cavity. Coronal section through the gall-bladder and liver. *a*, Liver; *b*, duodenum; *c*, gall-stone; *d*, wall of the gall-bladder infiltrated with cancer; *e*, cancerous infiltration in the neighboring liver-tissue; *f*, portion of duodenum which is infiltrated with cancer and adherent to the rest of the new growth. (Life size.)

extra-uterine life, in the period of childhood or later; in which case traumatism not infrequently furnishes the immediate occasion for the beginning of the development of the tumors.

To this group belong the osteomata, chondromata, angiomata, gliomata, fibromata (nerve- and skin-fibromata), sarcomata, and adenomata. Furthermore, many teratoid tumors and cysts must also be placed in this group, inasmuch as they will be found, on closer examination, to represent the following conditions: residua of fœtal formations; a transposition or a monogerminal implantation of the germs of certain tissues; an implantation of rudimentary portions of a twin embryo; a bigerminal implantation; and probably also pathological proliferations of male or female sexual cells.

A second group is developed after traumatic injuries of the tissues, and it is reckoned that such a traumatic origin can be definitely determined in from seven to fourteen per cent. of the cases. The cause may be a

single injury, as a stab or a blow or a crushing or a fracture; or it may be a repeated mechanical irritation, like that due to rubbing, scratching, etc.

In a third group of cases the development of the new growth follows an inflammation, especially if accompanied by ulceration and the formation of a scar. This inflammation and ulceration may or may not owe their origin to some specific injurious influence. Cancer of the gall-bladder, for example (Fig. 219, *d*, *e*), occurs almost invariably in gall-bladders which contained gall-stones, and which therefore have been the seat of chronic inflammation. Cancer of the stomach may form in the edge of an ulcer or in its scar-tissue after it has healed. Sometimes cancer develops in the skin, or in the mucous membrane of the pharynx or larynx, in the base of a tuberculous or syphilitic granuloma, or in the scar which follows one of these processes.

The tumors of a fourth group seem to owe their development to the unequal atrophy of the elements which make up a tissue, as a result of which certain opposing forces are removed or lessened. This is especially true of epithelial growths (cancers), developed either in advanced age or in organs which, having just passed through a period of increased functional activity, are undergoing atrophy. In this way we can explain the development of cancer of the skin, for example, by saying that the connective tissue of the skin is undergoing a certain atrophy, which is connected with relaxation of its strata, while the epithelium is still possessed of its full power of reproduction.

Cohnheim formerly advanced the theory that all true tumors grew from distinct tumor-tissues, which were only persisting centres of embryonic tissue. This view receives no support, either from the results of clinical observation or from those of anatomical investigation of the tissues.

That the etiology of tumors is not always the same is shown by the variety of the conditions under which they arise.

It is hard to say what is the nature of the influence which causes the cells to produce an atypical form of tissue. In this connection one is likely to think, at first, of the causes which underlie hypertrophy and regeneration of tissue. There are, on the one hand, special congenital predisposing influences, or the various irritations which stimulate the formative activity of the cells; and, on the other, those influences which tend to lessen or even to remove the hindrances to growth. But it still remains a puzzle why tissues which are not typical should be produced, and should so participate in the development of the organism that they can be considered as playing a useful part. In their effort to explain this phenomenon, which is associated with an increase in the capacity for living and for multiplying, even under pathological conditions (including that in which cells gain an entrance into and are transported through the lymph- and blood-channels), many authors have been disposed to find the cause in the presence of parasites. But, according to our present knowledge, we are by no means justified in attributing the development of true tumors, of autonomous new growths, to the influence of parasites. The development and life-history of tumors speak against this hypothesis, and so does especially the formation of metastases; for there can be no doubt that these metastatic nodules are due to the proliferation of living tumor cells which have been carried in the lymph or blood stream.

Ribbert is of the opinion that the cause of the pathological proliferation of tissue which leads to the formation of a tumor is the separation of cells or groups of cells from their normal connection with the rest of the body; this separation taking place either before birth (during some disturbance of intra-uterine growth) or afterward as the result of external influences. Nevertheless, such transplantations or separations of cell-masses take place very often both in uterine life and afterward (e.g., after the infliction of a wound or as the result of the formation of an ulcer; in cicatrices; in infectious granulation-growths) without any subsequent development of a tumor. At best, *such transplantations of tissue constitute only one of the predisposing causes*, and consequently some additional factor will still be necessary if the atypical progressive growth of tissue —that is, the development of a tumor—is to be started. Besides, the development of a tumor is in no wise dependent on a transplantation of tissue. It can just as well start in

normally placed cells—a statement which can be directly proved in the case of epithelial tumors.

Our knowledge of the cause of tumors up to the present time may be thus summed up: Hereditary and acquired conditions of certain cells and cell-groups, which express themselves in a tendency to increased formative activity and to the production of atypical tissue, lead to the formation of tumors. This growth may be prepared for, favored, or started by the transplantation of cells or groups of cells; but it is often facilitated by changes that take place in the neighborhood of the cells concerned. No general reliable scheme can be given for the development of tumors. The relations differ, not merely according to the particular type of tumor, but also among individual cases belonging to the same type. It must not be forgotten that the formations which we class together as tumors have a very different significance, and many of them ought rather to be classed under other headings (malformations).

§ 108. **When a tumor has arisen in any tissue it continues to grow independently.** The tumor draws upon the vessels of the neighboring tissue for its nutrition, or it may grow independently by division of its

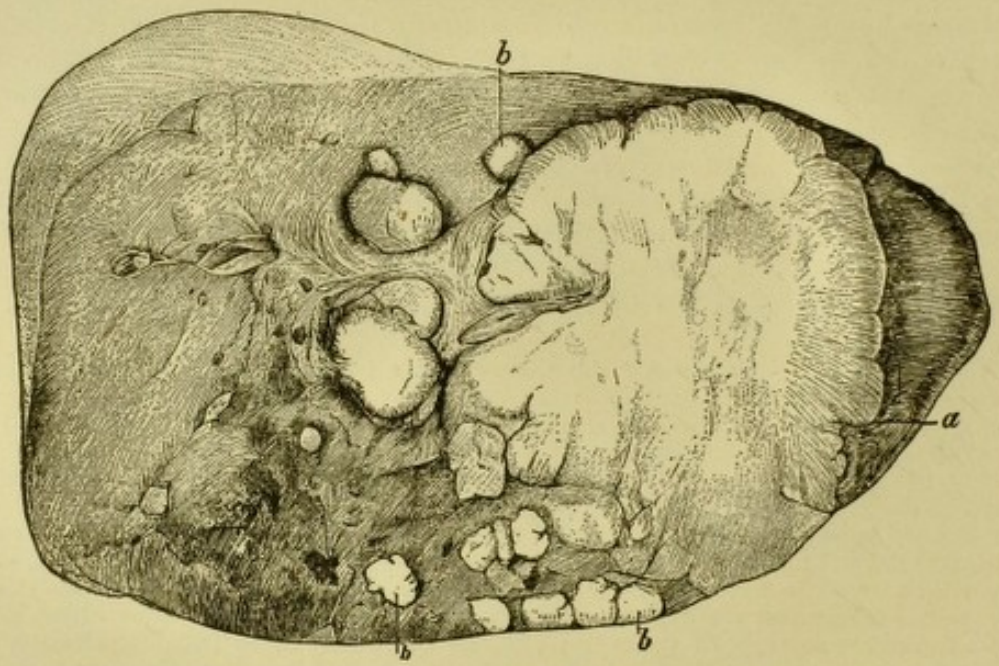


FIG. 220.—Section through a primary carcinoma of the liver, *a*, with multiple metastases, *b*, in the liver-substance. (Three-sevenths life size.)

own cells. In many cases the tumor increases only by **interstitial expansive growth,** and the neighboring tissues are simply displaced and pressed together. In other cases the tumor **grows by infiltration**, and *forces its way into the intercellular spaces of the surrounding tissues*, so that new territories are thus brought under the influence of the tumor. By this process a part of the cells of the invaded tissue are often stimulated to proliferation, so that an increase of the tumor takes place by an *appositional growth*, in which the cells both of the tumor and of the surrounding tissue take part.

The characteristic feature of **growth by infiltration** consists in the *involvement, in the disease, of the tissues or organs which bound the original site of the tumor.* Moreover, *the tissue of organs which are simply adjacent to the organ originally affected may become involved by contiguity* (Fig. 219, *e*, *f*). If tumor-cells find an entrance into any of the larger cavities of the body, they may spread on its surfaces and lead to the development of tumors.

If, in the process of infiltrative growth, **a tumor breaks into a**

lymph-vessel or a blood-vessel—something which always happens in tumors called carcinomata and sarcomata—and if *cells of the tumors possessed of the power of development* escape into the vessel, **tumor metas-**

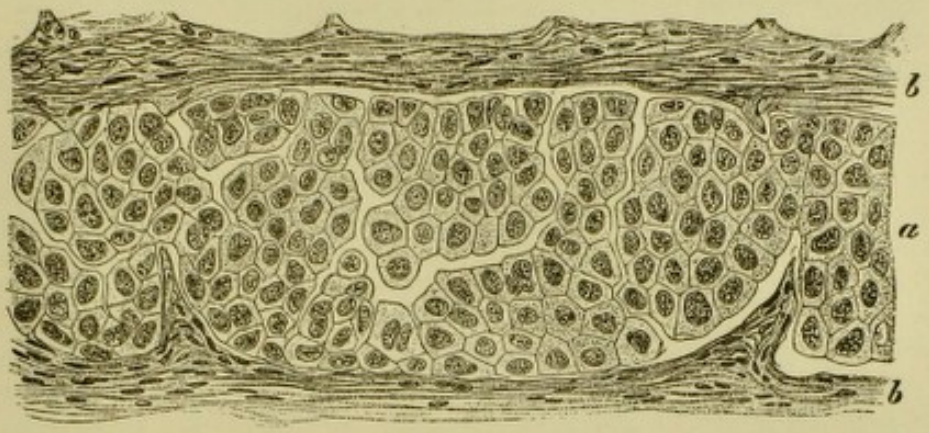


FIG. 221.—Filling of a periglandular lymph-vessel (in the region of the axilla) with cancer cells from a carcinoma of the mammary gland. (Müller's fluid; hæmatoxylin.) *a*, Cancer cells; *b*, wall of the lymph-vessel. Magnified 300 diameters.

tases are likely to follow; that is, there is likely to be a development of disconnected **daughter-tumors.** These secondary tumors may develop in the organ in which the primary tumor has its seat (Fig. 220, *b*), but

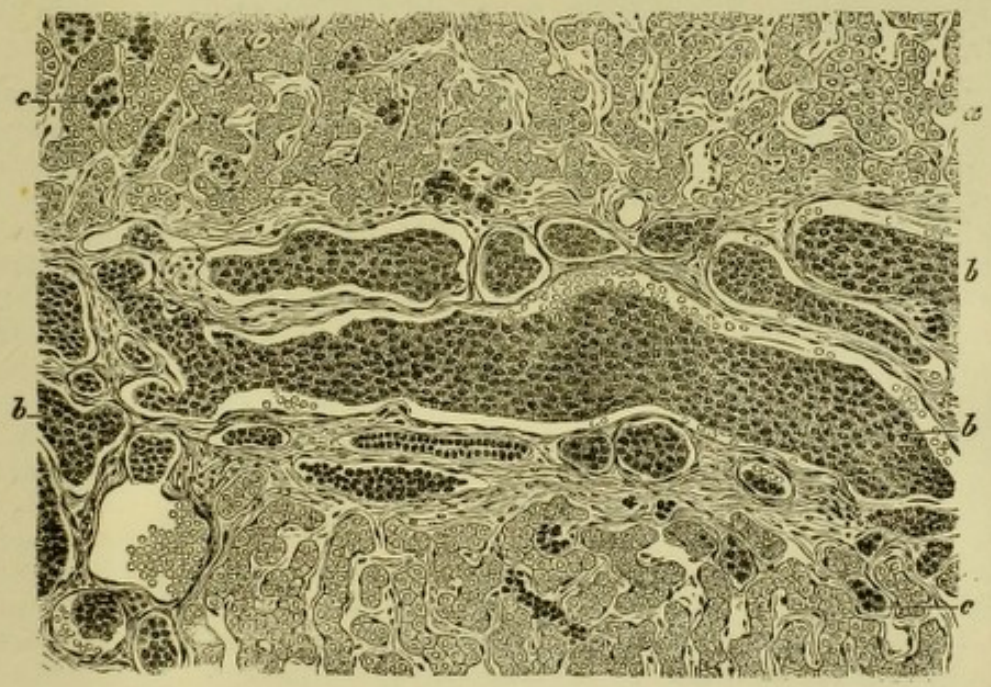


FIG. 222.—Metastatic development of a carcinoma in the branches of the vena portæ and in the hepatic capillary vessels. (Müller's fluid; hæmatoxylin; eosin.) *a*, Tissue of the liver; *b*, plugs of cancer cells in the vena portæ; *c*, cancer cells in the capillaries. Magnified 100 diameters.

they usually develop rapidly in other organs as well: in the case of the lymph-vessels in the lymph-glands, and in the case of the blood-vessels in those organs to which the living cells are carried by the blood (cf. § 18).

The secondary tumors are developed directly from the transported cells. In **metastasis by the lymph-channels** the lymph-vessels are first filled with tumor-cells which have developed from the transported cells

(Fig. 221, *a*). The surrounding tissue joins in this growth, new blood-vessels are formed, and in this way a tumor develops, usually in the form of smaller and larger *nodules;* but it may also happen that *the lymph-channels are more evenly distended by the growth* (Fig. 221, *a*),

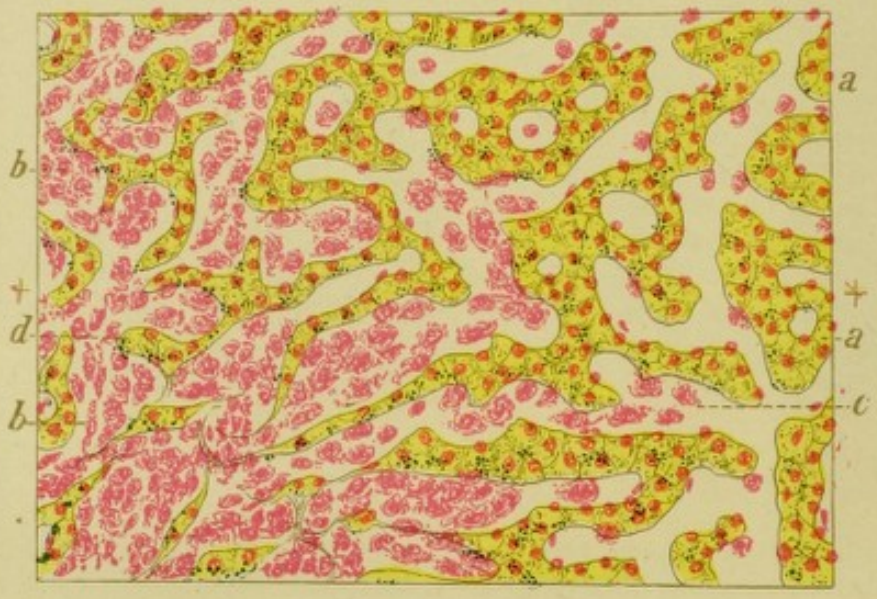


FIG. 223.—Metastatic sarcoma of the liver following primary sarcoma of the parotid. (Flemming's mixture; safranin; picric acid.) *a*, Broad framework of liver-cells; *b*, sarcomatous tissue developed in the vessels; *c*, single tumor-cells in the liver-capillaries; *d*, framework of liver-cells which have undergone atrophy and fatty degeneration. Magnified 150 diameters.

without any real formation of nodules; or at most little swellings occur in the course of the lymph-vessels. If the metastasis takes place in *lymph-glands*, these swell up into nodules of smaller or larger size, and the tumor-tissue gradually takes the place of the gland-tissue.

When the *metastasis takes place through the blood-vessels* the first development begins with the tumor-cells which form the embolus in artery, capillary, or vein; and under certain conditions the vessels (Fig. 222, *b*, *c*, and Fig. 223, *b*, *c*) may be filled throughout a considerable extent by the growing tumor-cells. The tissue in which the tumor embolus develops remains passive at first, and its specific components—e.g., gland-cells (Fig. 223, *d*) and muscle-cells—undergo atrophy and finally disappear. Later, the blood-vessels and connective tissue take part in building up the secondary tumor.

In its further development the secondary nodule becomes sharply differentiated from its surroundings and increases in bulk. But often enough, at least in places, growth by infiltration persists, and under proper conditions widespread diffuse tumors develop—as, for instance, in the liver (Fig. 223) and in bone-marrow.

The number of metastases taking place by lymph- or blood-channels varies greatly in different cases, and may be limited to one organ or may affect many. In rare cases the seeds of the original tumor may spread through almost the whole body, so that larger and smaller nodules appear in quick succession in the most diverse parts—in gland, muscles, skin, etc. This is possible when a tumor situated in the lung or in a bronchial gland breaks into a pulmonary vein.

If a bit of tumor capable of forming metastases is transplanted from one animal to another of the same species, it sometimes happens that it will develop in the second animal. We may therefore have such a

thing as *a metastasis from one animal to another*. In a similar way we may have, in operations upon man, transplantation of bits of tumor from one part of the body to another, and these may continue their growth in the new situation.

Side by side with the progressive development of tumors we find very often indeed **retrogressive changes**; and especially in rapidly growing cellular tumors, which increase by infiltrating the surrounding tissues, we may find, to a marked degree, fatty or myxomatous degeneration, pigmentation, necrobiotic changes, and hemorrhagic infarction, so that the *tissue often sloughs completely*. This rapid breaking down of the tissue is due in part to the fact that in carcinomata the proliferation of the epithelium advances into the blood-vessels, throughout a wide area, and thus causes them to become plugged. The destruction of the cells in nodular tumors, in case it is followed by a resorption of the products of degeneration, may lead to *shrinking and the formation of cicatricial contractions*. Very often, too, we find *cysts containing the products of degeneration*, and even *ulcers;* and in the case of carcinomata of the mucous membranes, the parts of the tumor which grow up above the surface are apt eventually to disintegrate and disappear. Retrogressive changes usually do not occur in slowly growing dense tumors.

Necrosis and disintegration of the tumor-tissues seldom terminate in a **cure**. This is most likely to happen if a polypoid new-growth becomes totally necrotic (for example, as a result of twisting of its peduncle) and sloughs away. Usually in tumors which have a tendency to undergo retrogressive changes and to disintegrate, while the older portions are falling to pieces, the tumor is constantly growing at the periphery and constantly involving new tissues.

If a tumor is extirpated, recovery may take place; but to insure this all parts of the tumor must be removed or destroyed. This is most readily accomplished in the case of slow-growing tumors which grow by expansion and have sharply defined borders. In tumors which grow by infiltration it is very difficult to define the limit of the tumor, which often extends far beyond the point where any change in the tissue is apparent. Consequently, in such cases, sooner or later a **recurrence** is apt to take place in the operation scar, the recurrence growing from portions of the original tumor which were not removed (Fig. 224, *a*). Such recurrences behave exactly like the original tumor, and can also form metastases (Fig. 224, *c*).

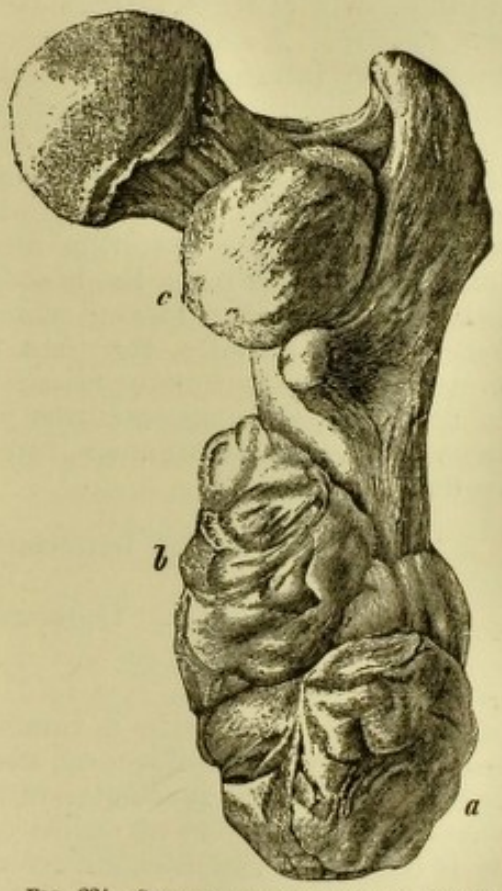


FIG. 224.—Sarcoma recurrent in the stump of a femur after amputation. *a*. Fungous tumor springing from the bone-marrow; *b*, *c*, periosteal nodules. (One-half life size.)

Tumors are usually classed as **benign** and **malignant**, according to their clinical and anatomical characteristics. The *benign tumors*, as a

rule, *grow slowly by expansion, and do not form metastases.* The *malignant tumors*, on the other hand, *grow rapidly and by infiltration, undergo degenerative changes more readily*, and *give rise to metastases.* The **malignant tumors**, generally speaking, are the carcinomata and sarcomata. It must be remembered, though, that the malignancy of a tumor depends on its location as well as on its nature. Thus a benign growth can cause malignant symptoms if its presence interferes with the functions of vital organs. So, for example, every tumor of the brain or of its membranes becomes a dangerous affection at the moment when it interferes with the functions of the brain; and such benign tumors as fibromata of the uterus, for example, as soon as they grow large enough to press upon and displace other organs, must be looked upon as destructive growths.

When a tumor has existed for a certain period there often is produced an appreciable falling-off of nutrition in the body—a marasmus, commonly called the **cachexia of tumors.** This occurs for the most part in connection with the malignant growths called cancer and sarcoma, and may be caused, at least in part, by the great demands which the rapid growth of these tumors and their metastases make upon the nutritive supply. A still more important cause may lie in the fact that the tumor may interfere with the taking in of nutritive material. For example, in carcinoma of the œsophagus, stomach, or intestine, the function of the affected organ is profoundly interfered with, and the assimilation of food may be almost completely prevented. It must be further observed that, by the degeneration of the tumor and the continuous secretion from the resulting ulcers, often a great deal of albuminous material escapes from the body; while from the putrefactive processes substances are often formed which, when absorbed, act injuriously upon the system. Finally, the pain which is often experienced in a tumor may rob the unfortunate patient of his sleep. Whether the tumor itself, in certain cases, manufactures substances which are poisonous to the body in general is unknown, but the possibility of such a thing cannot be denied.

II. The Different Varieties of Tumors.

1. Connective-Tissue Tumors.

(a) Fibroma.

§ 109. A **fibroma** is a tumor composed of *connective tissue.* It is usually in the form of a *node*, sharply differentiated from the surrounding tissue; usually it affects only one part of an organ, but in exceptional cases it may convert an entire organ into a single great mass of tumor. If it occurs on the free surface of a mucous membrane or the skin, it often forms a *papilloma.*

The consistence of the fibroma depends on the character of the connective tissue. It is often hard and tough, creaks under the knife (*desmoid tumor*), and presents, when cut, a white tissue much like tendon; and in other cases it is soft and flaccid, presents a grayish-white cut surface, and is somewhat translucent. In still other cases the bands of connective tissue are white and glistening, yet the tumor as a whole is more open in its structure and is correspondingly flaccid.

There are all gradations between these hard and soft extremes, and even in one tumor different parts may possess different characteristics.

The hard kinds, as seen through the microscope, appear to be chiefly composed of thick bundles of coarse fibres (Fig. 225, *a*, *b*), among which are sprinkled a larger or smaller number of cells. In those kinds which are less hard the bundles of fibres are correspondingly more delicate (Fig. 226). If obstruction of the circulation and œdema supervene, the bundles of fibres (Fig. 226, *b*) may be pressed apart, and the cells (*c*) which lie upon them may become swollen (*d*). By reason of these changes the tissue is rendered softer.

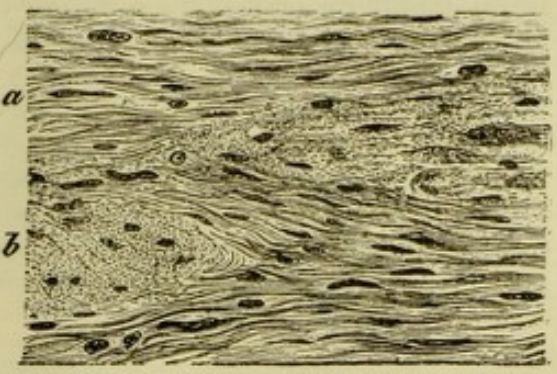


FIG. 225.—Dense fibroma of the lobule of the ear. (Alcohol; hæmatoxylin.) *a*, Longitudinal section; *b*, transverse section, of bundles of fibres. Magnified 400 diameters.

The softer kinds of fibroma, which present a translucent, gray-white surface on incision, are usually richer in cells; so that it is possible, by tearing a bit of the tissue to pieces, to isolate spindle-shaped cells (nuclei with tails). The intervening tissue is relatively less; the fibrillæ are more tender and are arranged in narrower bundles. Sections through such tumors, when stained, appear full of nuclei (Fig. 227, *b*).

The fibromata develop from actively growing cells of the connective tissue, and usually it is possible to find places which are richer in cells than the mass of the tissue, and in which the cells appear not only as small spindles, but also as round cells, or as short, thick spindles, or even as star-shaped cells. The change from this new-formed tissue rich in cells to mature connective tissue is brought about in the same way as was described in the chapter relating to Hyperplasia of Connective Tissue.

Fibromata may occur in any tissue which contains connective tissue in any form. They are very common, for example, in the nerves, skin, periosteum, fasciæ, uterus, and nasal mucous membrane; they are less common in the ovary, mamma, intestinal tract, etc. In the mamma the fibromata develop especially around the canaliculi, so that the latter are found to be surrounded by connective tissue rich in cells (Fig. 227, *b*).

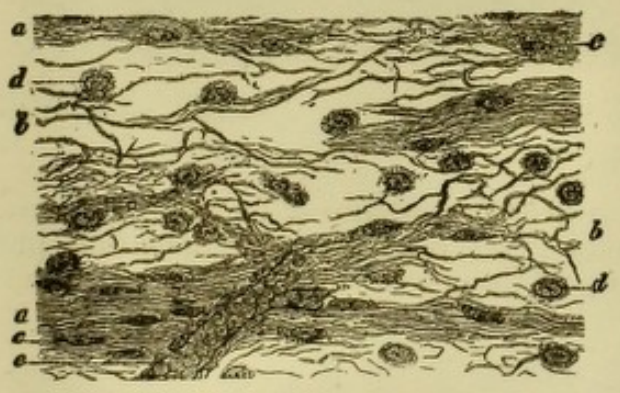


FIG. 226.—Section through an œdematous fibroma of the uterus. (Osmic acid; glycerin.) The bundles of connective-tissue fibres, which lie close together at *a*, are pressed apart at *b* by the fluid; *c*, spindle-shaped cells; *d*, swollen round cells; *e*, blood-vessel. Magnified about 200 diameters.

Fibromata do not form metastases, but a number of them often occur together, especially along the course of nerves and in the skin (see under Neurofibroma, § 118). Moreover, it is not uncommon to see several centres of growth in a single tumor; that is, the mass of the tumor is made up of several nodules or bands which are separated from one another by ordinary connective tissue (Fig. 227, *b*). Fibromata are dangerous only by reason of their size or their position.

Fibromata may undergo fatty degeneration, or may soften and disintegrate, so that cavities are formed inside of them. These may also break through, and so give rise to ulcers. The blood-supply varies greatly, and is sometimes abundant, sometimes scanty. Sometimes the blood-vessels are dilated, so that throughout the tissue there seem to be large canals or clefts, from which blood escapes when the tumor is examined in a fresh state. Dilated lymph-channels are also sometimes observed.

If the basic substance of a fibroma is strongly saturated with fluid, and the fibrillæ are pressed apart, we have an *œdematous fibroma*, closely resembling the umbilical cord in appearance.

The term *keloid* is applied to a tumor of the skin which, in its fully developed state, is composed of tough fibrous tissue; and which, furthermore, presents sometimes a knobbed and hard appearance, at other times

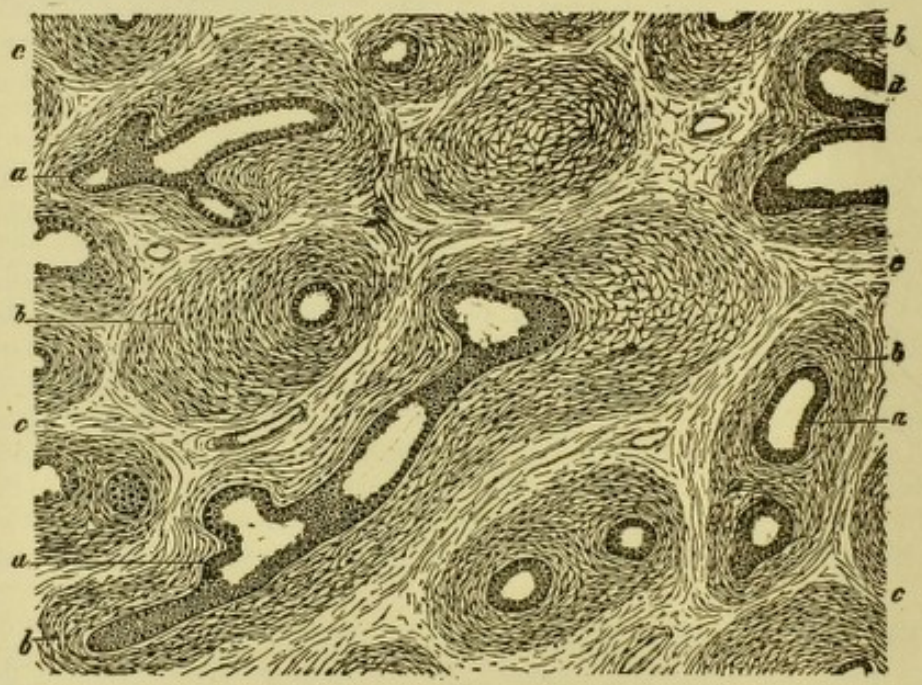


FIG. 227.—Pericanalicular fibroma of breast. (Müller's fluid; alum carmine; eosin.) *a*, Tubules of gland; *b*, pericanalicular connective tissue, newly formed and full of cells; *c*, connective tissue with few cells. Magnified 40 diameters.

that of a star-shaped growth or a growth made up of bands and ridges. It commonly develops as a sequel to some injury or inflammation, but it may also develop independently of these processes.

(b) Myxoma.

§ 110. A **myxoma** is a tumor consisting chiefly of *mucous tissue*, and is made up of cells and a liquid or gelatinous intercellular substance. The cells are for the most part of irregular shape, and are provided with processes of varying length (Fig. 228) which anastomose with one another (Fig. 229, *a*). The tissue is markedly translucent, soft, and shows plainly its blood-vessels when they are filled with blood. Gelatinous masses or a tenacious fluid, both of which swell up in water, may be obtained from the cut surface.

No tumor is ever completely made up of myxomatous tissue; it is

found usually in combination with other kinds of tumor-tissue, especially with connective tissue, fat, cartilage, and sarcomatous tissue. For this reason the tumors are called **fibromyxomata, lipomyxomata** (Fig. 231), **chondromyxomata** (Fig. 234, *c*), and **myxosarcomata** (Fig. 229).

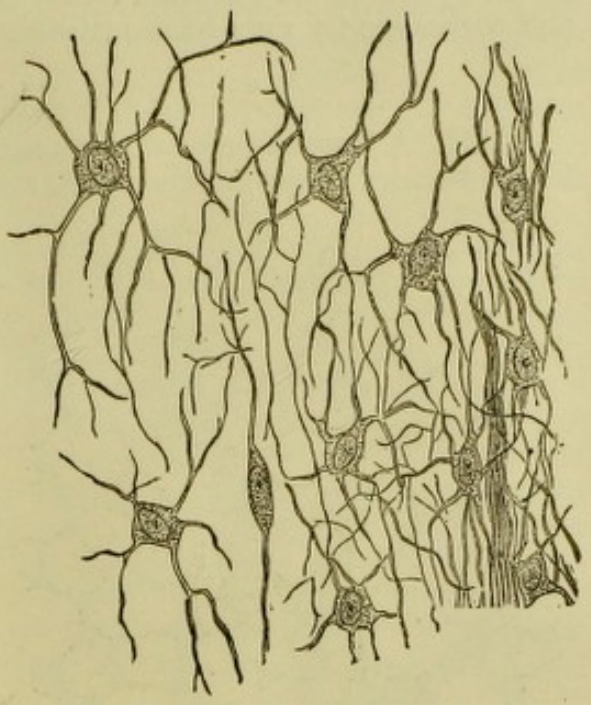


FIG. 228.—Cells from a myxoma of the periosteum of the femur. (Gold preparation.) Magnified 400 diameters.

Myxomatous tissue may be developed from fibrous tissue, this transformation being due to the fact that a fluid containing mucin collects in the meshes of the fibrillæ and then gradually causes the latter to disappear. When adipose tissue becomes myxomatous the fat in the fat-cells first breaks up into smaller drops (Fig. 231, *b*, *c*), and then disappears from the cells altogether; after which the latter contract and become star-shaped (*d*), while a jelly-like material containing mucin appears between the cells. When cartilage is transformed into myxomatous tissue a mucoid degeneration takes place in the basic substance, while the cells change their shape (cf. Fig. 234, *c*, *d*). Myxosarcomata (Fig. 229) may develop out of myxomata through an increase in the proliferative activity of certain groups of cells, or they may develop from sarcomata through the accumulation of mucus between the cells of the tumor.

Myxomata, myxofibromata, and myxolipomata are developed most frequently in the connective tissue of periosteum, skin, fasciæ, and sheaths of muscles, or in subcutaneous and subserous fatty tissue, or in

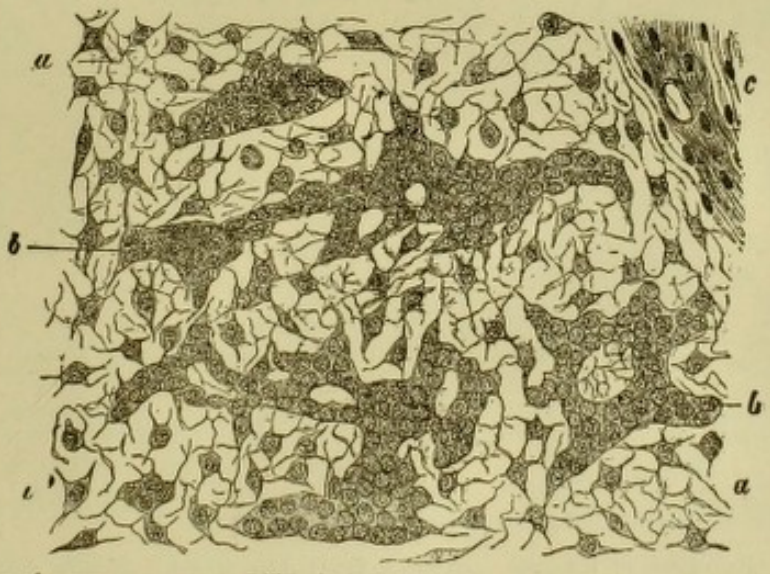


FIG. 229.—Section of a myxosarcoma. (Müller's fluid; carmine; glycerin.) *a*, Mucous tissue; *b*, strings of cells; *c*, fibrous tissue. Magnified 250 diameters.

bone-marrow. Myxochondromata occur in the parotid, and are even quite common there.

They are always benign tumors, which very rarely form metastases. Myxosarcomata, on the other hand, have the characteristics of sarcomata, and consequently may form metastases.

(c) Lipoma.

§ 111. A **lipoma** is a tumor composed of *adipose tissue* (Fig. 230). These tumors are sometimes soft, sometimes solid, usually nodular and lobulated, and they often reach great size. Their structure is very like normal subcutaneous fat-tissue; that is, they are composed of lobules of fat, which are held together by thicker or thinner connective-tissue septa.

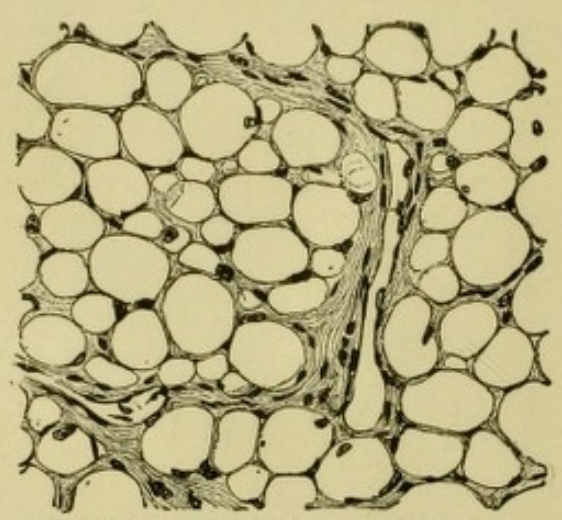


FIG. 230.—Lipoma from the region of the shoulder, with relatively small fat-cells. (Müller's fluid; hæmatoxylin.) Magnified 300 diameters.

Microscopically, too, a lipoma greatly resembles the lobules of subcutaneous fat (Fig. 230), although the arrangement in clusters, like clusters of grapes, is usually lacking. If fat-tissue and mucous tissue grow together, as often happens, the tumor is then called a **lipomyxoma** (Fig. 231); or if there is a great deal of fibrous tissue, it is called a **lipofibroma** or a **fibrolipoma.**

Usually lipomata develop from fat-tissue, but they may also grow from connective tissue that has normally no fat. Calcification, necrosis, gangrene, and sloughing may all occur in large lipomata. These tumors

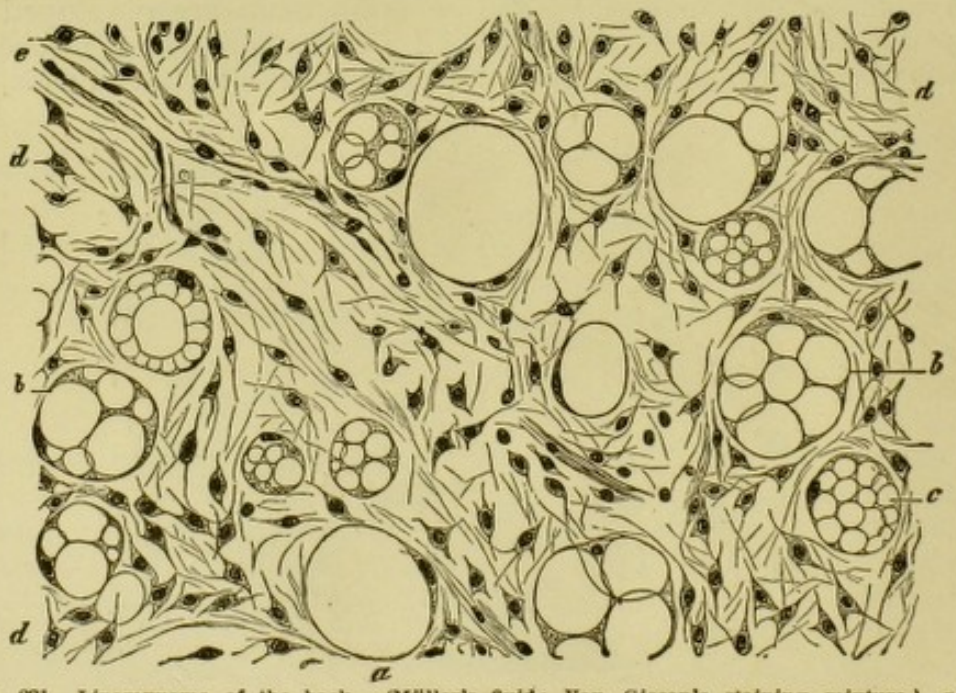


FIG. 231.—Lipomyxoma of the back. (Müller's fluid; Van Gieson's staining mixture.) *a*, Large fat-cells; *b*, *c*, fat-cells in which the fat has broken up into small drops; *d*, mucous tissue; *e*, blood-vessel. Magnified 300 diameters.

do not form metastases, but sometimes many of them appear at one time. A complete disappearance of a lipoma does not occur, even when the individual undergoes a marked general loss of flesh.

Lipomata are sometimes observed even in new-born children, as, for instance, in those cases in which they are found in or over the clefts belonging to spina bifida; but they much more often develop for the first time in later years. The favorite seats of these growths are the subcutaneous tissues of the back, buttocks, neck, axilla, abdomen, and thigh; but they may also be found in the connective tissue separating individual muscles, in the subserous adipose tissue, in the kidneys, in the intestine, in the mamma, under the aponeurosis upon the forehead, in the meninges, in the hand, in the fingers, in the joints, etc. They sometimes also occur as multiple growths, and may then show a tendency to occupy symmetrically placed parts of the body. A rare condition, which occurs in men, is that which is characterized by a new growth of fat on the neck and throat. This condition, which has been described particularly by English authors, manifests itself in the form of knobbed and lobulated alterations of the skin in this region. Madelung gives to the condition the name of *fatty neck*. The development of fat in these cases takes place partly in the subcutaneous tissue and partly in and under the fasciæ and between the muscles. When this process of fat-production extends to the trunk, to the upper extremities, etc., conditions will be established which resemble very closely general obesity.

(d) Chondroma.

§ 112. A **chondroma** or **enchondroma** is a tumor consisting essentially of *cartilage*. The amount of connective tissue found in its structure, covering its surface or penetrating its interior as a framework for the blood-vessels,

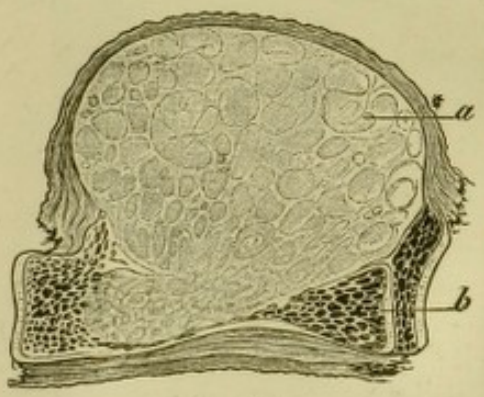


FIG. 232.

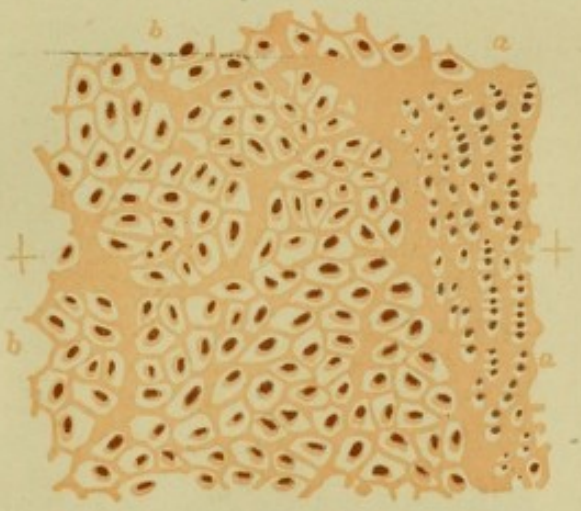


FIG. 233.

FIG. 232.—Periosteal chondroma of a digital phalanx, seen in longitudinal section. *a*, Chondroma; *b*, phalanx. Natural size.

FIG. 233.—Section through a chondroma of the ribs. Cartilage containing many cells. *a*, Small, *b*, large cells. (Preparation stained with hæmatoxylin and carmine, and mounted in Canada balsam.) Magnified 80 diameters.

is so slight as to be quite lost sight of when compared with the cartilaginous tissue.

Cartilaginous tumors are usually developed in those places in which cartilage is found normally—that is to say, in some part of the osseous

system or in the cartilaginous part of the respiratory apparatus; but they do also occur in tissues which normally have no cartilage, as, for example, in the salivary glands, and particularly in the parotid, in the testicle, and more rarely in other organs. They may develop in bones, from remains of cartilage left intact at the time of ossification; but they are more apt to arise in the marrow or in the periosteum (Fig. 232). These tumors vary greatly in size. The small ones are usually spherical in shape; the larger ones knobbed or lobulated. The individual nodules are separated from one another by connective tissue. Several of them often occur at the same time, particularly in the hands and feet, although they may also develop in other parts of the skeleton.

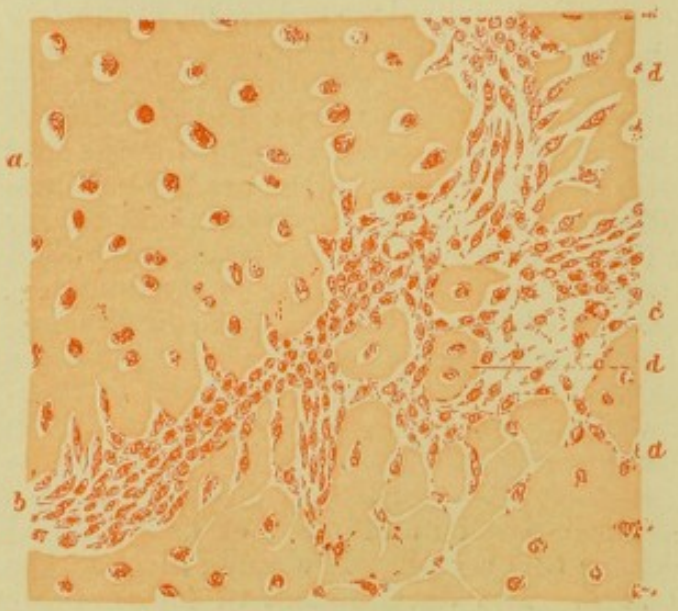


FIG. 234.—Chondromyxosarcoma of the parotid gland. (Alcohol; carmine.) *a*, Cartilage tissue; *b*, sarcoma tissue; *c*, mucous tissue; *d*, cartilage in process of breaking down and being converted into sarcoma and mucous tissue. Magnified 80 diameters.

The tissue of an enchondroma is usually that of hyaline cartilage (Fig. 233); less often is it composed of reticular or fibro-cartilage. Still there are often fibrous patches in the hyaline cartilage. The periphery

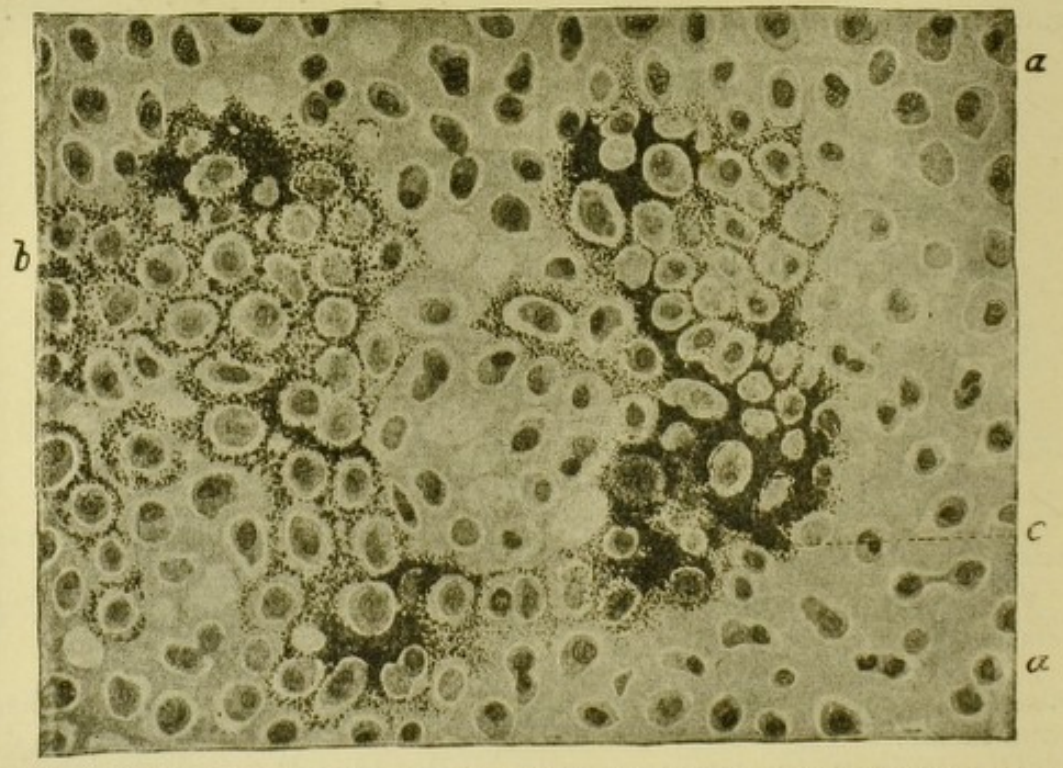


FIG. 235.—Periosteal chondroma of the calcaneus, with areas of calcification. (Müller's fluid; hæmatoxylin.) *a*, Hyaline cartilage; *b*, *c*, calcified cartilage. Magnified 250 diameters.

is often composed of fibrous tissue, which constitutes a sort of perichondrium.

The number, size, form, and arrangement of the cells vary greatly in different enchondromata, and also in the same tumor. Certain ones contain many cells (Fig. 233), others few; then, again, some have small cells and others large; and others still have both large and small cells.

The cells themselves have sometimes capsules and sometimes none; sometimes they lie in groups in a mother-capsule, sometimes the individual cells are scattered about in a regular manner. All the varieties of cartilage which exist normally may be found in tumors. Accordingly we find cells of different forms, the majority of them, however, being of the round form. Nevertheless it is common enough to find spindle- and star-shaped cells, especially in the neighborhood of the connective-tissue bands, which separate the tumor into lobules or surround it as a

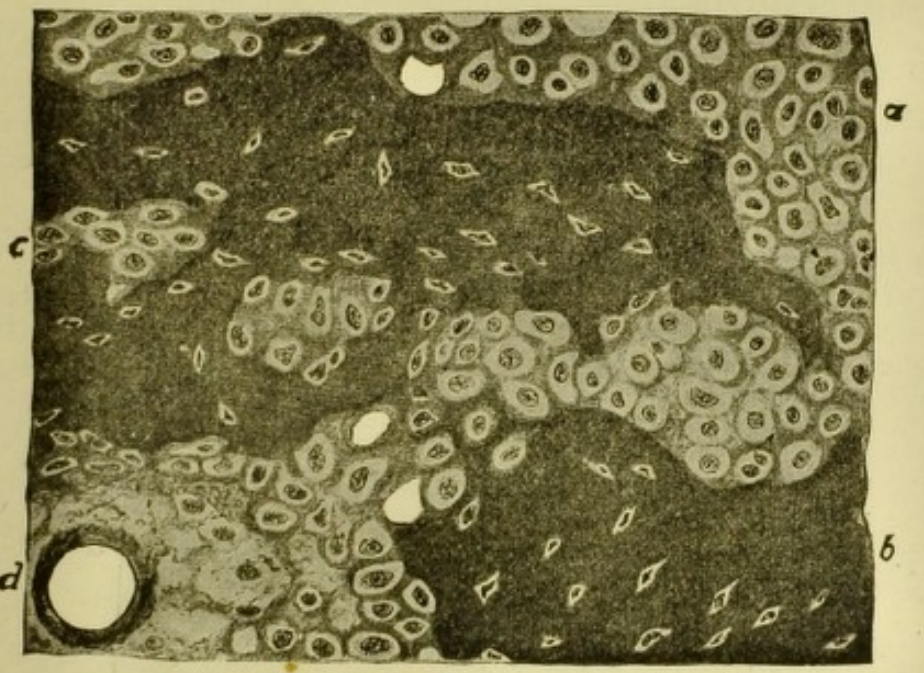


FIG. 236.—Osteochondroma of the humerus. (Alcohol; picric acid; hæmatoxylin; carmine.) *a*, Hyaline cartilage; *b*, bone; *c*, cartilage which is being converted into bone; *d*, blood-vessel. Magnified 250 diameters.

whole. What was said in § 89 holds good here with reference to the method of development. Sometimes cartilage forms the matrix, sometimes bone-marrow, or periosteum, or bone, or one of the forms of connective tissue. Cartilaginous tumors growing from cartilage have been denominated *ecchondroses*.

The tissue of enchondromata is often subject to retrograde metamorphoses. Some of the cells often contain fat-drops. In large tumors the basic substance often undergoes a mucoid degeneration and becomes fluid. The result is either the formation of *mucous tissue* (Fig. 234, *c*), thus giving rise to a *chondromyxoma;* or the intercellular substance undergoes complete liquefaction and the cells are destroyed, in which case *cysts* with fluid contents are formed—the result of softening processes. In other cases cartilage calcifies (Fig. 235, *b*, *c*), or genuine *bone* may be formed (Fig. 236, *c*, *b*), so that the name **osteochondroma** must be employed in designating such a growth. By excessive proliferation of the

cells of the cartilage, sarcomatous tissue may result, and the neoplasm becomes a **chondrosarcoma** (Fig. 234, *b*).

An enchondroma is usually a benign growth, although in certain cases of mixed tumors metastases may occur.

In the vicinity of the place where the sphenoid and the occipital bones unite, in the median line of the clivus, there sometimes appears a very small tumor to which Virchow has given the name of an **ecchondrosis physalifera spheno-occipitalis**. This little tumor either occupies the space between the bone and the dura mater, or at its highest point it pierces the latter and penetrates into the arachnoid and the pia. In its typical form the tumor consists of bladder-like cells, not unlike the cells of plant life, and it takes its start from the medullary portion of the bone and also in some measure from its superficial portions. In addition to the tissue which is peculiar to the tumor there may enter into its composition a certain amount of cartilage and bone; a circumstance which has led Virchow to look upon the growth as a chondroma which has developed from remains of the spheno-occipital cartilage, and which is characterized by having cells that have undergone a peculiar bladder-like degeneration. However, the characteristic structure of the tissue rather favors the view, originally put forward by H. Müller and recently adopted by Ribbert, that this little tumor is the outcome of a proliferative activity on the part of some remains of the chorda (*chordoma*).

(e) *Osteoma.*

§ 113. An **osteoma** is a tumor consisting of *bone*. Tumors of this nature are generally found in connection with the osseous system (Figs. 237–239), but they may occur elsewhere.

New growths of bone in connection with a normal bone have been variously designated according to their location and relations. If a new growth of bone is confined to a limited area it is called an *osteophyte*, or if of considerable size, an *exostosis*. Circumscribed bony growths inside of bones are called *enostoses*. New growths of bone which are not attached

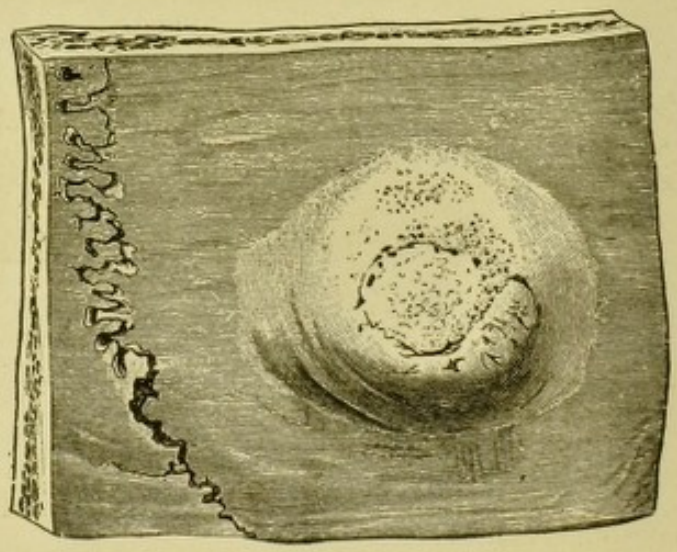


FIG. 237.—Ivory-like exostosis of the parietal bone. Natural size.

to old bone are of four sorts: *movable periosteal exostoses*, which are surrounded by the tissues of the periosteum, but are separate from the bone; *parosteal osteomata*, which have their seat near a bone; *disconnected osteomata*, which are removed to some distance from any bone and are situated in tendons and muscles; and finally, *heteroplastic osteomata*, which occur in other organs, as, for example, in the lungs, in the mucous membrane of the bronchial tubes, in the skin, in the mamma, etc.

The teeth, too, may have excrescences. If they are formed from the

cement, they are called *dental osteomata;* if from the dentine, *odontomata*. We can divide osteomata into hard or *eburneous* (*osteoma durum* or *eburneum*) (Figs. 237 and 239) and softer *spongy forms* (*osteoma spongiosum* or *medullare*) (Figs. 238 and 240). The former consist of a firm, compact tissue like the cortical portion of the shafts of long bones, and have very narrow nutrient canals (Fig. 239, *a*); the latter are made up of thinner and more delicate masses of bone-tissue with wide medullary spaces (Fig. 240), imitating in their structure the cancellous tissue of bones.

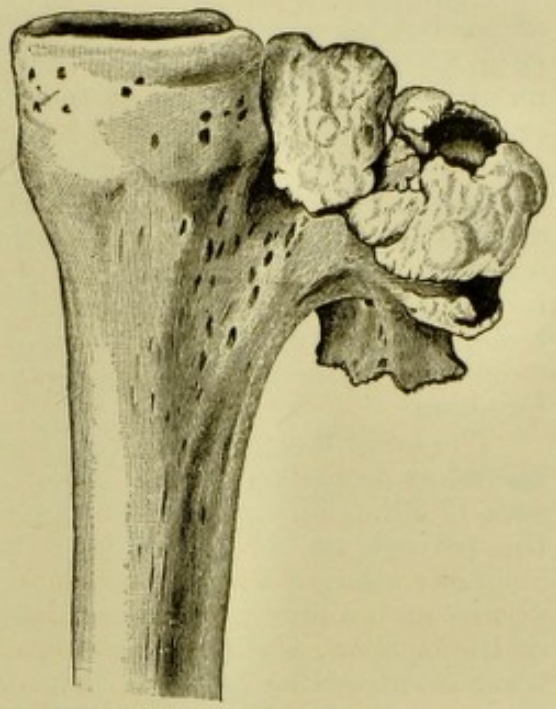


FIG. 238.—Cartilaginous exostosis of the upper diaphysis of the tibia. Reduced about one-half.

Sometimes the surface is regular and smooth, so that the whole tumor has the appearance of a cone with a rounded top (Fig. 237), or that of a ball, or that of a knob attached to a stem; or it may be irregular in shape, rough and warty (Fig. 238). The former is the case with the ivory-like nodules which most commonly appear as exostoses on the skull (Figs. 237 and 239), while the latter is true of the spongy exostoses and the disconnected and

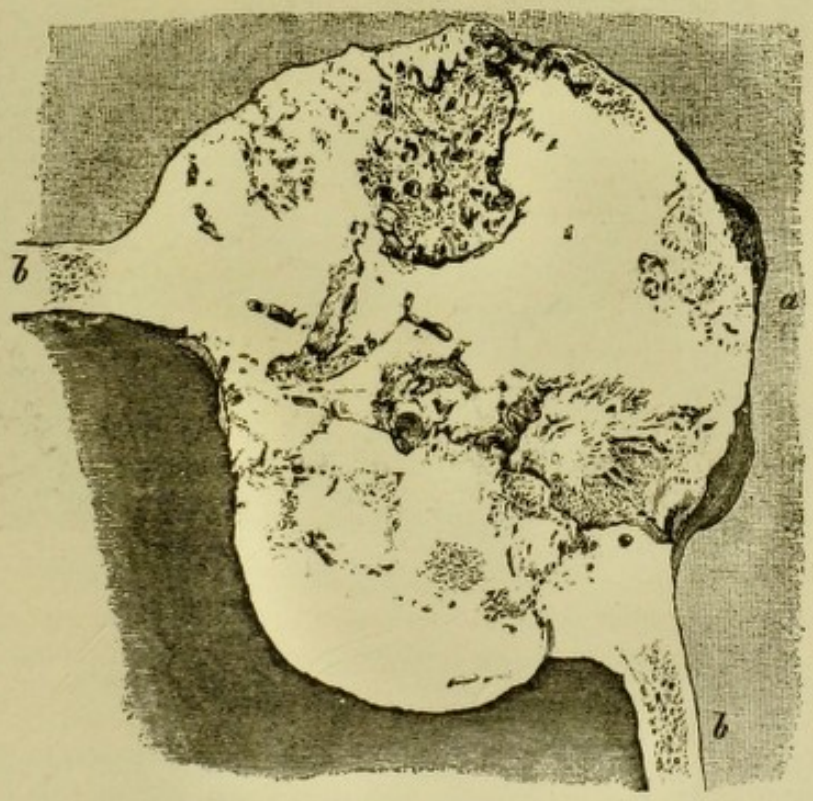


FIG. 239.—Eburneous osteoma of occipital bone, seen in frontal section. *a*, Osteoma; *b*, wall of cranium. (Eight-ninths life size.)

heteroplastic osteomata, such as are observed, for instance, in the falx of the dura mater (Fig. 240).

Osteomata occur either *singly* or in *multiple form*, and the latter mode of occurrence is rather common. The ivory-like exostoses of the skull (Fig. 239) and the osteomata of the dura mater often develop in great numbers, and circumscribed bony growths may form in large numbers on the bones of the trunk and lower extremities. In such cases the epiphyses or points of insertion of tendons, or both together, are the favorite seats. Such growths are evidently to be referred to an inherited disposition, on the part of the points affected, to overgrowth, or else to a disturbance in the development of the skeleton. Sometimes a transmitted tendency can be proved. Thin discs and splinter-like pieces of bone, such as are found, in rare cases, in the lungs or in the mucous membrane of the air passages, may also at times be encountered in large numbers.

The bony tissue is developed partly through the formation of osteoblasts, as described in § 89, partly through the metaplasia of formed tissues (§ 93). The matrix is formed chiefly from the connective tissue of the periosteum, as well as from that of the site whence the osteoma springs; also from the cartilage and the marrow. If an exostosis develops in such a manner that cartilage is first formed from the periosteum or the marrow, and then bone develops out of this, we apply to this the term *cartilaginous exostosis* (Fig. 238). But if this intermediate stage

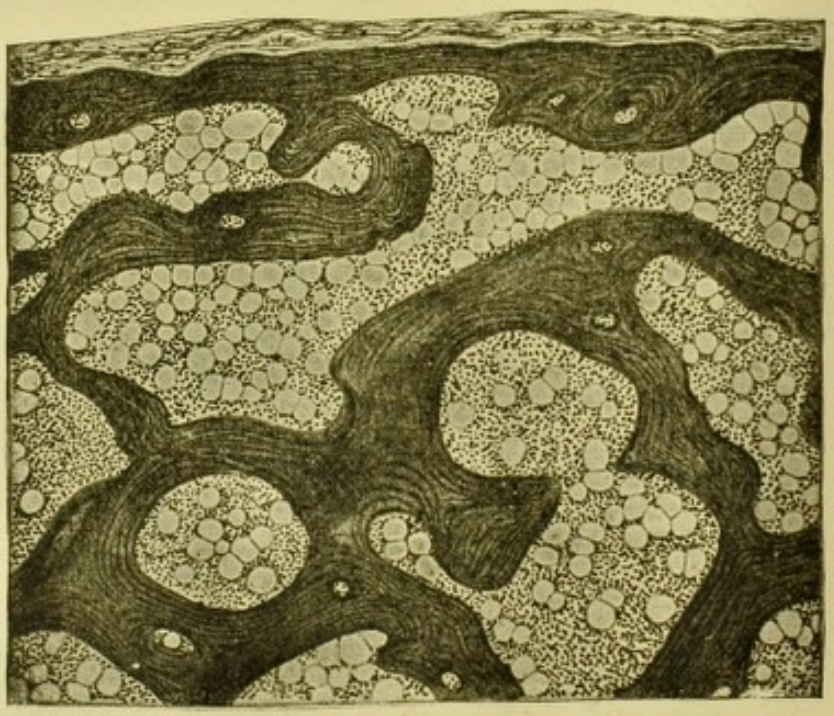


FIG. 240.—Osteoma of the dura mater. (Alcohol; picric acid; hæmatoxylin; carmine.) Magnified 40 diameters.

of cartilage is wanting, and the exostosis develops directly from the proliferating periosteum, then we term the growth a *connective-tissue exostosis* (Figs. 237, 239, and 240).

If a tumor is made up of connective tissue and bone in such a manner that the connective tissue makes up a considerable portion of the tumor, and does not simply represent the periosteum and marrow of the

bone, the tumor is called an **osteofibroma**. Such tumors generally spring from the osseous system. If there is an abundant formation of bone in a chondroma, the name **osteochondroma** is used. Osteochondromata (Figs. 236 and 241) are also usually connected with the long bones. The new growth may develop in the periosteum (Fig. 241, *c*),

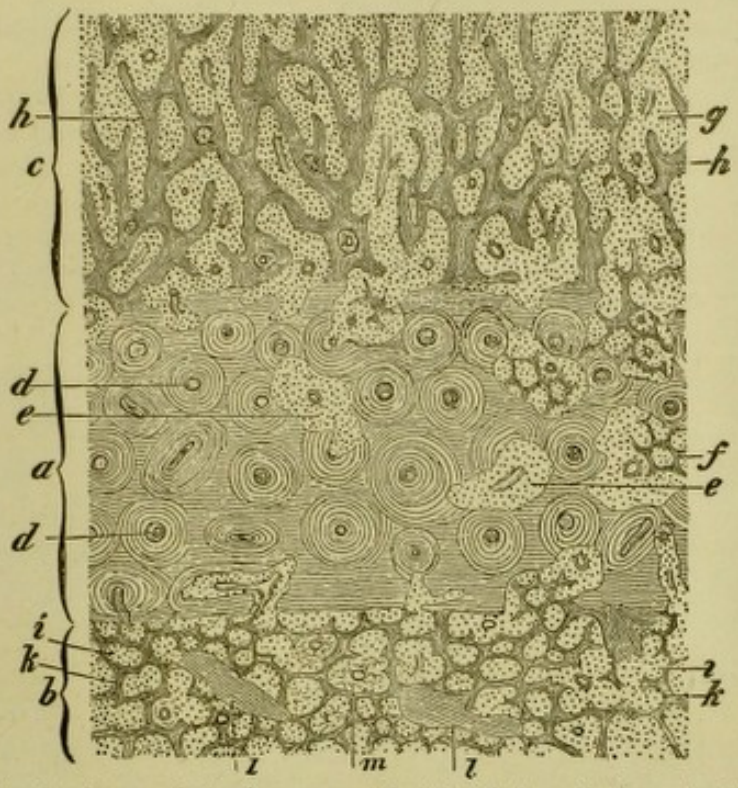


FIG. 241.—Osteochondroma of the humerus. (Alcohol; picric acid; hæmatoxylin; carmine.) *a*, Cortical part of the humerus; *b*, medullary cavity; *c*, layer of new bone deposited by the periosteum; *d*, normal Haversian canals; *e*, dilated Haversian canals filled with cartilage, which canals, at *f*, contain newly formed bone; *g*, cartilage which has been produced by the periosteum, and which, at *h*, contains bone-trabeculæ; *i*, cartilage produced by the tissues of the bone-marrow and containing, at *k*, bone-trabeculæ; *l*, old bone-trabeculæ; *m*, remnant of bone-marrow. Simply enlarged by means of a magnifying lens.

or in the marrow (*a*, *b*). An abundant growth of bone-trabeculæ (*f*, *h*, *k*) in the cartilage (*e*, *g*, *i*) gives the tissue a firm, hard consistence.

Many of the new growths of bone which come under observation are not tumors in the strict sense of the term, but hyperplasias resulting from excessive growth or inflammatory processes. This is true of many osteophytes and exostoses, and also, to a certain extent, of the parostoses and disconnected osteomata. Scales of bone which occasionally form in the falx of the dura mater, and which possess a normal medullary substance (Fig. 240), are to be considered as dislocated or misplaced portions of the embryonic skeleton. The formations of bone which occur in the deltoid muscle and in the adductors of the thigh from constant carrying of a musket and horseback-riding must be looked upon as tumors which owe their origin to a local congenital predisposition; for the connective tissue belonging to muscles shows itself possessed of qualities which, as a rule, belong only to the periosteum and bone-marrow. The so-called *myositis ossificans*—that peculiar disease of the muscles which is characterized by a progressive ossification, in childhood, of their connective tissue—is to be interpreted in the same way.

(f) Hæmangiomata and Lymphangiomata.

§ 114. Under the name **angioma** are grouped *those new growths in the structure of which blood-vessels or lymph-vessels constitute such an important part as to determine the character of the tumor.*

Vascular tumors which arise from blood-vessels are called **hæmangiomata,** or *angiomata* in the restricted sense of this term; while those which arise from lymph-vessels are called **lymphangiomata.** They consist to a large degree of growths which may be looked upon as *malformations* of a more or less considerable vascular area. Four principal varieties may be distinguished: *hæmangioma simplex, hæmangioma cavernosum, hæmangioma hypertrophicum,* and *angioma arteriale racemosum.*

Hæmangioma simplex, or **telangiectasia,** are terms used to describe a formation in which there are an *abnormal number of normal blood-ves-*

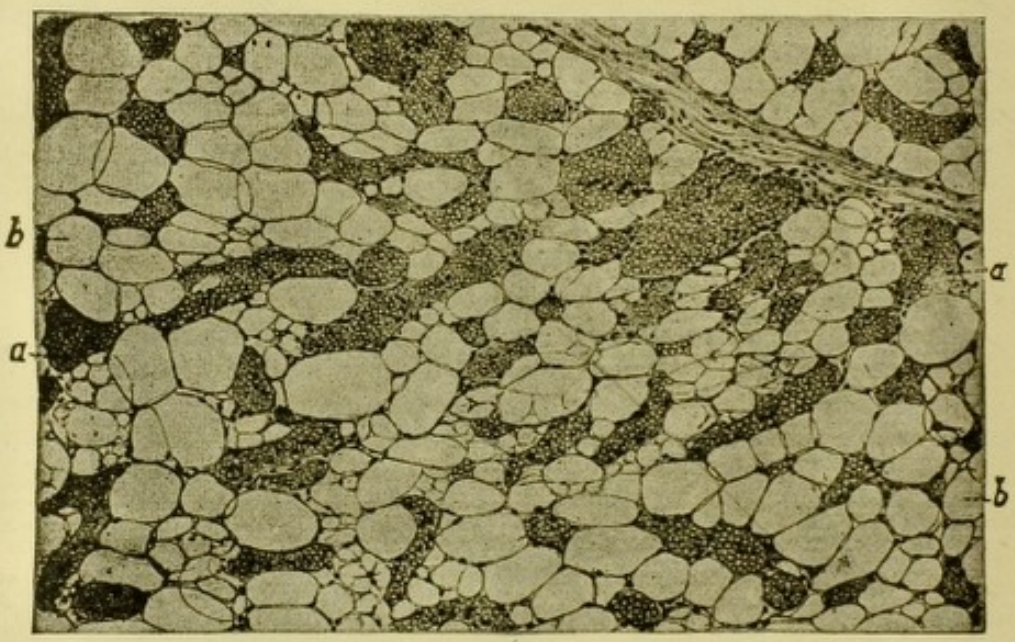


FIG. 242.—Telangiectasia of the panniculus adiposus of the abdominal walls. (Formalin; hæmatoxylin; eosin.) *a*, Blood-vessels filled with blood; *b*, adipose tissue. Magnified 80 diameters.

sels, or *abnormally broad capillaries and veins, whose structure, in part at least, is abnormal.*

Such formations are most often found in the skin and in the subcutaneous tissue. They are usually congenital, but grow after birth. They are called **vascular nævi** (*nævi vasculosi*), and are often found in places where fœtal clefts have closed (*fissural angiomata*). It is often impossible to speak of such a formation as a true tumor, for the skin may not be raised at all. But there are also telangiectases which deserve the name of tumor. In these not only the skin, but also the subcutaneous tissue, may be the seat of the disease; and the tumor presents itself either as a sharply defined growth or merely as a thickening of the skin. The smooth nævus vasculosus, on the other hand, is a superficial substitution of another tissue for that of the skin. The color of the affected part is either *bright red* (*nævus flammeus*) or *bluish red* (*nævus vinosus*). Usually the line of demarcation between healthy and affected skin is not a sharp one. On the border of the chief discoloration or in

its neighborhood are often little circumscribed red spots, presenting sometimes the appearance of outrunners from the centre of the disease.

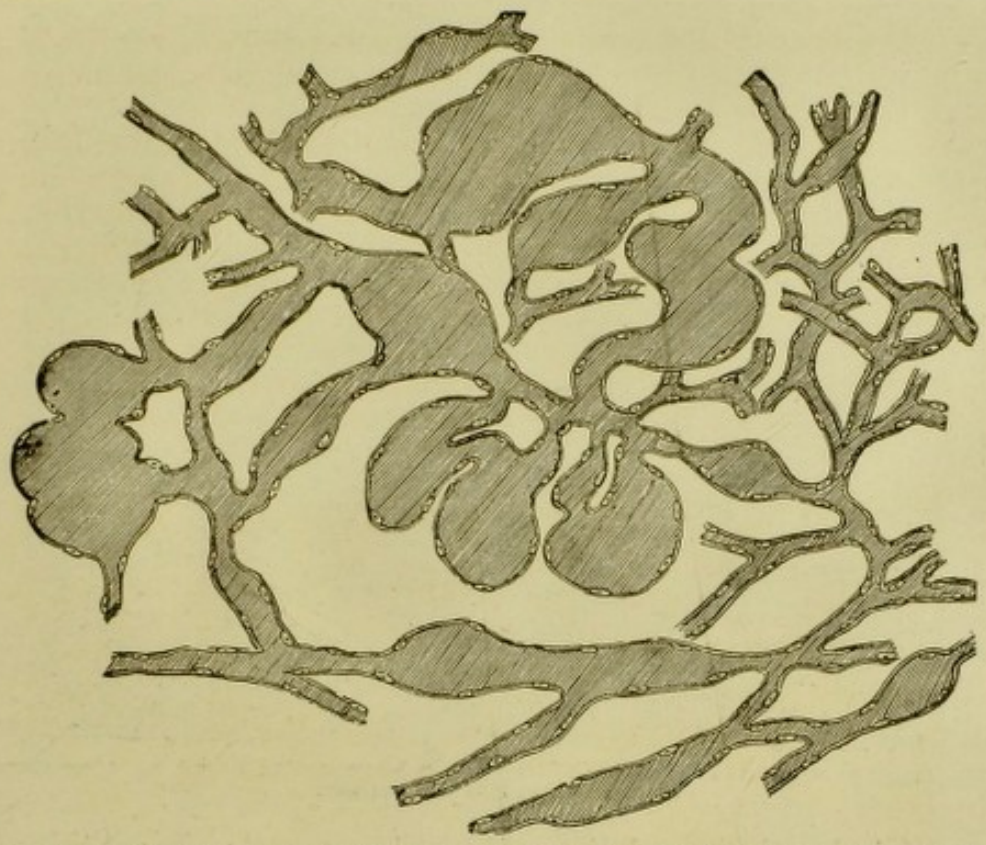


FIG. 243.—Dilated capillaries from a telangiectatic tumor of the brain, all the attached portions of tumor-tissue having been shaken off in water. Magnified 200 diameters.

The red color is produced by dilated vessels full of blood, which are situated either in the corium or in the subcutaneous adipose tissue (Fig. 242, *a*). There are also cases in which large areas of subcutaneous adipose tissue present a reddish appearance, by reason of the pathological development of new blood-vessels. More rarely than in skin do we find similar angiomata in glands (the breast), in bones, and in the brain (Fig. 243) and spinal cord and their membranes. On the other hand, we often find analogous alterations of the vessels in tumors—e.g., in gliomata or sarcomata.

If the vessels, which are usually abnormally abundant, are isolated, it becomes evident that the capillaries, or also the small veins (*angioma*

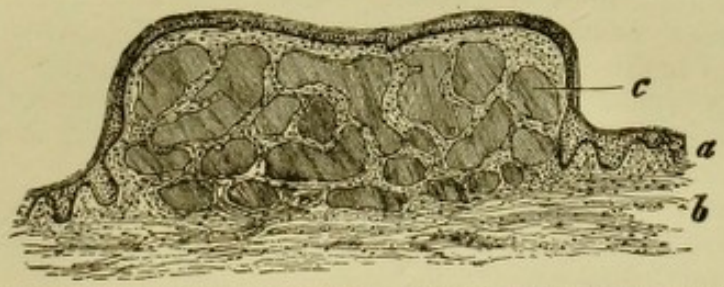


FIG. 244.—Angioma cavernosum cutaneum congenitum. (Müller's fluid; hæmatoxylin.) *a*, Epidermis; *b*, corium; *c*, cavernous blood-spaces. Magnified 20 diameters.

simplex venosum), are more or less dilated. These dilatations (Fig. 243) may be fusiform or cylindrical, sacculated, or spherical, and the

different forms of dilatations combine in the greatest variety of ways. The dilated blood-vessels are united with one another by capillaries of

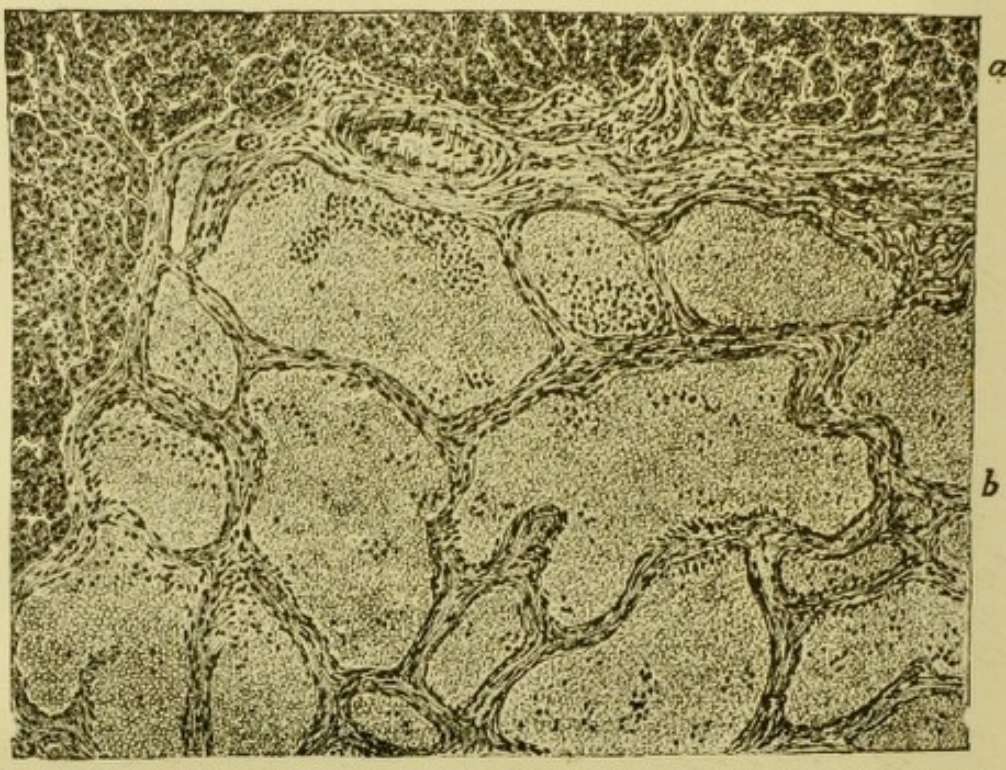


FIG. 245.—Angioma cavernosum hepatis. (Müller's fluid; hæmatoxylin; eosin.) *a*. Liver tissue; *b*, angioma. Magnified 100 diameters.

normal or slightly increased dimensions. The vessel walls are thin; that is to say, they are only slightly thicker than those of a normal capillary.

A **hæmangioma cavernosum**, or *cavernous tumor*, is a *new growth of blood-vessels which consists of a cavernous spongy tissue*, whose structure suggests that of the corpus cavernosum or spongiosum of the penis (Fig. 244 and Fig. 245). If the spaces are filled with blood the tumor has a bluish or dark reddish appearance.

A cavernous angioma, like a simple angioma, usually occurs in the skin (Fig. 244, *c*) or the subcutaneous tissue, where, at the time of its development, it appears like a pathological sketch of the vascular system. Sometimes it is a bluish-red spot (*nævus vasculosus vinosus*); sometimes it resembles a slightly elevated wart with a smooth surface (Fig. 244), or one with a bluish-red, somewhat irregular surface (*nævus vasculosus prominens, verruca vasculosa*); and finally, it may include more extensive areas of skin which are either discolored a bluish-red or are thickened, and if the development of cavernous tissue extends into the subcutaneous or even into the intermuscular connective tissue, there

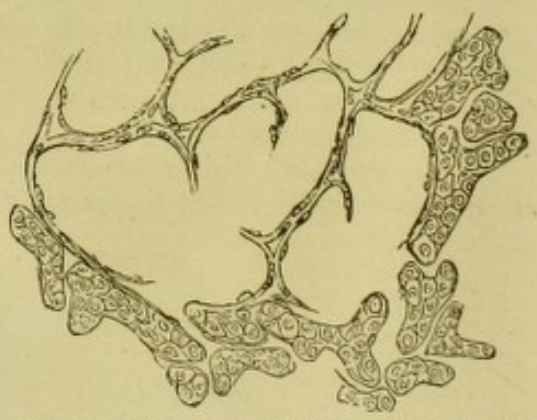


FIG. 246.—Section through the margin of a very small cavernous angioma of the liver, at a time when this margin was in process of active growth. (Carmine preparation.) Magnified 150 diameters.

may result *great tumors* or *disfiguring irregularities of the portions of the body affected* (*elephantiasis hæmangiomatosa*).

Hemorrhoids are the bluish-red, knotty, vascular tumors which form

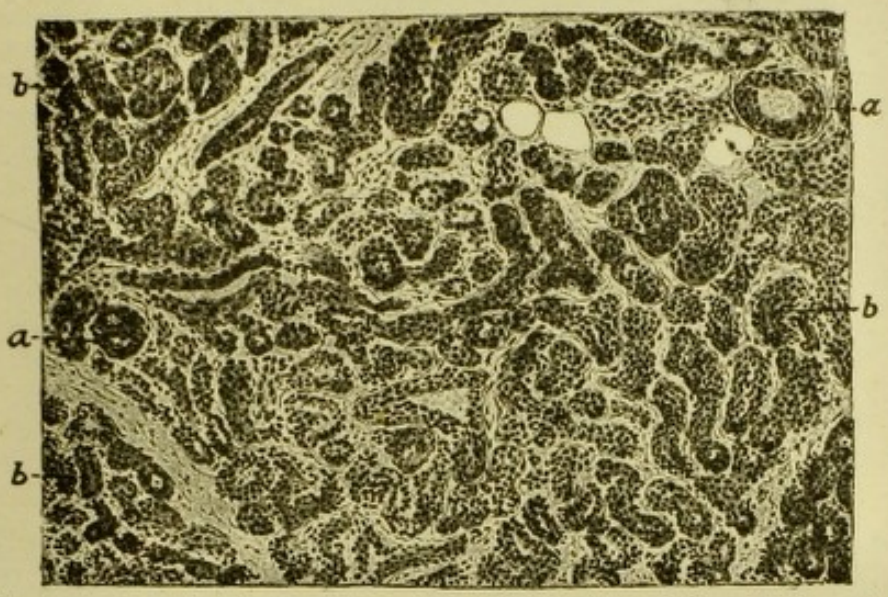


FIG. 247.—Angioma simplex hypertrophicum. (Formalin; hæmatoxylin.) *a*, Blood-vessels containing blood; *b*, empty and collapsed blood-vessels, with thick walls and richly supplied with nuclei. Magnified 100 diameters.

in the thickened mucous membrane of the anus. They are generally considered to be varicose dilatations of the vessels, brought about by obstruction to the blood current, and by chronic inflammatory processes. According to the investigations of Reinbach, these tumors are true angiomata, whose development, which may begin in early childhood, depends on a new formation and cavernous metamorphosis of the blood-vessels, and may be quite independent of any obstruction to the blood flow.

Within the body cavernous angiomata are most often found in *the liver* (Fig. 245, *a*, *b*), although they may also be found in the other organs — the kidneys, spleen, intestines, bladder, bones, muscles, uterus, brain, etc. In the liver they are found as dark-red areas, varying in size from that of a pin's head to that of a body several centimetres in diameter. They displace the substance of the liver and do not stand out above the surface of the organ. They are found in elderly persons, and owe their origin to a cavernous metamorphosis of the capillaries of the liver (Fig. 246); the liver cells perishing, while the walls of the capillaries proliferate. In the case of very small intra-acinous angiomata, one can make out the communication between the capillaries of the liver and the cavernous spaces (Fig. 246). Larger angiomata are separated from the substance of the

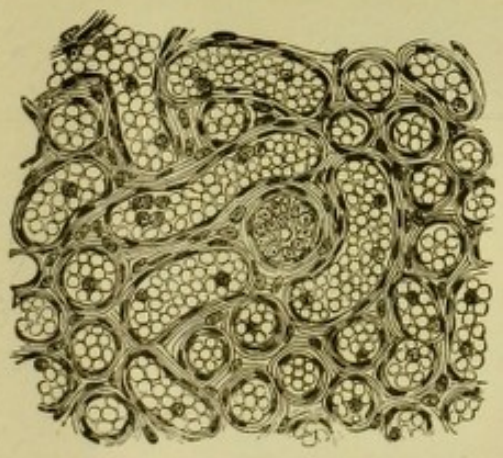


FIG. 248.—Angioma simplex hypertrophicum cutaneum et subcutaneum. (Alcohol; carmine.) In the middle of the section is the duct of a sweat-gland cut transversely. Magnified 200 diameters.

liver by a sort of a capsule (Fig. 245), which is formed in part of

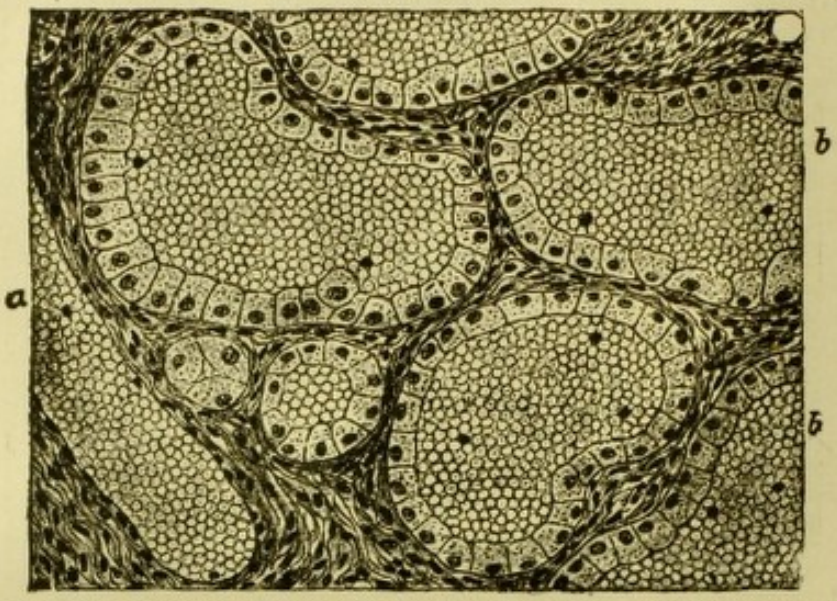


FIG. 249.—Angioma cavernosum hypertrophicum of the skull-cap. (Müller's fluid; hæmatoxylin.) *a*, Blood-vessels with flattened endothelium; *b*, blood-vessels with cuboidal and cylindrical endothelium. Magnified 250 diameters.

the capsule of Glisson, and in part of newly developed connective tissue.

The blood spaces of a cavernous angioma are lined with a flattened

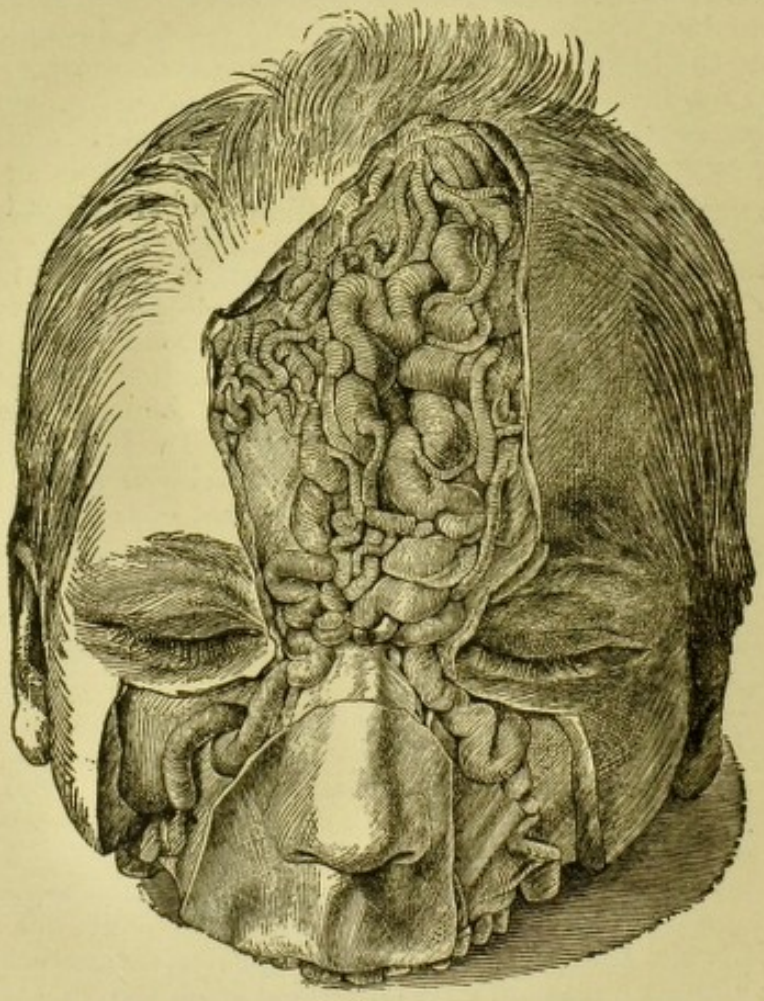


FIG. 250.—Angioma arteriale plexiforme of the frontal and anguiar arteries of both sides.

endothelium. The walls are usually thin; but their thickness, as well as the amount of connective tissue between the individual vessels, varies greatly. Some of the blood spaces may undergo a fibrous degeneration, in connection with the formation of a thrombus.

Hæmangioma hypertrophicum, in its typical form (*Hæmangioma simplex hypertrophicum*), occurs most frequently in the skin and subcutaneous tissue, where it forms a circumscribed nodule, not unlike the soft, smooth warts. The pathologically altered vessels may lie in the papillæ or in the corium or in the subcutaneous tissue. They present themselves either as narrow tubes filled with blood (Fig. 247, *a*, and Fig. 248), whose walls are more or less thick and abnormally rich in cells; or else as firm strings of cells (Fig. 247, *b*), which are either collapsed, thick-walled vessels, or possess no lumen whatever.

In very rare instances it happens that an hypertrophy of the walls takes place in an angioma which, from the calibre of its vessels, is properly classed as cavernous; and this hypertrophy is due to the fact that the pavement endothelial cells are altered to cubical or cylindrical cells (Fig. 249, *b*). Such a tumor may therefore be called an *angioma cavernosum hypertrophicum* (or, in some cases, angiosarcoma endotheliale).

A cirsoid aneurism, or **angioma arteriale racemosum**, or **angioma arteriale plexiforme** (Fig. 250), is a condition in which the *arteries* of a whole group *are dilated, tortuous, and thickened*, so that they form a convolution of enlarged arteries. They feel to the palpating finger like a bunch of earthworms. Many of these angiomata, which are found particularly on the head, and which may cause erosion of bone, are congenital in origin. Others appear to be acquired, and develop in consequence of a traumatism; and yet it is possible that, already before the injury was inflicted, certain special conditions existed at the affected point.

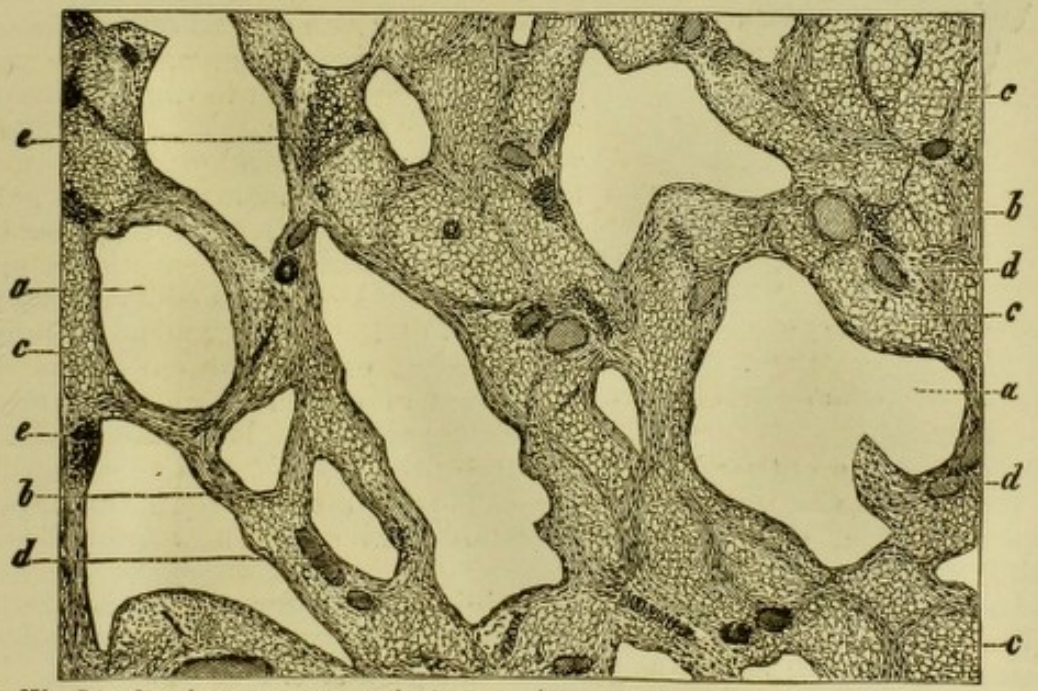


FIG. 251.—Lymphangioma cavernosum subcutaneum. (Alcohol; alum carmine.) *a*, Ectatic lymph-vessels; *b*, fibrous tissue; *c*, fat; *d*, larger blood-vessels; *e*, cellular tissue. Magnified 20 diameters.

§ 115. **Angioma lymphaticum**, or **lymphangioma** (Fig. 251), is composed of a tissue the greater part of which is made up of *dilated lymph-vessels*. The different forms are: *lymphangioma simplex*, or *telan-*

giectasia lymphatica ; lymphangioma cavernosum ; lympnangioma cystoides ; and *lymphangioma hypertrophicum.* The fluid contained in the cavities is usually a clear and bright lymph, but sometimes it is milky.

In the **simple lymphangioma** the lymph-vessels to a greater or less distance are dilated, and their walls are usually thickened. In the **cavernous lymphangioma** (Fig. 251) the vessels are still more increased both in number and in size, while the intervening tissue is diminished in quantity, so that even to the naked eye the tissue appears spongy. The **cystic lymphangiomata** contain cysts from the size of a pea to that of a walnut or greater. The tissue between the dilated lymph-vessels is, according to the part from which the tumor springs, connective tissue, or fat (Fig. 251, *c*), or muscle, or some other tissue. Sometimes this tissue includes foci of lymphadenoid tissue (*e*). Moreover, it may present the signs of active proliferation.

FIG. 252.—Large, hard pigmented nævus of the back, buttocks, and thighs, with scattered smaller pigmented spots on the upper part of the body. (After Röhring.)

Lymphangiomata are sometimes congenital, and at other times they make their first appearance only later on in life. As a congenital phenomenon ectasia of the lymph-vessels is observed in different forms, particularly in the tongue (*macroglossia*), in the palate, in the lips (*macrocheilia*), in the skin (*nævus lymphaticus*), in subcutaneous tissue, in the neck (*hygroma colli congenitum*), in the vulva, etc. *Lymphangiomata of the skin* spread out over more or less extensive areas, and they may give rise to smooth or to slightly uneven elevations of the skin. When the blood-vessels are well developed they may lend a reddish appearance to the part. The bursting of dilated lymph-vessels which lie immediately beneath the epithelium, may keep up a constant moist condition of the surface and so establish a lymphorrhœa. If the cavernous development of the subcutaneous lymph-vessels spreads over large areas of the skin, conditions outwardly resembling those of *elephantiasis* may result. In such cases the intervening tissue usually takes part in the hypertrophic growth, or there will be established a fibrous elephantiasis, with lymphangiectasia.

In rare cases *chylangiomata*, containing chyle, appear in the course of the lymph-vessels of the intestine or mesentery. *Cystic lymphangiomata of the peritoneum* are also extremely rare.

The pathological formations, which may be grouped under the single heading of **hypertrophic lymphangiomata**, consist of peculiar alterations of the skin, which either are congenital or else first manifest themselves in early youth. They are commonly termed pigmented nævi, lentigines, ephelides, and fleshy warts.

The *pigmented nævi* (*nævi pigmentosi*), or *melanomata*, form larger or smaller plaques situated on the same level with the surrounding skin

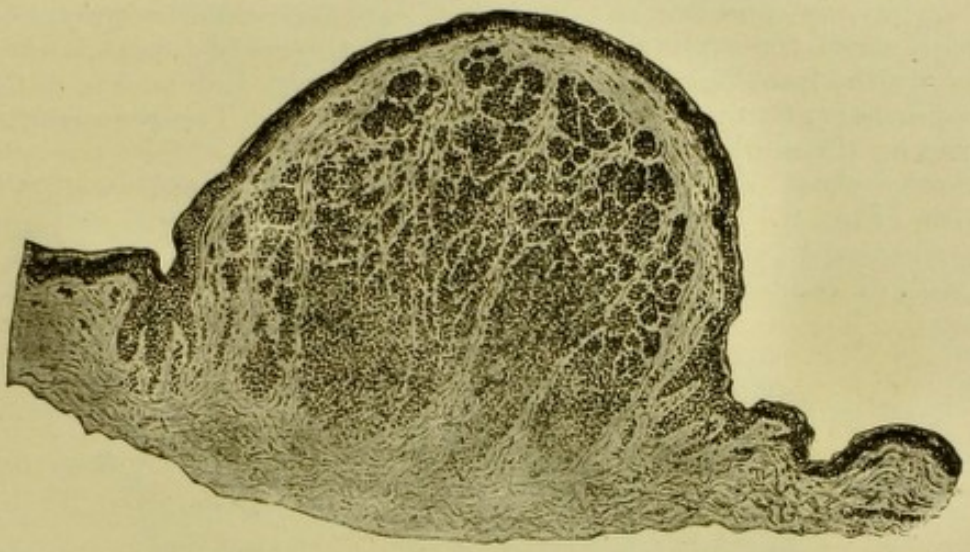


FIG. 253.—Lymphangioma hypertrophicum. Section through a small, soft, smooth wart. (Formalin; hæmatoxylin; eosin.) Magnified 40 diameters.

(nævus spilus), or raised above it like warts (nævus prominens, nævus verrucosus), and often studded with hairs (nævus pilosus). They are pale brown or dark brown or black (Fig. 252), and are usually covered by normal, less often by hypertrophied epidermis. They are usually small, but they may be as large as an ordinary plate, and in rare instances they may cover a large part of the body.

Lentigines appear at any time after birth, and on any part of the surface of the body; and when once formed they remain for life. They

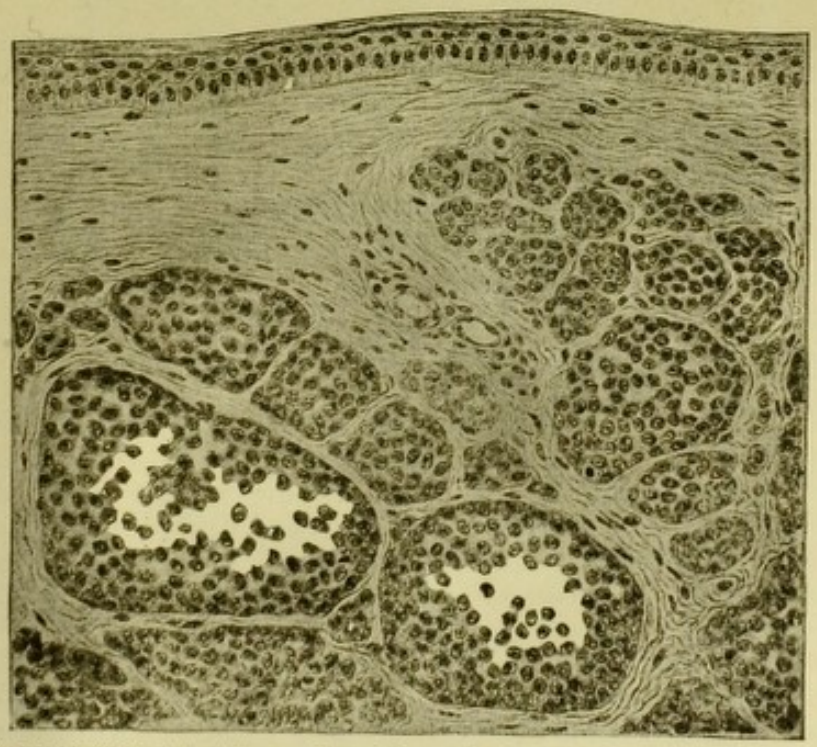


FIG. 254.—Lymphangioma hypertrophicum. Rounded summit of a rather large, soft, smooth wart. (Formalin; hæmatoxylin eosin.) Sharply limited nests of cells in the corium. Magnified 250 diameters.

closely resemble the little pigmented nævi, and form well-defined spots of a yellow or brown or almost black color, and as large as a pin-head or larger.

Freckles, or *ephelides*, are ill-defined, angular, pale-brown spots, not elevated above the surface, which appear in the early years of life especially on the face, hands, and seldom elsewhere, and which either remain permanently or in course of time disappear. The pigmentation is favored by the sunlight.

Fleshy warts (*verrucæ carneæ*) are non-pigmented, well-defined, smooth (Fig. 253), or slightly roughened, or very uneven papillary growths caused by a normal or hypertrophic epithelium (Fig. 253, *a*).

In all of the pathological formations just described the connective-

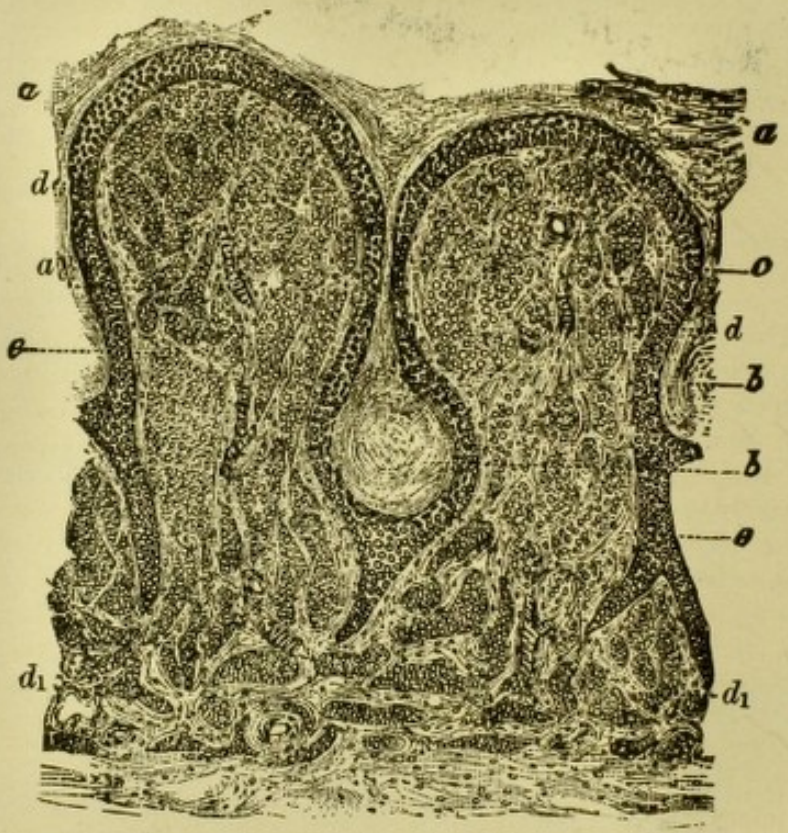


FIG. 255.—Section through two papillæ of a papillomatous fleshy wart. *a*, Thickened horny layer of epidermis; *b*, epithelial pearls; *c*, rete Malpighii; *d*, nests and strings of cells in the papillæ; d_1, nests and cells in the reticular layer; *e*, connective tissue. (Preparation stained with carmine.) Magnified 50 diameters.

tissue framework incloses *masses of cells*, either in round groups or drawn out into bands (Fig. 253, Fig. 254, Fig. 255, *d*, d_1). They lie partly in the papillæ and partly in the corium, and are more abundant in those cases in which the growth is elevated above the surface of the skin. In the pigmented growths the cells of the cell-nests may also be bearers of the pigment, which either occurs in the form of separate brown and yellow granules, or else is diffused throughout the substance of the cells. In many instances, however, the pigment is to be found mainly in the connective-tissue cells of the fibrous portions of the growth.

The cells of the cell-nests are comparatively large (Fig. 254), and they possess an abundant protoplasm and a bright, bladder-like nucleus. From the position which they occupy and from the appearance which they present, one is warranted in drawing the conclusion that they are

the product of the proliferation of the endothelial cells of the lymph-vessels. Accordingly, it would appear to be proper to place these growths in the category of the endotheliomata or in that of the lymphangiosarcomata, but the limited extent to which they grow makes it seem more correct to classify them among the lymphangiomata (compare § 123). The aggregations of cells which are found in the hypertrophic form of lymphangioma may, to a certain extent, be spread out somewhat diffusely through the tissues, as also occurs in the case of an hypertrophic hæmangioma. When this happens, the peculiarities of structure which characterize this form of growth will be lost.

Unna, Kromayer, and Delbanco hold the view that the cell-nests of the cellular nævi are of epithelial origin, representing portions of the surface epithelium which have dropped down to a lower level; and Kromayer goes so far as to assume a metaplasia of epithelium from the surface to the connective-tissue stratum. I have not at my disposal any preparations which show the first stages in the development of these nævi. More recent exhaustive studies relating to nævi and fleshy warts have failed to reveal any connection between the cell-nests and the epithelium, and consequently I favor the belief —notwithstanding the investigations of these last-named authors—that the pathology which is given in the main body of the text, in regard to these nævi and fleshy warts, is that which most perfectly harmonizes with their anatomy and clinical behavior, both when they are fully developed and when they undergo a change into malignant sarcomas (compare § 123).

(*g*) *Myoma.*

§ 116. **Myoma** is the name applied to a tumor whose chief structural elements are *newly developed muscular fibres.* An obvious division is into *leiomyomata* if the muscular fibres are of the smooth variety, and *rhabdomyomata* if the fibres are striped.

Leiomyomata, called also *myomata lævicellulares,* occur most frequently in the uterus, less often in the Fallopian tubes, in the uterine ligaments, in the labia majora, and in the muscular layers of the alimentary tract and urinary channels. In these localities they form rounded and nodulated tumors of various sizes. In exceptional cases they are found in the skin and subcutaneous tissue, where they form small nodules which only rarely attain the size of a pigeon's egg. They occur either singly or in larger number, and may appear in early childhood or even before birth (Marc).

If the new growth takes place in muscular organs, it proceeds from the muscular layer, forming in its development bundles of muscle-fibres (Fig. 256), interwoven in various directions, and furnishing, therefore, in sections, a variety of pictures. Submucous myomata of the uterus may include in their substance uterine glands. Myomata which develop on the dorsal wall of the body of the uterus, and close to the angle formed by the Fallopian tube, may include in their substance a varying number of gland-tubules which come from the Wolffian body (von Recklinghausen). When this happens, it is proper to call such tumors *adenomyomata.* They differ from the ordinary spherical myomata, which have sharply defined limits, in these respects: their boundaries are ill-defined; and, furthermore, a few individual glands may, through the accumulation of secretion in them, become converted into cysts. According to Ricker, the ordinary myomata of the uterus may contain epithelial tubes, which perhaps owe their origin to some portion of Müller's duct which has become displaced during intra-uterine life. In the skin and subcutaneous tissue, so far as there are any observations on the subject, the new growth of muscle-fibres has its origin in the mus-

cularis of the vessels (Fig. 257), which layer not only becomes thickened (*c*), but also gives off separate offshoots of muscular fibres (*b*). This new formation of muscular tissue may easily be associated with the pathological formation of blood-vessels (*a*), and from this combination will result tumors that may properly be called *angiomyomata* (Fig. 257). According to the observations of Jadassohn, myomata of the skin may also spring from the erector muscles of the hairs—the arrectores pilorum.

A certain amount of connective tissue takes part in the formation of a myoma, and often assumes such importance that the tumor deserves the name **myofibroma** or **fibromyoma.** For example, most of the myomata of the uterus are myofibromata. The fibrous connective-tissue portions of the tumor appear glistening white, while the muscular parts are reddish-white or bright reddish-gray. The fusiform muscle-fibres may be isolated by teasing a fresh bit of tumor, or, better, a bit which has macerated for twenty-four hours in twenty-per-cent. sulphuric acid,

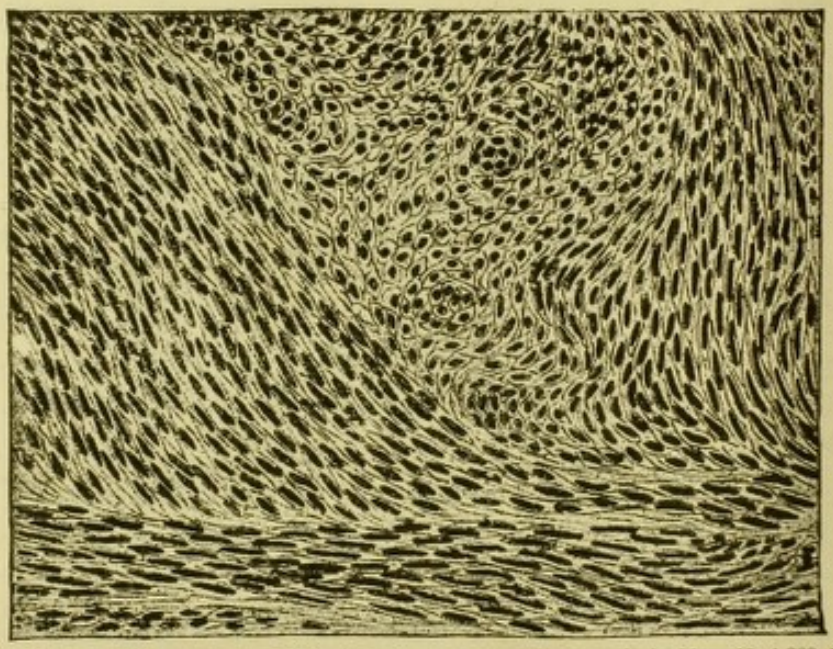


FIG. 256.—Myoma of the uterus. (Müller's fluid; hæmatoxylin; eosin.) Magnified 300 diameters.

or for twenty to thirty minutes in thirty-four-per-cent. potassic hydrate. In a longitudinal section the muscular fibres are best recognized by the staff-like nuclei (Fig. 256 and Fig. 257, *b*), as well as by the regular arrangement of the cells in bands or parallel lines. In cross-section the muscle-cells appear as little areas whose rounded boundary lines are somewhat flattened by pressure one against the other, while in the centre of each of these areas is the nucleus cut transversely (Fig. 256).

Leiomyomata are thoroughly benign tumors, although they often attain a very large size, and sometimes undergo a change into sarcomatous tissue. In fibromyomata of the uterus we often have processes of fatty degeneration and softening, which destroy the tumor or lead to the formation of cystic cavities. Calcification may also occur. A myofibroma may become a pure fibroma through the degeneration and disappearance of the muscular fibres.

A **rhabdomyoma** (Zenker), or *myoma striocellulare* (Virchow), is a rare tumor whose essential part is made up of striated muscle-fibres either well or poorly developed. When well developed the muscular

fibres form nucleated bands of various widths, which show a transverse (Fig. 258, *a*, *b*, *c*) and in places also a longitudinal striation (*e*, *f*).

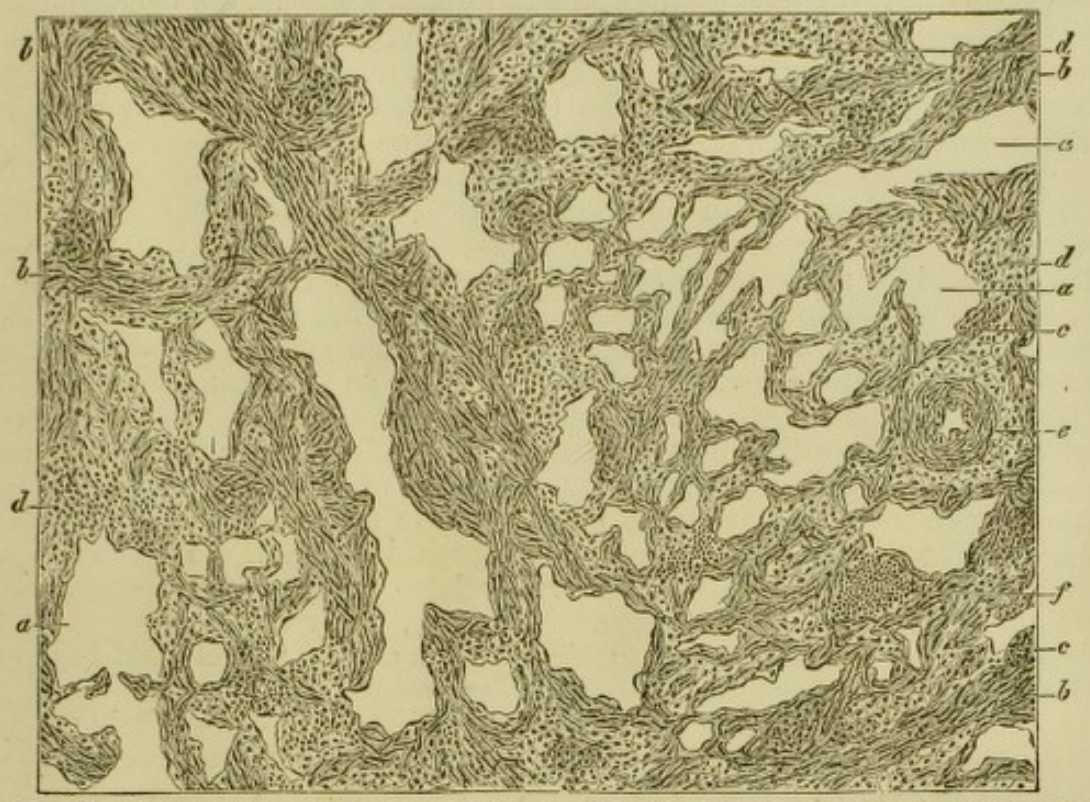


FIG. 257.—Subcutaneous angiomyoma of the back. (Alcohol; hæmatoxylin; eosin.) *a*, Cavernous blood-vessels; muscular strings cut longitudinally at *b*, transversely at *c*; *d*, connective tissue; *e*, artery with hypertrophied muscular layer; *f*, group of lymph-cells. Magnified 50 diameters.

The ill-developed forms consist of narrow bands without transverse striation (*d*); of spindle-cells with long-drawn-out thread-like processes without transverse striation (*g*) or with partial striation (*f*); and also of round cells of different sizes, which show either a radial or a concentric striation (*h*, *i*). Besides these there are also cells which possess

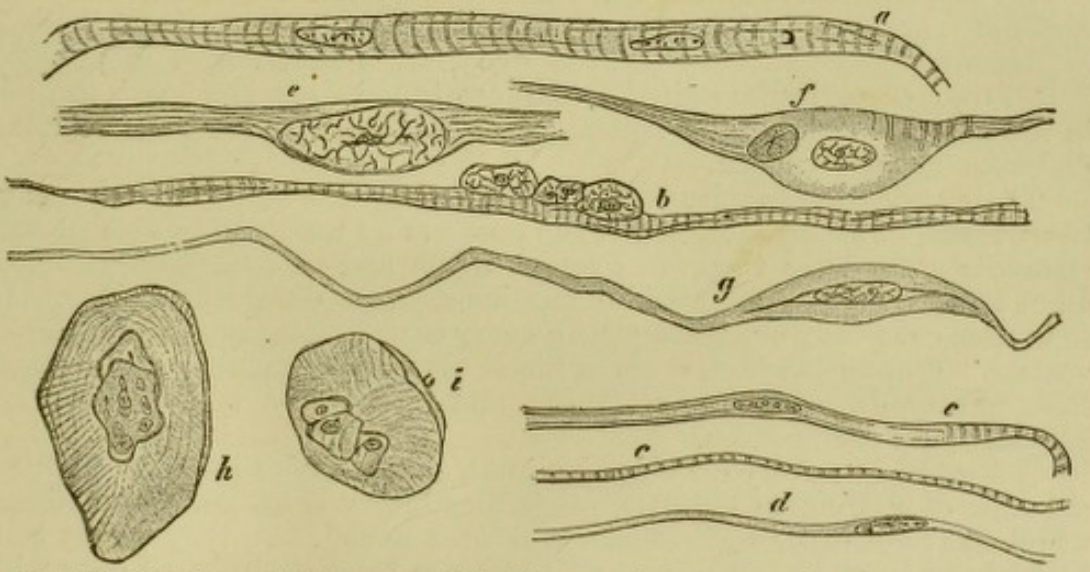


FIG. 258.—Cells from a rhabdomyoma. (After Ribbert and Wolfensberger.) *a*, *b*, *c*, Fibres of various sizes with transverse striation; *d*, small nucleated fibre without striæ; *e*, spindle-cell with longitudinal striæ; *f*, spindle-cell with longitudinal and transverse striæ; *g*, spindle-cells, non-striated, with elongated processes; *h*, *i*, round cells with concentric and radial striation.

no especial characteristic, so that it is impossible to decide whether they are young undeveloped muscle-cells or simple cells of the connective tissue. The bands as well as the spindles are usually in bundles, and interwoven among themselves. It is usually not possible to demonstrate with certainty, on the surface of the fibres, a sarcolemma; but various delicate membranes have been described by different authors which apparently were fragments of a sarcolemma.

Rhabdomyomata occur most frequently in the kidney or in its pelvis, in the testicle, and in the uterus; seldom in other localities, as, for example, in the vagina, in the bladder, in the muscles, in the heart, in the nerves, in the subcutaneous tissue, in the mediastinum, in the œsophagus, etc. They form nodular tumors of varying size, and if situated on the surface of a mucous membrane the new growth is polypoid or papillomatous in shape. They may develop as well from transversely striated muscular tissue as from smooth muscular fibres. In the kidney and testicle they either form well-defined nodules or else they cause the destruction of the whole organ. The growth of these tumors is due apparently to misplaced portions of embryonic muscle-tissue, and consequently the condition is generally congenital. But these tumors may first develop at an advanced age. Sometimes another tissue—e.g., cartilage—is included in the tumor. Moreover, fairly well-developed muscular fibres are found in complicated tumors of the testicle and kidney. (Compare the paragraphs relating to Teratomata.)

If a tumor contains only a few cells which can be definitely recognized as muscle-fibres, while most of the cells have no specific character, it is usually called a *myosarcoma*.

(*h*) *Glioma and Ganglionic Neuroglioma.*

§ 117. **Gliomata** are tumors which grow from the *cells of the stroma of the central nervous system*, and which, when fully developed, consist essentially of these cells. In the brain they form growths which for the most part are not sharply defined from the normal brain-substance, but pass into the latter by insensible gradations. They often, therefore, convey the impression of a local swelling of the brain, and only the difference in color, and a comparison of the healthy with the pathological tissues, suffice to convince the eye that a real tumor is present. When they occur in the spinal cord these tumors are most apt to arise in the neighborhood of the central canal, and may spread over a considerable length of the cord.

Their appearance varies considerably: sometimes they are light gray, translucent, of about the color of the cortex, and moderately firm in consistence; sometimes they are grayish-white and of firmer consistence; and at other times they may be reddish-gray or dark red in color. In the latter case they are traversed in every direction by numerous dilated vessels. Gliomata which contain much blood often exhibit hemorrhagic foci. Fatty degeneration, softening, and destruction of the tissue are also common occurrences.

A section of a fully developed glioma shows under the microscope a network of extremely delicate glistening fibres (Fig. 259, B), among which are embedded numerous short oval nuclei. A very scanty cell-protoplasm surrounds these nuclei, and can be distinguished only with difficulty. When the tissue is investigated in the fresh state or after maceration in Müller's fluid, it is easy to detect that these nuclei belong

to cells (astrocytes) that are characterized by the great number of fine branching processes which they possess, and which extend in every direction (Fig. 259, A). By the employment of suitable staining mixtures one may demonstrate, even in sections, the connection between some, at least, of the fibres (Fig. 260).

The cells closely resemble normal glia-cells, although at times they are much larger, and, in some instances, more spherical in shape. A few of them contain two, three, or even four nuclei.

Investigations with reference to the development of gliomata have proved that the glia-cells are the mother-cells of the tumor. The ganglion-cells do not take any part in the proliferative processes. The abundance of cells in a glioma varies greatly. Sometimes the cells preponderate decidedly, and then at other times the stroma is the more prominent part of the texture. A simultaneous proliferation of the cells of the perivascular connective tissue produces a gliosarcoma.

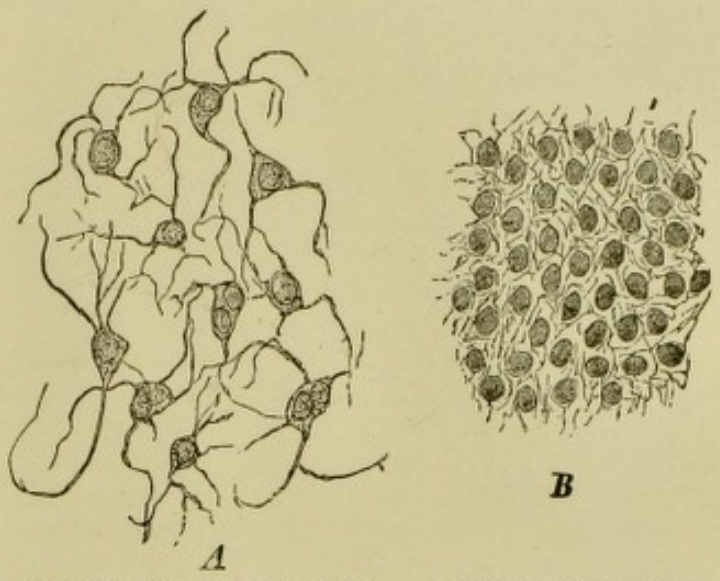


FIG. 259.—Glioma of the cerebrum. *A*, Cells isolated by teasing, and stained with carmine; *B*, section from the same tumor after hardening in Müller's fluid. (Staining with Bismarck brown.) Magnified 350 diameters.

There is often a great increase in the number of blood-vessels, and in some places they may be ectatic.

Gliomata usually occur singly, and do not furnish metastases. Their etiology is unknown. Some gliomata probably originate from imperfectly developed portions of the brain and spinal cord. Traumatism may furnish the exciting cause for their development.

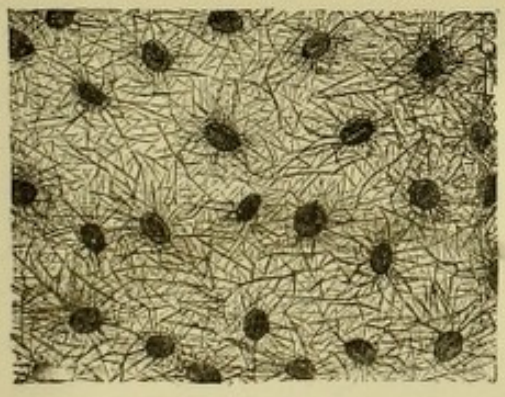


FIG. 260.—Section of a glioma of the cerebrum, with astrocytes. (Müller's fluid; hæmatoxylin, according to Mallory's method.) Magnified 500 diameters.

The name **glioma** is also applied to a tumor of the retina which is observed only in childhood. These growths, a certain proportion of which are of congenital origin, develop in the retina and are evidently due to some disturbance in the development of that organ. They have a soft consistence, are white or grayish-red in color, and are rich in cells. The major portion of the tumor consists of small, round, or irregularly shaped cells, poor in protoplasm, and greatly resembling the cells of the nuclear layer. They possess in places smaller or larger processes. These cells are found best preserved in the neighborhood of the blood-vessels, while in other portions they often show

signs of having undergone degenerative changes. The tumor may also contain (Wintersteiner) ganglion cells, cylindrical cells, and peculiar cell forms like rosettes and bands, these latter being regarded as made up of fibres of the rods and cones. Wintersteiner therefore calls such a tumor a *neuroepithelioma*.

The glioma of the retina often shows areas of necrosis in its centre. If it develops further, it either breaks into the retrobulbar space or for-

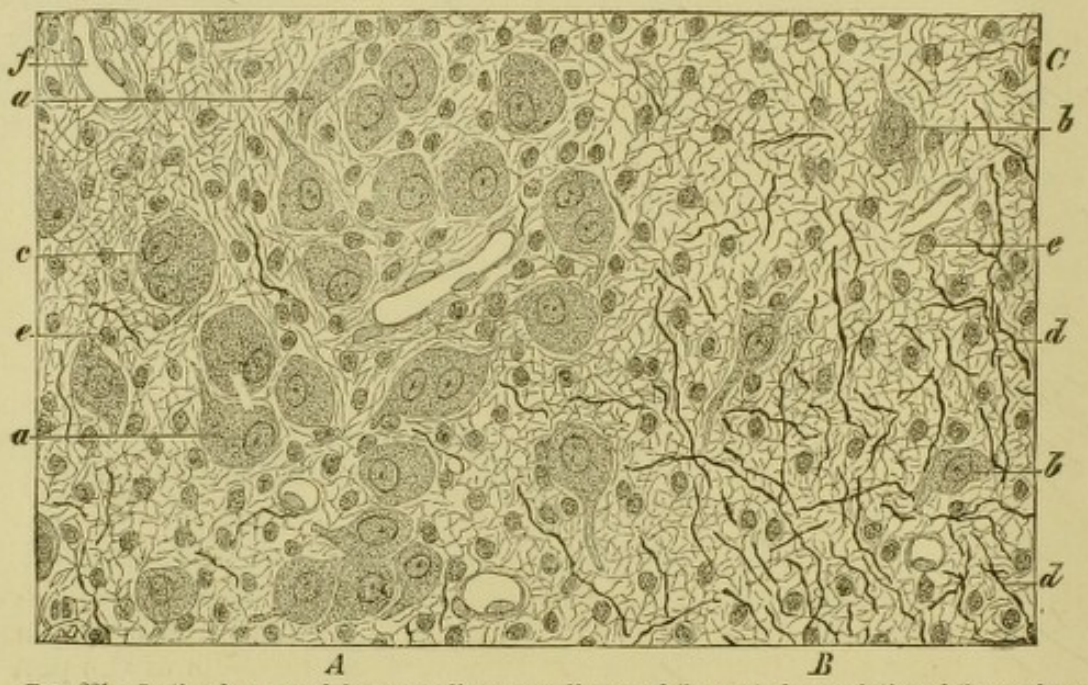


FIG. 261.—Section from a nodular neuroglioma ganglionare of the central convolution of the cerebrum. *A*, Portion of the tumor which is rich in ganglion-cells; *B*, portion containing nerve-fibres; *C*, jelly-like portion. *a*, Ganglion-cells in groups; *b*, individual ganglion-cells; *c*, ganglion-cells with two nuclei; *d*, nerve-fibres with medullary sheaths; *e*, glia-cells; *f*, blood-vessels. (Preparation treated by Weigert's method and mounted in Canada balsam. Details completed from another preparation which had been stained with hæmatoxyiin.) Magnified 300 diameters.

ward through the cornea and sclera. It recurs after excision, and forms metastases.

Neuroglioma ganglionare (Fig. 261) is a term applied to those new growths which arise in the *central nervous system*, are composed of hyperplastic *glia-tissue*, *ganglion-cells*, and *nerve-fibres*, and constitute either ill-defined swellings of the larger masses of the brain or circumscribed nodular enlargements of small sections of this organ. When examined by the naked eye the affected portions of the brain may still appear to be fairly normal; but as a general rule the distinction between gray and white substance is fainter than normal, and the tissue is throughout white or grayish-white or spotted white and gray, and at the same time more or less hardened.

These masses are chiefly made up of more or less dense glia-tissue containing a certain number of nerve-fibres (*d*) and ganglion-cells (*a*, *b*, *c*), not only in the region of the cortex, but also in that of the white substance.

Probably all such formations must be regarded as the result of a disturbance of the embryological development of the brain—that is, as local cerebral malformations, which have undergone further development after birth.

(i) Neuroma and Neurofibroma.

§ 118. The tumors called **neuromata** are observed most often in the ends of amputated nerves, where they form at times quite large swellings, which are either separated from the surrounding tissues by more or less sharply defined limits or are united to them without any such distinct line of separation. From their origin they have received the name of *amputation neuromata* (Fig. 262, *b*). The development of these neuromata is explained in the following manner: After the nerves are cut off, more or less connective tissue forms on the stump, and at the same time the axis-cylinders divide and grow out in length. In this manner the scar-tissue becomes supplied with nerves, which at first have no sheaths, but which very soon become covered with fibrous sheaths and ultimately with medullary ones. The mass of nerves penetrating into the granulation tissue may be very great, so that the connective tissue, after a certain length of time, may contain a rich supply of nerves, which, radiating from the end of the old nerve, spread through the fibrous tissue in every direction (Fig. 262, *b*). We have here, therefore, an instance of the useless regenerative growth of a nerve-stump—a growth which exceeds the physiological necessities of the nerve and so forms a tumor-like mass.

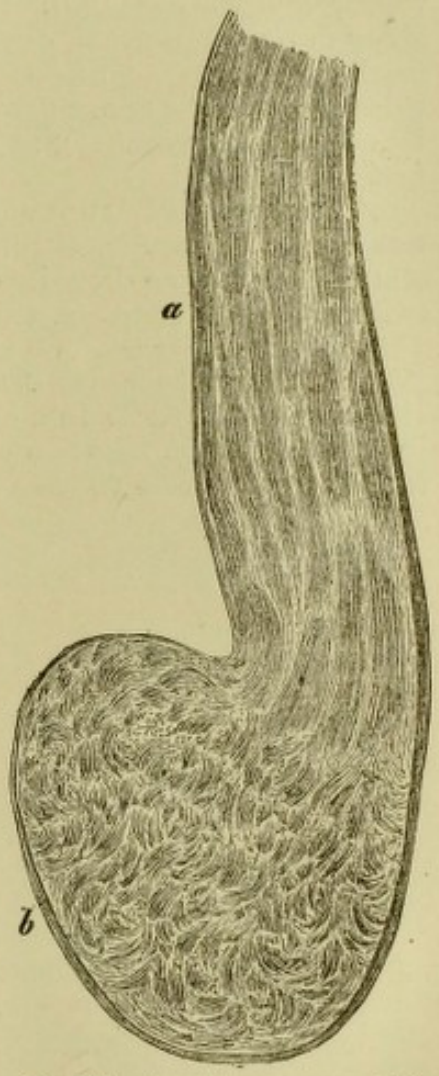


FIG. 262.—Amputation neuroma of the ischiatic nerve (nine years after amputation). Longitudinal section. *a*, Nerve; *b*, neuroma. (Drawn from a preparation which had been hardened in Müller's fluid.) Magnified 3 diameters.

Another form of the so-called neuroma develops spontaneously in the course of a nerve, without any outside provocation. This tumor owes its origin to an *increase of the connective tissue of the nerve*, usually of the outer, more rarely of the inner layers of the endoneurium; as a result of which the nerve-bundles, at the point where the tumor is developing, are inclosed in a more or less thick layer of connective tissue, usually of a loose sort (Fig. 263, *b*, *d*); or these bundles are split open by the growth of connective tissue into separate individual fibres. Sometimes the perineurium is also involved in the proliferative process. Where nerves lie together in a large bundle the epineurium as well as the endoneurium and perineurium of the smaller nerve-bundles may be affected by this process, but this is usually not the case.

These tumors, structurally considered, are not neuromata, but **neurofibromata or fibromata of the nerves.** A number of them are usually present at the same time, and they may occur in all the peripheral nerves, although, as a rule, they are limited to a definite area of nerve-

distribution. The nodules are sometimes situated along the nerve-trunk, sometimes on the finest branches, usually of the cutaneous nerves. These soft connective-tissue nodules, which are scattered about through the skin in smaller or larger numbers, are termed **multiple fibromata of the skin.** The finest nodules are demonstrable only with a microscope, but the usual size is from that of a pea to that of a hazel-nut. Individual tumors may reach the size of a man's fist, the nerve-fibres being quite lost sight of in the great mass of connective tissue, whose continued growth may even cause them to waste away entirely. In addition to this formation of well-defined nodules there may also be, throughout the area of distribution of the affected nerves, *a diffuse thickening of the nerve-fibres, due to hypertrophy of the connective tissue.* And finally, with the conditions mentioned may be associated a hypertrophic thickening of the connective tissue of the skin proper and of the subcutaneous tissue, resulting in *alterations of the skin not unlike those observed in elephantiasis.*

A third form of neuroma is the **cirsoid neuroma** (Bruns) or **plexiform neuroma** (Verneuil), a tumor which is characterized by the circumstance that in the domain of several nerve-branches a convolution of twisted and interwoven, thickened and nodular nerves develops (Fig. 264). An examination of the individual cords reveals this also to be a *fibromatosis of the nerves* (Fig. 263), the excessive growth of the endoneurium resulting partly in a diffuse thickening of the nerve-fibres, partly in a nodular one. But in this case attention should be directed to the fact that the nerves in the territory involved are not only thickened, but

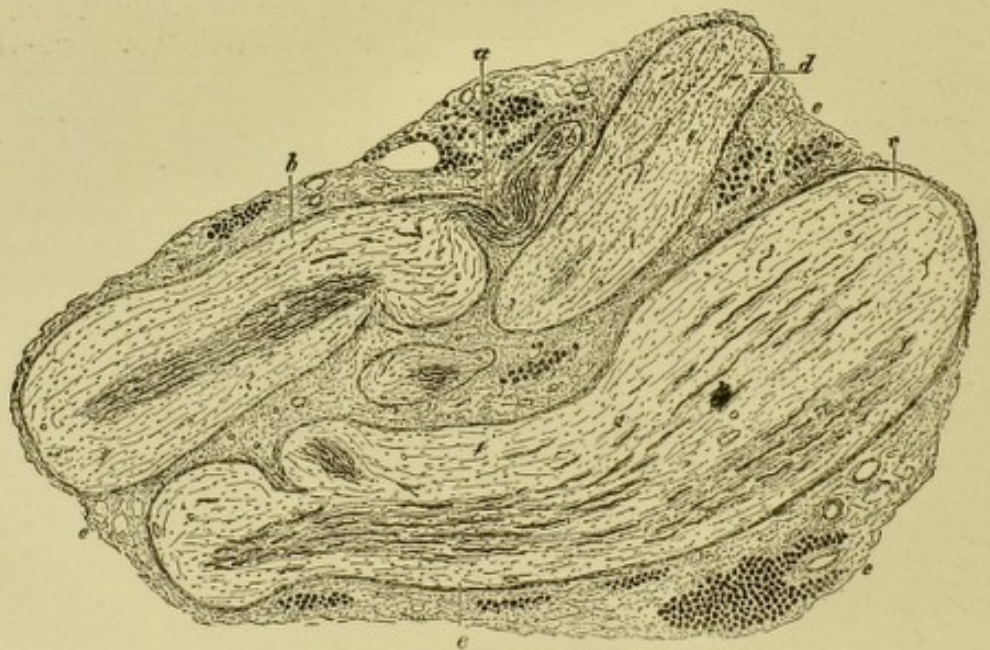


FIG. 263.—Nerves from a cirsoid neuroma which involved the cheek and lower jaw and presented a close resemblance to elephantiasis. (Flemming's mixture; safranin.) *a*, *b*, Nerve, the outer layers of whose endoneurium have undergone decided proliferation; the nerve-fibres proper occupy the axis of the entire mass; *c*, nerve with markedly proliferated endoneurium and separated nerve-fibres; *d*, thickened nerve showing a small bundle of nerve-fibres at the left end; *e*, loose connective tissue, rich in nuclei, lying between the nerves and containing fat-tissue. Magnified 8 diameters.

also actually *increased in length*, and consequently *rendered tortuous;* and, furthermore, that the nerves are *increased in number*, so that the sum total of the nerves situated in the skin and subcutaneous tissue is greater than it should be under normal conditions. The conditions here, therefore, are those of a genuine neuroma, a *neuroma verum*, in

combination with fibromatosis. Most of the nerves in this tumor are medullated (neuroma myelinicum). It is difficult to determine to what extent tumors of this nature contain nerve-fibres which are non-medullated (neuroma amyelinicum); nevertheless cases have been reported in which most of the fibres were found to be non-medullated. Cirsoid neuromata occur on the head, body, and extremities, and are usually characterized by *gross alterations of the skin which remind one strongly of elephantiasis.*

Neurofibromata and cirsoid neuromata do not cause metastases, but in certain cases neuromata take on a sarcomatous and consequently a malignant character. *Hereditary transmission* and *congenital predisposition* have been proved to be concerned in both forms of neuromata.

FIG. 264.—Cirsoid neuroma of the sacral region. (From a drawing by P. Bruns.) The nodular, twisted, and interwoven nerves are dissected out at *a*, while at *b* they are still covered by connective tissue. (Life size.)

(*k*) *Sarcoma.*

§ 119. **A sarcoma** is a *connective-tissue tumor in which the cellular elements are much more prominent than the intercellular substance, not only on account of their number, but often also by reason of their size.* The sarcomata are therefore closely related to undeveloped connective tissue, and a comparison between sarcoma and embryonic tissue is by no means far-fetched.

Sarcomata develop either in a previously normal tissue belonging to the group of connective substances—as, for example, in the skin, in the subcutaneous tissue, in the intermuscular connective tissue, in the periosteum, in the spinal cord, in the membranes of the brain, in the connective-tissue framework of glandular organs, etc.—or else in a fully formed connective-tissue tumor—as, for example, a fibroma, a myoma, a chondroma, an hypertrophic lymphangioma, etc. Finally, the decidua uteri may also serve as a starting-point for the development of a sarcoma. The transformation of the parent tissue into tumor-tissue takes place by growth and multiplication of the existing cells. The cells usually divide by mitosis, and the faster the tumor grows the more numerous are the mitoses. Besides the typical mitoses there are atypical forms of all sorts; sometimes also nuclei broken into fragments. Direct segmentation of nuclei occurs more rarely.

When fully developed, sarcomata form tumors which are separated from the surrounding tissues by more or less sharply defined limits. They may grow in any part of the body where there is connective tissue, but they are found in certain regions far more frequently than in others. For example, they are found much oftener in the skin, fasciæ, inter-

muscular connective tissue, bone, periosteum, brain, and ovaries than in the liver, the intestine, the uterus, and the lungs.

The development and form of the cells vary considerably in different sarcomata. The intercellular substance is sometimes scanty, soft, and delicate; at other times it is more abundant, and resembles in character rather the basic structure of the developed normal connective substances.

The amount of the intercellular substance has a marked influence upon the consistence and color of the tumors. The **medullary variety** presents a marrow-white or grayish-white cut surface, and is rich in cells and poor in intercellular substance. A hard and dense tumor is poorer in cells and richer in fibrous intercellular tissue. Such tumors shade by insensible gradations into fibromata. Varieties upon the border-line are called **fibrosarcomata.** The cut surface of a sarcoma presents throughout very nearly the same appearance, unless retrograde changes or an unequal distribution of blood-vessels cause differences. It is usually uniformly smooth and of a milk-white color in the medullary forms, or clear grayish-white and somewhat translucent, or of a bright grayish-red or grayish-brown, in the firmer varieties. The hard varieties are of a brilliant-white or yellowish-white color.

The development of blood-vessels varies in sarcomata. Sometimes the vessels are remarkably numerous and broad—in fact, ectatic (*telangiectatic sarcomata*). Usually the vessels have walls easily distinguishable from the tumor-substance, but the tumor-cells themselves may also constitute the outer cells of the walls of the vessels; and in such a case the cells of the walls of the vessels also take part in the growth of the tumor. Lymph-vessels have not been demonstrated in sarcomata.

Retrograde changes—such as fatty degeneration, mucoid degeneration, liquefaction, cheesy degeneration, necrosis, hemorrhage, gangrene, ulceration, etc.—are common occurrences in sarcomata.

Sarcomatous tumors may be divided into three classes. The first of these includes the *simple sarcomata*—sarcomata in the narrower sense, that is, tumors which are formed according to the type of fœtal connective tissue, and which show, therefore, a more or less even distribution of the cells, without any formation of separated foci or groups of cells. The second class includes those sarcomata which show *a particular arrangement and grouping of the individual elements*, so that in appearance they resemble the epithelial tumors. The third class is characterized by *secondary changes in the cells, in the intercellular substance, and in the blood-vessels*—changes which give to the tumor a peculiar appearance.

The *etiology of sarcomata* is not a simple one. They occur oftener in youth than in old age. Some develop in fœtal life and owe their origin to some local malformation. Sometimes they develop as the result of a trauma. A parasitic origin has not been demonstrated. Usually there is a single primary tumor; but multiple primary sarcomata are sometimes observed, as, for example, in the skin and in the bone-marrow. The softer tumors lead to metastases.

§ 120. **Simple sarcomata** include both the soft medullary forms and those of a firmer consistence, which shade off insensibly into the fibrosarcomata and the fibromata. Among these forms several subordinate varieties may be distinguished, according to the character of the cells.

Small round-celled sarcomata are very soft, rapidly growing tumors, which develop especially in the connective tissue of the limbs and supporting framework of the body, and also in the skin, testicles, ovaries,

and lymphatic glands. The cut surface of a section of one of these growths appears milky white, and sometimes shows caseous or softened areas. If scraped the surface yields a milky fluid. The structure is very simple. The tumor is composed almost wholly of round cells and vessels (Fig. 265, *c*). The cells are small and frail; they have very little protoplasm, and a spherical or slightly oval, rather large and bladder-like nucleus (*c*), which seems to be more highly developed than the nuclei in lymphatic elements.

Between the cells lies a very scanty amount of granular and delicately fibrillated intercellular substance. The vessels traverse the masses of cells in the form of very thin-walled canals. If the tumor is examined at its very margin of growth among the muscular fibres, its tissue will be found to present an aggregation of round cells (Fig. 265, *b*, *c*) in the connective tissue lying between the muscles. Often in close proximity

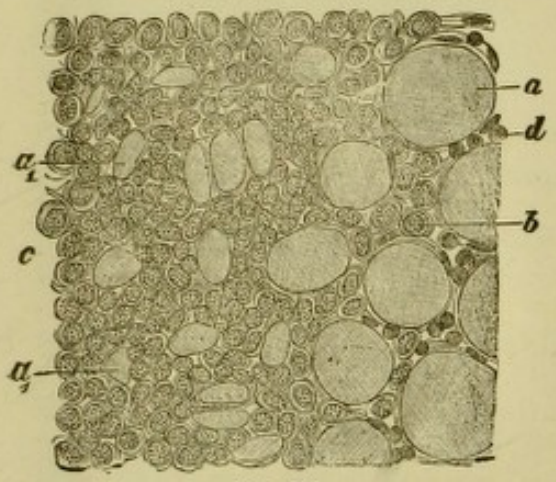


FIG. 265.

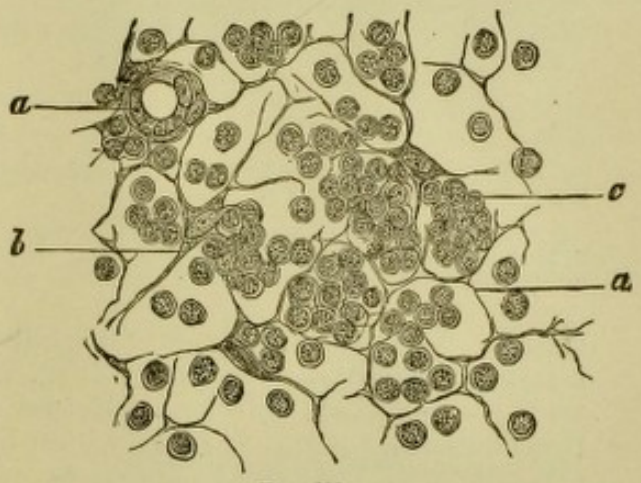


FIG. 266.

FIG. 265.—Section through the margin of a sarcoma of the intermuscular connective tissue of the neck. (Alcohol; carmine.) *a*, Normal muscle cut transversely; a_1, atrophied muscle cut transversely; *b*, round cells of the sarcoma growing between the muscle-fibres; *c*, mature tumor-tissue; *d*, round cells of the character of white blood-corpuscles. Magnified 300 diameters.

FIG. 266.—Section from lymphosarcoma of the mucous membrane of the nose, after shaking it about in water to free it from the greater number of its cells. (Alcohol; carmine.) *a*, Reticulum; *b*, cells of the reticulum; *c*, round cells; *d*, blood-vessel with actively growing cells. Magnified 300 diameters.

to the cells of the tumor there are lymphatic elements whose nuclei (*d*) stain more deeply than those of the tumor itself.

A second form of round-celled sarcoma is called **lymphosarcoma.** This tumor imitates in structure the lymphatic glands, at least to this extent: that the stroma which holds together large numbers of round cells, is composed of a vascular reticulum (Fig. 266, *a*), a part of which, at least, is made up of branching and anastomosing cells (*b*). These relations are easily made clear by shaking a section in a test-tube.

According to the degree of development of the reticulum which they possess, one may divide the *lymphosarcomata* into two forms—*the soft* and *the hard*. In the firmer specimens of this variety of new growth the reticular framework substance may present a more or less close resemblance to ordinary fibrous connective tissue.

Lymphosarcomata occur most frequently in the lymphatic glands and the lymphadenoid tissue of the mucous membranes and the spleen, but they are also found in other situations. The tumor, in its growth, involves, one after another, a more or less considerable portion of the lymphadenoid tissues enumerated.

Large round-celled sarcomata occur in the same localities where the small round-celled sarcomata are found, but their cells are much larger than those of the latter. These two forms of tumors resemble each other closely, although the large-celled variety is not so soft as the small-

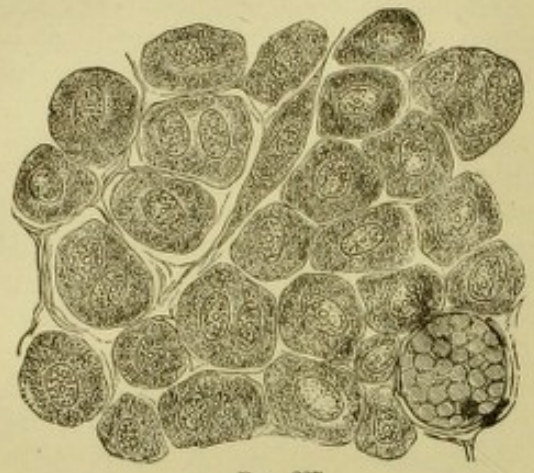


FIG. 267.

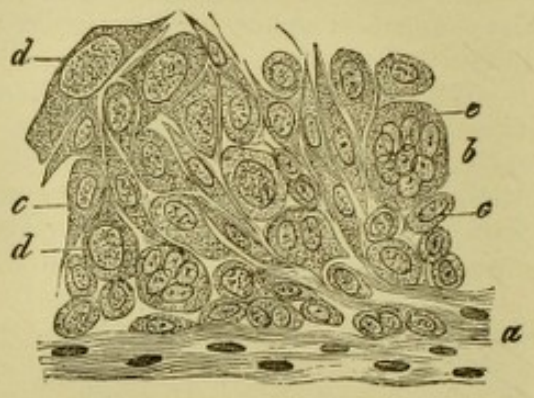


FIG. 268.

FIG. 267.—Section from a fungoid large round-celled sarcoma of the skin of the leg. (Carmine preparation.) Magnified 400 diameters.

FIG. 268.—Section of a sarcoma of the breast, with variously shaped cells. (Alcohol; Bismarck brown.) *a*, Connective tissue; *b*, sarcomatous tissue; *c*, smaller cells; *d*, cells with hypertrophic nuclei; *e*, multinuclear cells. Magnified 300 diameters.

celled. The cells are richly supplied with protoplasm, and possess large bladder-like oval nuclei (Fig. 267). Many of the cells have two nuclei, some more than two. Between the cells is a reticulated intercellular substance (Fig. 267), in which both spindle-shaped and branching cells unite to form an alveolar network in whose meshes the large round epithelioid cells lie. For this reason such tumors have been called *large round-celled alveolar sarcomata* (Billroth).

In other forms of large round-celled sarcomata the cells are of varying size (Fig. 268), and among them are many long or irregularly shaped cells, so that the tumor may well be called a **sarcoma with polymorphous cells.** The nuclei, too, vary much in size (Fig. 268) in these tumors, and there may be a large number of them in a single cell (*e*) (multinucleated giant cells).

The large round-celled sarcomata and the sarcomata with polymorphous cells are in general not so malignant as the small round-celled ones; but nevertheless they do give rise to metastases.

Spindle-celled sarcomata are among the commonest of tumors. They are usually much denser than the round-celled varieties, but they may also be of a soft *medullary character.* A cut section usually appears grayish or yellowish-white and somewhat translucent, or it may present a more or less reddish hue by reason of its vascularity. Medullary tumors whose cells have undergone fatty degeneration may have a pure white color. In general these tumors are much less malignant than the round-celled ones, but their character in this respect varies according to their location and their richness in cells.

According as the cells are large or small, we may distinguish **large spindle-celled and small spindle-celled sarcomata.** By teasing small bits of the tumor-tissue some of the cells may be isolated, and in this way very long spindles may occasionally be obtained (Fig. 269). The cells lie side by side, arranged in bundles, which in a section may be

cut transversely or obliquely or longitudinally—a proof that they are interwoven in different directions.

This arrangement of the spindle-cells in bundles is often very striking. In other cases it is entirely absent (Fig. 271), and for considerable distances the spindles will be found to lie in the same direction. Sometimes the direction of the spindles is determined by the direction of the blood-vessels—i.e., the individual bundles build each a sheath about its own blood-vessel.

Between the spindle-cells there may be a very small amount of intercellular substance, or it may not be possible in the section to demonstrate any intercellular substance. In other cases it is more abundant and of a fibrillary character. In such cases the cells have less protoplasm, so that often it is scarcely possible to demonstrate any protoplasm around the nucleus, and the processes at the poles of the cell seem to spring directly from the nucleus (nuclear fibres). Such varieties are dense and hard. They form the connecting-link between sarcomata and fibromata, and are called **fibrosarcomata.**

Sarcomata with polymorphous cells are also found among the spindle-celled sarcomata. They contain spindle-shaped, triangular, and prismatic cells, and also star-shaped cells and cells which are quite irregular in shape (Fig. 270).

Both in polymorphous-celled and in spindle-celled sarcomata are found more or less numerous giant cells (Figs. 268, 270, and 271), so

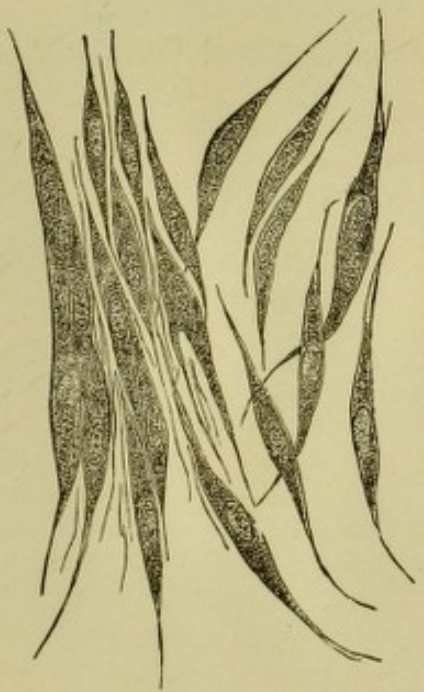


FIG. 269.

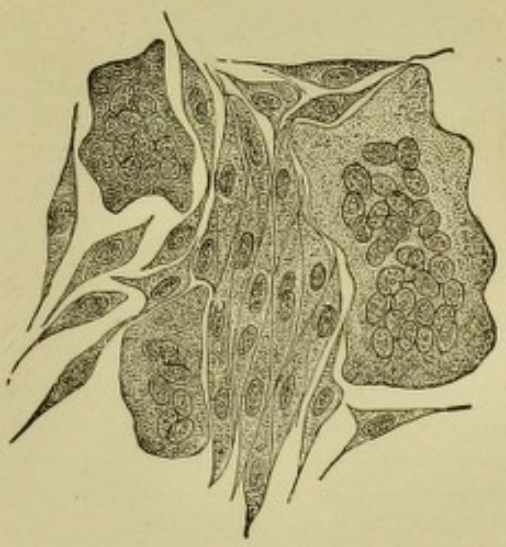


FIG. 270.

FIG. 269.—Spindle-cells from a large spindle-celled sarcoma of the cheek. (Teased preparation.) Magnified 400 diameters.

FIG. 270.—Cells from a medullary giant-celled sarcoma of the tibia. (Preparation stained with hæmatoxylin.) Magnified 400 diameters.

that the name of **giant-cell sarcoma** may properly be applied to these tumors. They develop most often from some part of the osseous system, but they are found in other parts of the body also.

If a sarcoma develops in a preëxisting new growth, a mixed form of

tumor results, to which the names **myxosarcoma** (Fig. 229), **chondrosarcoma** (Fig. 234), **myosarcoma**, etc., are given. If bone develops in a sarcoma, we have an **osteosarcoma.**

Lymphosarcoma of the lymph-glands and of the lymphatic system of the spleen and of the mucous membrane of the intestinal tract produces a peculiar condition of the affected

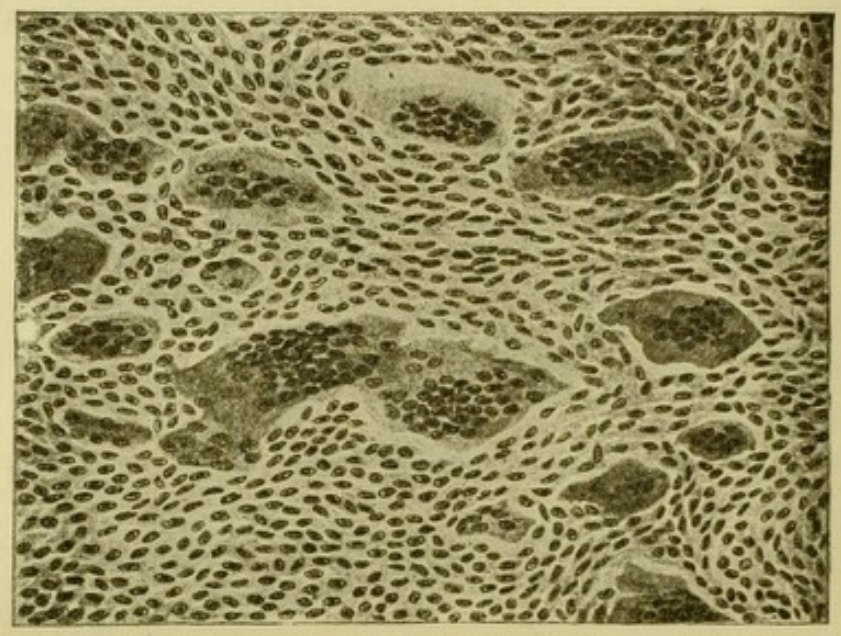


FIG. 271.—Giant-cell sarcoma of the upper jaw. (Müller's fluid; hæmatoxylin.) Magnified 400 diameters.

organs; the progressive increase in the lymphadenoid tissue leading to the formation of large nodules. Under these circumstances the characteristic structure of the lymphatic system is lost and the new-formed tissue also shows considerable variations from the structure of typical lymphadenoid tissue—e.g., fibrous thickening of the reticulum, or the production of giant cells. As similar growths also occur in other organs, such as the liver, the disease cannot be looked upon as a simple hypertrophy of the lymphadenoid tissue, but is closely associated with tumor building. It is possible that it may be an infectious disease.

§ 121. **Sarcomata which present an organoid structure** are found among those forms called **alveolar sarcomata** and **tubular sarcomata.** These growths are connective-tissue tumors in which the cells, especially the larger ones, are arranged in groups, so that it is possible to distinguish a *vascular stroma* and *separate aggregations of cells.* According to their genesis these tumors may be divided into two classes: endotheliomata and hæmangiosarcomata. There are also sarcomata of an alveolar type which possess stroma and cell-nests, but which cannot—so far as their development is concerned—be included with the above-named classes.

The **endotheliomata** are organoid sarcomata in which the large cells of the cell-masses and strings are derived from a *proliferation of the endothelium of the lymph-spaces and lymph-vessels.* They may therefore be called **lymphangiosarcomata.** They develop in previously healthy tissue, or in tumors already formed, especially in hypertrophic lymphangiomata (pigment spots and warts; cf. § 115), and in myxochondromata. The localities in which they are particularly likely to develop from healthy tissue are the membranes of the skull and the serous membranes of the great cavities of the body, but they may also develop in the same manner in other organs. When they develop from hypertrophic lym-

phangiomata, it is usually from such as are seated in the skin. Finally, when they take their start from a myxomatous tumor, the latter is apt to be one of the mixed growths found in the salivary glands, the palate, or the orbit.

Endotheliomata of the delicate membranes of the brain or spinal cord may be either nodular or flattened growths. Their mode of growth is the following: The flat endothelial cells which clothe the connective-tissue network of the subarachnoid tissue and of the pia become swollen and assume the appearance of cubical or even of cylindrical cells (Fig. 272, *d*, *e*). Consequently the new growth at first presents the characteristics of *tubular gland-like formations;* and, when the process of proliferation is active, even solid *nests of cells* may be formed. Inasmuch as the pia extends into the brain as a lymphatic sheath over the cerebral vessels, the further advancement of the new growth will take place in the form of cords of large cells (like epithelial cells) following the course of these vessels (Fig. 272, *f*, *g*, *h*).

Endotheliomata of the dura mater are formed by a proliferation of the endothelial cells of the lymph-vessels; and through a filling up of the

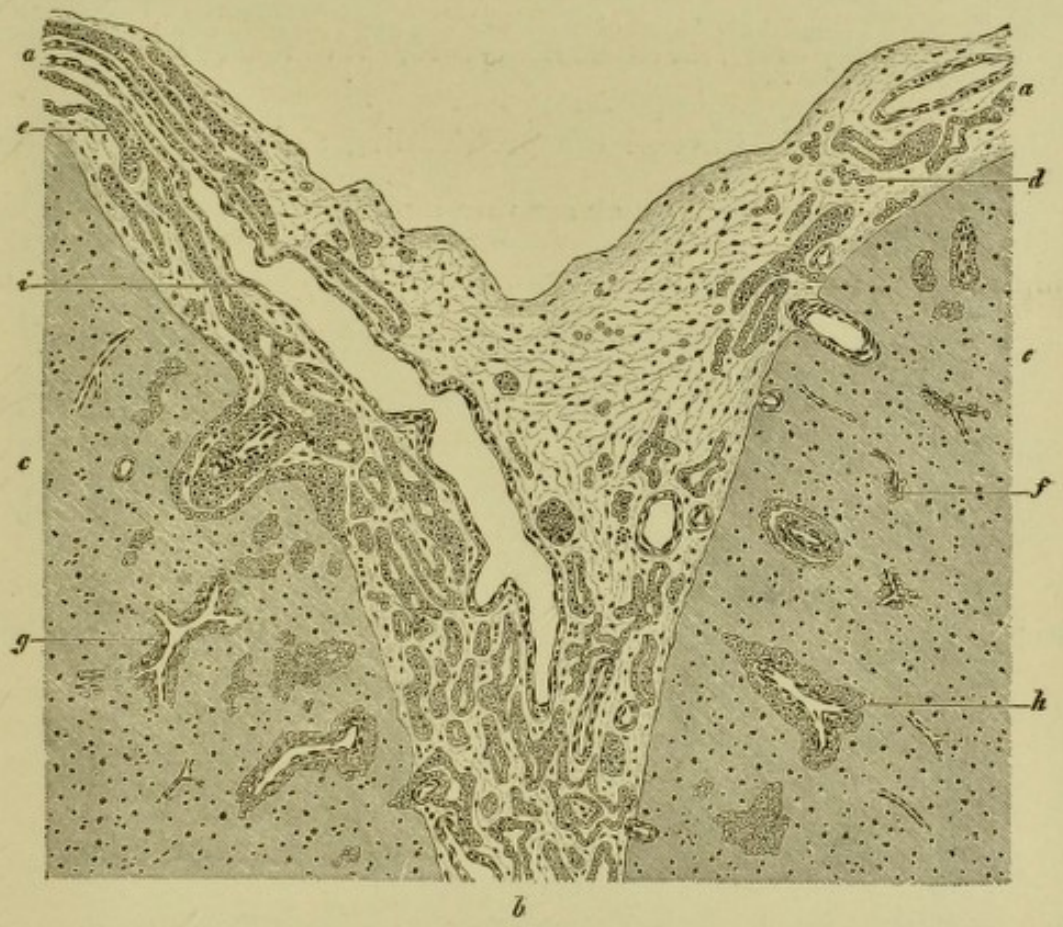


FIG. 272.—Section through an endothelioma of the pia mater and cerebral cortex, diffusely spread out over the surface of the brain and spinal cord. (Müller's fluid; hæmatoxylin.) *a*, Pia mater on the surface, *b*, in a sulcus, of the brain; c, cortex; *d*, *e*, endothelial growths in the subarachnoid spaces; *f*, *g*, *h*, endothelial growths in the pial sheaths of the cortical vessels; *i*, longitudinal section through a vein. Magnified 30 diameters.

same with large cells, there are formed anastomosing strings of cells (Fig. 273, *c*, *d*, *e*) which in some places may still preserve a lumen.

Endotheliomata of the pleura or of the peritoneum are usually flat growths with a certain number of nodular elevations. They are charac-

terized by strings of large cells (Fig. 274, *b*), which, following the course

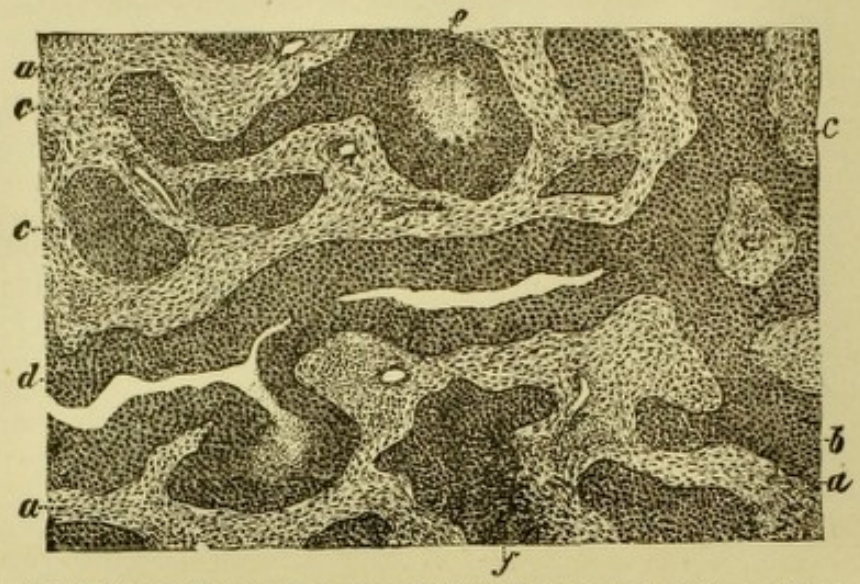


FIG. 273.—Endothelioma of the dura mater. (Müller's fluid; hæmatoxylin.) *a*, Stroma of connective tissue; *b*, an aggregation of small round cells; *c*, nests and cords of cells, resulting from the proliferation of the endothelium of the lymph-vessels; *d*, cord of endothelial cells with a lumen; *e*, area of fatty degeneration in a nest of endothelial cells; *f*, cord of cells, gradually mixing with the bordering connective tissue on the right. Magnified 25 diameters.

of the lymph-vessels, traverse the proliferating and already hypertrophied tissue of the serosa.

Endotheliomata of the mamma are rare tumors. They develop in the form of nodules, through the proliferation of the endothelium of the lymph-vessels and lymph-spaces (Fig. 275, *b*, *c*), and in the course of

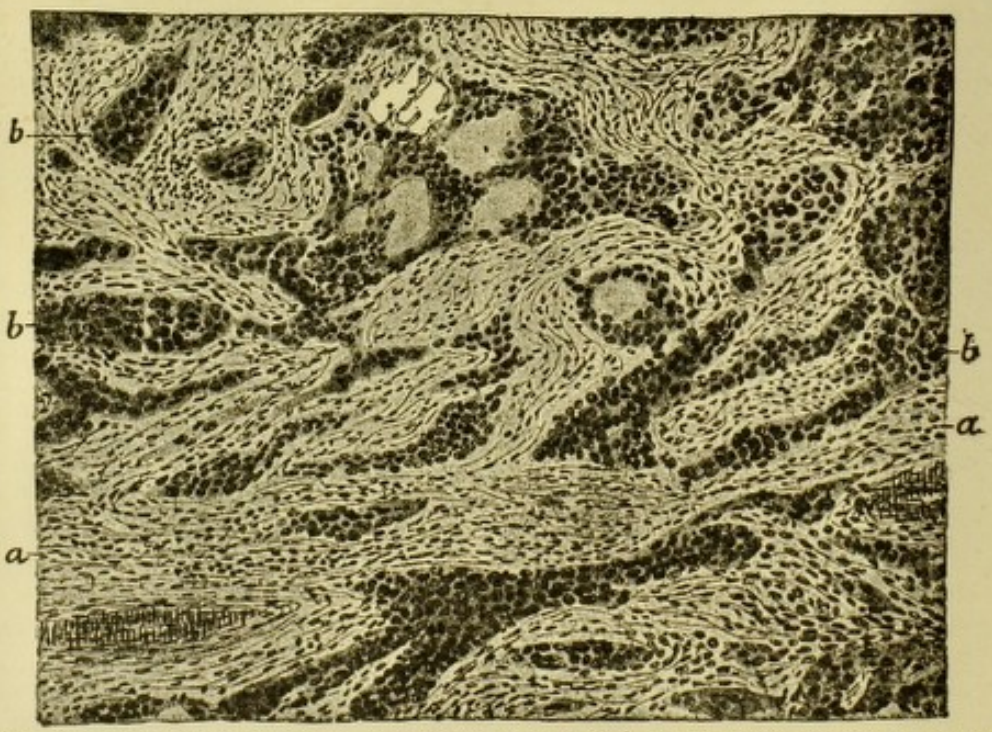


FIG. 274.—Endothelioma of the pleura. (Alcohol; hæmatoxylin.) *a*, Thickened connective tissue of the pleura, the result of proliferative activity; *b*, cord-like masses of cells. Magnified 100 diameters.

their growth they produce, in some places, large strings of cells (*c*), in others smaller clumps of cells. The proliferating cells vary much in

the size and composition, as well as in the form, of both the nucleus and the cell-body.

Endotheliomata of the skin, which develop from hypertrophic lymphangiomata (warts and moles), possess a structure similar to that of the original growth, and therefore also have cell-nests of varying size (Fig. 254).

The endothelial growths which occur in myxomata and myxochondromata form strings of cells of different shapes (Fig. 229, *b*); but it is to be remembered that similar growths spring from blood-vessels (Fig. 278, *c*, *d*), so that a definite conclusion in regard to the nature of the strings is often impossible.

The alveolar or tubular or plexiform structure of endotheliomata is sharply defined only in the early stages of the growth, and is likely to disappear, at least in part, as that growth progresses. This is due, on the one hand, to the fact that the endothelial proliferation extends, with-

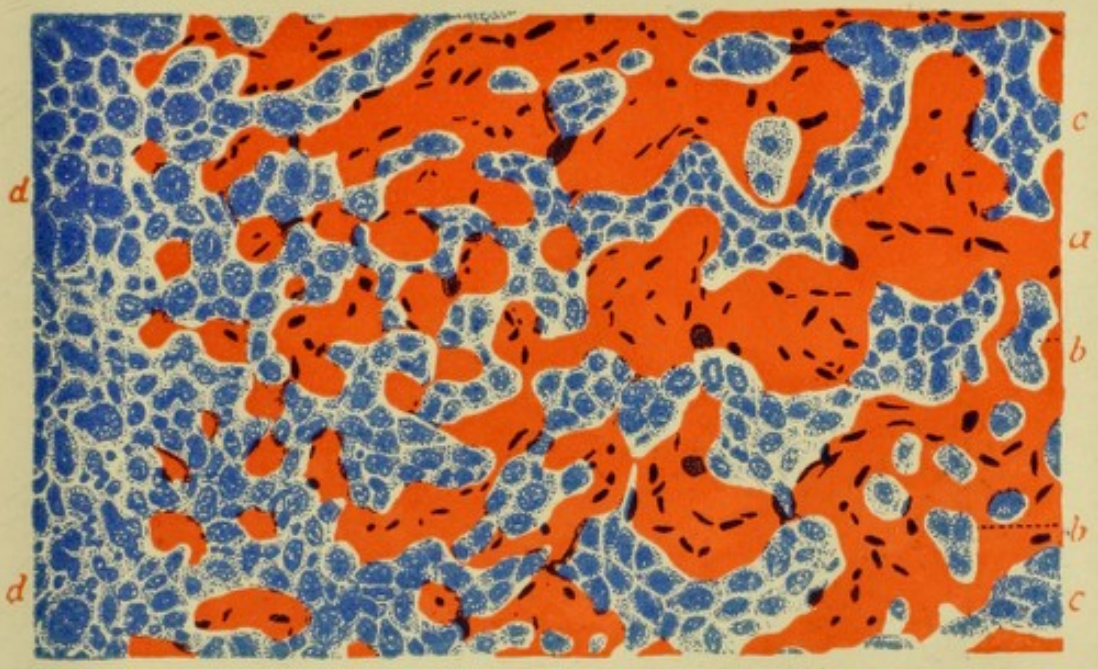


FIG. 275.—Endothelioma of the mammary gland. (Alcohol; hæmatoxylin; eosin.) *a*, Connective tissue; *b*, enlarged cells in the interstices of the connective tissue; *c*, cord-like masses of cells; *d*, diffuse growth of cells. Magnified 300 diameters.

out sharp limits, into the surrounding connective tissue (Fig. 273, *f*); and, on the other, to the circumstance that the connective-tissue cells themselves take on a new activity similar to that of the endothelial tissue. The result of this double proliferative activity is the production of a cellular new growth of considerable size and possessing the characters of an ordinary sarcoma (Fig. 275, *d*). Accordingly, no sharp dividing line can be drawn between the endotheliomata and the sarcomata; indeed, as a matter of fact, the former may gradually become altered into the latter.

The similarity in structure between the endotheliomata and the carcinomata raises the question whether it would not be better to designate the endotheliomata as *endothelial cancers*. The structure of the tumors would certainly justify us in following such a course, and yet at the same time I consider it better to avoid the use of this term. In the first place, the term endothelioma is in general use and is quite appropriate, so that the introduction of the term endothelial cancer would easily give rise to uncertainty. The term cancer is usually employed to designate an epithelial tumor, and consequently

it does not seem desirable to introduce two types of cancer—an epithelial and an endothelial variety.

I have classed as endotheliomata those tumors of the serous membranes which are characterized by the formation of strings of cells in the lymph-channels, and in so doing I have assumed that the strings of cells are derived from the endothelium of the lymph-vessels and lymph-spaces. I must admit, however, that I do not consider this supposition absolutely proved, in spite of the definite statements of certain authors (cf. Glockner). The possibility of their development out of the epithelium of the serosa is not excluded (Benda), and if it were, there would still remain the question whether it would not be better to reckon such tumors with the cancers, as is done with the corresponding tumors of the kidney and the ovary, the glandular cells of which organs are derived from the peritoneal epithelium.

§ 122. The **hæmangiosarcomata** or **angiosarcomata**, in the narrower sense of the term, make up a group of organoid sarcomata, in which the walls of the blood-vessels and their surroundings not only participate in a special manner in the building-up of the tumors, but also at the same time they constitute a characteristic portion of these growths.

In typical cases the substance of the tumor may be made up almost entirely of a mass of blood-vessels (Fig. 276, *a*), the walls of which are surrounded by thick layers of cells extending often to the endothelium (*b*). The thick-walled tubes of cells sometimes pursue an isolated course, and at other times they form anastomoses, thus furnishing a picture in which there is much twisting and curving of the parts (plexiform angiosarcoma).

The perivascular mantle of cells, which is a characteristic feature of an hæmangiosarcoma, may constitute the chief portion of the tumor (Fig. 276, *a*, *b*, *c*; Fig. 277, *a*), so that the remaining tissues, represent-

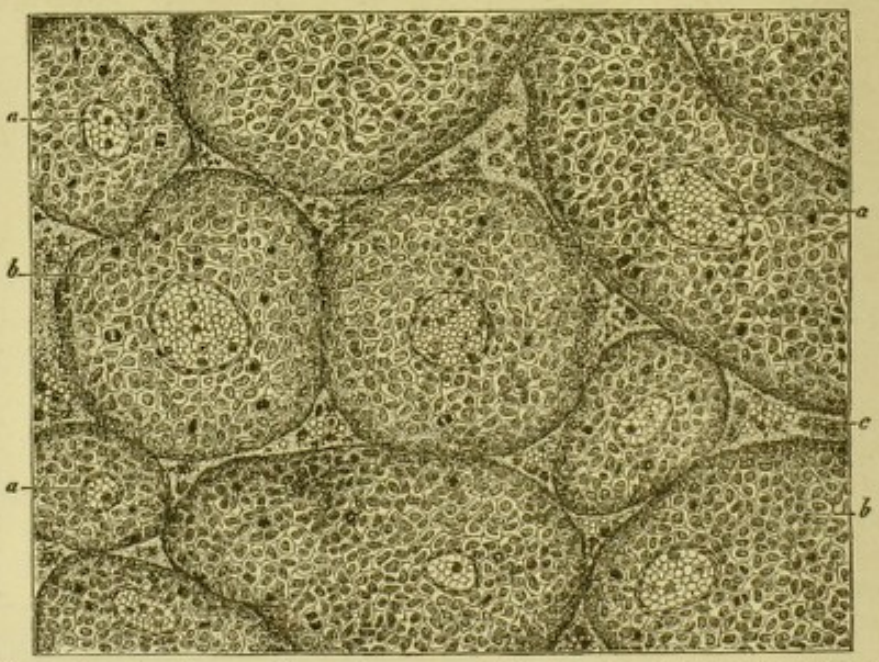


FIG. 276.—Section through a nodular angiosarcoma of the thyroid. (Flemming's mixture; safranin.) *a*, *a*, Vessels in section; *b*, perivascular cellular cylinder in cross-section, showing numerous mitoses; *c*, granular masses with scattered cells between the cellular cylinders. Magnified 80 diameters.

ing all that is left of the original structures, are decidedly put into the background. In other cases the strings of cells which are derived from the blood-vessels constitute only an insignificant portion of the tumor (Fig. 278, *d*); and while they give to certain parts of it a characteristic appearance, yet their bulk is far less than that of other con-

stituents—such, for example, as the cellular fibrous tissue and the cartilage tissue (Fig. 278, *b*, *a*), or the myxomatous tissue (Fig. 284). If there is a marked growth of the perivascular tubes of cells, and if these, in the course of their growth, become fused one with another (Fig. 277), the angiosarcoma will simply become an ordinary sarcoma, a transformation which invariably takes place in large tumors of this character.

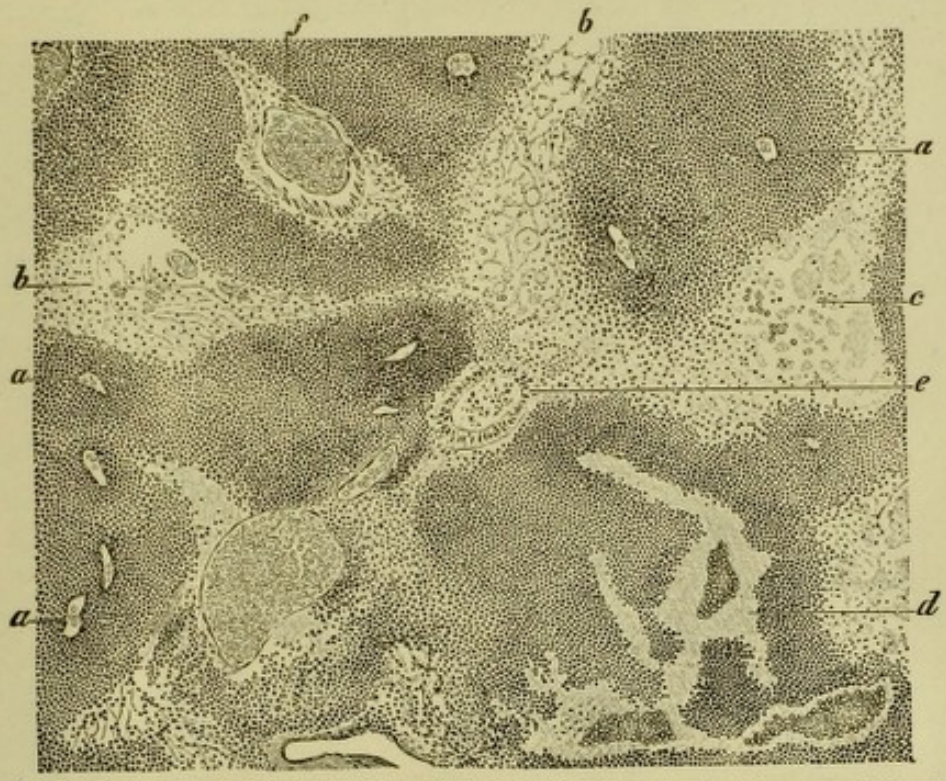


FIG. 277.—Angiosarcoma of the testicle. *a*, Closely packed masses of cells lying around the blood-vessels; *b*, parts of the tissue in which there are very few cells; *c*, hyaline scales; *d*, hyaline mass in which blood is imprisoned; *e*, seminiferous tubules; *f*, large vein. (Müller's fluid; hæmatoxylin; eosin.) Magnified 80 diameters.

Hæmangiosarcomata occur in various organs—in the testicles, kidneys, salivary glands, brain, mamma, bones, thyroid gland, and liver; but they are rarely encountered in the last-named organs.

Endotheliomata or lymphangiosarcomata and hæmangiosarcomata are not sharply differentiated from each other, and there are certain tumors which may properly be called by one or the other name. The perivascular development of the endothelial growth in the brain, in endothelioma of the pia (Fig. 272, *f*, *g*, *h*), merits also the name hæmangiosarcoma. If the endothelium of the blood-vessels of an hæmangiosarcoma proliferates (Fig. 284, *d*), the term endothelioma may also appropriately be employed.

If the cell-nests, in a lymphangioma of the skin, increase so greatly in number that the spaces between the vessels are completely filled with cells, while the framework of the tumor is composed entirely of the blood-vessels (Fig. 279), it is an open question whether the tumor should be called an endothelioma or a hæmangiosarcoma.

The term *angiosarcoma* is not used with the same meaning by all authors. Waldeyer introduced the name for tumors springing from the adventitia of blood-vessels. Kolaczek has extended its use so that it shall include also those which spring from the lymph-vessels, and many authors have followed his lead. It certainly is more correct, as well as more practical, to employ the name only for those tumors to which it was

originally given (i.e., for tumors which spring from blood-vessels), and to apply the name endothelioma to tumors starting from the endothelial cells of lymph-vessels and lymph-spaces. If, however, the application of the term is insisted upon for both classes of tumors, then it is very desirable that the terms *hæmangiosarcoma* and *lymphangiosarcoma* should be employed. The suggestion that the term *perithelioma* should be used in the place of hæmangiosarcoma has not met with a favorable reception, and besides it seems superfluous to introduce a new term with which to designate an angiosarcoma.

It is the custom with a number of authors to use the term angiosarcoma in all cases in which the blood-vessels and the sarcomatous tissue are so markedly developed that

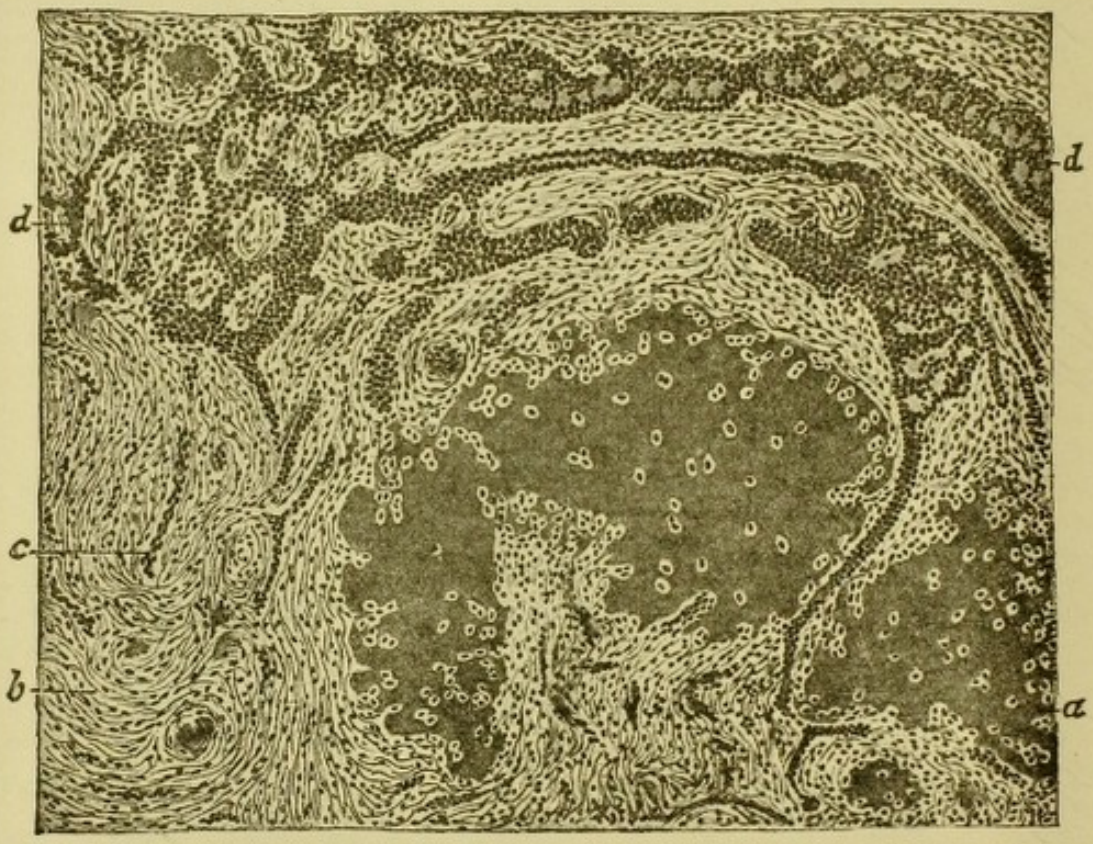


FIG. 278.—Chondrofibroma of one portion of the parotid gland, and angrosarcoma or another. (Müller's fluid; hæmatoxylin; eosin.) *a*, Area of cartilaginous growth; *b*, firm sarcomatous tissue; *c*, blood-vessels; *d*, cord-like masses of cells which have grown out from blood-vessels, and which show, here and there, small hyaline areas. Magnified 80 diameters.

they stand out in striking contrast. Such a special employment of the term is not to be commended.

§ 123. **Sarcomata which acquire a peculiar character, either because their cellular elements produce some special substance or because certain changes take place in the framework of the tumor,** are to be found both among the usual types of sarcoma and also among those which possess an organoid structure. The chief examples of tumors which belong in this category are the melanosarcomata, the chloromata, the osteoid sarcomata, the petrifying sarcomata, the psammomata, and the sarcomata in which there are hyaline formations.

Melanosarcomata are developed in tissues which contain pigmented connective-tissue cells—*chromatophores*. They are most often found in the choroid of the eye and in the skin. In the latter situation moles and birth-marks form their usual starting-point. They belong to the malignant sarcomata, which grow into the neighboring tissues, and form metastases. The fully developed tumor is in whole or in part smoky gray or black or brown, the color being due to the presence of round or

angular or fusiform or branching cells, which are either filled with yellowish-brown pigment granules (Fig. 279, *b*, *e*, and Fig. 280, *c*), or are stained a diffuse yellow. In sarcomata of an alveolar type, the pigment may lie in the large nests of cells or in the small cells of the framework. It is found to be especially abundant in the vicinity of the blood-vessels (Fig. 279, *e*, and Fig. 280, *d*), but this pigment is not hæmosiderin (cf. § 73).

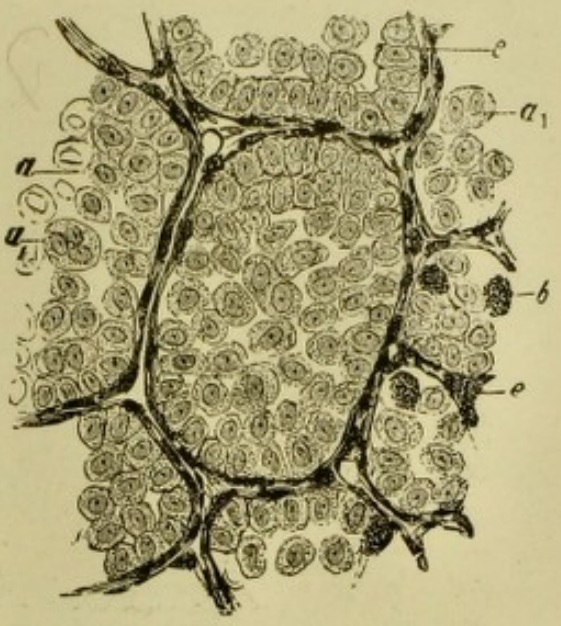


FIG. 279.—Section through a melanotic alveolar sarcoma of the skin. (Alcohol; hæmatoxylin.) *a*, Sarcoma-cell of an epithelial character containing one nucleus; a_1, the same, with more than one nucleus; *b*, cells containing pigment; *e*, stroma containing blood-vessels and pigment. Magnified 300 diameters.

The metastases are also more or less pigmented, and sometimes they are of even a darker shade than the mother tumor.

Chloromata are characterized by a color which appears bright green on the freshly cut surface, but changes to a dirty hue when the latter is exposed to the air for a short time. They develop most frequently from the periosteum of the cranium, and are formed of a tissue composed of round cells and a reticulated framework. They may therefore be reckoned among the lymphosarcomata.

According to Chiari and Huber, the green color is due to the pres-

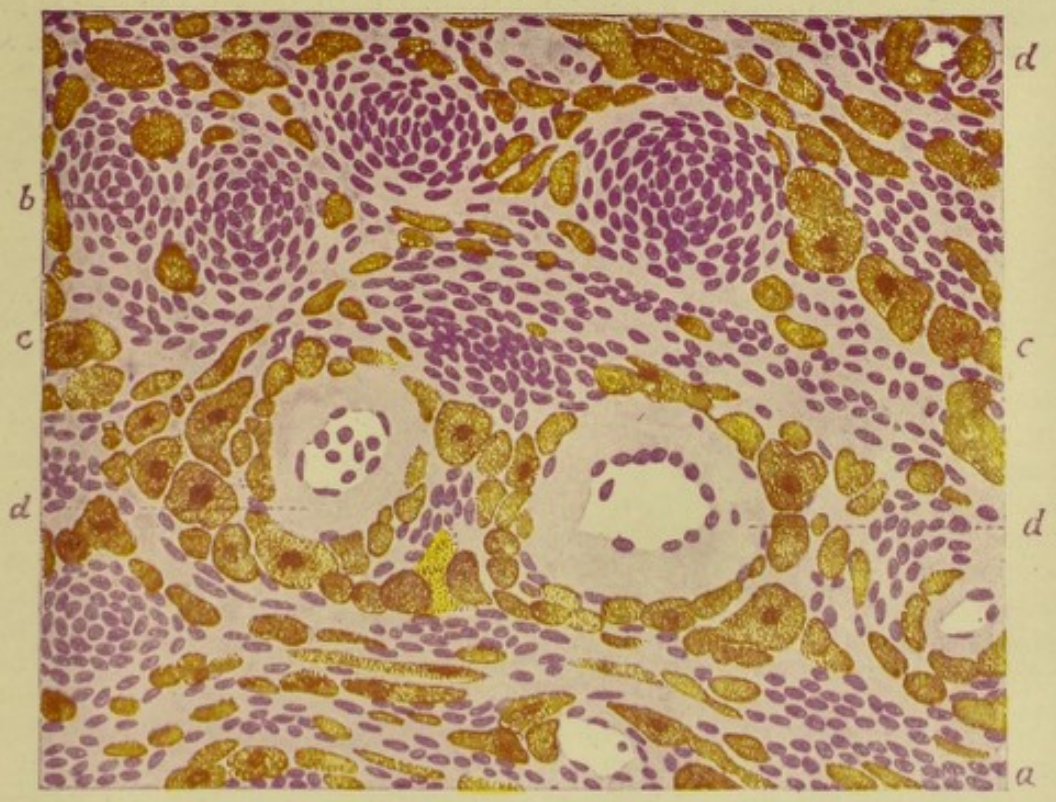


FIG. 280.—Melanosarcoma of the skin. (Alcohol; carmine; eosin.) *a*, Sarcoma tissue, rich in cells; *b*, nests of cells; *c*, pigment cells; d, blood-vessels with walls which have undergone hyaline degeneration. Magnified 300 diameters.

ence in the cells of small shining spherules which give the microchemical reaction of fat. The disappearance of the color in alcohol lends

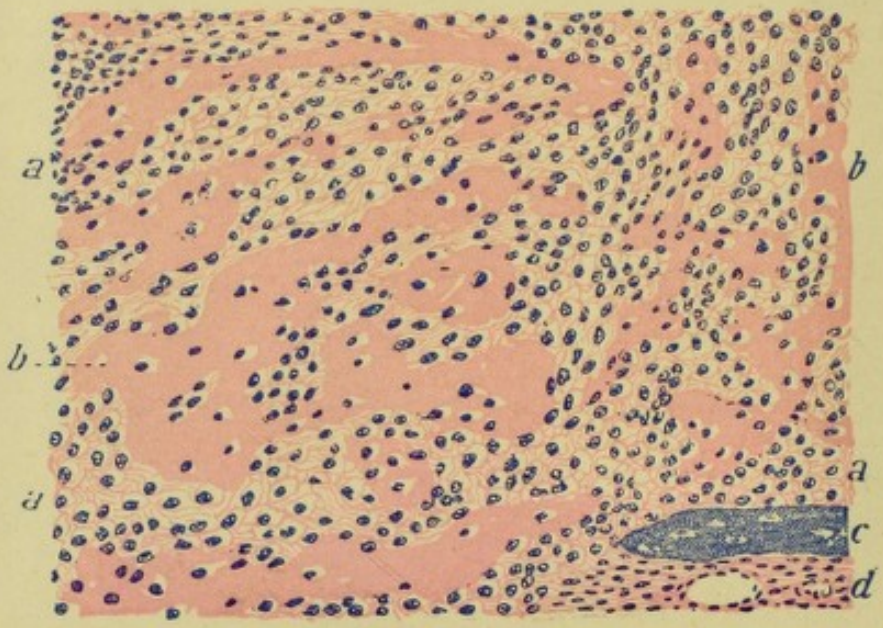


FIG. 281.—Osteoid sarcoma of the ethmoid bone. (Müller's fluid; hæmatoxylin; eosin.) *a*, Sarcoma-tissue; *b*, osteoid tissue; *c*, plate of old bone; *d*, vascular fibrous tissue. Magnified 45 diameters.

support to this statement. On the other hand, von Recklinghausen claims that the color is parenchymatous.

Osteoid sarcomata develop in the marrow of bones and in their periosteum, and are characterized by the fact that in certain portions of the framework of the growth a condensation of the tissue takes place, i.e., *trabeculæ of osteoid tissue* are formed (Fig. 281, *b*). A tumor of this na-

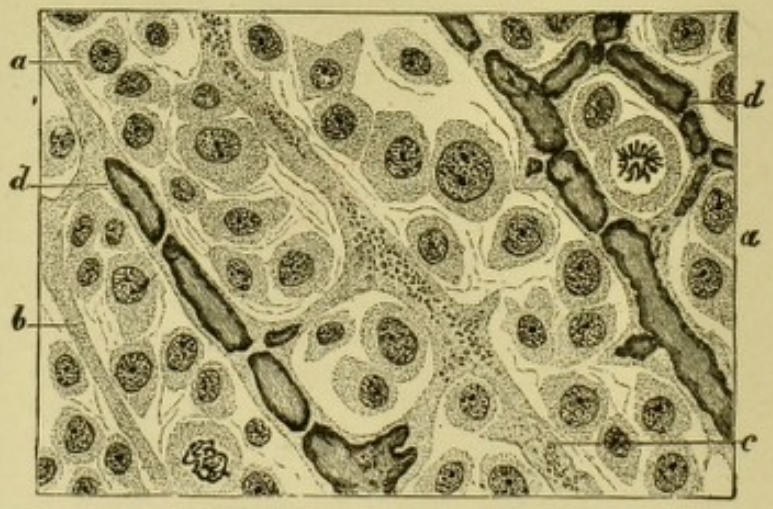


FIG. 282.—Petrifying large-celled sarcoma of the tibia. (Müller's fluid; hæmatoxylin; eosin.) *a*, Polymorphous tumor-cells; *b*, alveolar stroma; *c*, trabeculæ of the stroma with small calcareous concretions; *d*, petrified bands of the stroma. Magnified 265 diameters.

ture, while closely resembling an osteosarcoma, still differs from it in one respect: it contains no deposit of lime salts.

Petrifying sarcomata also develop most frequently in some part of the skeleton. They are characterized by the fact that trabeculæ of a delicate basis-substance develop among the cells of the tumor (Fig.

282, *c*) and afterward undergo calcification (*d*); thus giving a certain hardness to the tissue of the tumor. At the same time no actual bone-formation takes place.

Psammomata or *sand tumors* (acervulomata) are sarcomata or fibro-sarcomata of the dura, or of the soft membranes of the brain, or of the pineal gland, which contain *concretions of lime* in greater or less abundance. Some of these concretions are similar in structure to the normal cerebral sand, the basis of their formation being concentric layers of cells which have undergone hyaline degeneration (Fig. 283, *a*, *b*, *c*). Others are shaped more like a lance (*d*), and probably owe their origin to the deposit of lime salts in connective tissue which has undergone hyaline degeneration, or in blood-vessels which have previously passed through the same pathological change.

Psammomata usually occur in the form of round nodules. As a rule, several of them are found at the same time.

If the myxosarcomata are left out of the account it may be said that the **sarcomata which contain masses of hyaline substance** acquire this feature in one of the following three ways: *either the cells produce the*

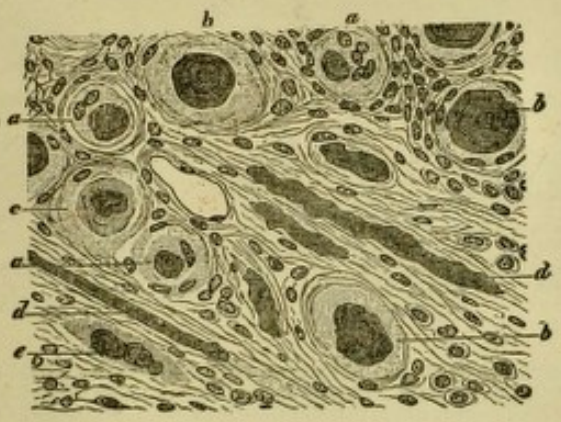


FIG. 283.—Section of a psammoma of the dura mater. (Alcohol; picric acid; hæmatoxylin; eosin.) *a*, Hyaline nucleated globule including a concretion; *b*, concretion with non-nucleated hyaline border, lying in fibrous tissue; *c*, concretion with hyaline border; *d*, lanceolate concretion in connective tissue; *e*, lanceolate formation containing three concretions. Magnified 200 diameters.

hyaline substance; or else they themselves become converted into this material; or, finally, both the fully developed connective tissue and the blood-vessels undergo a change into hyaline substance. The changes enumerated may take place not only in an ordinary sarcoma, but also in an endothelioma or an hæmangiosarcoma, although they occur far more commonly in the last-named tumors (Fig. 274, *b*; Fig. 278, *d*; Fig. 284). The hyaline masses are encountered in a variety of forms. They are sometimes round, sometimes club-shaped, sometimes like cords, sometimes like a net, and sometimes branching like the leaves of a cactus plant. They crowd apart the masses of cells and sometimes compel them to assume the aspect of cords. Billroth has described such tumors as *cylindromata*. In endotheliomata the hyaline degeneration may be associated with the formation of epithelial pearls—i.e., small bodies which are composed of cells that have been rendered flat and have been arranged, like the layers of an onion, around a central nucleus.

Hyaline degeneration of the walls of the blood-vessels and of the bundles of connective tissue results in a thickening of these structures (Fig. 280, *d*); and this thickening is sometimes uniformly, sometimes irregularly, distributed. *Hyaline products of the cells* have a tendency to assume a

spherical shape (Fig. 274, *b*; Fig. 278, *d*; Fig. 284, *c*, *d*). The disintegration of masses of cells of considerable size is followed by their conversion into large balls, or cords, or branching structures of hyaline material.

If, in the case of endotheliomata and angiosarcomata, the cord-like

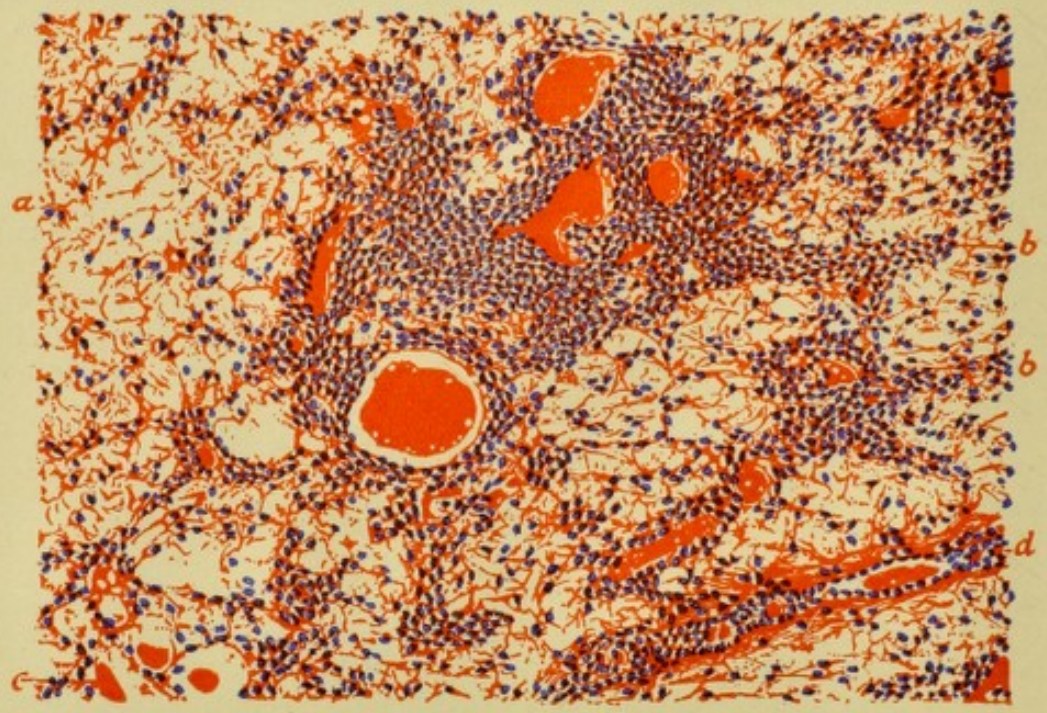


FIG. 284.—Myxoangiosarcoma of the parotid gland, with hyaline deposits. (Müller's fluid; hæmatoxylin; eosin.) *a*, Mucous tissue; *b*, cord-like masses of cells, in the midst of which are spheres of hyaline material; *c*, hyaline spheres in mucous tissue; *d*, blood-vessels with proliferating endothelium and hyaline masses. Magnified 100 diameters.

masses of cells which have developed in the lymph- or blood-vessels undergo a change into hyaline substance, there will be produced a variety of structures that closely resemble glands which contain colloid (Fig. 284, *d*), and that have even, in not a few instances, been mistaken for the latter.

Ribbert looks upon melanosarcomata as an independent variety of new growth. It is because they spring from the chromatophores that he believes they should be separated from the sarcomata and reckoned as a class by themselves. It is, however, to be noticed that, in addition to the chromatophores, other cells take on proliferative activity. Consequently the melanosarcomata can be considered only as sarcomata in the building up of which certain cells have taken part—cells which have the power of producing pigment.

2. *The Epithelial Tumors.*

(*a*) *General Remarks.*

§ 124. **Epithelial tumors** are new growths in the formation of which both vascular connective tissue and epithelial cells—i.e., tissues which are derived either from epidermal or from glandular epithelial cells—take part. The arrangement of connective tissue and epithelial cells follows in general that of the normal physiological arrangement of these tissues;

that is to say, the connective tissue either forms a layer the surface of which is covered with epithelium, as in the normal skin and mucous membranes, or else it forms a network in the meshes of which the epithelial cells are disposed, after the pattern of a normal gland. The imitation of the first-named structure leads to the formation of **papillary new growths**; that of the second, to the formation of more or less sharply defined **nodules** or **superficial patches of thickened tissue.**

The epithelial tumors may be divided into two groups, according to the physical characteristics and arrangement of the cells; one group including the **papillary epitheliomata, the adenomata,** and **the cystadenomata,** and the other **the carcinomata** and the **cystocarcinomata.** The chief clinical characteristic of the first group lies in the fact that it contains only benign tumors, *which are sharply differentiated from the surrounding tissues* and *do not form metastases.* The second group, on the other hand, includes the malignant new growths, *which grow by infiltration and form metastases.* However, the two groups are not sharply separated the one from the other, for papillary epitheliomata and adenomata may, through the occurrence of certain changes in the mode of multiplication and distribution of their epithelial cells, become converted into carcinomata.

(*b*) *Papillary Epitheliomata, Adenomata and Cystadenomata.*

§ 125. A **papillary epithelioma** is a new growth which is composed of a framework of connective-tissue papillæ covered with epithelial cells. It is therefore constructed in very much the same manner as are the papillæ of the skin. Nevertheless, there are certain differences: the papillæ are higher and often branched, and the epithelial covering as a whole is thicker.

Papillary epitheliomata of the skin appear in the form of *knobbed warts*, the slender papillæ of which (Fig. 285) are covered by epithelial cells that show a tendency, at least so far as the outermost layers are concerned, to become cornified (*ichthyotic warts* and *horny warts*). These warts may, like the fleshy warts (see § 115), appear in youth (*ichthyotic warts*) as well as in advanced age (*verruca senilis*). The first-

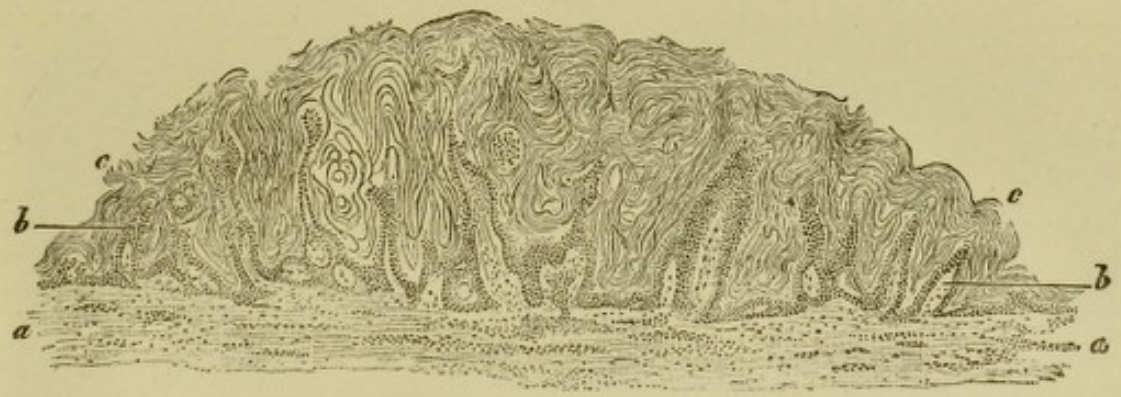


FIG. 285.—Papillary epithelioma or ichthyotic wart of the skin. (Müller's fluid; hæmatoxylin; eosin.) *a*, Corium; *b*, enlarged papillary body; *c*, laminated horny epithelium. Magnified 40 diameters.

named sort is a local malformation of the skin (Fig. 285), while the last-named is due to a pathological growth and cornification of the epithelium (Fig. 286, *c*, *d*), followed by an outgrowth of the peripheral portions of the same, in the form of papillæ. The development of what is

known as a *cornu cutaneum* or *cutaneous horn* (Fig. 121 and Fig. 122) is due to the excessive cornification of the epithelium covering hypertrophied papillæ; and in this process it will be found that the horny epithelial cells become piled up, with their long axes at right angles to the surrounding surfaces of the skin, in cylindrical or cone-shaped masses.

Papillary epitheliomata of the mucous membranes are encountered either in the form of wart-like, nodulated growths (Fig. 287, *e*, *f*), or in that of long, slender, papillary growths (Fig. 288, *a*) which spring from a small stem that often breaks up into a number of branches. The former variety is found especially in the larynx, rarely in the nose or urinary bladder; while the latter variety is seen in the urinary bladder, in the pelvis of the kidney, and upon the vaginal portion of the uterus, more rarely in the ureters, the gall-bladder, or the biliary passages.

In both varieties the individual excrescences are formed each one of a slender connective-tissue papilla (Fig. 289) which contains blood-vessels and is covered by a thick layer of epithelial cells. The character of the epithelium corresponds in general to that of the part in which the growth occurs, but there are papillomata which are covered with stratified, flat epithelial cells, although growing from a part (e.g., the nose) the normal epithelium of which is cylindrical in shape.

Papillary epitheliomata in dilatation cysts, which are also called **papillary cystomata,** occur most frequently in cysts of the ovary and in cysts of the lactiferous ducts of the mammary gland; more rarely they

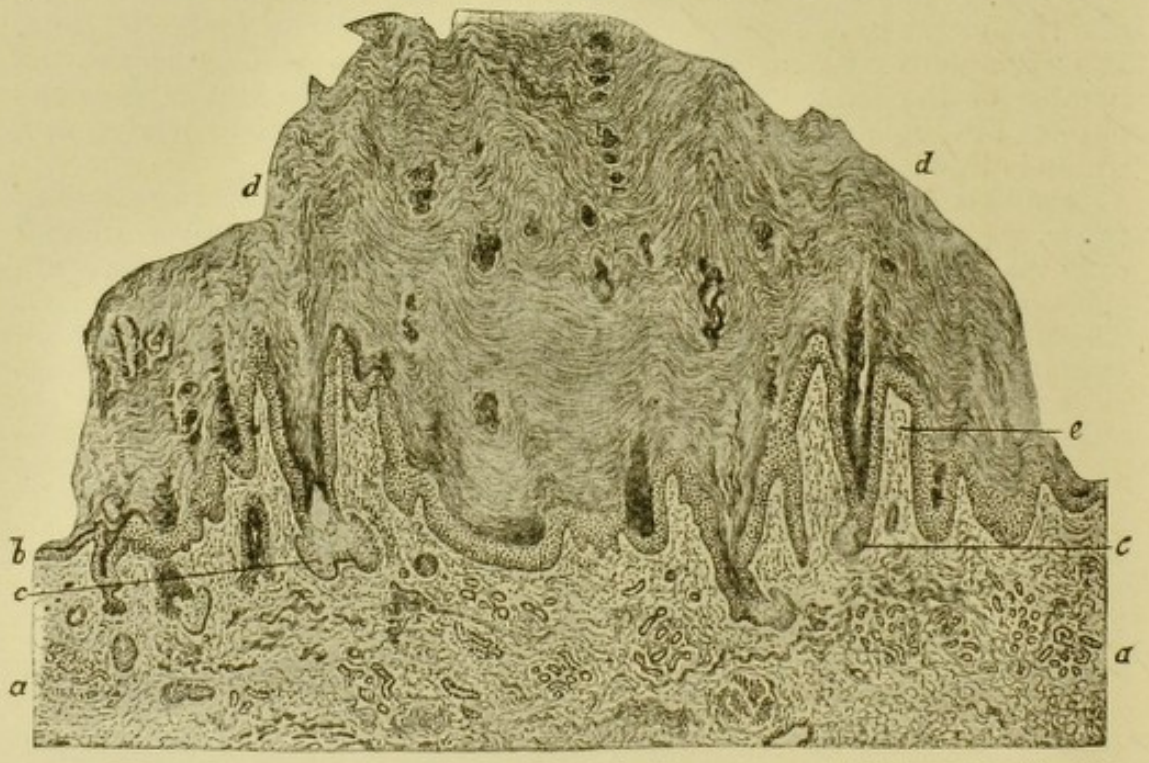


FIG. 286.—Senile horny wart of the skin of the forehead. (From a woman eighty-four years old.) (Alcohol; hæmatoxylin; eosin.) *a*, Corium; *b*, epithelium; *c*, atrophied sebaceous follicles, with horny epithelium at their outlets; *d*, hypertrophied horny layers; *e*, enlarged papillæ of the skin. Magnified 15 diameters.

are encountered in atheromata (dermoids) of the skin. They form little wart-like elevations, or cauliflower-like tumors which in some instances may fill up the whole cyst. Their structure is like that of the corresponding excrescences in papillary adenocystomata (cf. § 127), or the papillary epitheliomata of the skin or mucous membranes.

Papillary epitheliomata of the surface of the ovary develop in about the same manner as do those of the urinary bladder; but they are of rare occurrence. **Papillary epitheliomata of the ventricles of the brain** spring partly from the choroid plexus (telæ choroideæ), and partly from the ependyma.

It is difficult to draw a sharp dividing line between **papillary epi-**

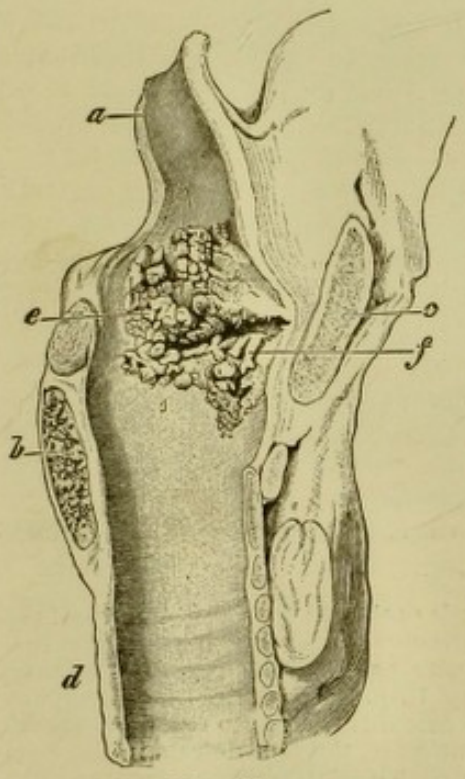


FIG. 287.

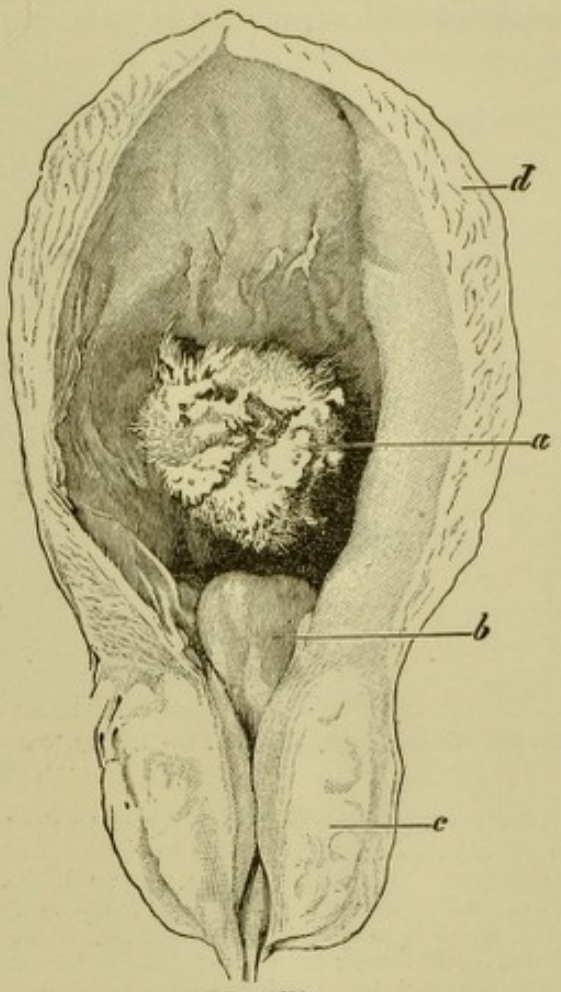


FIG. 288.

FIG. 287.—Papillary epithelioma of the larynx. *a*, Epiglottis; *b*, ossified cricoid cartilage; *c*, thyroid cartilage; *e*, *f*, papillary growths. Natural size.

FIG. 288.—Papillary epithelioma of the urinary bladder. *a*, Epithelioma; *b*, *c*, enlarged prostate; *d*, thickened wall of the bladder. Five-sixths natural size.

theliomata and other formations. Thus, inflammatory growths of the skin and mucous membranes—the **pointed condylomata**—which develop especially on the external genitals as the result of irritations of a chronic nature (cf. § 105), resemble the epitheliomata so closely that they can be told from them only by the history of an antecedent inflammation. If the connective-tissue framework of the papilloma is well developed, in comparison with the amount of epithelium that may be present, the tumor may be reckoned among the **papillary fibromata**. Whether such a classification of the growth is to be adopted or not in any particular instance, is a matter which must be left to the judgment of each observer. Finally, the benign papillary epitheliomata may also change into **carcinomata**, either by the growth of the epithelium, at the base of the papillæ, into the underlying connective tissue, or by the growth of the superficial epithelium, while in a condition of proliferation, into neighboring organs, as takes place, for example, in papillary epitheliomata of the ovary. As a general remark it may be said that the term *epithelioma* is often applied to *carcinomata which take their start from surface epithelium*, but it seems far better to reserve this term for the benign tumors described above.

Among the epitheliomata may be classed those formations which are called **cholesteatomata** or **pearl tumors**, and which owe their existence partly to inflammations, partly to misplacement of embryonal tissue. The most striking feature of the cholesteatoma is due to the presence of glistening white pearls which are made up of thin, scaly

epithelial cells pressed closely together, and which often inclose cholesterin. The principal localities in which these peculiar formations are found are the descending urinary passages, the cavities of the middle ear, the pia of the brain, and very rarely that of the spinal cord.

Pathological cornifications, accompanied by the formation of glistening white scales and the so-called pearls, occur in the *urinary passages* in the course of chronic inflam-

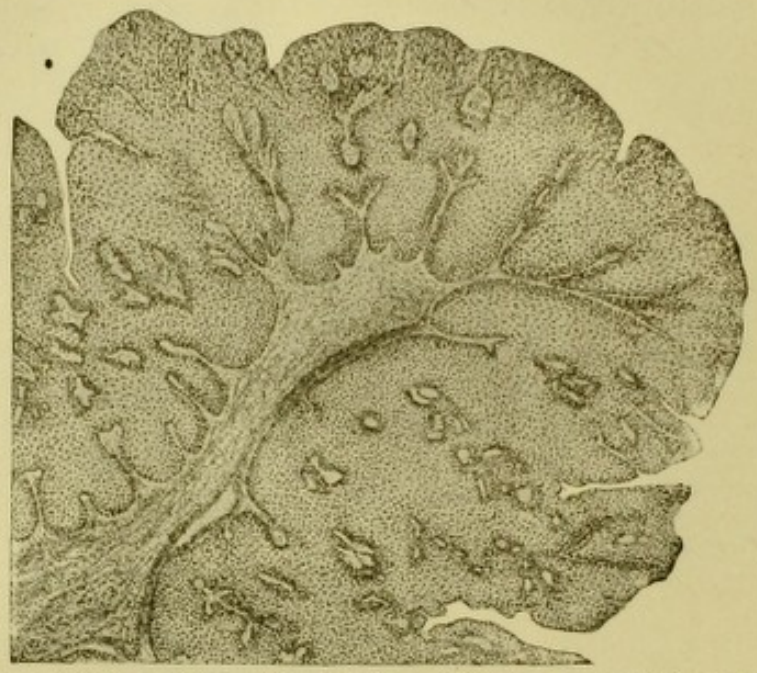


FIG. 289.—Papillary epithelioma of the urinary bladder. (Alcohol; hæmatoxylin; eosin.) Magnified 35 diameters.

mations. Cholesteatomata are found in the *tympanic cavity*, in the *mastoid antrum*, and in the *external auditory meatus* in the form of yellowish-white or bluish-white spherical masses, with concentric layers like an onion, and varying in size from that of a cherry pit to that of an egg. In these situations they may, by pressure upon the neighboring bone, cause it to disappear. Such cholesteatomata owe their origin to the proliferation of flat epithelium which has penetrated from the outer ear, through defects in the membrana tympani, into the spaces of the middle ear; in which localities they replace the cylindrical epithelium and, under special conditions (chronic inflammations), they form the spherical masses referred to above. They probably, in rare instances, also develop from epidermoidal cells which, during the period of embryonic life, have found their way into the cavities in question.

The *intracranial cholesteatomata* are situated at the base of the brain (seldom in the vertebral canal), in the vicinity of the lobus olfactorius, tuber cinereum, corpus callosum, plexus choroides, pons, medulla oblongata, and cerebellum, in which localities they form on the surface shining silky nodules of varying sizes, that extend to a greater or less distance into the substance of the brain. The nodules are single, but masses of cholesteatomata may become separated from the chief nodule and push their way into the neighboring tissues. According to Bostroem it is always possible to demonstrate, at any point that may be selected, the connection between the pia and the cholesteatoma; the nature of this connection being such that one can see how the scales of which the cholesteatoma is composed originate from a stratum of cells that rest upon vascular connective tissue, and how, furthermore, these latter cells present all the characteristics of epidermoidal cells. The cholesteatomata of the pia may therefore be called *epitheliomata* or *epidermoids* (Bostroem), and their development may be explained by the assumption that displaced epidermis germs have found their way into the pial layer at some time during early embryonal life. According to Bostroem this event occurs after the closure of the medullary canal and before the separation (by a process of constriction) of the secondary from the primary vesicle of the fore-brain or from the vesicle of the mid-brain; or—to state the case in somewhat different terms—it occurs between the closure of the medullary canal and the separation of the hind-brain vesicle from that of the cerebellum. We may therefore place the time of the occurrence of this event in the fourth or the fifth week of intra-uterine life. These epidermoids may accordingly be classified as belonging to the *teratoid tumors* (*q. v.*).

§ 126. **Adenomata** are usually *nodular tumors*. They possess sharply defined boundaries and are commonly seated either in the midst of a gland, or in the skin, or in a mucous membrane. In the last-named situation they quite often protrude from the surface in the form of a polypus. The absence of any tendency to grow as it were by filtration or to produce metastases justifies us in considering adenomata as *benign tumors*.

One of the characteristics of an adenoma is its power to **reproduce a tissue which resembles the glandular tissue of the parent organ** more or less closely. The tissues thus reproduced imitate either the *tubular* or the *acinous type* of gland, and yet these two forms are not sharply separated, the one from the other. *Papillary adenomata* owe their origin to the formation of papillary excrescences on the internal surface of the glandular tubes.

The stroma which supports the gland is composed in part of pre-existing connective tissue, in part of that which has been newly formed.

Adenomata develop in either normal tissues, in malformed tissues, in tissues which have been altered by disease (inflamed mucous membranes, cirrhotic livers, contracted kidneys), or *in the remains of* fœtal structures (Wolffian bodies, canalis neurentericus, remains of fusion-germs). The material for the new gland structure is furnished by the proliferation of the epithelium of the old gland, the steps of the process being quite like those which occur in the regeneration of normal gland tissue. The reason why new gland formation takes place in normal organs is beyond human ken. Glandular new formations that develop in tissues which have been altered by inflammation, and that ultimately assume many of the characteristics of tumors, may at first present the features of a regenerative or hyperplastic new growth; and on this account *the adenomata cannot be sharply differentiated from regenerative and hyperplastic growths*.

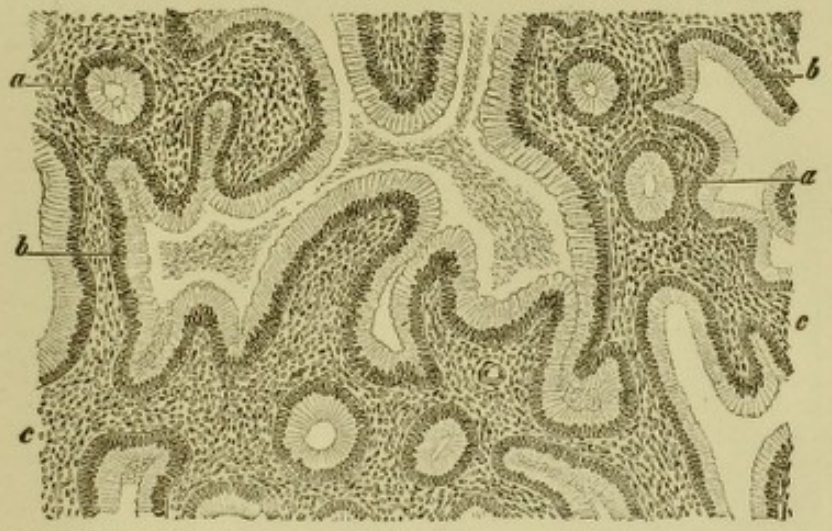


FIG. 290.—Adenoma tubulare (glandular polyp) of the intestine. (Alcohol; alum carmine.) *a*, Transverse sections, *b*, longitudinal sections, of gland-tubules; *c*, stroma, rich in cells. Magnified 100 diameters.

Tubular adenomata represent the commonest variety of adenomata. They occur especially in mucous membranes (Fig. 290) which are provided with slender tube-like glands (intestine, uterus), but they are also often found in such glands as the breast (Fig. 291), the liver, the ovary, and the kidney. These tumors, which vary in size from that of a pea

to that of a man's fist (they rarely exceed this), are characterized by the fact that they develop simple or branching gland tubules (Fig. 290, *a*, *b*,

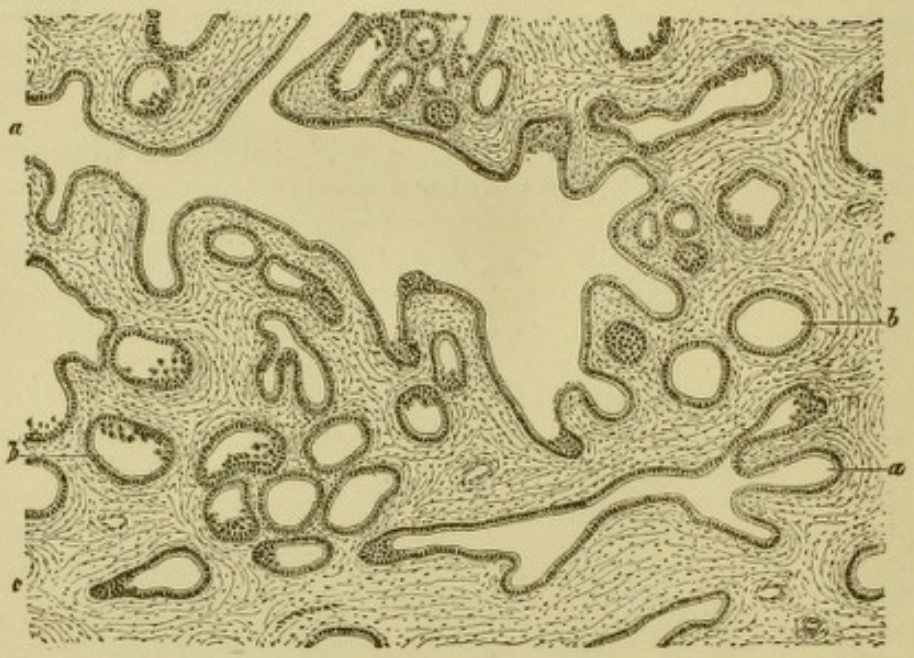


FIG. 291.—Tubular adenoma of the breast. (Alcohol; alum carmine.) *a*, Branching and dilated glandular ducts, cut longitudinally; *b*, the same, cut transversely; *c*, stroma. Magnified 30 diameters.

and Fig. 291, *a*, *b*) which are lined with a cylindrical or cubical epithelium.

Alveolar adenomata develop in glands (mamma, ovary, thyroid gland, sebaceous glands), and are characterized by the formation of numerous terminal berry-like alveoli (Fig. 292, *a*) as well as gland tubules (*b*).

A papillary adenoma owes its origin to the circumstance that at

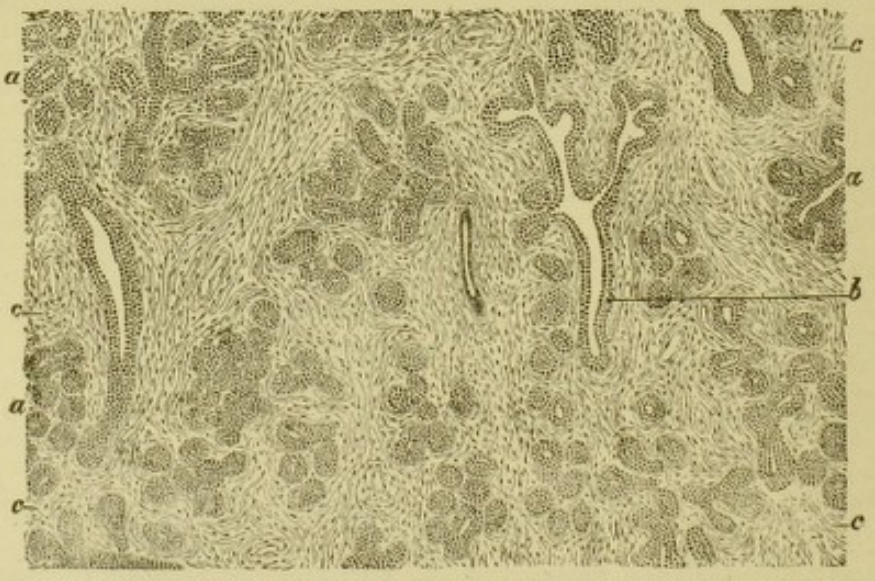


FIG. 292.—Alveolar adenoma of the breast. *a*, Terminal alveoli of gland; *b*, ducts of gland; *c*, connective-tissue stroma. (Alcohol; alum carmine.) Magnified 30 diameters.

different points in the tubules of an adenoma the epithelium multiplies and forms little elevations, into each of which a papilla of connective

tissue grows. Excrescences of this nature may multiply to such an ex-

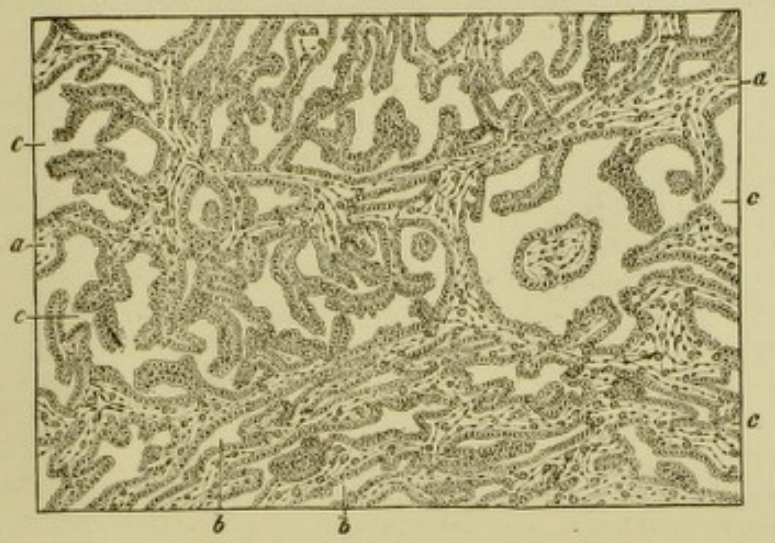


FIG. 293.—Adenoma tubulare papilliferum of the kidney. *a*, Connective-tissue stroma; *b*, glandular tubules with diverticula; *c*, tubules with markedly developed papillary excrescences. (Müller's fluid; hæmatoxylin.) Magnified 30 diameters.

tent as to fill the gland tubules, sometimes even to the point of stretching them (Fig. 293, *b*, *c*).

The **stroma of an adenoma** is sometimes slight, sometimes strongly developed, and consequently adenomata may be divided into a *hard va-*

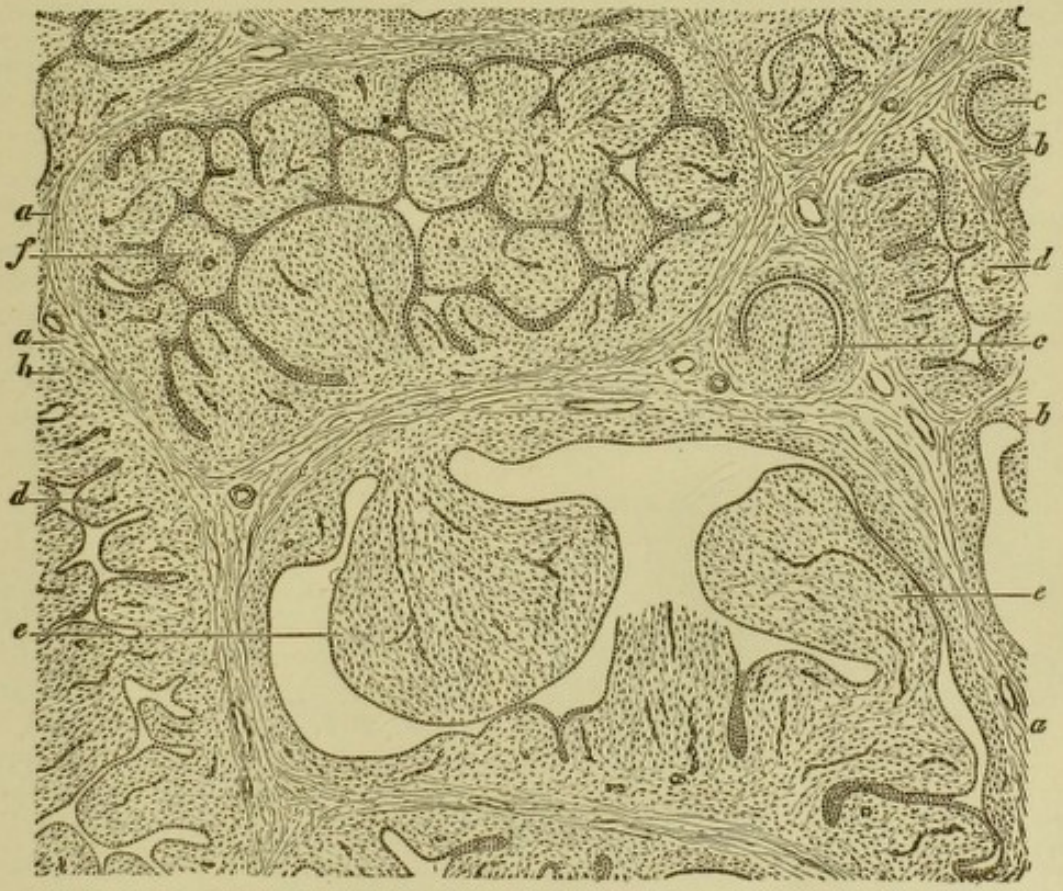


FIG. 294.—Intracanalicular fibroma of the breast (adenoma papilliferum). (Alcohol; alum carmine.) *a*, Dense fibrous tissue lying between the canals; *b*, pericanalicular tissue, rich in cells; *c*, *d*, *e*, nodular intracanalicular growths, cut longitudinally; *f*, intracanalicular growths, cut transversely. Magnified 25 diameters.

riety (mammary gland) and a *soft variety* (kidney, liver, ovary, testicle). If the connective tissue is particularly well developed, the term **fibro-adenoma**, or *fibrous adenoma*, may appropriately be employed. The mammary gland is the favorite seat of such a fibro-adenoma.

If—as happens rather often in the mammary gland—the growth of connective tissue in an adenoma does not take place in a diffuse manner, but remains confined to the immediate vicinity of the canaliculi (cf. Fig. 227), the tumor is commonly termed a *fibroma pericanaliculare;* and when, under the impulse of a more active growth at certain points, the connective tissue advances into the interior of the glandular spaces in the form of rather broad and short papillæ (*e*), it is proper to name the tumor in which this phenomenon has occurred a **fibroma intracanaliculare** (Fig. 294, *c*, *d*, *e*). It is also permissible, in accordance with its mode of origin, to apply to such a tumor the term **fibro-adenoma papilliferum.**

Adenomata cannot be sharply differentiated from tumor-like hypertrophies of the glands on the one hand, nor from carcinomata on the other. For example, if, after the healing of an ulceration in the intestine, the regenerative processes in the glands are so active that polypoid masses are formed, they may be called either *glandular hypertrophies* of the mucous membrane or *adenomata*, according to the conception which one has of the word tumor. In the same way different names may be applied to the glandular polyps which occur so often in the uterus.

The *carcinomatous nature* of a growth which resembles an adenoma (cf. § 129) is generally shown by the more marked epithelial proliferation and by its infiltrative mode of growth. There are, however, adenomata which are covered with a single layer of cylindrical epithelium and which show this same infiltrative manner of growing (especially in the intestine). Such growths have assumed a malignant character, and they must therefore be counted among the carcinomata. They should be called either *destructive adenomata*, or *adenocarcinomata*. On the other hand, there are also adenomata which manifest a markedly atypical growth of their epithelial elements, and which—for at least a long time—do not show any malignant characteristics. Adenomata of this nature are encountered in the mammary gland and in the mucous membrane of the uterus.

§ 127. A **cystadenoma** or **adenocystoma** is an *adenoma whose glandular canals are dilated by the presence of accumulated secretion*. As such tumors are almost always composed mainly of numerous cysts, they are also called **multilocular cystomata.** According to the character of the walls of the cysts, the tumor may be either a *smooth-walled* or *simple cystoma* (*cystoma simplex*), or a *papillary cystoma* (*cystoma papilliferum*).

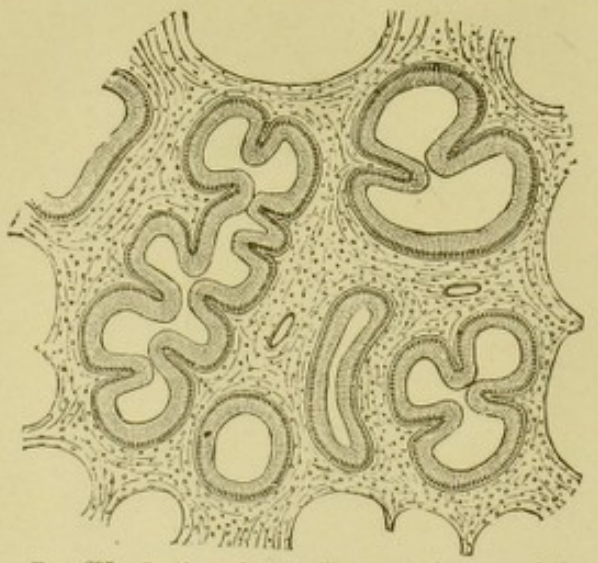


FIG. 295.—Section of a papillary cystadenoma of the ovary. (Müller's fluid; hæmatoxylin.) Magnified 40 diameters.

Smaller quantities of secretion can often be made out in ordinary adenomata (Fig. 290), and the interstices in both simple and papillary adenomata (Fig. 291, *a*, Fig. 294) may be so wide that they at once attract attention in a cross section of the growth. In cystadenomata this cyst formation is the striking thing about the picture.

The predecessors of the cysts are *gland tubules* of various shapes (Fig. 295 and Fig. 296, *b*), which lie in a more or less richly developed

connective-tissue stroma. Through the accumulation of secretion these tubules are gradually dilated, and in consequence numerous small cysts

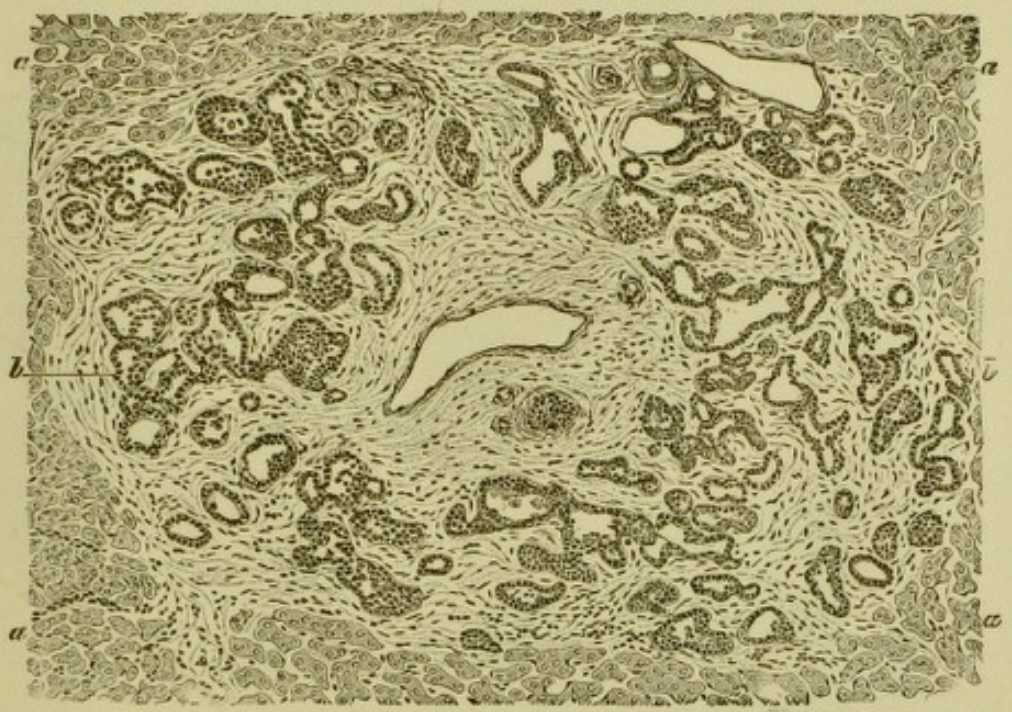


FIG. 296.—Adenocystoma of the gall-ducts, in the first stages of development. (Alcohol; hæmatoxylin.) *a*, Liver tissue; *b*, adenoma tissue in the midst of the periportal connective tissue. Magnified 100 diameters.

(Fig. 297), or else cysts both large and small (Figs. 298–301), are formed. The relations of these are often such that the tumor may con-

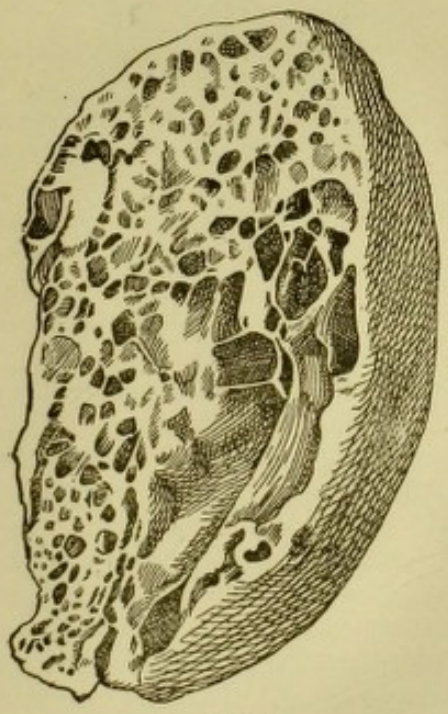


FIG. 297.

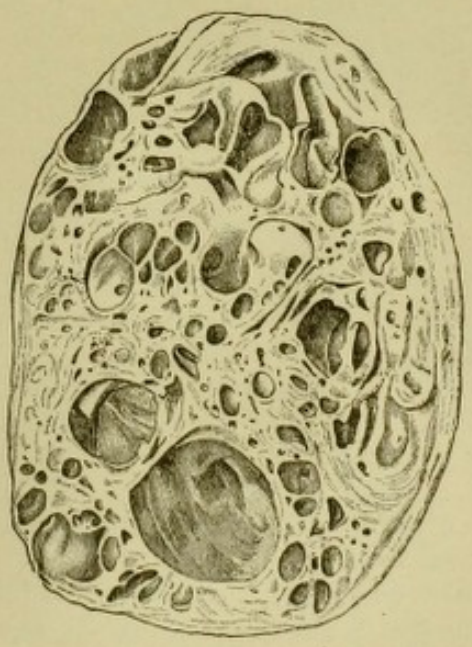


FIG. 298.

FIG. 297.—Portion of a section of a multilocular adenocystoma of the ovary. Reduced about one-sixth in size.

FIG. 298.—Section through an adenocystoma of the testicle of a four-year-old boy. (Life size.)

sist of a few large cysts (Fig. 301) in whose walls little cysts are located; or there will be found, by the side of large cysts (Fig. 299, *c*), masses of tissue which contain only very small cysts (*e*) or even appear solid

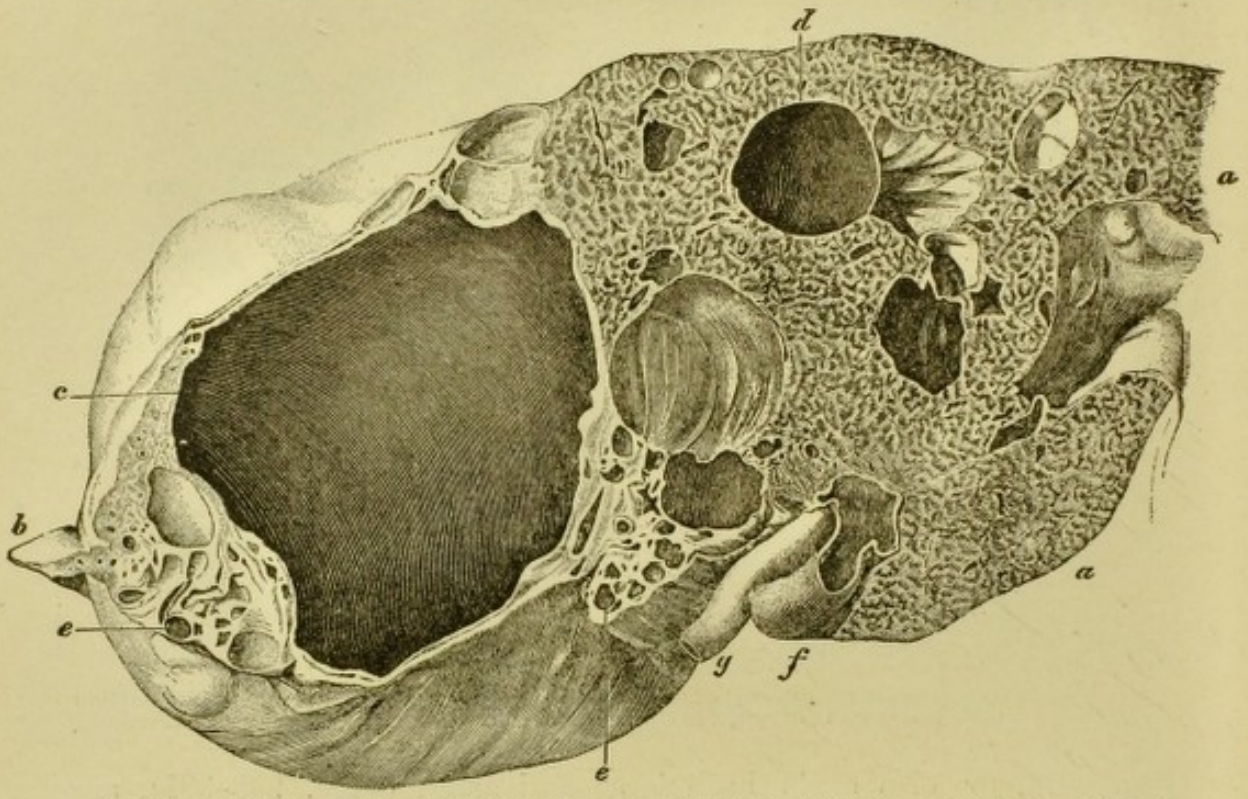


FIG. 299.—Multilocular adenocystoma of the liver, seen in section. *a*, Parenchyma of the liver; *b*, membranous margin of the left lobe; *c*, *d*, two of the larger cysts; *e*, group of smaller cysts, separated from one another only by connective tissue; *f*, portal vein; *g*, hepatic artery. (Two-thirds life size.)

—that is, they are composed of a tissue containing only undilated glands.

All the different types of cystomata may be found in the ovaries (Fig. 297 and Fig. 301), the testicles (Fig. 298), the liver (Fig. 299), the kidneys (Fig. 300), and the mammary glands.

Cystomata not infrequently develop in both ovaries at the same time, and may be associated with dermoid formations. Adenocystomata of the testicle often have foci of cartilage or other kinds of tissue in their stroma; and when this is found to be the fact, these tumors must be counted with the *teratomata* (§ 136).

The *epithelial lining* is usually composed of simple cylindrical epithelium, but the latter may be ciliated or cubical or squamous.

The *contents of the cysts* usually consist of a clear, often distinctly ropy fluid, which contains a substance like mucin (pseudomucin; cf. § 63). This substance is a product of the epithelial lining, and in it beaker-cells (Fig. 303, *c*) are often found. The fluid also often contains whitish flakes, products of fatty-degenerated cells, or it may be cloudy or more or less reddish or brownish in color from previous hemorrhages. When the cysts are numerous and they all contain an abundant secretion, the tumor may attain enormous proportions. In the ovary, for example, such tumors may reach a weight of from 10 to 20 kgm., or even more.

The **papillary adenocystomata** constitute a common variety of adenocystomata. They are characterized by the fact that sooner or later

papillary excrescences develop in the glands which have undergone cystic dilatation.

In the adenocystomata of the ovary these excrescences are usually slender and delicate, presenting—when seen *en masse*—a villous appearance; or they may occur in the form of cauliflower-like elevations which fill, to a large or a small extent, the cysts. (Both forms are shown in Fig. 302.) Minute papillary elevations, which occupy an extensive surface, may give to the inner lining of the cyst a velvety character similar to that of a mucous membrane. If the excrescences develop in the smallest cysts, completely filling their cavities, the whole tissue may again present the appearance of a dense, non-cystic, medullary tumor, but it is almost always possible to obtain a greater or less quantity of mucus from the cut surface.

The larger papillæ are always more or less branched (Fig. 303), and are made up of a stroma rich in cells (*a*). They are generally covered with tall cylindrical cells (*c*), which possess a strong resemblance to beaker cells. The contents of the cysts consist of a ropy mucus (*d*) which contains a larger or smaller number of cast-off epithelial cells, that have usually undergone mucoid degeneration, or the remains of

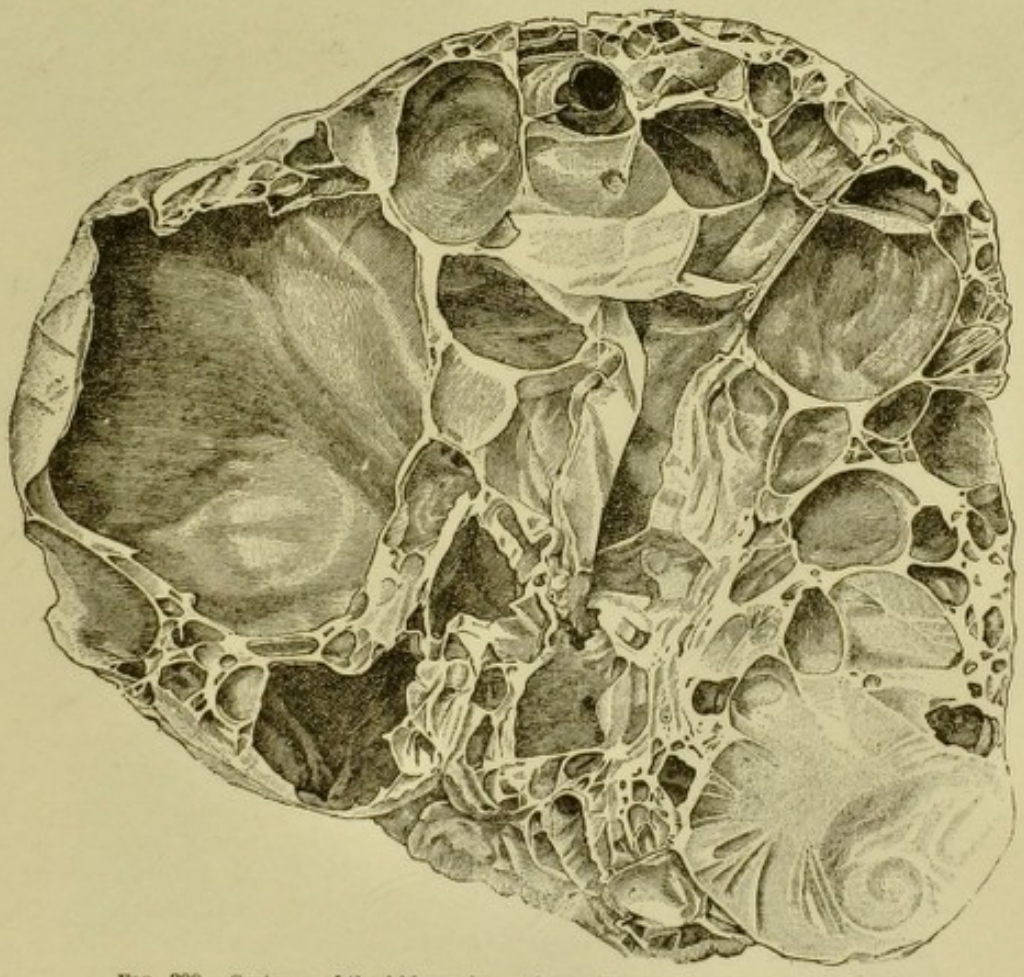


FIG. 300.—Cystoma of the kidney, in section. (Eleven-fourteenths life size.)

such cells. In rare cases the connective tissue of the papillæ undergoes mucoid degeneration (Fig. 304, *a*, *b*). When this takes place it is apt to swell up to a remarkable degree, and eventually to become converted into a ball of mucus, which is confined within an envelope of epithelium.

In adenocystomata of the liver, the testicle, and the kidney, papillary excrescences are either wanting altogether or else they are very small.

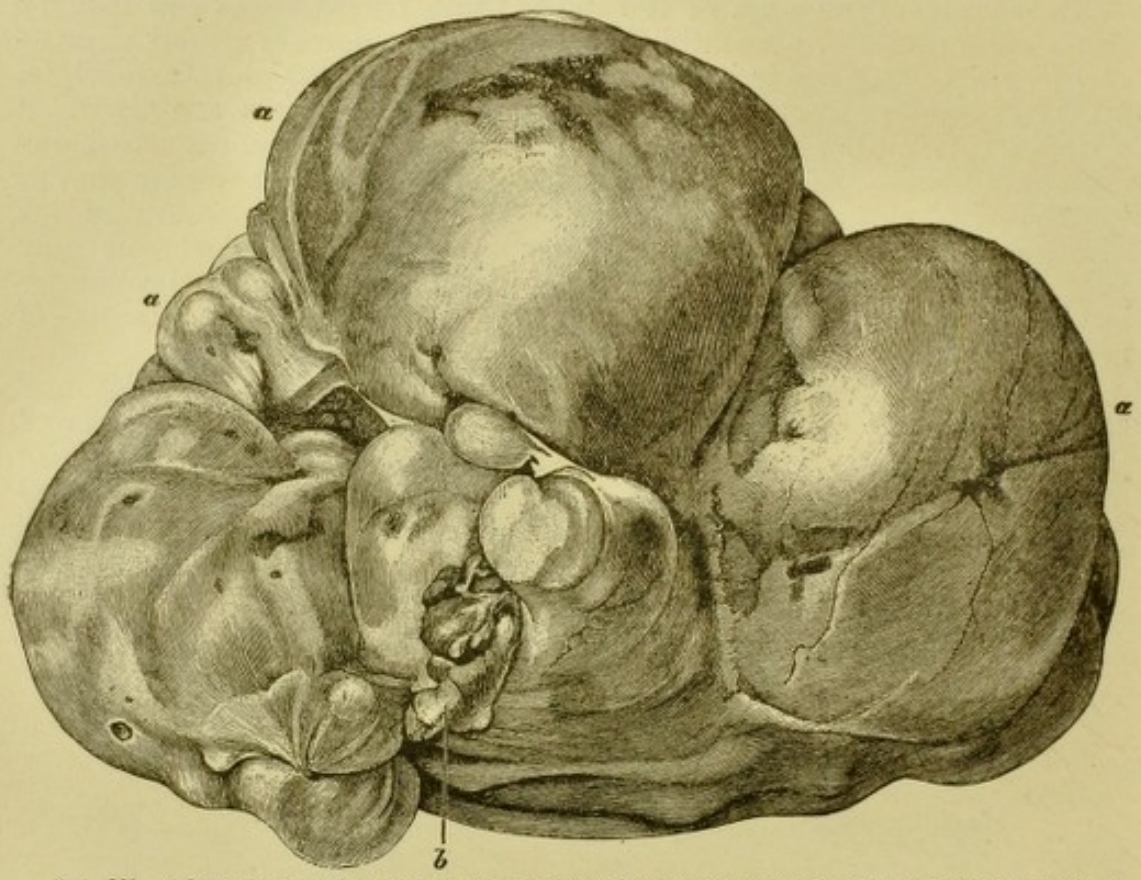


FIG. 301.—Adenocystoma of the ovary—partly of the simple variety, partly of a papillary character. *a*, Smooth-walled cysts; *b*, papillary growth which has broken through a cyst-wall. (It is soft and covered with the ordinary cylindrical epithelium of mucous membranes.) There were, in this case, metastatic nodules in the peritoneum. (Reduced by about one-third.)

In the papillary adenocystomata of the mammary gland the excrescences are usually thick and plump (Fig. 305), as is generally also the case with the papillary adenomata (Fig. 294). Accordingly in cross sections one

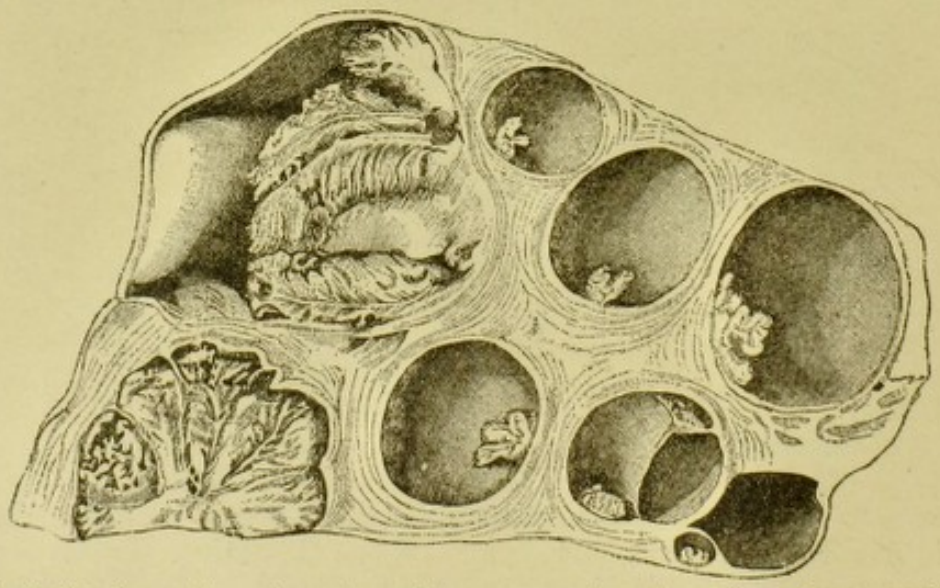


FIG. 302.—Portion of a papillary adenocystoma of the ovary, seen in section. (Drawn from a specimen hardened in chromic acid.) Four-fifths life-size.

finds the cystic spaces filled with polypoid growths of the greatest variety

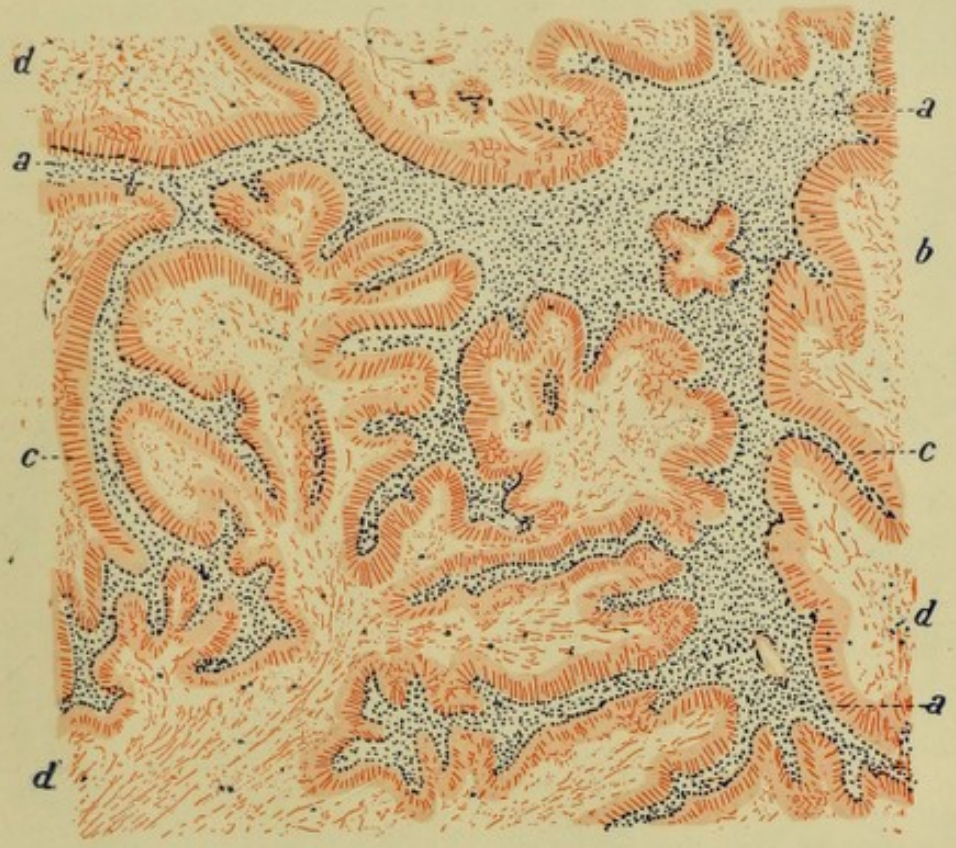


FIG. 303.—Papillary cystoma of the ovary. (Müller's fluid; hæmatoxylin; eosin.) *a*, Stroma with papillæ; *b*, gland-tube with small papillæ; *c*, tall cylindrical epithelium which lines the cyst-cavities and covers the papillæ; *d*, mucus filled with cells, in the interior of the cysts. Magnified 150 diameters.

of shapes (Fig. 305), and often flattened through mutual pressure, so that the surface of such a cross section looks like the cut surface of a cabbage.

FIG. 304.—Papillary adenocystoma of the ovary, with myxomatous degeneration of the connective tissue of the villi. (Müller's fluid; hæmatoxylin.) *a*, Fibrous stroma; *b*, papillæ which have undergone myxomatous degeneration; *c*, epithelium. Magnified 80 diameters.

As the connective-tissue portions of these tumors preponderate over the epithelial portions, many authorities include them among the connective-tissue tumors; and, according to the characteristics of the connective tissue, they have received such specific names as *cystofibromata,*

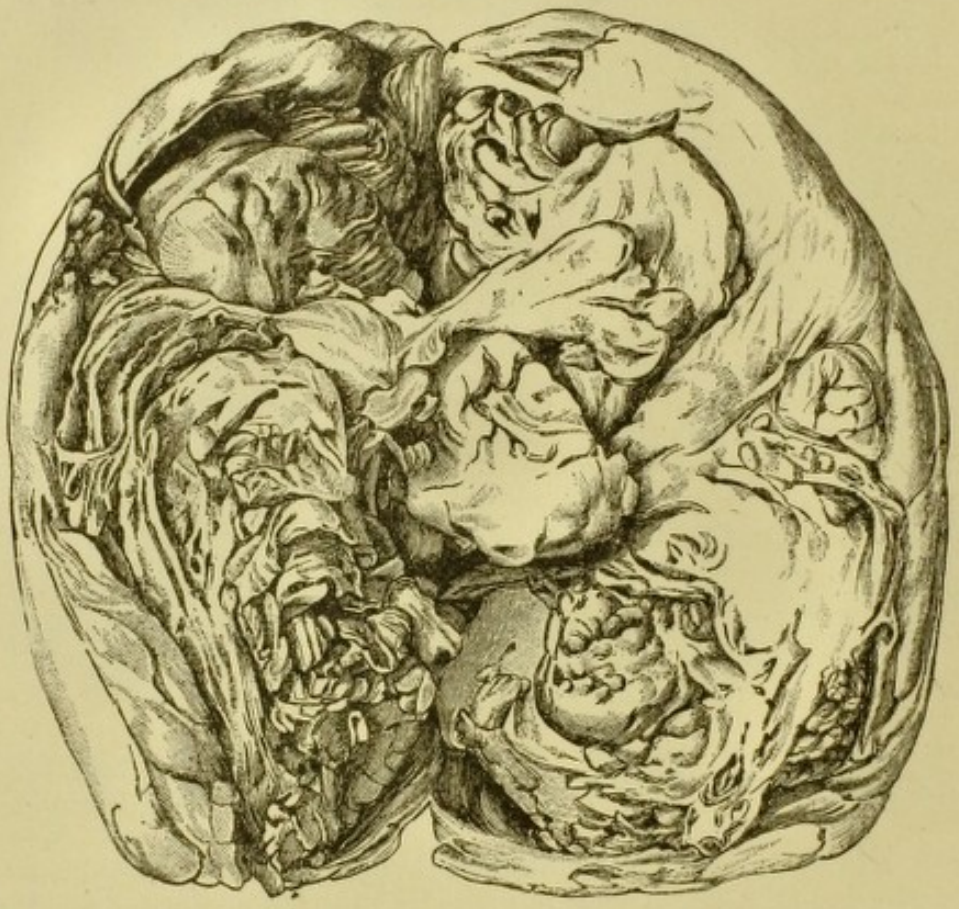


FIG. 305.—Papillary cystoma or intracanalicular papillary fibroma of the breast, laid open by a longitudinal incision. (One-half life size.)

cystomyxomata, and *cystosarcomata*. When the tumor is made up of leaf-like layers, it has been designated as a *sarcoma phyllodes*.

The *papillary adenocystomata* show a *certain malignancy* even when the papillæ are clothed with simple epithelium (cf. Cystocarcinomata). This tendency shows itself, for example, in the circumstance that the papillary growths break through the cyst wall, both when the tumor involves the ovary and when it has its seat in the mammary gland—in which location it may also break through the overlying skin. Papillary cystomata of the ovaries (Fig. 301, *b*) may thus give rise to metastases in the peritoneal cavity, and these in their turn may display the characteristics of papillary epitheliomata.

The adenocystomata must also be ranked as a variety of tumor which possesses no sharply defined limits. Thus, for example, papillary cystomata may also arise from the development of papillary excrescences in dilatation cysts which are formed from pre-existing glands (cf. § 125). Malformations of the organs (e.g., of the kidneys) may lead to the development of multilocular cystomata, the cystic dilatation affecting not only the urinary tubules, but also Müller's capsules. It has already been mentioned that teratomata may occur under the form of adenocystomata. Finally, there is also an intermediate form between cystadenoma and cystocarcinoma.

(c) *Carcinomata and Cystocarcinomata.*

§ 128. **Carcinomata** are *malignant epithelial tumors* which possess two special characteristics, viz., *they grow by a sort of infiltrative process* and *they are apt to form metastases.*

They develop:—

(1) In the skin, in mucous membranes, and in glands, all of which organs appeared to be normal before the carcinoma developed in them.

(2) In the skin, in mucous membranes, and in glands, which had undergone pathological changes before the carcinoma developed in them.

(3) In already existing papillary epitheliomata, adenomata, and adenocystomata.

(4) From the remains of epithelial fœtal structures and from epithelial tissues which have been displaced by disturbances of development and are already predisposed to become the seat of some pathological new growth.

(5) From the epithelial tissues of the villi of the chorion and placenta.

The most characteristic feature in the development of a carcinoma is the **atypical manner in which the epithelium sooner or later forces its way into the tissues which border upon the affected glands or the surface epithelium.** Usually this growth of epithelium is accompanied by a **growth of connective tissue,** but this is not absolutely essential to the development of a carcinoma. The tissue invaded by the epithelial growth—it matters not whether it be a gland, a muscle, a bone, or any other tissue—will ultimately be destroyed by the carcinoma.

The **cause of the atypical growth of epithelium** is not really known. It is merely possible to state that certain conditions predispose to such growth. Thus, for example, an *advanced age* predisposes to the development of carcinomata of the skin. In this period of life the connective tissue of the skin undergoes a certain amount of atrophy and loss of firmness of texture, while the epithelium, at least in part, continues to increase, and here and there, under certain circumstances, shows evidences of an increased activity (development of heavier hairs upon the nasal septum, upon the lobes of the ears, and in the eyebrows). Then again, carcinomata of the mucous membranes and of the glands usually appear in mature years, although they may develop in early adult life, and even in childhood.

Another *predisposing factor* in the formation of cancer is furnished *by the displacement and separation of epithelium*, as easily happens in the healing of ulcers (cf. Fig. 152), and also in infectious or non-infectious granulation growths; in both of which the epithelium penetrates into the interior not only from the margin of the granulations, but also from any point upon their surface. Consequently, carcinomata often develop in *ulcers*, in *scars*, in *infectious granulations* (e.g., in tuberculous lupus of the skin and mucous membranes), or in *tissues which have been changed by inflammation* of any kind.

All the predisposing factors which have been enumerated do not constitute the sole cause of the development of a carcinoma. They may exist for a long time without ever leading to the formation of a cancer. It appears, therefore, that something else must be added before the unlimited atypical growth of epithelium begins, and what this something is, is not known.

In recent years, the opinion has often been expressed and stoutly

maintained that **parasites** cause the growth of a carcinoma. Unfortunately, most of those things which have been described as parasites (viz., protozoa, and especially the sporozoa and the yeast fungi) have not been parasites at all, but degenerated nuclei and karyokinetic figures, or leucocytes (or the products of their destruction) which have been included in tumor cells, or products of the cell-protoplasm, especially keratohyalin and colloid.

In the few cases in which genuine parasites have been found in the tissues, they may perfectly well have entered after the tumor had begun to develop. Under such circumstances they can in no sense be looked upon as the cause of the development of the carcinoma.

There are certain portions of the alimentary canal which are more frequently involved in the development of carcinoma. Such are the rectum, the flexures of the colon, the pyloric and cardiac openings of the stomach, the œsophagus, the pharynx, the tongue, and the gums. A carcinoma may develop in any portion of the skin, but it is seen more frequently on the lips and the nose than it is on the remaining portions of the face, or on the extremities, and more frequently on these again than it is on the body. The parts of the sexual apparatus most often affected are the mammary gland and the cervical portion of the uterus. Less frequently, though still often enough, the ovaries, testicles, body of the uterus, vulva, vagina, and penis are affected. The liver, kidneys, urinary bladder, trachea, bronchi, lungs, and pancreas occupy a middle ground; while the larynx and the gall-bladder, on the other hand, are more frequently attacked.

Cancer usually develops in the form of *nodules, which are not sharply differentiated from their surroundings*, and which often rise above the surface of the mucous membrane as *sponge-like*, or *polypoid*, or *papillary masses*. They spread from the point at which they begin to develop by an **infiltrative sort of growth** of the epithelium, by which either the nodules are increased in size, or else an extensive thickening of the affected organ (the intestinal wall, for example) results. The ovaries, testicles, uterus, kidneys, etc., may be partly or wholly transformed into a carcinomatous mass. The epithelial infiltration, as it advances, may pass beyond the limits of the organ originally affected, and may involve the neighboring tissues and organs. Thus, for example, the infiltration may extend from the mammary gland to the contiguous fat and skin and muscle, from the gums to the maxillary bone, from the uterus to the vagina and the parametrium, as well as to the bladder and the rectum, from the gall-bladder to the liver, from the bronchi to the lungs, etc.

The **formation of metastases** may take place as well through the lymph- as through the blood-channels, and is of frequent occurrence by both routes. It leads, for the most part, to the formation of secondary nodules in the various organs, but it may assume such a character that quite large portions of the system of lymph-vessels—as, for example, the pulmonary lymph-vessels—may be simply dilated by the new growth, without the formation of separate nodules. The transportation of cancerous germs to the marrow of bones may result in the cancerous degeneration of the marrow of an entire bone or of several related bones. It is also to be noted that probably not every transplantation of cancer cells leads to the formation of a cancerous growth. There are grounds for the belief that in the majority of instances the cells which are thus transplanted perish.

The tissue of a carcinomatous tumor is sometimes soft like marrow, sometimes rather tough and solid; but it is almost always possible to scrape from its cut surface a certain amount of whitish, opaque fluid called *cancer juice* or *cancer milk*. It is often possible to make out, on the cut surface, a tough fibrous framework, in the meshes of which the softer masses lie, and from which they can often be squeezed by pressure, either in the form of fluid, or as plugs, or as a crumbling material.

The masses obtained by pressure and by scraping the cut surface are made up, for the most part, of the **atypically developed epithelial cells**, the so-called **cancer cells**, which are found in a *great variety of forms* and which often show degenerative changes, especially fatty degeneration. There is usually no true *secretion* emanating from the epithelial cells, and yet one sometimes encounters in the mucous membranes, in the ovaries, and in the mammary glands, carcinomata which produce mucin or pseudo-mucin; and the amount of the secretion thus produced may be great enough to form cysts, thus justifying the employment of the term *cystocarcinoma*.

Retrograde changes occur very often in cancers at an early stage, and are due partly to the lack of vitality of the new growth and partly to disturbances of the circulation, which may be caused either by the growth of cancer cells into the capillaries and veins or by external influences. These changes lead, in the first place, to a *breaking down of the cancer cells* in certain parts of the tumor, and then, after the broken-down material has been gotten rid of through absorption, a certain amount of shrinking of the tissues will take place at the corresponding spots. Depressions will thus be formed between the nodules. Such retracted areas are seen quite frequently in the primary nodules of the mammary gland and in the secondary nodules of the liver, lungs, and other internal organs. They have received the name of *cancer-umbilications*.

The retrograde changes often lead to a complete destruction of the cancerous tissue and the **formation of an ulcer.** This is observed more particularly in cases in which a mucous membrane is the part affected; a carcinoma in this locality usually revealing itself, at the time of the patient's death, in the form of an ulcer of greater or less extent. Similar ulcerative changes also occur in cancers of the mammary gland and of the external skin. In the latter situation, the cancer may present the appearance of a progressing, corrosive ulcer, an ulcus rodens. The border of such an ulcer is sometimes raised up like a wall or studded with nodules, while at other times it is sharply defined and only slightly infiltrated. The base is sometimes fissured and ragged, and covered with necrotic tissue, while at other times it is smooth.

The deeper tissues which border upon the ulcer are often abnormally hard, this change being due either to a cancerous infiltration or to a growth of connective tissue which has taken place as a sequel to the retrograde changes and the ulceration.

In recent years a large number of articles have been published by authors who have attempted to prove (successfully, as some of them have thought) that the formation of a cancer is due to parasites. Nevertheless, none of these treatises can be looked upon as furnishing satisfactory proof of the correctness of this hypothesis. Then, besides, it is extremely improbable that cancers owe their origin to infection. There are three facts which militate against the idea of a parasitic origin for these tumors: first, no parasites can be demonstrated in the beginning of the cancer's development; second, the whole course of the disease is quite different from that of an epithelial growth produced by parasites; and third, the formation of metastatic tumors is due, beyond all question, to the transportation of cancer cells.

§ 129. **Cancer of the skin** usually develops from the epidermis, and is characterized by the growth of the interpapillary portions of the same into the deeper parts of the chorion in the form of epithelial cones (Fig. 306, *d*) which fill up the interstices of the connective tissue. The

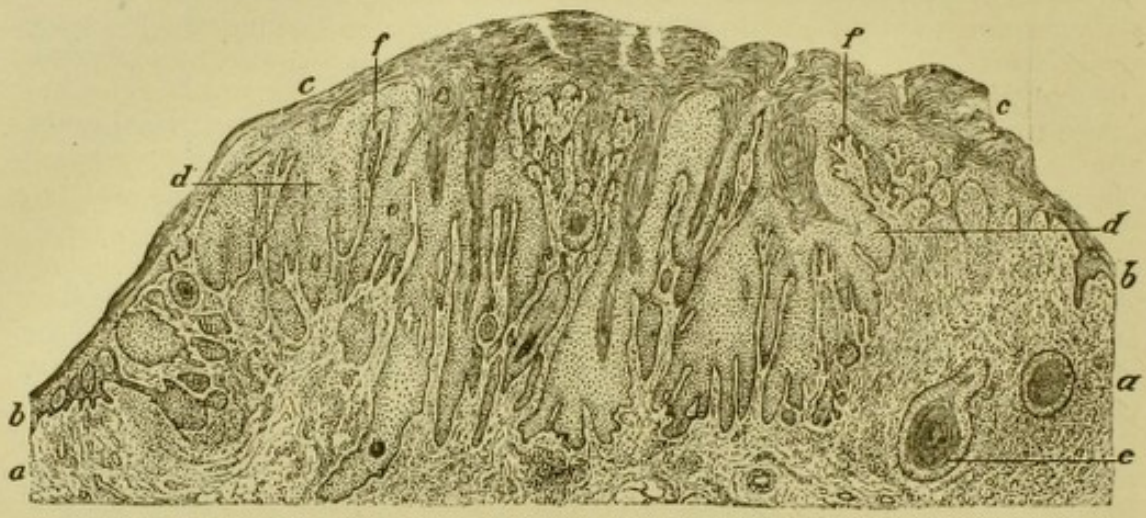


FIG. 306.—Transverse section through a carcinoma of the lip. (Alcohol; hæmatoxylin; eosin.) *a*, Corium, in a proliferating condition; *b*, epithelium; *c*, thickened horny layer; *d*, epithelial plugs extending down into the corium; *e*, epithelial plug cut obliquely and showing a pearl of horny substance; *f*, enlarged papillæ of the skin. Magnified 12 diameters.

stratum corneum (*c*) may also undergo hypertrophy along with the cells of the rete Malpighii, and penetrate deeply into the subjacent tissues as a part of the epithelial cones (*d*). Furthermore, the cones of epithelium may produce horny epithelial plates (*e*) after they have reached these deeper regions.

The *epithelium of the hair follicles and the sebaceous glands* may also take part in the formation of the cancer, and indeed there are cancers of the skin which develop entirely from the sebaceous glands, and which must therefore be reckoned among the glandular cancers.

The *connective tissue* may remain entirely passive while the epithelium grows into it, but sooner or later it is excited to growth (Fig. 306, *a*) and the papillæ are often changed to long, branching structures (*f*). Besides the *fibroblasts*, *leucocytes* are often found in the connective tissue, and these latter may make their way into the epithelium. They are especially abundant after disintegration of the tissues begins, and at that time the proliferating connective tissue presents all the appearances of inflammatory granulation tissue.

The mode of origin of a carcinoma that springs from a mucous membrane which is provided with flattened epithelium may be the same as that of a carcinoma of the skin—that is, it begins as a *proliferation of the epidermis* (Fig. 307, *a*, *c*). If glands are present these may take part in the cancerous development. It is a noteworthy fact that, in the growth of such a cancer, even those glands which possess cylindrical epithelium can furnish epithelial products which are exactly like those of the epidermis. The epithelial proliferation may at first advance within the canaliculi and lead to a diffuse thickening and stratification of the epithelium (Fig. 307, *f*), or to the formation of distinct excrescences (*e*). Later on, however, the growing epithelium breaks into the connective tissue.

The connective tissue acts as it does in cancer of the skin.

The **mode of origin of a mucous-membrane carcinoma which is made up of simple cylindrical epithelium** is the following: In cases in which the intestine is the seat of the disease the growth begins in the *tubular glands* or in the *crypts*, in both of which localities the epithelium first undergoes an active proliferation and then arranges itself in layers, while the glands, under the increasing pressure, undergo dilatation (Fig. 308, *b*). At a later stage the glands become changed into branching, atypically formed structures (*c*), which are lined with a stratified epithelium and grow into the surrounding tissues.

In comparatively rare cases newly formed atypical glands, in the intestinal or the gastric mucous membrane, may take on an infiltrative mode of growth (Fig. 309, *e*) at a time when they still carry a single layer of tall cylindrical epithelial cells, and portions of the growth bearing this characteristic may be found not merely in the submucous tis-

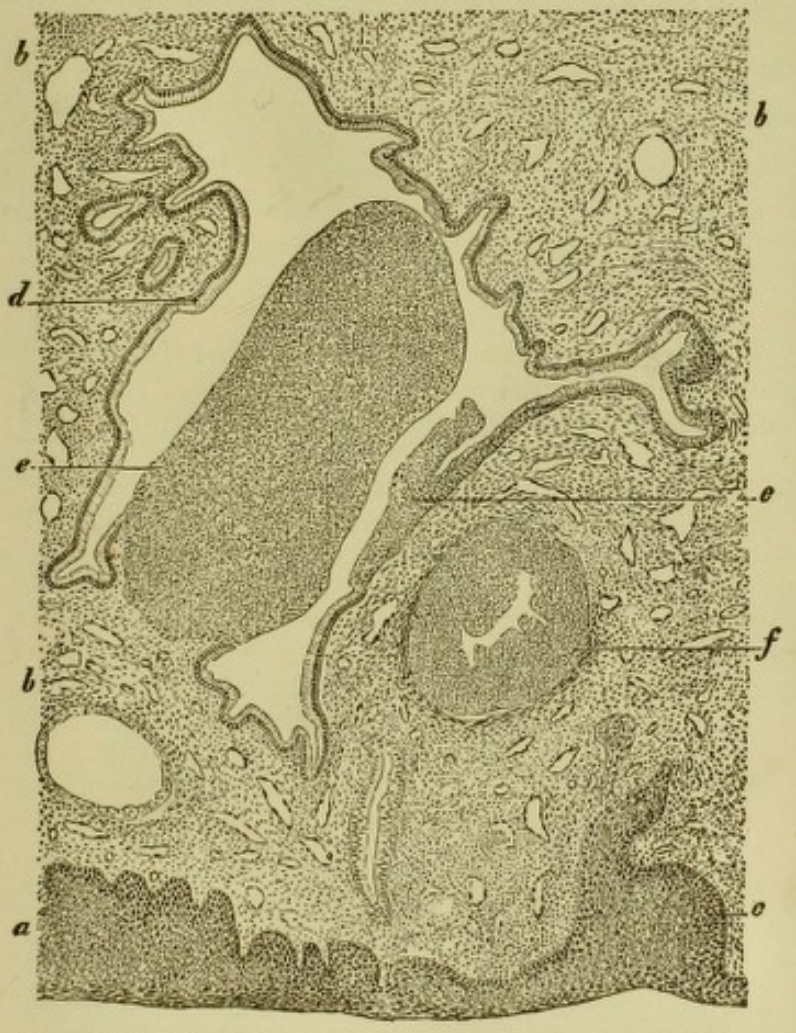


FIG. 307.—Commencing development of a carcinoma in the vaginal portion of the uterus. (Alcohol; Bismarck brown.) *a*, Epithelium; *b*, connective tissue; *c*, surface epithelium growing down into the deeper-lying tissues; *d*, dilated gland; *e*, epithelium of a gland growing out in the form of plugs; *f*, transverse section of a gland, the cylindrical epithelium of which has become converted into laminated epithelial scales. Magnified 45 diameters.

sues (Fig. 309, *b*), but also in the muscular layer (*c*) and even in the serosa (*d*).

The epithelial cells of the newly formed glands are usually more deeply stained than normal epithelium by the dyes which stain nuclei.

As in the case of carcinoma of the skin, the connective tissue sooner

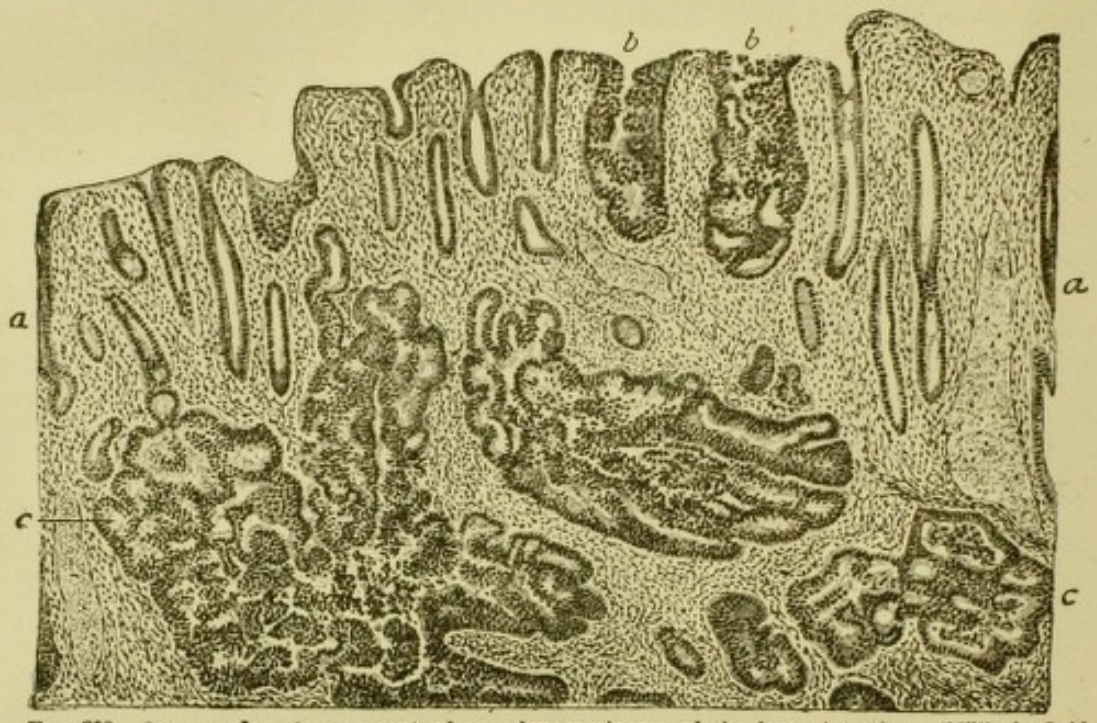


FIG. 308.—Commencing development of an adenocarcinoma of the large intestine. (Müller's fluid; hæmatoxylin; eosin.) *a*, Mucosa, with glandular tubules still unaffected; *b*, a part of the mucosa where the glandular tubules have been involved in the carcinomatous disease; *c*, foci of carcinomatous disease in the submucosa. Magnified 100 diameters.

or later takes on proliferative action, and with this proliferation there may be associated an emigration of leucocytes.

The **development of a cancer in a gland**, e.g., in the mammary

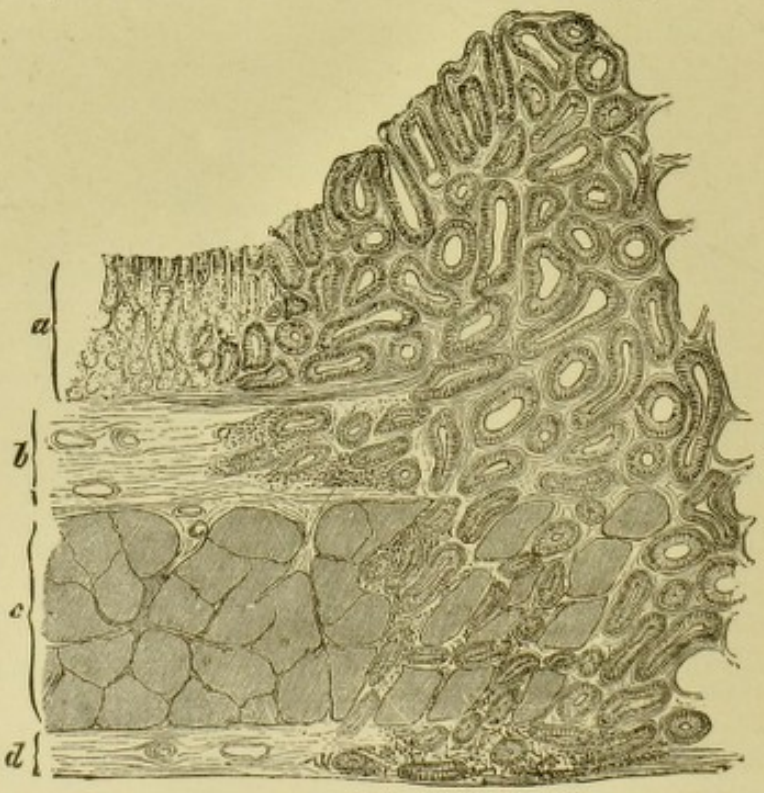


FIG. 309.—Section through the growing margin of a carcinoma adenomatosum of the stomach. (Alcohol; hæmatoxylin.) *a*, Mucosa; *b*, submucosa; *c*, muscularis; *d*, serosa; *e*, new growth proceeding from the mucosa and infiltrating the other layers. A round-celled infiltration appears in parts in conjunction with the development of tubules. Magnified 15 diameters.

gland, also begins with a *proliferation of the epithelium*, and in consequence of this proliferation the affected gland increases in breadth (Fig. 310, *a*) and often changes its form (*b*), and at the same time its lining epithelium may become stratified (*b*). When the epithelium breaks through into the interstices of the neighboring connective tissue, an epithelial infiltration of that tissue begins. The microscopical pictures presented by the growth will vary according to the structure of the gland from which the cancer originally developed, and also according to the variety of the cancer itself.

Through simple proliferation the connective tissue may contribute to the building up of the tumor, and yet in the early stages this participation may amount to little or nothing.

The **development of a cancer from an adenoma** or fibro-adenoma

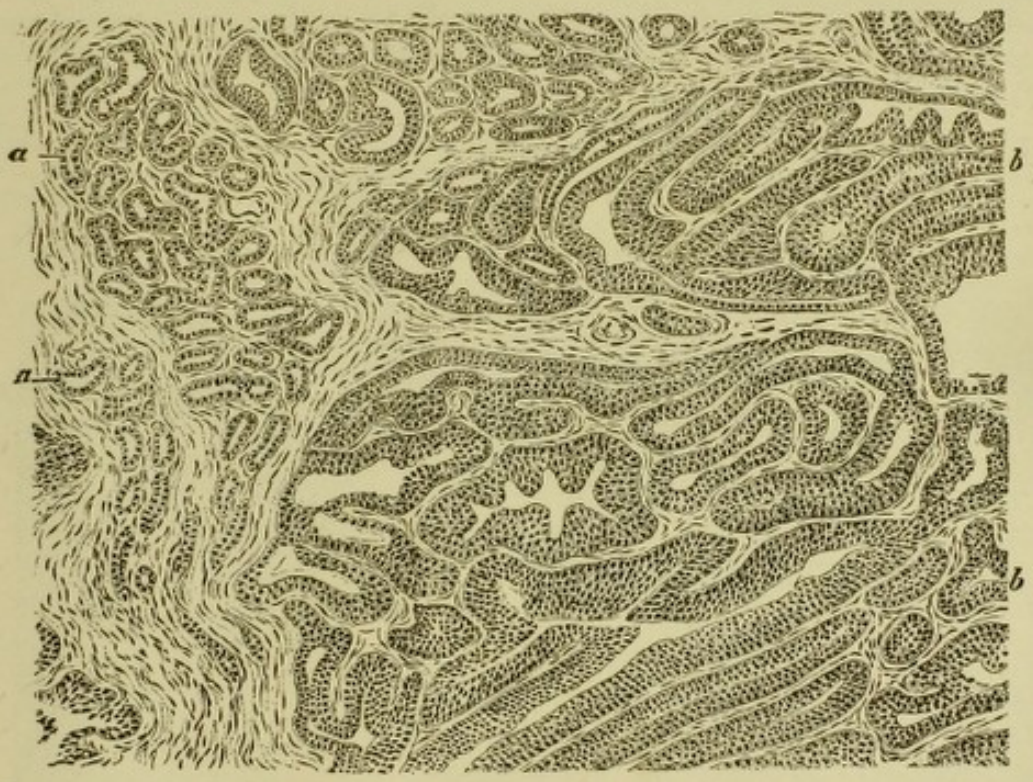


FIG. 310.—Cystocarcinoma of the mammary gland in an early stage of its development. (Tumor about as large as a bean.) *a*, Normal gland tissue; *b*, proliferating gland tissue. (Alcohol; hæmatoxylin.) Magnified 100 diameters.

(Fig. 311, *a*) also begins as a somewhat active *proliferation of the epithelium*, as a result of which the single layer of epithelial cells becomes stratified (*b*, *c*). The growth of the epithelium into the connective tissue, which often first takes place only at a much later stage, furnishes additional evidence of the malignancy, i.e., of the carcinomatous transformation, of the new growth.

The **development of a cancer from a papillary epithelioma** proceeds in the same manner as it does when the growth starts from previously normal skin or mucous membrane; that is to say, it is characterized by the infiltration of epithelium into the base upon which the epithelioma rests.

The **development of cancer from transplanted or misplaced epithelium**, or **from remains of fœtal structures**, proceeds in the same manner as it does when the growth springs from the epidermis or from glandular epithelium.

A carcinomatous transformation of chorionic or placental villi proceeds either from the fœtal *ectodermal epithelium* of the chorion and its villi, or from the cells which are known as the *syncytium* (which cells are situated upon the ectodermal epithelium, but are derived from the decidual uterine epithelium), or from both of these layers of cells. These carcinomatous growths spring from the points where the villi are attached to the main body of the uterus, and they penetrate from there into the adjacent tissues, especially into the blood-vessels (Fig. 312, *d*, *d*$_1$, *e*, *f*, *h*). Ultimately they lead to the formation of thrombi, to extensive destruction of uterine tissue, and to the establishment of metastatic carcinomatous foci. Myxomatous degeneration of the villi both of the chorion and of the placenta (hydatid mole) appears to favor the development of such cancerous growths. The expressions *placental carcinomata* and *chorionic carcinomata* seem to me on the whole to be commendable. A number of authorities apply to these growths the terms *malignant placentomata*, *malignant deciduomata*, and *destructive placental polyps*.

Ribbert believes, as has already been stated in § 107, that he has found the cause of the formation of cancer in a separation of single epithelial cells from their normal relations and a transplantation of them to points located between the cells of the connective tissue; and he looks upon the proliferation of the connective tissue as the first step in the development of a cancer. From the pictures furnished on preceding pages it is evi-

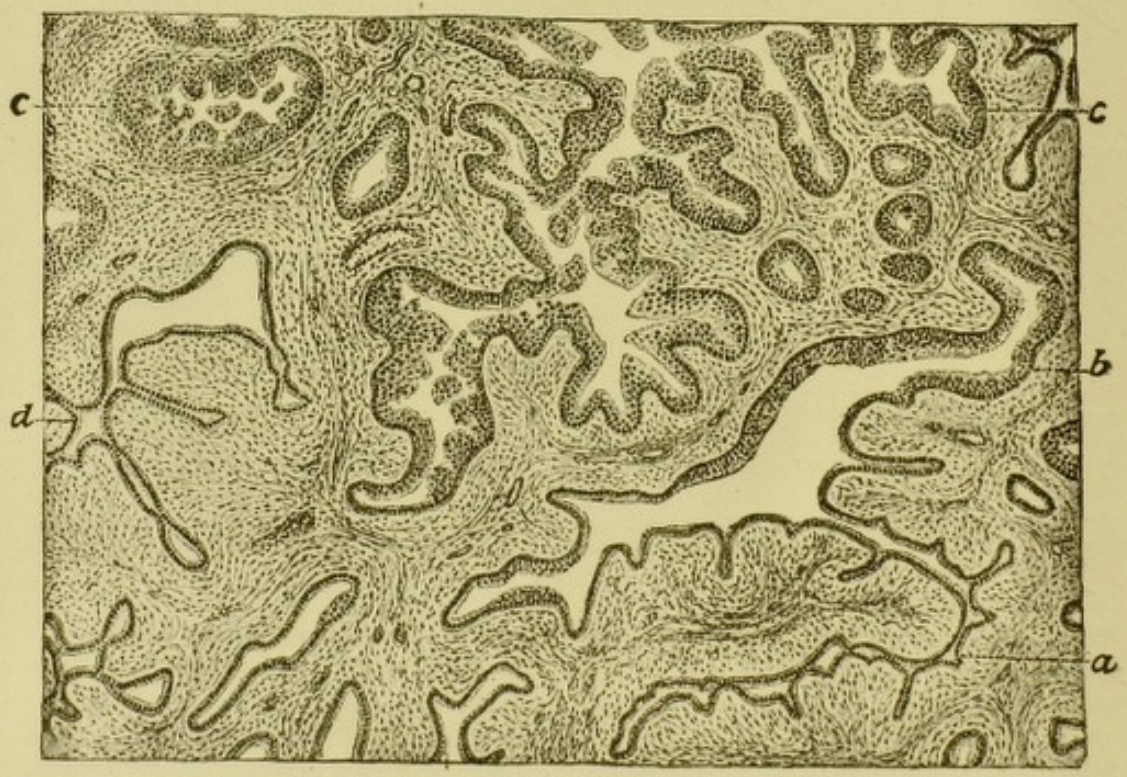


FIG. 311.—Tubular adenoma of the mammary gland, with beginning transformation into a carcinoma. (Formalin; hæmatoxylin.) *a*, Branching gland tubes lined with simple epithelium; the connective tissue which surrounds the tubes being rich in cells and in a proliferating condition; *b*, *c*, gland tubes, the epithelium of which is in some places still simple, while in others it has already reached a thickness of several layers. Magnified 100 diameters.

dent that this view of the development of cancer is not supported by the facts, but that, on the contrary, the proliferation of the epithelium can begin in normally placed surface or glandular epithelium, and that the starting-point for the development of a cancer lies in such proliferation and not in that of the connective tissue.

The transplantation of epithelium apparently favors the development of cancer, but does not of itself necessarily produce this result. The traumatic displacement of surface

epithelium in wounds may lead to the formation of the so-called **traumatic epithelial cysts,** that is, cysts which vary in size from that of a hemp seed to that of a nut, which are lined with epithelium, and which are filled, in case they come from the external skin, with a grumous mass of cast-off epithelial cells. They are usually found, after punctured wounds, on the palmar surface of the fingers or in the hollow of the hand.

Adenomata and **carcinomata** cannot always be sharply distinguished the one from the other, for the reason that tubular adenomata—especially those of the intestine,

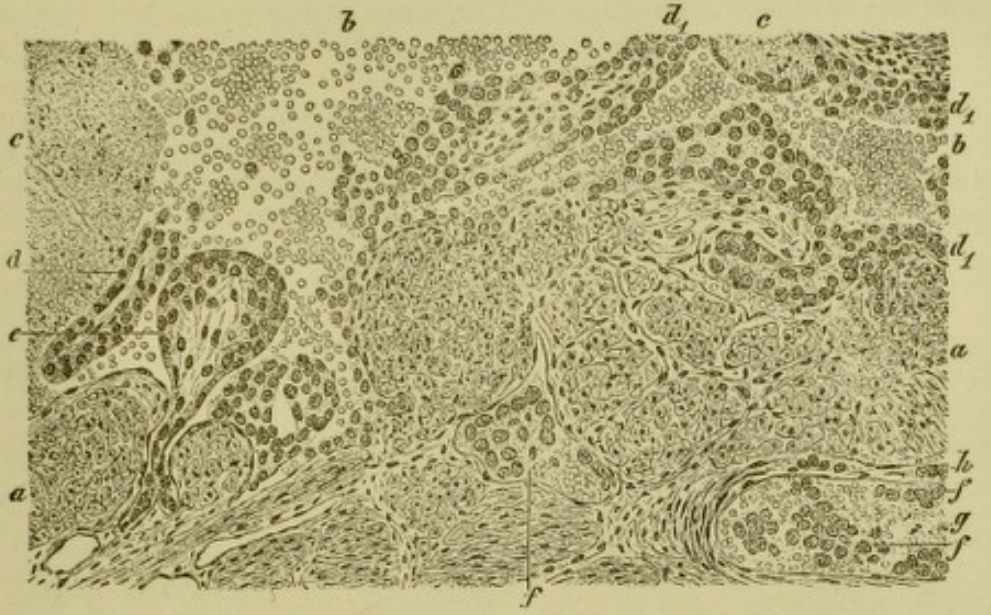


FIG. 312.—Placental carcinoma of the uterus (destructive placental polypus). (Compare von Kahlden: "Destruirende Placentarpolypen," *Centralbl. f. allg. Path.*, II., 1891.) *a*, Muscularis of the uterus; *b*, large blood-space; *c*, thrombus; *d*, d_1, intravascular growths of the epithelium which covers the villi of the chorion. These growths project into a large blood-space which has been broken into from the cavity of the uterus, and which contains several thrombi; and at some spots (as at *d*) they lie free in the blood-space, while at others (as at d_1), they are attached to the wall of the vessel; *e*, proliferating mass of cells which have forced their way into a rather small blood-vessel; *f*, an aggregation of proliferating chorionic epithelial cells within the veins of the muscularis of the uterus; *g*, thrombus; *h*, proliferating cells in the wall of a vein. Magnified 70 diameters.

more rarely those of the thyroid gland or the liver—although possessing a simple cylindrical epithelium, may grow by infiltration, break into the surrounding tissues (Fig. 309), and develop metastases. If a special name is to be applied to such forms, in order to distinguish them from the ordinary carcinoma adenomatosum, or adenocarcinoma, the terms **adenoma destruens,** or **malignum,** or **carcinomatosum,** may be employed. It is further to be noticed that benign adenomata, which have existed as such for a long time, may change into carcinomata.

To a certain extent the character of the parent tissue is preserved in the cells of the cancer, but a closer inspection shows a certain amount of change both in their morphological and in their physiological characters. Hansemann has called this alteration in the character of the cells *anaplasia*. It manifests itself in an alteration both in the form and in the structure of the cells which usually also manifest a different affinity for dye-stuffs. Then, in addition, a difference may be noted in the arrangement and relations of the cells, and in their relations to the surrounding tissues.

§ 130. The **structure of a carcinoma** is determined by its origin. The manner in which the epithelium proliferates, in the midst of connective tissue which may also take on proliferative action, makes it possible to distinguish a **connective-tissue stroma,** along which course the blood-vessels, from the **nests** and **strings of cells**—the **cancer plugs**, as they are called—which are embedded in that stroma. If the cancer penetrates into a tissue which has a specialized structure, the stroma may contain muscle fibres, bone trabeculæ, unchanged glandular tissue, etc., but these tissues are apt, in the course of time, to perish and disappear. In general, it may be said that a cancer possesses an alveolar structure in which the nests of cells sometimes suggest an imperfectly developed

acinous gland, at other times a tubular gland, thus justifying the establishment of *acinous* and *tubular types* of carcinoma. If the plugs of cells are solid, without a lumen, the tumor is spoken of as **carcinoma solidum**, or merely as **carcinoma.**

If there is a lumen in the cellular plugs, this circumstance will give to the growth a certain resemblance, in its anatomical structure, to the adenomata, and will therefore justify the employment of the term **carcinoma adenomatosum** or **adenocarcinoma** (Fig. 308, Fig. 309, and Fig. 310).

Several **forms of carcinoma** may be distinguished, in part according to the character of the epithelial cells, in part according to that of the groups which they compose, and finally in part according to certain changes which take place at a later stage of the growth. As the character of the cells is dependent upon the nature of the matrix in which they develop, so are certain types of carcinoma characteristic for certain re-

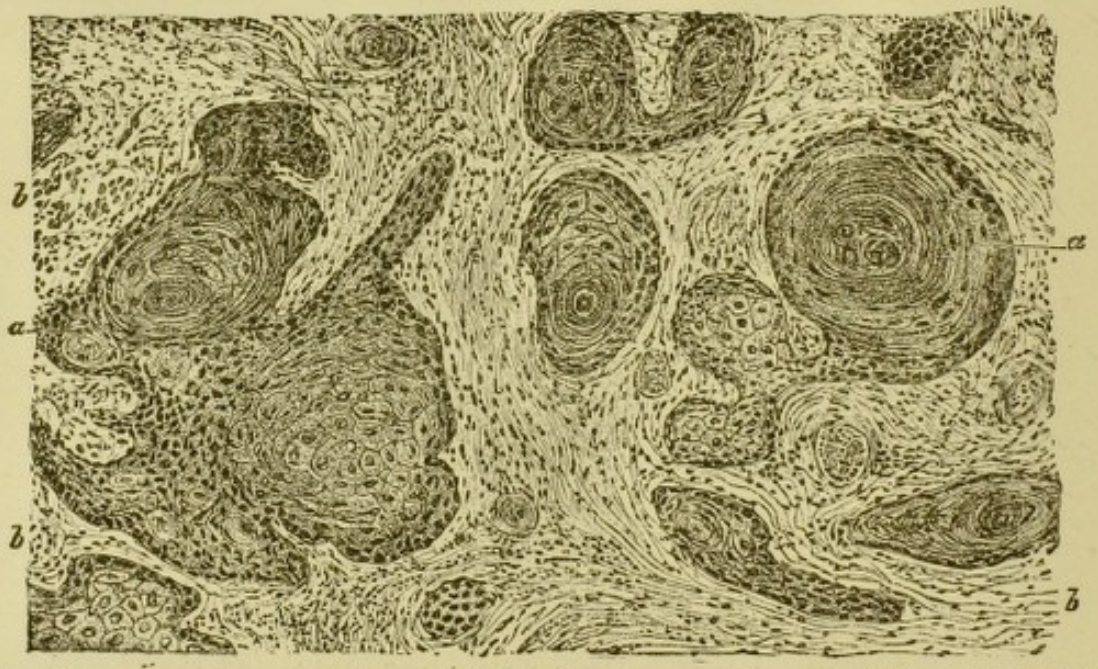


FIG. 313.—Horny carcinoma of the tongue. (Müller's fluid, hæmatoxylin; eosin.) *a*, Plugs of epithelium, with epithelial pearls; *b*, stroma. Magnified 100 diameters.

gions of the body; as a matter of fact, they appear almost exclusively in these parts of the body.

(1) **Flat-celled cancer** develops in those places where the skin or a mucous membrane is covered with flattened epithelium. It may develop, therefore, in the external skin, in the mouth, in the throat and the œsophagus, in the larynx, in the vaginal portion of the uterus, in the vagina, in the lower urinary passages, and especially in the bladder and external genitals. In rare cases flat-celled cancer may develop in a mucous membrane which is covered with cylindrical epithelial cells, e.g., in the trachea, or in remains of fœtal structures (i.e., in the remains of maxillary clefts or dermoids), or finally, in the ependyma of the ventricles of the brain. The flat-celled epithelial cancer is characterized by the formation of relatively large strings of cells (Fig. 313, *a*, and Fig. 314) of irregular shape; but besides these there are often small strings of cells, especially in those cases in which the cancerous growth has begun to involve larger areas of the mucous membrane. The epithelial

cells which are massed together in separate collections still show plainly the character of laminated flattened epithelium, but in consequence of their growth and multiplication within the interstices of the tissue they generally *assume a variety of shapes* (Fig. 314) and no longer manifest their typical characteristics. Very often the formation of keratohyalin and the change into a horny condition take place deep down in the centre of the larger epithelial plugs; and along with the process of cornification the cells arrange themselves in concentric laminæ like those of an onion (Fig. 313, *a*, Fig. 314, and Fig. 306, *e*). These rounded masses of laminated horny epithelium are called *epithelial pearls* or *horny bodies;* and hence the name *horny cancer* has been applied to such a tumor.

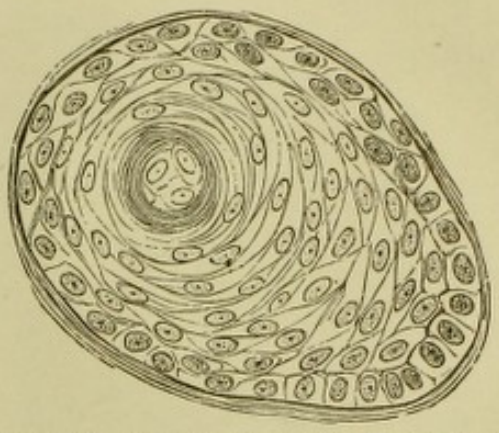


FIG. 314.—Epithelial plug from a cancer of the skin. Magnified 250 diameters.

(2) **Cylindrical epithelial cancer** develops especially in mucous membranes which are provided with cylindrical epithelium, i.e., in the intestine, in the stomach, in the respiratory passages, in the body of the uterus, and in the gall-bladder; but it is also found in glands, such as the ovary, mamma, liver, etc., and in the ventricles of the brain. Such a tumor exhibits, at least in the beginning of its growth, the character of a **carcinoma adenomatosum** or of an **adenocarcinoma** (Fig. 308, Fig. 309, Fig. 315, Fig. 316); that is, it forms epithelial structures which suggest glands and are made up of gland tubules of various shapes which are lined with a simple or stratified epithelium. When

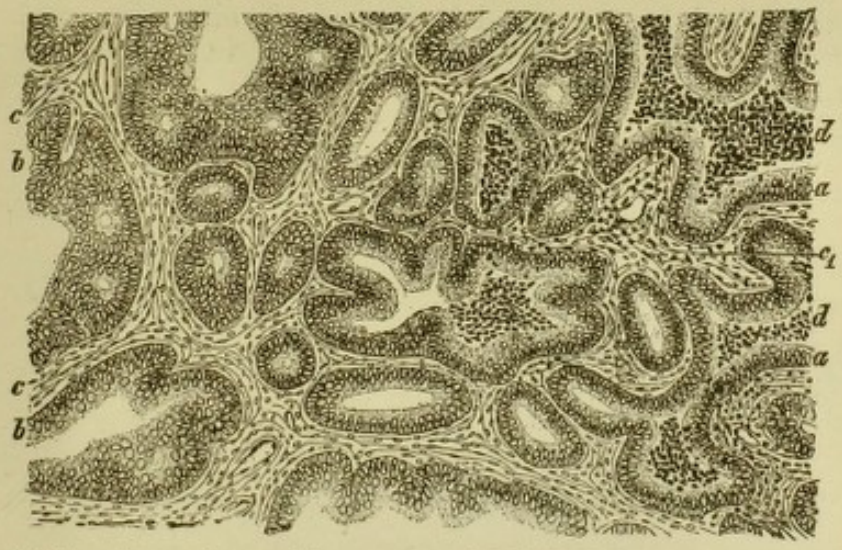


FIG. 315.—Tubular adenocarcinoma of the rectum. *a*, *b*, Epithelial gland-tubules; *c*, c_1, stroma; *d*, collection of leucocytes in the gland-tubules. (Alcohol; alum carmine.) Magnified 80 diameters.

the proliferative activity of the epithelial cells is unusually great, compact cell-nests without a lumen will be produced (Fig. 316).

The stroma of a cylindrical-celled cancer is usually poorly developed, so that the tumor possesses the character of a soft cancer—a **carcinoma medullare.** In some instances, however, the cancerous tissue possesses a firmer consistence.

(3) **Carcinoma simplex**, or *carcinoma in the narrower sense*, is a cancer whose especial characteristics are derived from the form and disposition

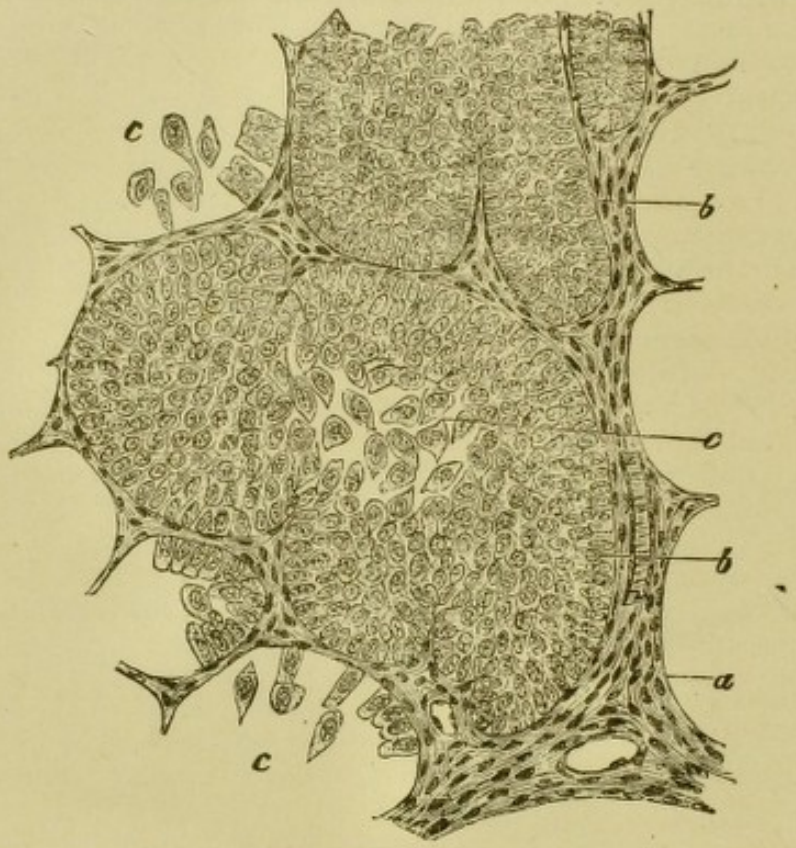


FIG. 316.—Adenocarcinoma of the fundus of the uterus. *a*, Stroma; *b*, plugs of carcinoma cells; *c*, isolated carcinoma cells. Magnified 150 diameters.

of the cells, which are arranged in irregularly shaped, compact groups (carcinoma solidum). It is most often found in glands, but may also develop in the mucous membranes or in the skin. The nests of cells are

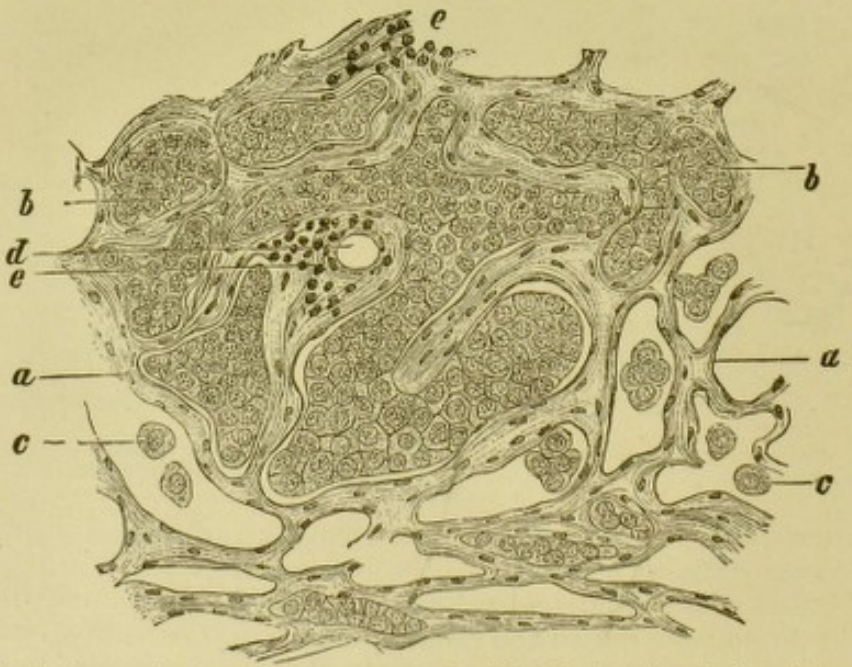


FIG. 317.—Carcinoma simplex of the mammary gland. (Alcohol; hæmatoxylin.) *a*, Stroma; *b*, plugs of carcinoma cells; *c*, scattered carcinoma cells; *d*, blood-vessel; *e*, infiltration of the stroma with small cells. Magnified 200 diameters.

in some cases shaped quite irregularly (Fig. 317), in others they are to a great extent round (Fig. 318), and finally in still others they are long drawn out or fusiform in shape (Fig. 319). These variations have led

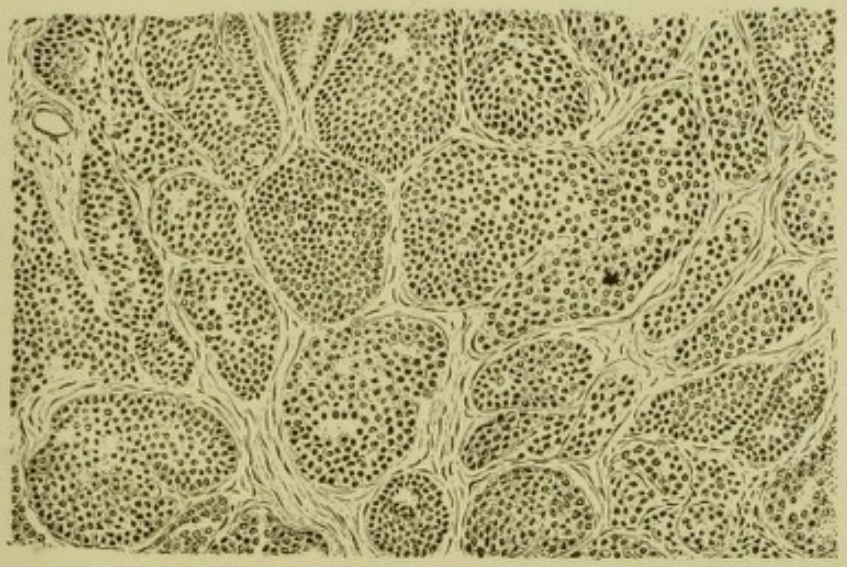


FIG. 318.—Acinous carcinoma of the mammary gland, with large nests of cells. (Müller's fluid; hæmatoxylin.) Magnified 100 diameters.

to the subdivision of these growths into **carcinoma acinosum** (Fig. 318) and **carcinoma tubulare** (Fig. 319). It is, however, to be observed that these different types may exist in the same tumor (Fig. 320, *e*, *f*, *g*), since the structure of the nests of cells is dependent partly upon the character of their own growth, partly upon that of the tissues in the midst of which they develop. Thus, for example, the cell-nests at the point of origin of the tumor may have a variety of shapes (*e*): some-

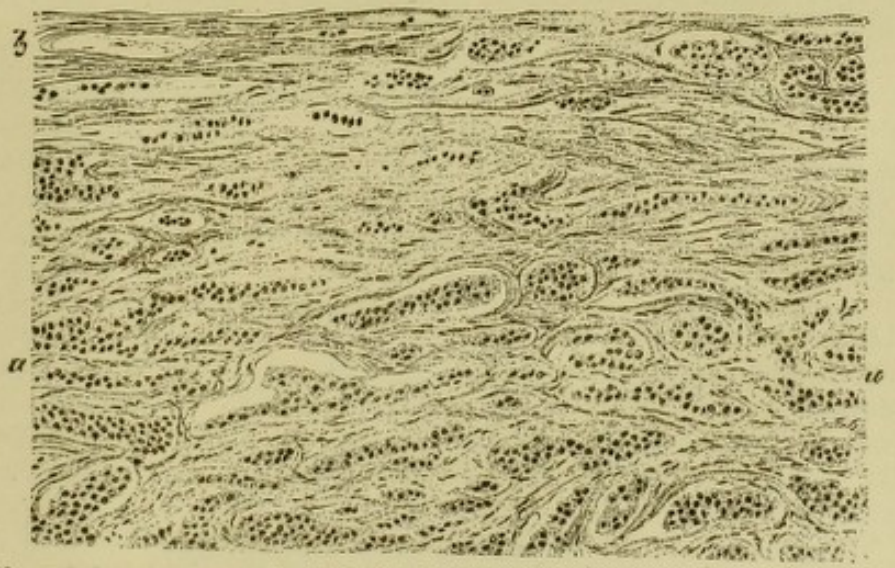


FIG. 319.—Tubular scirrhous carcinoma of the mammary gland. (Müller's fluid; hæmatoxylin.) *a*, Spot at which there are well-developed, oblong nests of cells; *b*, spot at which the nests of cells have broken down and have for the most part disappeared. Magnified 100 diameters.

what rounded in the adipose tissue (*f*), and small and fusiform when they develop in the unyielding connective tissue of the skin (*g*).

An abundant development of cell-nests within a delicate connective-tissue network results in a **carcinoma medullare.** A strong develop-

ment of the connective-tissue stroma with the formation of comparatively few cancer cells gives rise to a hard tumor which is called **carcinoma durum,** or **scirrhus** (Fig. 319).

A hard cancer may owe its origin to the fact that from the beginning the nests of cells are small and relatively scarce, while the connective-tis-

FIG. 320.—Section through a segment of a carcinoma of the breast. (Alcohol; hæmatoxylin.) *a*, Nipple; *b*, tissue of the mammary gland; *c*, skin; *d*, outlet-ducts of the gland; *e*, carcinomatous masses occupying the position of glandular tissue; *f*, lobules of fat already infiltrated with cancer; *g*, portion of skin also infiltrated with cancer; *h*, carcinomatous cell-nests in the nipple; *i*, normal lobules of the gland; *k*, infiltration of small cells in the connective tissue. Drawn with the aid of a lens.

sue stroma is abundant and firm. Such a condition of affairs is found when the epithelial proliferation takes place in firm connective tissue such as that of the breast or of the skin; and yet, on the other hand, newly formed connective tissue may possess the same characteristics. In the course of time, a cancer may grow harder by reason of the destruction of a part or of all of the nests of epithelial cells (Fig. 319, *b*), while the connective tissue increases. Accordingly, a cancer **which was originally soft may become hard;** that is, **as the induration of the connective tissue advances,** the **cancerous portions undergo a corresponding shrinkage.** Cancers of the breast or stomach or intestine often undergo such secondary induration, so that the nests of cancer cells may be wholly wanting in the tissues which have undergone this fibrous change.

(4) **Cancers which are characterized by peculiar secondary changes** are usually those in which the cancer cells form peculiar products or undergo peculiar metamorphoses. It happens less frequently that the stroma is the part which undergoes some alteration.

Mucoid cancer or **gelatinoid cancer—carcinoma mucosum** (*C. gelatinosum, C. colloides*)—owes its peculiar characteristics to the fact that the epithelial cells produce mucus (mucin or pseudo-mucin) or a gelatinous substance similar to colloid. This production of mucus occurs

in cancers of the intestine and breast and may be manifest in the very

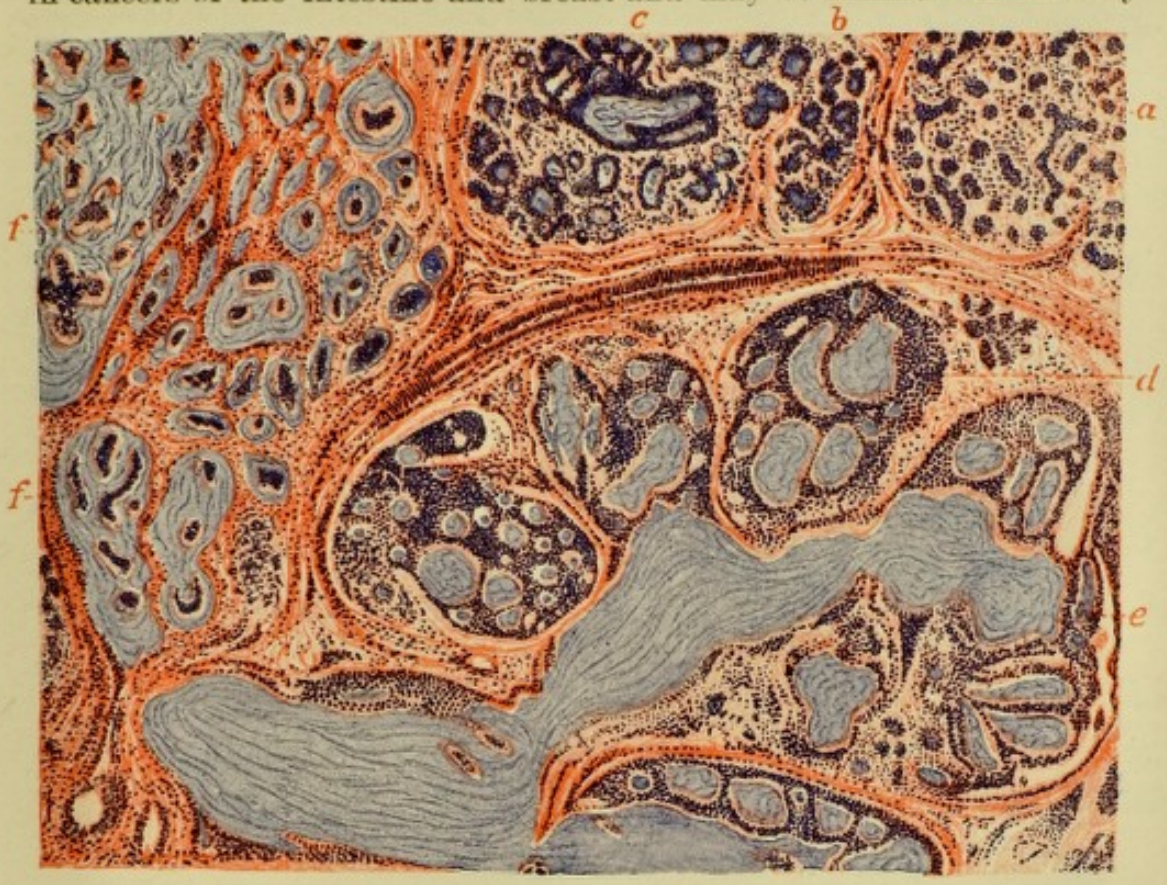


FIG. 321.—Mucous carcinoma of the mammary gland. (Müller's fluid; hæmatoxylin; eosin.) *a*, Normal gland tissue; *b*, *c*, first beginnings of the carcinomatous growth, in which the development of mucus may already be seen; *d*, rather large nests of cells, among which are masses of mucus; *e*, *f*, carcinomatous tissue in which the transformation into mucus is far advanced. Magnified 30 diameters.

beginning of the development of the growth (Fig. 321, *b*, *c*), so that the mucoid products of the cells collect in the centre of the cell-nests like the secretion of a gland. As time goes on, the rows of cells which sur-

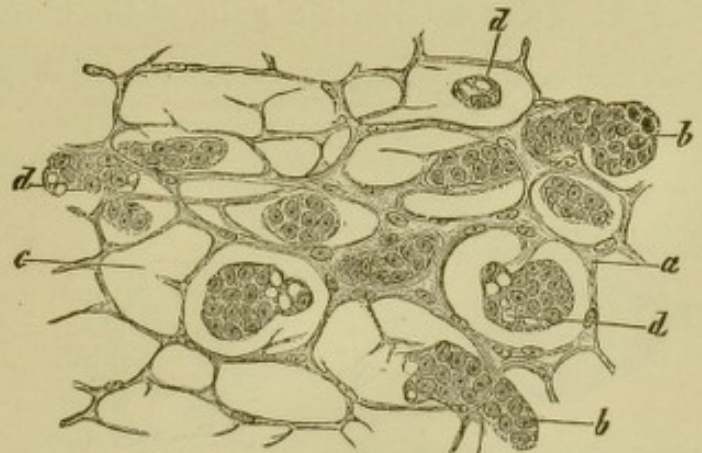


FIG. 322.—Mucous carcinoma of the mammary gland. (Alcohol; hæmatoxylin.) *a*, Stroma; *b*, plugs of carcinoma cells; *c*, alveoli which do not contain any carcinoma cells; *d*, cells with balls of mucus in their interior. Magnified 200 diameters.

round the mucoid material are usually broken through and the cells are loosened from their underlying support and crowded together in the

middle of the alveolus (Fig. 321, *d*, *e*, *f*). Ultimately, the epithelial cells are entirely destroyed.

In intestinal cancers the formation of mucus takes place in the beaker cells, which are similar to the normal beaker cells. In cancer of the breast the mucus forms in drops in the cancer cells (Fig. 322) and becomes free either by escaping from the cell or through the complete destruction of the cell itself.

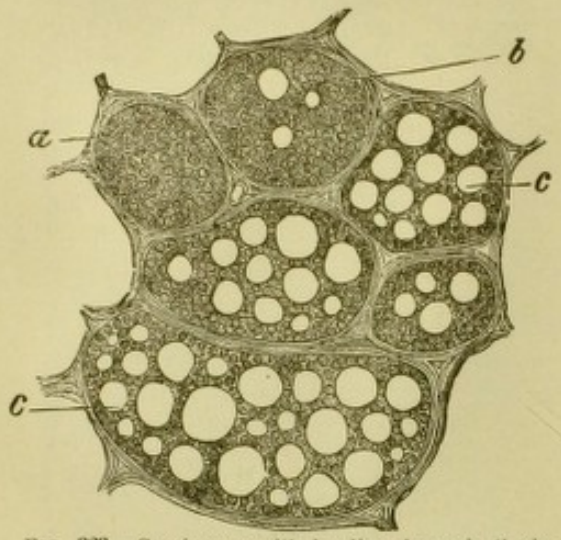


FIG. 323.—Carcinoma with hyaline drops in the interior of its nests of cells—carcinoma cylindromatosum. *a*, Cell-nests without; *b*, cell-nests with a few hyaline balls in their interior; *c*, cells which, through the formation of numerous hyaline balls, have been made to arrange themselves in the form of a network. Magnified 150 diameters.

If mucoid or colloid masses develop within the nests of cells, these nests may be studded by hyalin drops and so changed as to present the appearance of meshwork (Fig. 323). Such structures were formerly called *cylindromata* and classified with the corresponding sarcomata (§ 123). If any one wishes to retain this nomenclature he can speak of such a tumor as a *carcinoma cylindromatosum*, but it seems unnecessary to separate these tumors from the mucoid and gelatinoid cancers.

When the cancer cells grow to an extraordinarily large size, as occurs, for example, in flat-celled cancers or in cancers of the breast, the resulting tumor is termed a **carcinoma gigantico-cellulare.** If the increased size of the cells is due, not to an increase in the amount of protoplasm, but to the collection of drops of fluid in the cells and in their nuclei (Fig. 324), the cells are designated *physalides*, and the tumor *carcinoma physaliferum*.

If the stroma of a cancer undergoes a transformation into a mucoid tissue the name *carcinoma myxomatodes* may be applied to the tumor. This change, however, affects only certain parts of the tumor. In rare

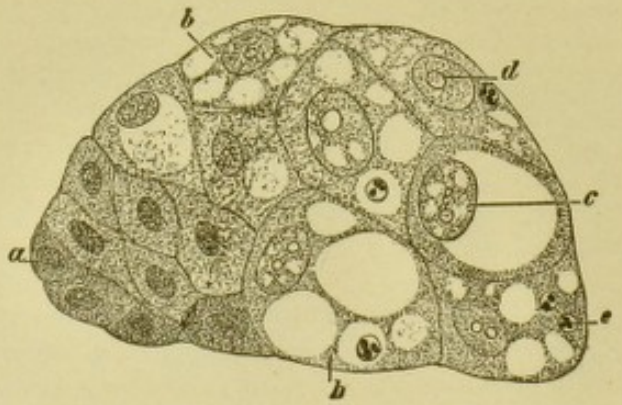


FIG. 324.—Enlarged dropsical cancer-cells from a carcinoma of the breast. *a*, Ordinary cancer-cells; *b*, dropsical cells containing in their interior clear drops of fluid; *c*, swollen nucleus; *d*, swollen nucleolus; *e*, wandering cells. (Müller's fluid; Bismarck brown.) Magnified 300 diameters.

cases the *connective tissue*, in parts of the tumor, also undergoes a *hyaline degeneration*.

Chalky deposits in carcinomata may take the form of concretions similar to those which occur in psammomata (vide § 123). The deposits may be either in the cells or in the connective tissue. They are observed in papillary adenomata and carcinomata of the ovary and in cancer of the breast. There are also more extensive calcifications which lead to complete *petrification*. Such tumors are observed in the skin and subcutaneous tissue, in the form of sharply defined, hard, rounded nodules. Some of these tumors—so far as one can judge from the descriptions—are to be reckoned among the carcinomata, while others of them are either calcified atheromata or adenomata of the sebaceous glands.

The cancers which develop from the surface epithelium were formerly called **cancroids** and **epitheliomata,** in contrast with other cancers which were supposed to grow from the connective tissue. The knowledge that the cancers which develop in glands are also epithelial formations makes such a distinction unnecessary. Nevertheless, the

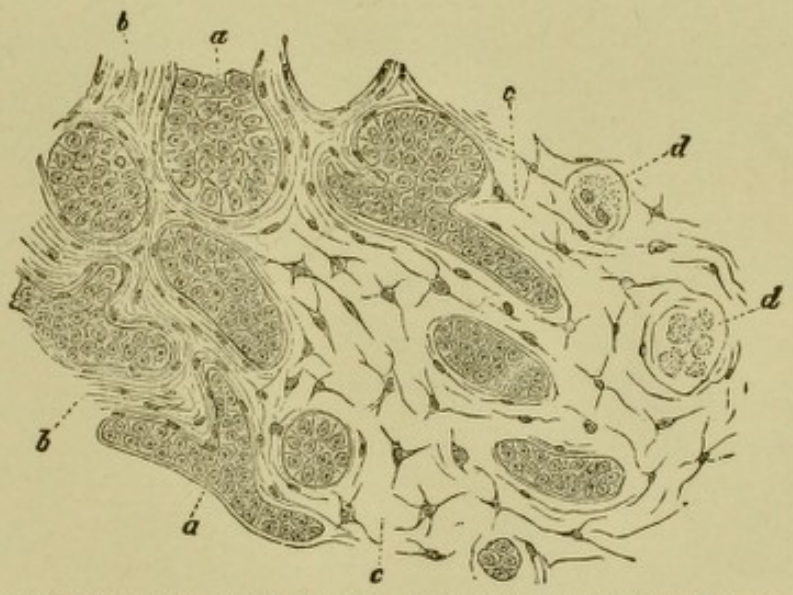


FIG. 325.—Myxomatous carcinoma of the stomach. (Müller's fluid; hæmatoxylin.) *a*, Plugs of cancer-cells; *b*, connective-tissue stroma; *c*, stroma of mucous tissue; *d*, cancer-cells which have undergone mucous degeneration. Magnified 200 diameters.

name cancroid is still much used. The term epithelioma ought to be reserved for benign epithelial tumors (§ 125).

Formerly a *carcinoma* was defined as a tumor which possesses an *alveolar structure* and gives lodgment to nests of cells in a connective-tissue stroma; and recently attempts have been made to restrict the use of the term carcinoma to growths which answer to this definition. The adoption of this definition, however, would be a step backward: it would bring together forms of tumors which, according to their origin, ought to be separated. Furthermore, in accordance with this idea one would have to distinguish an epithelial cancer from a connective-tissue cancer (endotheliomata, alveolar sarcomata), inasmuch as the epithelial nature of the cell-nests would no longer be a requisite for the placing of a tumor among the carcinomata.

Recently Lange has attempted to prove that the substance which gives to a mucoid cancer of the breast a gelatinoid appearance is a product of the connective tissue. I am entirely unable to indorse this opinion, but am convinced of the correctness of the view which is expressed in the main body of the text.

§ 131. The **cystocarcinomata** represent a form of new growth which stands in the same relation to simple cancer as the cystadenomata do to the adenomata. The majority of cancers furnish no demonstrable secretion, and yet in the group of the adenocarcinomata, for example, there are certain forms in which the epithelial cells produce mucus and also colloid (thyroid gland), and in adenocarcinomata of the liver a secretion

of bile has been observed (Schmidt). In cystocarcinomata the mucoid secretion of the epithelium may lead to the formation of quite large

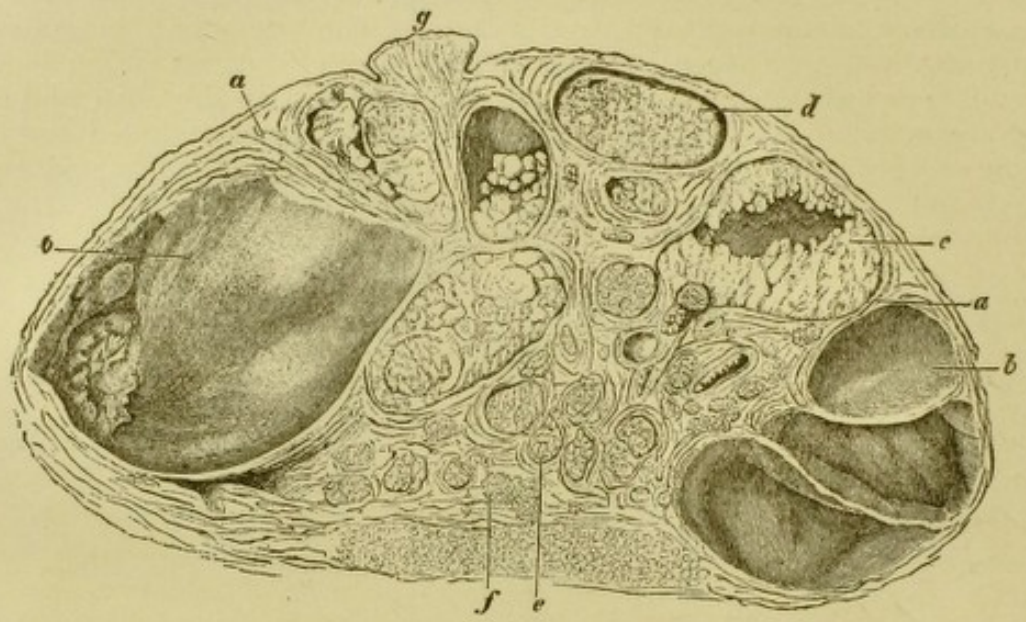


FIG. 326.—Papillary cystocarcinoma of the breast. *a*, Stroma; *b*, smooth-walled cysts; *c*, cysts studded on the inside with papillary growths; *d*, cysts completely filled with papillary growths; *e*, small encysted papillary growths; *f*, adenomatous growths; *g*, nipple of the breast. (Reduced in size by about one-third.)

spaces filled with fluid. These growths are observed particularly in the ovary and in the mammary gland, and the form which they assume is that of a **carcinoma papilliferum** (Fig. 326); for the cyst-spaces are either partially (*b*, *c*) or completely (*d*, *e*) filled with papillary growths. These excrescences present a soft, marrow-like appearance, and when

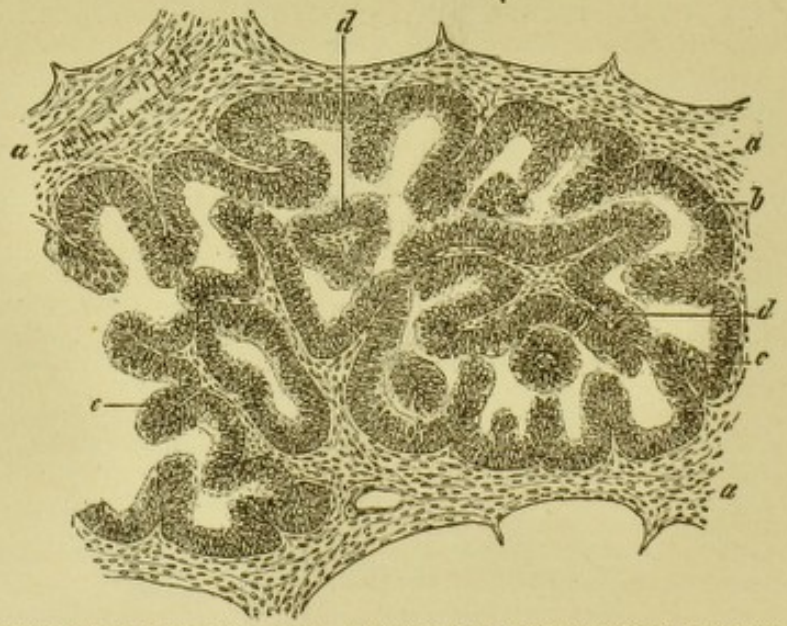


FIG. 327.—Papillary cystocarcinoma of the ovary. (Müller's fluid; hæmatoxylin.) *a*, Stroma; *b*, epithelium; *c*, *d*, papillæ. Magnified 80 diameters.

their number is very large they lend a marrow-like consistence to the entire tumor.

The cyst walls as well as the papillary growths, which branch in the same manner as do those of the papillary cystadenomata, are covered

with a thick, laminated stratum of epithelium (Fig. 327, *b*, *c*, *d*, and Fig. 328, *c*). The papillæ are generally slender structures (Fig. 327, *c*, *d*), but, through somewhat active proliferation of the connective tissue, or even through a mucoid degeneration of this tissue (Fig. 328, *b*), these may attain larger dimensions. If all of the connective tissue undergoes mucoid degeneration, the tumor will then consist of mucoid cysts inclosed in epithelium; and if at the same time the epithelium of adjoining papillæ breaks down and disappears, there will ultimately be nothing left beyond an epithelial stroma inclosing globules of mucus.

The metastases of cystocarcinomata may show cauliflower-like, papillary growths, and this is particularly the case when ovarian tumors

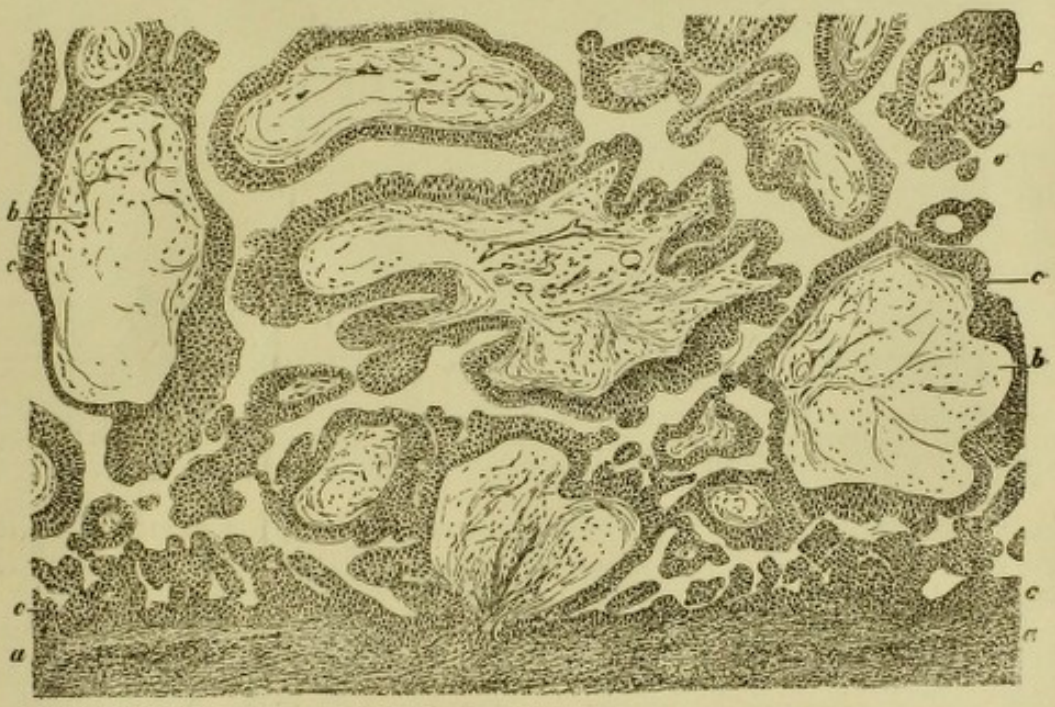


FIG. 328.—Papillary cystocarcinoma of the mammary gland, with papillæ which have undergone a myxomatous degeneration. (Müller's fluid; hæmatoxylin; eosin.) *a*, Firm connective tissue; *b*, papillæ which have become myxomatous; *c*, epithelium which has proliferated to such an extent as to form several layers. Magnified 80 diameters.

of this nature begin to spread throughout the peritoneal cavity. Other metastases show the characteristics of ordinary carcinomata.

§ 132. The **formation of metastases,** which occurs more frequently in cancer than in any other form of tumor, is the natural result of its infiltrative mode of growth. The cancer cells at first break into the lymph-vessels (Fig. 221) and then along these they pass on into the lymph-glands. In both situations there occurs at once a multiplication of the invading cancer cells (Fig. 221, and Fig. 329, *d*). In the lymph-glands, at a later stage, the cancer tissue takes the place of the lymphoid tissue. When this occurs the lymphocytes disappear, and the connective tissue of the lymph-gland serves as the framework for the cancer.

The development of cancer in the lymph-channels is limited either to the filling and distention of the same by the cancer cells (Fig. 221), or the latter may grow more vigorously at certain points and so lead to the formation of daughter nodules.

The piling up of epithelial cells in the lymph-vessels often extends over a large territory, and then—either through the pushing of some of

the lymph-channels out of their proper places, or perhaps even by aid of the thoracic duct—it often happens that *cancer cells are transported*

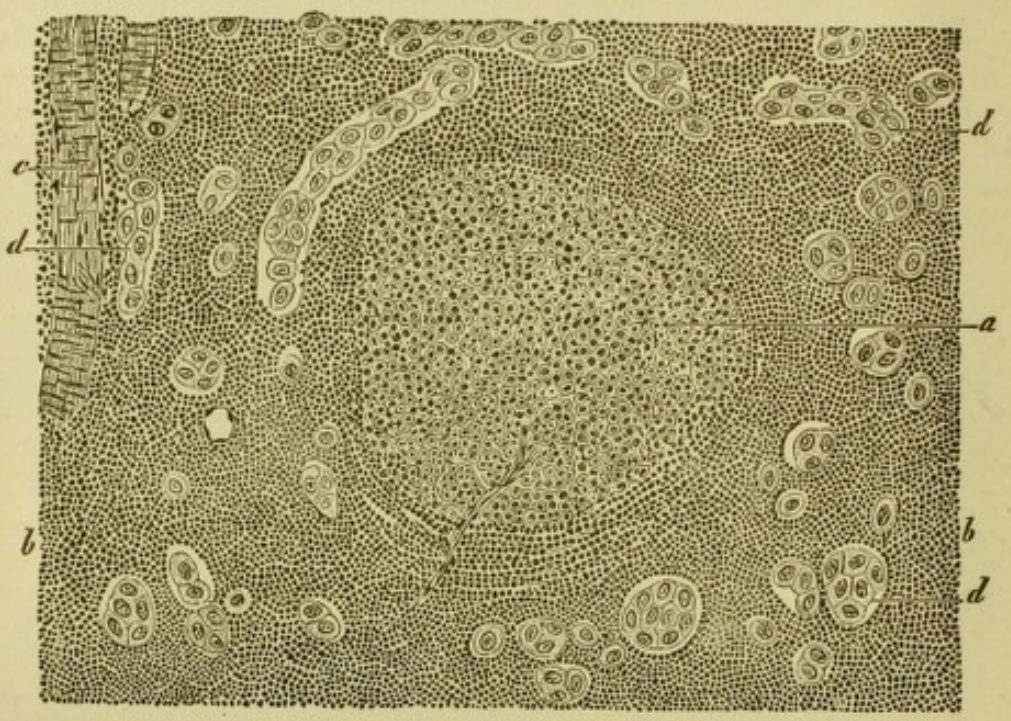


FIG. 329.—Section of an enlarged lymph-gland taken from the axilla. It shows the beginnings of a cancerous growth. (Alcohol; hæmatoxylin.) *a*, Aggregation of young cancer cells in a lymph-node; *b*, lymph-channels; *c*, artery; *d*, nests of fully developed cancer cells. Magnified 60 diameters.

along what appears to be a retrograde course. Thus, for example, in the case of a carcinoma of the stomach both the lymphatic vessels of the lungs and those of the upper extremities may become infected.

The epithelial cells, in their proliferative activity, are just as likely

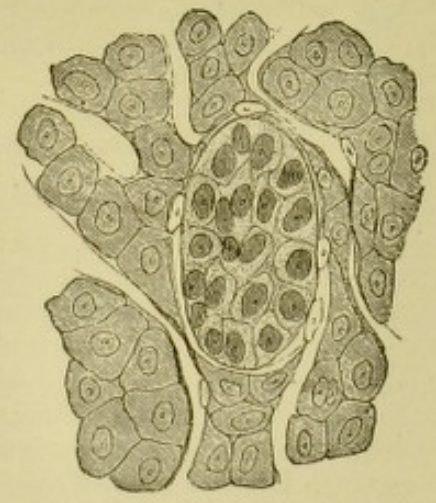


FIG. 330.

FIG. 331.

FIG. 330.—Metastatic collection of young cancer cells in the interior of a capillary blood-vessel of the liver. Specimen taken from an adenocarcinoma of the stomach. (Alcohol; hæmatoxylin.) Magnified 300 diameters.

FIG. 331.—Metastatic development of carcinoma within the capillaries of the liver; the primary growth being located in the pancreas. (Alcohol; carmine.) It will be observed that both cancer cells (in the form of nests) and connective tissue have developed in the interior of the capillaries. Magnified 250 diameters.

to break into the blood-vessels as into the lymphatics, and from the investigations of Goldmann it appears that cancers force their way into veins with surprising regularity. When this latter event occurs the lumen of the vein will be entirely occupied by cancer cells, while at a later stage the affected portions of the vessel become converted into cancer tissue, the framework for which is furnished by the proliferative activity of the vessel-wall. The transportation of cancer cells which have been set free in the blood-stream leads to the formation of metastases (Fig. 222, *b*, Fig. 330, and Fig. 331). Here also the cancer growth proceeds primarily from the invading epithelial cells, and a stroma for the new foci of disease is furnished by the vessel-walls and adjacent structures.

The daughter nodules increase in size, partly by direct proliferative growth, partly by the fusing together of neighboring blood-vessels and lymph-spaces which have been invaded by the disease.

In general the cancer metastases show a tendency to assume the nodular form. In the serous membranes and in the skin diffuse proliferations of tissue may occur, which present the character of dense infiltrations inclosing only the smaller-sized cancer nodules. Likewise the marrow of entire bones or of entire groups of bones may be involved in diffuse carcinomatous disease, and as this advances the bone substance gives place to cancer tissue, whose stroma often incloses newly formed osteoid tissue.

Portions of cancer removed while still in a living condition from one animal and inoculated into another of the same species continue to develop in the new locality and form daughter nodules exactly as occurs in the case of the metastases which form in the course of the original disease.

3. Teratoid Tumors and Cysts.

§ 133. Under the head of **teratoid tumors and cysts** may be grouped together all those tumor-like formations which are distinguished by the fact that the tissues from which they take their origin either do not normally appear at the site in question (*heterotopous growth*) or at least do not normally appear there at the time at which they are found (*heterochronous growth*). Part of the teratoid tumors and cysts, which may be correctly classed together as **teratomata**, exhibit moreover the peculiarity that they are composed of a great variety of tissues.

The teratoid tumors and cysts may be conveniently subdivided, according to their structure and their origin, into four groups, as follows: First, *the simple teratoid tumors;* second, *the simple teratoid cysts;* third, *the teratomata* which are *of complex structure and which are found in different parts of the body;* fourth, *the teratoid cysts and solid tumors of the germinal glands.*

Heterotopous tissue-growths, which are included in the same class with the teratoid tumors, may occur in the most various organs, but are found at certain sites more often than at others. Among the more common may be mentioned the following: Chondromata and chondromyxomata of the salivary glands and of the testicle, osteomata of the muscles, lipomata of the pia, rhabdomyomata of the kidneys, and tumors composed of the tissues of the suprarenal capsules within the kidney. The following are encountered somewhat rarely: chondromata and osteomata of the skin or of the mammary gland, rhabdomyomata of the testicle, etc.

The occurrence of tissue formations at points at which these tissues do not normally appear is to be explained only by the assumption of **misplaced germinal matter** or of a **displacement of tissue.** It is assumed, in other words, that during early embryonic life the embryonal cells of one organ must have found their way into the group of cells which constitute the first beginnings of another organ. Thus, for example, cells possessing the character of periosteum cells might find their way into a group of embryonic muscle cells. As regards the assumption of a displacement of tissue, it is conceivable that this may occur through some change in the natural position of a tissue which is either in course of development or is already actually developed. The subsequent appearance of pathological tissue formations constitutes the only ground upon which we are able to base the first assumption; while, as regards the other hypothesis, we occasionally find corroborative evidence, later on, in the anatomical relations. Thus, for example, in the retrograde changes which take place in hernias of the sacral portion of the spinal cord adipose tissue (Fig. 332, *i*) and muscular tissue (Fig. 332, *k*) may push their way into the spinal canal and the sac of the arachnoid and grow around the nerves. Arnold saw a case in which transposition of adipose tissue, gland tissue, cartilage, and glia tissue had taken place at the lower end of the trunk. In this case the patient had a myelocyst, with absence of the bony wall of the spinal column throughout the lumbar, sacral, and coccygeal regions. He also found, in a case of fatty teratoma of the frontal region, that there was a defect in the wall of the skull, and that through this opening the tumor on the outside was connected with an intracranial growth of a similar character.

Teratoid cysts may be divided into two great groups: on the one hand, *the ectodermal epithelial cysts*, and on the other, *the entodermal* and *mesodermal epithelial cysts.*

The **ectodermal cysts** vary in size from that of a pea to that of a man's fist, and their walls show ectodermal characteristics. For example, the sac may consist of a smooth connective-tissue membrane, lined with several layers of flat epithelium. Such cysts are known as **epidermoids.** Or else the sac may present the characteristics of true skin; that is, it is furnished with papillæ like those of the skin, with sebaceous glands, with hair follicles, with hair, with sweat glands, and also often with subcutaneous fat. These cysts have been named **dermoids,** or **dermoid cysts,** or **dermatocysts.**

The contents of the cysts are composed either entirely of cast-off horny cells, or else of such cells intermingled with fat and pale-colored hairs.

The localities in which such *epidermoids and dermoids are found* are the skin and the subcutaneous tissues, where they present themselves in the form of tumors which bear some resemblance to the *collections of cheesy material*, or *atheromata*, which owe their origin to the retention of secretion in the outlet channels of the sebaceous glands and in the hair-follicles. They are also encountered at the side of the *neck* and in the median line of the neck, either above or below the hyoid bone. They also occur in the thoracic cavity (more particularly in the *mediastinum*), in the *peritoneal cavity* (rarely), in the *pelvic cellular tissue*, in the *coccygeal region*, and in *the raphe of the perineum.* Finally, they also appear *within the cranium*—on the dura and also in the hypophysis. More often, however, such intracranial growths are designated as **cholesteatomata** or as **pearl tumors.** These vary in size from that of a pea to that

of an apple; they are globular or slightly nodulated tumors, with a white, satin-like surface, and they are composed in great part of non-nucleated, *thin cellular scales*, arranged in closely applied laminæ. These are invariably situated at some point on the pia (Bostroem), and it is the vascular pia, covered with laminated squamous epithelium, which, in the course of years, produces the delicate epithelial scales of which the tumor is composed, while the adjacent brain or arachnoid, which the tumor may rest against in places, does not share in the production of the horny scales. In rare cases the cholesteatomata contain *sebaceous material* and *small hairs* in addition to the epithelial scales. In these cases one may find, seated here and there upon the pia, dermal structures—i.e., true skin, provided with *sebaceous glands* and *hair follicles*, or, in other words, with the organs which produce the sebaceous material and the hairs. The simple cholesteatomata can therefore be designated as **epidermoids** (Bostroem), while those which contain hair may rightly be named **dermoids.** The cholesteatomata occur at the base of the brain, in the neighborhood of the olfactory lobe, the tuber cinereum, the corpus callosum, the choroid plexus, the pons, the medulla oblongata, the cerebellum, and very rarely the spinal cord.

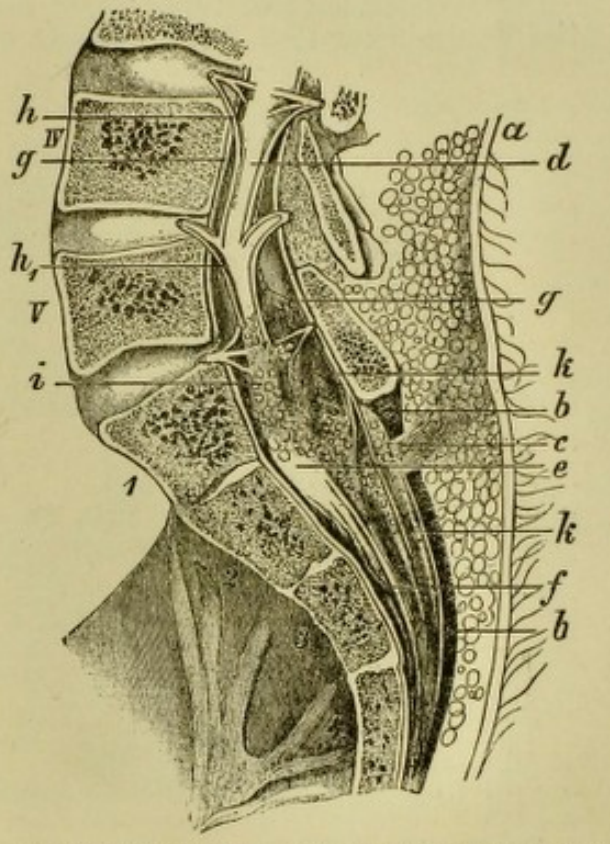


FIG. 332.—Spina bifida occulta, with myolipoma inside the vertebral canal. (Sagittal section about 1 cm. to the left of the median line. Reduced about one-half. Copied from von Recklinghausen.) *a*, Abnormally hairy skin; *b*, fibrous covering which forms the posterior wall of the sacral canal, with a slit-like opening at *c*; *d*, spinal cord; *e*, conus medullaris, lying in the second sacral vertebra (2) instead of in the second lumbar vertebra; *f*, cauda equina; *g*, dura mater; *h*, h_1, recurrent left anterior nerve-roots of the third and fourth lumbar nerves; *i*, fat; *k*, muscular tissue; IV, fourth, and V, fifth lumbar vertebræ; 1-4 sacral vertebræ.

Without doubt the dermoids and epidermoids under consideration owe their origin to a **transfer of the germinal epithelium** from its original position to the sites in question. In the case of the epidermoids, probably only embryonal epithelial cells are deposited, whereas in the case of the dermoids, embryonal dermal tissue is also deposited. The intracranial cholesteatomata originate probably in an early deposit of germinal epidermis in the pia. Mediastinal dermoids doubtless depend upon disturbances in the development of the thymus, which springs from ectoderm. Dermoids on the side of the neck originate in the remains of the branchial clefts, and particularly of the second. Those dermoids which hang down from the hyoid bone or lie behind it are probably to be regarded as the remains of the ductus thyreoglossus. Dermoids of the pelvic cellular tissue can be explained by attributing them to epithelial offshoots from the perineum, or they may be looked upon as outgrowths from the Wolffian duct.

Simple **entodermal** and **mesodermal epithelial cysts** are characterized by the fact that they are lined with epithelium composed of *cylindrical cells*, which often possess *cilia*. They are found particularly often in the broad ligaments of the uterus, and in the Fallopian tubes. They are also found at other points in the abdominal cavity, on the intestine, in the neighborhood of the trachea and the bronchi, in the lungs, on the pleura, in the neck, in the tongue, in glandular organs, etc. They form cysts which vary in size from that of a pin's head to that of a man's fist

The occurrence of these cysts may be explained in most cases by the assumption that **fœtal glands or canals,** which normally should

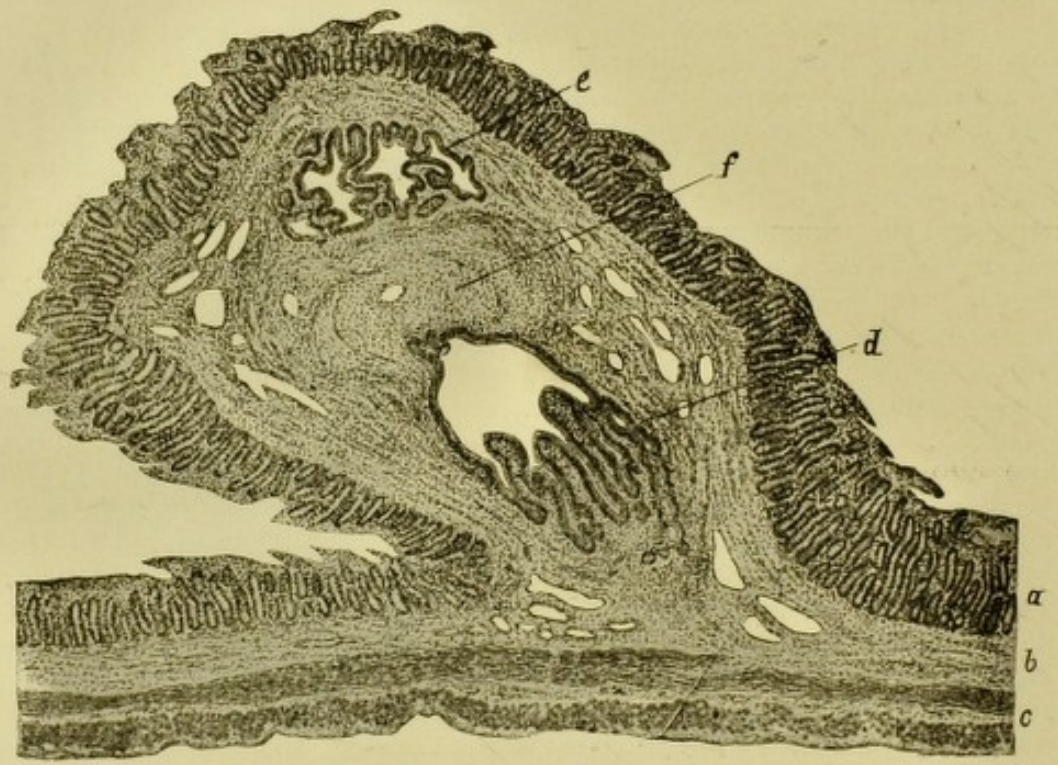


FIG. 333.—Adenoma-like isolation of a part of the mucous membrane of the small intestine. The isolated portion lies in the submucosa and gives rise to a ridge-like prominence of the mucous membrane, about 2 cm. in length. (Alcohol; hæmatoxylin.) Specimen taken from a child six weeks old. *a*, *b*, *c*, Normal intestinal wall; *d*, *e*, portions of mucous membrane lodged in the submucosa; *f*, mucous tissue rich in cells. Magnified 35 diameters.

disappear early in life, **have continued to exist,** or else that **portions of entodermal or mesodermal epithelial tubes, which have become separated from the original structure by a process of constriction, have served as the starting-point for their formation.** Thus, for example, the cysts on the side of the neck may owe their origin to remains of the internal branchial clefts; those at the back part of the tongue to the remains of the ductus thyreoglossus or to the epithelial buds and glands which develop from it; and those which are located in the œsophagus or in some part of the respiratory apparatus to separated portions of the intestinal canal or of the air passages, or to remains of the connecting link between the two. In the broad ligaments and the Fallopian tubes the cysts spring from remains of the canals of the Wolffian body; in the abdominal cavity they originate in part from separated portions of the intestine (*entero-cysts*) and in part from the urachus (*urachus-cysts*). Inside the glands—for example, in the liver or in the kidneys—portions of the gland tubules may become separated dur-

ing the process of development (*adeno-cysts*), and from these, at a later period, cysts may develop.

Cysts located in some part of the central nervous system, or in its immediate neighborhood, may take their origin from the medullary tube (*myelo-cysts*).

The mode of origin of cysts lined with cylindrical epithelium can be inferred, in the majority of cases, only from their position and from the character of their walls, and yet in these cases there is no room for doubt concerning their origin. Our conclusions are of the most positive character in those cases in which the portion of tissue separated (Fig. 333, *d*, *e*) is small, and still retains plainly the character of the mother structure.

The significance of ectodermal, entodermal, and mesodermal cysts depends upon their position, size, and the secondary changes which occur in them. The size varies from that of the head of a pin to that of a man's head. Among the secondary changes—aside from simple *inflammations*—the development of *adenomata* and *carcinomata* should be mentioned. It is in this manner that remains of the Wolffian body, which are present in the dorsal wall of the uterus and the angles of the tubes (von Recklinghausen) often develop into cystadenomata or adenomyomata. In dermoids squamous epithelial cancers (branchiogenic and subcutaneous carcinomata) and probably also cylindrical epithelial cancers may originate from portions of intestinal mucous membrane (Fig. 333) which have become separated from the parent organ by a process of constriction. Cysts, cystadenomata, and carcinomata may develop in the jaw from similarly separated portions of the embryonic dental epithelium.

Cholesteatomata of the pia are regarded by many authors (Virchow, Eppinger) as endothelial structures, although it seems to me that the structure of these formations speaks against such an assumption. If a cholesteatoma possesses hairs which can develop only in hair-follicles, any other than an ectodermal origin is excluded. And it is not clear why cholesteatomata free from hair should have a totally different genesis from those bearing hair. Bostroem, who has made exhaustive studies of this subject, also arrives at the same conclusion, and I believe that his researches demonstrate its correctness.

§ 134. **Teratoid cysts of a more complicated structure** and **solid teratomata,** originating outside the reproductive glands, appear in the same localities as the simple teratoid cysts, but show a particular predilection for the region of the coccyx. The complex character of these cysts is shown by the fact that cartilage, bone, fat, mucous glands, smooth and transversely striated muscle fibres, nerve tissue, and tissue similar to that of sarcomata and carcinomata may be found in the cyst-wall. Dermoid cysts may also contain teeth, and even ciliated epithelial cysts. *Solid teratomata* occur, in the first place, in the form of *hairy polypi* (in the cavities of the nose, throat, and mouth)—that is, in the form of polypoid growths which are covered with a hairy skin, and which are made up essentially of fat, but which may also contain muscle fibres and cartilage, bony structures, teeth, and cysts. Then, in the next place, tumor-like growths, of the most complicated structure, may appear in the cranium, the neck, the lower jaw, and by preference in the coccygeal region. They contain the most diverse tissues, such as connective tissue, fat, cartilage, bone, gland tissue, muscle, nerve tissue, and brain substance, as well as ectodermal and entodermal cysts. They may further inclose rudimentary or completely formed parts of the

body, or at least masses which can be readily recognized as representing parts of the body.

The complex teratoid cysts and solid teratomata are, in many cases, to be regarded as **local disturbances in development** which are characterized by the fact that in the earlier stages of embryonic life a **displacement of tissue** or a **separation of tissue by constriction** has taken place **in a single individual** (*monogerminal tissue-implantation; autochthonous teratomata*). Hairy polypi of the throat, as well as the cystic and solid teratomata found at the base of the skull or in the hypophysis, can be explained by assuming that a dislocation of ectodermal tissue has taken place. If teratoid cysts of the mediastinum contain cartilage and mucous glands, the presence of these tissues may be explained by the vicinity of the trachea. In the case of teratomata in the region of the coccyx the manifold character of the growth may be explained by the fact that not only portions of the terminal vertebræ, of the pelvis, and of muscular tissue, but also remains of the neuroenteric canal, of the hind-gut, and of the medullary tube take part in the formation of the tumor. It is also possible that in intracranial teratomata, as in simple dermoids, the basis for the growth is furnished by embryonic tissues which have been displaced. Then besides, in these growths there is always the possibility that we may be dealing with the presence of a **rudimentary twin**, or, in other words, that a *bigerminal implantation* has taken place; and such an assumption is warranted in all those cases in which the teratoma contains completed or rudimentary parts of the body, or tissue formations, which cannot be explained by assuming that at the spot in question the tissue elements of a single fœtus have undergone displacement (compare § 153).

§ 135. **Teratomata of the ovary and of the testicle** occur partly in the form of dermoid cysts, and partly in that of solid tumors in which multiple cystic formations are present. The dermoid cysts are encountered chiefly in the ovary, while the solid tumors occur more frequently in the testicle.

The so-called **dermoid cysts of the ovary** form rather thick-walled cysts which vary in size from that of a pea to that of a man's fist, and which are filled with fatty material inclosing pale hairs. At some one point in the wall of the cyst there will be found *a projecting mass of tissue, which is studded with hairs and often also with teeth* (Fig. 334, *b*, *c*, *d*). This mass of tissue varies greatly in appearance in different cases, *at one time being provided with villi, at another time presenting the aspect of a tuberosity or of a shallow elevation, and at still another time extending like a diaphragm across the cavity of the cyst.* The uppermost layer of this prominence possesses all the characteristic parts of skin, viz., hair-follicles with hairs, sebaceous glands, and sweat glands (sometimes showing cystic degeneration). In the deeper layers are found other tissue formations, such as cysts and tubules lined with ciliated cylindrical epithelium, bone, cartilage, muscle, brain substance, nerves, mucous glands, and intestinal mucosa, as well as pigmented structures resembling the rudimentary tissues of the eye. On the other hand, kidney tissue, or liver tissue, or heart muscle, has never been discovered in these growths. The ovary alongside the dermoid is destroyed or else only traces of it remain.

According to Wilms, to whom we are indebted for the most laborious researches concerning these growths, ovarian dermoids cannot be ex-

plained either by the assumption of a displacement of germinal matter, or by the assumption of an inclusion of a rudimentary twin. The latter view is excluded by the mere fact that in about fifteen per cent. of the cases dermoids occur at the same time on both sides. Wilms holds strongly to the view that these ovarian dermoids are *rudimentary embryos* or *rudimentary parasites, which develop from a single ovum*, and in support of this view he points to the facts, first, that these structures contain the constituent parts of all the germinal layers, and second, that in the formation of individual constituent parts a certain uniformity prevails. Thus, for example, under the ectoderm, which projects in-

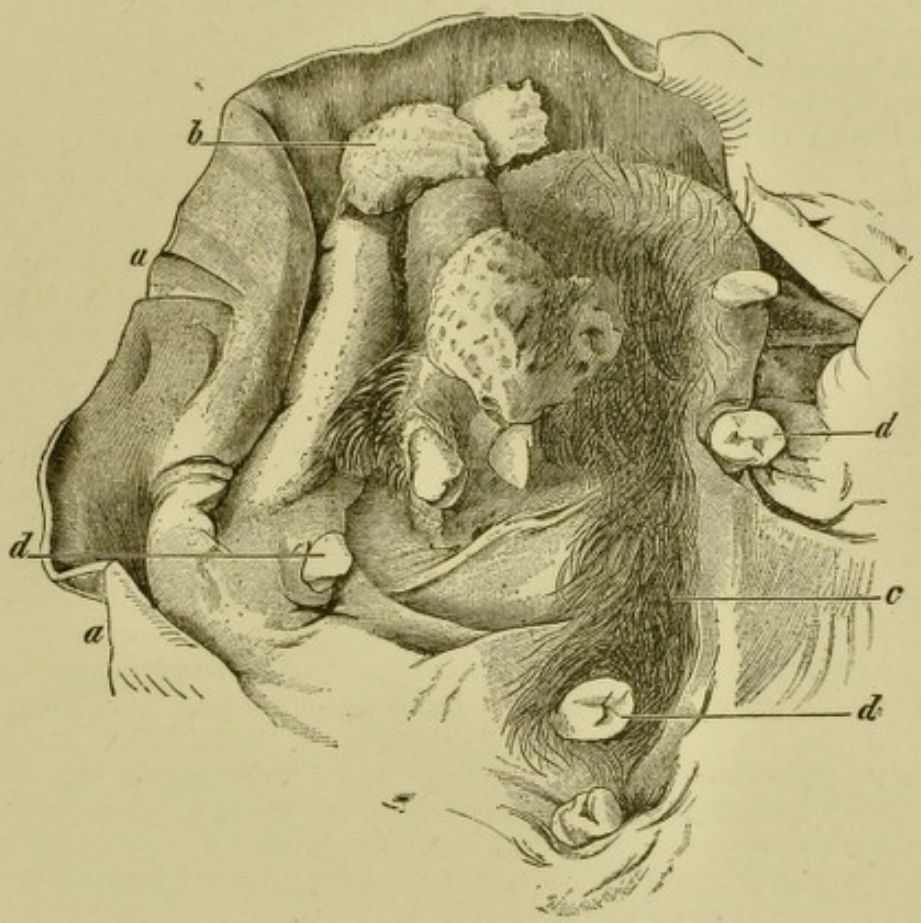


FIG. 334.—Portion of the wall of an ovarian dermoid cyst. *a*, Smooth part of the wall; *b*, projecting portion, made up of fatty and cutaneous tissues; *c*, uneven part of the wall, containing hairs and teeth (*d*), and bending upon itself in the upper portion. Life size.

ward and which is developed to a much higher degree than any of the other layers, bones are found which we are warranted in classifying as cranial and maxillary bones, and also at the same time brain substance is found along with the bones; whereas the entodermal tissues, which remain in a rudimentary condition, form the outer portion of the tumor.

Ovarian dermoids may develop at any period of life, but they occur most frequently in the middle period.

Solid teratomata of the ovary are much more rare than dermoid cysts, and they form *tumors* in which the greatest variety of tissue formations is to be found. These, which are distributed throughout the growth in the most disorderly manner, comprise epidermis, epithelial pearls, hairs, sebaceous glands, sweat glands, tubules, and cysts lined with ciliated epithelium, acinous glands, connective tissue rich in cells,

adipose tissue, muscle, cartilage, and bone—in other words, constituent parts of all the three germinal layers. In rare cases, teeth, intestine, thyroid gland, and a rudimentary brain may be present. Wilms is of the opinion that growths of this character have developed from a single ovum, and he therefore calls these teratomata *embryoid tumors*.

Teratomata of the testicle occur principally in forms which are described, according to their structure, as *adenocystomata*, *chondro-adenomata*, *chondrosarcomata*, *adenomyosarcomata* (Fig. 336), etc. In some cases the formation of cysts with fluid contents is a marked feature of the tumor (Fig. 298); in other cases cysts are found only in certain parts of the growth; and, finally, in still other cases the tumor is entirely solid. These growths sometimes attain the size of a child's head. In some instances they are congenital, but more commonly they develop in adult life and then grow rapidly.

The lining of the cyst presents as a rule the character of entodermal tissue, but in one and the same cyst these characteristics may differ

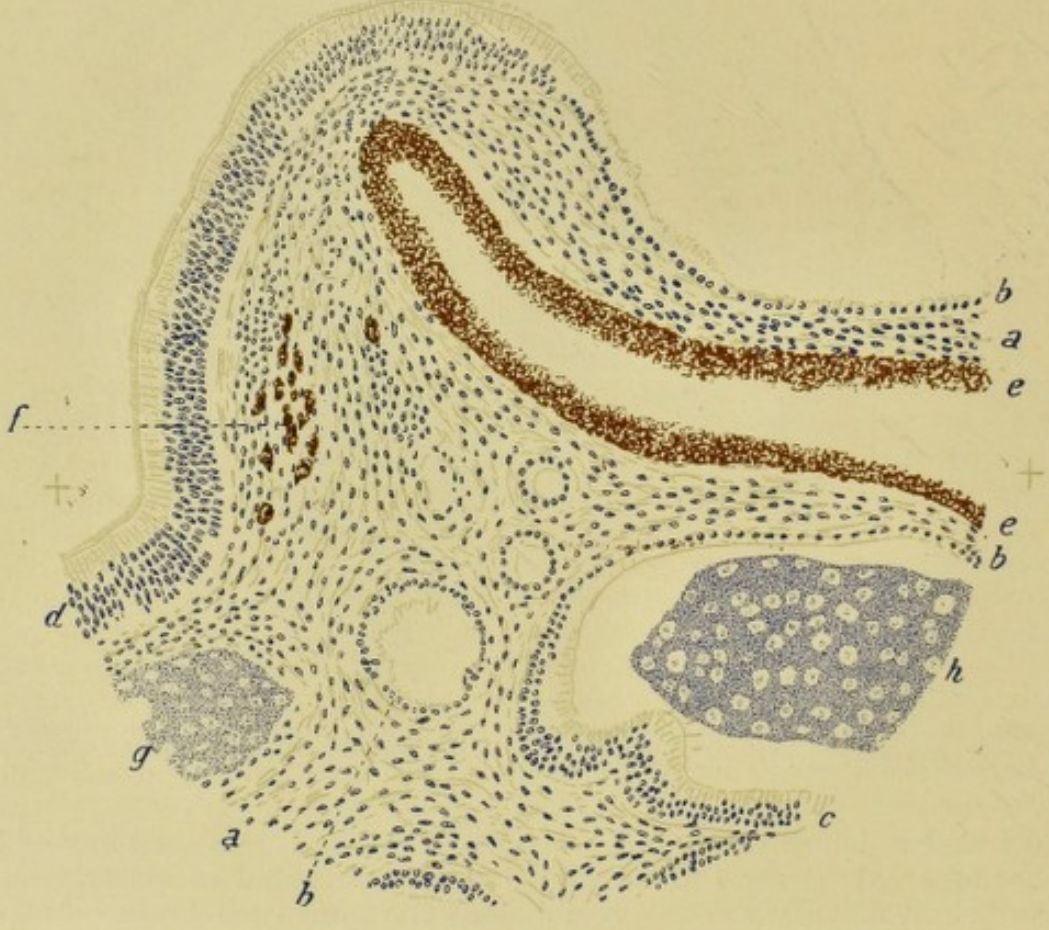


FIG. 335.—Congenital adenocystoma of the testicle, with formation of pigment and cartilage. (Müller's fluid; hæmatoxylin.) *a*, Connective-tissue stroma; *b*, simple cubical epithelium; *c*, stratified cylindrical epithelium; *d*, stratified ciliated cylindrical epithelium; *e*, pigmented epithelium lining a gland-tubule; *f*, pigmented connective-tissue cells; *g*, focus of cartilage in connective tissue; *h*, focus of cartilage in a gland-tubule. Magnified 100 diameters.

(Fig. 335). For example, at one point there may be a single layer of cubical epithelium (Fig. 335, *b*); at another, simple cylindrical epithelium, both with and without cilia; at still another, ciliated epithelium in layers; and finally, at a fourth, pigment epithelium (*e*).

Ectodermal epithelium is present only in scanty amount in these tu-

mors, and is then confined to a few groups of cells, some of which show the characters of cornified epithelium; then, again, it may be entirely absent, or, at all events, in the case of large tumors it cannot be demon-

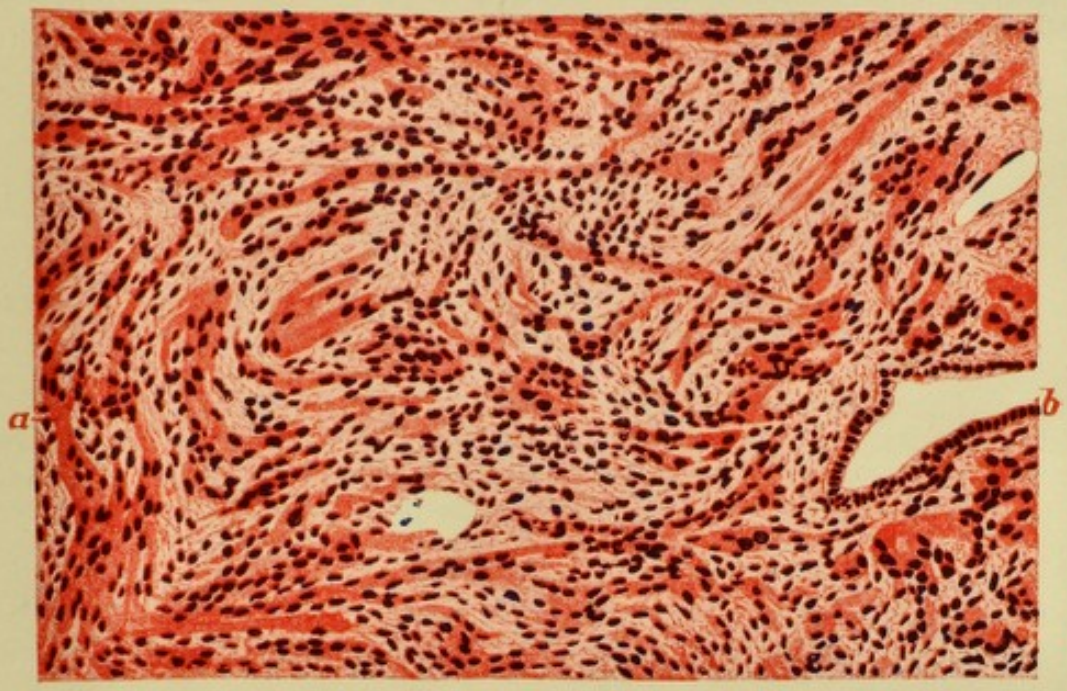


FIG. 336.—Adenorhabdomyoma (teratoma) of the testicle. (Formalin; hæmatoxylin; eosin.) *a*, Cellular tissue, with bands of muscles; *b*, gland tube. Magnified 100 diameters.

strated. In addition to cysts, glands which produce mucus may also be found in these tumors.

Among the framework substances connective tissue, mucous tissue, cartilage (Fig. 335, *g*, *h*), at times also muscle (Fig. 336, *a*), adipose tissue, and rarely bone, are present.

Wilms holds that these growths also are *embryoid tumors*—i.e., structures which are composed of all the germinal layers, and in the formation of which the entoderm and the mesoderm play the principal part. Furthermore he believes that these tumors develop from a *single sexual cell.* Other authors refer their origin to a displacement of germinal matter.

Dermoid cysts of the testicle are of rare occurrence. They develop, however, as often in children as in adults. In their structure they resemble very closely the ovarian dermoids. They have their origin in germinal material that represents all three germinal layers, and according to Wilms they also should be looked upon as *rudimentary parasites which have originated from a single sexual cell.*

The researches of Wilms were carried on in Bostroem's laboratory in Giessen on a very large amount of material, and the results of the study of individual cases of teratoid tumors of the reproductive glands agree so perfectly that the hypothesis advanced by him and Bostroem concerning the origin of these tumors appears to be well founded, and especially so in regard to the theory of the origin of the so-called dermoids. In respect to the other mixed tumors of the reproductive glands the assumption of a displacement of germinal matter cannot entirely be discarded.

Repin, Duval, and Delbert have announced similar views concerning teratomata of the sexual glands.

Waldeyer attributes the origin of dermoids of the ovary to germinal epithelium, and

he assumes that the cells of the latter, in their character of undeveloped eggs, can produce further products in the direction of an imperfect embryonic development.

Pilliet and Costes refer the origin of the teratoid tumors of the testicle to a further development of some ovarian tissue which remains at the hilus of the testicle, or to a development of the remains of the Wolffian body which, although forming a part of the testicle, play no useful part in its physiological work.

CHAPTER VIII.

Disturbances of Development and the Resulting Malformations.

I. General Considerations in Regard to Disturbances of Development and the Origin of Malformations.

§ 136. After the union of the sexual elements has taken place, the development of the embryo progresses by a continual division of nuclei and cells. Along with this division there arise in an orderly manner special groupings and differentiations of the cells, leading to the formation of special tissues and organs. The cell-proliferation, as well as the development of the individual cell-groups into special organs and parts of the body, depends upon internal causes, and is controlled by characteristics which the embryo has received by transfer of inheritable paternal or maternal characteristics which were in the ascendant at the moment of the union of the sexual elements, which are to be regarded as the carriers of inherited characteristics. It follows that not only the characteristics proper to the species, but also the special peculiarities of the individual, are predetermined in the germ, and the development of the embryo proceeds essentially under the control of self-contained moulding forces. And yet this development is not accomplished without an influence from the environment, in that the embryo of necessity receives nourishment from the maternal organism, and is exposed to mechanical influences on the part of its envelopes and the uterus. These influences may operate to modify the development of the fœtus.

In every species of animal, man included, the bodily form and the shape of the organs present a *particular type*, which experience has shown recurs continually, and which is therefore looked upon as *normal*. If there are departures, more or less marked, from this type, which are to be referred to an abnormal course of the intra-uterine development, the condition is called a **congenital malformation.** If the departure from the normal build is very great, so that the affected individual is grossly misformed, it is spoken of as a **monster.**

It is customary to use the term malformation to designate only such anomalies in the form of the whole body or individual parts of it as present to a mere external inspection rather striking departures from the normal. It is nevertheless entirely correct to use this term for pathological conditions of intra-uterine origin, which consist not so much in an abnormal change in form, but rather in a partial or faulty organization of the affected part or organ.

A **single malformation** is one which originates from a single individual, while a **double malformation** or a **double monster** is one which is made up from two individuals.

Malformations may arise in two ways: from internal causes and from external causes.

As **internal causes** may be reckoned all such as already exist in the germ, so that in the development of the embryo abnormal forms arise spontaneously, without intervention from without. When such a mal-

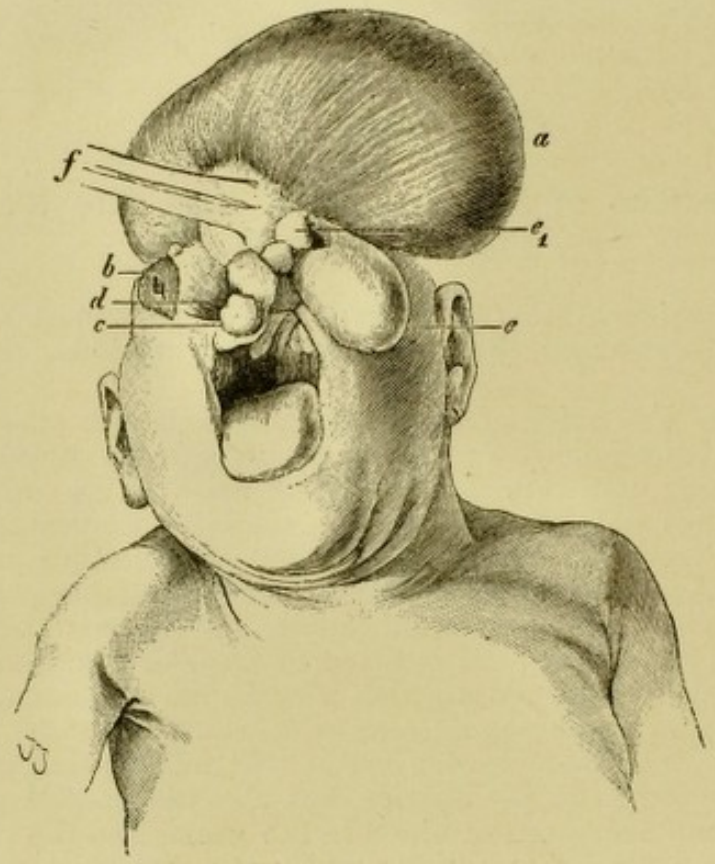


FIG. 337.—Malformation of the head, due to adhesions of the membranes to the frontal region (close adhesions of the placenta to the uterus). *a*, Cutaneous sac inclosing a vascular, spongy tissue containing abundant cysts; *b*, eye; *c*, distorted lip; *d*, funnel-shaped depression lined with mucous membrane; *e*, left, e_1, right, ala nasi; *f*, fibrous bands. (Reduced to three-fourths natural size.)

formation occurs for the first time in a family it must be regarded as a *primary germ-variation*. This is to be regarded in either of two ways: there may have been an abnormality of one or the other of the sexual nuclei which entered into union, or they may both have been normal, but from their union a variety has arisen which from our point of view is to be looked upon as pathological (cf. § 33). It is also possible that disturbances in the process of fecundation can give rise to pathological variations.

If a similar malformation has already occurred in a parent, the case may be one in which the defect has been *inherited*. If a malformation which has appeared is a peculiarity which was not present in one of the parents, but did occur in remoter ancestors, while it was wanting in the intermediate links, the occurrence is spoken of as *atavism*.

As primary germ-variations we find the very same malformations that occur by inheritance; in other words, only those malformations are inherited that have originally presented themselves as primary germ-variations. To these malformations that may be transmitted by inheritance belong an increase in the number of fingers or toes (polydactylism), malformations of the hands and feet, abnormal hairiness, harelip, and certain pathological conditions of the nervous system, as, for example, fibromata of the peripheral nerves.

Under **external causes** of malformations the first to be considered are *jarrings, pressure, disturbances in the supply of oxygen and nourishment*, and *infections*.

Jarrings of the uterus can very likely directly damage the egg at an early stage. At a later stage in the development of the embryo the damage worked by trauma is probably more often to be looked upon as the result of a tearing loose of the egg and bleeding from the decidua, leading to malnutrition of the egg. It is evident that bleeding from other causes, changes in and contaminations of the maternal blood, as they occur in infectious diseases, also disease of the uterus itself, will have a detrimental effect on the developing egg; yet all of these conditions probably lead more often to the death of the fœtus and to extrusion of the egg than to the development of a malformation. Infectious diseases of the mother may be transmitted to the fœtus and cause there characteristic disturbances. An abnormal pressure from the uterus or the membranes may be exerted upon the embryo, especially when the amniotic fluid is in small quantity. Deformities of the extremities—as, for example, club-foot, flat-foot, and club-hand (Fig. 340)—not rarely show signs of pressure having been exerted.

From the anatomical appearances in some malformations it appears that **pathological conditions of the amnion** are particularly likely to exert a damaging influence on the embryo, and may give rise to a variety of malformations.

This may be occasioned by *abnormal adhesions of the embryo and amnion*, as well as by *pressure of the amnion upon the embryonic rudiments*. Even at the birth of the child bands and threads of union can, not infre-

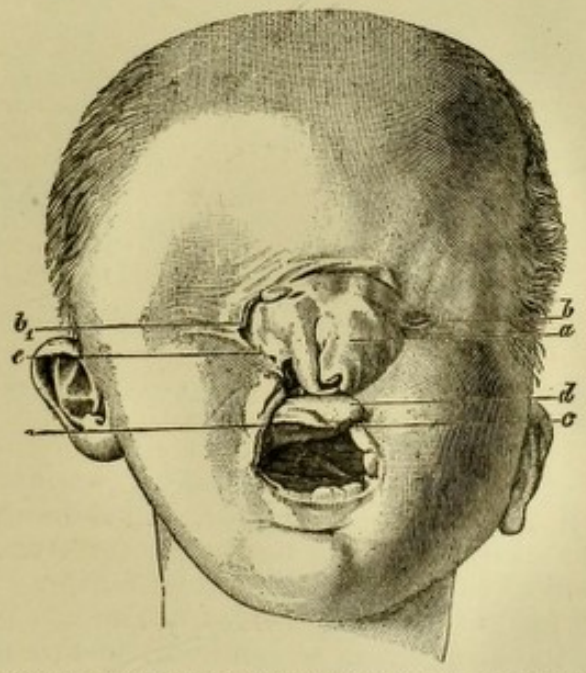


FIG. 338.—Malformation of the face, caused by amniotic adhesions and pressure (asymmetry of the face). *a*, Misshapen nose; *b*, b_1, rudimentary openings between the eyelids; *c*, c_1, clefts in the upper lip and alveolar process of the upper jaw; *d*, intermaxillary bone with prominent lip; *e*, oblique facial fissure, closed so as to make a furrow by scar-tissues.

quently, be made out (Fig. 337 *f*, and Fig. 338), and their connection with the misshapen portion of the child leaves no doubt that they stand in a causal relation to the malformation. Such adhesions may give rise to severe malformations of the cerebral (Fig. 337) or of the facial (Fig.

338) portions of the head. Not rarely portions of extremities are snared off by threads of the amnion (Fig. 339) and may be completely amputated and then absorbed.

How far these connections between the amnion and the fœtus are to be referred to a primary adherence and intergrowth, and how far to inflammations of later occurrence, is as yet a moot question. At birth these connections are often no longer visible and the affected region presents only a scar-like appearance (Fig. 338).

According to Dareste and Geoffroy St. Hilaire, an abnormal snugness of the amnion exerts also a damaging influence on the embryo. So it is also claimed that abnormal tightness of the cephalic cap of the

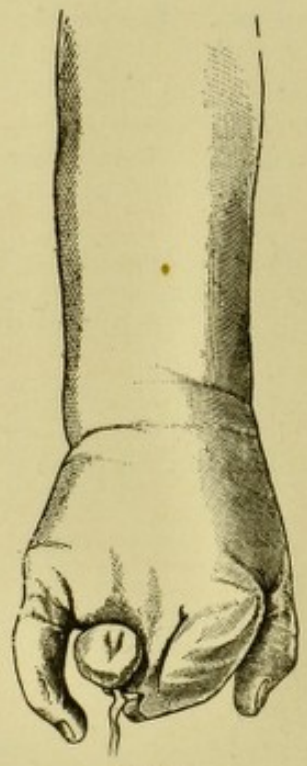


FIG. 339.

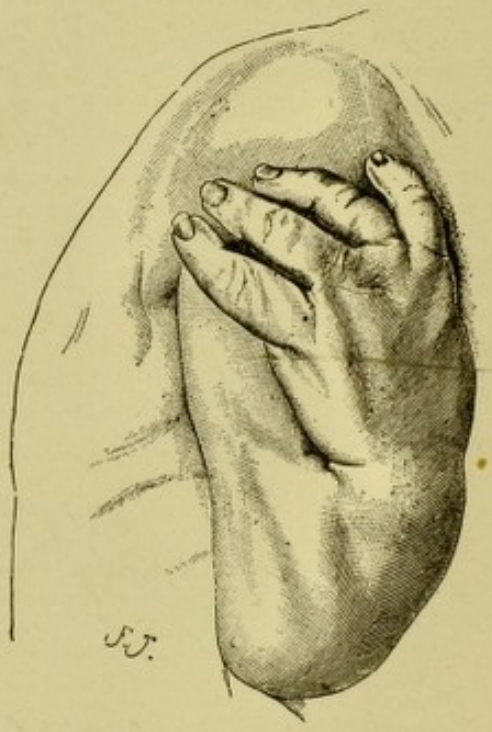


FIG. 340.

FIG. 339.—A hand stunted by amniotic adhesions; ring-finger snared off; middle and index fingers grown together and distorted. (Reduced one-sixth.)

FIG. 340.—A hand stunted and misshapen by pressure; thumb wanting; hand flattened; great bending and shortening of the forearm. (Reduced one-fifth.)

amnion is capable of causing the malformations known as anencephalia and exencephalia (§ 141), cyclopia (§ 141), and cebocephalia or arrhinencephalia (§ 141); while abnormal tightness of the caudal cap leads to stunted development of the lower extremities (§ 145). Marchand refers also phocomelia (§ 145) to pressure exerted at an early period. Finally, clefts which occur in the anterior abdominal and thoracic walls (§ 143) are associated with a deficient growth of the amnion; still the latter condition is often not so much the cause as it is a concomitant of the malformation, which may follow from a variety of causes, but is doubtless often to be classed with the spontaneous or primary malformations.

The period at which the damaging influences exert themselves naturally varies much, and so also does the extent of the damage. The earlier the damage occurs the more extensive it generally is. Malformations in the more restricted sense arise mostly in the first three

months, a period when the body and its individual parts are assuming their proper forms. Damage to the fœtus at a later period occasions *departures which in appearance are more nearly allied to those acquired after birth.*

Some malformations are **typical**—that is to say, they always reappear in the same form; while others, again, are entirely **atypical**, so that often the most astonishing anomalies of form arise. The latter are mostly the result of harmful influences operating secondarily from without, while the former may be regarded as chiefly due to internal causes. External influences, however, may also cause typical deformities.

Geoffroy St. Hilaire[1] discards entirely the teaching of primary abnormality of the germ (Haller and Winslow), and attributes arrests of development simply to mechanical influences. Panum[2] agrees with him in general, although he admits the possibility of a primary abnormality. In hens' eggs he produced malformations by temperature variations of the incubator, and also by varnishing the shells. Dareste[3] made similar experiments, and produced deformities due to arrests of development by setting the eggs on end, by varnishing the shells, by raising the temperature above 45° C., and also by irregular warming of the eggs.

Very recently L. Gerlach, Fol, Warynsky Richter, Roux, and Schultze have experimented in this direction, and have sought, with some success, to produce malformations in hen embryos by localized influence of radiant heat, variations of temperature, varnishing the eggs, changes of position, injuries, removal of a portion of the white of the egg, and by agitation. Roux, experimenting on frogs' eggs, found that, after destruction of one of the divisions formed by the primitive streak, the other continued its development to the formation of half an embryo, demonstrating that the portion on either side of the primitive streak contains within itself the developmental power to form the corresponding half of the body. But the body-half which is wanting may be later replaced by subsequent development from the undestroyed half, and a whole structure be produced, showing that a half contains powers to produce also the other half.

Schultze experimented on the eggs of amphibia. They normally assume a position in which the darkly pigmented protoplasm of lighter specific gravity lies above, and the heavier clear protoplasm, rich in yolk granules, lies below. Malformations may be produced by placing the eggs in an abnormal position and preventing their resuming the normal position; and the degree of malformation stands in direct relation to the size of the angle which the attraction of gravity makes with the abnormally placed axis of the egg. By turning the egg through an angle of 180° in the two-cell stage a double monster is regularly produced. By the same turning in the eight-cell stage, development is completely stopped. All this shows that gravity is another influence capable of causing disturbances of development, and that these disturbances arise from displacements consequent upon a sinking of the heavier and a rising of the lighter constituents of the egg.

According to investigations by O. Hertwig the eggs of Axolotl when kept in a 0.7-per-cent. solution of sodium chloride undergo a pathological development, which is, however, restricted to the central nervous system in the region of the head and buttocks. It would thus appear that the sodium-chloride solution affects only those portions of the ectoderm which are in the process of changing into ganglion cells; and, as a result, with otherwise normal development, there may be a loss of portions of the central nervous system.

For the production of a malformation, it is manifest that the damage to the embryo must not be too severe; otherwise the embryo will die. Above all, the activity of the circulatory apparatus must be preserved. If the embryo dies, it is either expelled from the uterus together with the membranes, or it is absorbed while the membranes continue for a time their development. A malformed fœtus cannot sink below a certain minimum of development without perishing at an early period, unless maintained as a sort of parasite upon another fœtus developing at the same time (cf. § 154).

§ 137. **Single malformations** may conveniently be divided, according to the sort of departure which characterizes them, into five groups. As **arrests of development**, or **monsters due to defective develop-**

[1] "Hist. gén. et partic. des anomalies de l'organisation chez l'homme et les animaux," Paris, 1832–37.

[2] "Untersuch. über die Entstehung der Missbildungen," Berlin, 1860.

[3] "Recherches sur la production artificielle des monstruosités," Paris, 1877.

ment, are classed all those malformations in which the whole or a part of the body is abnormally small and poorly developed (*hypoplasia*), and also the malformations characterized by absence or very great dwarfing (*agenesia*, *aplasia*) of individual organs or parts of the body. In this class belong absence of the brain or parts of it, or abnormal smallness of the brain; defects in the septa of the heart; absence and dwarfing of the extremities, etc.

Where parts of the body or organs are normally formed by the union of distinct centres of development, and by a primary or secondary arrest of development this union fails to take place, arrests of development may show themselves as *clefts* and *reduplications*. Thus imperfect development of the plates forming the anterior body-wall gives rise to clefts in the median line of the thorax and abdomen; failure of the maxillary processes of the first branchial arch to unite or to form a union with the intermaxillary process gives rise to clefts in the facial portion of the head. Deficient union of the early lateral halves of the female genital tract results in more or less extensive duplication of the uterus or vagina.

Where at an early stage the beginnings of two organs lie in proximity, they may unite so as to produce a *coalescence* or *adhesion* between two organs or parts normally distinct. So it may happen that the kidneys are more or less united, and the eyes may be more or less completely merged into a single organ. Such mergings of organs arise in two ways: from secondary union of divided organs, or from deficient separation of two organs which develop from a single focus.

Malformations due to excessive growth, or **monsters due to excessive development,** are characterized sometimes by the *abnormal size* of individual parts, sometimes by *multiplication* of their number. An extremity or a portion of a finger may attain an abnormal size (*partial giant growth*), or the whole body may be included in the abnormal growth (*general giant growth*). These are examples of increase in size of members. A multiplication of the number of parts occurs notably in the glands of the breast, the spleen, the suprarenal capsules, and the fingers. In the case of glandular organs, if additional ones occur, they are usually called *supernumerary organs* (*Nebenorgane*).

Malformations occur, also, through an **abnormal disposition of parts** (*monstra per fabricam alienam*). Under this head are included certain anomalies of the thoracic and abdominal organs which are characterized by abnormal positions of the organs, and also in part by the changes in relations between individual parts. In this class belongs the transposition of the organs of the thorax or abdomen, or of both at the same time (*situs transversus*). Various cases of defective formation in the heart and great vascular trunks may also be classed here, though more properly these conditions should be looked upon as arrests of development.

A fourth group of malformations is caused by the presence of **tissues in unusual situations** and the **persistence of fœtal structures,** as already spoken of in §§ 133 and 134.

Finally, a fifth group includes malformations exhibiting a **mixture of the sexual characteritics,** subdivided into *true and false hermaphrodites*. True hermaphrodites possess both a male and a female generative gland. False hermaphrodites are unisexual, but the remainder of the sexual apparatus does not correspond to the generative gland, or there is a simultaneous formation of organs belonging both to the male and

to the female. A part of these malformations are arrests of development; others are to be regarded as cases in which from the original bisexual embryonic formation the organs of both sexes have attained development, whereas normally the structures characteristic of one sex, instead of developing, dwindle away and persist only in a very rudimentary form.

§ 138. **Double monsters** (*monstra duplicia*) are instances of a duplication of the whole body or of parts of the body. The twins are always of the same sex, and are mostly united together at corresponding parts of the body. The duplicated parts exhibit sometimes equal, sometimes unequal development; in the latter case one of the parts is dwarfed and appears as a parasitic appendage to the well-developed individual. This permits a subdivision into an **equal** and an **unequal form of double monster.**

All double monsters come from a **single** *egg, and develop from a single germinal vesicle.*

Several views of the origin of double monsters may be entertained. First, it may be supposed that two embryonic areas arise in the wall of a single blastodermic vesicle, which grow, impinge one on the other, and blend to a greater or less extent. A second possibility is the formation within a single embryonic area of two primitive streaks and two medullary grooves, which either remain separate or partially merge one into another. A third case would be one in which the primitive streak was single, but the medullary groove was double either in a part or in the whole of its extent. Finally, it may be that a duplication takes place at a later period of development, and then affects only individual parts.

In all of the above possible modes of duplication the duplication takes place by a double formation, at a certain stage in development, of a part that is normally single. In the first instance the duplication dates from the period of formation of the embryonic area; in the rest it begins within the embryonic area. In the first three instances it affects the structures in the body-axis, in the fourth it is confined to such as do not lie in the body-axis.

To explain the formation of double monsters, it is essential to suppose a duplication of parts of the blastodermic vesicle or of the embryonic area. The only question is how far it may be possible for a doubling that has already taken place to disappear by a subsequent blending. Thus, if there are two entirely distinct embryonic areas, it may be asked whether only separate homologous twins can arise, or whether a merging can take place at an early stage. From the observations and experiments on this subject it may be accepted without question that embryonic areas which are already in the process of development can merge together.

The *causes of a duplication of the embryonic beginnings in a single blastodermic vesicle* are as yet little understood. Fol supposes that by an abnormal impregnation of the ovum by two, three, or more spermatozoa double and multiple monsters arise; but other observations (Born) indicate that ova impregnated by two or more spermatozoa do not develop. According to Marchand, the duplication of the embryonic beginnings is to be referred back to conditions existing within the ovum previous to fertilization or to the character of the fertilization. Wiedemann inclines to the view that the origin of the double monster dates from the moment of impregnation and is due to the impregnation of ova containing two blastodermic vesicles by two spermatozoa.

In recent years successful experiments have been made in the production of double monsters from the eggs of animals. They were conducted by Gerlach, O. Schultze, and

Born. Gerlach produced double monsters (anterior duplication) from hens' eggs by varnishing them before incubating, and leaving only a Y-shaped spot in the region of the primitive streak free. Schultze produced double monsters by turning frogs' eggs through an angle of 180° (cf. § 136). Born succeeded in uniting together portions of the larvæ of amphibia, not only of the same kind, but also of different species and families (rana esculenta with bombinato rigneus and with triton). From all these experiments the conclusion may with certainty be drawn that double formations may be produced from a normally constituted egg through secondary influences, and that neighboring embryonic elements may merge and grow one into the other.

II. Special Malformations in Man.

1. *Arrests of Development in a Single Individual.*

(a) Arrest in the Development of all the Embryonic Elements.

§ 139. **Arrest in the development of all the embryonic elements** manifests itself in two ways. If the disturbance is very marked, further development becomes impossible, and the embryo either dies at once or it becomes stunted and after a certain time perishes. If the disturbance is not so great a normally formed fœtus develops, but it remains small and weakly—in other words, **a dwarf is formed** (**nanosomia** or **microsomia**).

When a fœtus dies it is, in the majority of cases, expelled from the uterus along with its membranes (**abortion**). In the earliest periods of development the **embryo may disappear by absorption.** The membranes are usually expelled; but they may also remain for a time and suf-

FIG. 341.—Portion of a mole, presenting the form of a bunch of grapes. (Natural size.)

fer further changes. Most frequently they form **flesh-, thrombus-,** or **blood-moles**—fleshy masses consisting of the membranes and blood-clots. The clots form the chief bulk, come from the placenta materna, and are often the cause of the death of the fœtus. In the case of the so-called **grape-mole** (Fig. 341) the villi of the chorion or of the pla-

centa undergo an enormous dropsical swelling, as a result of which portions of the villi expand to bladder-like structures held together by delicate connecting strands. In this process the solid portions of the connective tissue are thrust apart by fluid and eventually undergo lique-

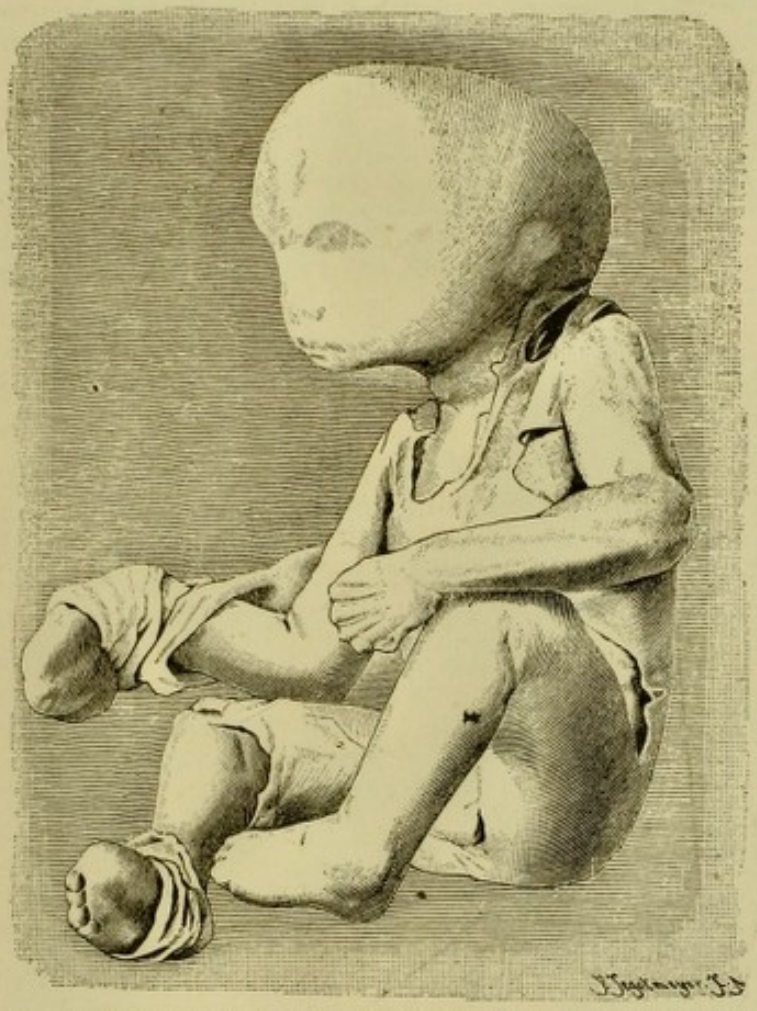


FIG. 342.—Lithopædion entirely inclosed in fibrous membranes. (Removed from abdominal cavity by operation two years after beginning of pregnancy.) Extra-uterine pregnancy caused by embryo breaking through uterine portion of a Fallopian tube into abdominal cavity. (Reduced one-third.)

faction, especially in the central portions. The epithelium of the villi shows in some places proliferation, in others dropsical degeneration.

The death of a fœtus in an advanced stage of development results, provided it be not expelled, in the formation of a **lithopædion.** This occurs most frequently in cases of extra-uterine pregnancy, in which the fœtus occupies an abnormal site, as in the peritoneal cavity, in a Fallopian tube, or in an ovary. If a fœtus so placed dies at such an advanced state of development that it cannot be absorbed, it may be carried in the maternal organism for years. Not infrequently its form is perfectly retained (Fig. 342), and the whole fœtus becomes enshrouded in an envelope of connective tissue. In other cases the fœtus, in the course of time, becomes converted into a partially fluid mass, which contains the osseous remains, as well as fat, cholesterin, and pigment, and is inclosed in a fibrous capsule. Usually lime salts are deposited in the new-formed capsule, as well as in the fœtal elements that remain.

All of these forms are included in the term lithopædion, but they are subdivided under three heads (Küchenmeister). The fœtus may be

mummified, but easily shelled out from calcified membranes (*lithocelyphos*). Or the fœtus may become adherent at a number of points with the membranes, and later these points become calcified, while the remaining parts undergo mummification (*lithocelyphopædion*). Or, again, the membranes may rupture and the fœtus be discharged free into the peritoneal cavity, and later become encrusted with lime-salts (*lithopædion* in the narrower sense).

According to observations of His,[1] an embryo may for one reason or another come to a standstill in its development, and yet be retained for weeks or even months in its envelopes. The first change that takes place at the approach of death is a great swelling of the central nervous system, which leads to deformities of the head. Later, the tissues become infiltrated with wandering cells, which make the boundaries between the organs vague. The whole embryo becomes soft and dark, and the superficial configuration of the body may become indistinct.

(b) Deficient Closure of the Cerebrospinal Canal and the Accompanying Malformations of the Nervous System.

§ 140. **Deficient closure of the vertebral canal** leads to the malformations known as **rachischisis** or **spina bifida.** Where the defect in the vertebral canal is broad so that at the bottom of the cleft the bodies of the vertebræ are seen covered by membrane the condition is usually called *rachischisis.* Where, at the site of the defect, there is a sac which protrudes, the malformation is usually called *spina bifida* or, more cor-

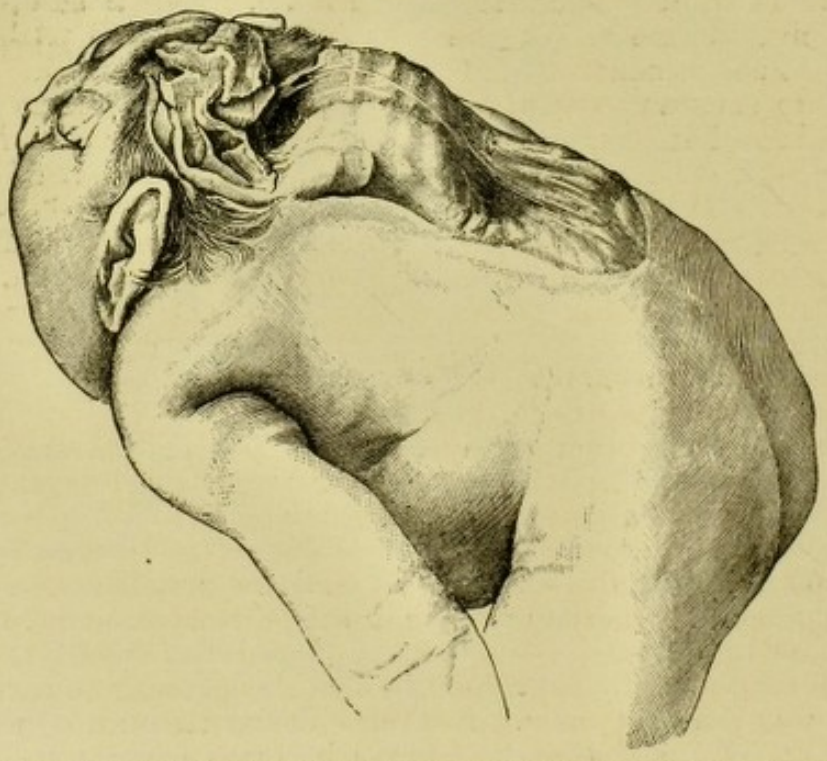


FIG. 343.—Craniorachischisis, with total absence of the brain and spinal cord. The skull is covered with irregular skin-like masses, the spinal furrow with a delicate envelope (pia mater). Kypholordotic bending and shortening of the spinal column. (Reduced one-sixth.)

rectly, *spina bifida cystica;* though to this formation the names *rachischisis cystica* or *hydrorachis cystica* may also be applied.

In **rachischisis totalis** (*holorachischisis*, Fig. 343) the bodies of the

[1] "Fragen d. path. Embryologie"; Intern. Beiträge, Festschr. f. Virchow, i., 1891.

vertebræ form a shallow groove open posteriorly, and usually covered only by a thin, transparent membrane; though, in rare cases, there are rudiments of spinal cord in the form of whitish bands and lines (*total or partial amyelia*).

The delicate membrane, which lines the furrow and rests upon the dura mater covering the bones, is the ventral portion of the pia mater spinalis. A part of the nerve-roots may have undergone development and be seen springing from rudiments of spinal cord or from spinal ganglia.

Partial rachischisis (*merorachischisis*) involves usually the sacro-lumbar or the upper cervical region, while the intermediate portions of the vertebral column are seldom the seat of malformation.

The dorsal surface of the vertebral bodies whose arches have remained rudimentary is mostly covered by a mass of velvety red tissue (Fig. 344, *c*) (von Recklinghausen) closed in by a delicate integument; though the amount of this tissue may be very small, or may even be wanting. External to this tissue-mass, which is not everywhere equally abundant, and which decreases at the sides, comes usually a delicate, transparent, vascular skin (Fig. 344, *e*); next, a zone of skin with an epidermis, but somewhat thinner than the normal skin, and often bearing abundant hairs (Fig. 344, *f*); then, finally, comes the normal skin.

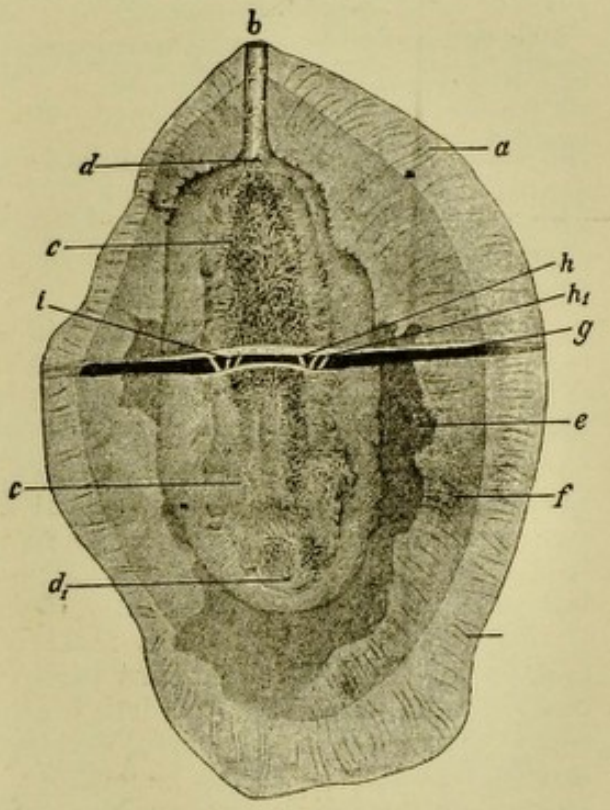


FIG. 344.—Rachischisis partialis. (After von Recklinghausen.) *a*, Outer skin with hairs; *b*, spinal cord, laid bare by dissection; *c*, area medullo-vasculosa; *d*, cranial, d_1, caudal polar furrow; *e*, zona epithelo-serosa; *f*, zona dermatica with hairs; *g*, space between dura mater and pia; *h*, anterior, h_1, posterior nerve-roots; *i*, ligamentum denticulatum.

The soft red tissue-mass (*c*) lying in the median line is the rudiment of the malformed spinal cord, and is an extremely vascular tissue, containing often more or less abundant parts of the spinal cord, as nerve-fibres, ganglion-cells, and glia-cells, and is therefore appropriately called *area medullo-vasculosa* (von Recklinghausen).

The area medullo-vasculosa is sometimes a continuous tissue; sometimes it is scattered in patches and bands, and forms only a delicate web. The cranial as well as the caudal extremity of this median area may end in a distinct furrow, designated respectively as the *cranial* and the *caudal polar furrow* (*Polgrube*—von Recklinghausen) (*d*, d_1). Anteriorly this is next to the spinal cord (*b*); in lumbrosacral rachischisis it is connected caudally with the filum terminale. The tegument on which the area lies is only the pia mater, which also continues into the red zone spoken of above (*e*), which, being covered also with epithelium, is designated as the *zona epithelo-serosa* (von Recklinghausen). The

prominent zone bordering this and covering the rudiments of the posterior vertebral arches (*f*), is formed of cutis and is known as the *zona dermatica*.

On the ventral side of the pia mater that forms the covering of the defect is a cavity (*g*), bounded on its deeper side by the dura mater and

FIG. 345.—Spina bifida sacralis. (After Froriep and Förster.) Girl of nineteen years, born with a tumor the size of a pigeon's egg over the upper sacral and lower lumbar regions, which enlarged from the sixth year on, while at the same time club-feet developed.

the external layer of the arachnoid; so that this space is in reality the ventral portion of the subarachnoid space, and, as is normal with this space, is crossed by the ligamentum denticulatum (*i*) and the nerve-roots (*h*, h_1), which, in the region of the area medullo-vasculosa, lose themselves in the pia-like tissue.

Spina bifida cystica or **rachicele** (*rachischisis cystica*) occurs in three types: *myelomeningocele*, *meningocele*, and *myelocystocele*. According to its site we may further distinguish a cervical, a dorsal, a lumbar, a lumbo-sacral, and a sacral spina bifida. In general a spina bifida is characterized by the development of a fluctuating tumor, which is in most cases visible externally behind the spinal column (*spina bifida posterior*); but instances also occur in which the sac projects anteriorly from the spinal canal (*spina bifida anterior*), and others in which it is too small to be visible externally (*spina bifida occulta*).

Myelomeningocele occurs most often as a *spina bifida lumbosacralis* and forms usually a tumor, at birth varying from the size of a nut to that of an apple and after birth increasing in size, in the region of the lower lumbar and upper sacral vertebræ. It is covered either by smooth or scar-like skin, or may be without any skin on its summit and there clothed by a reddish, mucosa-like tissue (area medullo-vasculosa). The portion devoid of skin may be drawn in like a scar. In rarer cases there may be no external tumor (spina bifida occulta), the site of the cleft being indicated only by a heavier growth of hair or by a depression.

On opening the sac, which is composed of the arachnoid (Fig. 346, *e*) and pia (*f*, f_1), while the dura (*g*) does not reach to the dorsal portion of the sac, one sees that the lower end of the cord (b_1) is drawn outward and that the cavity of the sac is crossed by nerve-roots (*i*, i_1). Occasional nerve-roots (*h*) may also spring from the column of the cord as it courses through the sac.

According to these findings there is an accumulation of fluid in the meninges, a *hydromeningocele* (hydrorrachis externa circumscripta), which is combined with a prolapse of the spinal cord, a *myelocele*. At the site of the protrusion the vertebral arches are defective, and this defect may reach as far as the hiatus sacralis. Smaller defects may involve only one or two vertebræ.

Dorsal and cervical myelomeningoceles are much rarer than those in the lumbo-sacral regions. The deficiency in the vertebral arch is usually confined to one or two vertebræ. The cord here is involved in the me-

ningocele in so far that portions are drawn outward in the form of a band or a cone.

Hydromeningocele spinalis arises from a hernial protrusion of spinal arachnoid, caused by a circumscribed collection of fluid in the subarachnoid space. It may occur at the upper end of the spinal column, when there exists a cleft of the superior cervical vertebræ, together with hernia of the brain in the occipital region. Most frequently, however, it occurs in the sacral region, and here the hernial protrusion takes place either through a defect in the vertebral arches and vertebral bodies, or through the hiatus sacralis, or between vertebral arches, or through intervertebral foramina. In most cases the dura has no share in the formation of the sac; but views differ on this point and some authors (Hildebrand) describe a dural sac. By a progressive accumulation of fluid the sacs may attain a very considerable size. Small meningoceles may remain concealed in the deep tissues.

In accordance with the direction the hernia takes we may distinguish a *meningocele* posterior and a *meningocele anterior*, the latter taking place through a defect in the bodies of the vertebræ (*rachischisis anterior*).

A **myelocystocele** or **hydromyelocele** (*syringomyelocele*) has its origin in an expansion of the central canal of the spinal cord, as a result of which a more or less considerable portion of the cord, together with its connective-tissue envelopes, becomes a cystic tumor. The dura is wanting in the portion of the sac which has protruded outside the vertebræ.

According to von Recklinghausen, the wall of these sacs is formed, in the main, of the spinal membranes, but is lined on the inner surface by a cylindrical epithelium, and has at some part of its inner surface an area medullo-vasculosa—usually on the ventral, seldom on the dorsal side. Corresponding with this condition, the nerve-roots, if they are present, spring mostly from the ventral, seldom from the dorsal wall of the sac. The cavity itself is crossed neither by bands nor by nerves.

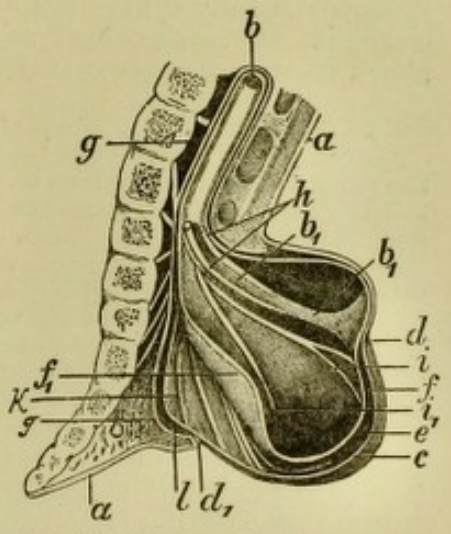


FIG. 346.—Myelomeningocele sacralis in sagittal section, a little to the left of the median line. (After von Recklinghausen.) *a*, Skin; *b*, spinal cord; b_1, column of the cord; *c*, area medullo-vasculosa; *d*, cranial, d_1, caudal polar groove; *e*, pia mater; *f*, arachnoid, somewhat separated from the pia mater; f_1, portion of the pia mater turned over; *g*, dura mater; *h*, recurrent roots of the fourth lumbar nerves; *i*, radix anterior, i_1, radix posterior of the fifth lumbar nerve, running free in the arachnoid sac; *k*, sacral nerve-roots between the arachnoid and pia; *l*, filum terminale.

Myelocystoceles occur, in the majority of cases, in conjunction with lateral clefts of the vertebral canal, and have a tendency also to be combined with *defects* and *asymmetries of the bodies of the vertebræ*, leading often to *shortening of the trunk;* sometimes affecting only the dorsal region, and sometimes including also the lumbar region. There is often, also, ecstrophy of the bladder, intestine, and abdominal cavity.

Myelocystoceles are mostly covered only by the outer skin, but are sometimes concealed deep down in the soft parts. They may furthermore be combined with meningoceles, producing **myelocystomeningoceles.**

In cases of rachischisis there is sometimes a **division of the spinal cord into two parts** (*diastematomyelia*), usually where the rachischisis

is total—that is, where generally only rudiments of spinal cord are indicated. Where there is partial rachischisis such divisions are rarer; but the separate cords are more fully developed, and the fibrous and bony envelopes may, at the beginning and end of the cleft, send dividing septa between them. Cases occur in which each cord-half shows an H-shaped area of gray matter.

The *production of rachischisis* is to be referred back to agenesia and hypoplasia of the medullary folds, which should form the medullary groove of the vertebral arches; and the agenesia of the spinal cord is also to be referred back to the very earliest period. Whether it be a question of primary agenesia, already predetermined in the elemental germ, or whether damaging influences from without, perhaps toxic substances (Hertwig), pressure from without or growing in of membranes, may have secondarily checked development or destroyed parts already formed, it is in most cases difficult to determine; yet the symmetrical distribution of the arrested development tends to support the former view.

In cases of *spina bifida* with hernial protrusion, the local *defects in the bony vertebral column* and *the deficient development of the dura mater*, which is usually wanting at the site of the protrusion, are to be regarded as the primary defects. The growth of the sac may be explained by congestive and inflammatory transudation, and relics of inflammatory changes, as thickenings and membranous adhesions, may even sometimes be demonstrated in the pia.

In the earliest embryonic period, the medullary groove is formed by the development on either side of the median line of wall-like elevations of the ectoderm. By converging growth of these elevations the medullary groove is closed and formed into the neural canal. Thereupon the masses of cells (primitive vertebral plates) lying at the sides of the newly formed canal, form an envelope about it, which gives rise in the first place to a membranous, non-articulated, vertebral column. This, at the beginning of the second month, becomes studded with discrete cartilaginous elements, from which in the course of the further development the vertebral bodies and arches are formed, while between them appear the intervertebral discs and the vertebral ligaments. The development of the cartilaginous vertebræ is not completed until the fourth month, and until then the dorsal covering of the neural canal consists of the united portions of the membranous vertebral column. The cartilaginous vertebræ are replaced in the course of development by bone.

As to the origin of myelocystoceles and myelocystomeningoceles, one cannot, according to von Recklinghausen, ascribe as a cause either the persistence of a connection between the neural canal and the epiblast, or an excessive stretching of the medullary groove-wall through bending of the axis of the embryo. According to him, the myelocystocele is a deficient growth in the long axis of the vertebral column, characterized anatomically by shortness of the column, by failing of vertebræ or portions of vertebræ, by separation of bony wedges from the bodies of the vertebræ, and by unilateral defects in the arches. The neural canal, then, pursuing its normal development, becomes too long for the vertebral canal, undergoes in consequence curling or kinking, and there is a tendency to a partial protrusion at the point where the bend is sharpest. Marchand, on the other hand, holds that this hypothesis does not fit all cases, and Arnold also believes that the causal relations between arrests of development in the muscle-plates and vertebral elements on the one hand, and those of the neural canal on the other hand, are not constant, but that a variety of disturbing influences may give rise to one or more of these anomalies.

According to O. Hertwig, the ordinary spina bifida is an arrest of development dependent upon a partially prevented closure of the primitive mouth cleft.

§ 141. **Faulty development of the cranial vault** and the associated **hindrance to the development of the brain** lead to the malformations which are termed *cranioschisis*, *acrania*, *hemicrania*, *microcephalus*, *anencephalus*, *exencephalus*, *micrencephalus*, and *cephalocele*.

Acrania and **hemicrania** or **cranioschisis** are the results of an agene-

sia or hypoplasia of the bony and membranous portions of the cranial vault, which has either arisen as a primary disturbance of growth, or

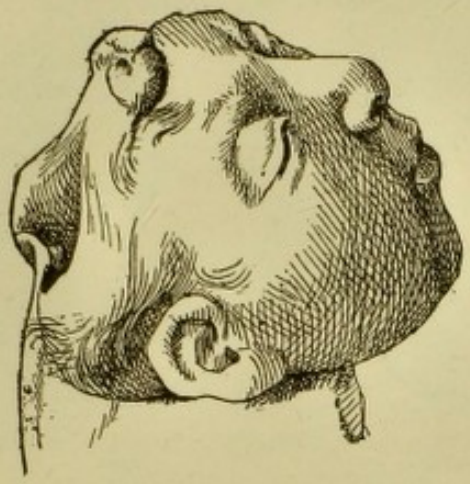


FIG. 347.—Anencephalia et acrania. (Reduced one-half.)

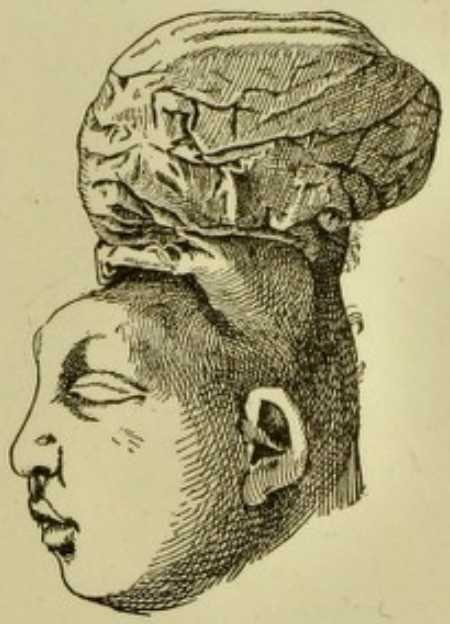


FIG. 348.—Cranioschisis with exencephalia.

has been caused by harmful external influences, damaging the primitive cerebral elements.

In acrania both the bony portion and the skin of the cranial vault are wanting (Fig. 347 and Fig. 349) almost entirely; the surface of the base of the skull is covered only by a skin-like, vascular tissue.

If the defect in the cranial vault is extensive enough to include also the arches of the vertebræ, there is produced the condition known as **craniorachischisis** (Fig. 343). In this case the spinal column is mostly shortened and bent, the head in consequence being drawn sharply backward and the face turned upward. When the eyes bulge out, owing to

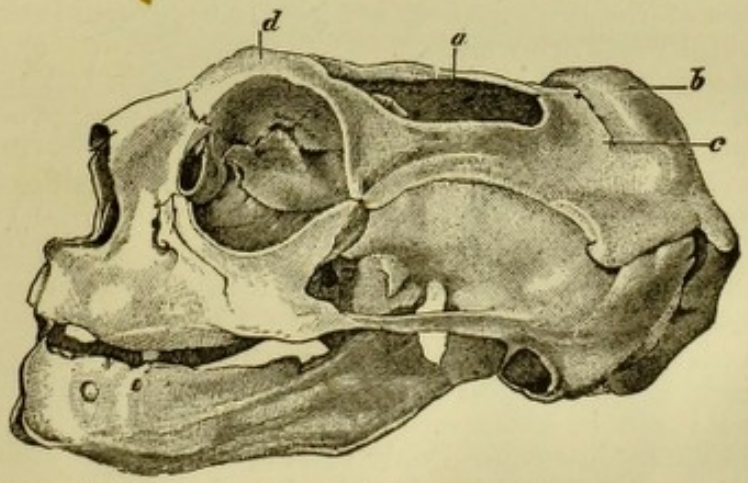


FIG. 349.—Partial agenesia of the bones of the cranium in anencephalia. *a*, Defect; *b*, occipital portion of skull; *c*, parietal bone; *d*, frontal bone. (Reduced one-fifth.)

deficient development of the forehead, the malformations resemble frogs (*frog fœtus*).

In hemicrania the flat bones of the cranial vault have undergone

more or less extensive development (Fig. 349, *b*, *c*, *d*) and form a cranial cavity, which is, however, of small capacity, inasmuch as the flat bones of the vault are elevated but a short distance above the base of the skull. If the bones of the vault which have undergone but feeble development yet unite with one another after the normal manner, there is produced a simple

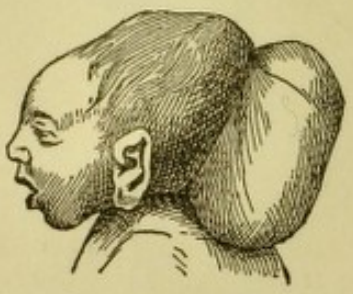


FIG. 350.—Hydrencephalocele occipitalis.

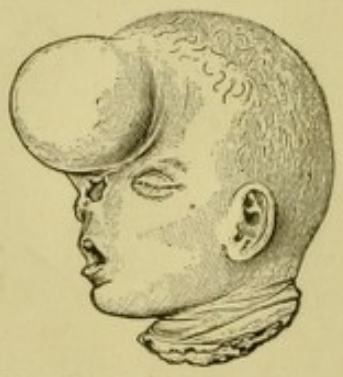


FIG. 351.—Encephalomeningocele nasofrontalis.

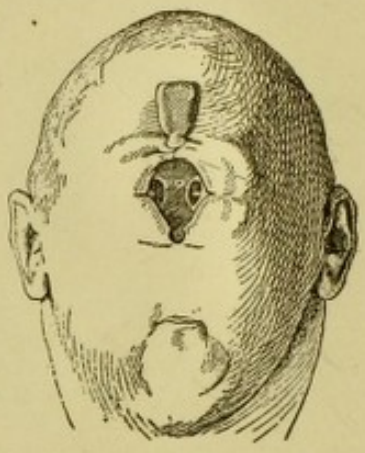


FIG. 352.—Synophthalmus or cyclopia.

microcephalus. This may be already present at birth, or it may be produced later by insufficient development of the skull.

Acrania and hemicrania are often associated with **total anencephalus,** and the base of the skull is covered only by a vascular, spongy, skin-like mass, composed of a connective tissue rich in blood-vessels, mostly spotted with hemorrhages and containing either no brain substance or only undeveloped rudiments (*area cerebro-vasculosa*).

In other instances the meninges contain, beside cystic cavities and gland-like remnants of the medullary plate, also more or less developed brain substance, which usually protrudes through the defect in the cranial vault, causing **exencephalus** (Fig. 348 and Fig. 337). The hernial masses are either covered by only a soft membrane, representing the meninges, or they may have also a covering of skin.

With microcephalus there is also **micrencephalus,** that is an abnormal smallness of the brain. Either there is a general lack of development, or special parts are wanting.

Where the cranium is in general properly closed, but presents **partial deficiencies,** portions of the cranial contents may protrude in the form of a hernial sac, and it is hence spoken of as a **hernia cerebri** or **cephalocele** (Fig. 350 and Fig. 351). Defects of ossification (Ackermann), or deficient resistance of the membranous cranial envelope, are doubtless usually the primary cause; but adhesions of the meninges with the amnion (St. Hilaire) may also be a cause. On the extracranial portion of the sac the dura mater is lacking (Muscatello).

The size of the protruding sac varies greatly. It may be so small as to be found only by careful examination, or it may be so large as to approach the brain in volume. When accumulation of fluid in the subarachnoid space has caused only the arachnoid and pia to protrude, the tumor is a **meningocele**; when brain-substance also protrudes, it is a **meningo-encephalocele.** A protrusion of brain-substance and pia without accumulation of fluid is called an **encephalocele**; if the protruding brain-substance contains part of a ventricle filled with fluid it is called a **hydrencephalocele.**

These brain-hernias appear mostly in the occipital region (*hernia*

occipitalis) close above the foramen magnum (Fig. 350) and at the root of the nose (*hernia cyncipitalis*). In the latter region it may involve more especially the frontal bone (*hernia nasofrontalis*, Fig. 351), or the ethmoid (*hernia naso-ethmoidalis*) or the lachrymal bone (*hernia naso-orbitalis*). More rarely hernias occur at the sides of the skull (*herniæ laterales*) or at the base (*herniæ basales*). The latter may bulge toward the nasopharynx (*hernia sphenopharyngea*) or the orbits (*hernia sphenoorbitalis*) or the sphenomaxillary fossa (*hernia sphenomaxillaris*).

Marked stunting in the development of the anterior of the three cerebral vesicles may leave the cerebrum single (St. Hilaire's *cyclencephalia* or *cyclocephalia*), while at the same time a deficient separation of the ocular vesicles takes place. When the stunting is very marked, only a single eye may be formed in the middle of the forehead, or there may be two united together and lying in a single orbit (Fig. 352); and this malformation is called **cyclopia** or **synophthalmia**, and **arrhinencephalia** (Kundrat). The nose is also stunted (Fig. 352), being present only as a cutaneous tag attached above the eye and devoid of bony foundation (*ethmocephalia*).

When the eyes are separate, yet abnormally close together, the nose in general may be normal, but at the root it is very small (*cebocephalia*).

In the severer forms of the malformation the ethmoid and the nasal septum may be wanting, and the upper lip and palate may be cleft in the median line, or laterally on one or on both sides (Kundrat). In the

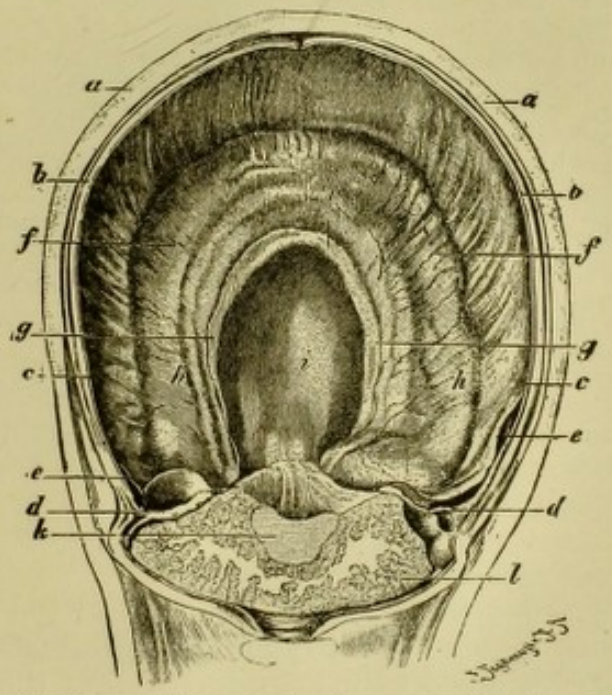


FIG. 353.—Cranial cavity of a synophthalmus microstomus opened by a frontal section (viewed from behind). *a*, Skin and subcutaneous tissue; *b*, cranial vault; *c*, dura mater; *d*, tentorium; *e*, arachnoid; *f*, posterior surface of the cerebrum, consisting merely of a thin-walled sac covered with pia mater; *g*, tumefied border of the cerebral sac; *h*, subarachnoid space behind the cerebral sac; *i*, cavity of the cerebral sac, communicating with the subarachnoid space by the enlarged transverse fissure; *k*, section through the corpora quadrigemina; *l*, section through the cerebellum; *m*, the atlas. (Four-fifths natural size.)

milder forms the forehead is merely reduced in size and pointed like a wedge.

In the severest grades of these malformations the cerebrum consists of a sac (Fig. 353, *f*, *i*) occupying more or less of the cranial cavity and filled with a clear fluid; where the sac does not lie against the cranial

wall the intervening space is taken up by fluid distending the subarachnoid space (*h*). In milder instances only individual portions of the brain are wanting in development, those mostly affected being the olfactory nerve and olfactory bulb, the corpus callosum, a part of the convolutions, etc. The optic thalami are often blended together. The chiasma and optic tracts may be either wanting or present. The corpora quadrigemina (*k*), the pons, the medulla oblongata, and the cerebellum (*l*) are usually unaffected.

Spinal cord and brain develop from the neural canal. In the portion that is to become the brain, the neural canal changes at an early period into three vesicles. The anterior of the three, the forebrain, throws out from its lateral portions the primary optic vesicle, while the middle portion grows forward and upward and divides into the prosencephalon and the thalamencephalon. From the former are developed the cerebral hemispheres, the corpora striata, the corpus callosum, and the fornix. From the thalamencephalon are formed the optic thalami and the floor of the third ventricle. The second cerebral vesicle or mesencephalon forms the corpora quadrigemina, while the third divides into epencephalon and metencephalon, from which are formed the pons, the cerebellum, and the medulla oblongata.

The cerebral portion of the neural canal becomes inclosed in the primitive vertebral plates of the head, which form the membranous primordial skull. The basal portions change to cartilage in the second fœtal month. In the third month both the cartilages of the base and the membranous vault begin to ossify.

According to G. St. Hilaire, Förster, and Panum, acrania and anencephalus are to be ascribed to an abnormal accumulation of fluid in the cerebral vesicles, a *hydrocephalus*, occurring before the fourth month. Dareste and Perls oppose this view and point out that in acrania the base of the skull is mostly bulged inward, hence is not pressed outward; and they look for the cause of acrania in a pressure upon the skull exerted from without (Perls) and caused by the head cap of the amnion being very snug and retarding the development of the cranium. Lebedeff looks for the cause of acrania in an abnormally sharp bending of the body of the embryo, which he conceives to occur in case the cephalic end of the embryo grows abnormally in the longitudinal axis or in case the cephalic covering lags behind in its development.

By the sharp bending the change of the medullary groove into a neural canal is thought to be prevented, or the canal after its formation to be destroyed. From this could be explained also the absence later of the brain as well as of the teguments and bones of the cranium. The cystic formations in the teguments lying upon the base of the skull Lebedeff would have formed from the folds of the medullary groove, which sink into the mesoderm and then become snared off.

Hertwig thinks it possible that chemical substances, circulating in the blood or secreted from the wall of the uterus, may destroy the earliest beginnings of the brain.

It is very probable that acrania has not in every instance the same origin. While in one case the influences brought forward by Perls and Lebedeff, or adhesions with the membranes, may arrest the development of skull and brain, yet in other cases the malformation should probably be looked upon as a primary agenesia already predetermined in the germ.

(c) Malformations of the Face and Neck.

§ 142. The development of the **face** is subject not infrequently to disturbances leading to more or less marked malformations, which may appear alone or be combined with malformations of the cranial portion of the head. When the frontal process and the maxillary processes of the first branchial arch remain in an entirely rudimentary state, or are more or less completely destroyed by pathological processes, there is present at the site where the face should be merely a surface or cleft (**aprosopia** and **schistoprosopia**), which may or may not be combined with malformations of the nose and eyes.

But more frequent than these large defects are smaller clefts involving the lip, the alveolar process of the upper jaw, the upper jaw itself, and the hard and soft palates (**cheilo-gnatho-palatoschisis**). This malformation establishes a communication between the mouth and the

nasal cavity (Fig. 354). The hard palate, where it abuts against the vomer, is cleft in the median line where it meets the soft palate. In the alveolar process of the upper jaw the cleft runs between the eye-tooth and the lateral incisor, or between the lateral and central incisors. The malformation may be bilateral or unilateral, primary and hereditary or secondarily acquired, one of the causes of the latter condition being amniotic adhesions (Fig. 337).

Frequently the cleft involves only special portions of the region above mentioned, as the upper lip (*harelip, labium leporinum*), or, what is rarer, only the hard or only the soft palate. The mildest degree is indicated by a *notch* or a *cicatricial line in the lip*, or by a *bifurcation of the uvula*.

Prosoposchisis (Fig. 338, *e*) is the term applied to a cleft running obliquely from the mouth to an orbit. It is usually associated with malformations of the brain. Morian distinguishes three varieties. The first commences on the upper lip as a harelip, passes into the nostril, thence around the ala nasi toward the orbit, and may extend even beyond the orbit. The second variety begins likewise in the region of a harelip, but extends outward from the nose toward the orbit. The third variety extends from the corner of the mouth outward through the cheek, toward the canthus of the eye, and divides the superior maxillary process externally to the canine tooth. A *transverse cleft of the cheek* also occurs, coursing from the corner of the mouth toward the temporal region.

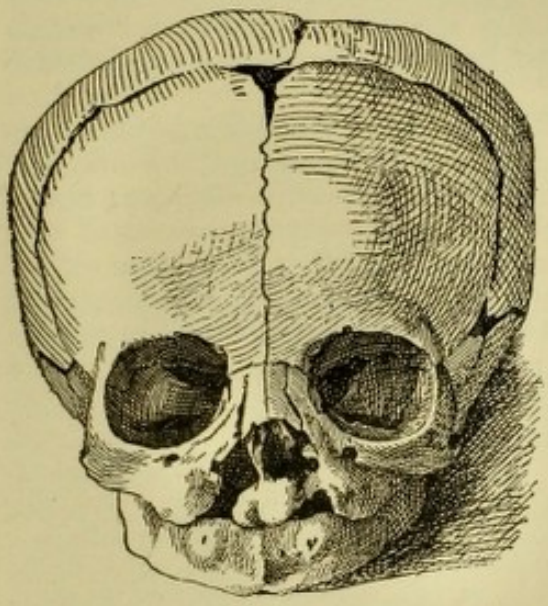


FIG. 354.—Double cheilognatho-palatoschisis.

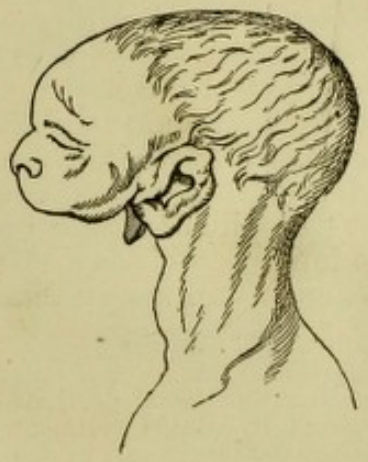


FIG. 355.—Agnathia and synotia (Guardan).

Median facial clefts also occur, and may involve the nose and upper jaw, and also the lower jaw, or even extend as far down as the sternum. With this malformation the tongue may also be cleft (Wölfler).

All of the above-described clefts may be confined to small portions of the regions mentioned, and may also attain various depths.

When the inferior maxillary process of the first branchial arch is tardy in its development, the inferior maxilla becomes also imperfectly developed, and may be entirely wanting, producing the malformations known as **brachygnathia** and **agnathia** (Fig. 355), and the appearance presented is as if the lower half of the face had been cut away; the ears are sometimes so close to each other as to touch (*synotia*). Usually the

superior maxillary processes are also imperfectly developed, and frequently the ear is misshapen.

Malformations of the mouth, as abnormally large size (*macrostomia*), abnormally small size (*microstomia*), closure (*atresia oris*), and duplication (*distomia*), are all rare.

When the embryonic external branchial clefts or internal branchial pockets fail in part to close, fistulæ opening either externally or internally, or closed cysts, remain. The former condition is called **fistula colli congenita.** The mouths of the external fistulæ are generally found at the side of the neck, more rarely approaching, or actually in, the median line; those of the internal fistulæ open into the pharynx, trachea, or larynx. Frequently slight remains of the branchial pockets form merely diverticula of the latter organs. The fistulæ are mostly clothed with a mucous epithelium, sometimes ciliated, originating, therefore, from the visceral branchial pockets—according to von Kostanecki and von Mielecki, mostly from the second. In rare cases a complete branchial fistula is found, having both an external and an internal opening.

The **branchial cysts** which arise from the branchial pockets are sometimes clothed with mucous membrane (ciliated epithelium), are filled with fluid, and receive the name of *hydrocele colli congenita;* sometimes they are lined with an epidermal covering, contain masses of epidermal cells, and are therefore reckoned among the *atheromata* and *dermoid cysts.* Arrests in development of the anterior end of the branchial arch (mesobranchial field) and in the region of the third branchial pocket (the site of origin of the thymus) and branchial cleft may lead to the formation of *dermoids in the submental region, at the root of the tongue, and in the mediastinum.* (Compare § 133.)

The face and neck are developed in part from a single embryonic rudiment, in part from paired rudiments. The latter are represented in the branchial or visceral arches growing from the lateral portions of the base of the skull ventrally in the primitive throat-wall. The single rudiment, called the frontal process, is a prolongation downward of the base and vault of the skull, and is, in fact, the anterior end of the skull. Between the individual branchial arches there are at a certain period cleft-like depressions or branchial pockets.

The frontal process and the first branchial arch form the borders of the great primitive mouth, which has a diamond shape. In the course of development the first branchial arch sends out two processes, of which the shorter applies itself to the under surface of the forehead and forms the upper jaw, while from the lower and longer one the lower jaw develops. The frontal process, which forms the anterior border of the mouth, produces a wide and long forehead and then pushes on two lateral processes, called lateral nasal processes. By further differentiation of the central portion of the frontal process the septum narium is formed, which, by means of two spurs called the inner nasal processes, produces the borders of the nostril and the nasal furrow. The lateral nasal processes are the lateral portions of the skull, and develop within themselves later the ethmoid labyrinth, the cartilaginous roof, and the sides of the anterior portion of the nares. At a certain stage they form with the superior maxillary process a fissure running from the nasal furrow to the eye, and called the lachrymal fissure.

The mouth is at first simply a great cavern, but is soon subdivided into a lower and larger digestive and an upper and smaller respiratory portion. This is done by the development, from the superior maxillary processes of the first branchial arch, of the plates which are to form the palate, and which begin in the eighth week to unite with one another and also with the lower edge of the nasal septum. The union of these lateral plates to form the palate begins anteriorly and progresses backward.

The union of the contiguous surfaces of the frontal and nasal processes with the superior maxillary processes forms the cheek and a continuous superior maxillary border, from which are developed later the lip and the alveolar process of the upper jaw-bone and the intermaxillary bones, while the nose develops from the frontal process. The intermaxillary bones are formed as two entirely distinct symmetrical bones, but unite early one with the other, and both with the upper jaw-bones.

(d) Faulty Closure of the Abdominal and Thoracic Cavities, and the Accompanying Malformations.

§ 143. The construction of the body-form from the flat embryonic layers begins by a turning over and drawing together of the layers at the periphery of the embryonic area, so that they become transformed into two tubes, one of which is the abdominal wall, the other the alimentary canal.

The infolding of these layers takes place at the cephalic and caudal ends as well as at the sides; and as these folds approach one another from all directions, those which are to form the abdominal wall produce a tube whose interior finally communicates only at the parietal umbilicus, by means of a tubular prolongation, with the cavity of the extra-embryonic portion of the blastodermic membrane. While these lateral and ventral walls of the embryo are being thus formed, within the body the intestinal furrow closes to form a tube which is in communication at only one point—namely, at the visceral umbilicus (within the above-mentioned communication of the abdominal cavity)—with the cavity of the umbilical vesicle, the channel between the two being called the omphalomesenteric duct.

FIG. 356.—Hernia funiculi umbilicalis. (Two-thirds normal size.)

The omphalomesenteric duct becomes obliterated in the sixth week. The complete closure of the abdominal cavity follows in the eighth week.

Arrests of development in the formation of the abdominal wall may take place at various points and be more or less marked. They are most frequent in the region of the umbilicus, where the closure of the abdominal cavity occurs latest. When faulty development of the abdominal wall at this point—leaving the abdominal cavity closed over a greater or less area only by peritoneum and the covering of the umbilical cord (the amnion)—gives rise to hernial protrusion over this area (Fig. 356), the condition is called **omphalocele, hernia funiculi umbilicalis,** or **umbilical hernia.** The remnant of the cord is situated either on the summit of the protrusion or at one side, and is more or less shortened.

The anterior abdominal walls may entirely or almost fail to unite—conditions which are called **fissura abdominalis, gastroschisis completa,** and **thoracogastroschisis,** and are characterized by the unde-

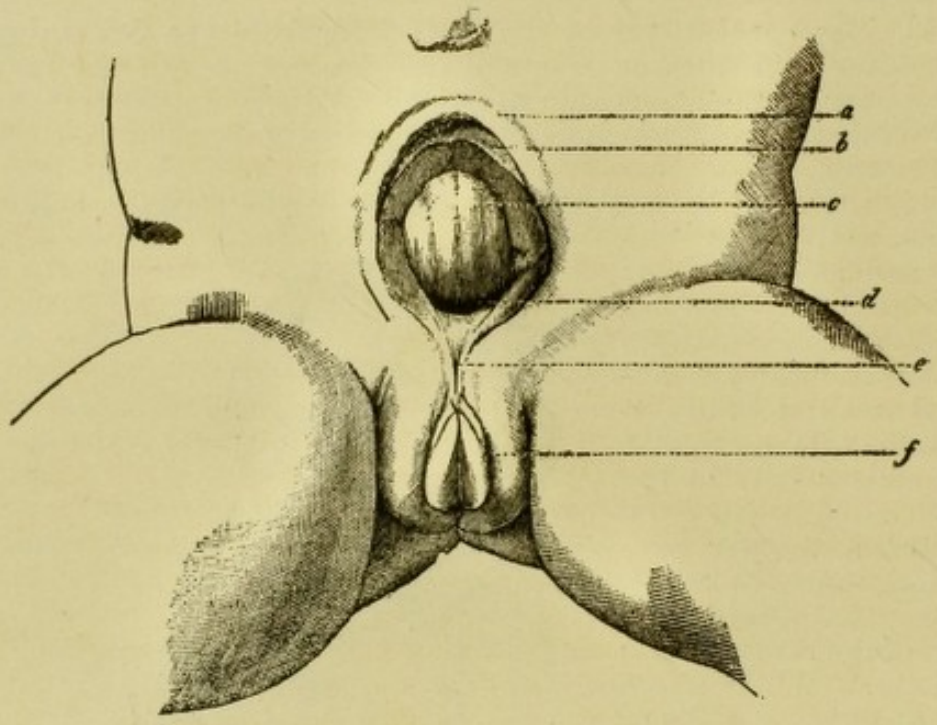


FIG. 357.—Fissura abdominis et vesicæ urinariæ, in a girl eighteen days old. *a*, Border of the skin; *b*, peritoneum; *c*, bladder; *d*, small bladder-cavity composed of the trigone; *e*, trough-like urethra; *f*, the labia minora.

veloped abdominal coverings not having been separated from the amnion, but running into it. The greater bulk of the abdominal contents then lie in a sac composed of peritoneum and amnion; or the peritoneum may be wanting also. The umbilical cord is also often wanting, and the umbilical vessels run to the placenta without joining one another.

Failure of the chest-wall to close is called **thoracoschisis.** The heart, covered with the pericardium or entirely free, may push out through an opening in the cardiac region. This condition is called **ectopia cordis.**

When the failure to close is confined to the sternal region it is called **fissura sterni.** This may involve the whole sternum or only a part of it; it may affect only the bones, or it may affect the skin also.

When the urinary bladder prolapses through a cleft in the abdominal wall, the condition is known as **ectopia vesicæ urinariæ.**

Clefts of the abdominal wall, whether total or partial, are not infrequently complicated by clefts of the parts lying behind the abdominal wall. When a cleft of the lower abdominal wall is combined with a cleft of the bladder also, so that the posterior wall of the bladder protrudes through the abdominal opening (Fig. 357, *c*), the condition is called **fissura** or **ecstrophia** or **inversio vesicæ urinariæ.** Sometimes the pelvic girdle and the urethra are also cleft, converting the latter into an exposed trough (Fig. 357, *e*). The ecstrophy is then said to be complicated with **fissura genitalis** and **epispadias.**

When an abdominal fissure, or an abdominal fissure together with ecstrophy of the bladder, is complicated with fissure of the intestine,

the condition is called **fissura abdominalis intestinalis** or **vesico-intestinalis.** The intestinal fissure is situated in the cæcum or in the beginning of the colon, and the mucous membrane of the intestine protrudes in the same manner as the posterior wall of the bladder; and hence it is called **ecstrophia** or **inversio intestini.**

If the omphalomesenteric duct does not undergo its normal atrophy, an appendix of intestine, called **Meckel's diverticulum,** remains. This diverticulum proceeds from the outer surface of the gut, having generally the appearance of a glove-finger, and either ends blindly or is attached at the umbilicus, sometimes being dilated at the ends. It may be adherent in the umbilical ring, and its mucous surface may protrude (*ectopia intestini, adenoma umbilicale*). In very rare cases a cyst lined with mucous membrane is found in the abdominal wall (*cyst of the vitelline duct*).

Umbilical hernia and clefts in the upper part of the abdominal wall are often combined with craniorachischisis, while ecstrophy of the bladder and intestine is often combined with myelocystocele; and von Recklinghausen regards the two malformations as bearing some relation to each other. Large abdominal clefts are furthermore often associated with lordotic or scoliotic curvatures of the spinal column.

(c) Malformations of the External Genitalia and of Parts belonging to the Anal Region, caused by Arrested Development.

§ 144. Malformations of the **external genital organs** may be associated with malformations of the abdominal wall, the bladder, and the internal genital organs, or they may occur without these associations. **Total absence of the external genitalia** may be the only defect, but it usually forms only a part of a more extensive malformation of the parts of that region, and, as a rule, is associated with defects in the internal genital organs (Fig. 360).

A dwarfed condition of the penis is not rare, and when it exists

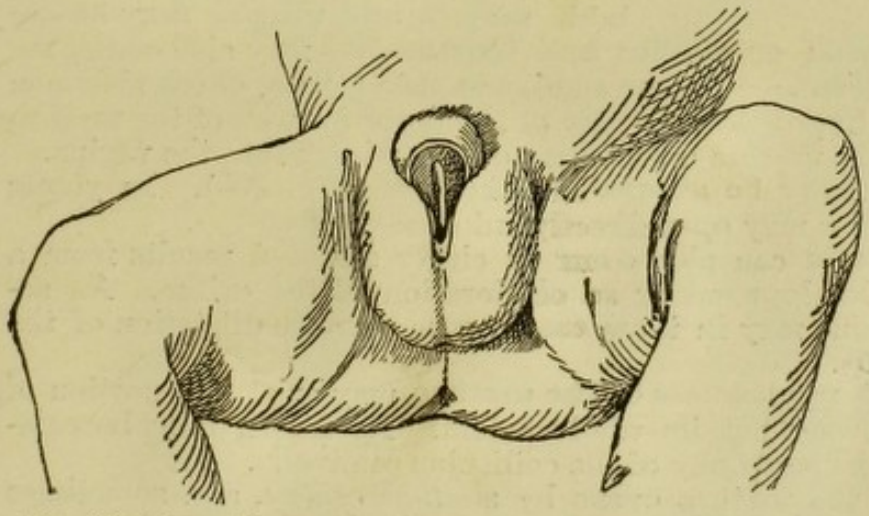


FIG. 358.—Hypospadias, associated with a stunted penis. (Reduced one-fourth.)

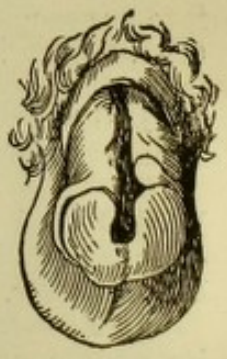


FIG. 359.—Epispadias. (After Ahlfeld.)

the organ presents externally a more or less close resemblance to a clitoris. It is usually associated with **hypospadias,** the urethral opening being beneath the glans, the body, or the root of the penis (Fig. 358),

or, in extreme cases, behind the scrotum (*hypospadias perineoscrotalis*). The same degrees of hypospadias may exist in penises otherwise normal, being due simply to a more or less complete covering of the sexual furrow from which the urethra normally develops.

Epispadias (Fig. 359) is the term applied to the condition in which the urethra opens upon the dorsal aspect of the penis. It is less common than hypospadias, and results from an incomplete or retarded closing of the pelvic cavity, of such a character that the cloaca is divided into an anal and a genital portion (Thiersch). Sometimes the two penile halves may remain separate, with or without ectrophy of the bladder or an incomplete closure of the abdominal cavity.

FIG. 360.—Complete absence of the urethra and external genitals, with extreme distention of the abdomen by an accumulation of urine in the bladder; and compression and dwarfing of the lower extremities. (In the posterior wall of the bladder there were rudiments of tubes and ovaries.)

Hypertrophy of the prepuce is not of rare occurrence. If a narrowing of the preputial opening is associated with it, and the prepuce cannot be pushed back over the glans, it is customary to speak of the condition as an **hypertrophic phimosis.** Entire **absence of the prepuce** is rare, *abnormal shortness* more frequent.

Deficient development of the scrotum is usually associated with retention of the testes in the abdominal cavity or in the inguinal canal, and causes the external genitals to look like those of the female—a result which is heightened when the penis is small or ill developed.

In the female the **clitoris and the labia majora and minora may be deficiently developed; epispadias and hypospadias** may also occur, the former associated with ectrophy and incomplete closure of the abdomen (Fig. 357). In hypospadias a part of the posterior wall of the urethra is wanting and the urethra opens more or less widely into the vagina.

The **urethra may be absent** in either sex (Fig. 360). In young females the bladder may open directly into the vagina.

Urethral atresia can also occur in either sex, and results from a local defective development or an obliteration of the orifice. An accumulation of urine may in these cases cause extreme dilatation of the bladder (Fig. 360).

An **abnormal narrowness of the urethra** may exist in a portion of its course or throughout its whole extent. Its lumen may be compromised by an hypertrophy of the colliculus seminalis.

Occasionally the urethra opens by *multiple orifices*, and sometimes there is a blind canal in the glans penis, lying beside the normal urethra.

Atresia ani simplex is a term used to denote a condition in which the anus is closed and at the same time the bowel well developed. It may arise from a failure of the ectoderm to fold in at the anal site, or it may be (Frank) that a cloaca already existing and opening outwardly has closed by subsequent adhesion.

If the rectum does not end directly above the anal skin, but higher up, there is beside the atresia ani also an **atresia recti**, a malformation which may occur also when the anus is fully developed.

When there is, together with absence of the anus, also an arrested development of the vaginal wall, which should grow downward between the sinus urogenitalis and the bowel and unite with the perineum, there remains a persistent **cloaca** in which the sinus urogenitalis and the termination of the bowel unite. In other cases are found **fistulous communications between the rectum** on the one hand, and **the bladder** or **urethra** (in boys) or **the vagina** or **uterus** on the other hand (*atresia ani vesicalis, urethralis, vaginalis, uterina*).

In rare cases of anal closure the bowel may communicate with the outer world by **external fistulæ** in the perineum, the scrotum, or the sacrum.

(f) Malformations of the Extremities due to Arrest of Development.

§ 145. **Defective development of the extremities** is not rare, and may owe its origin to a deficiency in the primary differentiation of the embryo, be secondary to some disturbance in the development of the limb or the bones, or result from constrictions caused by strands of the membranes or loops of the umbilical cord. The cause of such defective development of the extremities may sometimes be referred to precedent malformations of the central nervous system.

They are grouped into the following classes, according to the degree of malformation:

1. *Amelus.* The extremities are either all entirely wanting or are represented by mere stumps or wart-like rudiments (Fig. 361).

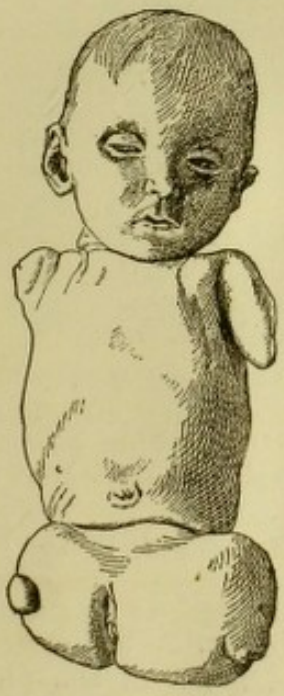


FIG. 361.—Amelus.

FIG. 362.—Micromelus with cretinitic facies.

2. *Peromelus.* All the extremities are dwarfed.

3. *Phocomelus.* The hands and feet are developed, but are attached directly to the shoulder and pelvis respectively.

4. *Micromelus* (microbrachius, micropus). The extremities are fully differentiated, but remain abnormally small (Fig. 362).

5. *Abrachius* and *apus*. Absence of the upper extremities with well-developed lower extremities, or *vice versa*.

6. *Perobrachius* and *peropus*. The arms and thighs well developed; the forearms, hands, legs, and feet malformed.

7. *Monobrachius* and *monopus*. Absence of a single upper or lower extremity.

8. *Sympus, sirenomelia, symmyelia*. The lower extremities are coalescent in a position of semi-rotation around their axes, so that their external aspects are in contact (Figs. 363 and 364). The pelvis is usually absent, as are also the external genitals, bladder, urethra, and anus.

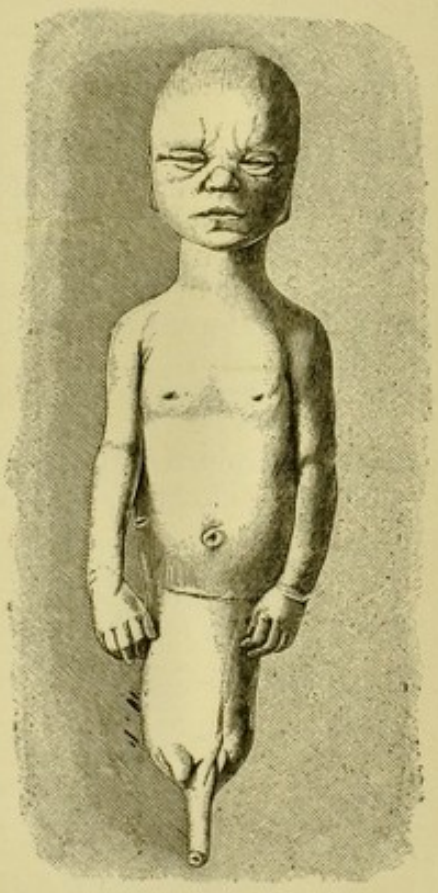


FIG. 363.—Sympus apus.

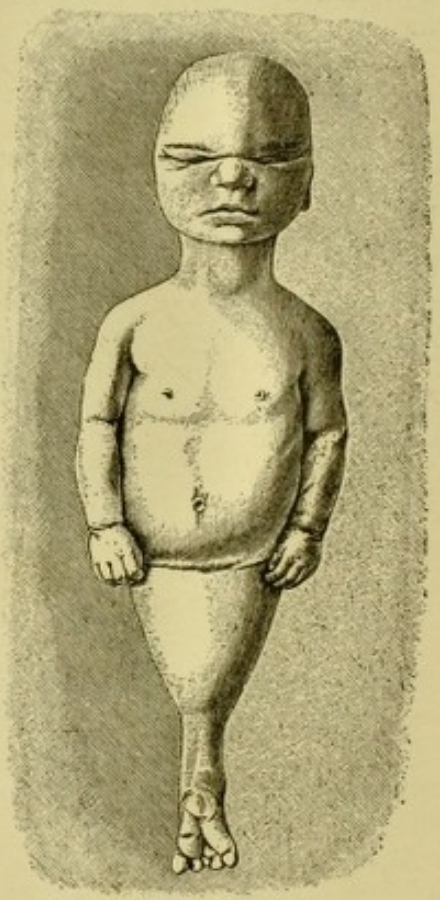


FIG. 364.—Sympus dipus.

The feet may be entirely wanting (*sympus apus*) and only a few toes be present (Fig. 363), or in other cases (Fig. 364) a single foot (*sympus monopus*) or both feet (*sympus dipus*) may be present.

9. *Absence of individual bones* may exist in any part of the extremities (Fig. 365).

10. *Perodactylism—dwarfing of the fingers or toes*—is encountered in a great many forms. In general, the condition is due either to imperfect development, or to the entire absence of some of the phalanges (Fig. 367, and Fig. 369, *c*) or frequently to the presence of membranous (Fig. 366 and Fig. 368) or even bony (Fig. 367 and Fig. 369, *d*, *e*) connections between the fingers (*syndactylism*).

If only the lateral fingers or toes become developed, while the middle are lacking, the forms arise to which the terms *cleft hand* and *cleft*

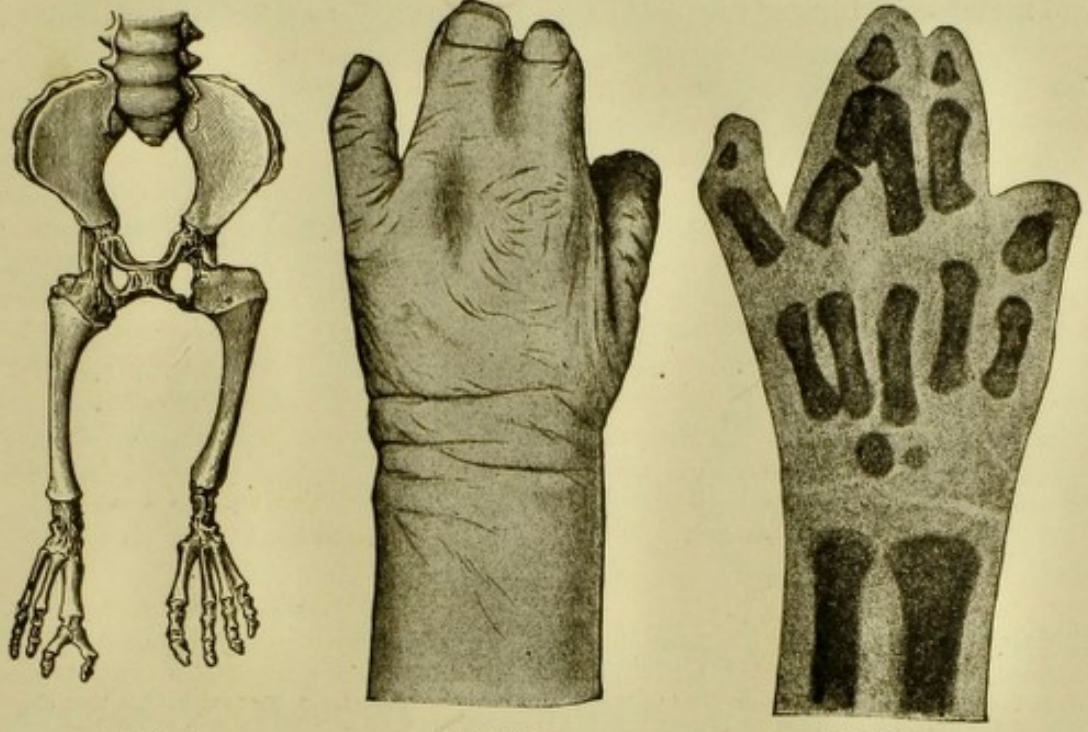


FIG. 365. FIG. 366. FIG. 367.

FIG. 365.—Absence of the femur and fibula. Diminution in the number of the phalanges. One-half natural size.

FIG. 366.—Perodactylism with syndactylism. Left hand of a new-born child. Seven-eighths natural size.

FIG. 367.—Picture of the hand shown in Fig. 366 when illuminated by the Röntgen rays. Seven-eighths natural size.

foot (Kümmel) are applied. When the fingers are badly malformed there are apt to be malformations and defects in the region of the tarsal

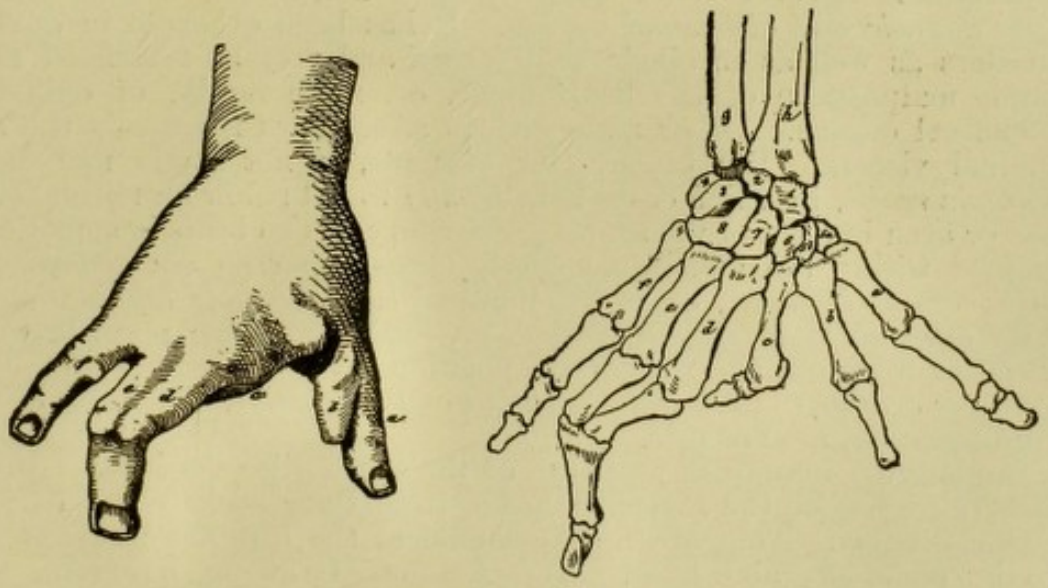


FIG. 368. FIG. 369.

FIG. 368.—Malformation of the right hand (perochirus) with coalescence of the fingers. (After Otto.) *a*, Supernumerary thumb; *b*, thumb proper; *c*, dwarfed index-finger; *d*, middle finger; *e*, ring-finger; *f*, little finger.

FIG. 369.—Bones of the perochirus depicted in Fig. 368, shown in their dorsal aspect. (After Otto.) *a–f*, Same as in Fig. 368; *g*, ulna; *h*, radius; 1, os naviculare; 2, os lunatum; 3, os triangulare; 4, os pisiforme; 5*a*, os multangulum majus superfluum; 5*b*, os multangulum ordinarium; 6, os multangulum minus; 7, os capitatum; 8, os hamatum.

and metatarsal bones (Fig. 371) (or of the carpal and metacarpal bones).

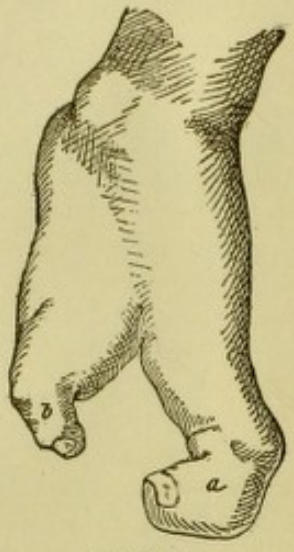


FIG. 370.

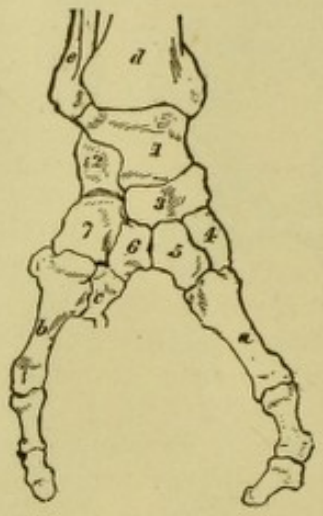


FIG. 371.

FIG. 370.—Peropus dexter. (After Otto.) *a*, Great toe; *b*, little toe.

FIG. 371.—Bones of the foot depicted in Fig. 370, in the dorsal aspect. *a*, Big toe; *b*, little toe; *c*, rudiment of the third toe; *d*, tibia; *e*, fibula; 1, talus; 2, calcaneus; 3, os naviculare; 4, os cuneiforme majus; 5, os cuneiforme minus; 6, os cuneiforme tertium; 7, os cubiforme.

These conditions are designated respectively *peropus* and *perochirus*. The lack of a hand or a foot is designated as *achirus* or *apus*.

2. *Abnormal Positions of the Internal Organs and of the Extremities.*

§ 146. Of the abnormal positions of the internal organs, the most important is the **situs inversus viscerum**—i.e., a *lateral transposition of the thoracic and abdominal viscera*. It has been observed in double monsters as well as in single individuals, and may be restricted to a simple malposition of the heart alone, or, more rarely, of only the abdominal organs. Other malpositions affect most frequently the abdominal viscera. The kidney, for example, is not rarely malplaced (*dystopia renis*), in which cases it is usually found below its normal site, near or even in front of the sacral promontory. The testis is sometimes retained within the abdominal cavity (*ectopia interna seu abdominalis testis; cryptorchismus*), or in the inguinal canal (*ectopia inguinalis*), or at the external ring (*ectopia pubica*), or, finally, at some point between the latter situation and its normal position (*ectopia cruroscrotalis, perinealis*, or *cruralis*). *Abnormal positions of the intestine*, especially of the large intestine, are not rare.

Among the abnormal positions of the extremities **congenital luxations** (slipping of the articular heads from their sockets) are of particular interest. They are most common at the hip, more rare at the elbow, shoulder, and knee. Von Ammon, Grawitz, Krönlein, and Holtzmann, regard them as in part the result of a local arrested development, but mechanical influences may also lead to luxation. At the hip the acetabular socket remains small and imperfect, and the head of the femur is more or less incompletely developed. The small acetabulum is in the normal location, the head of the femur, on the contrary, is displaced, usually backward (luxatio iliaca). At birth the ligamentum

teres is always intact, and the capsule of the joint embraces both the acetabulum and the head of the femur. After considerable use of the extremity, the ligamentum teres stretches and may tear apart; the capsule is stretched to a baglike form, and at the point where it is pressed against the bone it may become perforated A new joint may then be formed by the proliferation of the surrounding tissues.

Abnormal positions of the feet and hands are to be attributed sometimes to disturbances of development, sometimes to mechanical influences upon the extremities when they are growing. The most important of these deformities is the **congenital club-foot (pes equinovarus)**, which, according to Eschricht, is due to an arrest of development, leaving the foot in its fœtal position, with malformation of the bones and their articular surfaces. The inner border of the foot is sharply elevated and the foot at the same time is in plantar flexion. The collum tali is elongated in an anterior and inferior direction (Hüter, Adams). If the children learn to walk, they tread upon the outer side of the foot, which thereby becomes flattened, while the foot becomes still more sharply turned inward.

The congenital club-foot, though, as stated, usually the result of arrest of development, may occasionally be caused by an abnormal pressure due to a relatively small uterus (Volkmann). Under these conditions the positions known as **pes calcaneus** and **pes valgus** may be produced. They are characterized in part by a strong dorsal flexion, in part by a twisting of the foot. Frequently the evidences of the pressure to which the feet have been subjected are seen in an atrophic condition of the skin and the relative positions of the bones.

The position of the hand designated as **clubbed-hand** or **talipomanus** is caused by a rudimentary development of the radius, and is usually associated with other malpositions in the individual.

3. *Malpositions the Result of Excessive Growth or Multiplication of Organs or Parts of the Body.*

§ 147. A malformation known as **general giant growth** is the result of an excessive growth of the whole body, which may take place *in utero* or in after-life. During extra-uterine life growth far beyond the usual maximum may take place.

Partial giant growth may also take place *in utero* or after birth, and usually affects portions of the extremities or the head. During extra-uterine life trauma sometimes gives an impulse to a pathological excess of growth.

In these hypertrophies of an extremity—as, for example, a finger—the structure of the part may preserve its general normal relations, all its constituents participating in the abnormal development. In other cases certain tissues monopolize the growth, as, for example, the soft parts, especially the fat. Furthermore, the enlarged soft parts may show a pathological structure, as exemplified by cases in which the blood- or lymph-vessels are abnormally developed. When the extremities are the seat of this growth the condition is usually designated as **elephantiasis.** When the thickened portions are sharply circumscribed they are usually regarded as **tumors,** and, according to their structures, are classed with the angiomata, lymphangiomata, or fibromata. On the trunk the hypertrophies usually resemble elephantiasis, but sometimes

they assume the form of a neoplasm. The same is true when the parts affected belong to the face; the lips, cheeks, and tongue being not infrequently enlarged and distorted by a hyperplasia of the connective tissue richly endowed with lymphatic vessels.

Circumscribed hypertrophies of the bones occur in various parts of the skeleton, and are sometimes multiple. The bones of the head—those of the skull as well as those of the face—may be the seat of hypertrophy, which may be so extensive as to cause a deformity of one or both of these regions, a condition known as *leontiasis ossea* (Fig. 124). Circumscribed hypertrophies also lead to the formation of *osteomata* or *exostoses*, often multiple. The bones of the hip and of the extremities may present hypertrophies which may involve single bones only, or may result in the formation of atypical, frequently multiple, masses of bone.

§ 148. **Supernumerary organs,** or a **multiplication of the parts of the skeleton and of the muscular system,** are not uncommon, and are the result either of changes occurring early in the development of the parts, or of the persistence of parts that are normally suppressed as development advances, in which latter case they may perhaps be regarded as examples of atavism.

1. **Duplications at the extremities.**

A duplication of a whole extremity, without involving either the shoulder or the pelvis, has never been observed in man. Duplication of the hands and feet is rare, but a number of cases are on record (Fig. 372). The number of fingers may reach nine or ten.

Supernumerary fingers (polydactylism) on a simple hand, where the extra fingers are attached at the radial or ulnar side

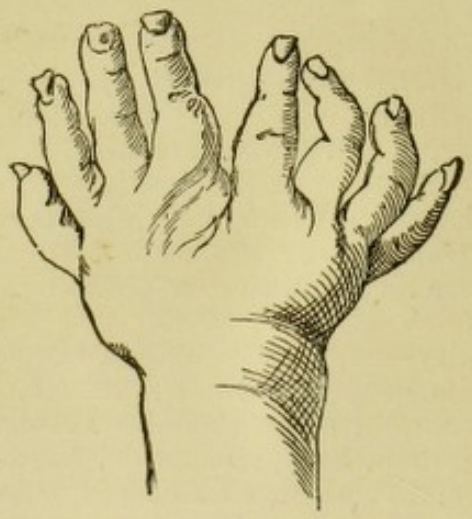


FIG. 372.—Polydactylism with duplication of the hand. (After Lancereaux.)

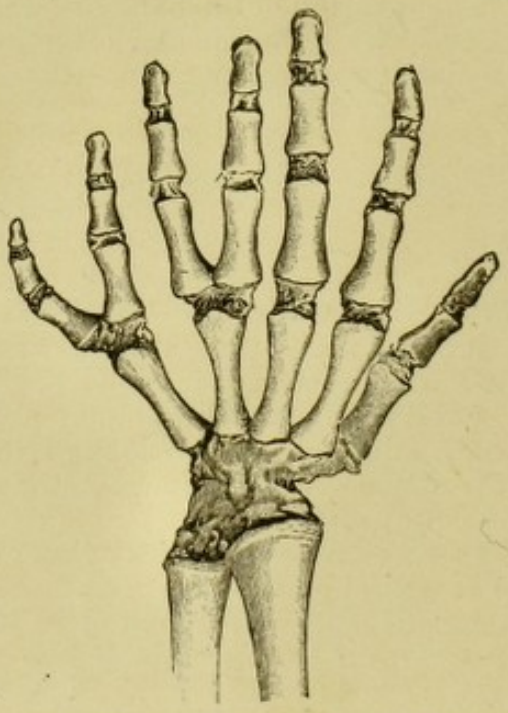


FIG. 373.—Polydactylism in a new-born child. (Skeleton only.) Duplication of the phalanges of the fourth and fifth fingers. Natural size.

of the hand, or intercalated between the normal fingers, are more common than a duplication of the whole hand (Fig. 369, *a*, and Fig. 373). Similar anomalies occur on the lower extremities. Frequently the du-

plication involves only the first, or the first two, terminal joints of the fingers (Fig. 374 and Fig. 375). When attached to the edge of the hand the fingers may be well developed (Fig. 373), or they may be mere rudiments. Occasionally they appear as small pedunculated fibrous tumors. In the fully

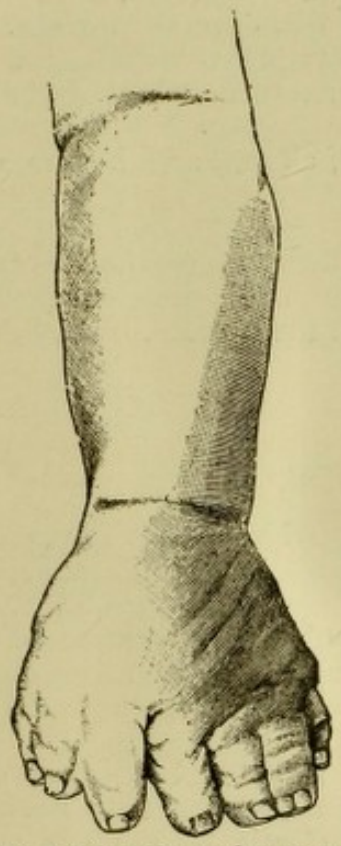


FIG. 374.—Polydactylism and syndactylism of the left hand. (Reduced one-fifth.)

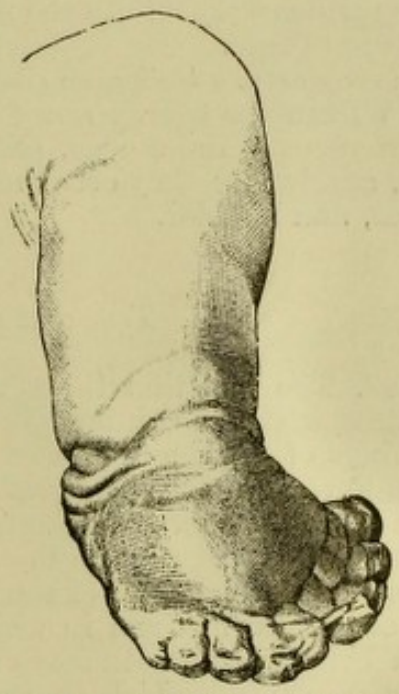


FIG. 375.—Polydactylism and syndactylism of the right foot. (Reduced one-fifth.)

developed supernumerary fingers the phalanges (Fig. 373) may articulate with the metacarpal or metatarsal bones of neighboring fingers, or with supernumerary bones of the hand or foot, which in turn may articulate with supernumerary carpal or tarsal bones (Fig. 369, 5 *a*).

Polydactylism is sometimes inherited, sometimes the result of intrauterine influences and therefore independent of heredity.

2. **Supernumerary nipples and breasts** (**hyperthelia, hypermastia**) are not uncommon anomalies in both sexes, and are probably to be regarded as examples of atavism. They are usually situated on the thorax, along two lines running from the axillæ to the inguinal regions; but they may rarely be in other places—e.g., the axilla, shoulder, abdomen, back, or thigh. They are usually small, but may acquire functional activity when pregnancy takes place. Supernumerary nipples may reach as high a number as ten.

3. *The formation in men of breasts* resembling those of women (**gynæcomastia**) is rare in well-developed men with perfect sexual organs (see Hermaphrodism, § 149); but it not infrequently happens that the male breast suffers moderate enlargement at puberty.

4. **Duplication of the penis** with the formation of two urethræ, is of very rare occurrence.

5. **Supernumerary bones and muscles** are of frequent occurrence. *Extra vertebræ* may be developed at any part of the spinal column, and, at the lower end, may result in the formation of a **tail.** Besides the true tails containing bones, there are, according to Virchow, two forms

of false or imperfect tails, which contain neither bone nor cartilage. One of these forms he regards as a prolongation of the spinal column, while the other he looks upon as a cutaneous appendage of various make-up, which may sometimes be classed with the teratomata. The true tails are very rare, and, according to Bartels, are usually the result of an elongation or separation of the vertebræ rather than of the presence of supernumerary bones.

Supernumerary ribs in the neck or loins, as well as a forking of the ribs, are not rare.

Supernumerary teeth also occur.

6. Within the thorax and abdomen **duplications of the viscera** are most frequent in the spleen, pancreas, suprarenal bodies, ureters, renal pelves, and lungs; they occur more rarely in the ovaries, liver, kidneys, testicles, and bladder.

4. *True and False Hermaphrodism.*

§ 149. The fact that the sexual organs of both sexes develop from structures that are originally common to both, and which contain the beginnings of all the organs of both sexes, makes it *a priori* probable that malformations might result through an unequal development of the organs on the two sides of the body, or through a simultaneous development of organs peculiar to the two sexes, or, finally, through a lack of harmonious development of the external and internal genitalia.

Those malformations in which a single individual acquires sexual organs belonging to both sexes are grouped under the title **hermaphrodism** (Fig. 376). If both sexual glands (testis, ovary) are present the case is designated as **hermaphrodismus verus.** If the combination of the two sexes consists merely of a simultaneous development of male and female genital passages, or of internal organs belonging to one sex and sexual passages belonging to or simulating the other sex, the case is one of false hermaphrodism or **pseudohermaphrodismus.** The true sex is determined by the nature of the essential sexual glands present (ovary, testis).

The bodily habit of hermaphrodites frequently shows a curious blending of male and female characteristics. For example, the breasts, neck, and shoulders may approach the female type, while a development of the beard, face, larynx, and voice may correspond to the male type. In false hermaphrodites the bodily habitus may by no means always correspond to the true nature of the sex of the individual; a male may resemble a female, and *vice versa*.

The following **chief forms of hermaphrodism** are enumerated by Klebs:

I. **Hermaphrodismus verus,** or **androgynes.**

1. *Hermaphrodismus verus bilateralis*, characterized by the presence of both testis and ovary on both sides, or the presence on both sides of a compound organ containing testicular and ovarian structures. According to Klebs, no certainly authentic case of this kind is on record for the human species. Heppner asserts, however, that he found both ovary and testis in the broad ligaments of an individual with hermaphroditic external genitals and possessed of a vagina, uterus, and Fallopian tubes.

2. *Hermaphrodismus verus unilateralis.* Cases in which both sexual

glands are present on one side, while only one is present on the other side of the body. No authentic case of this malformation is on record.

3. *Hermaphrodismus verus lateralis.* These are cases in which there is an ovary on one side, a testis on the other. They have been frequently described in human beings (Rudolph, Stark, Berthold, Barkow, H. Meyer, Klebs, Messner, and others), but usually without exact microscopical examination. In the cases in which that has been undertaken, ovarian structures had not been made out with certainty until Obolonsky made a histological study of a case in the collection of the German university in Prague, and established the fact of a testis on the right (Fig. 376, *o*) and an ovary (*k*) on the left side. The broad ligament on the right side contained a testis (*o*), an epididymis (*p*), a vas deferens (*q*),

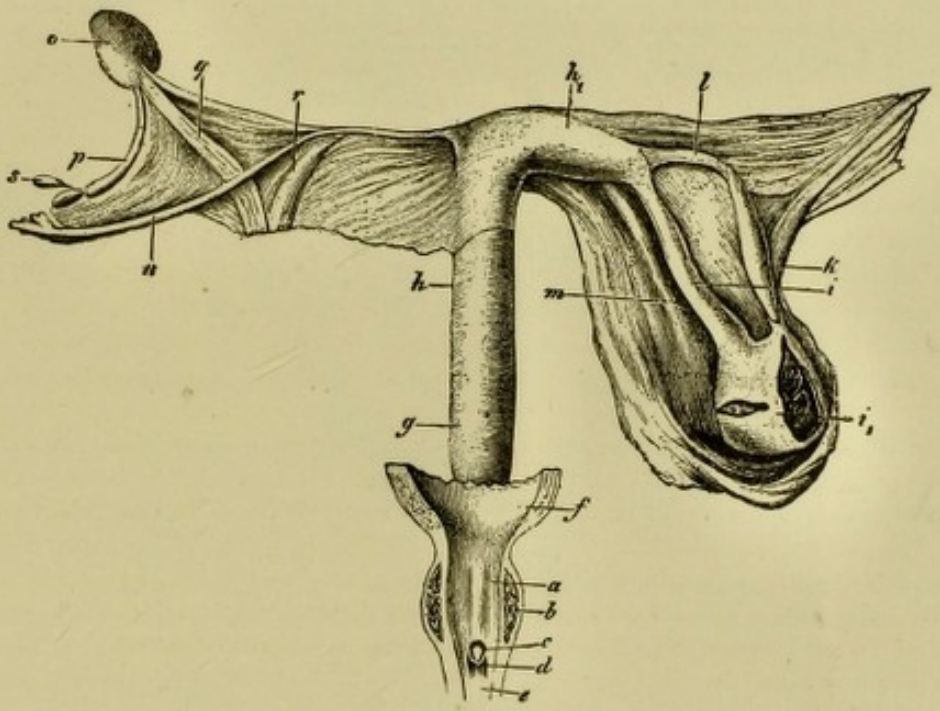


FIG. 376.—Hermaphrodismus verus lateralis. (After Obolonsky.) *a*, Urethra; *b*, prostate; *c*, colliculus seminalis; *d*, hymen; *e*, urogenital canal; *f*, bladder; *g*, vagina; *h*, uterus; h_1, left uterine horn; *i*, left tube; i_1, infundibuliform extremity of left tube; *k*, left ovary; *l*, ovarian ligament; *m*, left round ligament; *n*, right tube; *o*, right testis; *p*, epididymis; *q*, right vas deferens; *r*, right round ligament (About one-half natural size. Specimen in the pathological collection of the German Pathological Institute in Prague.)

a rudimentary tube (*n*), and a round ligament (*r*). The left broad ligament contained an ovary (*k*) with an ovarian ligament (*l*) and a well-developed tube (*i*). There was also a uterus (*h*), vagina (*g*), and a prostate (*b*). According to published observations of cases falling in this class, the sexual passages corresponding to the glands may all be developed or some of them may be lacking. The external genitals are malformed, and combine structures belonging to both sexes.

II. **Hermaphrodismus spurius,** or **pseudohermaphrodismus,** characterized by bisexual development of the external genitals and genital passages, associated with a unisexual development of the essential sexual glands. The most pronounced cases occur in males who, besides their proper sexual organs, possess more or less well-developed vagina, uterus, and tubes. It is much rarer to find that portions of the Wolffian duct have developed in females.

In male false hermaphrodites the external genitals are frequently

malformed and approach the female type, while in the female they resemble the male (Fig. 377).

This resemblance is brought about in the male when the penis is stunted, its ventral furrow fails to close (hypospadias), and the two halves of the scrotum remain separate, resembling the labia majora (especially when the testes do not descend), in which case there is usually a depression at the root of the penis between the scrotal halves. In the female the male genitalia are simulated by a development of the clitoris into a sort of penis (Fig. 377, *a*), a union of the labia, and narrowing or even closing of the ostium vaginæ. The vagina and urethra

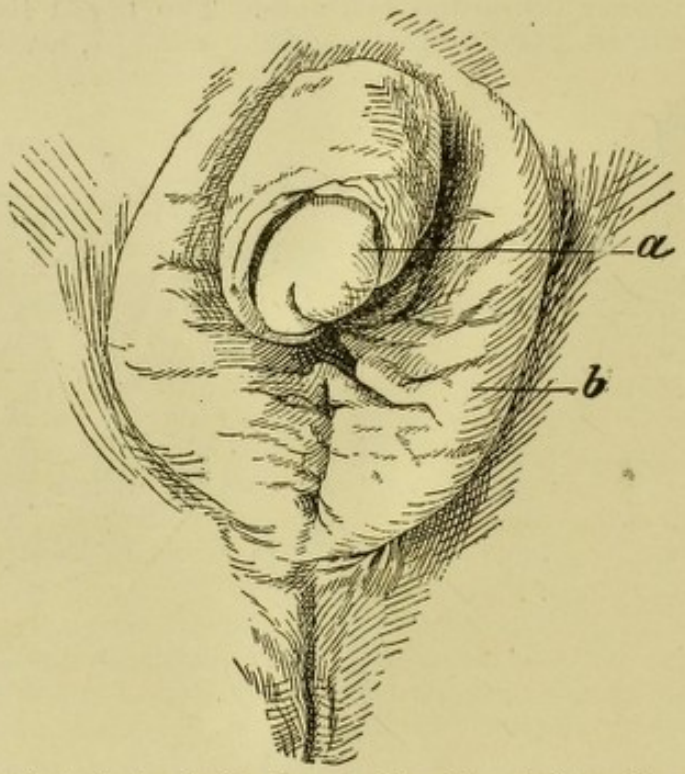


FIG. 377.—External genitalia of a female false hermaphrodite with vaginal stenosis. *a*, Clitoris resembling penis; *b*, labia majora. (Five-sixths natural size.)

may have a common opening or separate openings beneath the penile clitoris.

Malformation of the external genitals does not necessarily imply malformations in other portions of the sexual apparatus.

1. *Pseudohermaphrodismus masculinus* occurs in three varieties:

First, *pseudohermaphrodismus masculinus internus*. The external genitalia belong to the male type, and the prostate is also developed, but is usually pierced, generally at the colliculus seminalis, by a canal which communicates with the urethra and passes above into a rudimentary or more or less well-developed vagina, and occasionally uterus, and even tubes. The male organs may be well developed or more or less malformed.

Second, *pseudohermaphrodismus masculinus completus* or *externus et internus*. Vagina, uterus, and tubes are present, either more or less completely developed or in a rudimentary state, and the external genitalia more or less resemble the female type. The penis exhibits the condition of hypospadias resembling the clitoris, and at its root there is usually an orifice leading into a vestibule which divides into a urethra

and a vagina. Sometimes the vestibule and vagina are separate. In rare cases the external genitals appear normal, but the penis contains two canals, one, the upper, being the urethra, the other the sexual passage. When the ducts of Müller are highly developed the vasa deferentia are frequently defective, and sometimes the vesiculæ seminales are wanting.

Third, *pseudohermaphrodismus masculinus externus*. Only the external genitalia depart from the male type, resembling more or less perfectly those parts in the female. As in these cases the bodily habitus often simulates that of the female, they may readily cause a mistake in the sex.

2. *Pseudohermaphrodismus femininus* also occurs in three varieties, but is rarer than masculine false hermaphrodism.

In *pseudohermaphrodismus femininus internus* rudiments of the Wolffian ducts, lying in the broad ligaments or in the uterovaginal walls, and sometimes extending to the clitoris, are found in individuals with well-developed external genitals.

Pseudohermaphrodismus femininus externus is characterized by external genitalia resembling those of the male (Fig. 377).

Pseudohermaphrodismus femininus externus et internus, in which the external genitals resemble the male and there is a persistence of parts of the Wolffian ducts, has been recorded in only two cases (Manec, Bouillaud, and L. de Crecchio). In one of the cases there was a prostate, in the other a prostate pierced by the vagina, an ejaculatory duct, and a sac resembling a seminal vesicle, which opened into the vagina.

The **internal sexual organs** develop from elements which in the beginning are the same and undifferentiated in the two sexes. These elements are a sexual gland lying antero-internally to the *Wolffian body* and a *sexual canal* known as Müller's duct. The latter develops beside the *Wolffian duct* and, like it, empties into the lower end of the bladder or into the sinus urogenitalis.

In the male the duct of Müller nearly disappears, only a trace, the vesicula prostatica or uterus masculinus, remaining; the primitive sexual gland unites with a part of the Wolffian body, which becomes the epididymis, another small portion forming the vasa aberrantia testis (organ of Giraldès), while the chief bulk of the organ disappears, and the Wolffian duct becomes the vas deferens and vesicula seminalis.

In the female the Wolffian body and its duct disappear, leaving only a trace, the parovarium, behind. From the ducts of Müller, which coalesce at their lower ends, develop the vagina, uterus, and Fallopian tubes, the extreme upper end often persisting as a little sac, the hydatid of Morgagni.

The sexual gland first appears in the fifth week. It is produced in mammalia (and probably in man) by a thickening of the peritoneal epithelium, which becomes the germinal epithelium of the organ (Waldeyer), while the mesoderm also proliferates. Whether the seminal tubules are derived from the peritoneal epithelium (Bornhaupt, Egli), or whether they are derived from the Wolffian body (Waldeyer), is still a mooted question (Kölliker). The ova spring from the germinal epithelium. The environing cells of the Graafian follicle are regarded by Waldeyer as also derived from the germinal epithelium, while Kölliker thinks they are probably derived from the Wolffian body.

The significance of the *pedunculate and non-pedunculate hydatids*, situated in varying numbers near the globus major, is not as yet fully determined (Kölliker). According to Waldeyer, the *hydatid of Morgagni* is to be regarded as a remnant of Müller's duct. Roth thinks it may also stand in close relation to the Wolffian body, inasmuch as occasionally a vas aberrans of the epididymis communicates with it.

The ducts of Müller and the Wolffian ducts join in the female to form a single strand. At the end of the second month the ducts of Müller coalesce, at first near their centres and then farther down, to form the *uterus* and the *vagina*. The Wolffian ducts gradually disappear or are represented by mere remnants, situated at birth in the broad ligaments (Kölliker) or in the walls of the uterus (Beigel). Riedel holds that they persist throughout life in about one-third of the cases, consisting of a strand of cylindrical epithelium surrounded by muscular tissue, or of a mere muscular bundle lying in front and to the side of the uterus and vagina.

The **external genitals** begin to develop even before the separation of the intestinal and genito-urinary orifices, by the formation, in the sixth week, of a median genital eminence just in front of the cloaca, and of two lateral sexual folds. Toward the end of the second month the eminence becomes more prominent and its lower surface is furrowed. In the third month the cloaca becomes divided to form the anal and genito-urinary orifices. In the male the genital eminence develops into the penis, the glans becoming recognizable in the third month, and the furrow closing to form a tube (the urethra) in the fourth month. Meanwhile the two genital folds unite to form the scrotum.

The prepuce is formed in the fourth month. The prostate starts in the third month as a thickening of the tissues at the junction of the urethra and sexual passages, its glandular portions springing from the epithelium of the canal and extending into the surrounding fibrous tissue.

In the female embryo the genital furrows and genital folds do not unite, so that the sinus urogenitalis remains short. The genital eminence becomes the clitoris, the folds become the labia majora, the borders of the genital furrows the labia minora.

5. *Double Monsters.*

(a) Classification of Double Monsters.

§ 150. **Twin formations** lying within a single chorion may be divided into two large groups: in one group they are *entirely distinct one from the other*, in the second group *portions of the bodies are united.*

FIG. 378.—Acardiacus acephalus, showing a rudimentary development of the lower extremities (acardiacus amorphus).

In the group of **twins entirely separate** one from the other, there are again two types to be distinguished: that in which *both twins are fully developed*, and that in which *one twin is stunted.*

Twins joined together by portions of their bodies may in the same way be again divided into two groups, namely, into the *equally and the unequally developed.*

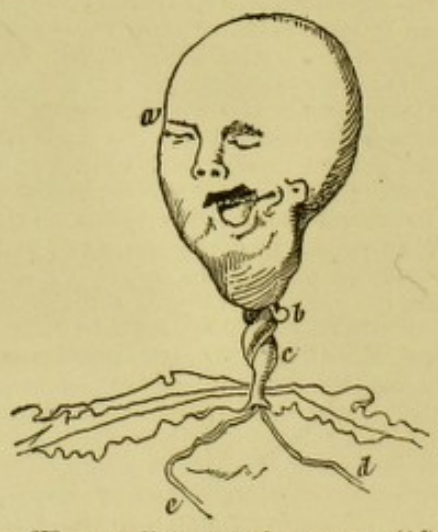


FIG. 379.—Acardiacus pseudoacormus. (After Barkow.) *a*, Head; *b*, rudiment of the left upper extremity; *c*, rudimentary intestine; *d*, artery; *e*, vein.

In reference to the situation of duplicated parts of the body one may distinguish (Foerster, Marchand):

1. Monstra duplicia katadidyma or duplicitas anterior.
2. Monstra duplicia anadidyma or duplicitas posterior.
3. Monstra duplicia anakatadidyma or duplicitas parallela.

They may further be conveniently grouped in three families (Taruffi):

FIG. 380.

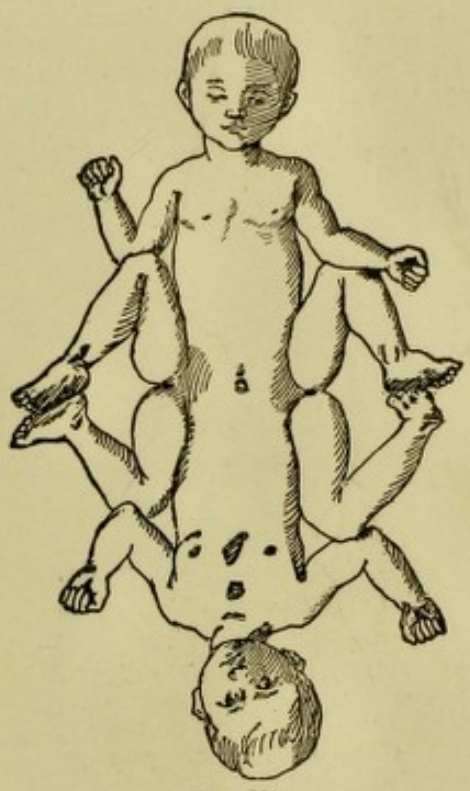


FIG. 381.

FIG. 380.—Pygopagus. (From Marchand.) A, B, The two twins; *a*, *b*, the separate umbilical cords; *c*, the two cords united into one; *d*, the common placenta. There is a single coccyx and sacrum (from the second vertebra downward), and the lower end of medullary is canal single. The two intestinal canals terminate in a single anus; while all the other sexual organs are double, there is a common vestibule for the two vaginæ.

FIG. 381.—Ischiopagus. (From Levy.)

1. Twins united mainly by the epigastrium and thorax.
2. Twins united mainly by the heads.
3. Twins united mainly by the pelves.

Ahlfeld divided double monsters into two main groups, *those with complete* and *those with partial duplication of the axial structures*.

In very rare instances **triple monsters** are found.

(b) The Chief Forms of Double Monsters.

§ 151. **Twins separated from each other** and lying within the same chorion are designated **homologous twins.** They are always of the same sex, have usually a common placenta, and resemble one another very closely. If from any cause one of the twins dies after its body has been developed, it may be pressed flat by the farther growth of its fellow. A **fœtus papyraceus** results.

When twins possess a common placenta within which the blood-vessels have abundant anastomotic connections, the heart of the stronger

twin may work the circulation alone, and thereby cause alterations in the direction of the blood stream in the weaker fœtus. The result of this is that the latter suffers grave disturbances in its development and becomes an **acardiacus**, a *monster without a heart*, and develops either no heart at all or only a rudimentary heart. In most of these cases *the head also fails to develop* (*acardiacus acephalus*) or remains *rudimentary* (*acardiacus paracephalus*), and generally there is also no development, or only in a rudimentary form, of the upper extremities, the thoracic walls and lungs and the liver; while the abdomen,

FIG. 382.—Diprosopus distomus tetrophthalmus diotus dibrachius.

FIG. 383.—Craniopagus parietalis.

pelvis, and lower extremities are more or less perfectly formed (Fig. 378). According to the development of the extremities one may distinguish the following varieties: *acardiacus paracephalus* (or *acephalus*) *sympus*, *monopus*, *dipus*, *monobrachius*, *dibrachius*.

In rarer cases there is no distinct formation of any part of the body and there results an *acardiacus amorphus*, a shapeless mass, mostly without indication of extremities, and having inside only rudiments of organs.

An *acardiacus pseudoacormus* is a very rare formation (Fig. 379). In this monster only the head (*a*) is developed, while merely small rudiments of the rest of the body are present.

§ 152. **Twins equally developed and bound together** occur in the following principal types:

1. **Duplicitas anterior** (*monstra duplicia katadidyma*), duplication of the anterior portions of the body with union of the posterior portions.

Pygopagus (Fig. 380). Union of the twins in the region of the coccyx or of the sacrum. According as the union is more or less extensive, the sacrum, coccyx, lower end of the medullary canal, anal opening, lower end of the bowel, and the sexual apparatus are duplicated or partly single.

Ischiopagus (Fig. 381). Union of the twins in the pelvis, through which it comes to form a wide ring, while the two sacra are opposite one another. The anus, the end of the bowel, and the sexual organs may be single or duplicated, and the number of the lower extremities from two to four.

Dicephalus and diprosopus (Fig. 382). This duplication is limited to the upper part of the trunk and the head, or to the neck and head alone, or, finally, only to portions of the head. As the external blending increases, there comes also a unification of the internal organs, the spinal cord, brain, etc. According to the number of the lower and upper extremities one may distinguish *dicephalus tetrapus, dipus, tetrabrachius, dibrachius.* When the heads have blended one may distinguish *diprosopus tetrophthalmus, triophthalmus, diophthalmus, tetrotus, triotus, diotus, distomus, monostomus, tribrachius, dibrachius.*

FIG. 384.—Cephalothoracopagus or syncephalus with janus head. Both anterior and posterior faces are malformed, having only one eye, and a nose resembling a proboscis situated above the eye.

FIG. 385.—Thoracopagus tribrachius tripus. The hand of the third arm, common to both halves, has two dorsal surfaces, and the laterally distorted fingers possess nails on both sides. The third foot has eight toes.

The mildest grades of duplicitas anterior are the rare cases of *duplication of the jaw* or *of the mouth* and *the nose*.

2. **Duplicitas posterior** (*monstra duplicia anadidyma*). This is a union of the twins at the head and thence farther downward, with duplication of the posterior parts of the body.

Craniopagus (Fig. 383). This is a union of the twins in the cranial part

FIG. 386.—Polymelos. (From Lancereaux.)

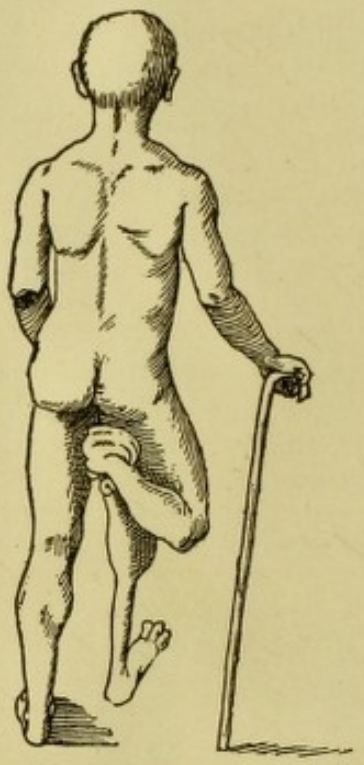


FIG. 387.—Polymelos. (From Liesching.)

of the head. According to the site of union one distinguishes *craniopagus parietalis, frontalis, occipitalis*. When union is extensive, portions of the brain are also single.

Cephalothorocopagus s. **Syncephalus** (Fig. 384). A union of the twins in the region of the forehead, face, and partly also the belly. In the region of the united heads, there is an anterior and a posterior face (*janus, janiceps*). The two faces may be equally (*janus symmetros*) or unequally (*janus asymmetros*) developed. The internal organs show varying degrees of blending and singleness.

Dipygus. Duplication is confined to the lower half of the body and the lower extremities, while the upper parts are either wholly single or only partly cleft. The duplication of the spinal cord may begin at various elevations. One may distinguish various forms based on the number of the extremities. The mildest grades of duplication are confined to the lower end of the spinal column, the anus, and the external sexual organs.

3. **Duplicitas parallela** (*monstra duplicia anakadidyma*). Duplication at the anterior and posterior ends of the body with parallel positions of the two trunks.

Thoracopagus (Fig. 385). Union of the twins by the chests. According to the seat and extent of the union, as well as according to the number of extremities present, one may distinguish various forms, as: *Xiphopagus* (union at the xiphoid process of the sternum), *sternopagus* (union at the sternum), *thoracopagus tetrabrachius, tribrachius, dibrachius, tetrapus, tripus, dipus*. If portions of the faces have melted to-

gether as well, there results a *prosopothoracopagus*. Melting together and resulting singleness of the internal organs vary along with the degree of outward blending. The heart may be double or single, in the latter case being malformed. This monstrosity is comparatively frequent.

Rachipagus. Blending of the twins in the region of the spinal column is very rare.

§ 153. **Twins joined together but unequally developed** may occur in any of the double forms described in § 152. If the development of one of the twins remains only rudimentary and no heart develops, its nourishment can come only from its developed fellow. The well-developed one is then known as the **autosite** and the rudimentary one as the **parasite.** If the parasite is only very rudimentary, it is classed with the **bigerminal teratomata** (cf. § 134).

At the *posterior end of the body* a rudimentary parasitic double monstrosity occurs in the form of *increase in the number of the extremities*, a *polymelos* (Fig. 386 and Fig. 387). The extra extremities may be one or two in number and may have undergone more or less perfect development. The malformation may be regarded as a *dipygus parasiticus*. In the coccygeal region it is not rare to find *teratomata*, in which the presence of rudimentary extremities (Fig. 388 *a*, *b*, *c*) or various body portions leaves no doubt that what presents itself to external view as a tumor, covered as it is by the skin of the autosite, is in reality to be

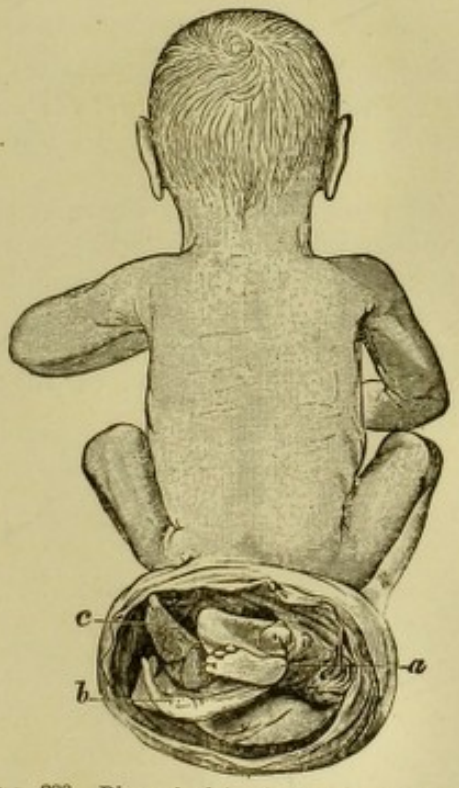


FIG. 388.—Bigerminal teratoma of the coccygeal region. (Pyopagus parasiticus.) *a*, *b*, *c*, Extremities, which are lying in a sac formed by the skin of the autosite.

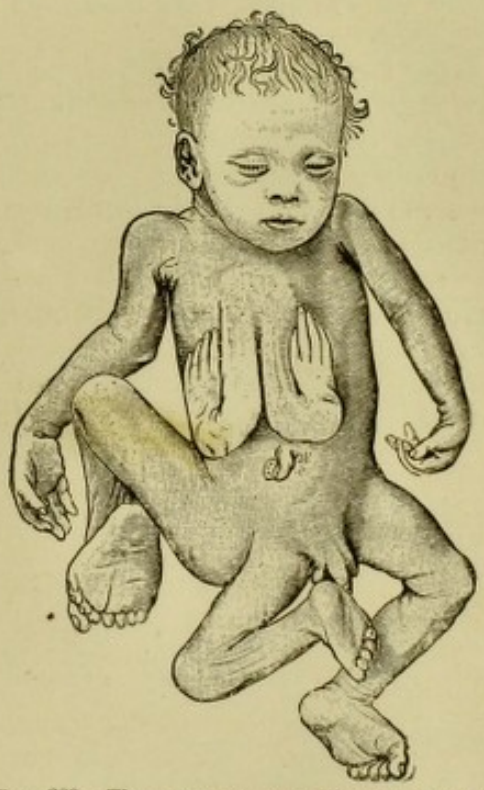


FIG. 389.—Thoracopagus parasiticus (polymelos). Three legs spring from the pelvis, and one of them has a double foot. Two upper extremities project from the anterior wall of the chest.

regarded as a double monster, a *rudimentary pygopagus* (Fig. 388) or else a *dipygus parasiticus*. The parasite is called an *epipygus*.

On the trunk, also, *extra extremities* occur (Fig. 389), or a *headless*

trunk with extremities (Fig. 390), or a *rudimentary one only, without extremities;* or, finally, *teratomata*, formations which one may regard as *thoracopagus parasiticus* and as *dipygus parasiticus*. The malformation is also often called an *epigastrius*.

Where such teratomata lie beneath the skin of the belly or chest of, or are within the abdominal or the thoracic cavity of, the autosite, the conditions are known as *inclusio fœtalis subcutanea* or *abdominalis* or *mediastinalis*. The abdominal inclusion is also called *engastrius*.

Fig. 390.

Fig. 391.

Fig. 390.—Dipygus parasiticus. (From Schenk von Graefenberg.) Parasite springs from the thorax of the autosite.

Fig. 391.—Epignathus. (After Lancereaux.)

In the *region of the head* a rudimentary twin-formation is most frequent in the mouth, being usually a formless mass, firmly adherent to the base of the skull, called an *epignathus* (Fig. 391) and composed of skin, connective tissue, cartilage, bone, brain substance, teeth, intestinal elements and muscles, rarely containing well-formed extremities.

On other parts of the head rudimentary twin-formations or bigerminal teratomata are very rare (cf. § 134).

CHAPTER IX.

Fission-fungi which Exist as Parasites and the Diseases Caused by Them.

I. General Considerations in Regard to the Schizomycetes or Fission-fungi.

1. *General Morphology and Biology of the Fission-fungi.*

§ 154. The **schizomycetes** or **fission-fungi,** also frequently called collectively **bacteria,** belong to the *protophytes*—i.e., to the very smallest, simplest plants. Many of them are so small that they stand upon the very border-line of invisibility even with the use of the strongest system of lenses. When they occur in animal tissues they are therefore often to be distinguished from disintegrated cell-products of the tissues only with the greatest trouble—i.e., only by the use of different reagents or methods of staining.

The *fission-fungi* throughout are *devoid of chlorophyll and are unicellular organisms,* but they are often found aggregated in smaller and larger colonies.

The form and character of the individual cells, as well as their growth, their division and reproduction, are different, and at present these differences are used to group the bacteria into different genera. The **cocci,** often also called micrococci, constitute the first genus of fission-fungi, and constantly occur as spherical or oval cells, and were formerly often called *sphærobacteria* (Cohn). Six forms of growth can be distinguished according to their grouping in the process of reproduction: *double cocci* or *diplococci, chain-cocci* or *streptococci, clustered cocci* or *staphylococci, tablet-formed cocci* or *merismopedia, packet-shaped cocci* or *sarcinæ,* and *tubular cocci* or *ascococci.*

The **bacilli** (rod-shaped bacteria) form the second class, which was formerly divided by Cohn into *microbacteria* and *desmobacteria,* according to the length of the rods. Hence they may also be classified as *short rods* and *long rods.* Along with the designation *bacillus* many authors employ the name *clostridium* for bacilli which assume spindle and club shapes in the formation of spores. Long threads are also often called *leptothrix.*

The **spirilla** (screw-like coiled rods) form the third genus. Screws with short, wide turns are called *spirilla,* those with drawn-out turns *vibrios,* those with a long, narrowly twisted screw, *spirochaëte.* They may also be subdivided, according to their length, into *short screws* and *long screws.*

All of the bacteria as yet referred to occur either in one single form of growth or in a very limited cycle of forms of growth, and may therefore be grouped together as **monomorphic** or **oligomorphic bacteria.**

Cohn, to whom we are indebted for the fundamental investigations of the bacteria, united under this term exclusively these oligomorphic organisms.

By many authors, however, organisms which display in their individual development a long series of forms of growth—i.e., forming spherical cells as well as rods and simple and branched threads—have also been classified as bacteria. These can be brought together in a second group—the **polymorphous bacteria**—where belong especially such fungi as *leptothrix*, *cladothrix*, *beggiatoa*, and *crenothrix*.

The fission-fungi are all made up of a plasma, or **cell-contents**, surrounded by a **cell-membrane**, both, according to Nencki, consisting for the most part of an albuminous substance, or **mycoprotein**. According to A. Fischer the contents are formed of a protoplasmic tube without a nucleus, but with a central collection of fluid. Bütschli, Schottelius, and others conceive the recognizable central bodies in the single bacteria to be nuclei. According to Nägeli, Zopf, and others, many fission-fungi possess a membrane consisting of cellulose, or at least of a carbohydrate very nearly resembling cellulose. This membrane becomes turgid under certain conditions of growth in many of the bacteria, and forms a *capsule* having a hyaline appearance.

In all forms of the bacteria except the cocci wandering **motion** has been observed, which is brought about by means of fine **flagellate threads** in lively vibration. In addition there is a slow oscillatory or a gliding and creeping motion carried on by the contractile and flexile plasma. Both forms of motion appear only under certain conditions of nutrition and growth and only in certain species.

Multiplication of the bacteria takes place by **transverse division** of the cell, which previously grows out longitudinally. In some forms division can take place in two or even in all three dimensions of space. After division the cells separate immediately or remain for a time hanging together. If they hang together after dividing according to the first method, they **form threads** (*streptococci*, *leptothrix*); according to the second method, **colonies in a plane are formed** (*merismopedia*); according to the third method, **colonies are formed in a solid body** (*sarcinæ*). Long threads can become segmented into shorter pieces.

According to the investigations of Buchner, Longard, and Riedlin, the period of reproduction—i.e., the length of time from one cell-division to the next—in the cholera-spirillum under favorable conditions of nutrition varies from fifteen to forty minutes.

If the bacteria in the period of rest aggregate into clumps in consequence of constantly progressing reproduction, or by the accumulation of neighboring cells anywhere in great masses, there are often formed glutinous colonies which are called **zoöglœa**. The jelly is formed out of the cell-membranes of the fission-fungi, and, according to Nencki, it also consists of mycoprotein. The glutinous masses can assume the most various shapes, and reach at times a considerable size, forming clumps or patches or ropes of from one to three or more centimetres in diameter.

Under certain circumstances many of the fission-fungi form **spores**. These are cells which are distinguished by the fact that they remain alive under conditions in which the ordinary vegetative forms die; and moreover, when they are put into fresh nutrient solutions, they can produce a new generation. Most frequently the *spore-formation is endogenic* —i.e., the spore arises inside of a cell, especially in bacilli, and is de-

veloped out of the protoplasm of the cell. In the latter a small granule appears, which grows out into an oblong or round, highly refractive, sharply contoured body, always remaining smaller than the mother-cell. The spore becomes free after the disintegration of the mother-cell. The formation of *arthrospores*, observed in micrococci, is said to take place by the assumption directly of the characteristics of spores by individual members of a colony or of one of the series of generations, while at the same time they either remain externally unaltered or take on other morphological peculiarities.

In old cultures the bacteria nearly always show **degeneration forms** which are swollen and distorted, and take the stain poorly and irregularly.

Babes and Ernst, by special methods of staining with Löffler's methylene blue, hæmatoxylin, and Platner's nuclear black, have found in the interior of different bacteria granules which, according to their behavior, probably bear some relation to the cell-division and to the spore-formation. Ernst designates the bodies found by him as *sporogenic granules*, since he was able to trace in some bacteria the transition of these into spores. He is inclined to attribute to them the nature of a cell-nucleus, a view assented to by Bütschli. Bunge looks upon the bodies described by Ernst as cell-granules, which have no connection with spore formation, and describes other bodies, staining with Löffler's solution, as the predecessors of the spores.

§ 155. The fission-fungi, owing to the absence of chlorophyl in them, are restricted in their **nutrition** entirely to ready-formed **organic substances** which are soluble in water and which are supplied to them in an abundance of **water.** They need, moreover, **various mineral substances,** especially sulphur, phosphorus, potassium or rubidium, or cæsium and calcium, or magnesium or barium or strontium.

They are capable of taking their necessary *carbon* from most of the carbohydrates that are soluble in water. They can derive their carbon from dilute solutions of compounds which in greater concentration are destructive, as, for example, benzoic acid, alcohol, salicylic acid, phenol, etc.

The fission-fungi derive their *nitrogen* from *albuminous matter;* they also obtain it from those compounds which are designated as *amins* (methylamin, ethylamin, propylamin), *amido-acids* (asparagin, leucin), and *amides* (oxamide, urea); and they may obtain it from the *ammonia salts*, and partly also from *nitrates.* The albuminates are changed into peptones, previous to their assimilation, by a ferment given off from the fission-fungi. Free nitrogen cannot be assimilated as such. Nitrogenous and non-nitrogenous compounds are not only assimilable as such, but also in combination. The fission-fungi can derive their nitrogen from ammonia and nitric acid only in the presence of organic carbon compounds.

According to Nägeli, *sulphur* is essential to the fission-fungi, and they take it from sulphates, sulphites, and hyposulphites. They take the other *mineral substances* enumerated above from various salts. If along with abundance of nutrient material there is too little water present, all further growth ceases; still many fission-fungi are able to dispense with water temporarily. Spores suffer very little from the effects of drying.

Some of the fission-fungi are restricted, for their nourishment, mainly or exclusively to dead organisms or to solutions of organic matter, and belong, therefore, to the **saprophytes.** Others are also able to

derive their nutrition from living animals or plants, and are therefore to be reckoned among the **parasites.**

If the fission-fungi get into water containing no nutritive material, many of them die in time. The spores resist the longest in this respect.

Free **oxygen** is necessary for the growth of many bacteria; others can dispense with it so long as they are under favorable conditions in other respects; still others develop only where oxygen is cut off. The first of these are called *obligatory aërobes*, the second *facultative anaërobes*, the third *obligatory anaërobes*.

Facultative anaërobes produce in part fermentation by their multiplication in the absence of oxygen; but, according to the investigations of Flügge and Liborius, fermentative phenomena seem also often to be absent. Pathogenic bacteria, according to Liborius, are facultative or obligatory anaërobes.

Carbon dioxide has no influence upon the development of many bacteria, as, for example, upon the typhoid-fever bacilli and upon the Friedländer pneumonia-bacilli. Upon others, on the contrary, it has an inhibitory action, as, for example, upon *Bacillus indicus*, *Proteus vulgaris*, and *Bacillus phosphorescens*, the bacilli of anthrax and of cholera, the pus-cocci, and others (C. Fränkel). The bacilli of anthrax, of cholera Asiatica, and of rabbit septicæmia die out in a few hours in artificial Seltzer water, but the spores of anthrax-bacilli keep alive indefinitely (Hochstetter).

Intense **light** has an injurious or destructive effect upon the development of many bacteria, and consequently infected water can be disinfected by light (Buchner). In *Bacillus anthracis* the virulence can be weakened by sunlight (Arnold, Gaillard). Anthrax-spores die out when exposed for a long time to light and air (Arloing, Roux). According to Geisler, the green, violet, and ultra-violet are the rays which are particularly injurious to them.

According to Nägeli, Hauser, Buchner, Zopf, and others, *different conditions of nutrition act in modifying the form and dimensions of the fission-fungi.* For example, bacilli cultivated in different nutrient solutions have different lengths as well as different thicknesses. In many varieties, moreover, it is said that, in one nutrient solution, the change is generally into spherical cells and short rods, while in another, on the contrary, it is into long threads (Zopf). Finally, the *physiological properties can also change under different modifications of nutrition.*

The **temperature** of the medium surrounding the bacteria acts generally in such a way that when there is a fall the vital processes become weaker and slower, and finally cease, whereas with elevation of the temperature they rise to a certain maximum, and at a slight excess above this suddenly cease; still higher temperatures kill the fungi. The maximum of permissible temperature lies at a different height for different fungi, and is also partially dependent upon the character of the nutrient substance.

A low temperature stops development in all. They fall into a state of numbness, but do not die even at very cold temperatures. The rigidity due to cold develops in the individual forms at different temperatures. The most favorable temperature for the *Bacillus anthracis* lies between 30° and 40° C.; at temperatures above 44° C. and below 15° C. there is cessation of development. Many bacilli form spores only at high temperatures.

Boiling water and *steam* at 100° C. kill all bacteria and bacterial

spores if allowed to act for some time. Bacteria and their spores bear higher temperatures in dry air, so that a temperature of 140° C. for three hours is necessary to kill the latter. Many bacteria are killed at a temperature of from 60° to 70° C., provided it is kept up for a very long time.

Anthrax-bacilli multiply within certain limits more and more slowly the lower the temperature is. Between 30° and 40° C. growth and spore-formation usually cease at the end of twenty-four hours. At 25° C. the time required rises to from thirty-five to forty hours. At 23° C. forty-eight to fifty hours are required for the spore-formation; at 20° C., seventy-two hours. At 18° C. spores appear at the end of five days; at 16° C., after seven days. Below 15° C. all growth and spore formation cease (Koch). Spore-formation still takes place even at 42° C.

In hot, dry air, bacilli free from spores do not withstand a temperature a little over 100° C. for an hour and a half. In hot, dry air, spores of the bacilli are destroyed at a temperature of 140° C. at the end of three hours.

Anthrax-spores die in *boiling water* in two hours, in *confined steam* in ten minutes; but the spores of the garden-earth bacillus are not killed in this time. The action of steam at 105° C. for a period of ten minutes kills all spores. *Watery vapor* in motion kills all spores in from ten to fifteen minutes, and penetrates very well into the objects to be disinfected (Koch, Gaffky, Löffler).

According to Arloing and Duclaux, anthrax-bacilli die in from twenty-four to thirty hours when exposed to the direct rays of the sun; spores in from six to eight weeks.

§ 156. If fission-fungi find themselves in a medium which suits them, their multiplication can still be brought to a standstill provided the fluid contains **substances which hinder their growth and even kill them.** This effect is produced by many substances—sublimate, lysol, carbolic acid, iodine, etc.—even in comparatively great dilution. Other substances operate injuriously upon the bacteria only when they are in stronger concentration. The point at which the multiplication is hindered is always reached at much greater dilution than that at which the bacteria are killed. Spores are much more resistant than the vegetative forms.

Many bacteria are very sensitive to acids, so that even a small degree of acidity hinders the growth. This is true, for example, of the organism of anthrax and of the Fränkel-Weichselbaum pneumococcus. But still some are able to grow with a moderate amount of acid in the nutrient fluid. As a general rule they are specially sensitive to the mineral acids, but the presence of a large amount of citric, butyric, acetic, and lactic acid also hinders the multiplication. In this connection belongs the fact that the products of decomposition caused by the fermentative action of the fungi at a certain degree of concentration are injurious to the development of the fungi, and finally stop their growth entirely. Thus in butyric-acid and lactic-acid fermentation the quantity of butyric acid and of lactic acid gradually formed may finally cause cessation of the growth of the fungus. A similar result occurs in the bacterial putrefaction of albumin, since the products, such as phenol, indol, skatol, phenyl acetic acid, phenyl propionic acid, etc., hinder the further development of the bacteria. The fission-fungi are less sensitive to alkalies, and many of them can bear a tolerably high degree of alkalinity in the nutrient fluid; but, on the other hand, there are certain forms which do not flourish in alkaline fluids—e.g., acetic-acid fungus.

Multiplication also ceases in the presence of a superabundance of nutrient material—i.e., with an **insufficent amount of water.** The fact that fruit preserved in sugar, and salted and dried flesh, do not become foul depends upon this. Food-stuffs can also be preserved by depriving them of water and by the addition of substances which are dissolved in the tissue-fluids, and in this way increase the proportion of

solid matter. The limit at which development takes place is reached at a much higher degree of humidity for the fission-fungi and yeast-fungi than for mould-fungi.

According to investigations of Pfeffer and Ali-Cohen, many motile bacteria show chemotactic properties—i.e., they are attracted or repelled by chemical substances dissolved in water. The bacteria swimming around in the fluid consequently collect together at places where there are chemical substances which attract. Typhoid-fever bacilli and cholera-spirilla, for example, are attracted by the juice of a potato (Ali-Cohen). Potassium salts, peptone, and dextrin also act by attraction, but the individual bacteria behave differently toward these substances (Pfeffer). Free acids, alkalies, and alcohol have a repulsive action.

If a nutrient fluid contains other lower fungi besides the bacteria there often takes place a **competition between the different micro-organisms,** and fission-fungi, budding fungi, and mould-fungi can crowd one another out. In a similar manner a **reciprocal crowding out occurs among the fission-fungi themselves.** Thus, for example, cocci can be supplanted and destroyed by bacilli, or one form of bacillus by another. This would happen where either the composition or the temperature of the nutrient fluid is more favorable for one or for the other, or also where one species of bacteria forms products which act injuriously upon the other, or where one form grows more rapidly than the other and in this way takes away the necessary nutrient material from the competitor.

According to the investigations made by Pasteur, Emmerich, Bouchard, Woodhead, Blagovestchensky, and others, the antagonism between many bacteria shows its influence even in inoculation experiments upon animals. By simultaneous inoculation with different bacteria it sometimes happens that the development of a pathogenic fission-fungus in the body of a susceptible animal is hindered. Thus, for example, the development of the anthrax-bacillus can be hindered by a simultaneous inoculation with erysipelas-cocci (Emmerich) or with the *Bacillus pyocyaneus* (Bouchard).

If, for example (Nägeli), fission-fungi, yeast-fungi, and mould-fungi are introduced together into a solution of sugar, the fission-fungi alone increase and cause lactic-acid fermentation. If to the same solution five per cent of tartaric acid is added, the budding fungi alone multiply and cause alcoholic fermentation. If four or five per cent of tartaric acid is added, only the vegetation of mould is obtained. The addition of the tartaric acid does not make the life of the other fungi impossible, but only favors the development of one over the other. In the same way the budding fungi alone develop in grape-juice, although other germs find their way into it, and the fission-fungi can multiply and produce acetic acid only after all the sugar is used up. Mould-fungi, which destroy the acid, can develop on the vinegar. Subsequently fission-fungi again appear and produce putrefaction.

§ 157. **The growth and multiplication of the fission-fungi always cause chemical transformations of the nutrient material,** and these are brought about in part *by the influence of the ferments* secreted by the bacteria, in part directly *through the metabolic processes* occurring within the cells themselves.

Among the *ferments* or *enzymes* are to be mentioned especially the *proteolytic* or *albumin-dissolving enzymes* (*bacterio-trypsins*), which bring about the solution of the albuminous bodies, and thereby cause the destruction of the peptone molecule. The bacteria further give rise to *diastatic ferments*, which change starch into sugar, likewise to *inverting*

ferments which transform cane-sugar (disaccharid) into grape-sugar (monosaccharid).

One of the first **chemical results of the bacterial metabolism**,—or, in other words, of the vital activity of the fission-fungi aided by their enzymes—is the breaking up of complex organic compounds. By many authors all these processes are designated as **fermentations**, while other authors (Lehmann) only speak of fermentations, when a fission-fungus breaks down a given food material with particular ease, and thereby gives rise to a special product, or, may be, several, in marked quantities, along with or in place of its other metabolic products. Other authors, still, limit the term fermentation to the destruction of the carbohydrates.

In the **decompositions caused by the fission-fungi** many widely different products are formed, which vary according to the composition of the nutrient material and the character of the fission-fungus. For fermentation to take place proper fermentable material is necessary. Many fungi can cause fermentation as well in the presence as in the absence of oxygen, while to some of them a paucity of oxygen is essential.

Among the **products of the bacteria**, which are of especial importance to the physician, are those which **act poisonously** and **cause tissue changes**, and to which belong particularly those substances which are described as *ptomaïns*, *toxins*, and *toxalbumins*.

The **ptomaïns** are basic, crystallizable, nitrogenous products of the destruction of albumin by bacteria; they are also known as the *alkaloids of putrefaction* or *cadaveric alkaloids*. When they display poisonous properties, they are classified among the **toxins**. The best known among them are sepsin, putrescin (dimethylethylendiamin), cadaverin (pentamethylendiamin), collidin (pyridin derivative), peptotoxin, neuridin, neurin, cholin, gadinin, and also substances resembling muscarin.

The **toxalbumins** are amorphous poisons, which occur in bouillon cultures of many of the bacteria. They are precipitated by the same methods that cause the precipitation of albumin, and hence are looked upon by most investigators as *albuminous bodies*. Nevertheless it is to be remarked that they are possibly, in part, bodies only carried down along with the precipitated albumin; and the proof (Brieger) that the specific poisons of tetanus and diphtheria, which have been classified among the toxalbumins, have been shown to be free from albumin argues for such a conception. It appears therefore more correct to classify these specific poisons also as **toxins**. They constitute those poisons which determine the special form of the intoxication in the various infectious diseases.

Among other decompositions worthy of note which are caused by bacteria are: the formation of lactic acid, formic acid, acetic acid, propionic acid, butyric acid, also often alcohol and carbonic acid from sugar; the formation of acids (acetic acid, butyric acid, propionic acid, valerianic acid, succinic acid, formic acid, carbonic acid) from alcohol and organic acids; the formation of indol, skatol, phenol, cresol, pyrocatechin, hydrochinon, hydroparacumaric acid, and paroxyphenylacetic acid (von Nencki, Salkowski, Brieger), and finally hydrogen sulphide, ammonia, carbonic acid, and water from albumin; the formation of ammonium carbonate from urea; the transformation of nitrous and nitric acids into free nitrogen; the reduction of nitrates to nitrites and to ammonia, etc. Finally, there are also in the soil living bacteria—

the nitrobacteria—which are able to form nitrous and nitric acids from ammonia (Winogradsky).

Along with the nitrification of nitrogen there takes place simultaneously a destruction of the earthy alkali carbonates, as shown by the fact that the nitrobacteria are able, in the absence of organic carbon compounds, to derive the carbon necessary for the building up of their cells from the *salts of carbonic acid*. There takes place, therefore, as a result of the vital activity of these organisms, a synthesis of organic material out of inorganic substances.

Under the influence of the fission-fungi there are formed *bitter, sharp, disgusting substances* that are but little known. Milk that has become bitter affords an example of this. Furthermore, fungi occasionally produce *pigments* of red, yellow, green, blue, and violet color. Thus, for example, a blood-red coating of *Bacillus prodigiosus* forms on bread (bleeding bread); moreover, bandages and pus sometimes turn blue in consequence of the presence of the *Micrococcus cyaneus*. In very many cultures a fluorescent coloring material is formed.

The *phosphorescent phenomena* to be seen not infrequently on putrefying sea-fish depend also upon bacterial products of decomposition, as proven by Pflüger, and appear where there is a lively reproduction of the bacteria.

The first investigations to establish the changes characteristic of putrefaction were made by Th. Schwann and Franz Schulze,[1] in the middle of the fifties, and upon the results of their experiments they expressed the opinion that fermentation and putrefaction depend upon the presence of very small organisms. Almost at the same time (1857) Cagnard-Latour observed the multiplication of yeast-cells in alcoholic fermentation. The observation made by Schwann was subsequently corroborated by Helmholtz. H. Schroeder and von Dusch then showed that by filtering through cotton-wool the air admitted to a fluid capable of fermentation, and also by the action of higher temperatures, the appearance of fermentation may be hindered.

Since the investigations of Schwann there have been advanced many hypotheses upon the cause of fermentation, especially upon the alcoholic fermentation caused by the yeast-fungi. Certain authorities have sought to bring these processes into immediate relationship with the life of the cells that cause the fermentation; others have sought to separate them from the latter. According to Liebig, the process is due to a molecular movement which an unformed ferment or a body in a state of chemical activity—i.e., decomposing—imparts to other bodies whose elements are not held strongly together. According to Hoppe-Seyler and Traube,[2] the cells excrete certain substances, so-called unformed ferments, which cause decomposition by contact action—i.e., merely by their presence, without taking part chemically or entering themselves into a compound.

According to Pasteur,[3] fermentation is dependent directly upon the life of the fermentative cells. It occurs only when free oxygen is lacking to the cells, so that these have to take the oxygen from the chemical compounds in the nutrient fluid. In this way the molecular balance of the latter is destroyed. According to von Nencki, also, anaërobiosis is to be regarded as the cause of the different kinds of fermentation.

According to Nägeli's *molecular-physical theory*,[4] fermentation is a transfer of molecular motion from the living protoplasm to the material undergoing fermentation. This motion is present in the molecules, groups of atoms, and atoms of all substances. The compounds forming the living protoplasm remain themselves unchanged, but by the transfer of molecular motion they destroy the equipoise in the molecules of the fermenting substance, and these become disintegrated.

According to E. and H. Buchner there can be obtained from yeast, by a pressure of 400–500 atmospheres, a cell-juice which causes fermentation in sugar solution directly. Fermentation is therefore not bound up with the life of the cells, but is caused by a cell

[1] *Poggend. Annal.*, 29 Bd., ref. in *Schmidt's Jahrb.*, 1866.

[2] Cf. Hoppe-Seyler, *Pflüger's Arch.*, 12 Bd., 1875, and "Physiol. Chemie."

[3] *Ann. de Chim. et de Phys.*, tome 58, 1860, et tome 64, 1862; *Comptes rend. de l'Acad. des Sciences*, tomes 45, 46, 47, 52, 56, 80; and Duclaux, "Ferments et Maladies," Paris, 1882.

[4] *Abhandl. d. Bayr. Akad., Math.-physik. Kl.*, iii., 76, 1879.

substance—"zymase"—which apparently is secreted by the cell, and on the surface of the latter splits the fermentable sugar into alcohol and carbonic acid.

H. Buchner is of the opinion that the specific toxins (for example of tetanus and of diphtheria) also are ingredients of the plasma of the bacilli concerned.

The power to produce fermentation—i.e, decomposition—in the nutrient fluid is very likely not only a property of fission-fungi and yeast-fungi, but also of the cells of more highly organized beings, therefore also of man. According to Voit,[1] the decomposition of the dissolved albumin circulating in the organism is attributable to a fermentative activity of the cells. Pasteur has shown that fruit and leaves possess fermentative properties under suitable conditions.

Along with fermentation and putrefaction which result from fungi, there are other decompositions of organic substances in the production of which the fungi have no part. These consist mainly in a slow oxidation or burning, in which carbon dioxide and water are formed, and, in the case of nitrogenous substances, also ammonia. This form of decomposition takes place under conditions in which atmospheric air and moisture are in contact with organic matter. Moreover, it also takes place in the living organism. In dead organic matter this answers partially to the process usually called *mouldering*.

2. *General Considerations concerning the Pathogenic Fission-fungi and their Behavior in the Human Organism.*

§ 158. As has been already explained in §§ 12, 13, and 14, there are among the fission-fungi numerous species which are capable of producing disease processes in the human organism, and they are therefore called **pathogenic fission-fungi.** The first condition of such action is evidently that the bacteria concerned must possess properties enabling them to multiply in the tissues of the living human body. They must

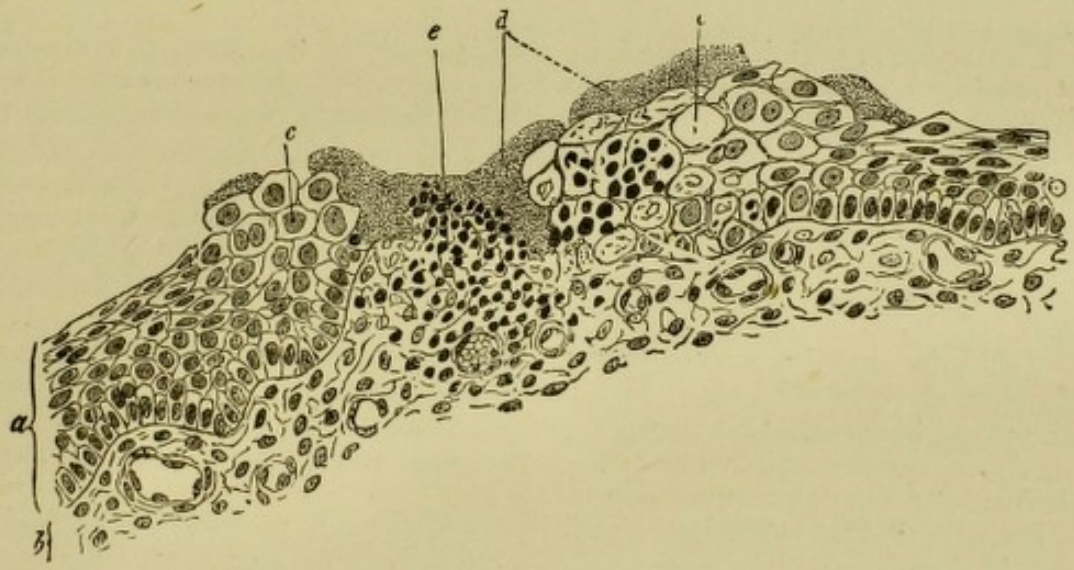


FIG. 392.—Section through a vocal cord of a child with streptococcus colonies upon and in the epithelium. *a*, Epithelium; *b*, connective tissue of the mucous membrane; *c*, swollen, degenerated epithelium, in part devoid of nuclei; *d*, layer of cocci; *e*, reactive small-cell infiltration, partly inside the degenerated epithelium, partly in the connective tissue. Magnified 200 diameters.

consequently find in the tissues the suitable nutrient material, and in the body-temperature the warmth necessary to their growth. The tissues, moreover, must not contain substances which are a hindrance to their growth (cf. §§ 29 and 30).

If pathogenic fission-fungi succeed in growing in the tissues of the body—i.e., if **infection** takes place (cf. § 14)—their action is in general characterized, at the point of multiplication, by *degeneration* (Fig. 392,

[1] "Physiologie des Sauerstoffwechsels," Leipsic, 1881.

d), *necrosis*, *inflammation* (*e*), and *new growth of tissue*, while the *toxins* produced by them *cause manifestations of poisoning*.

But in individual cases the disease process assumes different forms, in that the distribution of the bacteria in the organism and their local action, as well as the production of poisons, differ greatly with the different forms of bacteria.

With many of them the *local action* upon the tissues comes to the front; with others the *general intoxication*. Many bacteria *confine themselves to the region in which they have found entrance; others advance uninterruptedly into the surrounding neighborhood;* still others are carried by the lymph- and blood-currents and lead to the formation of *metastatic foci;* and finally, still others *increase in the blood*.

If a spread of the bacteria takes place through the blood, the *bacteria may go from the mother to the fœtus* during pregnancy, since the placenta forms no certain filter against pathogenic bacteria. This has been proved, for example, for anthrax-bacilli, for the bacilli of symptomatic anthrax, for the bacilli of glanders, for the spirilla of relapsing fever, for the bacilli of typhoid, and for the pneumococcus. According to certain observations of Malvoz, Birch-Hirschfeld, and Latis, changes in the placenta, such as hemorrhages, loss of epithelium, alterations of the vessel-walls, favor the transmigration of the bacteria. Bacteria—as, for example, anthrax-bacilli—can grow through the tissues. The passing over of bacteria from the mother to the fœtus presupposes, as a rule, that after the entrance of these organisms into the circulating blood of the mother, the latter shall remain alive at least long enough to allow of the transmigration.

The *bacteria* which succeed in multiplying in the human body *die out again, in many cases, in a short time*, and the diseases caused by them proceed to *recovery* (cf. § 28). Nevertheless it also not infrequently happens that *they are preserved for a long time in the body*, and either continuously *cause disease processes*, or, on the other hand, remain in a state of inactivity, so that no disease processes of any kind are recognizable *till, after a shorter or longer period of latency, a lively multiplication takes place*, and along with it *new manifestations of disease show themselves*.

Not infrequently a **secondary infection** associates itself with an infection already existing. The relation between the two infections is either that the second occurred accidentally after the first became established, or, on the other hand, that the way was prepared by the first infection for the subsequent one (cf. § 14).

Finally, **double infection**, in which two or even more forms of bacteria come to development in the tissues simultaneously and exert their destructive influence upon them, is not an infrequent occurrence.

§ 159. Each pathogenic fission-fungus has a **specific action** upon the tissues of the human body; but, nevertheless, *different species of fission-fungi may exert similar action*. Thus, for example, various bacteria can cause suppuration. Consequently it is only in a certain proportion of cases that the morbid changes in the tissues are so characteristic that the species of the pathogenic fission-fungus can be recognized with certainty.

It has been demonstrated, moreover, that **the pathogenic properties of the bacteria are not entirely constant**; that, on the contrary, their virulence varies, so that bacteria that cause severe or fatal infection may

become changed through external circumstances; that is to say, may become weakened so that they either lose entirely the power to produce processes of disease in the organism, or at least can cause only mild forms of disease. This peculiarity is not alone of theoretical interest, but is also of high practical interest. It explains, on the one hand, to a certain extent, why a certain infection does not always run the same course, and, moreover, why alongside of severe attacks light ones also occur. On the other hand, it affords us the possibility of obtaining *material for inoculation* from attenuated cultures of bacteria, by means of which slight degrees of infection and also slight degrees of intoxication can be produced, which protect the organism from severe infection, or cure an infection that has already taken place (cf. § 30).

Attenuation of the pathogenic properties of a fission-fungus can be effected by allowing higher temperatures, oxygen or light, or chemical antiseptic substances to act in a suitable manner upon the cultures as well as by cultivating the fungus in the body of animals possessing little susceptibility. In some forms, as in the diplococcus of pneumonia, it is only necessary to cultivate the bacteria in question upon artificial media to bring about attenuation; in others, such as the bacillus of chicken-cholera, prolonged exposure of the culture to the air suffices to bring about an attenuation. If it is desired to preserve the virulence of the pneumococci for a long time, it is necessary, from time to time, to inoculate the bacteria cultivated upon artificial media into rabbits, which are very susceptible animals. The glanders-bacilli and tubercle-bacilli and cholera-spirilla lose virulence if cultivated for a long time uninterruptedly upon artificial nutrient media. The streptococcus of erysipelas becomes so attenuated by continued cultivation in bouillon or nutrient jelly that it is no longer capable of killing even mice (Emmerich).

It is possible to make only hypotheses in regard to the explanation of the nature of the attenuation of virulence of the bacteria by the methods above mentioned. If the bacteria cultivated for a long time upon artificial media change in virulence, perhaps this can be partially explained by assuming that in a series of generations the less virulent varieties, which certainly must often appear, gradually win the superiority. In the attenuation of virulence by heat, chemical reagents, etc., however, this explanation is not permissible. In this case it turns very likely upon a general weakening, a degeneration of the protoplasm. This assumption is in accord with the fact that such bacteria show a diminution in energy of growth.

According to the investigations of Pasteur and of Koch, the virulence of anthrax-bacilli may be so attenuated by cultivation at 43° C. for about six days, or at 42° C. for about thirty days, that guinea-pigs are no longer killed by the inoculation.

A considerable attenuation of the anthrax-bacillus is obtained even by ten minutes' heating at 55° C. (Toussaint), or by heating at 52° C. for fifteen minutes, or at 50° C. for twenty minutes (Chauveau); moreover, the same result is also obtained by the action of oxygen at high pressure (Chauveau). The bacilli weakened by the influence of high temperature for a short time regain their virulence very quickly by recultivation; the bacilli, on the contrary, which have been weakened at lower temperatures remain attenuated through numerous generations. Spores of the bacillus of blackleg are rendered harmless by a temperature of 85° C. in six hours (Arloing, Thomas, Cornevin) without suffering any diminution in their power of reproduction. Moreover, the bacilli can be weakened without killing them by weak solutions of sublimate, thymol, eucalyptus-oil, nitrate of silver, etc.

The addition of carbolic acid in the proportion of 1 : 600 to the culture-fluid permits of the development of anthrax-bacilli, but destroys their virulence in twenty-nine days (Chamberland, Roux). In the same way attenuation is obtained by addition of bichro-

mate of potash (from 1 : 2000 to 1 : 5000). Carbolic acid added in the proportion of 1 : 800 prevents at the same time the formation of spores.

The poison of rabies, which kills rabbits in a short time on inoculation, may be attenuated by drying at temperatures of from 22° to 26° C. (Pasteur). According to Protopopoff, it is mainly the higher temperature which produces the attenuation.

If the bacilli of swine-erysipelas (Pasteur) are inoculated continuously into pigeons the virulence is so increased that not only pigeons die more quickly from the inoculation than at the beginning, but also hogs. But when, on the contrary, the swine-erysipelas bacilli are inoculated from rabbit to rabbit, they increase in virulence for rabbits, it is true, but lose in toxic power for swine.

3. *General Considerations in Regard to the Examination of Fission-fungi.*

§ 160. If bacteria are suspected in any tissue-fluid or in the parenchyma it is first sought to discover them by microscopic examination. Occasionally this succeeds by merely looking at a drop of the fluid or of a smear-preparation of the tissue-juice diluted with salt-solution or distilled water. In other cases it is necessary to apply coloring. In this case the fluid above mentioned is smeared on a cover-glass and allowed to dry. In order to fix the dried substance the cover-glass is then heated over a flame, allowed to cool, and stained. For this purpose methylene blue is used by preference, the solution consisting of a one-per-cent solution of the dye in a 1 : 10,000 solution of caustic potash. Aqueous solutions of fuchsin and methyl violet are also frequently used. For many bacteria special methods are also in use. In these methods the preparations are strongly overstained with a solution of gentian violet, or aniline-water fuchsin, or aqueous methyl violet, and the color is subsequently removed with weak acids or with iodine and alcohol (Gram's method). In this way it is often brought about that only the bacteria remain stained, sometimes even certain bacteria only.

If it is desired to show the presence of bacteria in tissues, the latter are cut in small pieces, hardened in absolute alcohol, then cut in thinnest possible sections, and stained by appropriate methods. Here again the staining, as above mentioned, with gentian violet, methyl violet, and fuchsin is especially often employed. Good object-glasses are necessary for the microscopic examination; if possible, oil-immersion lenses and illumination with substage condenser are to be employed.

If it has been possible to demonstrate the presence of bacteria in the tissues in any way, the attempt is next made to cultivate them. For this purpose the methods developed by Koch are generally employed. These, in principle, consist in distributing the fluid containing the bacteria uniformly in a solution of gelatin or agar previously warmed, and pouring out some of the mixture upon horizontal glass plates. The fluid containing the bacteria is obtained either by scraping the tissue or by rubbing up pieces of tissue in sterilized salt-solution. The gelatin and agar solutions are liquid at higher temperatures and solid at lower. When the solutions become solidified the individual bacteria or spores become developed at points separated from one another.

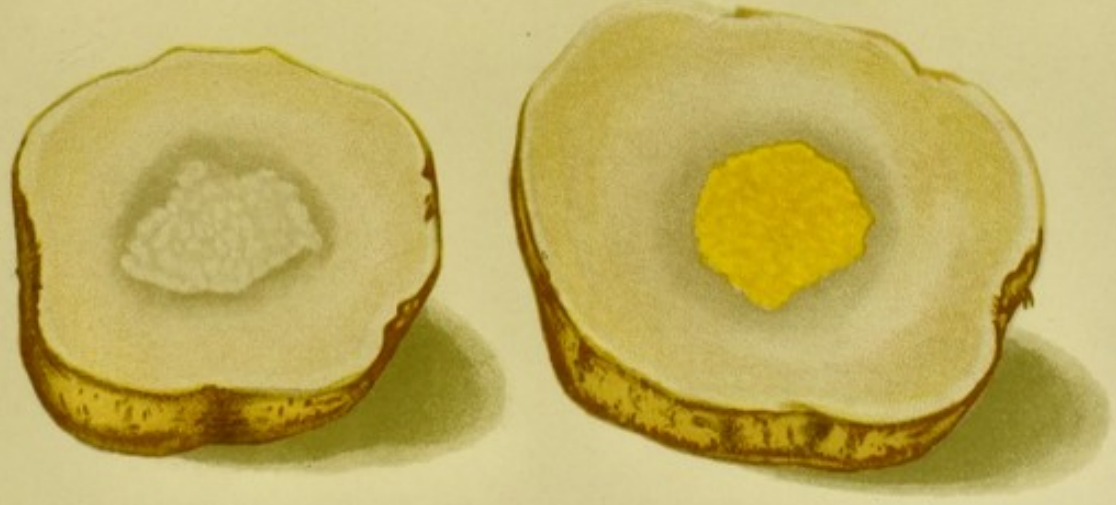
By a proper application of the method various colonies are subsequently obtained in the layer of gelatin spread out on the plate (Fig. 393). The colonies often differ from one another in appearance, even when examined with the naked eye. If the colonies are sufficiently separated from one another a small amount is to be taken from the individual colonies by means of a fine platinum needle, and transferred to a boiled potato (Plate I., Figs. 5 and 6), or to a gelatin plate free from bacteria,

1. Stab-culture of **Staphylococcus Pyogenes Aureus** in Agar-Agar.

2. Stab-culture of **Bacilli of Swine Erysipelas** in gelatine.

3. Stab-culture of **Cholera Spirilla** in gelatine.

4. Culture of **Tubercle Bacilli** upon coagulated blood-serum (after Koch).



5. Culture of **Anthrax Bacilli** upon a boiled potato.

6. Culture of **Staphylococcus Pyogenes Citreus** upon a boiled potato.

or upon the surface of the solidified nutrient fluid in a test-tube (Plate I., Fig. 4). Very often the infected needle is stuck into the solidified transparent medium contained in a test-tube (Plate I., Figs. 1–3).

If the culture on the gelatin plate is pure, and the whole procedure is carried out with the necessary care and avoidance of contamination, pure cultures are obtained by the above method. In stab-cultures (Plate I., Figs. 1–3) as well as in smear-cultures on potatoes (Figs. 5 and 6) and on any other nutrient medium (Fig. 4), often special peculiarities show themselves which make it possible for the practised observer to recognize the form of bacteria. Still it will occasionally happen that a thorough microscopic examination of the colonies will also have to be made.

It goes without saying that all the above manipulations must be carried out with care, and that care must be had for the absolute cleanliness of the instruments that come into use—of the glass plates and test-tubes,—and that the nutrient media must be free from bacteria. Suit-

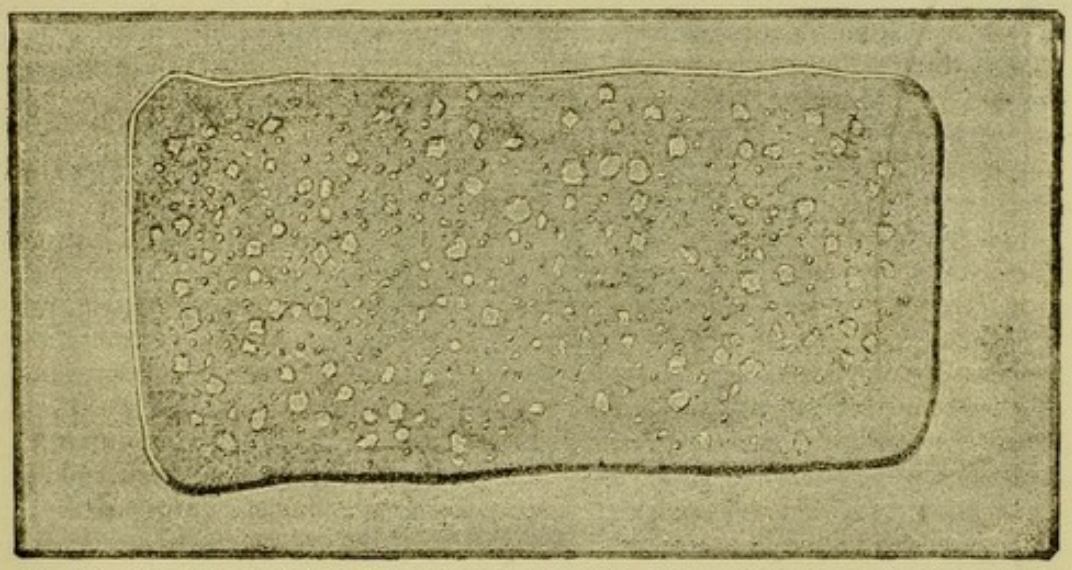


FIG. 333.—Gelatin plate containing colonies of small bacilli. These colonies are pellicle-like, with somewhat sinuous margins. Also small, round white colonies of cocci are present. Obtained from the exudate of a purulent peritonitus. (Diminished by one-third.)

able procedures are easiest learned in laboratories specially arranged for the purpose. The long-continued heating of the instruments used or their subjection to high temperatures plays an important rôle. The necessary guidance is furnished in the various books on bacteriological methods of examination which have appeared recently.

Infusion of meat containing peptone and gelatin is most usually employed for making plates. This consists of a watery infusion of chopped meat, to which a definite amount of peptone and salt is added. This is, moreover, neutralized with carbonate of soda, and enough gelatin added to give a solid consistence at ordinary temperatures. For stroke- and stab-cultures sometimes this same gelatin is used (Plate I., Figs. 2 and 3), sometimes a jelly made of a mixture of watery extract of meat, peptone, and agar-agar (Plate I., Fig. 1), sometimes blood-serum that has been brought to coagulation by warming (Fig. 4).

For stab-cultures the jelly is allowed to solidify with the test-tube in a perpendicular position (Fig. 3), for stroke-cultures in an oblique position (Fig. 4).

Sterilized bouillon is often used for cultures. The inoculated nutrient media are kept either at room-temperature or at higher temperatures of from 30° to 40° C. in an incubating-oven. The latter, however, is possible only with agar-agar, blood-serum, and potatoes, as the gelatin that is used becomes fluid at the temperature of the incubating-oven.

It goes without saying that the process just briefly described can be modified according to the exigencies of the case. Thus, for example, in cases in which the bacteria grow only at high temperatures it is necessary to use agar-agar plates and to do away with gelatin. Occasionally exudates formed on the mucous membranes (diphtheria) or small pieces of tissue which have been excised are introduced directly into the nutrient solution. If it is desired to examine the cultures directly under the microscope, hanging-drop cultures are made. For many bacteria—for example, for cholera-spirilla—the use of cultures in hanging drops is to be recommended. In this method a drop of sterilized bouillon hangs down from the under surface of a cover-glass and is inoculated from a previously purified culture of a fission-fungus. After this the cover-glass is laid over the excavation in a hollow-ground slide. If evaporation of the drop is avoided by closing off the external air from the cavity in the slide—which may be effected by sticking on the cover-glass with oil or vaseline—the multiplication of the bacteria can be directly observed for a long time.

If the bacteria are sought in water a small amount of the water is distributed in gelatin and plate-cultures are made. Earth may be rubbed up in sterilized salt-solution. Air is made to pass in definite amount through sterilized salt-solution, and the salt-solution infected in this way is then mixed with gelatin, and from this gelatin plates are made.

The culture of the bacteria on different media, accompanied by the microscopic examination of the different stages of development, serves for a more precise characterization, and at the same time also for the determination of the species of fission-fungus in question. After its peculiarities have been sufficiently studied in this way its development in the animal body is tested. As experimental animals those most usually employed are rabbits, dogs, guinea-pigs, rats, mice, and small birds. Bacteria to be tested are introduced sometimes under the skin, sometimes directly into the blood-current, sometimes by inoculation into the inner organs, sometimes by inhalation into the lungs, sometimes by administration with the food into the intestinal tract. The fungus can be regarded as pathogenic for the animal in question if it multiplies in the tissues of the latter and produces morbid conditions. If relatively large amounts are inoculated the experimental animal may, under certain conditions, die, even if the bacteria do not increase at all in its body; for the poisonous substances ready-formed in the culture and introduced by inoculation often suffice to kill the animal.

Experience has taught that only some of the bacterial infections which occur in man, if transmitted to animals by inoculation, run the same course as in man; that is to say, only those which also occur otherwise in animals. In other cases the pathogenic fission-fungi which occur in man or certain animals are, it is true, pathogenic for the experimental animals, but the morbid process shows a different localization and a different course. In still a third case the experimental animals are partially or completely immune.

Inversely, fission-fungi that are extremely pathogenic for the experimental animals are often innocuous for other animals and for man.

II. The Different Forms of Fission-fungi and the Infectious Diseases Caused by Them.

1. *The Cocci, or the Sphærobacteria, and the Morbid Processes Caused by Them.*

(a) *General Remarks upon the Cocci.*

§ 161. The **cocci** or **coccacei** (Zopf) are bacteria that always occur exclusively in the form of round or oval or lancet-shaped cells. In their multiplication by division they often form peculiar aggregations of cells hanging together, and it is customary to designate these by special names, according to the character of the different forms that appear. Since certain forms of cocci are specially apt to develop in definitely shaped aggregations, many authors have found in this circumstance a reason for making corresponding **varieties.** It is nevertheless to be noted that a given species does not always give rise to the same forms of growth, but may show variations called forth by the surrounding nutrient conditions.

Many of the cocci multiply by division in one plane only, viz., at right angles to the length of the elongated spherical cell.

FIG. 394.

FIG. 395.

FIG. 396.

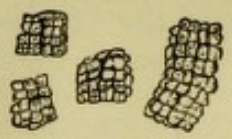


FIG. 397.

FIG. 394.—Streptococcus from a purulent peritoneal exudate of puerperal peritonitis. *a*, Separate cocci; *b*, diplococci; *c*, streptococci. Magnified 500 diameters.

FIG. 395.—Micrococcus colonies in a blood-capillary of the liver, as the cause of metastatic abscess-formation in pyæmic infection. Necrosis of the liver-cells. Magnified 400 diameters.

FIG. 396.—Cocci grouped in tetrads (merismopedia), from a softening infarction of the lung. Magnified 500 diameters.

FIG. 397.—Sarcina ventriculi. Magnified 400 diameters.

If in this case the spheres resulting by division remain together for some time in the form of double spheres, and if this form appears with especial frequency, they are called **diplococci** (Fig. 394, *b*). If, from a further continued division of the cells in one plane, rows of cocci (*torula-chains*) result, they are called **streptococci** (Fig. 394, *c*); and this term is used also as the name of a group. If the division of the cells takes place irregularly and the cells remain together thereafter, then the bacteria are generally known as **micrococci** (Zopf) or *heaped-cocci* (Fig. 395). By Ogston and Rosenbach the name **staphylococcus** or *grape-cocci* has been brought into use to indicate some of these forms. Larger collections of cells, which are held together by a gelatinous substance derived from the cell membranes, have been designated as *zoöglœa masses*. If the masses of cocci are united into larger collections by a gelatinous

envelope, then they are spoken of also as *ascococci* or *tubular collections of cocci* (Schlauchkokken).

Zopf introduced the name **merismopedia**, or *tablet-cocci*, for cocci which remain for a long time united in a four-celled tablet (Fig. 396). Others regard such bacteria as micrococci. The cocci that go by the name **sarcinæ** are characterized by dividing in three directions of space, so that compound cubical packets (Fig. 397) of round cells are formed from tetrads.

The cocci not infrequently show a tremulous molecular motion in fluids. Independent motion has not been observed with certainty. Spore-formation has not been observed in most of them. According to Cienkowski, van Tieghem, and Zopf, the *Coccus mesenterioides* (leuconostoc), that makes a frog-spawn-like coating on sugar or parsnips, forms arthrogenic spores. When this is about to occur some particular cell in a torula-chain becomes somewhat larger and glistening. According to Prazmowsky, *Micrococcus ureæ* also forms spores.

The **saprophytic cocci** grow upon very different nutrient substrata, and cause by their growth in suitable media various processes of decomposition. Many of them also produce pigment. *Micrococcus ureæ* (Pasteur, van Tieghem, Leube) causes fermentative processes in urine, and in consequence of these carbonate of ammonia is formed out of urea. *Micrococcus viscosus* is the cause of the slimy fermentation of wine. The cause of the *glow seen in foul meat* was found by Pflüger to be due to a micrococcus that forms slimy coatings on the surface of the meat.

Among the pigment-producers the best known are the *Micrococcus luteus*, the *Micrococcus aurantiacus*, the *Sarcina lutea*, the *Micrococcus cyaneus*, and the *Micrococcus violaceus*, which produce yellow, blue, and violet pigment respectively when grown on boiled eggs or potatoes.

Saprophytic cocci are found as well in the cavity of the mouth and in the intestines as on the surface of the skin, and occur occasionally also in the lungs. *Micrococcus hæmatodes* (Babes) is said to be the cause of red sweat, and produces red-colored zoöglœa masses.

Sarcina ventriculi (Fig. 397) occurs not infrequently in the stomach of man and animals, especially when abnormal fermentations are going on. According to Falkenheim, the stomach sarcina can be cultivated upon gelatin, forming round yellow colonies which show colorless spherical monococci, diplococci, and tetrads, but never contain cubical packets. They form these, however, in neutralized hay-infusion, and their growth causes the souring of the infusion. The membrane of the sarcina is said to consist of cellulose.

Micrococcus tetragenus (*merismopedia*) is often found in human sputum and consequently also in the mouth and throat; it is also found in the walls of tuberculous cavities or in hemorrhagic softening foci in the lungs, and forms tetrads (Fig. 396) in multiplying, the cells of which are held together by a slimy membrane. On gelatin it forms round or oval lemon-yellow colonies. It is pathogenic for white mice, developing in their blood. Gray house-mice are almost immune.

The **pathogenic cocci** cause acute inflammatory diseases, which for the most part go on to recovery after the destruction of the bacteria; but it not infrequently happens that the cocci maintain themselves for a long time in the body and give rise to chronic troubles.

(b) Pathogenic Cocci.

§ 162. **The streptococcus pyogenes** (Rosenbach) is a coccus which, in multiplying, forms *double spheres* and *chains of spheres* of different lengths, containing from four to twelve or more cells. This chain formation comes to an especially full development when the streptococcus is growing in fluids—in nutrient bouillon or fluid exudates,—yet it is also generally to be observed when these organisms are developing within the tissues.

The cocci stain very well by Gram's method, are facultative anaërobes, grow best at 37° C., and form small whitish colonies on gelatin and agar.

The streptococcus pyogenes is especially pathogenic for mice and rabbits (much less so for dogs and rats), but its virulence varies very much, and disappears rapidly from cultures on the ordinary nutrient

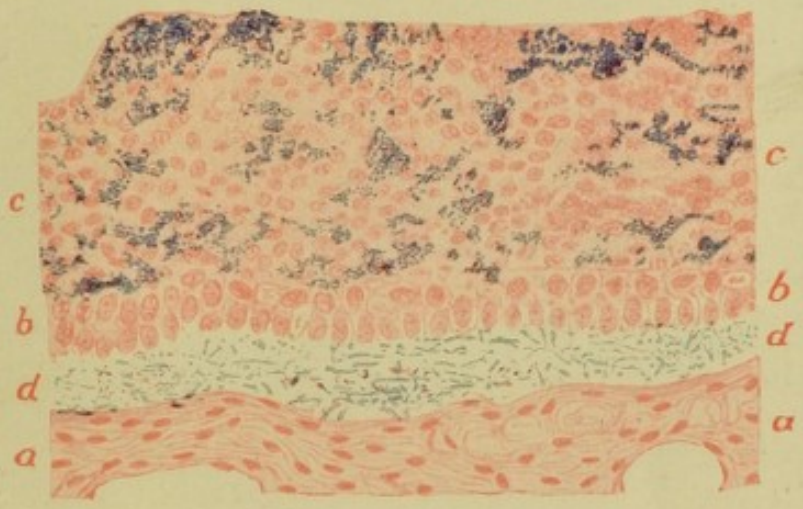


FIG. 398.—Streptococcus tracheitis in scarlet fever. (Alcohol; carmine; methyl violet; iodine.) *a*, Connective tissue; *b*, detached epithelium; *c*, membrane composed of cells and streptococci; *d*, fibrin threads. Magnified 300 diameters.

media. Virulence is retained for a relatively long time by cultures of the cocci in human serum or horse serum (serum two parts, and bouillon one part), or in a mixture of bouillon and ascitic fluid (Marmorek).

The *streptococcus pyogenes causes in man inflammations* which for the most part, but not always, assume a **purulent character.** Occasionally it is found also on the sound mucous membranes, for example, in the upper air-passages, or in the vagina and cervix uteri; and from this fact it is supposed that either its virulence is very slight, or that the mucous membranes offer a successful resistance to its entrance into their tissues.

An **infection with streptococci** occurs either in sound individuals, or in those who have received some injury, or finally as an accompaniment and consequence of other infections, such especially as scarlet fever, diphtheria, and pulmonary tuberculosis.

If it multiplies on the surface of the mucous membranes—for example, of the air-passages (Fig. 398)—it causes *inflammations* which may assume the character of a *desquamative* or *purulent catarrh* (*c*), or that of a process accompanied by *croupous exudations* (*d*). If it penetrates into the connective tissue of the submucosa, it causes most fre-

quently inflammations, which assume the character of a *phlegmon*, i.e., a more or less quickly spreading, sero-purulent, or purulent, or fibrino-

FIG. 399.—*Streptococcus pyogenes* from a phlegmonous inflammatory focus of the stomach. *a*, Leucocytes; *b*, leucocytes with streptococci inside; *c*, free streptococci. (Alcohol; Gram's method.) Magnified 500 diameters.

purulent, or sero-fibrinous inflammation, which may at certain points lead to suppuration and to abscess-formation. In the exudate the cocci in part lie free (Fig. 399, *c*), in part they are inclosed within the cells (*b*).

When the streptococcus spreads in the *corium*, into which it penetrates when there is a small wound of the skin, it utilizes the lymph-spaces and lymph-vessels (Fig. 400, *a*, and 401 *h*, *i*) as pathways and breeding-places, and causes a more or less severe inflammation, which may be recognized macroscopically by an advancing reddening and swelling of the skin, which is known as *erysipelas*. These external symptoms correspond to more or less severe serous and cellular infiltrations (Fig. 400, *d*, *e*, *f*, and Fig. 401, *m*), and often, also, to a cellulo-fibrinous exudation (m_1). In cases of severe infection with more highly virulent streptococci, the process can go on to liquefaction of the epithelium (Fig. 401, *e*, *f*, *g*, g_1), and to the formation of vesicles (Fig. 401, *c*; erysipelas bullosum), or even to necrosis and gangrene of the corium (Fig. 401, $l\,l_1$; erysipelas gangrænosum) and to suppurations of the tissue.

The spread and multiplication of the cocci in the *subcutaneous tissue* give rise to a spreading sero-purulent and fibrino-purulent inflammation, often with subsequent suppuration of the tissue. These forms of infection are designated as *phlegmons*.

In the *muscles* the streptococci select principally the connective tissue of the perimysium internum (Fig. 402, *a*) as the place in which they

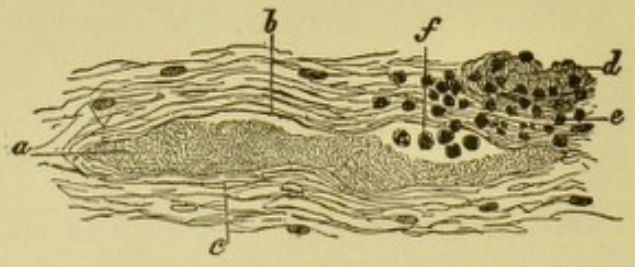


FIG. 400.—Colonies of *streptococcus erysipelatis*: *a*, in a lymph-vessel; *b*, in part composed of thickly packed spheres, in part of torula-chains; *c*, neighborhood of the lymph-vessel, with pale unstainable nuclei; *d*, vein; *e*, perivenous cellular infiltration of tissue; *f*, accumulation of cells in the lymph-vessel. Section of rabbit's ear two days after inoculation with erysipelas-cocci. (Alcohol; gentian violet.) Magnified 250 diameters.

multiply and spread, but they also penetrate into the sarcolemma tubes (*d*). Here also the consequences of infection are more or less severe inflammations, often going on to suppuration.

Infection of the *serous membranes* is followed by a sero-purulent or

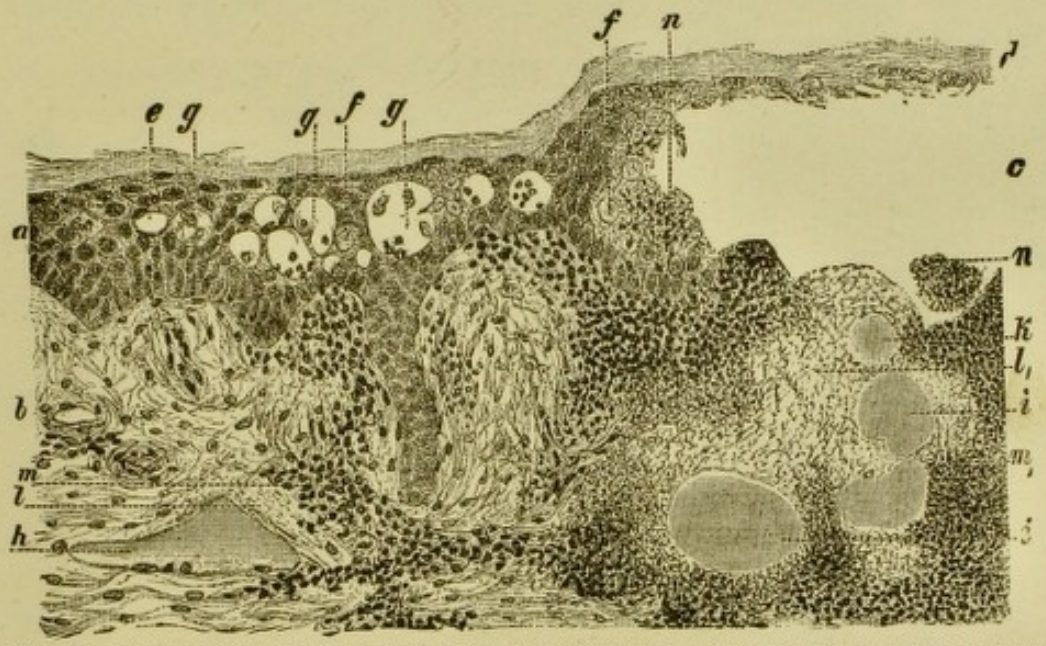


FIG. 401.—Section of the skin from a case of erysipelas bullosum. *a*, Epidermis; *b*, corium; *c*, bladder-like cavity; *d*, cover of this cavity; *e*, epithelial cell with vacuole; *f*, swollen cell with swollen nucleus; *g*, g_1, cavity caused by the melting down of epithelial cells, and containing fragments of the same and pus-corpuscles; *h*, lymph-vessel partially filled with streptococci; *i*, lymph-vessels completely filled with streptococci; *k*, colony of streptococci located in the midst of the tissues; *l*, l_1, necrotic tissue; *m*, cellular, m_1, fibrinocellular infiltration of the tissues; *n*, fibrinocellular exudation in the bladder-like cavity. (Alcohol; alum carmine.) Magnified 60 diameters.

fibrino-purulent exudation, during which the streptococci usually multiply abundantly in the free exudate.

Infection of the lungs causes the formation of purulent or croupous exudations in the lung alveoli.

The streptococcus infection may sooner or later cease, because the

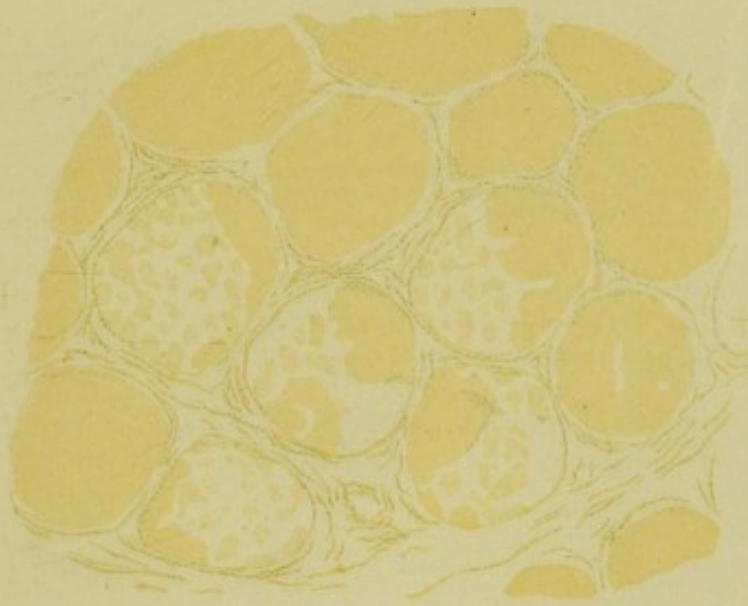


FIG. 402.—Pectoral muscle beset with large numbers of the *streptococcus pyogenes*, from a case of phlegmonous inflammation of the subcutaneous and intermuscular connective tissue, due to cadaveric poisoning. (The phlegmon of the wall of the chest developed two days after the finger was injured, and the intermediate lymph-vessels of the arm showed no evidences of being involved.) *a*, Perimysium internum full of streptococci; *b*, transversely cut muscular fibres, still intact; *c*, transversely cut muscular fibres which are beginning to degenerate; *d*, muscular fibres into which the cocci have penetrated. (Alcohol; gentian violet; vesuvin.) Magnified 350 diameters.

opposing forces of the organism limit the further spreading of the bacteria and destroy them. Often, however, the infection continues to spread until death occurs.

If the streptococci break into the lymph- and blood-vessels, *metastases* are often formed, and distant organs also become involved. In infection of the blood, an increase of the bacteria does not take place in the circulating blood, but occurs at points where they are brought to rest—as, for example, in the small vessels of the lung, of the heart, of the liver, of the kidneys, of the spleen, of the brain membranes, of the bone-marrow, of the joints, etc., or even on the valves of the heart. At the spot where the multiplication of the cocci takes place, an inflamma-

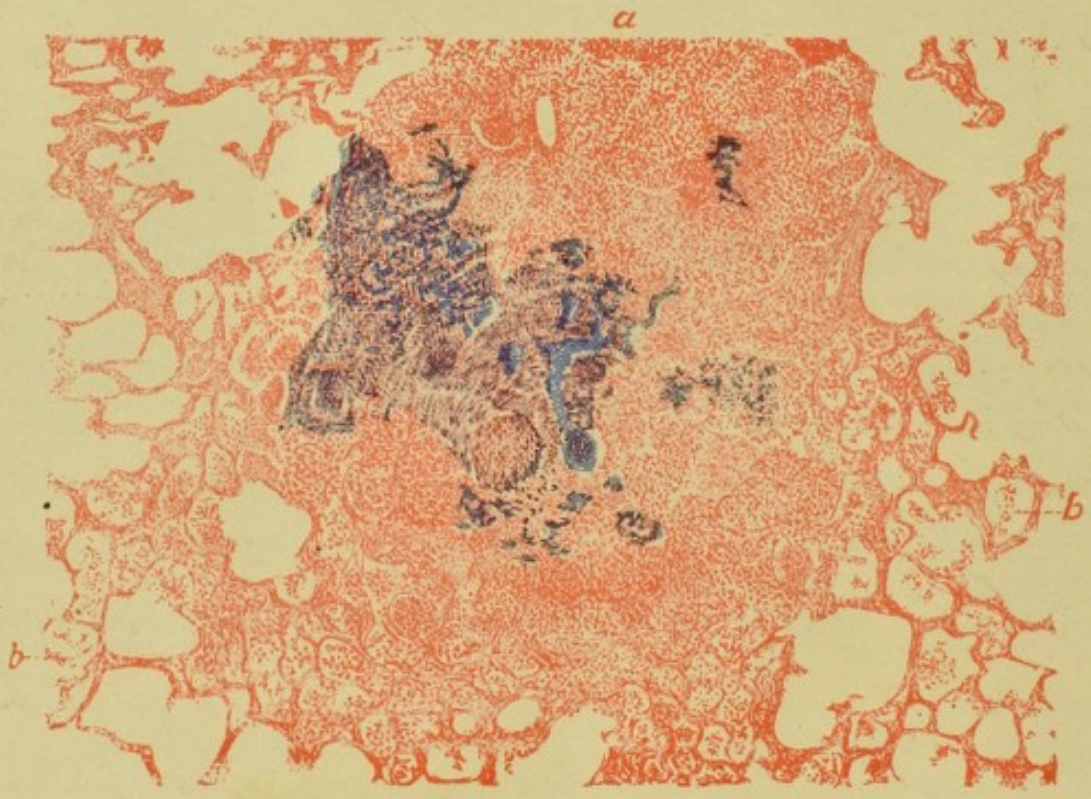


FIG. 403.—Metastatic hæmatogenous streptococcus-pneumonia following angina. (Alcohol; alum carmine; methyl violet; iodine.) *a*, Pneumonia area with streptococci (blue); *b*, inflamed lung-tissue surrounding the area. Magnified 80 diameters.

tion again develops, and it assumes the same characters in general as those manifested by the primary inflammation. The new inflammation, however, often appears less severe in character and may be more circumscribed.

A *hæmatogenous streptococcus-infection of the lung* leads to the formation of areas of inflammation (Fig. 403, *a*) which for the most part suppurate in the centre. In the *kidneys*, in the vessels of which a very extraordinary increase of the streptococci takes place, tissue-necrosis and suppuration likewise occur; and similar phenomena may also be recognized in other organs.

The *danger of a streptococcus infection* depends partly upon the *severe progressive local disease* of the tissue, partly upon the *intoxication, by means of toxins* (toxalbumins), which accompanies the local disease, and finds expression in the fever and severe systemic symptoms. If the symptoms of intoxication come strongly to the fore in the disease pic-

ture, then the infection is known as *septic intoxication*, as *toxæmia*, or as **septicæmia.** Preponderance of the metastatic suppuration leads to the form of disease designated as **pyæmia** or as *bacteriæmia.* If the symptoms of both these forms of infection appear together, then one speaks of the condition as a **septico-pyæmia** or a **pyo-septæmia.**

The course of a streptococcus infection, as well as the mode of entrance of the cocci into the body, can generally be recognized, because the infection usually starts from the injured outer skin or from deeply penetrating wounds, from the mucous membranes of the upper digestive and air passages, or—in the case of a woman who has recently given birth to a child—from the genital apparatus which has undergone some change during the act of parturition. Cases of **cryptogenetic infection,** however, are not so very rare. In these the first symptoms which are noticed at the bedside are those dependent upon disease of some internal organ, and it appears as if the infection had started primarily in this organ.

The individual areas of disease in streptococcus-infection can show very different degrees of severity of inflammation, and this depends in part upon the virulence of the bacteria, in part upon individual differences among those who are infected, in part upon the site of the infection, and in part upon the influence of preceding or accompanying pathological conditions. As regards this last factor it may be said that many infectious diseases (diphtheria, scarlet fever, tuberculosis, typhoid fever, influenza) increase the disposition to streptococcus-infection, and at the same time lower the patient's powers of resistance.

The biological characters of the streptococcus pyogenes are very variable, and this is shown as well in its behavior as a disease-producer as by the cultivations of streptococci taken from different cases. As a consequence of this, an endeavor has been made to form different species, and especially has the streptococcus which causes erysipelas been differentiated as a special form—the streptococcus erysipelatis. Further, according to the place in which it was found, it was customary to speak of a streptococcus puerperalis (Arloing), a streptococcus articulorum (Flügge), or a streptococcus scarlatinosus (Klein); or, according to the manner of its growth (von Lingelsheim), to distinguish a streptococcus longus and a streptococcus brevis, etc. These characters by themselves are certainly not sufficient to permit of all these forms being separated from one another as distinct species, and it seems therefore more correct, or at least more expedient, to consider the chain-forming pus-coccus as a single species, which, however, appears in many varieties.

In diphtheria and scarlet fever streptococcus infections of the throat and air-passages are exceedingly frequent, especially in the first, and as a consequence many authors (Baumgarten, Dahmer) are inclined to assign to the streptococcus a coördinate place with the diphtheria bacillus in the causation of diphtheria—the diphtheria bacilli predominating in the lighter cases, the streptococci in the severer. Pure streptococcus infections can also give rise to the picture of diphtheria. If both species of bacteria are present, their effects are combined; perhaps also the presence of the streptococci exalts the virulence of the diphtheria bacilli.

§ 163. The **diplococcus pneumoniæ** (Fränkel, Weichselbaum), or the **streptococcus lanceolatus** (Gamaleïa), or the **diplococcus lanceolatus** (Foà, Bordoni-Uffreduzzi)—also known as the *pneumococcus*—is a pathogenic streptococcus of frequent occurrence. It forms spherical, oval, and lance-shaped cocci (Fig. 404, *a*) that are generally, in the human body, surrounded by a transparent capsule and are grouped together in pairs (*b*, *d*), less frequently in chains of such pairs (*c*), or in large colonies (*d*).

The streptococcus pneumoniæ stains very readily with fuchsin and with gentian-violet, and with these staining solutions the capsule also becomes visible. The cocci are also stained by Gram's method.

These cocci are facultative anaërobes. They will not grow on gelatin at ordinary room-temperature, but on slightly alkaline blood-serum gelatin and agar-agar kept at a temperature above 22° C., best at the temperature of the human body. They form delicate, translucent, glistening cultures which suggest the deposit of dew on a cover-glass (Fränkel) and consist of diplococci and chain-cocci without capsules. The growth is, however, scanty, and easily dies out. Cultures do not succeed on potatoes.

The diplococcus pneumoniæ is the cause, in a large number of cases (according to Weichselbaum, in seventy-one per cent), of the lung affection called *croupous pneumonia*, in which the lung is the seat of an acute inflammation which is ushered in by a congestive hyperæmia. In the course of the disease the alveoli over large areas become filled with a coagulated exudate which consists of desquamated epithelium, leucocytes, red blood-corpuscles, fluid, and fibrin, and which under favorable conditions becomes liquefied and absorbed. Numbers of observations have shown that it can cause inflammatory processes bearing the characteristics of catarrhal bronchopneumonia—processes, therefore, which are distinguished by the appearance of an exudate partly serous, partly cellular. The cocci are found during the disease principally in the inflamed area of the lung, but they may also be met with in neighboring areas—in the pleura, and, under certain circumstances, in the pericardium, in the peritoneum, in the meninges, in the cavities adjacent to the nose, in the cellular tissue of the neck, in the mediastinum, in the submucous tissue of the soft palate and throat, even in the conjunctiva (Weichselbaum); and in all of these localities they cause inflammatory changes. Occasionally they may be found in the juice of the spleen and in the blood, and are said to pass into the fœtus in pregnant women (Viti). They are therefore, under certain circumstances, *widely distributed throughout the body*. They may cause a serofibrinous inflammation in the meninges, the pleuræ, the pericardium, and the peritoneum, and under certain conditions they may also cause seropurulent and fibrinopurulent inflammation, without the appearance simultaneously of a pneumonia. They can, furthermore, cause inflammation of the endocardium, of the kidneys, of the joints, of the Fallopian tubes, of the uterine mucous membrane, of the parotid, of the thyroid, of the bone marrow, and of the periosteum; and this inflammation may cause suppuration. In many cases the mouth and the nose and throat—where they are occasionally also found in healthy individuals (Weichselbaum, Fränkel)—seem to form the portal of entrance. Accordingly, in cerebral and cerebrospinal meningitis (Weichselbaum) the maxillary cavity, the tympanic cavity, and the cribriform labyrinth often contain exudate with diplococci. The diplococci are found in the exudate in all the forms which we have enumerated. The gelatinous capsule may show a very variable thickness.

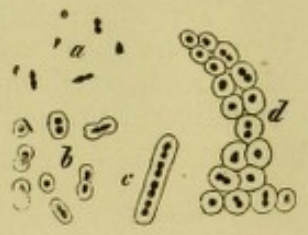


FIG. 404.—*Diplococcus pneumoniæ* of Weichselbaum and Fränkel. *a*, Cocci without a capsule; *b*, single cocci and double cocci in a gelatinous envelope; *c*, chain-cocci with a gelatinous envelope; *d*, colonies of cocci. Magnified 500 diameters.

Inoculated upon rabbits, guinea-pigs, and mice, they multiply in the form of capsule-cocci, especially in the blood and in the serous cavities, and may also cause pneumonia with bloody serous exudate (Weichselbaum). Rabbits are specially sensitive, as they die in from thirty-six

to forty-eight hours after subcutaneous inoculation, with symptoms of septicæmia. If pure cultures are injected into the pleural cavity of rabbits a pleurisy results, as well as a splenization of the lung in which the parenchyma is filled with a bloody serous exudate. The sputum of a pneumonia patient is pathogenic for rabbits, since it contains the cocci.

According to A. Fränkel, the cocci lose their poisonous properties very easily, especially if they are cultivated in milk; and if it is desired to retain the virulence they must be inoculated from time to time into susceptible animals. Cultivation of the cocci at 42° C. for one or two days destroys their virulence.

The *diplococcus pneumoniæ* belongs to those bacteria whose *physiological characteristics are very variable*. Foà distinguishes, according to the principal places in which they are encountered, a *pneumococcus* and a *meningococcus*. In *cerebrospinal meningitis* cocci have been found which in part resemble the streptococcus pyogenes (streptococcus meningitidis, Bonome), in part the diplococcus pneumoniæ (diplococcus intracellularis meningitidis, Weichselbaum). Whether these forms represent distinct species or are only varieties of the species mentioned has not as yet been definitely determined. Jäger is of the opinion that the **diplococcus intracellularis meningitidis** is the *cause of epidemic cerebrospinal meningitis*, and is entirely distinct from the pneumococcus. Sporadic meningitis may, on the other hand, be caused also by the pneumococcus.

According to Emmerich, in bouillon cultures there is formed, at the bottom of the vessel, a sediment containing some resistant forms which remain capable of development for months. Rabbits may be rendered completely immune (Emmerich) by repeated injections of much-diluted cultures (five thousand times diluted) of increasing virulence, so that 30 c.c. of cultures of full virulence are borne without any striking disturbance. The injected bacteria are killed in the course of a few days. The serum of immunized rabbits can cure pneumococcus infection in rabbits and mice.

§ 164. The **staphylococcus pyogenes aureus** (Rosenbach) or **micrococcus pyogenes** (Lehmann) is composed of spherical cells, which occur singly or in pairs, and by their multiplication generally form grape-like clusters and swarms. The cocci stain easily with the different aniline dyes, and also by Gram's method. They are facultative anaërobes, but grow better in the presence of air.

The staphylococcus thrives well on all the artificial media at the room-temperature, but grows better at 37° C. It forms whitish colonies, which produce pigment in the parts exposed to the air, and become colored orange-yellow (Fig. 1 of Plate I.). The color is most marked on agar and potato. Gelatin is slowly liquefied. When grape-sugar is present lactic-acid, acetic acid, and valerianic acid are formed. Actively poisonous products are formed in bouillon cultures. The staphylococcus pyogenes is one of the most frequently occurring of the pathogenic bacteria, and is, with the streptococcus pyogenes, the most common cause of **suppuration**, so that these two species have been frequently designated, in the narrower sense of the term, as **pus-cocci.** It is widely distributed throughout the external world, and has been demonstrated in milk, in washing-water and waste water, as well as in the air of operating-rooms and sick-rooms. Increasing in the tissues of the human organism (Fig. 405, *c*, c_1, and Fig. 406, *d*, *e*) it causes *tissue-degenerations* and *tissue-necroses*, on which supervenes an *inflammation* (Fig. 405, *d*, *e*, and Fig. 406, *e*, *f*, *g*) which generally assumes a *purulent character*. Not infrequently, however, the inflammation is less severe, i.e., does not go on to *suppuration of the tissues*.

The suppurations caused by the action of the staphylococcus are generally circumscribed, and also have less tendency to spread rapidly to the neighboring tissues than have the suppurations which are caused by streptococci. In the skin they cause more particularly those inflam-

mations which are termed *acne*, *eczema*, *furuncle*, and *cutaneous* and *subcutaneous abscesses*. In the bones they are the most frequent cause of the suppurative diseases of the bone-marrow and periosteum, which are designated as *septic osteomyelitis* and *periostitis*. They often give rise to *purulent inflammations* of the *liver*, *lungs*, *pleura*, *peritoneum*, *brain*, *brain membranes*, *muscles*, *myocardium*, *spleen*, *kidneys*, *joints*, etc., and are also often the cause of very severe, at times purulent, *inflammations of the endocardium* (Fig. 406). Inasmuch as the virulence of the staphylococci fluctuates, they can cause, in all the above-mentioned places and also elsewhere, *lighter transitory inflammations*, which heal with or without scar-formation.

The *portal of entrance* of the staphylococci is generally to be recognized without difficulty (especially in the case of wounds), and the same is true also of the route which they have followed when a metastasis occurs in some internal organ, in which event inflammations of the

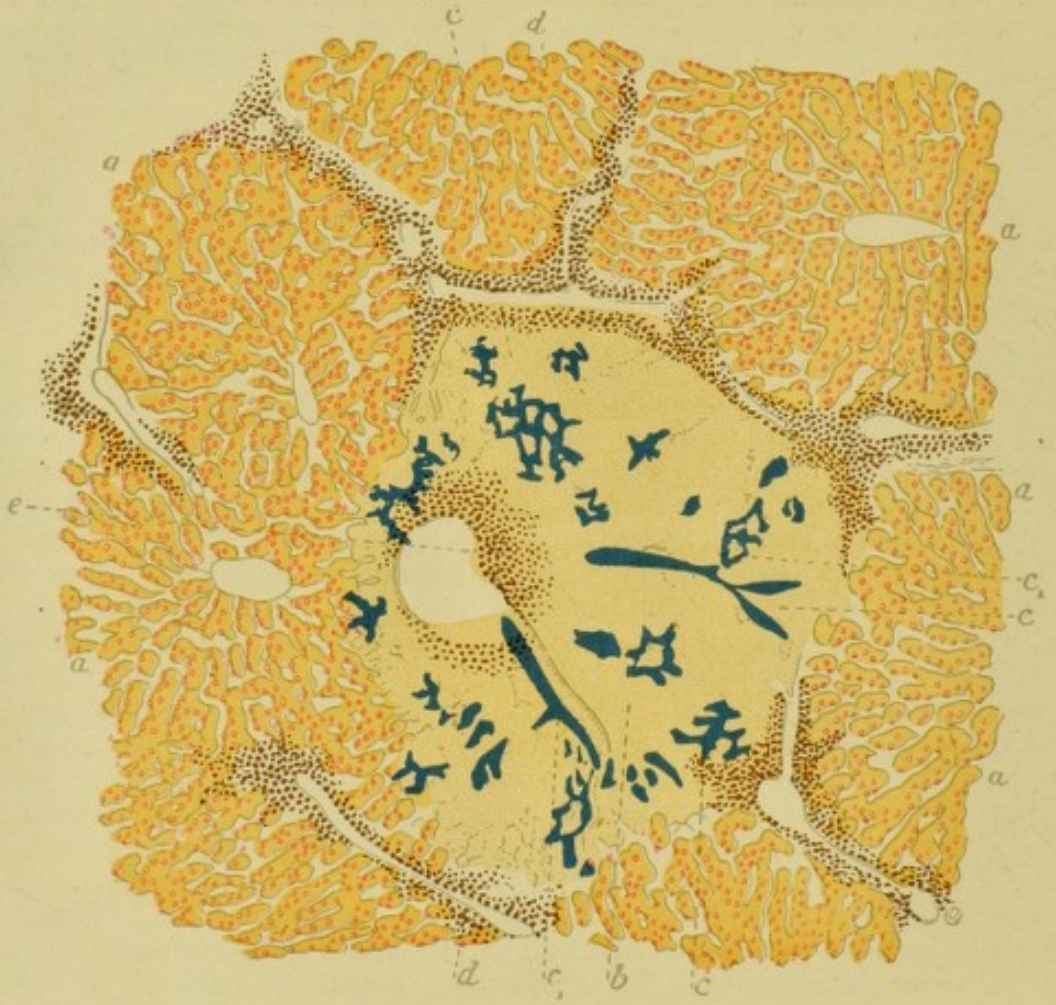


FIG. 405.—Metastatic aggregation of micrococci in the liver. (Alcohol; Gram's method; vesuvin.) *a*, Normal lobule; *b*, necrotic lobule; *c*, c_1, capillaries and veins filled with micrococci; *d*, periportal small-cell infiltration; *e*, a collection of small round cells partly inside, partly outside a vein into which a venula centralis filled with micrococci opens. Magnified 40 diameters.

lymph-vessels (lymphangitis) and of the blood-vessels (phlebitis, arteritis) make their appearance. **Cryptogenetic infections,** however, are not of rare occurrence, and they are of such a character that the myocardium or the endocardium or the bone-marrow or some other part of the body may be the first locality in which disease can be recognized.

Spreading of the staphylococci by means of the blood—an event which leads to multiple localization, with abscess-formation—is designated, as in the case of the spreading of the streptococci, as **pyæmia**; when the disease is complicated by the development of severe symptoms of poison-

FIG. 406.—Endocarditis pustulosa caused by *staphylococcus pyogenes aureus*. (Alcohol; Gram's method; vesuvin.) *a*, Tissue of the posterior segment of the mitral valve; *b*, threads of tendon; *c*, pustular protuberance of the upper surface of the mitral valve; *d*, *staphylococcus pyogenes aureus*; *e*, staphylococci intermixed with pus-corpuscles; *f*, pus-corpuscles with cocci; *g*, small abscess. Magnified 60 diameters.

ing, the term **septicæmia** is employed; and when there is a combination of both processes it is usual to designate the condition as **septico-pyæmia** (comp. § 162).

The *staphylococcus pyogenes aureus is also pathogenic for animals*—horses, dogs, cattle, goats, sheep, rabbits, guinea-pigs, and mice—and especially is this true for those named first. It gives rise to suppurations in these animals. In artificial cultures its virulence readily diminishes. The inoculation of susceptible animals with cultures of very great virulence causes a gelatinous-œdema.

The **staphylococcus pyogenes albus** (Rosenbach) and the **staphylococcus pyogenes citreus** (Passet) are very closely related to the staphylococcus pyogenes aureus, and apparently are only varieties of this organism. The first forms white colonies, the other citron-yellow colonies (Plate I., Fig. 6). These bacteria are found in the same localities as are the golden-yellow pus-cocci, and their mode of action is the same as that of the latter, but they are not encountered so frequently as is the aureus.

The staphylococcus pyogenes aureus usually occurs alone in the pus-foci, yet, not infrequently, other pus-cocci or even bacilli are also found accompanying it—for example, the bacterium coli commune, or the typhoid bacilli.

§ 165. **Micrococcus gonorrhœæ sive gonococcus** (Fig. 407) is a coccus which was first described by Neisser in 1879. It is constantly present in the purulent catarrh, called gonorrhœa, of the male and female urethra and the female genital canal (especially that of the uterus), as well as in the secretion of blennorrhœa of the eye, and it is also regarded as the cause of the gonorrhœa and of the blennorrhœa of the eye. Besides the specific cocci, other cocci may also be present in the gonorrhœal secretion, some of them resembling the specific cocci very closely. The secretion may, moreover, also contain the pus-cocci.

The gonococcus can be cultivated on coagulated human blood-serum.

on blood-serum gelatin, on human blood-serum agar, and on urine agar; and it forms on the surface of the nutrient medium a yellowish-gray layer with a smooth surface. It dies out easily, and grows only at comparatively high temperatures.

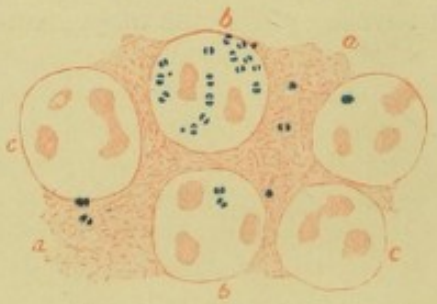


FIG. 407.—Gonococci in the secretion from the urethra in fresh gonorrhœa. (Methylene blue; eosin.) *a*, Mucus with separate cocci and diplococci; *b*, pus-cells with diplococci; *c*, pus-cells without diplococci. Magnified 700 diameters.

Animals enjoy immunity from infection by inoculation. Efforts were made by Bockhart and Bumm to inoculate human beings with gonococci cultivated on artificial media, and they obtained in this way a purulent catarrh of the inoculated mucous membrane. The experiments of Bumm, particularly upon two women, seem to have given a positive result.

The coccus forms mostly clumps in the purulent secretion of the mucous membrane affected with gonorrhœa. It appears largely in the form of diplococci with the opposing surfaces flattened (Fig. 407), partly free (*a*) and partly inclosed in cells (*b*); it stains readily with aniline dyes, but becomes decolorized by Gram's method.

The gonococcus penetrates into the epithelial layer of the mucous membrane and lies sometimes between and sometimes within the epithelial cells and in leucocytes. Only the superficial layers of the connective tissue are penetrated. It causes inflammations which assume the character of *purulent catarrhs*, and which are accompanied by cellular infil-

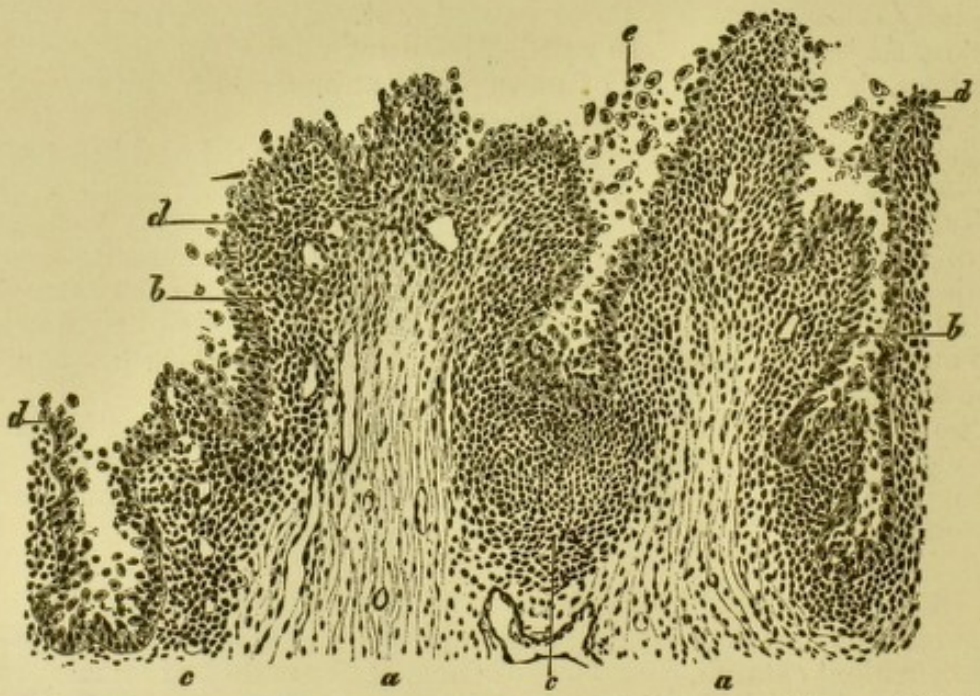


FIG. 408.—Gonorrhœal urethritis. Section through the wrinkled mucous membrane. (Müller's fluid; hæmatoxylin; eosin.) *a*, Normal connective tissue; *b*, *c*, inflamed, infiltrated, and proliferating connective tissue of the mucous membrane; *d*, infiltrated and desquamating epithelium; *e*, detached epithelial cells and pus corpuscles. Magnified 400 diameters.

tration of the tissues of the mucous membrane (408, *b*, *c*, *d*) and by desquamation of the epithelium. The male and female urethra and the adjoining parts of the genital ducts and glands, and the urinary passages

form the chief points of localization. The extent to which the inflammations following gonorrhœa (peri-urethral abscesses, inflammations of the prostate gland, of the epididymis, of the seminal vesicles, of the bladder, of Bartholin's glands, of the tubes, of the ovary, of the pelvic peritoneum, and of the joints) are due to the spread of the gonococcus on the one hand, or to secondary infection with the pus-cocci on the other, is still a matter of dispute. From the investigations which have thus far been made it can no longer be doubted that the gonococcus may become widely spread over the mucous membranes. It has also been found repeatedly in inflamed Fallopian tubes, ovaries, and joints, in perimetritic and parametritic inflammatory foci and in peri-urethral abscesses, and is to be regarded as the cause of the inflammation. Still the processes leading to suppuration, and also the metastases in remote organs, seem to depend oftener upon the presence of pus-cocci.

The gonorrhœal infection is at the outset an acute process, but can become chronic, and is cured only with great difficulty because the gonococci maintain themselves here and there in the urethra, in the Fallopian tubes, etc., for years, and cause inflammation.

§ 166. **Cocci** have been determined as the undoubted **exciting causes of animal diseases** in the case of a large number of those which are of an infectious nature, and that this statement is correct in regard to still others has been rendered at least probable. As has already been mentioned before, the streptococcus pyogenes, the diplococcus pneumoniæ, and the micrococcus pyogenes aureus are pathogenic for various animals, and the latter variety especially may often cause spontaneous suppurative inflammations in animals—i.e., inflammations which have not been caused by the experimenter. On the other hand, diseases have also been produced experimentally in animals by various cocci which are not pathogenic for man. Furthermore, in several spontaneously occurring diseases of animals, cocci have also been demonstrated, and it is not unlikely that they are the exciting causes.

1. According to Schütz,[1] Sand and Jensen,[2] and Poels,[3] the strangles of horses is an infectious disease in which the mucous membranes of the upper respiratory tract are the seat of a mucopurulent inflammation, in which, moreover, the lymph-glands pertaining to the part become swollen and some of them suppurate. It is caused by a *coccus in chains*, which may be cultivated and which produces strangles in horses on inoculation (Schütz).

2. According to Schütz,[4] the *epidemic lung-disease of horses, infectious pneumonia*, is caused by an oval *coccus*, which is not identical with the *diplococcus pneumoniæ* of Fränkel or the *bacillus pneumoniæ* of Friedländer, and consequently not identical with the fission-fungus described by Perroncito[5] in the pneumonia of horses, and held to be identical with the *diplococcus pneumoniæ*.

3. According to Semmer and Archangelski,[6] the microparasite of cattle-pest is a micrococcus. According to Metschnikoff and Gamaleïa,[7] it is a bacillus. The disease is anatomically distinguished by inflammation of the intestinal tract, bearing partly a croupous and diphtheritic character, as well as by swelling and sometimes even by necrosis of Peyer's plaques.

[1] "Der Streptococcus der Druse der Pferde," *Arch. f. wissensch. u. prakt. Thierheilk.*, xiv., 1888, and *Zeitsch. f. Hygiene*, iii.

[2] "Die Aetiologie der Druse," *Deutsche Zeitsch. f. Thiermed.*, xiii.

[3] "Die Mikrokokken der Druse der Pferde," *Fortsch. d. Med.*, vi.

[4] "Die Ursachen der Brustseuche des Pferdes," *Archiv f. wissensch. u. prakt. Thierheilk.*, 1887, and *Virch. Arch.*, 107 Bd., 1887.

[5] *Arch. Ital. de biol.*, vii., 1886.

[6] *Centralbl. f. d. med. Wiss.*, 1883, and *D. Zeitschr. f. Thiermed.*, xi.

[7] *Centralbl. f. Bakt.*, i., 633.

4. According to Poels and Nolen,[1] monococci and diplococci, some of them with a gelatinous capsule, are found constantly in the lungs and pleural exudate, in *contagious pleuropneumonia of cattle.* On gelatin and agar-agar they make mostly white colonies that later become cream-colored. Pure cultures injected into the lungs of rabbits, guinea-pigs, dogs, and cows cause pneumonic changes. Cornil and Babes found various bacteria in the exudate.

5. In the *udder-inflammations* of domestic animals, which occur sometimes sporadically, sometimes epidemically, different *micrococci* and *streptococci* have been described, and have also been designated by various names.[2]

6. According to Johne[3] the cerebrospinal meningitis, which occurs epidemically among horses, is caused by the *diplococcus intracellularis* (Weichselbaum, § 163).

7. Babes found in hæmoglobinuria of cattle—a disease that occurs in epidemics in Roumania—a coccus resembling the gonococcus, which he regards as the cause of the disease.[4]

8. According to Semmer, Friedberger, and Mathis,[5] the *distemper of dogs* is also caused by a coccus.

9. *The foot-and-mouth disease of cattle*, according to Klein, is caused by a streptococcus.[6] In recent years, Schottelius[7] and Kurth[8] and others have also found cocci in the organs of animals sick of the foot-and-mouth disease; but the bacteria described do not correspond with one another, and the pathological significance is doubtful.[9]

10. According to Rivolta and Johne,[10] and Rabe,[11] there occurs in horses a peculiar tumor-like growth of the connective tissue, called by Johne *mycofibroma* or *mycodesmoid*, which is caused by a micrococcus that grows in the animal tissues in round or grape-cluster-like colonies. These quickly become surrounded by a hyaline capsule, and are therefore to be reckoned as ascococci (*Micrococcus ascoformans*). The tumefaction consists, similarly to that of actinomycosis, of connective tissue, inclosing small foci of proliferation, which break down into pus. The foci harbor the fungi. They seem to develop oftenest in the spermatic cord, after castration. They appear, however, in other parts of the body.[12]

11. According to Eberth[13] and M. Wolff[14] a large number of the gray parrots (*Psittacus erithacus*) imported into Europe die of a *streptococcus mycosis.* The micrococci are present in nearly all the organs, but especially in the capillaries of the liver and their neighborhood, where they cause necroses of the liver-cells, but no suppuration.

12. According to Eberth,[15] some of the pseudotuberculous processes occurring in guinea-pigs represent a chronic suppuration that is produced by cocci, and that sometimes leads to metastases in other organs.

[1] *Fortschr. der Med.*,, 1886.

[2] Hess and Bergeaud: "Contag. Euterentzündung, gelber Galt gennant," *Schweiz. Arch. f. Thierheilk.*, 30 Bd., 1888; Frank: "Euterentzündungen," *Deut. Zeitschr. f. Thiermed.*, ii., 1876; Kitt: "Euterentzündung," "Lehrb. d. path. anat. Diagnostik," Stuttgart, 1894.

[3] "Seuchenartige Cerebrospinalmeningitis d. Pferde," *Deut. Zeitschr. f. Thiermed.*, xxii., 1887.

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[6] *Centralbl. f. d. med. Wiss.*, 1886.

[7] "Ueber einen bakter. Befund bei Maul- u. Klauenseuche," *Centralbl. f. Bakt.*, xi., 1892.

[8] "Bakt. Untersuch. bei Maul- u. Klauenseuche," "Arb. aus dem Reichsgesundheitsamt," viii., 1893.

[9] Johne: *Deutsche Zeitsch. f. Thiermed.*, xix., 1893; Löffler und Frosch: *Centralblatt f. Bakt.*, xxii., S. 257, 1897.

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[11] *Deutsche Zeitsch. f. Thiermed.*, xii.

[12] Kitt, "Der *Micrococcus ascoformans* und das Mykofibrom des Pferdes," *Centralbl. f. Bakt.*, iii., 1888.

[13] *Virch. Arch.*, 80 Bd.

[14] *Virch. Arch.*, 92 Bd.

[15] *Virch. Arch.*, 100 Bd.

2. *The Bacilli and the Polymorphous Bacteria, and the Morbid Processes Caused by Them.*

(a) General Remarks upon Bacilli and upon Polymorphous Bacteria.

§ 167. Under the name **Bacilli** or **Bacillacei** (A. Fischer) or *Bacteriacei* (Zopf) can be classified all those bacteria which appear in the form of straight rods, or rods that are only slightly bent in one plane. By many authors (Cohn, Hüppe, Lehmann) the bacillacei are divided into two groups: *bacterium* and *bacillus*. Of these the latter is distinguished by the formation of endogenous spores, while spore-formation is lacking in bacterium.

The **bacilli** multiply by division. The rods grow in length and divide into approximately equal parts by the appearance of a transverse wall of division. If the division of the rod that is growing out in length does not take place for some time, or if the division between the different

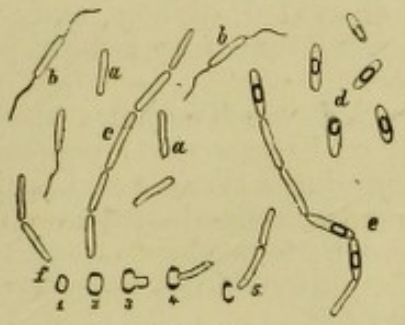


FIG. 409.

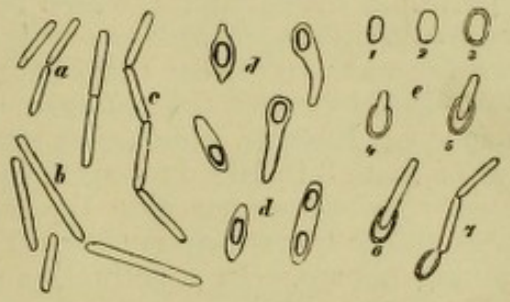


FIG. 410.

FIG. 409.—*Bacillus subtilis* in different stages of development. (After Prazmowski.) *a*, Separate rods; *b*, rods with flagella; *c*, chains of rods; *d*, separate cells with spores; *e*, chains of rods with spores; f_1–f_5, germination of spores. Magnified 800 diameters.

FIG. 410.—*Clostridium butyricum*. (After Prazmowski.) *a*, Short rods; *b*, long rods; *c*, chains of rods; *d*, cells with spores; e_1–e_7, germination of spores. Magnified 800 diameters.

parts is not easily recognized, there result long jointless rods or threads (Fig. 410, *b*). If the divided rods remain hanging together they form chains of rods (Fig. 409, *c*, and Fig. 410, *c*). In many forms of bacteria the ends are blunt, in others rounded or even pointed.

In many bacilli resting stages as well as swarming stages are observed, in which the flagella serve as organs of locomotion (Fig. 339, *b*). The flagella are situated sometimes at the ends, sometimes on the sides of the rods, and may occur in large numbers.

In many bacilli endogenic **spore-formation** is observed (Fig. 409, *d*, *e*, and Fig. 410, *d*), in which the spore sometimes lies in the middle, sometimes in the end of the cell. Not infrequently the spores appear in jointed threads. The germination of spores results in the formation of new rods (Fig. 409, f_1–f_5, and Fig. 410, e_1–e_7).

A noticeable change of shape does not usually take place in the rods in spore-formation. In other cases the rods assume a spindle shape or club shape or pear shape (Fig. 410, *d*), and this has been taken as ground for establishing a special group, *clostridium*. Numbers of authors, nevertheless, reckon these forms also with the bacilli.

In the non-pathogenic bacilli spore-formation and germination have been more exactly studied, especially in *bacillus subtilis* and *bacillus*

amylobacter, and these offer good examples of the processes which come under consideration in this connection.

Bacillus subtilis is a fission-fungus whose spores are very widely distributed in the ground, in hay (the hay bacillus), and in the air. Cultivated upon slices of potato or upon dung of herbivorous animals, it forms whitish-yellow clumps; on liquids, thin and thick pellicles. It requires oxygen for its development.

The fully grown cells (Fig. 409, *a*) are 6 μ long. The snake-like motions sometimes seen are produced by one or two flagella (*b*). The growth of the rods is at first in the form of undivided threads; when these are segmented chains of bacilli are formed. The separate cells may develop in their interior glistening, sharply contoured spores (*d*, *e*), which lie either in the middle or nearer to one end. Subsequently the cells out of which the spores have been formed perish. In germination the spore (Fig. 409, f_1–f_5) becomes pale and loses its glistening appearance and its sharp contour. Then at each pole a shadow appears, while the spore begins a tremulous motion. After a time the contents of the spore project from the side of the membrane in the form of a germinal diverticulum, which becomes elongated, divides, and produces swarming staves. The empty spore membrane may remain preserved for a time after the exit of the embryo.

Bacillus butyricus (*bacillus amylobacter* of van Tieghem, *vibrion butyrique* of Pasteur, *clostridium butyricum* of Prazmowski) possesses staves of from 3 to 10 μ in length, and also produces threads and chains of rods. In spore-formation the cells become spindle-shaped or club-shaped and tadpole-shaped (Fig. 410, *d*), and then produce one or two glistening spores. In germination after absorption of the spore membrane a germinal tubule protrudes from one of the two poles (Fig. 410, e_1–e_7). This becomes prolonged and forms new staves by segmentation.

Bacillus butyricus needs no oxygen for its development, and produces butyric-acid fermentation, with evolution of carbonic-acid gas, in solutions of starch, dextrin, sugar, or glycerin. In starch or glycerin or nutrient fluids containing cellulose the bacilli stain blue with iodine.

The **polymorphous bacteria** are distinguished from the bacilli by the fact that they form, besides rods, also long, short-jointed threads, at times also true branchings of the threads; and also, in a few instances, a basal, non-growing, and an apical growing end can be differentiated. In this category belong the fungi known as the leptothrix, beggiatoa, crenothrix, and cladothrix. They are here placed with the bacilli, because, on the one hand, their botanical position is not determined, while, on the other, so far as they are pathogenic, they conform most closely to the bacilli in their biological characters.

Saprophytic bacilli cause many kinds of fermentation by their growth in nutrient fluids; many of them also form pigments.

Bacillus prodigiosus grows on potatoes and bread, as well as on agar-agar and nutrient gelatin. It liquefies the latter, and produces a red coloring-matter which is soluble in alcohol. The coloring-matter develops only where oxygen is present. In the growth in milk the coloring-matter is contained in the fat-droplets. The bacilli themselves are always colorless.

Bacillus fluorescens liquefaciens produces in gelatin whitish cultures, and in the neighborhood of these the gelatin becomes liquefied, while the gelatin in the more remote surrounding portions fluoresces with a yellowish-green color.

Bacillus cyanogenes (Neelsen, Hueppe), when cultivated in sterilized milk, produces a slate-gray color that changes to intense blue on the addition of acid. In unsterilized milk, where lactic-acid bacteria develop simultaneously, the blue color appears without the addition of acid. On potatoes it forms yellowish slimy cultures, in the neighborhood of which the substance of the potato is colored grayish-blue (Flügge).

Bacillus acidi lactici causes fermentation of sugar of milk in lactic acid, and produces coagulation of casein. The cultures obtained in gelatin are of a white color.

Bacillus caucasicus (*dispora caucasica*) forms one of the fungus conglomerates that is called kefyr ferment, which the inhabitants of the Caucasian Mountains use in the preparation, from milk, of the alcoholic drink called kefyr. The kefyr ferment consists of small granules which contain yeast-cells along with rods. The bacilli occasionally show motile forms and develop on the ends of each rod a round spore. By their growth in the milk the milk-sugar is probably converted into glucose, while the yeast-cells produce alcoholic fermentation. According to Hueppe, the kefyr granules contain still other bacteria that peptonize casein.

Hauser described, under the name of **Proteus vulgaris** (Bacterium vulgare, of Lehmann), a form of bacillus which very often occurs in putrefying animal substances and causes the foul putrefaction. It forms staves of very varied length, and produces when cultivated in meat (Carbone) æthylendiamin, gadinin, and trimethylamin, of which the first two bases are poisonous for animals. According to observations of Bordoni-Uffreduzzi, Foà, Bonome, and Banti, certain bacilli closely resembling the proteus of Hauser seem to be pathogenic for human beings and capable of causing blood infection as well as intestinal affections.

Bacillus aceticus (*mycoderma aceti*) is a bacillus which converts the alcohol of fermented beverages into vinegar.

Bacillus pyocyaneus occurs occasionally in bandages from suppurating wounds, and causes a greenish-blue discoloration. The bacilli are small and slender. The cultures show different forms of growth. Gelatin is liquefied and turned green. The coloring-matter called pyocyanin is soluble in chloroform and crystallizes out of solution in long blue needles. The bacillus is pathogenic for rabbits, guinea-pigs, pigeons, and frogs, and causes on inoculation sometimes local ulceration, sometimes general infection. According to Kossel, Kramhals, and others, it may also be *pathogenic for man*, and from suppurating wounds may cause septic intoxication with enlargement of the spleen and enteritis.

The **pathogenic bacilli** and **polymorphous bacteria** cause diseases, sometimes acute, sometimes chronic, of which the first either end in death, or, by the destruction of the bacteria, go on to recovery. At the same time it occasionally happens that even in the acute diseases the bacteria maintain themselves for a long time in the body. The chronic diseases are especially characterized by the fact that the bacteria live and increase in the body, so that the disease assumes a progressive character, and sometimes quickly, sometimes more slowly, new regions are taken possession of by the bacteria and become altered by them.

(b) Pathogenic Bacilli and Polymorphous Bacteria.

§ 168. **Bacillus anthracis** (*Bactéridie du charbon*) is the *cause of anthrax*, an infectious disease which occurs mainly in cattle and sheep, but which is occasionally transferred to human beings. It is a fission-fungus that can multiply inside the tissues as well as in the blood when inoculated into a susceptible animal organism.

The **anthrax-bacilli** (Fig. 411) are from 3 to 10 μ long and from 1 to 1.5 μ broad. In the

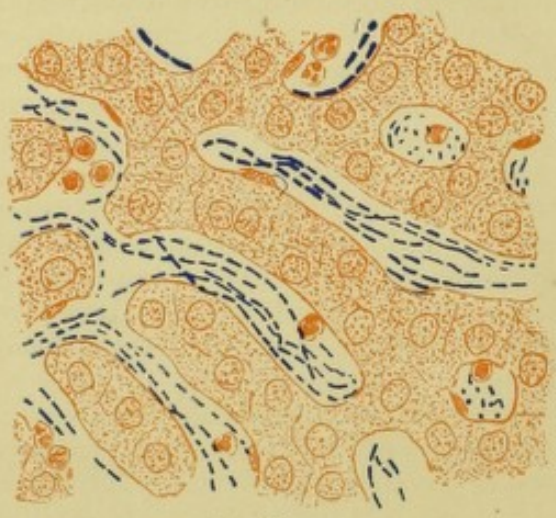


FIG. 411.

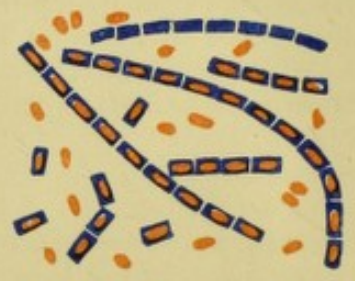


FIG. 412.

FIG. 411.—Section of liver with capillaries containing numbers of anthrax-bacilli and a few leucocytes. (Alcohol; gentian violet; vesuvin.) Magnified 300 diameters.

FIG. 412.—Anthrax-bacilli containing spores, and free spores that have escaped from the bacilli. (Cover-glass preparation treated with fuchsin and methylene blue, from a culture of the bacilli on a potato, under the stimulation of heat in an incubator.) Magnified 800 diameters.

blood of animals dead of anthrax they lie separate or in thread-like jointed bands of from two to ten staves. The ends are as a rule sharply cut across (Figs. 411 and 412), more seldom slightly concave or even convex (Johne). According to Serafini, Günther, and Johne, they possess a gelatinous capsule, which can be best made visible in dried preparations by staining with methylene blue (Günther). They can be cultivated upon blood-serum, upon gelatin, in bouillon, on slices of potatoes and turnips, in infusions of pease and mashed seeds of different kinds, in the presence of oxygen.

They grow most quickly at a temperature which varies from 30° to 40° C. Development is impossible at a temperature below 15° C. and above 43° C.; it is also impossible in the absence of oxygen.

If the conditions above mentioned are present, the staves grow in length, and may, in a few hours, form threads of considerable length, devoid of membranes. These are made up of short segments that are rendered visible by treatment with iodine or with some coloring-material (Fig. 412). Ten hours later, the clear contents of the threads become granular, and at regular intervals bright glistening bodies become apparent, which enlarge into strongly refractive spores (Fig. 412). Later on, the threads disintegrate and the spores become free.

According to Brefeld, Prazmowski, Klein, and others, the spore consists of a protoplasmatic centre which is surrounded by a double membrane, the exosporium and the endosporium. In germination the former is ruptured and the latter becomes the membrane of the liberated embryo. The liberated embryo multiplies by division.

Swarming is not observable during the entire process of development; the bacilli are always motionless.

The anthrax-bacilli easily die under the influence of high temperatures when subjected to drying, and in the presence of a nutrient medium which has become putrefied. The spores, on the contrary, are very resistant, and consequently are the ordinary medium of the transfer of the disease.

Colonies in gelatin show a wavy, irregularly shaped margin, and consist of wavy, curly bands of threads that subsequently grow out of the culture in various directions. The gelatin becomes liquefied in the immediate neighborhood of the culture. On slices of potato they form grayish-white cultures that appear slightly granular (Plate I., Fig. 5), with distinct outline. They form a whitish coating on blood-serum.

Stab-cultures in gelatin are white, and in the process of growth they radiate at right angles from the track of inoculation, especially near the surface. After liquefaction of the gelatin they sink to the bottom.

If the bacilli or spores get into the blood they multiply and produce the staves above described, which can be stained with various aniline

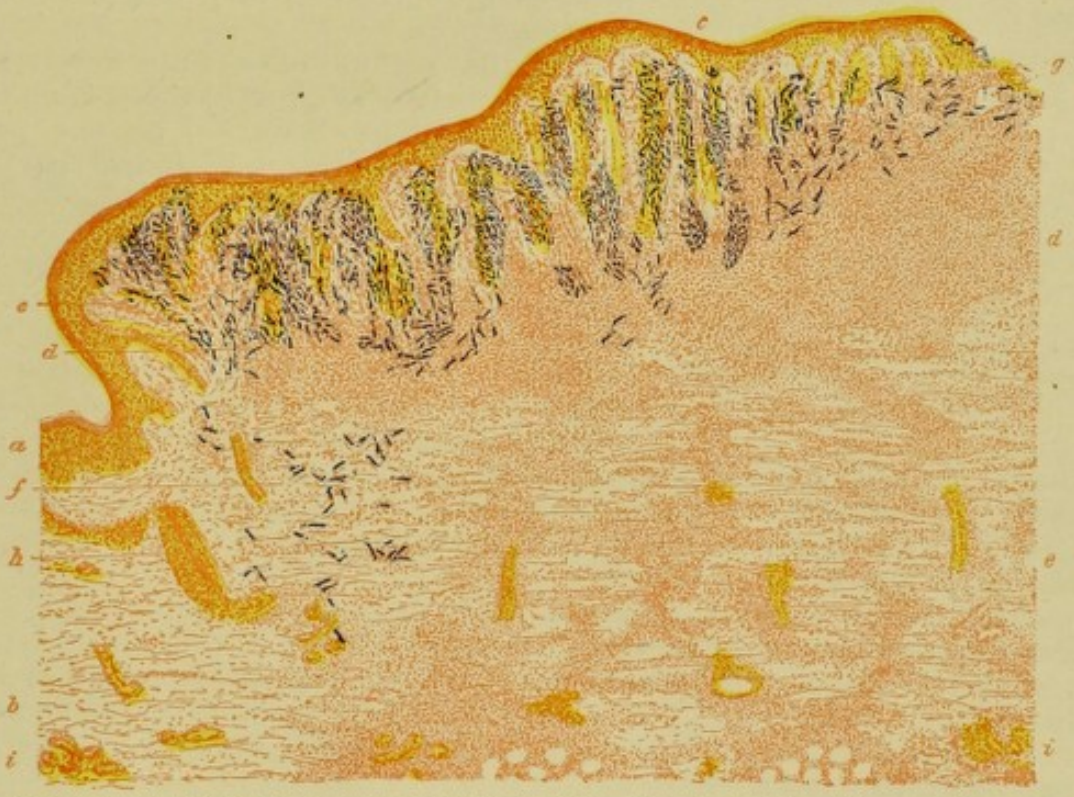


FIG. 413.—Section through an anthrax-pustule ten days old, extirpated from the arm of a man. *a*, Epidermis; *b*, corium; *c*, papillary body, œdematous, swollen, filled with exudate and bacilli; *d*, external layer of the corium infiltrated with cells; d_1, the same containing bacilli; *e*, deeper layers of the corium containing bands of cells; *f*, tissues of the skin interspersed with bacilli and cells; *g*, bloody exudate on the surface containing bacilli; *h*, hair-follicle; *i*, sweat-gland coil. (Alcohol; Gram's method; vesuvin.) Magnified 35 diameters.

colors, and also by the employment of Gram's method. Sections of hardened organs show that they are present in large numbers in the capillaries (Fig. 411), especially of the spleen, of the liver, of the lungs, and of the kidneys. The contiguous parenchyma of the tissue usually appears unchanged; still the local growth of the bacilli may produce degeneration of tissue and necrosis. If an infection of the blood takes place during pregnancy the infection may go over to the fœtus.

If anthrax-bacilli or their spores get through little wounds of the skin in human beings they develop a somewhat elevated pustule with arched or flattened surface (Fig. 413), usually from six millimetres up to several centimetres in diameter. The pustule is red or possibly more of a yellowish color. It is often in time covered with vesicles, or after the loss of epithelium it becomes moist; and by the drying of this exudate, which is often bloody, a scab is formed (Fig. 413, *g*). Infection takes place in persons that butcher or bury, or prepare the skins of animals affected with anthrax; occasionally also it is conveyed through the sting of a fly that has taken up the blood of an animal affected with anthrax.

The centre may become depressed by the formation of the scab in the middle, the edges forming a wall around. The neighborhood of the pustule is sometimes little changed and sometimes red and swollen, and may be occupied by small yellowish or bluish-red vesicles. If the process remains local the sloughing pustule may be thrown off. Infection of the blood is followed by fatal consequences. In rare cases infection shows itself in a widespread, intense œdematous swelling of the tissues without the formation of a circumscribed pustule.

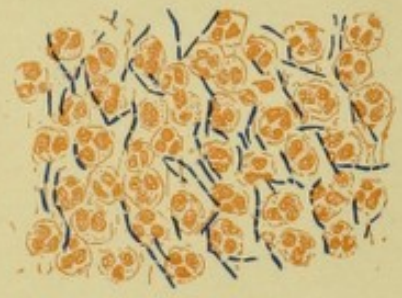


FIG. 414.—Section from a portion of an anthrax-pustule (Fig. 413) where the tissues contained bacilli. Magnified 350 diameters.

In the region of a fully developed anthrax-pustule (Fig. 413) the corium (*d*, d_1) and papillary body (*c*) become permeated by a cellular, serous, and bloody exudate as well as by bacilli. The bacilli lie in the external portions of the corium (d_1) and in the papillary body (*c*); but they can penetrate into the deeper layers of the corium (*f*). In the region of the papillary body (*c*) the exudate is sanguinolent. Vesicles filled with bloody fluid result if the exudate extends up to the epithelial covering and if the deeper portions of the latter become liquefied, thereby permitting the superficial portions to be lifted up by the exuded fluid. If the upper layers of skin are lost the bloody fluid containing bacilli (*g*) appears on the surface.

The cellular infiltration has its seat mainly in the corium (*d*, d_1, *e*), and it makes the impression as if the great massing of cells would form, to a certain extent, a protection against the further encroachment of the bacteria. The cells that accumulate are for the most part polynuclear leucocytes (Fig. 414). The bacilli lie partly within the cells, and partly between them.

If infection with anthrax-spores takes place in the intestinal canal—an event which occurs with special frequency in the small intestine, and only infrequently in the stomach and large intestine—reddish-black or reddish-brown hemorrhagic foci, the size of a lentil or bean, with a grayish-yellow or greenish-yellow discolored slough in the middle, will develop. In other cases the crests of the folds of the mucous membrane are swollen and show hemorrhagic infiltration, and the most prominent parts show evidences of sloughing. The mucosa and submucosa are infiltrated with blood in the region of the foci; the surrounding tissue is œdematous and hyperæmic. In these foci, as well as in their surroundings, the tissue contains bacilli, especially in the blood- and lymph-vessels, and they may be equally well seen in the swollen lymph-glands.

According to observations of Eppinger and Paltauf, primary lung infection occurs by inhalation of anthrax-spores, usually proving fatal in from two to seven days. Individuals who have to handle the hair of animals that have died of anthrax are specially exposed, and the infection of the men or women who are busied in the sorting of rags in paper-factories—an infection which is known as *rag-sorters' disease*—is, in a part of the cases, nothing more than an anthrax infection. The bacilli are very probably taken into the lungs in the form of spores with the inspired air, and develop in the bronchi and alveoli, in the spaces that contain the tissue-juices of the lung and pleura, and in the bronchial glands, and they also penetrate into the vessels. Their multiplication causes inflammatory processes in the lung, as well as the pouring out of a bloody serous exudate in the pleural space and in the mediastinal tissues, and swelling of the lymph-glands. It may also lead to formation of necrotic foci in the lung and in the bronchial and tracheal mucous membrane.

Mice, rabbits, sheep, horses, and sparrows are very susceptible to anthrax. White rats, dogs, and Algerian sheep are less susceptible or enjoy complete immunity. Cattle become easily infected through the intestines by taking in the spores into the alimentary canal, but are less susceptible to inoculation. Formation of spores does not take place in the tissues and in the blood.

By cultivating the bacilli at from 42° to 43° C. (Toussaint, Pasteur, Koch) it is possible to weaken their activity, so that first sheep are not killed, then rabbits and guinea-pigs, and finally even mice are no longer killed by inoculation. If the temperature is near 43° C., this condition can be reached in six days; at 42° C. it may take sixty days before the virulence becomes weakened to this extent (Koch). By first inoculating with bacilli that kill mice, but are harmless for guinea-pigs, and by a second inoculation with bacilli that will kill guinea-pigs, but not strong rabbits, sheep and cattle can be rendered immune, but not mice, guinea-pigs, or rabbits. Practically, however, this protective inoculation cannot be employed, because it is necessary to inoculate with very virulent material in order to protect from natural infection with spores introduced into the intestines; and consequently a large per cent—from ten to fifteen per cent—die from the protective inoculation itself. Moreover, the protection is only of short duration, and the inoculation must be repeated in about a year.

According to observations of Roux and Chamberland, the anthrax-bacilli can, while retaining their full virulence, be permanently deprived of the power of producing spores by cultivation in bouillon to which a small amount (1 : 2000) of potassium permanganate or carbolic acid (1–2 : 1000) has been added.

According to Koch, anthrax-bacilli can be cultivated on potatoes and alkaline or neutral infusions of hay, on cold infusions of pea-straw, on mashed barley and mashed wheat, in the juice of turnips, wheat, leguminous seeds, and numerous dead plants, in the presence of a sufficient quantity of water. Consequently the bacilli grow and develop outside the body—e.g., in marshes and on river-banks (R. Koch). The entrance into the animal body is to be regarded as an occasional excursion of the ectogenic bacillus. According to Soyka, the development of spores takes place very quickly in a moist medium containing the necessary nutrient material. According to Kitt, cattle-dung forms a nutrient substratum for the bacilli.

§ 169. The **bacillus typhi abdominalis** (Fig. 415), or the *bacterium typhi*, is a fission-fungus which appears mostly in the form of plump staves 2 to 3 μ long, with rounded ends growing out into long pseudo-threads in cultures. It is recognized as the cause of typhoid fever. When examined alive in cultures it shows lively, independent locomotion, caused by flagella (Fig. 416) which are attached to the sides of the staves as well as to the ends. The flagella can be made visible by proper staining-methods. The bacillus was first observed and described by Eberth and Koch, and afterward cultivated pure by Gaffky. A.

Pfeiffer showed its presence in the dejecta of typhoid patients, and his observations have been corroborated often since. According to Seitz, Hueppe, Neumann, and others, it may also be present in the urine of typhoid patients.

It may be well stained in cover-glass preparations with gentian violet, alkaline methylene blue, and Bismarck brown; by treatment with

FIG. 415.—Typhoid bacilli from a pure culture. Smear preparation. (Methylene blue.) Magnified 1,000 diameters.

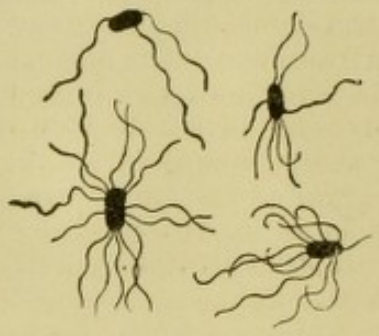


FIG. 416.—Typhoid bacilli with flagella. (After Bunge). Magnified 1,200 diameters.

iodine according to Gram's method it may be decolorized. The detection of the bacilli in sections of hardened organs is somewhat difficult, because the cell-nuclei also become stained, and because the bacilli are not uniformly distributed, but usually lie in clumps in the tissue.

The bacillus may be cultivated as well in nutrient gelatin, agar-agar, and blood-serum as in milk and on slices of potato. It forms a coating on the latter that can scarcely be distinguished by the naked eye. But if the surface is touched with a platinum wire it becomes apparent that it is covered with a pellicle, and the microscopic examination shows that this consists of bacilli.

On gelatin and agar-agar the bacilli form whitish-gray, flat cultures of irregular shape. *Gelatin is not liquefied.* Milk in which the bacilli are grown is not changed externally.

Cultures flourish at room-temperature as well as at body-temperature. Ordinary potato-cultures kept between 30° and 42° C. produce staves which have glistening granules in their poles. Gaffky interpreted these granules as spores, and formerly most authors accepted this interpretation. According to Buchner and Pfuhl, however, these granules at the poles are degeneration forms occurring especially when the culture contains an acid. The polar granules represent condensed protoplasm, and consequently stain in fresh preparations more quickly with the aniline dyes than do the other parts. The clear, colorless flakes on the ends of the staves that are seen on dried and stained bacilli, and which were regarded as identical with the polar granules and declared to be spores, result, according to Buchner, from the formation of hollows in the ends of the staves, due to retraction of the tube of protoplasm on the death and drying of the bacilli. Consequently spore-formation has not been proved to exist.

In moist earth (Grancher, Deschamps), in pure and impure water, typhoid-bacilli may remain alive for weeks. They do not die out for many weeks in artificial Seltzer water (Hochstetter). In privy-vaults and fæcal masses, or in earth saturated with fæcal matter, they may survive, under certain circumstances, for weeks and months (Finkler, Uffelmann, Karlinski).

Inoculation of the bacilli in animals used ordinarily for experimental purposes does not produce a disease corresponding to typhoid fever in man. Still experiments of Sirotinin, Beumer, Peiper, and others have shown that the typhoid-bacilli produce active toxins and toxalbumins (Brieger) which kill animals in larger doses, causing hyperæmia and swelling of the intestinal follicles, of the mesenteric glands, and of the spleen. Cultures injected into the tissues produce locally more or less severe inflammation.

The bacilli or their spores get into the human organism probably with the drinking-water and food; still an infection through the lungs is not to be excluded. According to the results of the anatomical examination, they develop in the wall of the intestines, in the region of the solitary and of the agminated follicles of the small and large intestines, as well as in the mesenteric lymph-glands and in the spleen. In the first of these localities they cause an inflammatory infiltration of the mucosa and submucosa (Fig. 417, a_1, b_1) that is extraordinarily rich in cells, and appears in the form of flat or somewhat elevated and rounded areas above the inner surface of the intestines. An exudation of fibrin in the form of threads may take place both on the free surface and in the deeper layers. Occasionally cellular inflammatory foci limited in area occur also in the muscularis (c_1) and in the serosa (d_1). A part of the infiltrated tissue usually sloughs and is then cast off, so that ulcers

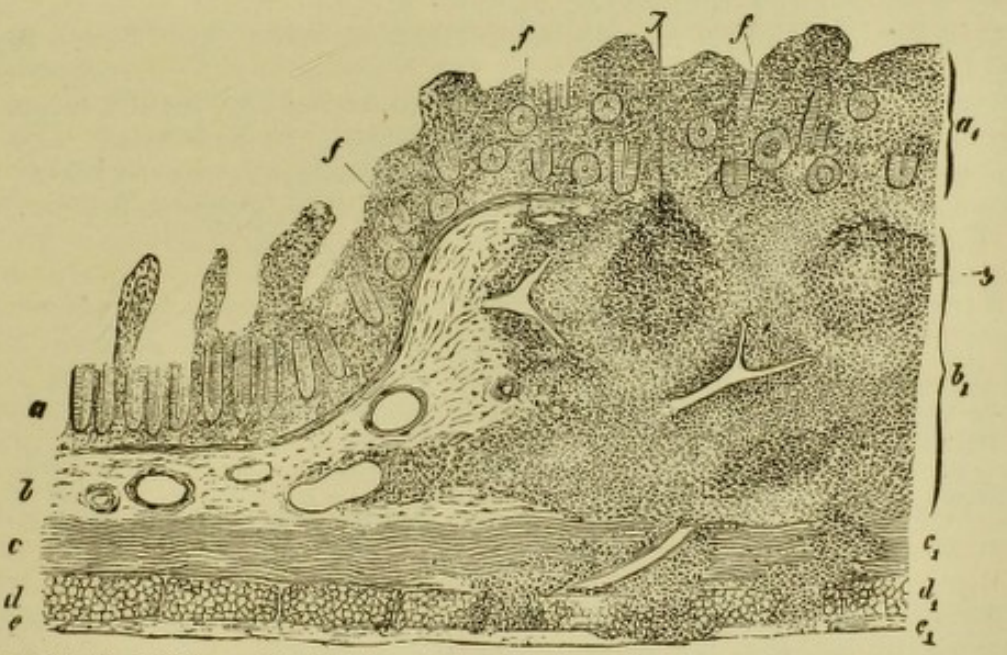


FIG. 417.—Typhoid fever. Section through the edge of a swollen Peyer's plaque. (Alcohol; Bismarck brown.) *a*, Mucosa; *b*, submucosa; *c*, muscularis interna; *d*, muscularis externa; *e*, serosa; a_1, b_1, c_1, d_1, e_1, the different layers of the intestine infiltrated; *f*, *f*, sections of a Lieberkühn's gland; *g*, follicle. Magnified 15 diameters.

are formed. In another part the swelling may subside by the absorption of the infiltration.

The swelling of the lymph-glands, which is sometimes due to the accumulation of cells and fluid, may also be caused by an exudation of thready fibrin. It is a condition which either ends in recovery by the absorption of the infiltration, or leads to partial necrosis of tissue. In the spleen the pulp in particular swells, while its vessels are greatly dilated with blood, and later its parenchyma becomes crowded full of cells and fluid.

According to recent investigations, *the bacilli are usually distributed to other parts of the body*, and it is probable that the inflammatory exudates in the lung which occasionally appear in the course of typhoid fever depend in part upon the growth of the bacilli in the lung. Still it must be borne in mind that inflammations due to inhalation of irritating substances very often occur in the lungs of typhoid patients, and also that *secondary infections* with cocci start from the ulcers and may cause metastatic inflammations in the different tissues. The swellings of the mucosa and submucosa and of the perichondrial tissue in the palate, throat, and larynx that often occur, and that depend upon inflammatory infiltration, are partly the consequences of specific infection and partly of secondary disease. Typhoid bacilli have been demonstrated in the liver, in the gall-bladder, in the roseola patches, in the kidneys, in the central nervous system, in the testicle, in the pleuritic and peritoneal effusions, in the periosteum, and in the bone marrow, etc., in part by means of the microscope, in part by the use of methods of cultivation. They can cause degeneration and inflammation in all of these places and give rise to suppuration in the tissues, so that inflammations arising in the course of a typhoid infection are due sometimes to the dissemination and localization of the typhoid bacilli, sometimes to secondary infections, and sometimes to mixed infections.

Neuhauss was able to find typhoid bacilli even in the spleen of a fœtus four months old, whose mother aborted while suffering from typhoid fever. Reher, Eberth, Chantemesse, Widal, and Ernst report similar instances.

Since the typhoid bacilli produce active toxins and toxalbumins, the morbid phenomena are to be referred largely to poisoning. In the course of typhoid fever bactericidal substances develop in the blood, and these cause a degeneration of the typhoid bacilli. (Comp. § 28. Note also the Widal-Gruber reaction which is there given.)

The cultures of typhoid-bacilli show few characteristic properties, and are consequently difficult to distinguish from other widely distributed bacteria. Thus their properties are very similar to those of the *bacillus coli communis* (cf. § 170). As a differential mark, it is asserted that the typhoid-bacilli produce no indol, whereas other similar bacteria—for instance, the *bacillus coli*—produce indol, so that the cultures of the latter turn red on the addition of potassium nitrite and sulphuric acid. In two-per-cent grape-sugar bouillon the typhoid-bacillus produces no gas, whereas the *bacillus coli* develops gas. Finally the typhoid-bacillus produces faint acidity in milk, but no coagulation; whereas the *bacillus coli* causes strong acidity and curdling of the milk in from twenty-four to forty-eight hours at 37° C.

§ 170. The **bacillus coli communis,** or the *bacterium coli commune* (Escherich), is a fission-fungus constantly present in the abdominal canal of man as well as of mammalian animals. The bacilli are staves 2 to 3 μ long and 0.3 to 0.4 μ thick. They are capable of locomotion by means of flagella, which may number as many as twenty on one staff (Bunge, Luksch, Günther). The bacilli grow at room-temperature as well as at the temperature of the incubator. In the depth of the gelatin they form small, round white colonies, on the surface pellicle-like colonies. On potatoes a yellow juicy coating is formed, of the same shade of color as maize or pease (Günther). Spore-formation does not occur. The bacilli cannot be stained by Gram's method.

The *bacillus coli* is very similar to the typhoid-bacillus; still it may be distinguished from this by proper methods of cultivation and by the employment of suitable reactions (cf. § 169). Formerly it was regarded

as a harmless saprophyte of the large intestines, but it can no longer be doubted, according to recent investigations, that pathogenic properties are also attributable to it, and that it is capable of causing *degenerations* and *inflammations* in various tissues. Thus, under suitable conditions, such as perforation or incarceration of the intestines, or impacted fæces, it may get into the peritoneal cavity and cause purulent inflammation, or at least take part with other bacteria in the production of inflammation. It gets, moreover, not infrequently, into the gall-ducts and gall-bladder, and seems capable of causing inflammations of varying intensity. Moreover, the bacillus has also been found, in some cases of septic disease, in the exudate of the membranes of the brain; furthermore, in pericarditis, pyelitis, pyelonephritis, cystitis, bronchopneumonia, strumitis, scarlatinal angina, and acute yellow atrophy of the liver (Stroebe, von Kahlden); and one cannot doubt that it is the active morbific cause in these diseases.

The similarity between the *bacillus coli* and the typhoid-bacillus has caused various authors to assume that the two bacilli represent only varieties of one kind, and that consequently the two forms may pass over into each other. Still, at present the opinion prevails that the two bacilli are to be entirely separated from each other (cf. § 169). As there are other bacilli that much resemble the *bacillus coli*, and often are not to be distinguished with certainty from it, it may well be assumed that the publications on the *bacillus coli* have not always dealt with the same bacterium.

§ 171. The **bacillus pneumoniæ** was discovered by Friedländer and Frobenius. This bacillus, it was assumed, was able to cause inflammations, especially inflammations of the lungs, of the nose (ozæna), of the middle-ear, and of the meninges, and less frequently of other organs. It is looked upon by Friedländer as the chief cause of croupous pneumonia, but this view is without doubt incorrect (comp. § 163). According to Weichselbaum it has been demonstrated in only about five per cent of the cases of lobar pneumonia. Baumgarten and others go so far as to maintain that its pathogenic significance is not yet firmly established, because other bacteria are always found present with it in the lungs.

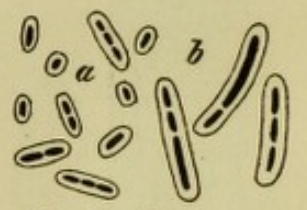


FIG. 418.—*Bacillus pneumoniæ* of Friedländer. *a*, Oval cells and rows of cells with gelatinous capsule; *b*, staves with gelatinous capsule. Magnified 500 diameters.

The bacilli lie in the alveolar exudate, as well as in the pleuritic exudates that form at the same time as the inflammation of the lungs. They appear sometimes in the form of staves (Fig. 418, *b*), sometimes in the form of oval cells (*a*), and not infrequently they are joined together so as to form short chains. Since the oval cells are more numerous than the staff forms, the bacillus was originally reckoned with the cocci.

The bacilli possess a hyaline, mucin-like capsule, soluble in alkalies, insoluble in acetic acid, which forms a common sheath around the chains of the bacilli (Fig. 418). Independent motion has not been observed.

The bacillus loses its color when stained with gentian violet and treated with iodine and alcohol, and may be easily distinguished in this way from the diplococcus. In order to stain it along with the capsule in sections, Friedländer recommends the employment of an acid solution of gentian violet, consisting of 50 parts of concentrated alcoholic solution of gentian violet, 100 parts of distilled water, and 10 parts of

acetic acid. After staining for twenty-four hours the sections are washed out in a 0.1-per-cent solution of acetic acid for a short time.

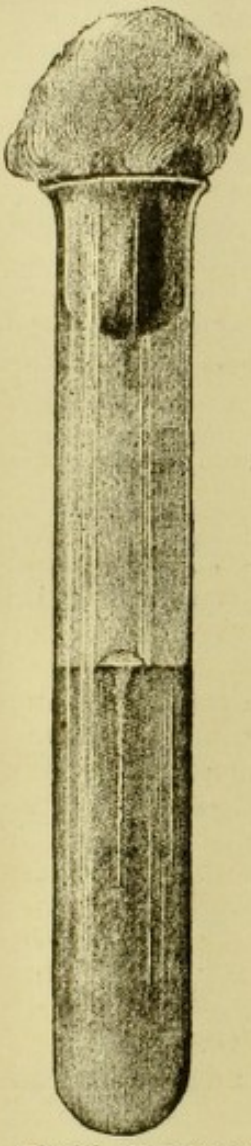


FIG. 419.—Nail-shaped stab-culture of Friedländer's pneumococcus in gelatin.

The bacilli grow in nutrient gelatin at room-temperature, and form porcelain-white, knob-shaped cultures on the surface of the gelatin. The oval and staff-shaped cells possess no capsule. Stab-cultures in gelatin are nail-shaped (Fig. 419), this appearance being due to the fact that the bacilli form a knob-shaped prominence at the entrance of the canal of inoculation. This is a peculiarity that the pneumonia-bacilli share with many other bacteria. On blood-serum they form gray, transparent colonies, on agar-agar grayish-white, on potatoes grayish-white or yellowish-white, creamy colonies. Spore-formation is not observed.

Rabbits are almost entirely refractory to inoculation of the lung; mice, on the contrary, die with pleurisy and disseminated pneumonia in from eighteen to twenty hours after injection of the bacilli into the lung, and the exudate as well as the blood is found to contain bacilli with gelatinous capsule, some lying free, some inclosed in cells. A typical lobar pneumonia cannot be produced in the ordinary experimental animals.

The bacterium of Friedländer, according to Fricke, is the principal representative of a group of bacteria which are gathered together under the name bacillus mucosus capsulatus, and represent varieties of a single species. The fission-fungus described as the ozæna bacillus is identical with the pneumonia bacillus, and apparently so also is the bacillus from the milk fæces of nursing children, known as the bacterium lactis aërogenes, to which is attached possibly a greater etiological significance as the cause of many diarrhœas.

§ 172. A bacillus was described in 1892 by R. Pfeiffer as the **influenza-bacillus** (Fig. 420), and the discovery has been frequently corroborated since; it is regarded as the cause of the influenza. In individuals who are sick of influenza it is found in the catarrhally affected air-passages, occasionally also in the lungs. The small bronchi may contain enormous numbers of the bacilli in pure culture. It is assumed that the multiplication of these organisms in the respiratory tracts causes inflammation, and that at the same time they produce poisons which on being absorbed cause the morbid phenomena peculiar to influenza. Canon states that the bacilli go over into the blood. The inflammatory changes which take place in different internal organs during the progress of influenza may be referred in part to the influenza bacilli, in part to the poisons which they produce, and finally in part to secondary infections.

The influenza-bacilli are very small, thin staves with rounded ends (Fig. 420), which lie separate or joined in twos, and may be stained with the usual aniline dyes, but not by Gram's method. They may be cultivated at body-temperature upon blood-agar or on agar that is smeared with human or pigeon's blood, and they form small, drop-like colonies as clear as water. They do not grow, on the contrary, upon

the other usual media. Spore-formation is not observed. In apes a catarrhal inflammation of the respiratory passages can be produced by intratracheal injection of pure cultures. Rabbits may be poisoned by inoculation of cultures, and they acquire, in consequence of the poisoning, a paralytic weakness of the muscles and dyspnœa. According to Cantani the poison produced by the influenza-bacilli exerts its effect chiefly upon the central nervous system.

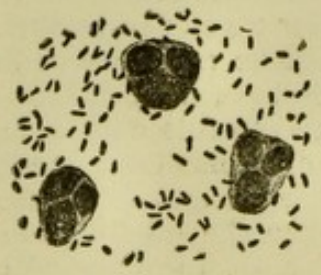


FIG. 420. — Influenza bacilli from the sputum, together with pus corpuscles. (Fuchsin.) Magnified 1,000 diameters.

§ 173. The **bacillus diphtheriæ** (Fig. 421) is a bacillus, first accurately studied by Löffler, which is found in the croupous membrane that occurs in diphtheria, and is very probably the cause of diphtheria. In the internal organs, such as the spleen and lymph-glands, the bacilli are either entirely absent or they are present in such small numbers that they can be detected only by methods of cultivation.

The bacilli are from 1.5 to 3 μ in length, and are often somewhat swollen at the ends. In cultures rods of various lengths are formed, the ends of which are thickened like clubs or pointed (Fig. 421). Stained bacilli appear spotted or granular. The best solution to use for staining is one composed of 30 c.c. of concentrated alcoholic solution of methylene blue and 100 c.c. of 0.0001-per-cent solution of potassium hydroxide, after which the preparation is treated for some seconds with 0.5 per cent acetic acid, and then with alcohol. In stained preparations the bacilli are often segmented. They also stain by Gram's method, provided the treatment with iodine solution and alcohol is done quickly.

The diphtheria bacilli grow best in the presence of air (Löffler) on a mixture of three parts of calf's or sheep's serum and one part of neutralized veal bouillon, to which one per cent of peptone, one per cent of grape sugar, and 0.5 per cent of common salt are added; or on blood-serum and on agar-agar with an addition of ten per cent of glycerin or of nutrient bouillon containing sugar (Kolisko, Paltauf, Kitasato). They form grayish-white colonies. For their development they require a temperature above 20° C., and grow best at from 33° to 37° C. The bacilli are resistant to drying, but they are soon destroyed by moist heat. Spore-formation has not been observed.

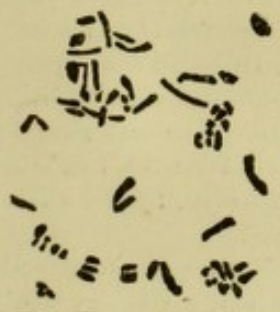


FIG. 421.—Diphtheria bacilli from a pure culture. Smear preparation. (Methylene blue.) Magnified 1,000 diameters.

Guinea-pigs inoculated subcutaneously with cultures of the bacilli (Löffler, Roux, Yersin) die in two or three days. At the point of inoculation there is found a whitish deposit and hemorrhagic œdema. The point of inoculation contains bacilli; the internal organs, on the contrary, are free. In rabbits, chickens, and pigeons, the *introduction of cultures into the trachea through a wound* is followed by the formation of a pseudo-membrane. *Inoculations of the conjunctiva in rabbits and of the vagina in guinea-pigs* are also followed by inflammation and by the formation of a false membrane. Sheep, horses, cats, dogs, cows, rabbits, and pigeons are susceptible to subcutaneous inoculation. Rats and white mice are nearly immune.

Roux, Yersin, Löffler, Spronck, and others observed subsequent

paralysis in pigeons and guinea-pigs that had survived inoculation. Roux and Yersin assert that intravenous injection of filtered cultures—i.e., bouillon-cultures containing no bacilli—causes in guinea-pigs and rabbits a severe illness characterized by paralysis, and fatal consequences in two or three days.

The virulence of the cultures varies greatly. The diphtheria bacilli produce, both in the human body and in cultures, **toxins** which are precipitable with alcohol and are obtained as a whitish powder. This poison has been classed among the toxalbumins; however, according to Brieger and Boer, it is not an albuminous body, and is formed also when the bacilli are grown in alkaline urine (Guinochet). According to Kossel the poison is formed in the interior of the bacterial cells from the nutrient material, and is then secreted.

The poison, injected subcutaneously in watery solution into animals, causes local tissue-necrosis, hemorrhagic œdema, and inflammation; taken up by the body fluids, it produces exudates in the pleura, nephritis, fatty degeneration of the liver, and paralyses.

Diphtheria in man is characterized by an inflammation extending mostly over the mucous membrane of the throat, palate, palatal arches, and the upper respiratory passages. It appears as *a febrile infectious disease combined with symptoms of intoxication, and gives rise locally to croupous exudates*, partly also to diphtheritic desquamation (cf. § 96, Fig. 178 and Fig. 179). The croupous membranes constitute the most striking feature. They are spread over the throat and the nose usually in limited flat patches, more rarely uniformly over larger areas, or they may form a continuous lining upon the larynx and air-passages. Underneath the croupous membrane the epithelium is mostly lost, the connective tissue of the mucous membrane hyperæmic, infiltrated, and swollen (Fig. 180). In severe cases the superficial layer of connective tissue is necrotic in places, most frequently on the tonsils, which are more or less swollen, often to a very marked degree. Deeper down in the tissues, the lymph-glands, especially those in the neck in near proximity, are swollen, and often show, on microscopic examination, small foci in which the cells are necrotic and disintegrated. Of the internal organs the kidneys especially are usually changed, in that there is a more or less high degree of fatty degeneration in the epithelium and capillary walls, not infrequently also an œdematous swelling and foci of small-cell infiltration. In the spleen, in the interior of the white-looking follicles, areas of degeneration are often found, in which a larger or smaller number of the cells are necrotic, some of them being already in a disorganized state and having no nuclei. In the blood many leucocytes show fatty degeneration. Degenerative changes and areas of inflammation are not infrequently found in the heart muscle, and in the intestine there is tumefaction of the follicular apparatus.

The lungs are not notably changed by the diphtheria poison; still bronchopneumonias often occur which are due to inhalation of the irritating contents of the bronchi, or to an extension of the bronchial inflammation upon the respiratory parenchyma.

The *local inflammations of the mucous membranes* as well as the *symptoms of intoxication* can be *caused only by the diphtheria bacilli and their toxins*, but it is to be remembered that *streptococci* also are with great regularity found in the diseased areas, and that a *pure streptococcus infection* may also call forth the clinical and anatomical picture of "diphtheria." If both species of bacteria are present, then the harmful action

of the one is supported by that of the other, and it appears that the presence of the streptococci increases the virulence of the diphtheria bacilli. In severe forms of diphtheria, streptococci are usually present in great numbers; yet every streptococcus infection does not warrant a bad prognosis, for the virulence of the cocci also varies considerably.

In the course of the infection due to the diphtheria bacilli, *antitoxins* arise in the body which nullify the poisonous action of the toxins; they aid and make possible recovery from the disease. This formation of antitoxins also follows the inoculation of animals with attenuated bacilli, and on this depends the possibility of obtaining from animals (sheep, horses), which are repeatedly inoculated with bacilli of increasing virulence, a serum which contains an antitoxin valuable for therapeutic purposes (comp. § 30).

Lehmann and Neumann call the diphtheria bacillus *coryne bacterium* on account of the club-like shape of the rods. Inasmuch as the bacillus can also form branched threads in cultures, they count it among the *hyphomycetes*, among which the tubercle bacillus and the actinomyces-fungus (oöspora) are also classified by them and by others.

According to Löffler, von Hoffmann, Roux, Yersin, Babes, and others, bacilli designated as *pseudodiphtheria-bacilli* occur very often in the mouth and throat, which look like the diphtheria-bacilli and even in cultures can only with difficulty be distinguished from these. Since the diphtheria-bacilli may lose their virulence, it is not improbable (Roux, Yersin) that the two bacilli are varieties of one kind.

§ 174. The **bacillus tetani** (Kitasato) is a fine, slender bacillus (Fig. 422) which is widely distributed throughout the superficial layers of the earth, and is to be regarded as the cause of tetanus. According to observations of Nicolaier made in 1885, it is often possible, in mice, guinea-pigs, and rabbits, by a subcutaneous inoculation of earth taken from the superficial layers, to obtain typical tetanus with fatal termination.

FIG. 422.—Tetanus bacilli showing spore-formation. The spore is located at one pole.

The demonstration was first made by Rosenbach in the year 1886 that the bacilli found in traumatic tetanus and those found in tetanus due to frost-bite in human beings, in the region of the seat of injury, were one and the same, and that when inoculated into guinea-pigs and mice they cause genuine tetanus. Since then this discovery has been often corroborated. The bacillus is present neither in the soil nor in the infected wound in an isolated condition, and consequently inoculations have been made with mixtures of bacteria. The effort to isolate in cultures the bacillus that was regarded as the cause of tetanus was unsuccessfully made by most investigators. Kitasato in 1889, in Koch's laboratory, succeeded in isolating the tetanus-bacillus by allowing the mixed cultures to remain in the incubator a few days and heating for a half-hour or an hour at 80° C., and then subsequently making plate-cultures in an atmosphere of hydrogen. The bacteria growing along with the tetanus-bacillus are killed by the heating, while the tetanus-bacillus is preserved.

The tetanus-bacillus is anaërobic and grows very well in an atmosphere of hydrogen, but not in carbonic-acid gas. It grows in ordinary slightly alkaline agar-agar containing peptone, and in blood-serum and nutrient gelatin. It liquefies the latter with the production of gas. Addition of from 1.5 to 2 per cent grape-sugar accelerates the growth. The most favorable temperature is between 36° and 38° C. It forms long, thin, bristle-like staves that produce spores on one end (Fig. 422) which

cause a swelling of the end of the staff, giving rise to the name knobbed bacilli. It may grow out in cultures into long pseudothreads. The cultures give out an offensive odor; gelatin is slowly liquefied. The bacilli stain by Gram's method. They are motile except at the period of spore-formation, and they possess peritrichal flagella. Pure cultures inoculated into horses, asses, guinea-pigs, mice, rats, and rabbits cause tetanus; but rabbits must be inoculated with somewhat larger amounts. The tetanic contractures start first in the neighborhood of the point of inoculation. Suppuration does not occur at the point of inoculation. The bacilli are not to be found after the animal is dead, and are never found except at the seat of inoculation.

According to the experimental investigations of Kitasato, the filtrate which is obtained from bouillon-cultures of the bacilli, but which contains no bacilli, acts in the same way as the cultures containing the bacilli, and guinea-pigs especially are very sensitive to it. The blood or transudate from the thoracic cavity of an animal infected with tetanus, although free from bacilli, causes tetanus when inoculated into mice. It is consequently to be assumed that in tetanus it is a matter of *intoxication* with a poison (tetanotoxin) that is distributed throughout the blood. The poison is destroyed by heat (Kitasato)—a temperature of 65° C. and over—in a few minutes, and by direct sunlight in from fifteen to eighteen hours, and loses its effects in diffuse daylight in a few weeks. According to investigations of Brieger and Cohn, the purified poison gives no reaction for albumin, and consequently does not belong to the toxalbumins.

The infection, i.e., the intoxication, of man results in most cases from small wounds. Rheumatic tetanus, which does not start from wounds, may apparently arise from a multiplication of the bacilli in the bronchi (Carbone and Perrero). It follows from this that there are also tetanus bacilli which grow in the presence of oxygen. The tetanus-toxin acts principally upon the nervous system.

The **bacillus œdematis maligni** (*vibrion septique* of Pasteur) is an anaërobic bacillus which was first thoroughly investigated by R. Koch. It is found in various putrefying substances, and the spores almost never fail to be present in earth that is manured with foul liquids or liquid manure. The bacilli are from 3 to 3.5 μ long and from 1 to 1.1 μ broad, and often form long pseudothreads. They are similar to the anthrax-bacilli, but are somewhat more slender and rounded on the ends, not sharply cut across, and are occasionally motile. In spore-formation a swelling develops from one part of the rod, as in *bacillus butyricus*, so that spindle-shaped and tadpole-shaped forms result.

The bacillus is motile and possesses flagella on the ends as well as on the sides. It is not stained by Gram's method.

It grows in nutrient gelatin as well as in agar-agar and coagulated blood-serum, but it must be introduced deep down and cut off from the air. Nutrient gelatin with the addition of one or two per cent of grape-sugar is a specially favorable medium (Flügge). Nutrient gelatin and blood-serum are liquefied, the latter with the production of gas.

The bacillus can be readily obtained by sewing up garden-earth under the skin of a guinea-pig and by taking care that the air does not find access to the point of inoculation. The subsequent multiplication of the bacilli causes a progressive œdematous swelling of the subcutaneous tissue. At a more advanced stage the bacilli spread over the serous membranes, and into the spleen and other organs.

Mice, guinea-pigs, horses, sheep, and swine are susceptible to the bacilli; cattle are not (Arloing, Chauveau).

According to the observations of Brieger, Ehrlich, Chauveau, Arloing, and others, the œdema-bacilli also occasionally develop in the tissues of human beings, especially when the tissues are poorly nourished and the bacilli by any accident—e.g., by puncture of a hypodermic syringe—get into the depth of the tissues. They lead to a gangrenous process which is combined with bloody œdema and the development of gas.

According to Vaillard and Vincent, tetanus does not follow inoculation of tetanus-bacilli deprived of poison. Consequently it must be assumed that the bacilli can only multiply in the tissues of man and animals and lead to poisoning when special conditions are present, when the tetanus poison itself is also present at the same time, or when other bacteria, such as *bacillus prodigiosus*, get into the tissues. Blumenthal believes that the bacilli excrete a ferment which produces, within the organism, the tetanus poison.

According to investigations of Kitasato, Tizzoni, Cattani, Baquis, Behring, and others, susceptible animals may be made immune from tetanus, or, more properly speaking, poison-proof against the poison of tetanus. The blood of animals that have been rendered poison-proof possesses the property of destroying the poison of tetanus, and consequently it is possible to immunize susceptible animals with the curative serum obtained from this blood, or to cure tetanus that has already broken out in man or animals (cf. § 30).

As regards the bacteria of hemorrhagic infection, compare § 46.

§ 175. The **bacillus of the bubonic plague** was discovered in 1894 by Kitasato and Yersin, of the Japanese and French commission of investigation, while investigating an epidemic which had broken out in Hong-Kong. The plague bacillus is a small rod, rounded on the ends (like the bacillus of fowl-cholera), which stains easily with the basic aniline dyes, especially with methylene blue, and shows exquisite polar staining. It is decolorized by Gram's method. According to Zettnow the bacilli possess capsules. It is found in all those affected with the plague, especially in the swollen lymph-glands, but also in the spleen and in the blood. It can be cultivated on the various artificial media, and forms bluish-gray colonies, which contain rods of various lengths. It multiplies abundantly in bouillon containing sugar. Spores are not formed. The bacilli are easily destroyed by heating, but can withstand drying well.

Mice, rats, and pigs are especially susceptible to plague inoculation, and frogs also are said to be susceptible (Dewel). Inoculation of virulent cultures causes death in a few days, and the bacilli are then found in the blood as well as in the œdematous fluid at the point of inoculation. When less virulent cultures are inoculated, glandular swellings develop after a few days (Kolle), and the animals die only at the setting in of severe swelling of the glands in the second week. The bacilli are found in the swollen lymph-glands and in the blood.

The bubonic plague, which in Europe at the end of the seventeenth and the beginning of the eighteenth century still carried off the population in vast numbers (the "Black Death"), has since 1720 almost entirely disappeared from Europe, and has shown itself only here and there in Eastern Europe. In different districts of Asia (Yunnan in China, Arabia, Mesopotamia) the disease seems to be endemic, and to spread from time to time like the cholera.

Man seems to be infected principally through small wounds (Kitasato, Aoyama, Yersin), yet an infection by means of inhaled air cannot be ruled out. Rats and mice contribute essentially to the spreading of

epidemics. Insects that have come in contact with sick animals or men can likewise spread the infection. Marked glandular swellings, which may go on to suppuration, are the chief symptom of the disease, which generally ends in death. Besides these appear enlargement of the spleen, degenerative changes in the glandular abdominal organs, and hemorrhages. In the later stages of the disease the enlarged and suppurating lymph-glands may also contain streptococci beside the plague bacilli. Secondary infections also occur.

Experiments carried on by Haffkine make it appear probable that successful protective inoculations may be undertaken with killed cultures of the plague bacilli. Yersin states that an active curative serum for the treatment of those infected may be obtained from immunized animals.

From the investigations of Ducrey, Krefting and Petersen (comp. Petersen: "Ulcus Molle," *Arch. f. Derm.*, XXIX., 1894, and XXX., 1895), it seems probable that the **ulcus molle**, or *soft chancre*, is caused by a bacillus. This view is, however, combated by competent authors (Finger: "Die Syphilis und die venerischen Krankheiten," Leipsic, 1896), and the doctrine is advocated that the soft chancre does not possess a specific virus. It is to be noted also that attempts to cultivate the bacilli of chancre have not so far been successful.

According to communications from Sanarelli ("Sur la Fièvre jaune," *Ann. de l'Inst. Pasteur*, 1897, and *Centralbl. f. Bact.*, XXII.), which have but recently appeared, **yellow fever** seems to be caused by a bacillus which can be cultivated. Its isolation is often difficult, by reason of complicating secondary infections with bacterium coli, streptococci, etc.

§ 176. The **bacillus tuberculosis** is the cause of the infectious disease which is very frequent as well in man as in the domestic mammalia, and which is usually called **tuberculosis**, but is also sometimes called *Pearl disease* (*Perlsucht*) in animals.

The tubercle-bacilli, discovered and thoroughly investigated by Koch in the year 1882, form narrow staves (Fig. 423), from 1.5 to 3.5 μ in length, that are often slightly curved. Aniline dyes (fuchsin or gentian violet), in aqueous solution with the addition of an alkali or carbolic acid or aniline, are suitable for staining them. The bacilli once stained retain the dye even when the preparation is decolorized with dilute sulphuric or nitric acid, or with hydrochloric acid and alcohol.

The stained bacilli show not infrequently in their interior clear, glistening, unstained places, or are composed of little stained globules. Koch interpreted these clear portions formerly as spores, and this view was generally accepted for a long time. But, nevertheless, a germination of these structures cannot be proved, and at present the objects in question are no longer regarded as spores. Consequently the tubercle-bacilli produce no special resistant forms, but still the bacilli are more resistant against external influences—e.g., against drying—than are many other bacteria.

The tubercle-bacilli may be cultivated at the body-temperature and in the presence of oxygen upon solidified blood-serum, upon blood-serum gelatin, upon nutrient agar, and in bouillon; they multiply, however, very slowly, so that only on the seventh to tenth day, or even later, cultures appear at the point of inoculation in the form of dull-white flakes resembling little scales. Larger cultures form, on the surface of solidified blood-serum, white, irregularly shaped, dull coatings (Plate I., Fig. 4). According to Nocard, Roux, and Bischoff, the growth of the bacilli is greatly aided by the addition of from four to eight per cent of glycerin. Pawlowsky succeeded in cultivating them on potatoes in sealed

glass tubes. In cultures the tubercle bacilli also produce threads, which in some cases split into two branches.

At temperatures below 28° C. and above 42° C. the growth of the bacilli ceases. Sunlight kills the bacilli in a short time (Koch).

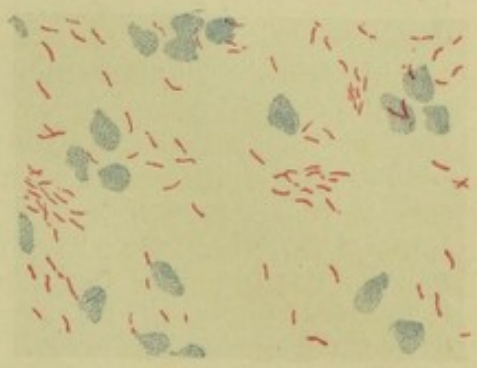


FIG. 423.—Tubercle-bacilli. Sputum of a man suffering from tuberculosis of the lung, spread in a thin layer on a cover-glass and stained with fuchsin and methylene blue. Magnified 400 diameters.

If the bacilli from pure cultures are inoculated into experimental animals, tuberculosis is produced in these; and the infection succeeds as well by inoculation under the skin or in the abdominal cavity or in the anterior chamber of the eye as by inhalation of an atomized suspension of the culture and by injection of the bacilli into the veins. Guinea-pigs and cats are specially susceptible; dogs, rats, and white mice, on the contrary, are less so.

The **infection of human beings and of animals** occurs from the taking up of the tubercle-bacilli from the lung or intestinal tract, or from wounds and ulcerations. In the alimentary canal the commonest points of entrance for the bacilli are the lymphadenoid apparatuses, the tonsils, and the intestinal lymph-follicles. Moreover, a direct transfer of the bacilli from the mother to the fœtus developing in the uterus also takes place.

In the external world the bacilli are spread mainly by the sputa, under certain conditions also by the fæces and by the urine; furthermore, they emanate from tuberculous ulcers of the skin or tuberculous organs taken from living or dead persons. Since the bacilli are tolerably resistant, they may remain preserved here, under certain conditions, for a long time, and can become mixed with the respired air as well as with

FIG. 424.

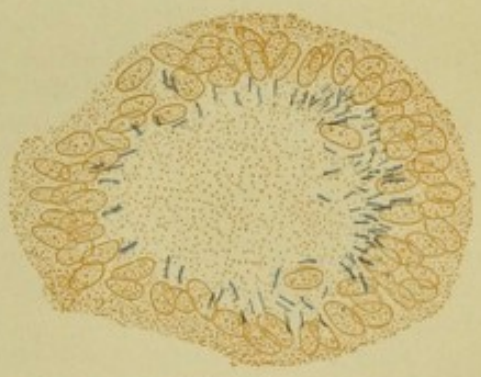


FIG. 425.

FIG. 424.—Tissue changes produced by a recent invasion of the tubercle-bacilli. (Diagrammatic, after Baumgarten.) *a*, Hyperplastic connective tissue; *b*, cross-section of a blood-vessel; *c*, karyomitoses in the connective tissue; *d*, mitoses of an endothelial cell of a vessel; *e*, emigrated leucocytes. Magnified 350 diameters.

FIG. 425.—A giant cell containing bacilli with necrotic centre, from a tubercle. Preparation stained with gentian violet and vesuvin, and mounted in Canada balsam. Magnified 350 diameters.

the food and drink. The milk of tuberculous cows contains the bacilli, especially when the udder is diseased; it seems, however, that the bacilli may also pass over to the milk when the udder is not demonstrably diseased (Hirschberg, Ernst, Leuch).

If the bacilli succeed in developing and multiplying in any tissue of the human body, they lead by a series of changes to the formation of *nodular masses of granulation tissue* or **tubercles,** which remain *devoid of blood-vessels,* and which, when they have arrived at a certain stage of development, *die out again.*

The first effect of the development of the bacilli in a tissue (Fig. 424) may be a *hyperplasia of the fixed cells of the tissue,* which begins with karyomitosis (*c*, *d*) and leads to the formation of epithelial-like protoplasmic cells (fibroblasts), which are usually designated as *epithelioid cells* (*a*). By reason of the fact that the process of cell-division repeats itself many times, there are produced collections of epithelioid cells (*a*) which form knot-like foci at the point where the bacilli multiply, and in these foci the bacilli lie, some of them between the cells, others in the cells themselves (Fig. 424).

By the hyperplastic development of cells the connective-tissue stroma of the original tissue is pushed more and more to one side, and even to

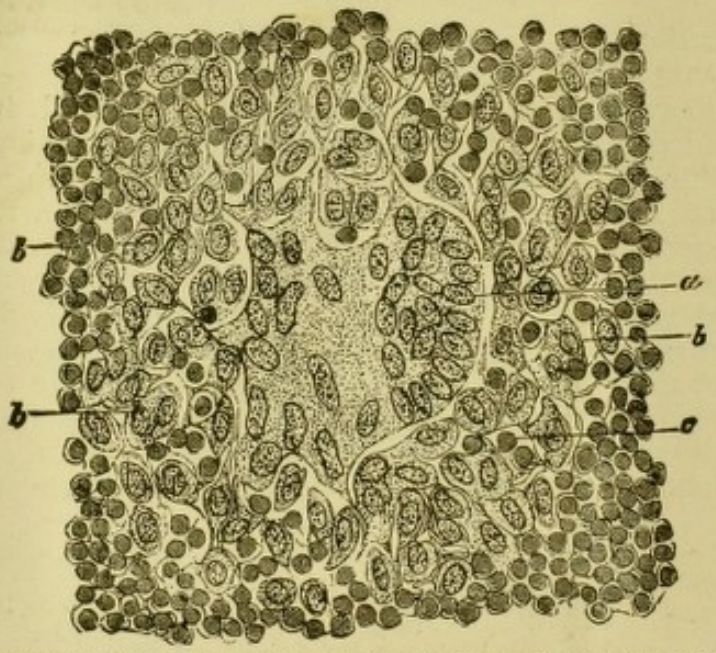


FIG. 426.—Tubercle from a fungous granulation of bone. *a*, Giant cells; *b*, epithelioid cells; *c*, lymphoid cells. (Müller's fluid; Bismarck brown.) Magnified 400 diameters.

some extent obliterated, so that the individual cells come finally to be separated from one another only by scanty fibres whose general arrangement is in the form of a net, which is consequently spoken of as the reticulum of the tubercle.

These exuberantly growing cells have for the most part one or two nuclei (Fig. 424, *a*, and Fig. 426, *b*); but usually cells containing several or many nuclei (*giant cells*) also appear (Fig. 425, Fig. 426, *a*) and these often inclose a very considerable number of large, oval, vesicular nuclei, as well as bacilli (Fig. 425). The nuclei of the giant-cells are nearly always distributed in the protoplasm in an irregular manner, sometimes grouped in the form of a wreath or horseshoe, sometimes massed together at one pole, sometimes at two or more points (Figs. 425 to 429). The nucleus-free part of the giant-cells, when they are properly stained, permits us to recognize conditions of degeneration and necrosis of the protoplasm which are brought about by the action of the bacilli present in the giant-cells (Fig. 425 and Fig. 429, *c*).

New vessels are not formed within the tubercles, and even the old vessels are obliterated by the hyperplasia.

To the hyperplasia already described is added, sooner or later, an

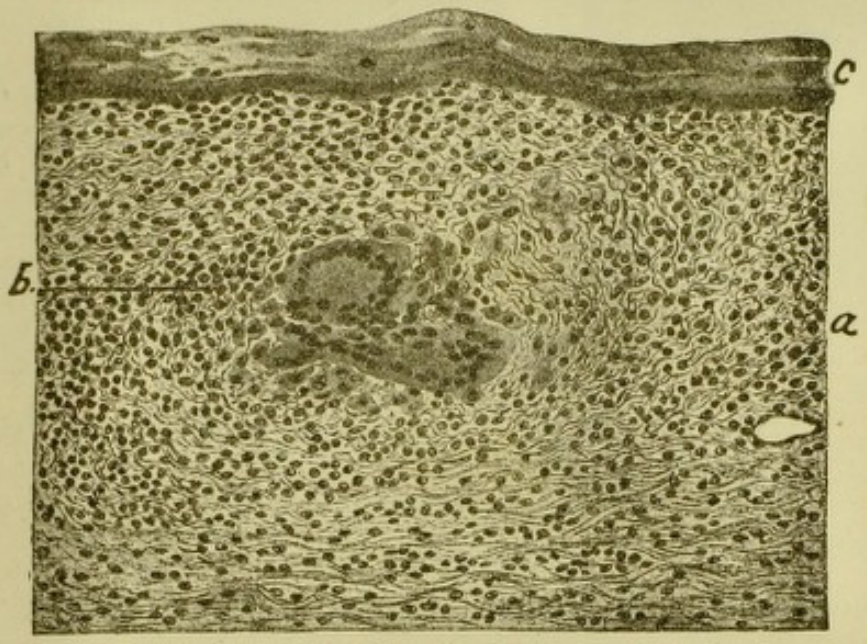


FIG. 427.—Tuberculosis of the pleura. (Alcohol; Van Gieson's mixture.) *a*, Thickened and proliferating pleura; *b*, tubercle, with giant cells; *c*, deposit of fibrin. Magnified 200 diameters.

inflammatory exudation, which is first recognized by the *massing together of the leucocytes* (Fig. 424, *e*, and Fig. 426, *c*).

The time at which the emigration of the cells begins varies according to the mode of invasion of the bacilli, and probably also according to

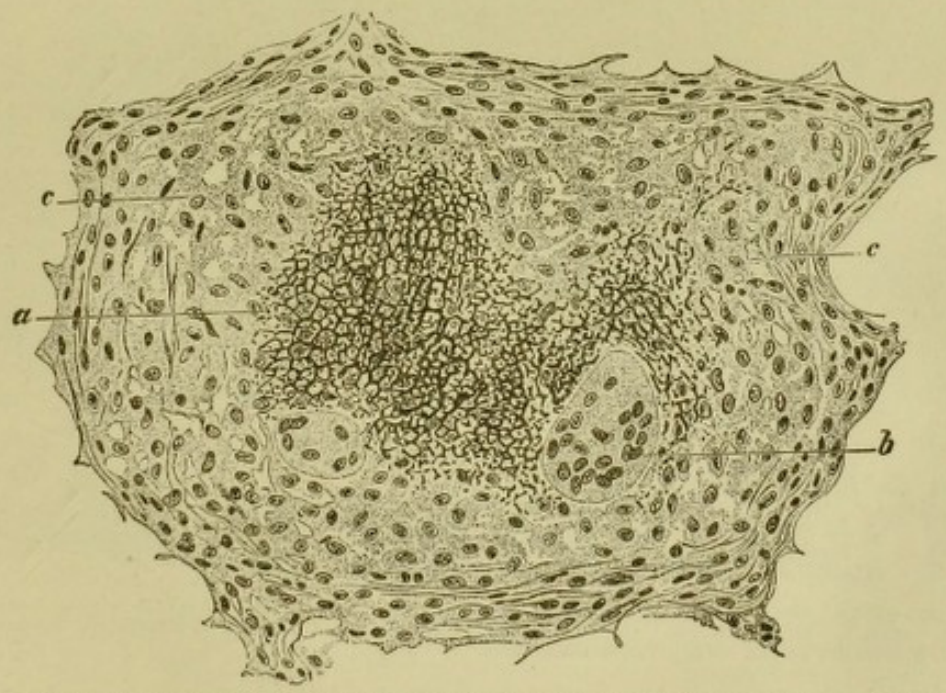


FIG. 428.—Large-cell tubercle from a tuberculous lung, with some exudation of fibrin. (Alcohol; fibrin stain.) *a*, Fibrin; *b*, giant cell; *c*, tissue composed of large cells. Magnified 300 diameters.

the character of the infected tissue. It takes place earliest when the tissue is at the same time subjected to some other pernicious influence,

e.g., to trauma. If a large-celled nodule has been formed by the excessive cell-reproduction, the emigration of cells leads first to an accumulation of small round cells at its periphery (Fig. 426, *c*, and Fig. 427, *b*) and then to an infiltration with round cells, which infiltration may become so marked that the large cells may be partly or entirely hidden. In this way a large-celled tubercle becomes a *small-celled tubercle.* If the emigration of the cells takes place very early, the tubercle assumes from the start the *character of a small-celled focus;* however, mononuclear fibroblasts, or even giant-cells may generally be made out in the midst of the focus (Fig. 427, *b*).

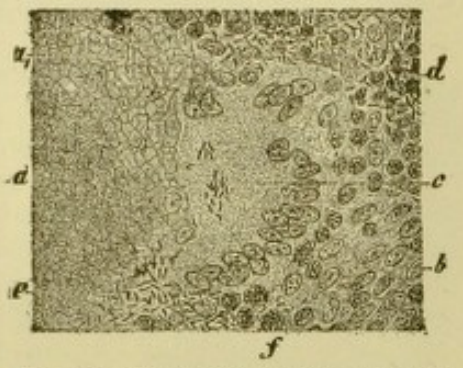


FIG. 429.—Tissue from a focus of tuberculous disease, showing bacilli and a limited area of cheesy degeneration. (Alcohol; fuchsin; aniline blue.) *a*, Granular cheesy material; a_1, cheesy material in the form of small, separate aggregations; *b*, fibrocellular tissue; *c*, partly necrotic giant cell with bacilli; *d*, cellular tissue invaded by bacilli; *e*, a similar invasion in tissue that is necrotic; *f*, bacilli inclosed in cells. Magnified 200 diameters.

With the emigration of the cells there is usually combined a serous exudation, and *fibrin* may be deposited in the tubercle itself (Fig. 428, *a*) as well as in the *surrounding tissue.*

The tubercle, when it has arrived at the height of its development, forms a small, *gray, translucent, cellular nodule* which may attain the size of a millet-seed, and which incloses among its tissues more or less numerous bacilli. When it has reached a certain size *retrograde changes* usually appear in the centre, in consequence of which the tubercle becomes cloudy and opaque, and presents a whitish, or grayish-white, or

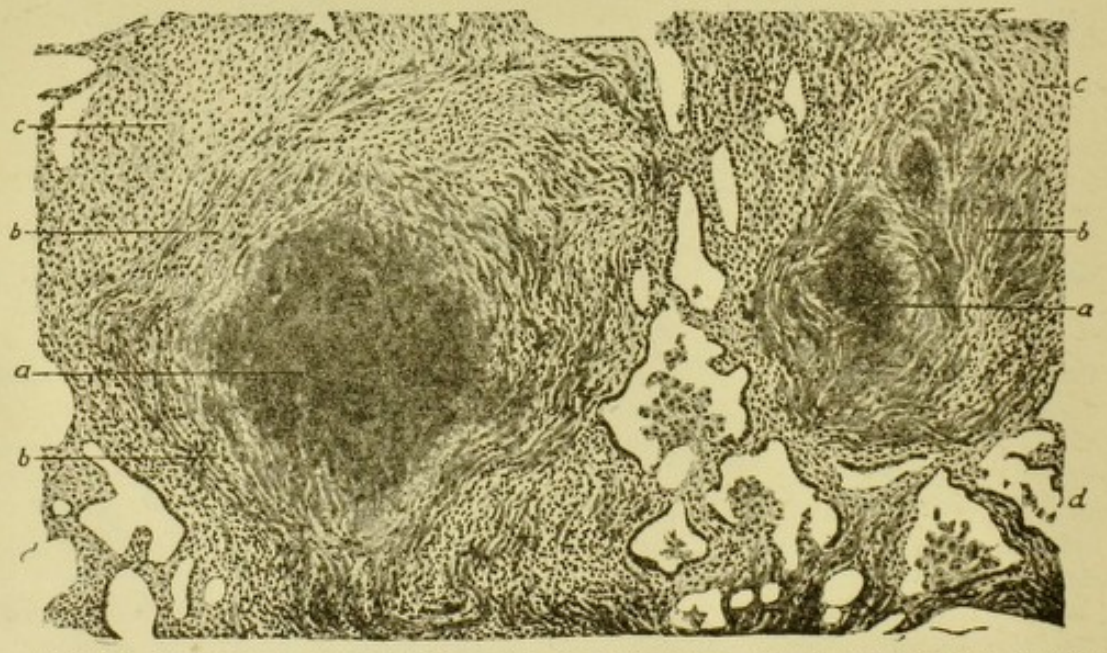


FIG. 430.—Partly cheesy and partly fibrous tubercle of the lungs. (Alcohol; Van Gieson.) *a*, Cheesy centre; *b*, dense, homogeneous connective tissue, containing but few nuclei; *c*, connective tissue rich in nuclei; *d*, pulmonary tissue. Magnified 80 diameters.

yellowish-white color—a change which is commonly termed cheesy degeneration of the tubercle.

The **caseation of the tubercle** depends partly upon a *necrobiosis* of the cells, partly upon a *deposition of coagulated substances* in the spaces

between the cells. The cell-necrosis is characterized by the death of the nuclei and the transformation of the cells into flake-like bodies, which later disintegrate and become granular (Fig. 429, *a*, a_1). The substance stratified between the cells is composed either of fibrin with a net-like arrangement (Fig. 428, *a*), or of a granular or hyaline fibrinoid substance, much resembling fibrin and arranged in nets. This substance does not take the Weigert fibrin-stain, but it stains yellow with Van Gieson's stain. In the further course of the caseous degeneration the fibrin and the fibrinoid substance are reduced to a granular mass, which fuses with the cell-detritus, so that the central part of the tubercle is then composed of a flake-like granular mass, which is only feebly stained with nuclear stains.

The caseous degeneration always attacks first the central parts of the tubercle, and generally also remains limited to these, but it may also affect the entire tubercle. If the caseous degeneration of the periphery does not occur, then the cellular character of the tubercle, after a shorter or longer time, undergoes at the periphery a *fibrous metamorphosis*, so that a **fibro-caseous tubercle** is formed (Fig. 430), the connective tissue of which is rich in cells and finely fibrous, or more coarsely fibrous, or hyaline and poor in cells (*b*). Generally, in the course of time, it becomes sharply differentiated from the caseous centre (*a*), so that the latter appears to be encapsulated by the connective tissue. If the tuberculosis runs a very favorable course, the centre instead of caseating may undergo a connective-tissue metamorphosis, so that the tubercle becomes a **fibrous nodule.**

The *infectious nature* of the disease known as *tuberculosis* had already been determined by the experimental transmission of tuberculosis to animals (Villemin, Lebert, Wyss, Cohnheim, Klebs, Langhans, and others) before the discovery of the tubercle bacillus. However, it was a long time before the view that tuberculosis is an infectious disease found general support, and the opposition (Middendorp) has even to-day not entirely disappeared.

The manifestations of tuberculosis, the appearance of caseating granulations in connection with insignificant wounds, were formerly attributed to the existence of an especial anomaly of the constitution, upon which it depended that infected individuals responded to lesions of the tissues arising in one way or another, not with the production of sound tissue, but with the formation of frail, caseating granulations. Among animals used for experiment this peculiarity was ascribed to those animals which are especially susceptible to tuberculosis, viz., guinea-pigs and rabbits; in man, on the other hand, this supposed constitutional anomaly was designated as *scrofulosis*, and it was believed to manifest itself in a tendency to inflammations of the skin and mucous membranes, to swellings of the glands, and to joint- and bone-diseases. Such a scrofulosis, however, does not exist. Pathological conditions which were, and still are, included under this name are for the most part manifestations of an already existing tuberculosis of the mucous membranes, likewise of the lymph glands and of the osseous system; and when inflammations of the mucous membranes and the skin, which are not of a tuberculous nature, recur frequently, and may, according to experience, in the course of time lead to tuberculosis (through secondary infection), then it is not a matter of an anomaly of the constitution, but of some other infection, for example, with pus cocci.

According to investigations of Koch, an active *poison*, *tuberculin*, can be extracted in aqueous glycerin solutions from pure cultures of the tubercle bacilli. For obtaining large amounts of tuberculin, cultures of six or eight weeks old, in slightly alkaline veal-broth to which one per cent of peptone and four or five per cent of glycerin are added, are especially favorable. The cultures are evaporated to about one-tenth the original volume by warming, and then are filtered through porcelain or siliceous-marl filters. In this way tuberculin is obtained free of bacteria, in a mixture which contains from forty to fifty per cent of glycerin, and thus is protected against decomposition. Tuberculin may be purified by suitable manipulation—i.e., precipitation with sixty per cent of alcohol—and then forms a white mass which is very probably an albuminous body (Koch), but can be ranked neither with the toxalbumins nor with the peptones, since it is very resistant to high temperatures and is precipitated with acetate of iron.

According to later communications from Koch a poisonously acting substance may also be obtained by expressing the contents of ground-up bacilli (comp. § 30). Both substances have been tried for the immunization of man against tuberculosis, yet a satisfactory result cannot be recorded (comp. § 30).

According to investigations of Prudden, Hodenpyl, Kostenitsch, Vissmann, Masur, and Kockel, dead tubercle-bacilli conveyed into the tissues of an animal by inoculation, or by injection into the blood-current, or by introduction into the respiratory passages, produce, at the point of introduction, inflammation and new growth of tissue very similar to that produced by the living bacilli. When introduced in large numbers, the dead bacilli may also produce suppuration. The process, however, caused by the dead bacilli differs from that caused by the living bacilli in the following respects: the dead bacilli become entirely destroyed in a few weeks, and the granulating nodules heal up by being changed into fibrous tissue; furthermore, the extent of the local new formation of tissue depends entirely upon the number of bacilli introduced; and, finally, no extension of the process takes place in the body. The dead bacilli contain, therefore, substances (proteins) which cause inflammation and later new growth of tissue.

Nocard, Roux, Mafucci, and C. Jones have observed that in cultures the *tubercle bacilli form threads with branchings*. Jones describes in these threads besides vacuoles also strongly refracting bodies, which he is inclined to take for spores. He further found in caseous pulmonary areas formations resembling the actinomyces-clubs, and looks upon these as well as upon the actinomyces-wedges as collections of a vitreous substance on the thread-fungi or even on the elastic fibres. He considers the tubercle bacillus as well as the actinomyces-fungus as a single-celled, non septum-forming, branching thread-fungus. Lehmann, who agrees with Jones, places the tubercle bacillus among the hyphomycetes and designates it as *mycobacterium*.

§ 177. **Tuberculosis** at its commencement is a **local disease** that oftenest appears in the lungs, the intestinal tract, and the skin; that is to say, in places that are accessible from without. But *cases of crypto-*

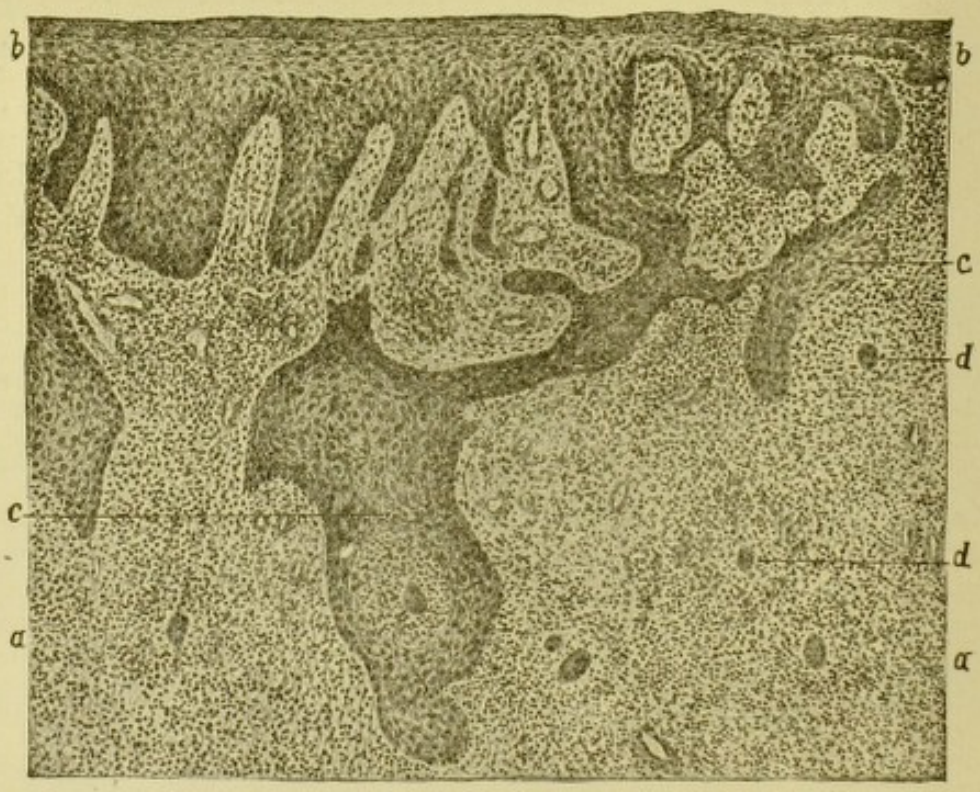


FIG. 431.—Lupus of the skin from the region of the knee, with atypical growth of epithelium. (Alcohol; Van Gieson.) *a*, Corium converted into granulation tissue in which there are scattered tubercles; *b*, epidermis; *c*, plugs of epithelium which have grown down into the deeper layers of the tissues; *d*, tubercles. Magnified 50 diameters.

genetic infection are by no means of rare occurrence; they are characterized by pathological changes which are concealed from view, deep down

in the parenchyma of some internal organ; as, for example, in the lymph-glands, in the epididymides, in the bones and joints, in the brain, and in the Fallopian tubes. So there remains no other possibility except to assume that the bacilli under certain circumstances get into the body without leaving behind a permanent change at the portal of entrance; that they develop first in distant organs to which they have been conveyed by way of the blood- or lymph-currents, and by their increase give rise to new formation of tissue and to emigration of white blood-corpuscles.

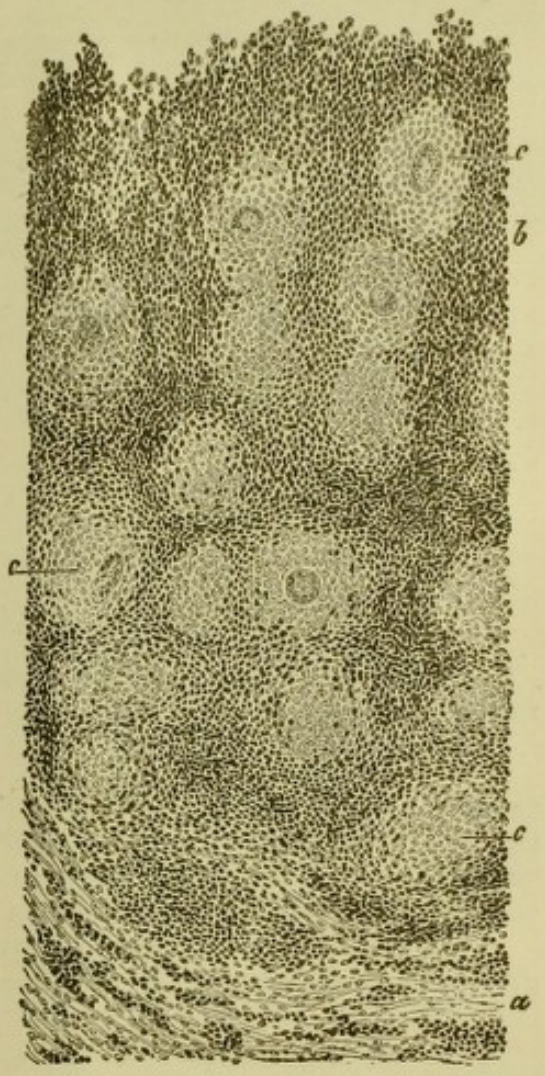


FIG. 432.—Growth of tuberculous granulations from the synovial membrane of the knee-joint. (Müller's fluid; Bismarck brown.) *a*, Connective tissue; *b*, granulation tissue; *c*, tubercles. Magnified 80 diameters.

The local disease begins with the formation of **miliary tubercles**, that is, cellular nodules of the kind already described, which arise in the tissue either singly or in great numbers simultaneously (in multiple infection) or one after the other (in secondary dissemination of the multiplying bacilli). The tissue in the neighborhood of the individual tubercles, and therefore also that between the tubercles, show sometimes more, sometimes less, pronounced appearances of inflammatory exudation and proliferation, especially cellular, by which processes the formation of **large granulating areas** very frequently occurs. In the mucous membranes and in the skin (Fig. 431, *a*) large areas of the mucosa and submucosa, and of the corium respectively, may, through the presence of such granulations, undergo thickenings of a nodular or flatly spread-out character. In the serous membranes large, flat, nodules may develop, and in their neighborhood the serosa will be thickened and covered with fibrinous exudate. In the synovial membrane of the joints and in the bursæ mucosæ soft fungous growths, the so-called *fungous granulations*, often develop; and in the lungs or in the glandular organs, in the periosteum, and in the bone-marrow, roundish gray-red or gray granulation-areas of different sizes, etc., make their appearance. All these areas have one feature in common, viz., that in their neighborhood are found inflammatory infiltrations and proliferations of the tissue, which assume the character of **granulation tissue** (Fig. 431, *a*; Fig. 432, *b*); and this granulation tissue contains in its substance characteristic formations—**tubercles** (Fig. 431, *d*, and Fig. 432, *c*)—which are non-vascular cellular nodules that often contain giant-cells. In gray-red looking tissues, rich in blood, these tubercles may often be recognized

with the naked eye, as gray, or—in case they have already undergone caseous degeneration—as white or yellowish-white nodules.

The *area of tuberculous granulation* when once formed continues to increase in its further development by *appositional growth*, whereby the

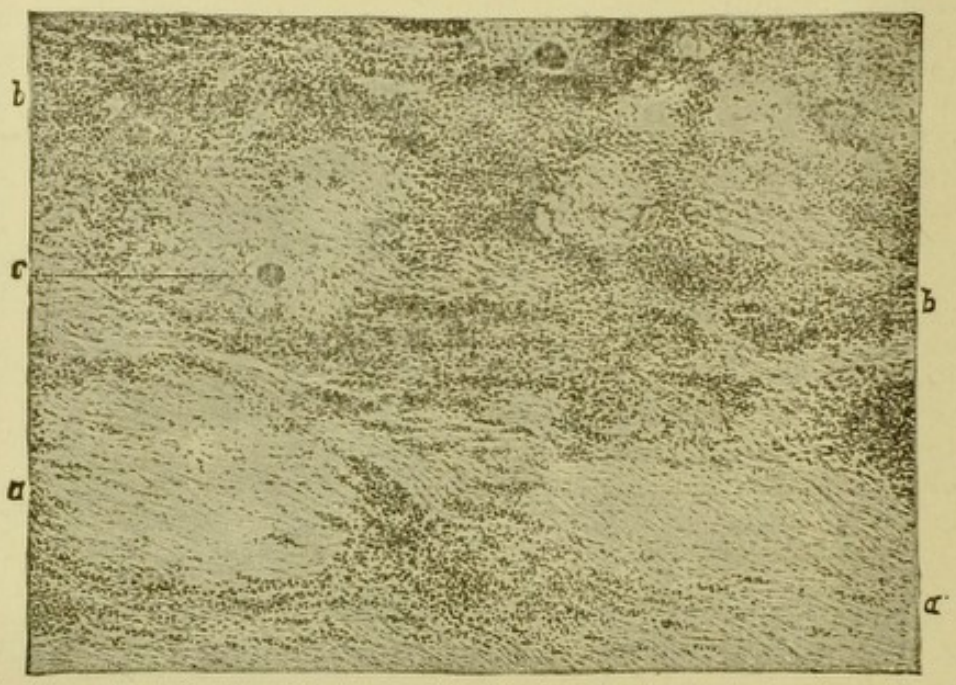


FIG. 433.—Tuberculous induration of the lungs. (Alcohol; hæmatoxylin; eosin.) *a*, Dense fibrous tissue; *b*, granulation tissue rich in cells; *c*, giant cells. Magnified 40 diameters.

same processes, which have just been described, are consummated in the periphery. The tissue altered by the tuberculous process may suffer various fates. The three principal terminations, which, however, are often combined in manifold ways, are the following:

In a first group of cases the production of connective tissue comes gradually to preponderate in the diseased area, and from this results a

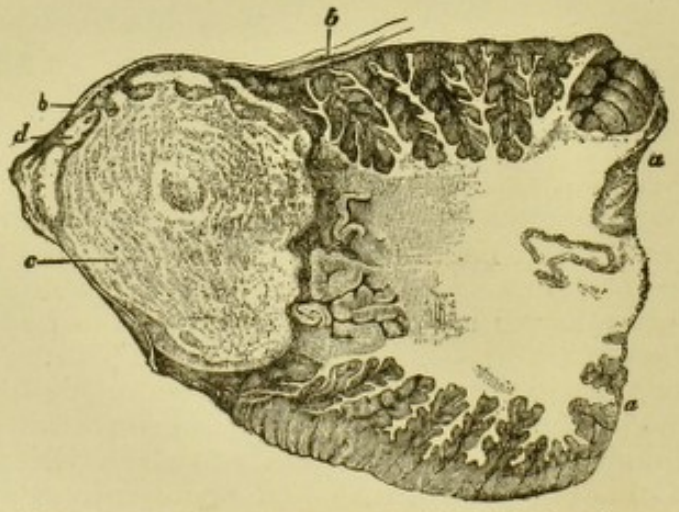


FIG. 434.—Large solitary tubercle of the pia mater cerebelli in vertical section. *a*, Cerebellum; *b*, dura mater grown to the tubercle; *c*, laminated tubercle; *d*, gray peripheral zone grown to the dura mater and beset with yellowish-white nodular deposits. Natural size.

connective-tissue induration of the part affected (Fig. 433). The tissue thus developed is a dense fibrous connective tissue (*a*), which for

years, however, continues to manifest characteristics different from those of ordinary scar-tissue. Thus, for example, it incloses more or less numerous *caseous foci*, and in its substance new foci of inflammatory activity are constantly developing; in consequence of which the *tissue remains rich in cells* (*b*), and here and there also still produces *giant-cells* and *characteristic tubercles*.

The second termination is that of **firm caseation** and of **fibro-caseous transformation.** When this termination occurs, rather firm caseous nodules are formed, as may be observed especially in the enlarged tuberculous lymph-glands, in the pia (Fig. 434, *c*), in the brain, in the spleen, etc. In the lungs this change is an almost constant accompani-

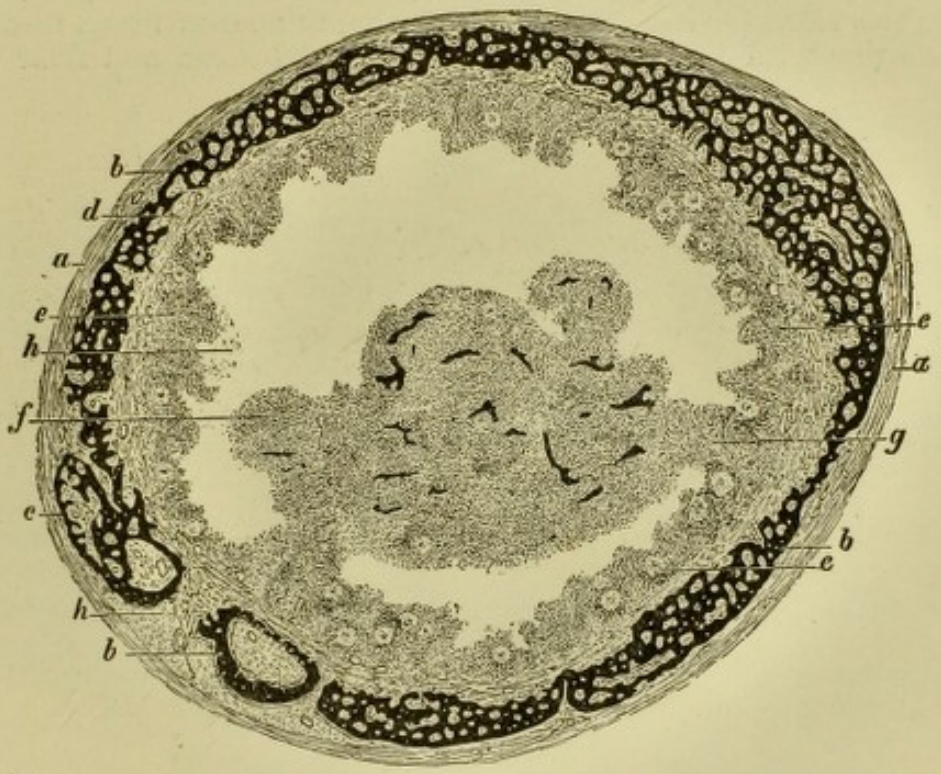


FIG. 435.—Tuberculous cavern in the tibia. (Alcohol : picric acid ; hæmatoxylin ; carmine.) *a*, Periosteum ; *b*, rarefied cortex ; *c*, periosteal bone-deposit ; *d*, fibrous tissue on the inner surface of the cortex ; *e*, granulation tissue containing tubercles ; *f*, sequestrum with scanty bone-scaffolding, permeated with granulations ; *g*, union of the granulations with the sequestrum ; *h*, cavity that had previously been filled with pus and caseous material. Magnified 4 diameters.

ment of the tuberculous indurations, which have caseous nodules in their centres.

In rare cases such nodules may attain very considerable dimensions in the pia and elsewhere, as in the brain, on the dura, and in different glandular organs (Fig. 434, *c*). Under these circumstances they constitute veritable tumors.

The third termination is that of **soft caseation, disintegration,** and **liquefaction,** which lead to the formation of **cold abscesses,** and, after their evacuation, to the formation of **caverns** or **cavities** and **fistulous passages,** and, when there is a wide opening, to **ulcers.**

Disintegration and cavity-formation occur especially often in the lungs, and may there lead to the formation of caverns as large and even larger than the fist. Then, too, they also occur not infrequently in caseating lymph glands, and in cheesy foci located in the kidneys, in the brain, in muscle tissue, and in bone (Fig. 435). The cavities contain at the

commencement the liquefied tuberculous tissue, in which the remains of the tissue originally present are often to be recognized in the form of sequestra (Fig. 435, *f*). After the contents of the cavity have been evacuated, its walls may furnish material enough to fill it once more, partly by secreting pus, partly by throwing off portions of necrotic tissue. Hemorrhages due to the erosion of blood-vessels are also not of infrequent occurrence.

The *walls of the caverns and abscesses* are generally lined with caseating granulations (*e*) containing tubercles, while the tissues lying outside these walls are in part indurated, and in part are also the seat of caseous foci.

Ulcers are formed most often in the mucous membranes (Fig. 436, *h*) and in the skin, for here the softening cheesy masses break through to the exterior with the greatest frequency. The edge and floor of the

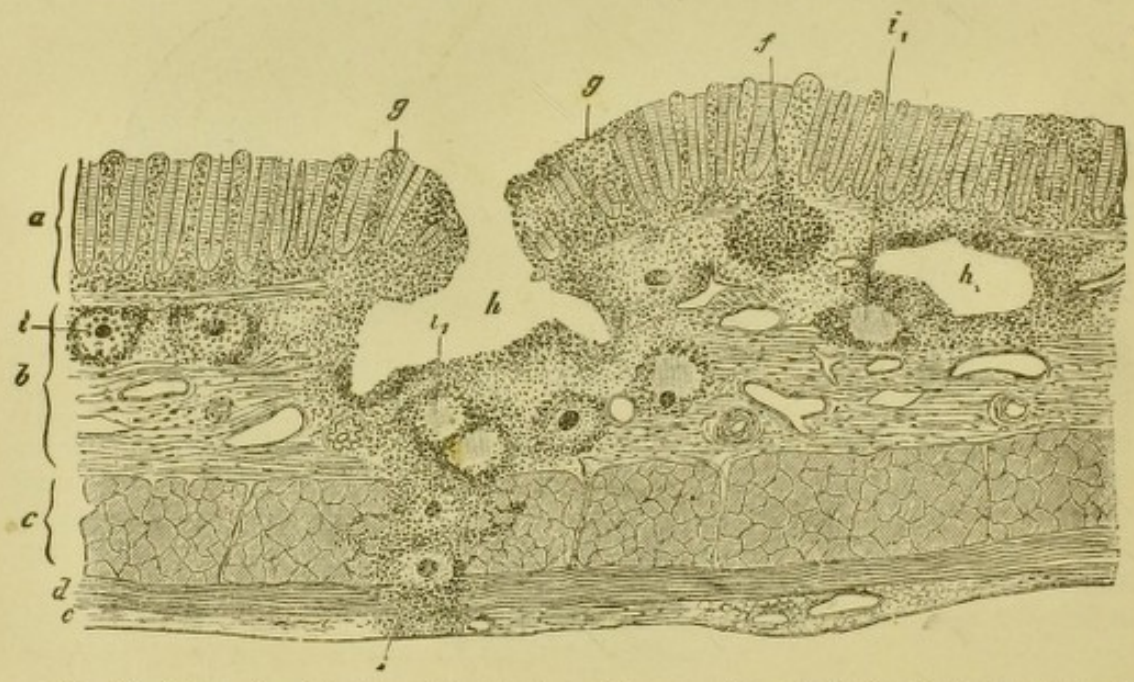


FIG. 436.—Tuberculous ulceration of the intestine, with an eruption of tubercles in the neighborhood. (Alcohol; Bismarck brown.) *a*, Mucosa; *b*, submucosa; *c*, muscularis interna; *d*, muscularis externa; *e*, serosa; *f*, solitary follicle; *g*, mucosa infiltrated with cells; *h*, ulcer; h_1, centre of softening; *i*, fresh, i_1, cheesy tubercles. Magnified 30 diameters.

ulcers are surrounded by infiltrated granulating inflammatory tissue, which often also contains tubercles.

The local disease may, in various stages of the tuberculosis, go on to **healing**, or at least (and this is the more common event) come to a **standstill** for a long time. If the bacilli are destroyed at the very beginning of the tuberculosis, a healing is possible which leaves behind it no recognizable scars. If healing and a standstill of the disease occur at some later stage, firm **cicatricial indurations** (Fig. 433) are formed. These indurations, however, still contain for the most part *caseous foci*, less frequently *small cavities*. In the lungs of individuals who for years have shown no symptoms of tuberculosis, such foci are to be found comparatively often; and in tuberculosis of the bones and joints the development of similar foci is not unusual, although here they are often combined with the pathological new formation of bone. At the same time the cicatrices, at least in the majority of cases, still possess marks characteristic of tuberculosis. Such are, for example, cheesy foci,

which may in part have become chalky, exuberant granulation-tissue, tubercles, and tubercle bacilli. In these cases, therefore, it is a question usually not of a complete healing but of a standstill of the disease.

During the entire course of the local disease, which by its progres-

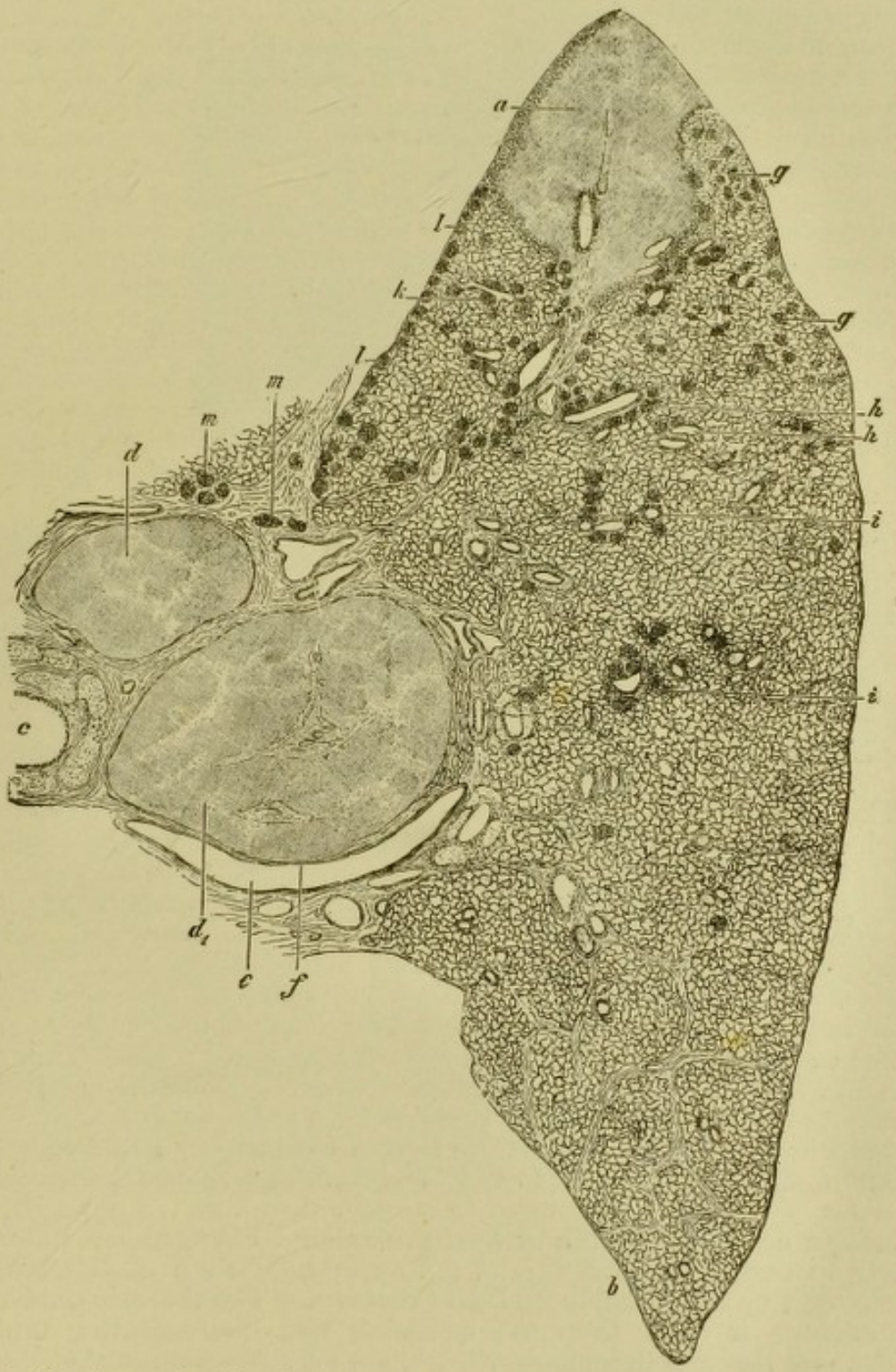


FIG. 437.—Commencing tuberculosis of the lungs in a child two years old. Horizontal section through the right lung. (Müller's fluid; carmine.) *a*, Cheesy focus near the anterior border; *b*, inner posterior border free from tubercles; *c*, transverse section of a bronchus; *d*, d_1, cheesy lymph-glands; *e*, pulmonary vein; *f*, point where the vein *e* has become adherent to the lymph-gland, d_1; cheesy degeneration of the vein-wall has also begun at the same point; *g*, tubercles in the lymph-vessels of the pulmonary parenchyma; *h*, periarterial, *i*, peribronchial, *k*, perivenous, *l*, pleural, tubercles; *m*, tubercles of a lymph-vessel lying in the tissue of the hilus of the lung. Magnified 3 diameters.

sive extension to the neighboring tissues manifests a certain harmfulness, there exists the further *danger of the formation of metastases*. The *intoxication*, which plays such an important rôle in many of the infectious diseases, and controls the picture of the disease, is not apparent

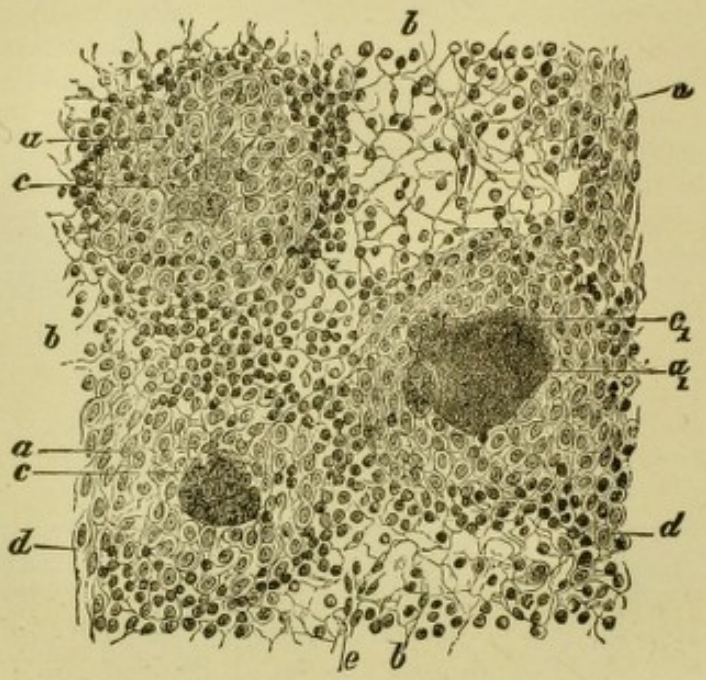


FIG. 438.—Eruption of tubercles in a lymph-gland. (Alcohol; hæmatoxylin.) *a*, Tubercles; a_1, caseated tubercle; *b*, lymphatic-gland tissue; *c*, giant cell in the centre of a tubercle; c_1, giant cell on the edge of an area of caseation; *d*, large-celled tissue between the tubercles; *e*, blood-vessel. Magnified 150 diameters.

in local tuberculosis, and there may be individuals with local skin-, lymph-gland-, or bone-tuberculosis who in other respects are entirely well.

The **formation of metastases** takes place primarily by way of the lymph-channels, and it belongs to the picture of advancing tuberculosis that, in the neighborhood of tuberculous areas, tubercles are developed in the lymph-spaces and lymph-vessels, i.e., in their walls (Fig. 436, *i*, and Fig. 437, *g*, *h*, *i*, *k*, *l*, *m*). The lymphogenous miliary tuberculosis is limited in some cases to the immediate neighborhood of the original disease, while in other cases it involves large regions, and may even—in the lung, for example—spread from a caseous tuberculous focus (Fig. 437, *a*) over a great part of the pulmonary lymphatic system (Fig. 437, *g*, *h*, *i*, *k*, *l*, *m*). These lymphangitic tubercles present the appearance of bright gray nodules, often surrounded by a red zone, and their structure will be found to be the same as that of the primary nodules.

The *lymph-glands* may also become involved very early, whereupon tubercles are developed in them (Fig. 438, *a*, a_1), and these lead, by successive crops, to a more or less pronounced enlargement and ultimately to caseation (Fig. 437, *d*, d_1), or to induration of the lymph-glands, or to a combination of both processes. The thoracic duct may also become infected from the caseating and disintegrating lymph-glands, and through this channel the blood may become infected.

Quite frequently *the formation of metastases takes place also by way of the blood-channels*. Thus, for example, the bacilli may enter the blood current along with the lymph of the thoracic duct, in the manner described above; or *they may*, as very often happens, *force a way for themselves*

directly into the circulating blood. In tuberculous tissues the bacilli may get directly into the small veins, but the arrest of the circulation and the occlusion of the vessels interfere generally with their further dissemination. But often enough they enter the larger veins—as, for example, through a *coalescence of the caseating lymph-glands*, at the hilus of the lungs (Fig. 437, d_1), with *neighboring veins* (e, f_1), whereby the tuberculous process spreads directly to the walls of the veins. But it may also happen that *numerous veins* in the neighborhood of tuberculous areas *become infected* with tubercle bacilli, so that the small veins of an entire vascular region may display well-marked tuberculous disease, i.e., they show inflammatory granulating hyperplasia of the vessel-walls, with the formation of tubercles and subsequent caseation (Fig. 339, *b*), and consequently, if thrombosis does not occur, large numbers of bacilli are likely to be given off from the diseased walls to the blood-stream. In rare cases even arteries, especially those of the lung, may become tuberculous through infection derived from their surroundings, and so may give off bacilli to the blood-stream.

The dispersal of the bacilli by means of the circulation has as a consequence a *hæmatogenous miliary tuberculosis*, i.e., an eruption of miliary tubercles (Fig. 440, *a*) at those places where the bacilli become lodged and where they multiply. Just where these places will be, and how

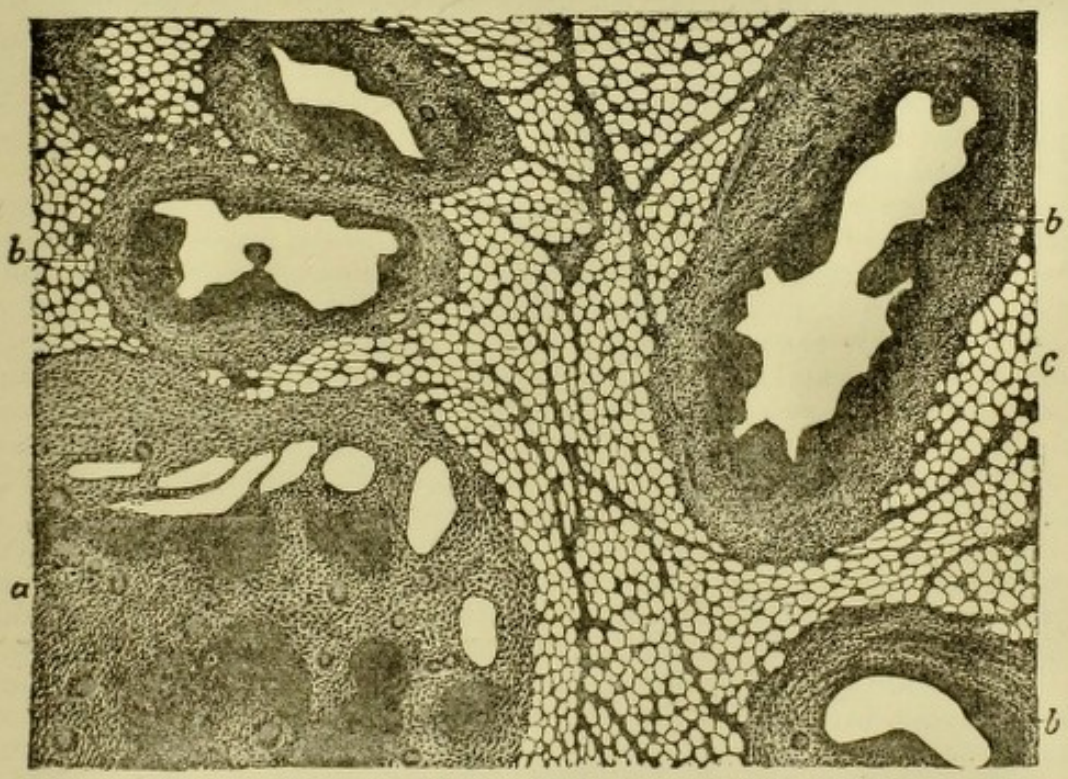


FIG. 439.—Tuberculous disease of the veins in the neighborhood of a retroperitoneal lymph-gland. (Formalin; hæmatoxylin; eosin.) *a*, Tuberculous lymph-gland, with giant cells and cheesy foci; at the periphery there are broad blood-vessels; *b*, veins which show a thickening of their walls due to a growth of tuberculous granulation tissue, while in the parts that are farthest away from the periphery they show areas of cheesy degeneration; *c*, adipose tissue. Magnified 30 diameters.

numerous the tubercles will be, are matters which are determined by the location of the point of invasion and by the number of the bacilli which have gotten into the blood. The entrance of many bacilli into the blood may lead to *general hæmatogenous miliary tuberculosis.*

If the bacilli have reached the blood in small numbers and have been

deposited in one organ only, and if death does not supervene, then there arises in this organ a *progressive local hæmatogenous tuberculosis*, which comports itself in the same manner as a primary infection coming from the exterior.

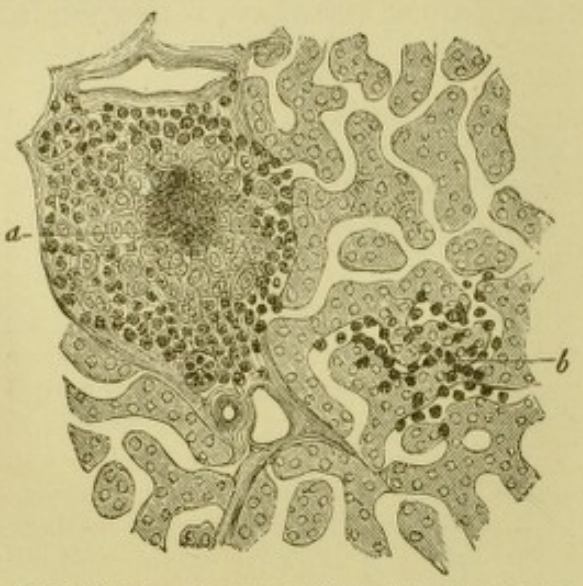


FIG. 440.—Hæmatogenous miliary tuberculosis of the liver. (Alcohol; carmine.) *a*, Fully developed tubercle in the connective tissue of the portal vein; *b*, accumulation of round cells. Magnified 150 diameters.

The *inflammation accompanying the hæmatogenous eruption of tubercles* is sometimes more, sometimes less pronounced, and is wont to be most severe in the meninges and in the lungs.

If an invasion of the bronchi takes place, say, from the softening of a caseous focus of the lung, or if a centre of softening in the kidney breaks through into the pelvis of that organ, then **the tubercle bacilli will be disseminated over the surface of the mucous membranes.** From the bronchi the bacilli spread into the trachea, the larynx, and the buccal cavity, and from there again into the digestive tract; and by aspiration, through deep, quick inspiration, they gain access to other as yet sound parts of the lung; from the kidneys they spread into the discharging urinary passages.

A *secondary infection* may also result from this spreading of the bacilli, yet only a small percentage of those which have thus escaped give rise to infection, and besides, there are, as experience teaches, only certain regions of the mucous membranes that are susceptible to infection. Thus, for example, in the case of the digestive tract, it is especially the tonsils and the lymphadenoid apparatus of the small and large intestines which are susceptible, while the œsophagus and stomach are nearly immune; and in the case of the discharging urinary passages, the susceptible parts are the pelvis of the kidney, the ureters, and the bladder, while the urethra nearly always remains free.

If the bacilli reach the **great body cavities,** they can also here spread over the surfaces, and the serous membranes respond to the infection with diffuse inflammation and with the formation of nodules (Fig. 441). Later, the formation of new connective tissue may follow.

If a woman is pregnant at a time when the tubercle bacilli are being disseminated throughout the body by the circulation, an **infection of the placenta** may take place, and from this an **infection of the fœtus** may also result, so that the child will be born already infected. Nevertheless, so far as experience covers this point, this occurrence is not common, and it is more usual for children of tuberculous parents to become infected after birth. A conceptional infection of the ovum by infected semen has not been demonstrated and is very unlikely.

Secondary infections are often associated with that by tubercle bacilli, and this occurs principally when the cavities or ulcers caused by tuberculosis are accessible from the exterior. Secondary infections appear most frequently in tuberculous lungs, and are caused chiefly by *streptococci* and *staphylococci*. Many authors are inclined to refer all

severe inflammatory exudations which accompany pulmonary tuberculosis to such secondary infections; but this is certainly not correct, for the formation of tubercles caused by tubercle bacilli can be accompanied by very pronounced inflammatory exudations, so that serous or serofibrinous, or pure fibrinous, or fibrino-purulent exudates may collect in considerable quantities in the tissues (in the lung-alveoli, on the pleura, in the subarachnoidal spaces, etc.). High (septic) fever, rapid destruction of tissue with a tendency to suppuration, and unusually severe inflammation point to secondary infections. However, it is very difficult to determine, unless a special investigation is directed to this point, whether a pure tuberculosis or a mixed infection exists.

The question as to *how often tuberculosis is transmitted by transfer of the bacilli from the mother to the child*, is still open. Nevertheless, according to the investigations of Schmorl, Birch-Hirschfeld, and Landouzy, in regard to miliary tuberculosis in pregnant women, it is proved that tubercle-bacilli occur in the spaces between the villi as well as in the blood of chorionic vessels, and that the liver of the fœtus may also contain bacilli. Furthermore, cases of tuberculosis of the placenta also occur which can be regarded as stages on the way of the tubercle-bacillus from the mother to the fruit (Schmorl, Kockel, Lungwitz).

Cases of tuberculosis appearing at an early period of life, reported by Demme, Baumgarten, Rilliet, Charrin, and others, speak in favor of a passage of the tubercle-bacilli from the mother to the fruit; so do also the statements of Armanni, Landouzy, and Martin, that the inoculation of portions of the organs of human fœtuses obtained from tuberculous mothers produces tuberculosis in guinea-pigs. But still more important are the experimental investigations which de Renzi and Gärtner made; for they succeeded, by inoculation of the pregnant female in guinea-pigs, white mice, and rabbits, in producing tuberculosis in the offspring in a certain number of cases, and con-

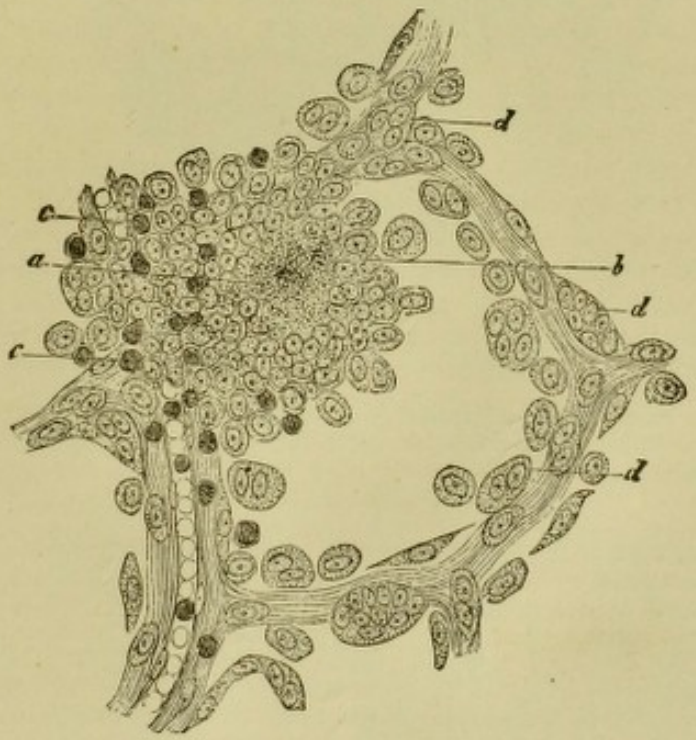


FIG. 441.—Tuberculosis omenti. (Müller's fluid; carmine.) *a*, Centre of a tubercle; *b*, cells of an epithelioid character; *c*, lymphatic elements; *d*, proliferating epithelium in the neighborhood. Magnified 200 diameters.

sequently Gärtner is of the opinion that under suitable conditions tubercle-bacilli may pass over from the mother to the fœtus in animals as well as in human beings. Finally, Maffucci and Baumgarten succeeded in effecting a transfer of tubercle-bacilli to impregnated hens' eggs, and in accomplishing this they ascertained that the infection did not disturb the development of the chicken, but, on the contrary, the bacilli that were taken

up by the embryo remained in the tissue of the latter without multiplying to any considerable extent, but subsequently caused tuberculosis in the body of the chick after it was hatched out.

The experiments cited above allow the assumption that the bacilli are transferred through the placenta from the mother to the fruit, and also that they may remain for a long time in the body of the embryo without causing any recognizable changes. Since, manifestly, congenital tuberculosis in human beings is extremely rare, while, on the other hand, tuberculosis in the first years of life is frequent, it is possible that in human beings also the infection may remain latent for a long time and not be always recognized by anatomical examination. The question whether conceptional tuberculosis, through the transference of the virus by means of the semen, actually occurs, is one which is open to discussion. The probability is that it does not occur. However, it is worthy of note that the semen and the contents of the seminal vesicles may contain tubercle bacilli, and this, not only in the case of tuberculosis of the testicles and epididymis, but also when the tuberculous patients have no recognizable tuberculous affection of the genital apparatus. Nevertheless, it must be kept in view, according to the investigations which have thus far been made, that tuberculosis is to be referred mostly to extra-uterine infection, and that children of tuberculous parents become so often affected with tuberculosis because, on the one hand, they are predisposed to tuberculosis, and, on the other, they are more exposed to the infection with the bacilli than are the children of healthy parents.

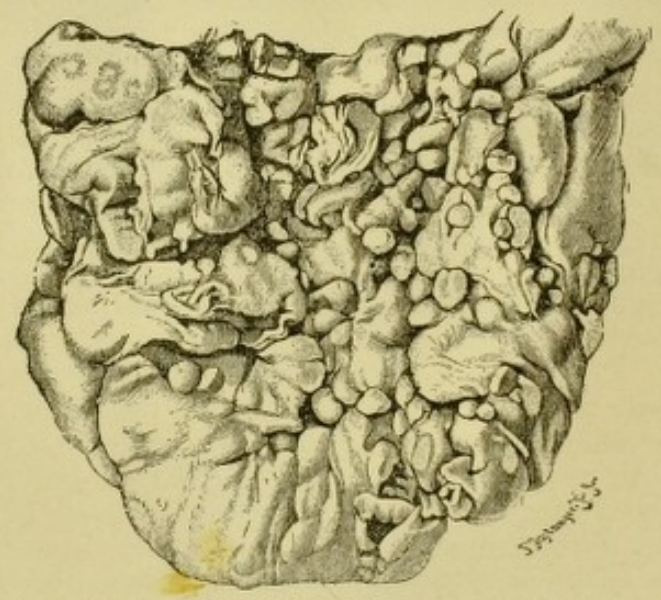


FIG. 442.—Growths from the pleura in a case of bovine tuberculosis (pearl-disease).

In animals a transference of tuberculosis to the fœtus seems occasionally to occur, according to the statement of Zippelius, Jessen, Pütz, Grothans, Malvoz, Lydtin, Brouvier, Adams, and others. Johne not only found nodules and larger consolidated areas in the lung and liver, and in various lymphatic glands of a calf fœtus, but he also established beyond a doubt the presence of the characteristic bacilli.

Tuberculosis of cattle and of the other domestic mammalia is a progressively spreading production of nodules, in which, along with small nodules, larger ones, the size of a potato and even larger, may form, and in which also there may be a certain amount of inflammatory action, resulting in exudations and in the production of connective tissue. The disease develops in cattle (Fig. 442), especially in the serous membranes, where the process is called the *pearl disease;* then it is also found with the next greatest frequency in the lymph-glands, the lung, the liver, the kidneys, etc. In the serous membranes the nodules often have a stem—i.e., are pedunculated, and they present some resemblance to sarcomatous growths. Along with caseation, calcification occurs strikingly often.

The nodules of tuberculosis of cattle and other domestic mammalia resemble precisely in structure the tubercles of human beings, and inasmuch as they contain the same bacilli, and inasmuch, furthermore, as the inoculation of calves with human tubercles produces typical tuberculosis (Bollinger), the hypothesis that the two kinds of tubercles are identical is certainly justified.

According to Maffucci, Rivolta, Straus, Gamaleïa, and others, **tuberculosis of birds**

is not caused by the same bacilli as those which produce the tuberculosis of man or other mammalia. Cultures of the tuberculosis of man are dry, warty or scaly, and lustreless; those of bird-tuberculosis are moist, folded, and soft, and can grow even at a temperature of 43° C. Dogs are entirely immune from bird-tuberculosis, but not from tuberculosis of man. According to the researches of Leray, intraperitoneal inoculation of mammalian tuberculosis causes in the liver and spleen of rabbits numerous caseous foci with few giant-cells and few bacilli; in the lungs, numerous caseous nodules with many bacilli. Inoculation with fowl-tuberculosis causes, on the other hand, non-caseating cellular growths, with giant-cells and with an immense number of bacilli.

According to Maffucci, Martin and Gärtner, the inoculation of human tuberculosis into a fowl is not followed by tuberculosis, but the bacilli remain alive for weeks in the body of the fowl. Pigeons (Anclair) die after intraperitoneal inoculation, but no tubercles are found in the tissues; the liver and lungs may still contain living bacilli after the lapse of fourteen days. In guinea-pigs the bacilli of human tuberculosis cause (Straus) much severer changes than the bacilli of fowl-tuberculosis. Whether man is susceptible to avian tuberculosis is as yet an open question.

According to Malassez, Pfeiffer, Eberth, Roger, Grancher, Zagari, and others, a disease very like tuberculosis occurs in guinea-pigs, rabbits, lambs, and horses, and this disease is also characterized by the production of caseous nodules and is caused by a pleomorphic bacillus that forms zoöglœa. The affection may be called **pseudotuberculosis** (Eberth, Pfeiffer). Malassez and Vignal call it *tuberculose zoöglèique*.

§ 178. At present a bacillus found by Lustgarten in syphilitic diseased foci is called the **bacillus of syphilis**, and it is possible that it has pathogenic significance and represents the *contagium of syphilis*. In favor of this, however, it can be said only that the bacilli have been found in various syphilitic foci in all stages; but it has not as yet been possible to cultivate these bacilli.

The bacillus resembles the tubercle-bacillus, is from 3 to 7 μ long, often bent, and somewhat swollen at the ends. According to Lustgarten, it may be made visible by a complicated staining-process, consisting in coloring the sections with aniline gentian-violet solution, then decolorizing them in permanganate of potassium, and washing them out in sulphurous acid. More recent authors have published other methods.

The bacilli are found in syphilitic foci of disease always in limited numbers only. They lie mostly in the cells (from one to four in a single cell) (Lustgarten), but also to some extent between the cells, and may also at times appear in the blood (Doutrelepont). The Lustgarten bacilli, at the present time, can hardly be used for differential diagnosis, since other bacilli, described as smegma-bacilli, found in the secretion from the prepuce and in the smegma between the labia majora and labia minora, stain by the method described by Lustgarten. According, however, to Doutrelepont, Klemperer, and Lewy, it is possible to distinguish these from one another by proper staining-methods—i.e., by carbolic-acid fuchsin.

The poison which on inoculation produces syphilis occurs only in the human organism, where it is alone reproduced. It is communicated to other individuals only by direct or indirect transfer. When inoculated into an organism it causes inflammatory processes of the most varied intensity and extent—from a simple, local, transitory hyperæmia to the production of large exudates or tumor-like granulations or extensive connective-tissue hyperplasias. If a child is begotten in the presence of syphilitic infection the disease may be transmitted to the child by the father as well as by the mother.

If the primary focus of inflammation is formed at the point of infection—which is usually some part of the skin, although it may be located in a mucous membrane (mouth, fauces, genital mucous membrane)—there is first a papule, which spreads over the surface and forms scales

in eight or ten days after its appearance. But it may ulcerate and give rise to the secretion of a serous or purulent fluid which dries to a scab. Simultaneously the bottom becomes indurated and produces a thick disc-like deposit in the skin or a thin parchment-like thickening. Occasionally there is at first a vesicle that becomes eroded, and then an ulcer that throws off but little exudate, but which is indurated at the bottom. In still other cases there exists first an ulcer, and the bottom becomes indurated subsequently.

The induration is called the **initial sclerosis**, or *Hunter's induration* (Fig. 443, *b*). The ulcer is called a *hard chancre*. The induration is caused mainly by an accumulation of small *round cells* (Fig. 443, *b*, and Fig. 444, *a*) in the interstices of the connective tissue. Occasionally *epithelioid cells* are formed (Fig. 444, *b*) and *isolated giant cells* (*c*). When this takes place the summit of development is reached; then the

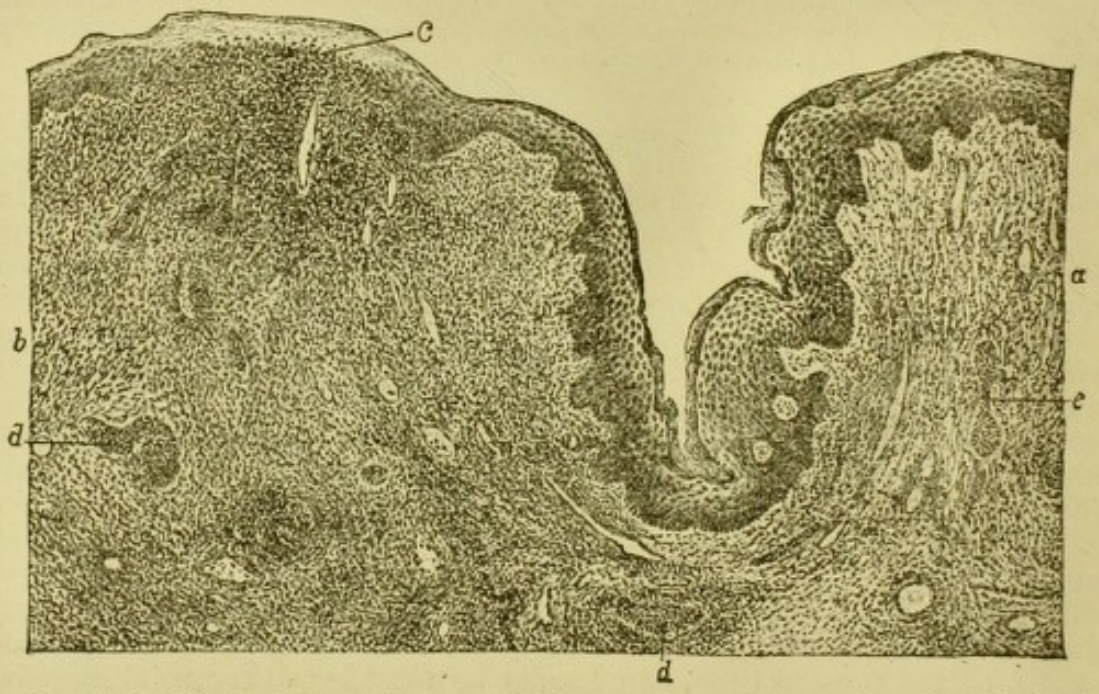


FIG. 443.—Initial sclerosis in syphilis. (Alcohol; hæmatoxylin; eosin.) *a*, Corium, slightly inflamed; *b*, initial sclerosis (connective tissue infiltrated with cells); *c*, a point where the cells have forced their way into the epithelium; *d*, *e*, lymph-vessels filled with leucocytes. Magnified 35 diameters.

greater part of the tissues disintegrates and ulcerates or becomes absorbed. Some of the cells are used in the formation of scar-tissue.

Within the area of the initial sclerosis, and in its immediate neighborhood, the lymph-vessels are dilated and filled with leucocytes. Then, after the lapse of a certain length of time, the lymph-glands, the skin, and the mucous membranes will become involved in the inflammation (secondary symptoms). Still later, there follow syphilitic inflammations of the intestines and of the bones; these are tertiary forms of the disease. These forms sometimes resemble other non-syphilitic inflammations, and sometimes special forms of granulation are produced. Syphilitic affections of the skin embraced under the term **syphilides** form sometimes only red blotches, sometimes small or large papillary excrescences, which may become associated with the formation of vesicles and pustules as well as with the formation of scales. Accordingly the various cutaneous syphilides have been called by different names, some of which are the following: *roseola syphilitica*, *papular*, *pustular*, *and ulcerating syphi-*

lides, and *psoriasis syphilitica*. A common element in all of these affections is a more or less high degree of inflammation, which is characterized by an infiltration of the tissues, partly also by hyperplasia. Thus, for example, there is found in the flattened elevations of the skin, which are known as the *large papular syphilide* or *condyloma latum*, an infiltration of the papillary body (Fig. 445, *i*), of the corium (*k*), and of the epithelium (*e*, *f*, *g*, *h*) with cells and fluid exudate; and this exudate coagulates when hardening of the parts occurs. Finally, these masses of exudate may reach the surface, in case the horny layer of the epidermis becomes macerated, and cause a moist condition of the condyloma. In the pustular syphilides the inflammation leads to a purulent melting of the epithelium, and, in the ulcerating form, also of the papillary body and of the corium, so that *ulcers* result.

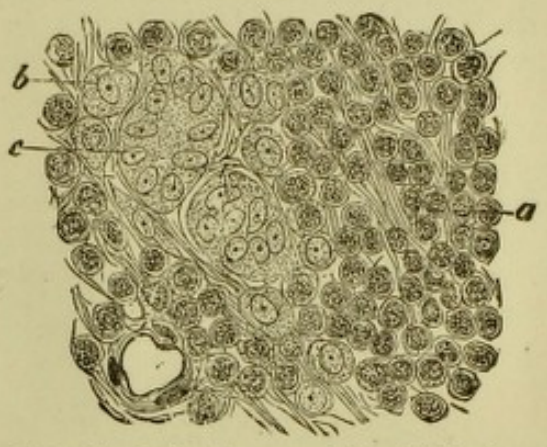


FIG. 444.—Section from a syphilitic initial sclerosis. (Alcohol; alum-carmine.) *a*, Round-cell infiltration; *b*, large mononuclear connective-tissue cells; *c*, polynuclear cells. Magnified 350 diameters.

Inflammatory changes similar to those in the skin appear, in the

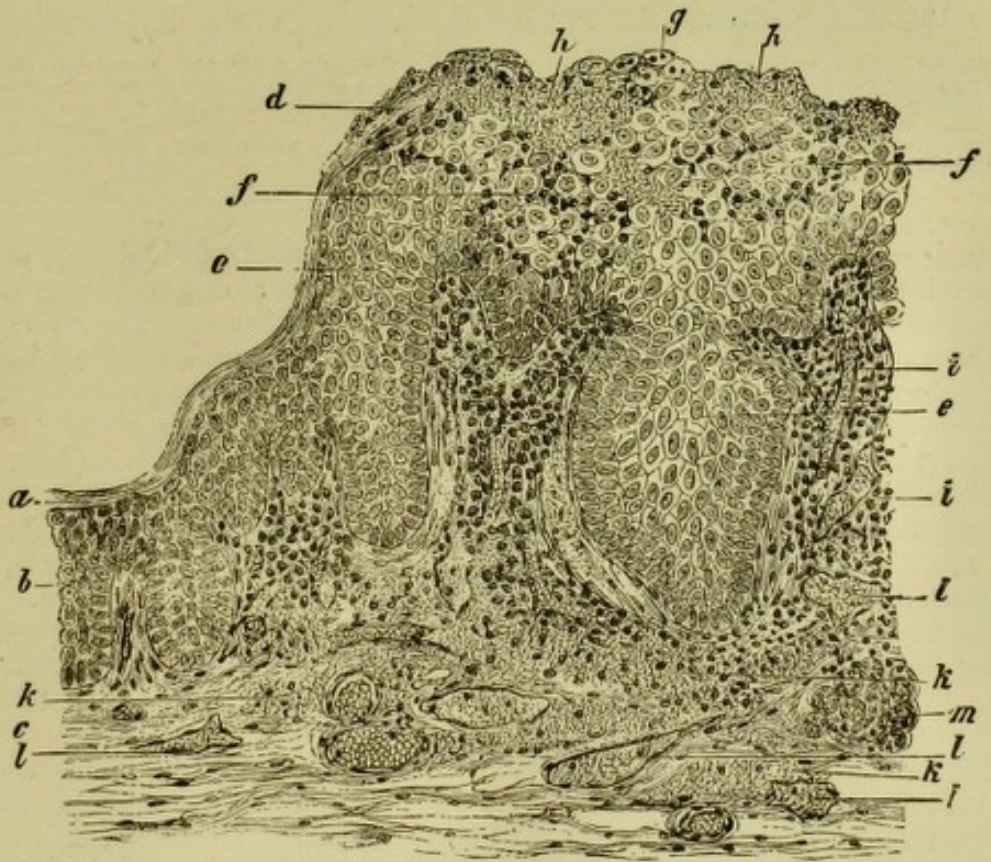


FIG. 445.—Condyloma latum ani. (Alcohol; Bismarck brown.) *a*, Horny layer; *b*, mucous layer of the epidermis; *c*, corium; *d*, loosened horny layer infiltrated with small cells; *e*, swollen mucous layer; *f*, swollen and infiltrated mucous layer; *g*, epithelial cells with round cells inside; *h*, coagulated granular masses; *i*, swollen papillary body infiltrated with cells and fluid; *k*, corium infiltrated with cells, fluid, and coagulated albumin; *l*, widened lymph-vessel filled with coagulum; *m*, sweat-gland. Magnified 150 diameters.

secondary stage of syphilis, also in the mucous membranes, especially of the mouth, fauces, and respiratory passages.

Syphilitic lesions of the tertiary stage, that appear in internal organs, in lymphatic glands, in bones, in muscles, in subcutaneous and submucous connective tissue, in the membranes of the brain, etc., constitute

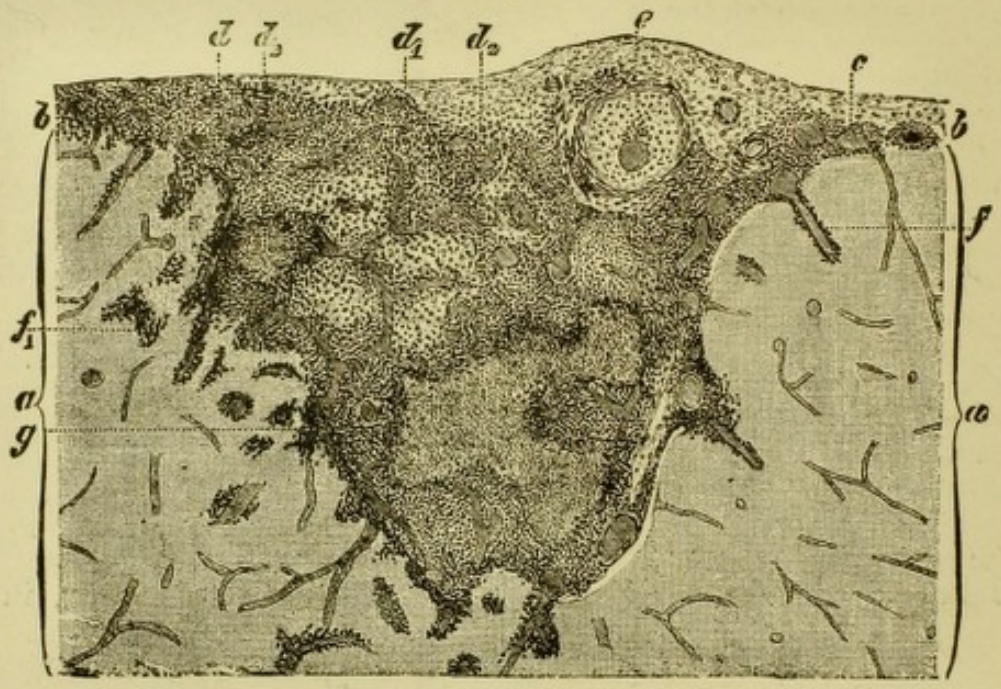


FIG. 446.—Meningo-encephalitis syphilitica gummosa. (Müller's fluid; alum-carmine.) *a*, Brain-cortex; *b*, pia mater; *c*, a vein surrounded by cellular exudate; *d*, fresh cellular granulation tissue; d_1, fibrocellular granulation tissue; d_2, caseated granulation tissue; *e*, artery with much thickened intima and adventitia infiltrated with cells; *f*, cellular infiltration of the pia-sheath of the cortical vessels; f_1, perivascular cellular infiltration of the cortical substance; *g*, diffusely spreading cellular infiltration invading the brain-cortex. Magnified 15 diameters.

formations that are usually designated as **gummata** (Virchow), except where they consist merely of a light grade of a degenerative or an inflammatory change, without characteristic features. In its earlier stages a gumma, as well as the broad condyloma, consists of an inflammation confined to one kind of tissue. But usually the gumma is richer in cells and attains a higher degree of development, as shown by the fact that a peculiar granulation tissue with new blood-vessels (Fig. 446, *d*, d_1) is formed. The gumma occurs especially in the periosteum, in the membranes of the brain, as well as in the parenchymatous organs of the abdomen, especially in the liver, the spleen, and the testicle, and shows a difference in the abundance of cells according to location. The forms which have a paucity of cells, and which are most often observed in the bones, have a soft consistence and present a gelatinous appearance on section, owing to the fact that the fluid portion of the node is in excess of the cellular mass. The tissue also undergoes a partial metamorphosis into mucous tissue. Forms rich in cells are met with especially in the soft membranes of the brain (Fig. 446), in the submucosa of various mucous membranes, in the skin, in the liver, in the testicle, and in the spleen. They form gray or grayish-white or grayish-red foci, sometimes spherical, as in the spleen and testicle, sometimes more irregularly shaped, as in the soft membranes of the brain; and in their light-gray or reddish-gray color, and somewhat transparent texture, they

resemble healthy *granulations*. Often, besides these lesions, diffuse inflammatory changes are also present in the affected organs.

Small foci of syphilitic infiltration quite often disappear quickly by absorption. In larger foci frequently suppuration or fatty and necrotic disintegration takes place. Disintegration of syphilitic foci of the skin and of the subcutaneous connective tissue, as well as of the mucosa and submucosa, leads to the formation of **ulcers** which, when a mucous membrane is the part affected, occur most frequently in the region of the mouth, throat, and upper air-passages (Fig. 448, *a*). In the interior of deeper-lying gumma-nodules caseous foci are not infrequently formed (Fig. 446, d_2 and Fig. 447, *a*). These are sometimes regularly spherical, sometimes irregularly shaped. The peripheral portions merge into callous connective tissue (Fig. 447, *b*, *c*, *d*) which incloses the caseous masses and radiates in bands into the surrounding tissue. *Papillary growths* (Fig. 448, *b*, *c*) not infrequently are formed in the neighborhood of the ulcers of the mucous membrane.

Necrotic remains of gumma-nodules which originally were cellular come under anatomical examination far more frequently than those which are still perfect; and yet in this changed condition they are still commonly designated as gumma-nodules. Not only the cellular hyper-

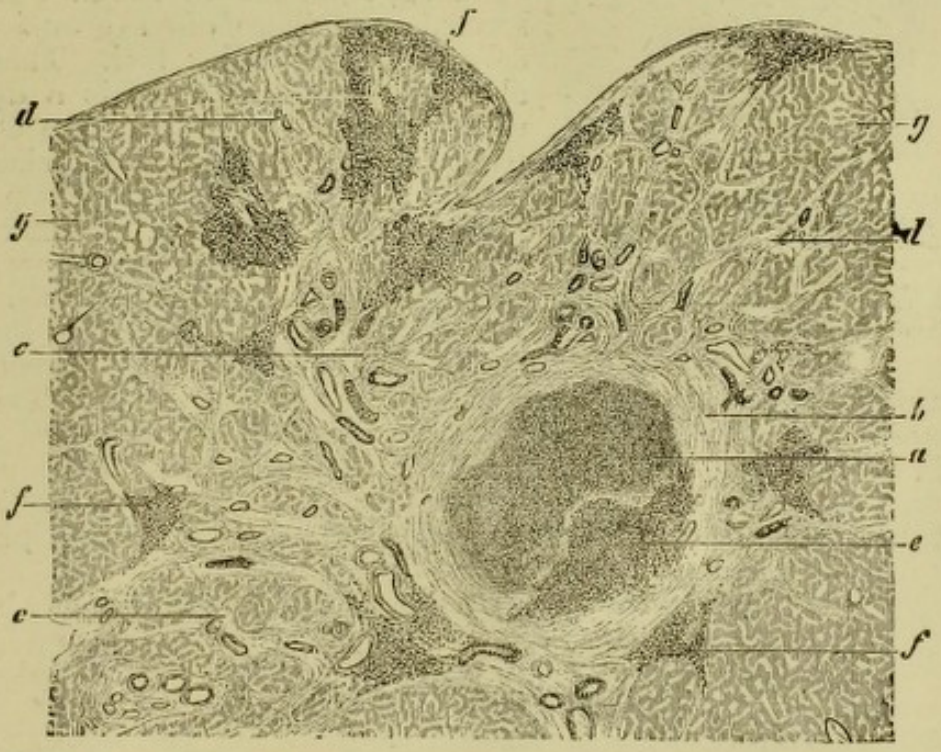


FIG. 447.—Gumma of the liver. (Alcohol; alum carmine.) *a*, Caseous nodule; *b*, homogeneous connective tissue; *c*, connective-tissue with remnants of liver-tissue; *d*, connective-tissue bands radiating into the liver-tissue; *e*, cellular foci at the edge of the caseous nodule; *f*, cellular foci within the connective-tissue rays; *g*, liver-tissue. Magnified 12 diameters.

plasia, but also the infiltrated tissue itself, is often involved in these necrotic changes.

The reason why syphilitic inflammation often results in disintegration of tissue and necrosis lies primarily in the character of the agent that produces the disease. Still a second circumstance is responsible for this manner of termination—namely, the extensive participation of the blood-vessels, especially of the arteries, in the inflammation.

When a syphilitic inflammation leads to a formation of granulations or to a connective-tissue hyperplasia the vessel-walls also become thickened, especially the intima (Fig. 446, *e*), so that the lumen of the vessel becomes narrowed and not infrequently even totally closed. Occasionally the syphilitic process is largely localized in the vessels.

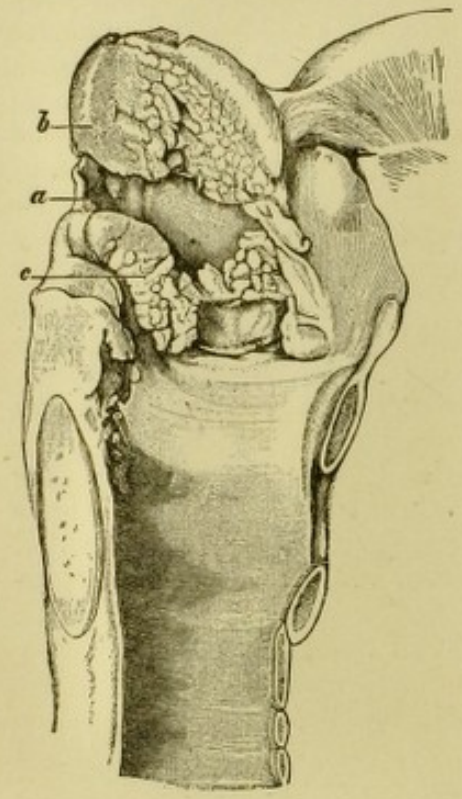


FIG. 448.—Syphilitic ulceration of the larynx. Sagittal section through the larynx and trachea. *a*, Ulcer; *b*, thickening and papillary growth on the epiglottis; *c*, thickening and papillary growths of the left wall of the larynx and of the superior thyro-arytenoid ligament. (Natural size.)

Hereditary syphilis is characterized mostly by peculiar tissue changes which differ not inconsiderably from the manifestations of acquired syphilis; but still changes also occur which agree with the latter. In the skin it causes macular as well as papular and pustular syphilides, which may lead to ulcerations. The spleen is usually more or less enlarged, and in individual cases may attain ten times its normal volume. In the liver intra- as well as perivascular aggregations of round cells are formed, and these often group themselves in small, thick foci. There are also cases in which there is a diffuse, widespread hyperplasia of the connective tissue, which lends a solid character and a peculiar brownish-yellow color to the liver. Moreover, in some cases there is a connective-tissue hyperplasia confined to the periportal tissue. The lung may present, throughout its substance or only in places, a thick gray or grayish-white character resembling sarcomatous tissue. This appearance in the altered area is due to the presence of connective tissue rich in cells (Fig. 450, *a*, *b*), containing only imperfectly developed alveoli (*e*, e_1) and bronchi (*d*, d_1), or none at all. In disease of limited extent there exists only a thickening of the peribronchial and perivas-

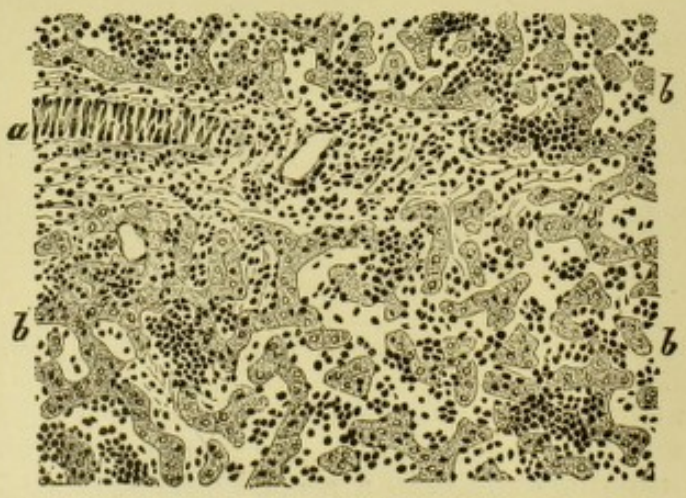


FIG. 449.—Congenital syphilitic hepatitis. (Müller's fluid; hæmatoxylin; eosin.) *a*, Periportal connective-tissue rich in cells (longitudinal section through an artery); *b*, glandular tissue beset with cells. Magnified 100 diameters.

cular tissue and of the interalveolar septa, in part associated with an accumulation of desquamated epithelial cells in the alveoli. In the kidneys and testicles the connective tissue may also be increased in places and enormously rich in cells. Syphilis thus often causes in glandular organs a *pathological development of the connective-tissue elements*, while the epithelial tissue remains behind in its development. In the blood the number of colorless corpuscles often seems increased. Finally, in the bones, not infrequently *disturbances in the endochondral ossification* occur—disturbances which are characterized mainly by irregularities in the formation of the medullary cavity, and in the deposition of lime-salts in the cartilage, and which lead to disturbances in the structure of the spongy subchondral bone-substance. By the formation

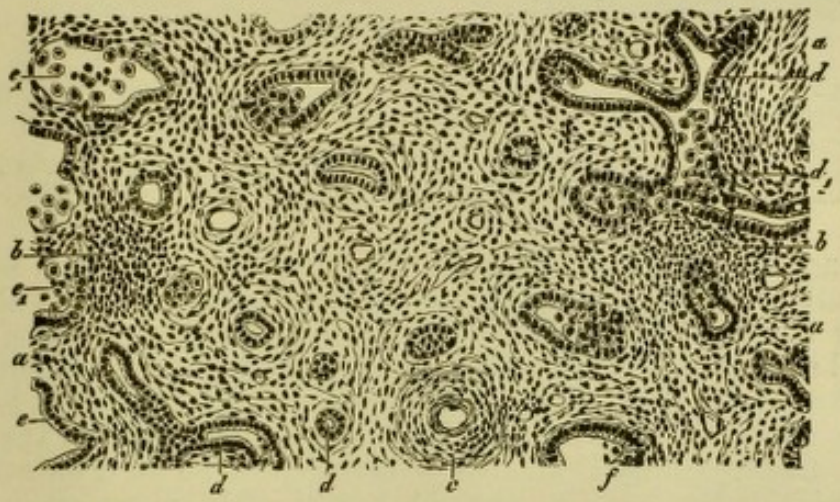


FIG. 450.—Changes in the lung in congenital syphilis. (Müller's fluid; hæmatoxylin; eosin.) *a*, Hyperplastic stroma rich in cells; *b*, foci of granulations rich in cells; *c*, arteries with thickened adventitia; *d*, d_1, gland-like bronchi, some of which contain desquamated epithelium and round cells; *e*, e_1, alveoli, some of which, e_1, contain desquamated epithelium and round cells. Magnified 60 diameters.

of hyperplastic granulations which undergo caseous degeneration, larger defects may occur in the bone-tissue.

Syphilis can be transferred to the fœtus as well by the sperm as by the ovum. The transmission from the father's side is the most usual. After conception, a transfer of syphilis from the mother to the fœtus may take place. Most frequently the transfer of syphilis occurs in the secondary stage. If infection and conception occur simultaneously, the intensity of the disease in the child is greatest; but, nevertheless, even freshly infected parents may produce healthy children (Neumann). The syphilis that is transferred by the mother during the first months of pregnancy kills the child. In the later months of pregnancy, syphilis, as a rule, is not transferred to the child (Neumann).

Mothers that bear children which have been infected with syphilis by the father may themselves remain healthy. It appears, therefore, that a certain immunity from syphilis does occur.

§ 179. The **bacillus lepræ** was first described by Armauer Hansen in 1880. It is a small, slender bacillus, from 4 to 6 μ long. It is regarded as the cause of **leprosy**—also called *elephantiasis Græcorum*. It is found constantly and in large numbers in the morbidly altered tissues (Figs. 451, 452, and 453).

The foci of disease in leprosy are characterized in general by a hyperplasia consisting of cells of different size, and of fibrous stroma (Fig. 451). The bacilli lie partly between (*e*), partly in the cells (*c*, *d*), and accumulate usually to a large extent in the latter. The cells in consequence swell enormously (*d*), and change into giant cells of one

or more nuclei (Fig. 452). The giant cells occasionally inclose large vacuoles which contain large numbers of bacilli, as well as granular, thready detritus of the liquefied protoplasm. The nuclei are preserved for a certain time, and are shoved over to the periphery by the vacuoles

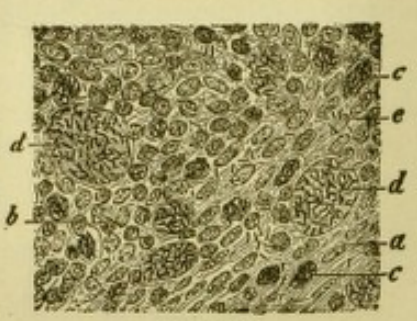


FIG. 451.

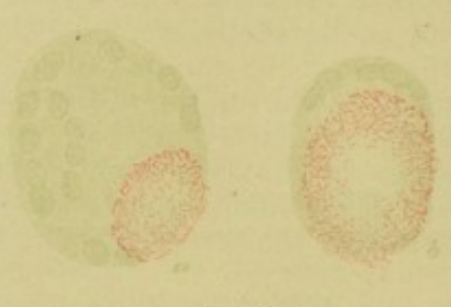


FIG. 452.

FIG. 451.—Tissue from a leprosy-nodule. (Alcohol; fuchsin; methylene blue.) *a*, Cellular fibrous tissue; *b*, round cells; *c*, *d*, medium- and very large-sized cells filled with bacilli; *e*, free bacilli. Magnified 200 diameters.

FIG. 452.—Two giant cells with vacuoles containing bacilli, from a leprous growth of the skin of the nose. (Alcohol; Gabbet's staining-method.) Magnified 400 diameters.

containing the bacilli. Later on, they too are destroyed, so that the entire cell then becomes a vesicle containing the bacilli (Fig. 451, *d*). Some of the cells in which the bacilli lie are tissue-cells which were present before the invasion, while others are newly formed cells.

The bacilli are surrounded by a slimy envelope (Neisser), and behave toward coloring-matters in much the same manner as do the tubercle-bacilli. Consequently the same procedure can be used for staining the former as the latter. The stained bacilli often show clear spots, or appear as if made up of stained granules.

According to Bordoni-Uffreduzzi and Neisser, the bacilli may be cultivated upon peptone-glycerin-blood-serum, upon gelatinized blood-serum, and upon boiled eggs. They grow out to threads of four times the original length, and are often swollen into club shape on the ends. It is still a contested point whether the bacilli form spores.

Inoculations of animals have as yet not given certainly positive results. It is true that it is claimed that the bacilli can multiply at the seat of inoculation, and that a hyperplasia may take place in rabbits (Damsch, Vossius); still a disease process extending over large areas of the body is not obtained. Schottelius and Bäumler obtained no positive results by inoculating apes with freshly excised pieces of leprous skin rubbed up so as to form an emulsion in warm bouillon and warm blood-serum. According to Campana and Wesener, the bacilli in the pieces that are inoculated are carried off by the wandering cells, but they cause no specific infection and do not multiply.

The infection of man takes place by mediate or immediate transference from individual to individual. The nasal secretion (Sticker) is particularly infectious, especially at those times when leprous suppurations are present in the nose. In leprous diseases of the respiratory passages the sputum may contain bacilli, and in the formation of nodules and ulcers of the skin the secretion of these ulcers may also contain the bacilli. Contagion seems to result most frequently from the nose; at least the early involvement of the anterior nasal region rather favors this supposition. In spreading in the body the bacilli make use mainly of the lymph-channels; they may, however, get into the blood.

The skin, the peripheral nerves, and the nose are mainly concerned in the disease; still the bacilli can multiply in other tissues—e.g., in the testicles, in the liver, in the ganglia, and in the spleen—and form foci of disease.

At the point of colonization the bacilli excite inflammation and hyperplasia. Granulation tissue containing blood-vessels is formed, and remains for a long time in a condition which is characterized by an abundance of cells. This forms the basis for nodules and tumors in the skin and the nose, and for spindle-shaped thickening of the nerves, and is the cause of the irritation and eventually of the degeneration and destruction of nerve-filaments. The bacilli, and the hyperplasia of the tissues caused by them, group themselves by preference around the hair-follicles (Fig. 453, *d*) and the ducts (*f*) and coils (*g*) of the sweat-glands; but this connection is not always to be made out in all of the hyperplastic foci (*h*). The bacilli may furthermore penetrate into the blood-vessels, the hair-follicles, and the sweat-glands (Touton), and thence come to the surface. In the nervous system they are found in the connective tissue as well as in the nerve-elements themselves, especially in the ganglion-cells (Sudakewitsch). The cells occupied by them undergo in time

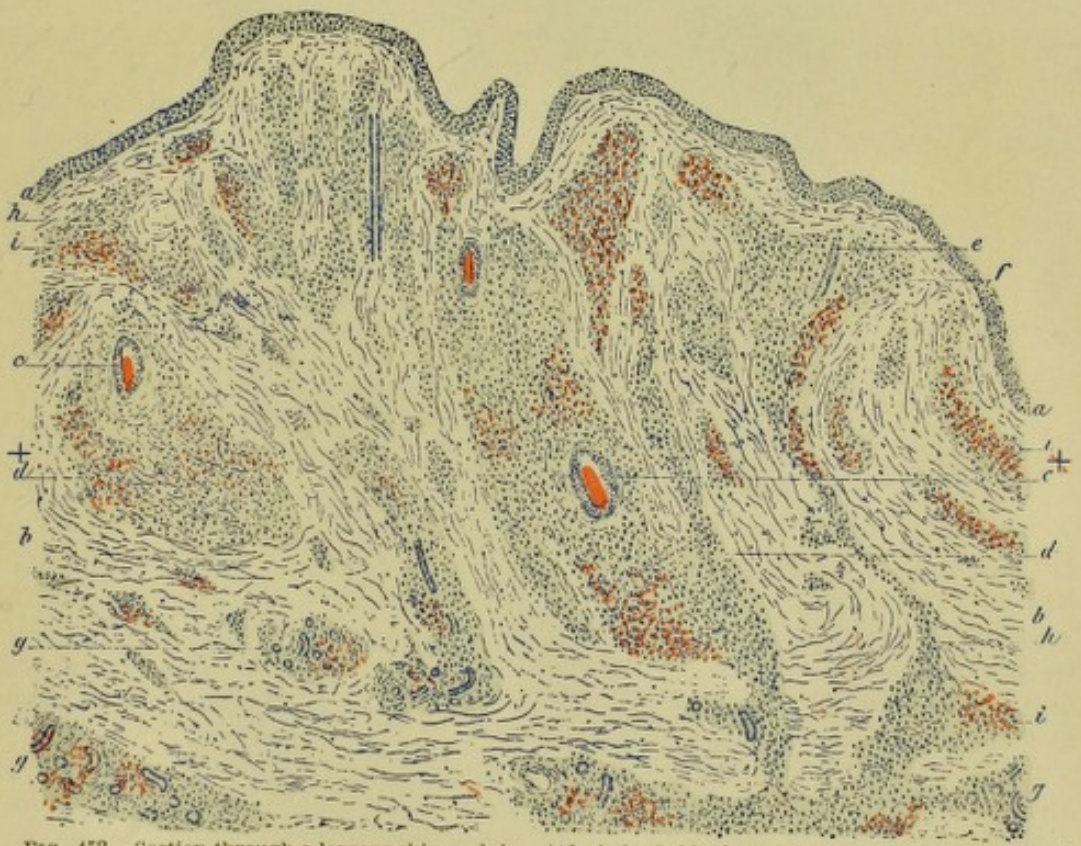


FIG. 453.—Section through a leprous skin-nodule. (Alcohol; Gabbet's staining-method.) *a*, Epidermis; *b*, corium; *c*, hair-follicle; *d*, leprous foci in the tissue surrounding the hair-follicles; *e*, duct of a sweat-gland; *f*, leprous foci in the neighborhood of *e*; *g*, leprous foci around the sweat-glands; *h*, leprosy-nodules in which no special connection with any elements of the skin can be recognized; *i*, foci of bacilli. Magnified 32 diameters.

degeneration, occasionally with hydropic swelling and the formation of vacuoles (Fig. 452).

The hyperplasia caused by the growth of the bacilli may almost disappear by disintegration and absorption of the cells after the condition has existed for years; but there always remain indurations rich in cells and pigmentation of the skin. Caseation never takes place.

Leprosy of the skin appears especially in the face, on the extensor surface of the knees and of the elbows, and on the posterior surface of the hands and feet. It begins by the formation of red spots, that either disappear, leaving pigmented spots behind, or become elevated into nodules of brown-red color—*lepra tuberosa* sive *tuberculosa* sive *nodosa*.

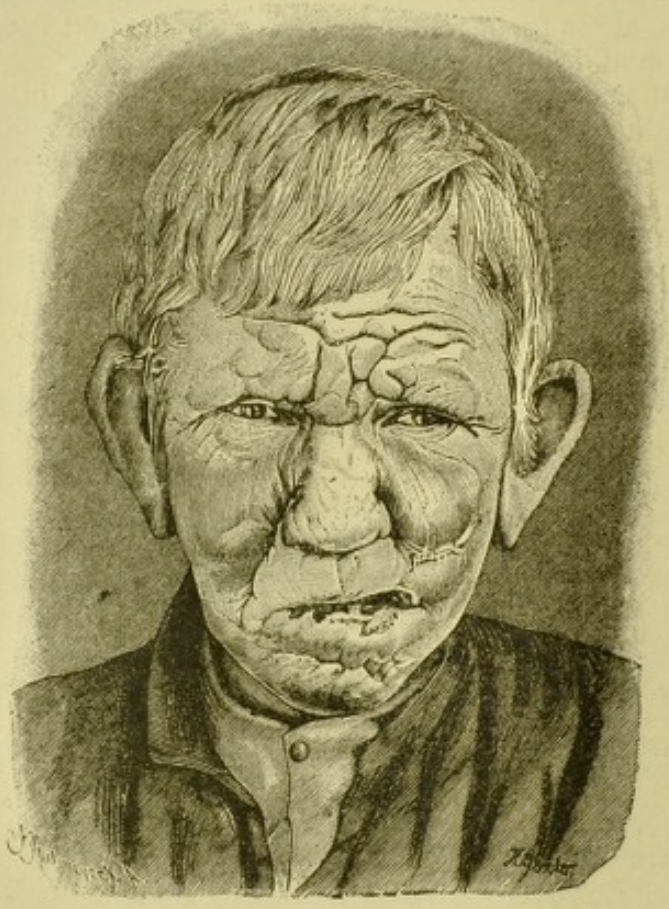


FIG. 454.—Leontiasis leprosa. (After G. Münch.)

In the region of the red spots the tissue contains large numbers of bacilli (Philippson), which for the most part lie within the vessels, and already at this stage the tissue-hyperplasia can be detected. According to investigations of Müller, the vesicular eruptions that occur in leprosy, and were formerly regarded as a sequel of a leprous disease of the nerves, are caused by the presence of bacilli.

The nodules remain for months unaltered, or they increase in size and become fused together into a single mass, so that very large tumors result, which have led to the name *facies leontina* (Fig. 454) being given to the distorted face.

The formation of ulcers which show no disposition to heal may result from *external influences*. New nodules appear occasionally, following an erysipelas-like reddening and swelling of the skin. The glands of the submaxillary and of the inguinal region swell to very large nodules.

Leprosy of the nerves (*lepra nervorum* sive *anæsthetica*) leads first to hyperæsthesia and pain, later to anæsthesia, more seldom to motor paralysis in the region of the affected nerves. The further consequences of the disease of the nerves are disturbances that show themselves in the skin in the form of white and brown spots (i.e., *lepra maculosa*, *morphœa*

nigra et alba), and in the bones and muscles in that of atrophy. Since those suffering from the disease are apt to injure themselves after the ap-

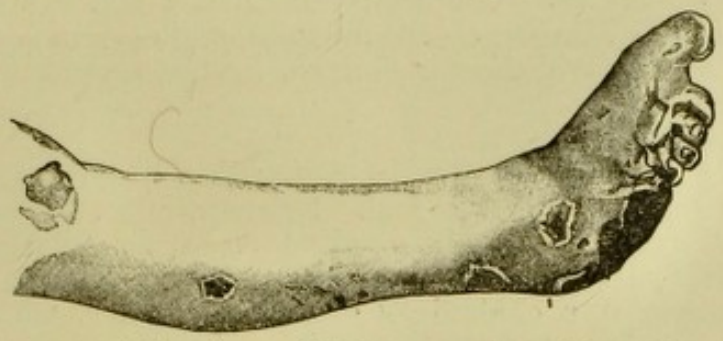


FIG. 455.—Lepra anæsthetica ulcerosa of the lower extremity and foot. (After G. Münch.)

pearance of anæsthesia, ulcers are often formed which cause deep erosions and may lead to the loss of entire phalanges (*lepra mutilans*) (Figs. 455 and 456).

Leprosy of the skin and leprosy of the nerves occur usually in combination, seldom separately. Along with the skin and the nerves, the central nervous system, the mucous membranes, the cornea, the cartilage, the liver, the spleen, the lymphatic glands, and the testicles may all become affected.

In Europe leprosy is confined mainly to Norway, Sweden, Finland,

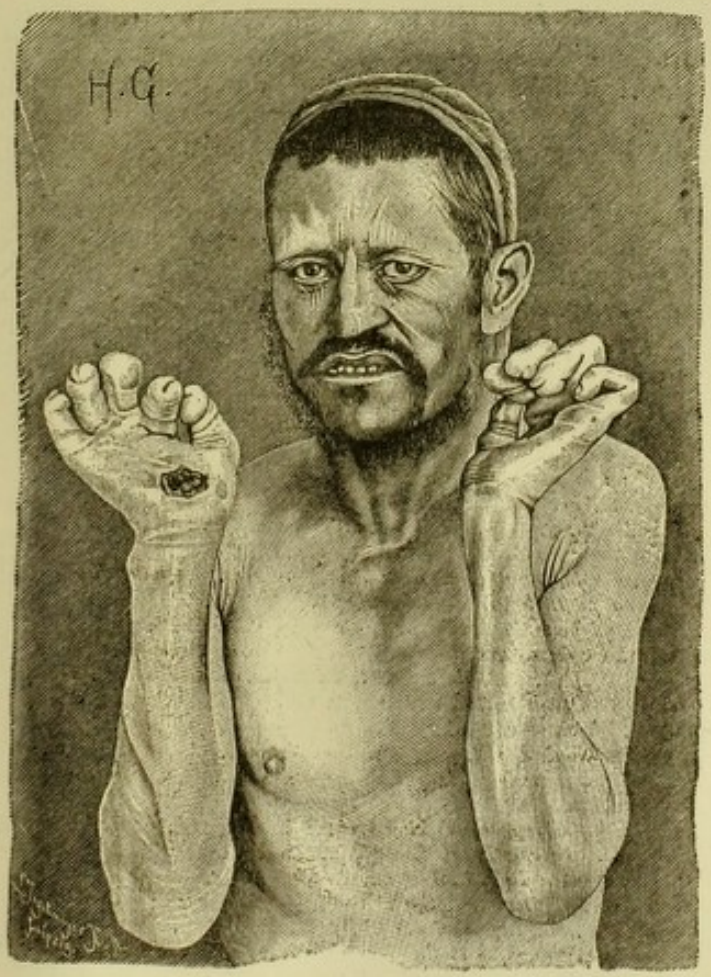


FIG. 456.—Lepra anæsthetica mutilans. Partial destruction of the fingers; ulcers in the hand. (After G. Münch.)

the Baltic Sea provinces of Russia, and the coast of the Mediterranean Sea. Sporadic cases of the disease, however, may occur in other regions. It occurs very frequently in Hindustan, China, Sumatra, Borneo, Java, and Mexico, on the northern and eastern coasts of South America, in Upper and Lower Guinea, in Cape Colony, and on the northern coast of Asia.

§ 180. The **bacillus mallei** is a bacillus discovered by Löffler, Schuetz, and Israel in glanders foci. Subsequently the observation was substantiated and the bacillus studied by Weichselbaum, Kitt, and others. It is to be regarded as the **cause of glanders** and of **farcy**, (*malleus*, *maliasmus*), a contagious disease of horses, which occurs in man only by transference from horses.

The glanders-bacilli are very small, slender bacilli, which occur in the foci of disease sometimes scattered, sometimes lying together in little clumps. For staining, alkaline methylene blue or gentian violet is usually employed.

The stained bacilli often show clear spots that are regarded by many as spores, but are interpreted by Löffler as forms of involution. The bacilli occur especially in the glanders foci, but occasionally also in the blood of the diseased individual (Löffler, Kitt).

The bacilli grow at temperatures varying from 30° to 40° C. on coagulated blood-serum, as well as on slices of boiled potato and on potato-pap. On the two latter they form amber-yellow coatings that later become red. On blood serum they form small, yellowish, transparent droplets which later become milky white. On agar-agar the colonies are grayish-white. Whether the bacilli form spores or not, is not yet determined.

Horses, asses, sheep, young dogs, goats, cats, guinea-pigs, and field-mice are suitable for inoculation. In cats, after inoculation, there develop in the testicles cellular foci, which are composed essentially of leucocytes (Fig. 457), and which lie partly inside the canaliculi (*b*, *c*), partly between them (*d*). Injection of the pus of glanders into the peritoneal cavity of male guinea-pigs causes the testicles to swell rapidly (Straus). After subcutaneous inoculations there results an ulcer at the seat of inoculation, and at the same time there is swelling of the neighboring lymph-glands. At a later stage nodules as well as nasal ulcers may be formed in the internal organs. In horses and asses typical glanders can be produced. Cattle, white mice, and house-mice are insusceptible.

The usual atrium of infection in horses is the mucous membrane of the nose. Then, next in order, the submaxillary glands become affected, and in the further course of the disease metastases develop in different organs. In the nasal mucous membrane, the infection may give rise either to a diffuse cellular infiltration of the mucous membrane, or, on the other hand, to subepithelial nodules the size of a millet-seed or a pea. In the chronic farcy of the skin larger nodules are developed, which join together in rows, forming worm-like cords.

The nodules of the mucous membrane break down easily. The cells of which they are composed bear precisely the character of pus-cells. By the disintegration, softening, and suppuration of the nodules, ulcers are formed with yellow infiltrated bottoms. They enlarge by a continuance of the process of nodular or more diffuse infiltration and subsequent disintegration of the edge, as well as by confluence of neighboring ulcers.

Horses that have died of glanders have often very extensive, irregularly shaped, elevated ulcers on the mucous membrane of the vomer. These ulcers have eroded edges and floors which are coated with a gray and yellow material; and besides these there are numerous small lenticular ulcerations and gray or yellow nodular foci which are on the point of breaking down. The whole process stands very nearly related to purulent inflammation. The healing of the ulcers is characterized by the formation of radiating scars.

The lymphatic glands in the neck are constantly the seat of inflammatory swelling. Of the internal organs the lungs particularly are affected. They either contain nodules which present, on section, a cheesy and disintegrated centre, while the periphery is grayish in color and rich in cells, or else foci of lobular pneumonia. The latter may

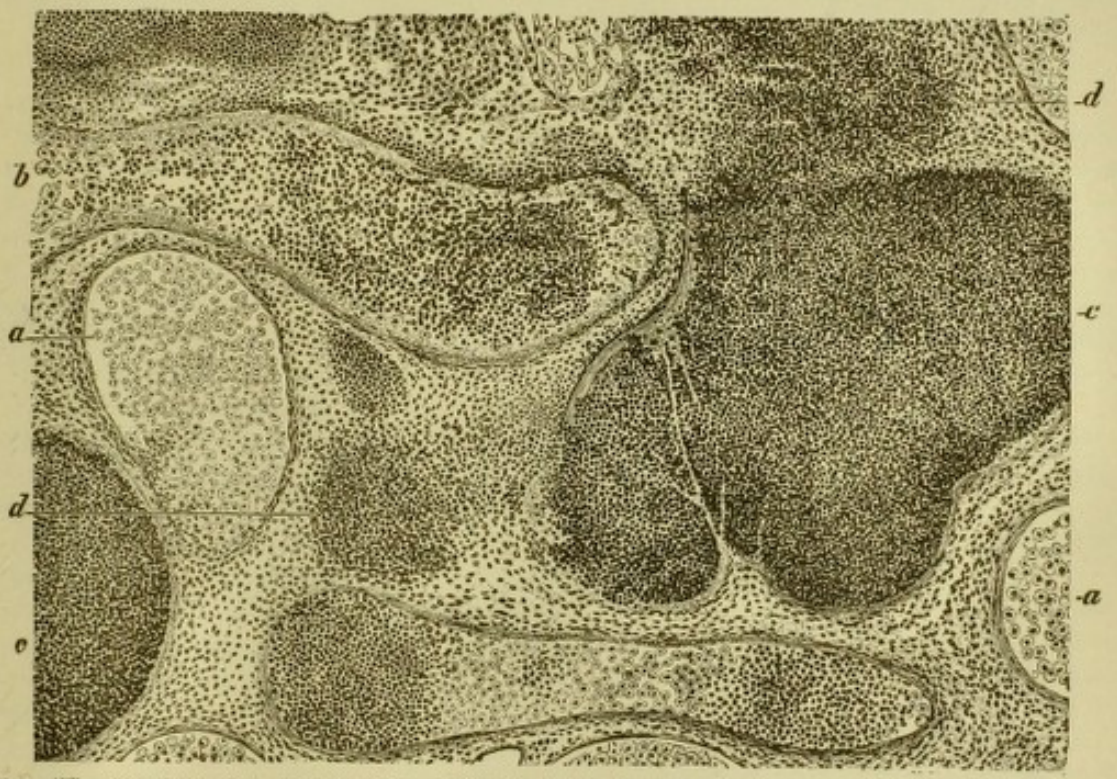


FIG. 457.—Glanders of a cat's testicle. (Müller's fluid; hæmatoxylin.) *a*, Seminiferous tubules; *b*, *c*, tubules filled with leucocytes; *d*, masses of leucocytes in the connective tissue. Magnified 100 diameters.

have either a light-gray or a more hemorrhagic appearance, or they may have already become opaque and of a yellowish-white color, by reason of fatty and caseous changes. Occasionally the mucous membrane of the intestinal tract may contain nodules of varied size, some of them light gray, and consequently rich in cells, some of them of an opaque, yellowish-white color, cheesy, or on the point of suppurating.

In farcy, which has more of a chronic course than glanders, the nodules which form in the skin and muscles consist of small-celled tissue which finally undergoes a retrograde metamorphosis, becomes caseated, and disintegrates.

In **human beings** the **infection with glanders-poison** takes place mostly through small wounds of the skin; it can, however, also appear primarily on the mucous membrane at the point where it joins the skin. In the skin and subcutaneous tissue the following lesions may develop: carbuncular and phlegmonous inflammations which may result in sup-

puration; nodular, vesicular, and pustular exanthemata; and suppurative inflammation of the lymphatic vessels and glands. In the mucous membranes of the respiratory passages catarrhs appear, and suppurating nodules and nodes are formed, which leave ulcers behind. In the internal organs metastatic, small-celled nodules are formed, that show a tendency to suppurate or to form extensive suppurative infiltrations or abscesses, especially in the muscles. In chronic farcy occasionally large nodules are formed in the skin and muscles, and these break down and give rise to ulcers that are slow to heal. In order to determine precisely what is the nature of the process it is scarcely possible to dispense with a bacteriological examination or with inoculations.

According to investigations of Kalning, Preusse, and others, a potent poison, *mallein*, can be extracted from cultures of the glanders-bacillus. This substance, when injected in small doses into horses suffering with glanders, causes febrile rise of temperature and may be used as a diagnostic aid.

§ 181. Under the name of the **bacilli of rhinoscleroma** (Fig. 458), Frisch, Pellizari, Chiari, Cornil, Alvarez, Köbner, Paltauf, von Eiselsberg, Dittrich, and others have described short rods with rounded ends which constantly occur in the morbid formation called *rhinoscleroma* or *scleroma respiratorium* (Bornhaupt, Wolkowitsch), and consequently are regarded as the cause of the disease. Staining succeeds best with methylene violet; the sections being left in the mixture for from twenty-four to forty-eight hours. After staining, the sections are treated with iodine water, or are left for from one to three days in absolute alcohol.

The bacilli possess mostly a hyaline capsule. According to Paltauf, von Eiselsberg, Dittrich, Wolkowitsch, and others, they may be cultivated on blood-serum, gelatin, agar-agar, and potatoes; and under these conditions they form capsules (Fig. 458). When cultivated in bouillon, on the contrary, they show no capsules (Dittrich). Stab-cultures in gelatin resemble very much the nail-cultures of the pneumonia-bacilli of Friedländer, but are of a transparent grayish-white color, and not dead white. The bacilli stain more readily than the pneumonia-bacilli, and also stain by Gram's method. Stepanow observed, in inoculations into the eyes of guinea-pigs, active inflammations and proliferating granulations containing the bacilli and hyaline-degenerated cells.

FIG. 458.—Bacilli of rhinoscleroma from an agar-agar culture. (Preparation of Stepanow; stained with gentian violet.) Magnified 750 diameters.

Rhinoscleroma is observed principally in east Austria and in southwest Russia; isolated cases occur also in Silesia, Italy, Egypt, Belgium, Sweden, and Switzerland, and in South America. It is a chronic progressive disease of the tissues which lasts for many years, usually beginning in the nose (Wolkowitsch), more rarely in the throat, larynx, or palate, and extending thence to the neighboring parts—the external nose, lips, tear-passage, trachea, etc. The affection in the nose is characterized by a thickening of its walls which in some cases is diffuse, but in others is lumpy or nodular. The external skin assumes a reddish or brownish-red color, becomes stiff and cracked, and is covered with scales. In the throat and respiratory passages tough cartilaginous infiltrations are sometimes found, and at other times shrunken scar-tissue. The infiltrations may appear at times in the form of nodules or nodes, at other times in that of tumors and flat thickened areas; or, finally, they may be spread out more diffusely. By the transformation of the infil-

tration into shrunken scar-tissue, extensive deformity of the affected organs may result. Deeply extending destruction of tissue is absent, but, on the other hand, superficial ulceration may take place. The infiltrated tissue on section appears yellowish and fatty, but not infrequently it shows a gray or grayish-red color. The tissue of the diseased portions consists partly of hyperplastic granulations, partly of fibrillated connective tissue. If the former extend to the epithelial covering there appear partly hyperplastic, partly degenerative processes in the epithe-

FIG. 459.

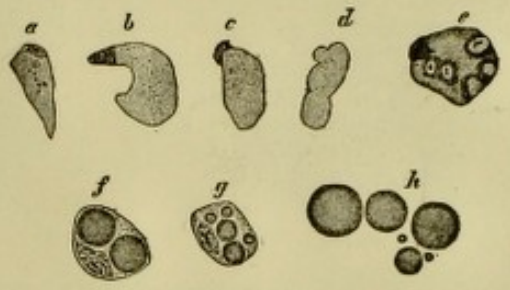


FIG. 460.

FIG. 459.—Section of rhinoscleromatous tissue, with numerous degenerated and vacuolated cells which inclose the bacilli. Preparation of Stepanow. (Osmic acid; hæmatoxylin.) Magnified 400 diameters.

FIG. 460.—Cells with hyaline degeneration and hyaline globules from rhinoscleromatous tissue of the vocal cord and of the nose. Preparation of Stepanow. *a*, *b*, *c*, *d*, Hyaline-degenerated cells with small bacilli; *e*, a hyaline cell with a capsulated bacillus; *f*, *g*, cells with hyaline globules; *h*, free hyaline globules. (*a*, *b*, *c*, *d*, stained with Löffler's solution; *e*, with hæmatoxylin; *f*, *g*, *h*, with fuchsin.) Magnified 500 diameters.

lial cells. The degeneration is characterized by the formation of vacuoles and by an infiltration of the parts with round cells. According to Stepanow, the vacuoles may contain bacilli.

The granulation tissue itself may show in many places no special peculiarities; it may, in fact, merely present the conditions that are found in other inflammatory infiltrations and proliferations of connective tissue. Other places, on the contrary, contain in smaller or larger numbers cells possessed of one vacuole, or completely degenerated and vacuolated, or reticulated in structure. In these gaps within the cells the bacilli can be detected (Fig. 459), some of which possess a gelatinous capsule. It is not to be doubted that the multiplication of the bacilli in the cells is the cause of the degeneration of the latter.

Along with the degenerated, vacuolated cells there occur cells of various shapes which have undergone hyaline degeneration (Fig. 460, *a*, *b*, *c*, *d*, *e*). These also contain bacilli with and without capsules, and also coccus-like forms. These cells may become changed into non-nucleated homogeneous scales by the loss of the nucleus (*d*). Finally, there are also cells inclosing hyaline spherules (Fig. 460, *f*, *g*), and these latter are also found lying free in the tissue (*h*). In places that are not yet affected with scar-degeneration the hyaline forms may be present in large numbers.

§ 182. The **actinomyces** or **ray-fungus** is a polymorphous fission-fungus, which appears in various forms of growth in the human and animal organism, as well as in artificial cultures. It is the cause of **actinomycosis**, a disease which occurs in man as well as among cattle, swine, and horses, and which is characterized by a progressively advancing inflam-

mation that produces in part granulations and connective tissue, in part pus. The botanical position of the fungus is still in dispute. Many classify it among the thread-fungi. It seems to be more correct, however, to place it *among the polymorphous bacteria.* Boström classifies it in the group *cladothrix.*

Areas which the fungus

FIG. 461.

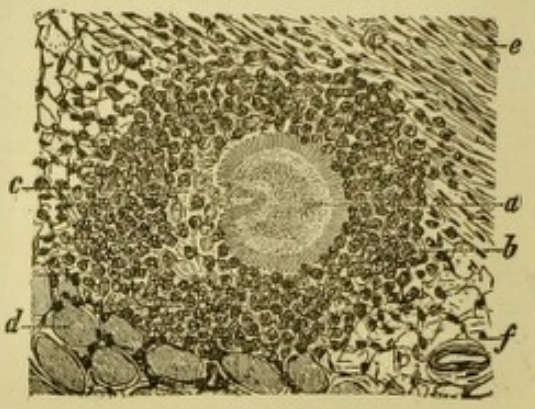


FIG. 462.

FIG. 461.—*Actinomyces hominis.* Teased preparation. Magnified 800 diameters.

FIG. 462.—Section from a tongue affected with actinomycosis. (Alcohol; alum-carmine.) *a*, Actinomyces kernel or gland; *b*, cellular nodule; *c*, pus corpuscles; *d*, cross-section of muscles; *e*, longitudinal section; *f*, cross-section of bands of connective tissue with blood-vessels. Magnified 200 diameters.

forms in the tissues were long ago observed by Langenbeck and Lebert, but their significance was not rightly interpreted. The observations of Hahn, supplemented by the investigations of Bollinger and Harz, first led to a correct interpretation of the ray-fungus occurring in domestic animals. Then Israel found a similar fungus in man, and Ponfick soon after gave his opinion in favor of the identity of actinomyces of cattle with the fungus discovered in human beings by Israel.

According to the investigations of Boström, the actinomyces is distinguished from the bacilli by the fact that in cultures on beef's blood-serum and on agar-agar, it forms *branching threads.* The threads of the cultures are partly straight, partly wavy, sometimes also twisted like a screw. They break up by transverse division into short rods and coccus-like forms that grow out again into threads under suitable conditions.

Within the human and animal organisms the fungus appears in areas which may be in the form of little granules scarcely recognizable with the naked eye, or in that of spherules as large as 2 mm. in diameter. The foci may be colorless and translucent, or white and opaque, sometimes yellow, sometimes brown, sometimes green, sometimes yellowish-green in color. Of the smaller ones, quite a number consist only of a mat of fine threads, some of them branching, others straight or wavy or coiled-up.

Most of the granules contain, moreover, peculiar club-shaped forms (Fig. 461) that constitute the termination of the threads; and if these club-shaped forms are present in large numbers, as is usually the case in the larger foci, they have a radiated arrangement (Fig. 462, *a*) and lend a ray-like appearance to the fungus colony. Occasionally there develop hand- and fan-like forms on the ends of the threads. According to Boström, all these peculiar forms result from a swelling of the membrane of the fungus threads, and are to be regarded as retrogressive forms that appear upon the exhaustion of the nutrient material.

The actinomyces is usually taken up with the food or with the respired air, and finds its first development often in the cavity of the

mouth. Since the threads and nodules of the actinomyces in many respects correspond exactly with the form of fungus called leptothrix, and, moreover, since the club-like swellings also occur on the ends of the threads of the latter (Israel), it is difficult to determine the presence of the actinomyces in the cavity of the mouth, in which situation, moreover, it seems not to form the characteristic nodules. It has been impossible up to the present time to detect the organism outside the human body. But it must be remarked that often little bits of some higher plants—the beard of grain, a splinter of wood—have been found in the pus from an actinomyces focus, and that swallowing parts of plants—a spike of grain (Bertha)—or the contamination of wounds with vegetable material, preceded actinomycosis in some cases; so that it is very probable that the fungus occurs upon higher plants and upon wood.

If the ray-fungus succeeds in settling in a tissue it calls forth an inflammation in its surroundings. While the germ that has penetrated the tissue develops a mycelium and a fungus-kernel (Fig. 462, *a*, and Fig. 463, *a*), a nodular inflammatory focus forms in its surroundings,

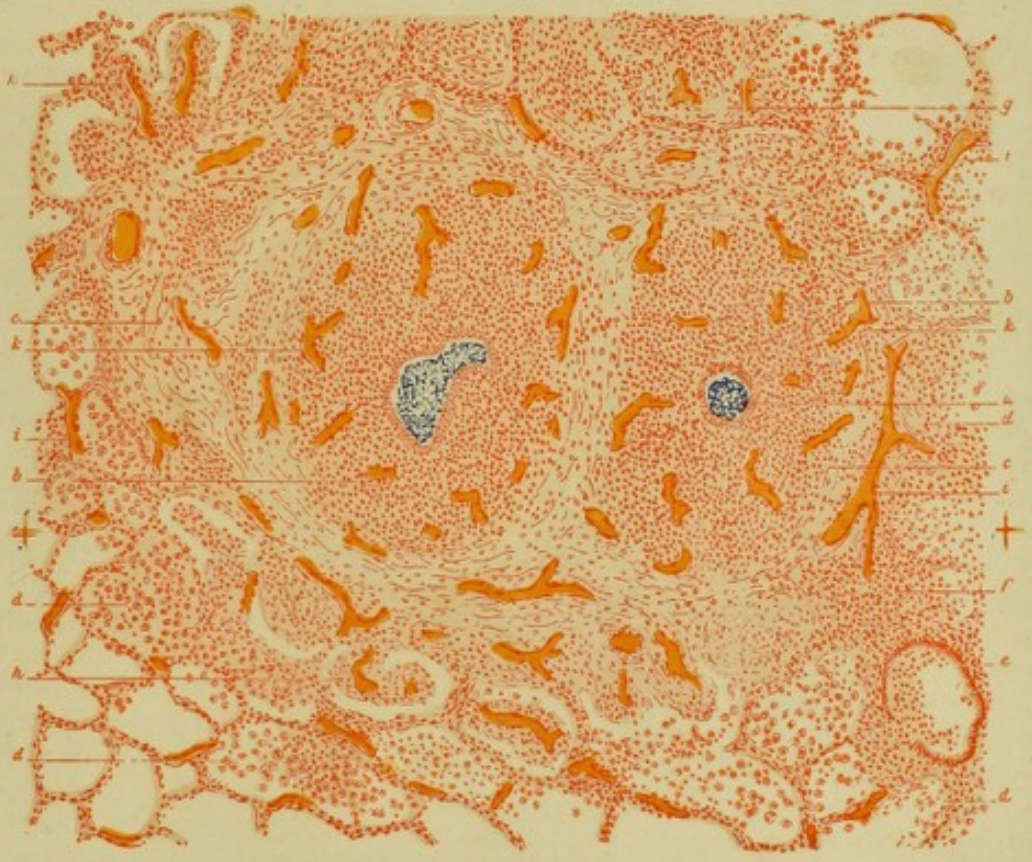


FIG. 463.—Actinomycosis of the lung. (Alcohol; carmine; Gram's method.) *a*, Fungus-kernel or gland; *b*, small-cell nodule; *c*, fibrous tissue; *d*, alveoli filled with large and small cells; *e*, bronchiolus with cellular-infiltrated wall; *f*, small-cell focus in the neighborhood of the bronchus, *e*; *g*, alveoli filled with vascularized connective tissue; *h*, connective-tissue hyperplasia in alveoli; *i*, blood-vessels of the lung; *k*, blood-vessels of the inflamed area. Magnified 45 diameters.

and this focus consists at first of small, round cells (Fig. 462, *b*, *c*, and Fig. 463, *b*), but later may also contain epithelioid cells and giant cells.

The fungus-kernels may multiply in the interior of a nodule and give rise to an enlargement of the latter, and it very often happens that cellular nodules the size of a pea and larger contain a large number of fungus foci, which are usually situated around the periphery. At the same time

new fungus foci, and consequently new cellular foci, may appear in the neighborhood. The further spread of the infection takes place by means of small rods and threads, which probably break off from the larger masses and are observed partly free in the tissue, partly inclosed in cells.

Larger nodules often undergo in time in the middle a purulent melting down, and so lead to the formation of small *abscesses*, which may join together to form large *pus-cavities* or *sinuses*. In the neighborhood of the cellular foci (Fig. 463) a lively *hyperplasia of the tissue* quickly develops, and this leads to the *formation of vessels* (*k*) and of young *granulation tissue*, which subsequently becomes *connective tissue*. If the connective-tissue hyperplasia attains very considerable proportions it leads to *induration* (Fig. 463), often also to *enlargement of the tissue*. The hyperplasia may finally penetrate into the small-cell foci and supplant these, and the fungi are probably destroyed in this way.

If the hyperplasia gets the upper hand a nodular new formation of tissue (Fig. 464, *a*) ensues in the course of weeks or months, and in cattle it can reach the size of a man's fist, and may even considerably exceed this size. The tumor consists partly of dense connective tissue, partly of granulation tissue, partly of a tissue in a transitional stage between these, and always contains small cellular foci, or even cavities formed by disintegration, with fungus-kernels, of the shape already described, lying in the purulent contents. When the fungus develops in the interior of the jaw-bone an active new bone-formation takes place simultaneously at the periphery (Fig. 464, *a*).

If the destruction of tissue and pus-production predominate over the hyperplasia there result more or less extensive sinuous cavities and branching fistulous tracts anastomosing with one another. The walls consist of granulations and hyperplastic connective tissue, and here and there contain fungus foci. The clumps of fungi may become partially calcified.

In cattle the process is situated mainly in the lower jaw, then also in the upper jaw (Fig. 464, *a*), in the tongue, in the throat-cavity, in the trachea, in the œsophagus, in the stomach, in the intestinal wall, in the skin, in the lung, and in the subcutaneous and intermuscular connective tissues. It leads here to the formation of more or less extensive nodular tumors of the character described, and was formerly given various names, such as osteosarcoma, bone-cancer, bone-tuberculosis, abscess of the jaw, wooden tongue, tuberculosis of the tongue, lymphoma, fibroma, worm-nodules, etc. In man the infection, so far as is known, may arise from any of the following localities: the mouth, the fauces, the œsophagus, the stomach, the intestine, the lungs, or some external spot which has received an injury. In the first-named locality the invasion of the actinomyces takes its start from carious teeth (cavities or fistulæ), or from any injury to the soft parts of the jaw or of the cheek. Thence the process encroaches upon the neighborhood, and may finally extend to the face and the hairy portions of the head, as well as upon the throat, the nape of the neck, the back, and the breast.

Where the process appears for the first time, tumefactions take place that subsequently partially soften and give rise to fluctuation. When the latter is the case, pus is formed that is sometimes thin fluid and sometimes more stringy, and contains the characteristic granules. If these abscesses break externally, fistulous tracts are formed, which either close again or continue to give off pus.

Accompanying the foci of suppuration, which are sometimes small, sometimes very extensive, there is formed constantly also more or less granulation tissue, which at times may be very abundant. In consequence of fatty degeneration and disintegration of its elements the granulation tissue often becomes partially whitish or yellowish or reddish-white in color, and permeates the morbid tissue in an irregular manner. In other portions it returns to a development of connective tissue, especially in places where the process does not spread any farther.

By this development of connective tissue a local healing of the process may take place, leaving behind a cicatricial induration. But usually in other places the process makes further progress, and under certain circumstances may lead to very extensive destruction. If it should encroach upon the bones of the spinal column or of the breast-wall these become roughened through superficial caries. In rare cases the jaw-bone may be attacked from the inside, as from an alveolus, and so undergo destruction. The process may spread inward from the base of the skull into the interior of the skull, and lead to actinomycotic meningitis and encephalitis.

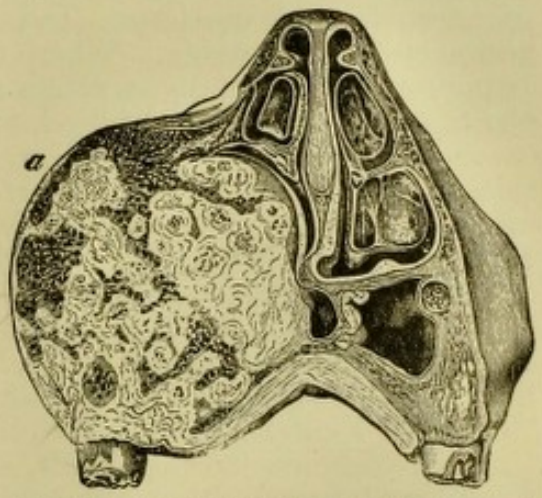


FIG. 464.—Frontal section through the nose and upper jaw of a cow affected with actinomycosis in the form of a tumor. *a*, Nodule consisting of connective tissue, bone, and small purulent foci. One-quarter natural size.

In primary infection of the respiratory apparatus the process takes the form of bronchopneumonic inflammations which are characterized by the formation of nodules (Fig. 463, *b*), and the latter, at an early stage, assume a yellowish-white color in their central portions. Here also cavities may be formed by disintegration of the inflammatory foci, and the contents of these will be found to consist of fluid, pus-corpuscles, fatty detritus, fatty globular granules, disintegrated red corpuscles, and masses of actinomyces. The tissue lying between the mycotic foci becomes to a greater or less extent affected with inflammatory thickening and induration (Fig. 463, *c*), and may change by connective-tissue hyperplasia to a callous slate-gray or gray-and-white-colored mass which is devoid of air and later contracts. In this way the larger part of the lung may become changed into a mass of connective tissue.

The process sooner or later spreads from the lung to the visceral pleura, and thence to the costal pleura or over to the pericardium. In consequence of this, inflammatory exudations, as well as proliferative processes, take place at the locations mentioned, and lead to adhesions between opposite surfaces of the pleura and of the pericardium. The cellular infiltration, as well as the pus-formation and the fatty degeneration and disintegration of the granulation tissue, may extend between the ribs to the outside from the costal pleura, and spread in the contiguous soft parts, in the connective tissue and muscles, and finally break through at different points externally. From the inside of the lung occasionally rupture takes place into the mediastinum and pericardium,

and finally into the heart. Under certain circumstances rupture takes place through the diaphragm into the abdominal cavity, or the process spreads from behind the mediastinum into the retroperitoneal connective tissue.

The secondary areas of destruction situated outside the lung often assume perfectly colossal proportions, whereas in the lung the process may spread only to a limited extent and then cicatrize. At one time the purulent softening predominates, at another the formation of granulations and indurations.

Actinomycosis originating in the intestinal tract begins with the formation of plaque-shaped, whitish patches of the fungus (Chiari), or of nodular mucous and submucous foci (Zemann) containing the fungus elements and leading to ulceration by undergoing necrosis. The process spreads from the intestine to the peritoneum and the retroperitoneal connective tissue, as well as to the organs adjacent to the original seat of disease—e.g., the liver. It finally breaks through the wall of the abdomen to the outside. Where the actinomyces patches develop, the inflammatory foci of hyperplasia are formed. If fæcal masses get into the tissues by a rupture of the intestine, fæcal abscesses are formed.

Metastases may occur in the course of the local disease, and this may take place by direct rupture of the fungus-growth into the blood-vessel, although this is rather unusual. From the intestines usually liver metastases result; from the lung there result skin, muscle, bone, brain, intestinal, and kidney metastases. The metastatic nodules behave like the primary foci. In rare cases primary foci of actinomyces occur in the internal organs—e.g., in the brain (Bollinger)—without our being able to discover any portal of entrance.

Johne, Ponfick, Boström, Wolff, and Israel have attempted inoculation experiments upon animals, and several of them (Johne, Ponfick, Wolff, and Israel) have obtained positive results, according to their statements. Wolff and Israel, by the inoculation of rabbits and guinea-pigs, obtained in almost all cases a characteristic morbid condition, with inflammatory foci containing the fungus-masses. They also succeeded in cultivating upon agar-agar the fungus which they had taken from the tumors.

A few years ago Eppinger[1] found a fission-fungus in the pus of an old brain-abscess which led to death by meningitis. The fungus is to be classed with the polymorphous bacteria. Eppinger called it **cladothrix asteroides,** and determined its characteristics by cultivation and inoculation upon animals. The disease caused by the fungus may be called **pseudotuberculosis cladothrichica,** inasmuch as there existed in the lungs and bronchial glands of the individuals so affected, changes similar to those which are observed in tuberculosis, and also since a disease suggestive of tuberculosis developed in guinea-pigs and rabbits on inoculation.

Buchholtz[2] saw in a lung which was infiltrated with the products of a pneumonia, and which contained a large cavity with ragged walls, the diseased lung-tissue thickly crowded with fine, branched, and many times broken threads, which could be stained by Gram's method. He considers the fungus, which he could not cultivate, as a pathogenic streptothrix.

According to Dunker[3] and Hertwig,[4] there occurs in hogs a ray-fungus which is always situated in the muscles, especially the intercostal muscles and those of the diaphragm and abdomen. It causes a degeneration of the muscle-fibres of the surrounding

[1] "Ueber eine neue pathogene Cladothrix und eine durch sie hervorgerufene Pseudotuberculosis," *Beiträge zur path. Anat. von Ziegler*, ix., 1891.

[2] "Ueber menschenpathogene Streptothrix," *Zeitschr. f. Hyg.*, xxiv., 1897

[3] *Zeitschrift f. Mikroskopie und Fleischschau*, iii., 1884.

[4] *Archiv f. wissensch. u. prak. Thierheilk.*, xii., 1886.

neighborhood, and hyperplasia of the connective tissue. The masses of fungi are also arranged radially, forming club shapes. They readily undergo calcification and then form white points in the flesh.

According to the investigations of Kanthack,[1] Boyce,[2] and Vincent,[3] it is very probable that the affection known as **Madura disease,** or **Madura foot,** or **mycetoma,** observed in India, represents a disease caused by a polymorphous fission-fungus nearly related to actinomyces and called by Vincent *streptothrix Maduræ*. The disease consists of a gradual swelling of one of the extremities, caused by nodular deposits which turn into abscesses and fistulous tracts, and which, on pressure, empty peculiar brown or black fish-roe- or truffle-like granules. The granules contain the fungus. Kanthack even regards the fungus as identical with actinomyces; but the investigations of Vincent and Boyce do not agree with this assumption. According to Boyce, the *streptothrix Maduræ* forms two varieties: a white one with white dichotomously dividing threads, and a black one with branching pigmented threads. Formerly it was assumed that the Madura disease was caused by a thread-fungus, the *Chionyphe Carteri*,[4] but there are no convincing investigations to support this assumption.

§ 183. In addition to those which have already been described there is a large number of **bacilli which are pathogenic for animals** and which at the same time may be the cause of infectious diseases in the human being. The most important animal diseases that owe their origin to bacilli are blackleg, or the symptomatic anthrax of cattle, swine-erysipelas, swine-plague, cattle-plague, and chicken-cholera.

The **bacillus of blackleg or symptomatic anthrax** (bactérie du charbon symptomatique) is a staff from 3 to 5 μ long and from 0.5 to 0.6 μ thick, with rounded ends, and sometimes possessing independent motion. According to the investigations of Bollinger, Feser, Arloing, Cornevin, Thomas, and others, it occurs constantly in blackleg.

Blackleg occurs especially in young cattle and lambs, and leads usually in two days to death. Anatomically it is characterized by a tumor-like swelling of the skin, caused by the exudation of a bloody serous fluid in the subcutaneous and intermuscular and muscular connective tissues, as well as by the evolution of gas in the affected portion. Bacilli are found in the region of the exudation and gas-production, as well as in the spleen and liver. They are not stained by Gram's method.

According to Arloing, Cornevin, and Thomas, the bacilli may be cultivated by exclusion of oxygen in chicken-broth to which a small amount of glycerin and sulphate of iron is added. Kitasato and Kitt cultivated them in guinea-pig broth, agar, and gelatin by excluding oxygen. They grow best at from 36° to 38° C., and form spores in the middle or toward the ends of the rods, the latter becoming somewhat swollen at the point where the spores form. Addition of sugar or glycerin to the nutrient medium accelerates the growth. If cattle or sheep are inoculated with bacilli which are attenuated by heat it is possible to give them immunity from the virulent bacilli. The following animals are susceptible to the bacilli of symptomatic anthrax: cattle, sheep, goats, rabbits, guinea-pigs, hogs, dogs, cats, chickens. Black rats enjoy immunity. Horses and asses assume an intermediate place.

If guinea-pigs are inoculated with virulent material—for example, with the dried juice of the muscle of cattle that have died of blackleg—there very quickly appears a rapidly spreading swelling which starts at the seat of inoculation, and is caused by an infiltration of the tissue with bloody œdematous fluid. The bacilli spread extraordinarily quickly, especially in the subcutaneous and intermuscular tissues, and they also penetrate into the muscles. They cause severe lesions of the vessels, leading to hemorrhage and to the exudation of a serous fluid; after a time an abundant emigration of leucocytes also takes place. Guinea-pigs usually die on the second or third day after the swelling has spread out over a portion of the body. The blood usually remains free from bacilli. Spores are not formed in the living body.[5]

[1] "Madura Disease and Actinomyces," *Journal of Pathology*, i., 1892.

[2] "Upon the Existence of more than one Fungus in Madura Disease," *Philos. Trans.*, vol. clxxxv., 1892; and *Hyg. Rundschau*, 1894.

[3] "Étude sur la parasite du pied de Madura," *Annal. de l'Inst. Pasteur*, 1894.

[4] Carter: "Mycetoma, or the Fungus Disease of India," London, 1874; Lewis and Cunningham: "The Fungus Disease of India," Calcutta, 1875; Hirsch: *Virchow's und Hirsch's Jahresbericht*, 1875 and 1876.

[5] Literature: Arloing, Cornevin et Thomas: "Le charbon symptomatique du bœuf," Paris, 1887; Hess: "Der Rauschbrand," *Thiermed. Vortr.*, No. 4, 1888; Kitasato: "Der

The **bacilli of swine-erysipelas** (Löffler, Lydtin, Schottelius, and Schuetz) vary from 0.6 to 1.8 μ long. At temperatures varying from 18° to 40° C. they may be cultivated in bouillon, in a mixture of meat infusion, peptone, and gelatin, in blood-serum, and in sour milk. In gelatin poured out on plates they form peculiar radiating, branching figures. In stab-cultures (Plate I., Fig. 2) whitish rays grow out from all sides of the line of inoculation like the bristles in a test-tube brush. The bacilli may form pseudothreads in cultures. Glistening spherules which they sometimes inclose are regarded as spores. With the pure cultures swine-erysipelas can be reproduced in susceptible hogs. House-mice and doves die in from two to four days after inoculation, and their blood contains numerous bacilli.

On inoculation in rabbits an erysipelas-like inflammation results, which leads either to general infection, with fatal termination, or to recovery. Guinea-pigs and chickens enjoy immunity.

According to investigations of Pasteur and Thuillier, which were corroborated by Schottelius and Schuetz, the toxic power of the bacillus for swine decreases by continued reinoculation into rabbits. Susceptible hogs inoculated with vaccine attenuated in this way do not die from the inoculation, and become insusceptible to the fully virulent bacilli.

Swine-erysipelas occurs especially among young highly bred (English) hogs, whereas the common breeds are entirely or nearly immune. The disease is characterized by fever as well as by the appearance of red spots, later becoming brown, on the neck, breast, and abdomen. At times intestinal hemorrhages occur. More than half of the infected animals die, usually in a few hours or within four days. The autopsy shows swelling of the intestinal mucous membrane, and here and there hemorrhagic infiltration; tumefaction of the follicles and ulcers, especially in the ileo-cæcal region; swelling of the mesenteric lymph-glands, and petechiæ in the serous membranes.

The bacilli are found in the blood, as well as in the lymph-glands, muscles, spleen, and kidneys, where they also lie in the vessels. Most of them are free, but some of them are inclosed within the leucocytes. They can be stained by Gram's method.[1]

The **bacillus of swine-plague** is a small bacillus, from 1.0 to 1.5 μ long, rounded at the ends, and for the most part staining only at the ends. It resembles the bacillus of chicken-cholera, and may be cultivated on various artificial media. It is looked upon as the cause of the disease known in Germany as Schweineseuche or Schweinepest, in England as hog-cholera or swine-fever, in America as swine-plague and as hog-cholera, in Sweden and Denmark as epidemic swine-disease. Yet it is not determined whether the epidemic swine-diseases of the different countries (with the exception of swine-erysipelas) are identical one with the other.

The anatomical alterations in epidemic swine-disease vary according to the location of the infection. In the lungs are found multiple necrotizing or hemorrhagic pneumonic areas and pleuritis. Intestinal infection leads to hemorrhagic and diphtheritic enteritis and (in chronic cases) to caseating inflammations, which are accompanied by corresponding involvement of the mesenteric lymph-glands, and at times by peritonitis also. The bacilli, besides being found in the diseased areas, are in acute cases also in great numbers in the blood. Swine, guinea-pigs, rabbits, and mice are susceptible to inoculations.[2]

Chicken-cholera, also called *typhoid of fowls*, is an epidemic disease which occurs in

Rauschbrandbacillus," *Zeitsch. f. Hyg.*, vi., 1889, and viii., 1890; Kitt: "Der Rauschbrand," *Centralbl. f. Bakt.*, i., 1887, and *Deutsche Zeitsch. f. Thiermed.*, xiii., 1887; Roger: "Charbon symptomatique," *Rev. de. Méd.*, 1891; Rogowitsch: "Wirkung der Rauschbrandbacillen," *Beiträge von Ziegler*, iv., 1889.

[1] Literature of swine-erysipelas: Hess: "Der Stäbchenrothlauf u. die Schweineseuche," *Thiermed. Vortr.*, i., 1888; Kitt: "Der Stäbchenrothlauf der Schweine und dessen Schutzimpfung," *Jahresb. d. Thierarzneisch.*, München, 1885–1886, Leipzig, 1887; Löffler: "Schweinerothlauf," *Arb. a. d. k. Ges.-Amte*, i., 1885; Lorenz: "Schutzimpfung gegen Schweinerothlauf," *Centralbl. f. Bakt.*, xv., 1894; Lydtin u. Schottelius: "Der Rothlauf der Schweine," Wiesbaden, 1895; Schütz: "Rothlauf d. Schweine," *Arb. a. d. k. Ges.-Amte*, i., 1885.

[2] Literature of swine-plague: Bleisch u. Fielder: "Schweineseuche," *Zeitschr. f. Hyg.*, vi., 1889; Frosch: "Ursachen der amerikanischen Schweineseuche," *Zeitschr. f. Hyg.*, ix., 1890; Raccuglia: "Bakt. d. amerikan. Swine-plague u. der deutschen Schweineseuche," *Centralbl. f. Bakt.*, viii., 1890; Selander: "Swinpest," *Ann. de l'Inst. Pasteur*, iv. Smith: "The Hog-cholera Group of Bacteria," *Centralbl. f. Bakt.*, xvi., 1894, p. 231; Friedberger u. Fröhner: "Pathol. der Hausthiere," 1896; "Jahresbr. von Baumgarten" (Salmon, Billings, Smith), 1886–1895; Schütz: "Schweineseuche," *Arb. a. d. k. Ges.-Amte*, i., 1886; Silberschmidt: "Swine-plague, Hog-cholera, Pneumoentéritis des Porcs," *Ann. de l'Inst. Pasteur*, 1895; Marek: Histologie der Schweineseuche," *Zeitschr. f. Thiermed.*, i. 1897.

chickens. The **bacillus of chicken-cholera** is a small bacillus from 1 to 1.2 μ long, often somewhat constricted in the middle. It was first studied by Perroncito, and then by Toussaint, Pasteur, Rivolta, Marchiafava, Celli, and Kitt. The disease is characterized clinically by great debility and stupor, occasionally also by diarrhœal intestinal discharges; anatomically by swelling of the spleen and liver, by hemorrhages and inflammations of the intestines, frequently also by pleuritis and pericarditis.

The bacilli are found in the blood, and consequently also in the capillaries of the various tissues. They may be cultivated on nutrient gelatin, on blood-serum, and in neutralized bouillon, as well as on potatoes, and they form whitish colonies. By inoculating or feeding chickens with the bacilli typical chicken-cholera can be produced. Pigeons, sparrows, pheasants, rabbits, and mice are susceptible to the bacilli. In sheep, horses, and guinea-pigs a local abscess at the seat of inoculation can be obtained.[1]

According to the view of Voges,[2] the German epidemic swine-disease, rabbit septicæmia, Wildseuche (deer-disease), Büffelseuche, chicken- and duck-cholera, the American swine-disease, swine-fever and Frettchenseuche (ferret disease), are all caused by the same disease-producer—the **bacterium of hemorrhagic septicæmia,** and are one and the same disease, to which he and Hueppe give the name of *hemorrhagic septicæmia.*

The **bacillus diphtheriæ columbarum** is a small, slender bacillus which Löffler[3] isolated from the exudate of a pigeon dead of diphtheria. It is probably[4] the cause of pigeon-diphtheria, a disease resembling human diphtheria. Löffler was able to reproduce the disease in pigeons, but not in chickens, by inoculating pure cultures into the mucous membrane of the mouth. Mice died about five days after inoculation, and the bacilli were found in the blood-vessels of all the organs.

According to Löffler (*l.c.*), a *bacillus* is also found in the **diphtheria of calves;** but he did not succeed in cultivating it pure or in proving its pathogenic significance.

Diphtheria of fowls and *diphtheria of calves* are etiologically different from the diphtheria of human beings.[5]

Besides the above, there are many bacilli which have been described as the cause of diseases occurring among animals. Thus, for example, according to Hoflich,[6] and Enderlen,[7] the frequently occurring *pyelonephritis of cattle* is caused by a *bacillus.* Likewise, according to Nocard,[8] the worm-disease of the ox, which formerly occurred frequently in France, and, according to Oreste and Armanni,[9] and von Ratz,[10] the plague occurring among the Italian buffalo, known as the *barbone dei bufali*, are caused by a bacillus (considered by Voges to be the bacterium of hemorrhagic septicæmia). According to Bang,[11] bacilli should be considered the cause of the epidemic-like abortion of cows. Siegel and Busenius[12] have described a bacillus as the cause of foot-and-mouth disease. but according to C. Fränkel[13] its pathogenic character remains to be proven. Whether a micro-organism described by Babes and Proca[14] can be looked upon as the cause of foot-and-mouth disease, is not at the present time determined.

[1] Literature: Gamaleïa: "Aetiologie der Hühnercholera," *Centralbl. f. Bakt.*, iv., 1888; Kitt: "Geflügelcholera," *Centralbl. f. Bakt.*, i., 1887, and *Deutsche Zeitsch f. Thiermed.*, xiii., 1888; Pasteur: *Compt. rend.*, xc., 1880; Wertheim: "Cholera gallinarum," *Archiv f. exper. Path.*, 26 Bd., 1889; Zürn: "Die Krankheiten des Hausgeflügels," Weimar, 1882.

[2] "Krit. Studien u. experim. Untersuch. über die Bakt. d. hämorrhag. Septikämie und die durch sie bewirkten Krankheitsformen," *Zeitschr. f. Hyg.*, xxiii., 1896.

[3] *Mittheil a. d. k. Gesundheitsamte*, ii.

[4] Babes and Puscarin: "Untersuch. über die Diphtherie der Tauben," *Zeitschr. f. Hyg.*, viii., 1890.

[5] Esser: "Ist die Diphtherie des Menschen auf Kälber übertragbar?" *Fortschr. d. Med.*, vi., p. 324; Löffler: *Mittheil a. d. k. Gesundheitsamte*, 1884; Pütz: *Fortschritte d. Med.*, v., p. 187.

[6] "Die Pyelonephritis bacillosa des Rindes," *Monatsch. f. prakt. Thierheilk.*, ii., ref. *Centralbl. f. Bakt.*, x.

[7] "Primäre infectiöse Pyelonephritis beim Rinde," *D. Zeitschr. f. Thiermed.*, xvii., 1891, ref. *Centralbl. f. Bakt.* x.

[8] "Note sur la maladie des bœufs de la Guadeloupe connue sous le nom de Farcin," *Ann. de l'Inst. Pasteur*, ii., 1888.

[9] "Studii e recerche entormo ol barbone dei bufali," ref. *Centralbl. f. Bakt.*, ii., 1887.

[10] "Die Barbonekrankheit," *D. Zeitschr. f. Thiermed.*, xxii., 1896.

[11] "Aetiologie des seuchenhaften Verwerfens," *Zeitschr. f. Thiermed.*, i., 1887.

[12] "Krankheitserreger der Mund- und Klauenseuche," *D. med. Woch.*, 1897.

[13] "Der Siegel'sche Bacillus," *Hygien. Rundschau*, vii., 1897.

[14] "Aetiologie der Maul- und Klauenseuche," *Centralbl. f. Bakt.*, xxi., 1897.

3. *The Spirilla and the Morbid Processes Caused by Them.*

(*a*) *General Remarks upon the Spirilla.*

§ 184. The **spirilla** or **spirillaceæ** or **spirobacteria** are divided into two genera, one of them called *Spirillum*, the other *Spirochaëte*. Many authorities recognize a third variety, viz., that of *vibrio*.

The genus **Spirillum** is characterized by the formation of stiff, short, shallow spirals, which sometimes have flagella and possess lively motion. Wavy staves are also called **Vibriones** by many authors.

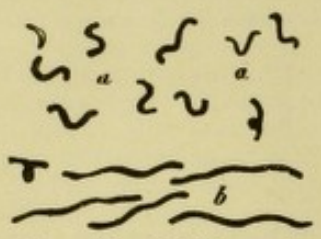


FIG. 465.—*Spirillum* sive *vibrio rugula*, *b*, and *spirillum undula*, *a*, obtained from a cold infusion of finely chopped earthworms. Drawn from a dried preparation treated with gentian violet. Magnified 600 diameters.

Spirillum sive *vibrio rugula* (Fig. 465, *b*) forms staves from 6 to 16 μ long and from 0.5 to 2.5 μ thick, simply bent or having a shallow turn, which move themselves by means of a flagellum. The spirillum occurs in water from swamps, in fæces, and in slime from the teeth.

Spirillum sive *vibrio serpens* form thin threads from 11 to 28 μ long, with three or four wavy bands. It occurs in stagnant fluids.

Spirillum tenue has threads from 3 to 15 μ long, very thin, with from two to five spiral turns.

Spirillum undula (Fig. 465, *a*) is a thread 1 or 1.5 μ thick and from 8 to 12 μ long, bearing on its end a flagellum and having from one and a half to three turns. It occurs in various putrefying fluids and executes rapid twisting and darting motions.

Spirillum volutans possesses threads 1.5 or 2 μ thick and from 25 to 30 μ long, with from two and a half to three and a half turns, bearing a flagellum at both ends.

The species **Spirochaëte** (Fig. 468) is characterized by flexible, long, sharply turned spirals.

Spirochaëte plicatilis forms threads from 100 to 225 μ long, very fine and closely turned. It is very abundant in water from marshes and gutters, and executes very rapid movements.

Spirochaëte buccalis sive *denticola* is from 10 to 20 μ long, pointed at both ends, and is not infrequently observed in the secretion from the cavities of the mouth and nose (cf. Fig. 176). It seems to have no pathogenic significance.

The spirilla, so far as they are not pathogenic, are little known, and investigations particularly as to their life-history are wanting. They are present in large numbers in the contents of privy-vaults. According to Prazmowski, *spirillum rugula* causes decomposition of cellulose and forms spores at the ends of the spirilla. According to Weibel, a vibrio which occurs in nasal slime has manifold forms of growth. Esmarch succeeded in cultivating a spirillum, called by him *spirillum rubrum*, in the different ordinary media. In bouillon it forms spirals of from forty-three to fifty turns. Short spirilla execute lively motions, but long spirilla, on the contrary, sluggish motions, or they may be motionless. Colonies in solid media are at first pale, but assume afterward in portions not in contact with air a wine-red color. In spirilla of old cultures three or four dull, glistening spots occur that do not stain and are probably to be interpreted as spores. Cultures containing

spirilla of this kind are more resistant to drying than others; but they are, on the contrary, very easily killed by heat.

The long spirals may break up into short segments possessing only about three-quarters of a turn, and these grow out in length and again divide.

Kitasato and Kutscher have also succeeded in cultivating spirilla.

(*b*) *The Pathogenic Spirilla.*

§ 185. **Spirillum choleræ Asiaticæ** (or *vibrio choleræ*), also called *comma-bacillus* (*bacille virgule cholérigène*), was discovered by R. Koch in 1884 and recognized as the cause of Asiatic cholera (Fig. 382). It forms a small, comma-shaped, curved staff from 0.8 to 2 μ long (Fig. 466).

Cultures of the cholera-spirilla are obtained upon a great variety of slightly alkaline media. The temperatures favorable for their growth are between 25° and 30° C. Between 16° and 8° C. they are still capable of puny development.

On gelatin plates they form round, flat, yellowish discs which liquefy the gelatin only slowly. With low magnifying powers they appear irregular in outline, and the surface granular or grooved and rough; it conveys the impression as if the surface were strewn with small particles of glass (Koch). By the liquefaction of the gelatin in the immediate neighborhood a funnel-shaped cavity is formed, and the colony sinks down finally to the bottom of the cavity.

Stab-cultures in gelatin form in two days a whitish cord corresponding to the line of inoculation (Plate I., Fig. 3). The gelatin becomes liquefied immediately around the line of inoculation. The canal widens out upward into a funnel filled with liquefied gelatin below and with air above. The widening of the funnel of the canal of inoculation takes place slowly, so that its edge reaches the wall of the tube only after five or six days.

On potatoes at from 30° to 35° C. the spirilla form light-brown cultures, on agar-agar grayish-yellow slimy cultures. They grow, moreover, also in bouillon, blood-serum, and milk.

FIG. 466.—Cholera-spirilla from a pure culture. Cover-glass preparation colored with fuchsin. Magnified 400 diameters.

They do not increase in pure water (Bolton), but do so in water that is contaminated with substances which furnish nutrient material.

The cholera-spirilla are aërobic, but they also are able to grow when oxygen is cut off. According to the investigations of Hueppe, cultivation in the presence of a paucity of oxygen increases the toxic power of the cultures; but, on the contrary, the resisting power against injurious agents—e.g., against acids and similar substances—is diminished; with free admission of oxygen the reverse takes place. Pfeiffer, however, found that young cultures cultivated in oxygen also contained poison. The spirilla present in fresh dejecta are easy to kill (Hueppe) and but little suited for infection, whereas the growth of the spirilla outside the body increases their resisting power against the stomach-juices, etc., and makes them more suitable for the infection of new individuals. They are readily destroyed by desiccation in free air (Guyon), by high temperatures, and by boiling for a short time. They are easily supplanted by saprophytic

bacteria when the nutrient material and the temperature are not entirely suitable. In privy-soil they die out quickly, according to Koch. They are readily destroyed by acids, corrosive sublimate, and carbolic acid. According to the observations of Koch, they can be preserved in well-water thirty days, in sewage seven days, on moist linen three or four days. Nicati and Rietsch found them alive after eighty-one days in water taken from the harbor of Marseilles.

In cultures they form sometimes short rods more or less curved (Fig. 466) and often hanging together in twos, sometimes long spirals. Along with these forms there also occur straight staves, and sometimes the majority of the rods that are present show the curve only imperfectly or not at all. In fluid media to which oxygen has access they show lively motility, which is easily seen in a hanging drop. According to the investigations of Löffler, the motility is caused by a single flagellum on one end.

When the nutrient material is exhausted to a certain extent, involution-forms often appear, in which the rods are sometimes shrunken, sometimes swollen, thus causing them to present a variety of forms. Globular swelling, as well as uncolored places (in stained preparations) caused by degeneration, have often been erroneously regarded as phenomena of fructification. Formation of spores has not been proved. If hydrochloric or sulphuric acid is added to cultures of the cholera-bacilli in culture-media containing peptone, the cultures assume a rose or Burgundy-red color, due to the formation of a coloring-matter—*cholera red.* A suitable culture-medium for this reaction is a meat-infusion containing peptone, or a one-per-cent solution (rendered alkaline) of peptone containing one per cent of salt. According to Salkowski, this is a nitroso-indol reaction.

When they get into the intestinal tract of human beings the spirilla develop in the small as well as in the large intestines, so far as they are not destroyed by the action of the gastric juice and are not hindered in their development by other influences. Their growth is followed by an extensive transudation from the intestinal mucous membrane, so that the intestine is filled with a fluid resembling meal-soup or rice-water, in which flakes of desquamated and slimy epithelial cells float about.

The spirilla are always present in large numbers in the contents of the intestine, and are also found in the lumina of the intestinal glands, and they may penetrate from there between and under the epithelial cells.

In fresh cases the presence of the spirilla may be demonstrated usually by making a cover-glass preparation stained with methylene blue or with fuchsin. The fresh dejecta, as well as foul clothing, are suitable for the examination, since, according to Koch's observations, the spirilla can multiply for a while vigorously on moist linen and moist earth. In old cases the detection of the spirilla is more difficult, but nevertheless succeeds in all cases, according to a number of authors, and is attainable most surely by making plate-cultures. In order to facilitate the separation of the cholera-spirilla from the other intestinal bacteria, Schottelius recommends the mixing of the dejecta with double the amount of meat-infusion rendered slightly alkaline, and allowing the mixture to remain uncovered at a temperature of from 30° to 40° C. for twelve hours. The spirilla, requiring oxygen as they do, develop especially on the surface, and may be easily transferred thence to plate-cultures. Koch recommends for this purpose a solution of peptone with salt.

The presence of cholera-spirilla in the intestines excites inflammation, which finds expression at the start in reddening, swelling, transudation, mucoid degeneration of the epithelium, and desquamation; subsequently also in hemorrhages, formation of sloughs, and ulceration. It is characterized constantly by a more or less abundant cellular infiltration of the tissues. The solitary follicles and Peyer's plaques are swollen even in fresh cases. Death may take place in a few hours or in from one to three days. If the disease lasts longer the contents of the intestines become more consistent and the intestinal mucous membrane shows ulcerative changes.

According to present experience, the spirilla produce poisonous substances which cause local damage to the mucous membrane of the intestinal canal, phenomena of intoxication, and paralysis of the vessels. In the liver and kidneys there often result small foci of degeneration, and within these the cells of the glands are cloudy or fatty and affected with hyaline degeneration or necrosis. Moreover, the kidneys very often show cloudiness caused by toxic degeneration of the epithelium; also there is occasionally swelling of the cortex. Frequently there are also ecchymoses in the epicardium; in the later stages also patches of necrosis in the mucous membrane of the vagina. The presence of the spirilla for a long time in the intestines may be followed by the formation of ulcers. Eventually they are crowded out by the putrefactive bacteria present in the intestines, and die out. A new intoxication, not dependent upon the original spirilla, may result from absorption of the products of putrid decomposition.

According to Koch, Nicati, and Rietsch, the cholera-bacilli may be contained in the material vomited. Nicati, Rietsch, Tizzoni, and Cattani also found them in the ductus choledochus and in the gall-bladder. According to the statement of these authors, the spirilla do not usually get into the blood, and are also absent from the internal organs; nevertheless, in cases of severe infection, they may gain access to all parts of the body.

Koch detected the spirilla in a tank in India which furnished the inhabitants with their entire supply of water for drinking and other purposes at a time when a part of the inhabitants were sick and dying of cholera. Since then they have been often detected during cholera epidemics in water-supplies.

According to the investigations of Nicati, Rietsch, van Ermengem, and Koch, symptoms resembling cholera can be produced in experimental animals by the introduction of cholera-spirilla into the intestinal canal. This succeeds when cultures are introduced directly into the duodenum or small intestines (Nicati and Rietsch); also (Koch) by rendering the gastric juice of the animals (guinea-pigs) alkaline with a five-per-cent solution of soda, then quieting the bowels by injecting into the abdominal cavity 1 c.c. of tincture of opium to every 200 gm. of weight of the animal, and finally introducing one or several drops of a pure culture into the stomach.

Animals inoculated in this way die with severe symptoms of collapse. The small intestines are found to be filled with a watery, flocculent fluid containing numbers of spirilla; the intestinal mucous membrane is reddened and swollen.

Asiatic cholera is endemic in Lower Bengal, and never entirely disappears there. Thence it spreads at times over India and over a larger or smaller territory of the earth by transportation. Since the spirilla

easily perish outside the body, the transportation must be effected mainly by persons suffering from cholera. Infection probably occurs exclusively from the intestinal canal by the introduction of infected beverages or food or some other substance into the mouth. But it is certain that the introduction of cholera-spirilla into the intestinal canal is not always followed by the disease.

Moreover, it not infrequently happens that the spirilla increase in the intestines, but cause only slight changes, so that the infected person suffers no severe trouble, and the diagnosis can be made only by the detection of the spirilla in the stool.

If the cholera-spirilla get into the drinking-water or water-supply in general, and succeed in multiplying, the cholera may develop with extraordinary rapidity in the locality. If, on the contrary, the infection follows by direct or indirect contagion from one person to another, the spread takes place more slowly, since it is limited to those who come in contact with the sick person or with the articles contaminated by the latter. The period of incubation lasts one or two days.

In the intestines of convalescents, according to investigations of Kolle, the spirilla may continue to live for a long time and to multiply, without giving rise to any symptoms that point to their presence. Kolle was able to detect them in a number of cases after from five to eighteen days, and in some cases even after from twenty to forty-eight days.

Once recovered from the disease, the affected individual enjoys immunity for a certain length of time. This immunity is to be ascribed to the presence in the body of bactericidal substances; and by means of these same substances it is possible to protect the body against an attack of cholera. In those, however, who have already contracted the disease, this protective effect is of no avail (compare § 30).

The poison which the cholera-spirilla produce, and which mainly causes the symptoms of cholera infection, is unknown. Gamaleïa believes that it is a nucleo-albumin, Scholl that it is a peptone (cholera toxopeptone). Pfeiffer is of the opinion that it is a component part of the cell-body. According to Metschnikoff and others it is excreted by the cells. Emmerich and Tsuboi seek to prove that the morbid phenomena in cholera are due to a nitrite-poisoning. They call attention to the fact that nitrites in small doses cause retching, vomiting, discharge of thin-gruel fæces, fall of temperature, weakness of the heart, cyanosis, and cramps of the extremities and muscles of the neck—in other words, symptoms resembling an attack of cholera; and, moreover, that the cholera-spirilla are able to make nitrites out of the nitrates contained in nutrient substances.

The virulence of cholera-cultures differs greatly, according to the source and the age. With increasing age the virulence decreases. Guinea-pigs, although very susceptible to intraperitoneal infection with cholera, may be protected from infection by intraperitoneal inoculation with attenuated cultures; but no absolute immunity can be brought about in this way. Blood-serum of human beings that have recovered from an attack of cholera shows protective properties for guinea-pigs some weeks after the attack.

The production of the nitroso-indol reaction in cultures of the cholera-spirilla is due to the fact that the cholera-spirilla not only produce indol in peptone solution, but also nitrites. For this reason, nitrous acid is liberated by the addition of hydrochloric or of sulphuric acid, and makes a red color with the indol. With the Finkler spirillum, the spirillum of Metschnikoff, and the spirillum of Deneke, which also produce indol, the red color of the cultures occurs only when potassium nitrite is added along with sulphuric acid, or when nitrous acid is added.

The following spirilla resemble the cholera-spirilla:

1. *Spirillum of Finkler and Prior*, found by the authors named in the dejecta of persons suffering from cholera nostras, when these have stood for some time in a vessel. The spirilla are very much like the cholera-spirilla, only somewhat longer and thicker. In plate cultures they are distinguished from the latter in that the small colonies are not distinctly granular and have a sharp contour. Gelatin is rapidly, not slowly, liquefied and consequently after twenty-four hours a sac-like tube (Fig. 467) filled with a cloudy fluid is formed in stab-cultures and rapidly spreads to the walls of the tube.

According to Flügge, even in forty-eight hours at room-temperature they form a grayish-yellow slimy coating, sharply marked off from the substance of the potato by its whitish border; whereas the cholera-spirilla do not grow at room-temperature at all, and at a higher temperature form a brown coating.

They, moreover, cause a foul-smelling decomposition and are rather resistant to drying. When introduced into the intestines of guinea-pigs by the method above described, they operate similarly to the cholera-spirilla, but less intensely.

It is very questionable whether the Finkler-Prior spirilla have pathological significance for cholera nostras, since the dejecta from which the investigators made their culture were not fresh, and other authors in similar cases have not found the spirilla.[1] Knisl[2] found them in the contents of the cæcum of a suicide.

2. *Spirillum tyrogenum*, found in cheese by Deneke[3] in Flügge's Institute, is also very much like the cholera-spirillum, but it is somewhat smaller and the long spiral threads are more narrowly wound. Cultures on gelatin plates form at first sharply contoured discs that appear dark with lower magnifying powers. They liquefy the gelatin much more quickly than do the Koch spirilla. In the line of puncture they behave similarly to the Finkler-Prior spirilla, but do not grow on potatoes.

3. *Spirillum sputigenum* is a spirillum whose shape is that of a curved staff, somewhat longer and thinner than the cholera-spirillum. It occurs in saliva and cannot be cultivated on the media that are in use.

4. *Vibrio of Metschnikoff*[4] is a fission-fungus that Gamaleïa was able to isolate in an epidemic of chickens in Odessa which was characterized by the appearance of diarrhœa and enteritis. On cultivation it shows very great resemblance to the Koch spirillum. The spirillum is most easily obtained pure by inoculating pigeons with the blood of diseased chickens. The pigeons die in from twelve to twenty hours and show the spirilla in the blood and in the intestinal tract.

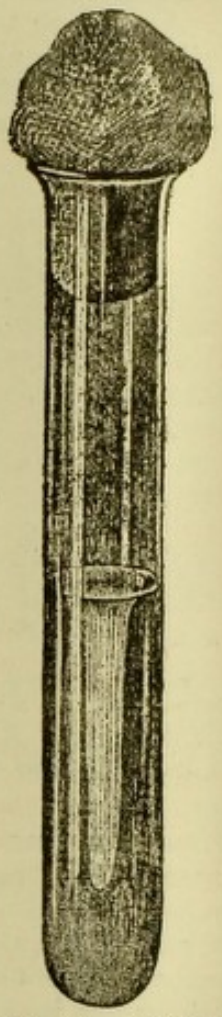


FIG. 467. — Stab-culture of the Finkler-Prior bacillus in gelatin.

§ 186. The **spirochaëte Obermeieri** (Fig. 468) is found constantly in the blood of patients suffering from **relapsing fever** during the attack of fever, and the multiplication of these organisms in the body is the cause of the disease.

The spirochaëte is from 16 to 40 μ long and possesses numerous turns. In a fresh drop of blood it exhibits lively motion. Carter and Koch succeeded in producing the disease by inoculating apes with the spirochaëte; but nothing definite is known as to its mode of development and habitat outside the blood. It is also unknown where it or its spores are to be found in the afebrile stages of the disease. In apes an attack of fever occurs only after several days have elapsed since the subcutaneous injection of blood containing the spirochaëte. According to the pathologico-anatomical results observed in man, it is to be noted

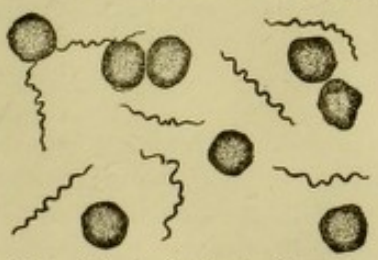


FIG. 468.—*Spirochaëte Obermeieri* from the blood of a person suffering from relapsing fever. (From a dried preparation treated with methyl violet.) Magnified 500 diameters.

[1] Kartulis: "Zur Aetiologie der Cholera nostras," *Zeitschrift f. Hyg.*, vi., 1889.

[2] *Münchener ärztliches Intelligenzblatt*, 1885.

[3] *Deutsche med. Wochenschrift*, 1885.

[4] Gamaleïa: "*Vibrio Metschnikovi* et ses rapports avec le microbe du choléra asiatique," *Ann. de l'Institut Pasteur*, ii., 1888; iii., 1889; and Pfeiffer, "Ueber den *Vibrio Metschnikovi* und sein Verhältniss zur Cholera asiatica," *Zeitsch. f. Hyg.*, vii., 1889.

that the spleen is enlarged and often contains numerous yellowish foci of degeneration, and often also anæmic infarctions.

According to the investigations of Nikiforoff, the histological examination of the spleen reveals extensive necrosis of cells and cell-degeneration (Fig. 469, *c*), as well as exudation of fibrin in the veins of the pulp and hyperplastic processes in the cells of this part of the spleen.

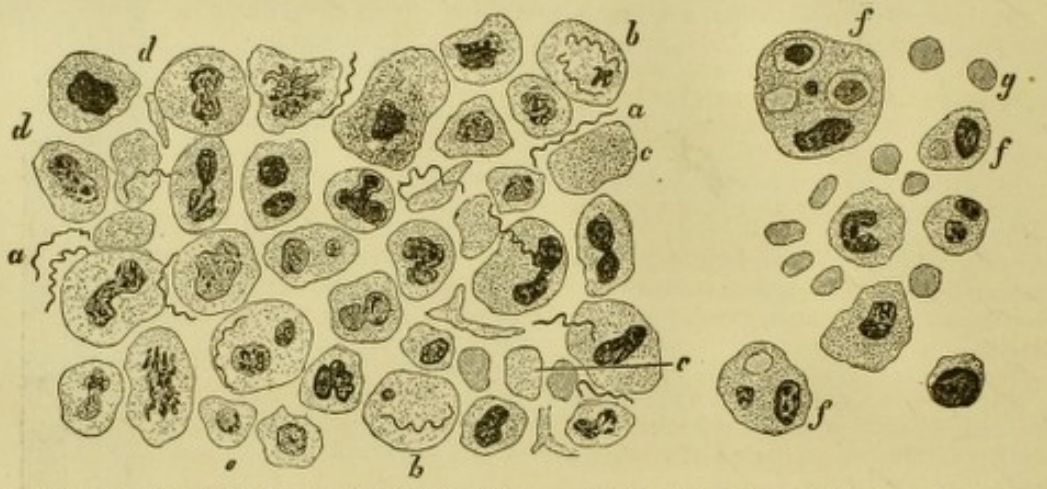


FIG. 469.—Portion of the tissue and isolated cells from a follicle of the spleen which has undergone partial necrosis; from a case of relapsing fever. (From Nikiforoff.) (Bichromate of potassium and sublimate solution; methylene blue.) *a*, Free spirilla; *b*, lymphocytes containing spirilla; *c*, non-nucleated lymphocytes; *d*, large, *e*, small pulp cell with only one nucleus; *f*, phagocytes which contain leucocytes and red blood-corpuscles, and débris of the same; *g*, free red blood-corpuscles. Magnified about 600 diameters.

Moreover, numerous large pulp-cells inclose decolorized red blood-corpuscles or fragments of these. Finally, numerous spirilla are found, especially in places which, while not entirely necrotic, nevertheless contain degenerated and necrotic cells, partly free, partly inclosed in leucocytes. Of the remaining cells some are well preserved, while others are just beginning to show signs of disintegration.

For staining this variety of spirilla in preparations dried on cover-glasses, alkaline methylene blue and fuchsin are most suitable.

CHAPTER X.

Mould-fungi and Yeast-fungi, and the Diseases Caused by Them.

§ 187. **Mould-fungi** and **yeast- or budding-fungi** belong to the non-chlorophyl-bearing thallophytes, as the fission-fungi do. They have no near connection, particularly in the phylogenetic sense, with the fission-fungi. On the other hand, they stand in very close relationship with one another.

Mould-fungi and yeast-fungi, like the fission-fungi, are compelled to derive their nutrition from organic substances containing carbon. The majority find it in dead organic substances, and therefore belong to the *saprophytes*. Some of them are capable of deriving nutrition from living tissues, and are to be classed, occasionally at any rate, as *parasites*. In human beings both kinds occur.

Outside the organism the mould-fungi are universally known as the producers of the different mouldy coverings that so often develop on organic substances. They belong to various groups of fungi.

The yeast-fungi are the producers of alcoholic fermentation and they form the scum on the top of alcoholic beverages.

§ 188. **Yeast-fungi** are found in man in the form of naked or single-capsuled, oval or roundish cells of various sizes. They occur chiefly as harmless **saprophytes**, and by far most frequently in the upper part of the intestinal canal—in the stomach—where they nearly always occur; and when beverages which are undergoing alcoholic fermentation are taken, they may be present in large numbers, and may also multiply. In the bladder, in case the urine contains sugar, they may likewise multiply and cause fermentation of the urine, with evolution of carbonic acid gas.

As **parasites** no importance had been attached to them until very recently, but the researches of Busse, Sanfelice, Curtis, and others have made it certain that there are also *species of saccharomyces of pathogenic importance*. According to these observations the pathogenic yeasts can multiply in various tissues, in the skin, in the periosteum, in the lungs, and in glandular organs, and can cause suppurating inflammations as well also as the formation of granulations and hyperplasia of the connective tissue, all of which processes run a course similar to that of an actinomycosis infection. The yeast cells in these centres of inflammation are for the most part provided with a capsule, and may be present in large numbers, so that they may cause by their mass tumor-like swellings. Through degeneration of the oval yeast cells crescentic forms may also develop.

In solutions containing sugar the budding-fungi produce oval cells (Fig. 470). Reproduction takes place by means of budding and constriction (Fig. 470), i.e., on any portion of the mother-cell there arises

an excrescence, which is constricted off after it reaches the size of the mother-cell. Under certain conditions the cells can grow out into threads, but no subsequent segmentation takes place in these threads; jointed threads result from budding (Cienkowsky, Grawitz). Diluted nutrient fluid favors the formation of threads.

FIG. 470.—*Saccharomyces ellipsoideus.* Magnified 400 diameters.

Mould-fungi are found in man partly in the form of simple or branching, unjointed or jointed threads of varying thickness; partly in that of oblong or even globular cells. The threads are called **hyphæ** (Figs. 471 and 472), and the mass which they form **mycelium**; the spherical or long oval or short cylindrical cells, which often hang together like a rosary, are called *spores* or, better, **conidia spores** (Figs. 471 and 472). Fructification on special fruit-bearers inside the body is only rarely observed.

The mould-fungi are partly **saprophytes** and partly **parasites**, and are found, with but few exceptions, only in localities exposed to the outside, as on the skin, in the intestinal canal, in the respiratory apparatus, in the external auditory canal, in the vagina, etc. Only exceptionally, and under special conditions, do they penetrate to the internal organs, as, for example, the brain. It is clear that the living tissues of the human organism do not afford a suitable nutrient medium for the mould-fungi, and the living activity of the tissue-cells for the most part does not allow development and multiplication of these. The need for oxygen does not allow the mould-fungi to develop in many tissues, and the body-temperature is, moreover, too high for many of these fungi. The chemical composition of the tissues also does not form a favorable mixture of nutrient material for the mould-fungi.

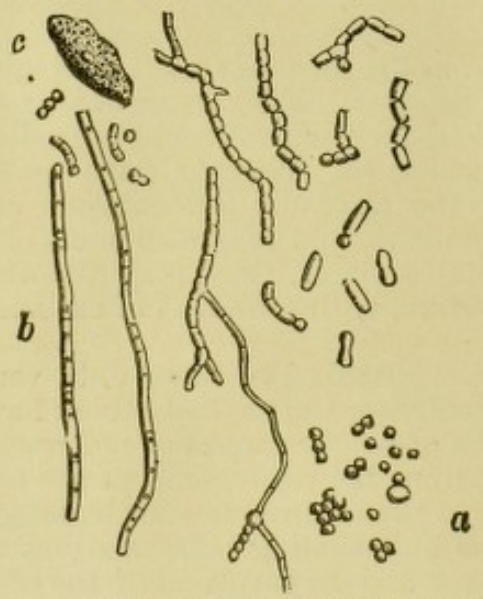


FIG. 471.—Hyphæ, conidia, and epithelial cells from a fresh specimen of favus. (After Neumann.)

Mould-fungi that grow as saprophytes occur most frequently in the *alimentary canal* in man, and here again most frequently in the *mouth*, *throat*, and *œsophagus*; and

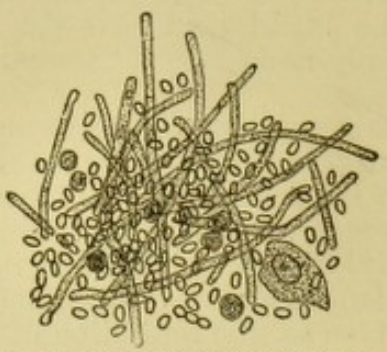


FIG. 472.—From a deposit of aphthæ on the tongue of a man who died of typhoid fever. Magnified 300 diameters.

they develop in these localities particularly when the ingesta or desquamated cells lie undisturbed in one position for a long time, and when the function of these organs happens to be below par. They are recognizable by their power to form threads and conidia.

In the *external auditory canal* the mould-fungi are especially apt to grow in abnormal masses that fill up the passage and that consist, in

some instances, of the secretion of the sebaceous glands of the ear, in others of inflammatory exudates and desquamated epithelium, and in still others of substances introduced from without.

Inside the *lung* the mould-fungi occasionally grow in the necrotic walls of cavities formed by disintegration, such as occur especially in tuberculosis, and they also grow in necrotic and gangrenous hemorrhagic infarctions. In the region of the air-passages they are oftenest observed in bronchiectases.

In the intestinal canal, as well as in the ear and in the lung, the mould-fungi usually form white deposits on or in the tissues. On the appearance of fructification (upon special fruit-bearers) they may, however, in places present a brown, gray, or black appearance. In the intestinal canal beverages and food may give them various colors.

These fungi have their habitat first in dead material, but they may penetrate thence more or less widely into living tissue; and cases have been observed in which they had even penetrated into the circulation

FIG. 473.—Section through an aphthæ-covered œsophagus of a small child. (Alcohol; carmine; Gram's method.) *a*, Normal epithelium; *b*, connective tissue; *c*, swollen and desquamated epithelium permeated with the growth of fungus threads; *d*, epithelium infiltrated with cells; *e*, masses of cocci and bacilli; *f*, cellular focus in the connective tissue. Magnified 100 diameters.

and were carried by the blood-current to distant organs. Thus the fungus-growth called **aphthæ**, which appears mostly in the cavity of the mouth, the throat, the œsophagus, more seldom in the stomach, in the small intestines, and in the vagina, and on the nipple of the breast of nursing women, cannot be regarded as a pure parasite, but, on the contrary, as a **parasitic growth** which penetrates into living epithelium (Fig. 473, *c*) and even into the connective tissue lying below. It is true that aphthæ for the most part occur only in sucklings and in depleted sick persons who are no longer able to cleanse the mouth, throat, and œsophagus, and whose condition of nutrition has suffered. Consequently special local primary conditions are necessary for its development, and the primary colonization of the fungus probably occurs in substances that have died. Still an active penetration in living tissue takes place—first into the epithelium (*c*, *d*), and then often also into the connective tissue (*a*, *f*) and into the blood-vessels—and from these portals of invasion even metastases may develop in internal organs. Thus, Zenker observed fungus threads and conidia in an abscess of the brain, and Paltauf reported a case in which a mould-fungus was con-

veyed from an intestinal ulcer to the brain and lung. Schmorl described aphthæ metastases from the kidneys.

The *mould-fungi which grow in the lung* do not always confine themselves to tissue that has died out or to the interior of the bronchus; they can also get into living, respiratory parenchyma (although rarely, it is

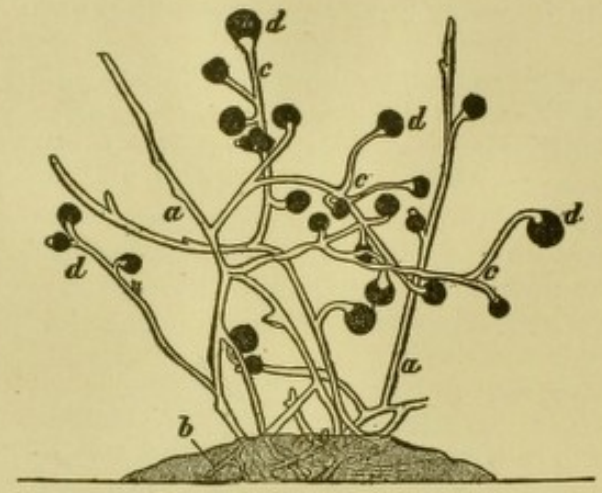


FIG. 474.—*Mucor corymbifer* in fructification. *a*, Aërial hyphæ; *b*, mycelium lying within the nutrient gelatin; *c*, branching fruit-bearers; *d*, sporangia. (Preparation from a culture made on a glass slide.) Magnified 100 diameters.

true), and when they invade this locality they form small white nodular masses (Boyce) in the neighborhood of which the lung-tissue is infiltrated.

Local **colonizations of mould-fungi which penetrate into living tissue** exercise a more or less considerable irritation in the neighborhood, and cause *degeneration* (Fig. 473, *c*) *and inflammation of the tissue.* This can be observed in mycosis of the lung, as well as in intestinal mycosis (*c*, *d*, *f*) and mycosis of the ear. When they have penetrated into the lung they form growths which are similar to the actinomyces nodules and are surrounded by an accumulation of cells (Boyce). Their action, however, is always limited, and, furthermore, they produce no substances which are injurious to the whole organism or cause symptoms of poisoning. The finding, as has been frequently reported, of mould-fungi in abscesses of the internal organs is probably to be interpreted in this way: that, along with fission-fungi which cause suppuration, thread-fungi get into the tissues and thence also into the circulation. A general spreading of mould-fungi does not occur even in these cases, because the further development remains confined to the location of the metastasis.

The forms of mould-fungi which are saprophytic, or at least pathogenic only under certain circumstances and to a limited extent, belong to the **Mucor, Aspergillus,** and **Eurotium** families. Several species have been obtained from the ear, and have been designated as *aspergillus fumigatus* (Fresen), *aspergillus flavus* sive *flavescens* (Brefeld, Wreden), *aspergillus niger* sive *nigricans* (van Tieghem, Wreden, Wilhelm), *aspergillus nidulans* (Eidam), *eurotium malignum* (Lindt), *mucor corymbifer*, and *trichothecium roseum;* and, so far as is known, these are the same species which occasionally occur in the respiratory apparatus.

In most cases the kind of mould-fungus cannot be immediately deter-

mined; it is first necessary to make cultures of the fungus upon suitable nutrient media—such, for example, as a decoction of bread, or an infusion of bread with agar-agar, potatoes, gelatin, etc. On these the conidia which are sown grow out to germinal tubes, and form simple or branching unicellular or multicellular threads on which the peculiarly constructed fruit-bearers characteristic of the species arise and eventually produce conidia. Many form spores by copulation of cells of mycelia, and this happens especially when the supply of oxygen is lessened (Brefeld, Siebenmann).

In the mucor varieties there appear special *fruit-bearers* which differ in the different species—at one time having a single stem, at another being branched (Fig. 474, *c*)—and on the ends of which button-like swellings develop. It is from these knob-like ends that *sporangia* (*d*)—i.e., globular vesicles filled with conidia spores—grow.

Mucor corymbifer, for example, forms branching fruit-bearers (Fig. 474, *c*). The sporangia on the ends possess a smooth membrane and inclose at the time of ripening yellowish conidia spores.

The aspergilli form *conidia-bearers* which swell out spherically above and then produce numerous *sterigmata*—i.e., pedicle-like outgrowths, radially arranged, thickly crowded, shooting out from the upper half of the sphere. Each sterigma subsequently has at its end a *chain of conidia spores* (Fig. 475, *a*, *b*), which owe their formation to a constricting process.

The *botanical position of the aphthæ-fungus* is still doubtful. Formerly it was called *oïdium albicans*, and reckoned, consequently, with the family Oïdium, which occurs, in different species, upon organic substances in the form of downy coatings. When cultivated from conidia it produces hyphæ, which become jointed and form conidia by transverse division of the threads, but form no peculiar fruit-bearers.

According to Rees, Grawitz, and Kehrer, the aphthæ-fungus grows by budding and by the growing out of mycelia and conidia, which in

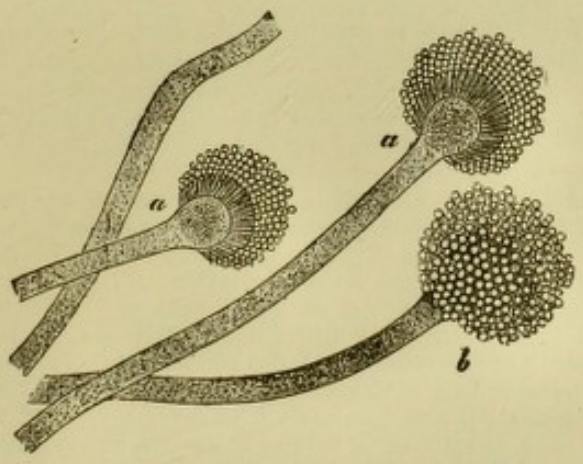


FIG. 475.—Hyphæ of *aspergillus fumigatus*, with conidia-bearers. *a*, Fruit-heads in optical cross-section; *b*, fruit-heads seen from above. Magnified 300 diameters.

turn produce at their ends, by a process of constriction, new conidia, in a manner similar to that which takes place in the yeast-fungi which belong among the mould-fungi. Consequently this fungus should be termed *mycoderma albicans*. Linossier and Roux are, however, of the opinion that the aphthæ-fungus does not belong at all to the saccharomycetes and they regard its proper classification at present as impossible.

According to Plaut, it is identical with a mould-fungus (*monilia candida*) which very frequently appears in nature. Kehrer suspects that it is a species of a higher fungus that has become degenerated by parasitism.

According to Neumayer, all kinds of yeasts are able to resist the effects of the digestive juices and can travel through the intestinal canal of human beings without being killed. Unless some fermentable substance is introduced at the same time they are entirely harmless. They exert some action on the intestinal canal only when fermentable substances are introduced along with them, and then abnormal products of fermentation result which act as an irritant on the intestinal canal.

Busse found (1894) yeast-cells developing in great numbers in the disease areas of a woman, thirty-one years of age, who died from multiple inflammations of the bones, skin, lungs, kidneys, and spleen, which were in part tumor-like, in part abscess-forming, and it is safe, according to his discovery, to look upon the yeast as the cause of the disease. The yeast could be cultivated easily on suitable nutrient media. Mice were especially susceptible to inoculations of the cultures, and died in from four to eighty-three days after inoculation, and the yeast-cells were found to have increased markedly, not only at the point of inoculation but also in the internal organs. Hyperplasia of the tissue took place only after a long duration of the infection.

Sanfelice experimented with yeast from fruit juices, and found among these one species pathogenic for guinea-pigs (saccharomyces neoformans) and one pathogenic for chickens and dogs (saccharomyces lithogenes). Curtis found, in multiple myxosarcoma-like growths of the skin, yeast-cells which were pathogenic for rats, mice, and dogs.

Sanfelice, Corselli, Frisco, Roncali, Binaghi, and others believe that blastomycetes may be the cause of true tumors, like sarcoma and carcinoma, but true tumors have never been obtained by experimental inoculations with yeast-cells—only inflammatory hyperplasia of the tissues; and the discovery of yeast-cell-like figures in true tumors does not permit of the conclusion that the tumors have been produced by the yeast-cells, even if a part of those seen were genuine yeast cells. According to the investigations of Koch, Löffler, Lichtheim, Hückel and Lindt the conidia of aspergillus fumigatus, A. flavescens, A. nidulans, eurotium malignum, mucor rhizipodiformis, M. corymbifer, M. pusillus, and M. ramosus flourish at the body-temperature, and when introduced into the blood-current of animals grow out into the tissues and form hyphæ; but there is no new production of conidia, and consequently no progressive infection of the animal extending beyond the area within which the spores have been introduced. Conidia of *mucor rhizopodiformis* and *mucor corymbifer*, when introduced into the blood-current of rabbits, grow mainly in the kidneys and in the lymphatic apparatus of the intestines, where they cause hemorrhagic inflammation.

Aspergillus mycoses of the respiratory apparatus are not rare **in animals**, especially birds, and the growth of the mycelium causes necrosis of the tissue and inflammation. According to Chantemesse, *aspergillus fumigatus* causes in doves a disease of the mouth, lungs, liver, and kidney. The two former affections are not unlike diphtheria, while the two latter closely resemble tuberculosis, and may consequently be called *pseudotuberculosis aspergillina*. According to Potain, the infection may be transferred to man and cause ulcerative disease of the lung.

Eurotium and *Aspergillus*, according to Siebenmann, are two different families, having, however, very great similarity with each other, since both the mycelium and the conidia-bearers are similarly formed. The main differences between the two are these: Eurotium produces perithecia in the form of glistening, light-yellow or sulphur-yellow, translucent bodies the size of a grain of sand, that are delicate and easily crushed, and these bodies develop continuously until completely mature spores, capable of germination, are formed. On the other hand, the genuine Aspergillus forms a hard, woody sclerotium usually embedded in a thick white matted mass of mycelia. The development of these takes place in two periods. The second part of the development takes place only when the sclerotium finds a lodgment upon a moist substratum.

Aspergillus flavus of Brefeld (*Eurotium aspergillus flavus* of de Bary) forms golden-yellow, greenish, and brown growths, the fruit-heads are round, yellow or olive green or brown; conidia round, seldom oval, sulphur yellow to brown, with minute warts on the surface; diameter from 5 to 7 μ. *Aspergillus fumigatus* of Fresen (*aspergillus nigrescens* of Robin) forms greenish or bluish or gray growths; the fruit-heads are long and shaped like an inverted tenpin; the conidia are round, seldom oval, smooth, mostly clear and colorless; diameter from 2.5 to 3 μ. *Aspergillus niger* of van Tieghem (*eurotium aspergillus niger* of de Bary) forms dark chocolate-brown growths; the conidia are round, brownish black or grayish brown when ripe; surface smooth or with warty thickenings; diameter from 3.6 to 5 μ.

Aspergillus can develop upon the injured sclera and bring about purulent inflam-

mation. Leber[1] cultivated it upon the sclera and in the anterior chamber of the eye of rabbits. Finally, aspergillus also appears in the pelvis of the kidney. Babes[2] found conidia and hyphæ of a thread-fungus in ulcers of the skin which were covered by scabs, and gave to it the name *oïdium subtile cutis*.

§ 189. **Thread fungi** are to be regarded as **causes of disease in a few affections of the skin**; that is, in *favus*, *herpes tonsurans*, *pityriasis versicolor*, *sycosis parasitaria*, and in *onychomycosis*. In all of these diseases the epithelial parts of the skin contain colonizations of hyphæ and conidia, and there remains no doubt that their presence causes to some extent hyperplasia and inflammation.

The **fungus of favus** (Fig. 471) is usually called **achorion Schönleini**; it was discovered by Schönlein in the year 1839.

Favus (*tinea favosa*, *scall*) has its habitat especially in the hairy portions of the skin of the head, more seldom on other parts—for example, in the substance of the nails. It is characterized by the formation of discs (*favus scutula*), varying in size from that of a lentil to that of a nickel, is sulphur yellow, and indented and pierced by a hair. In an abortive course it may merely form scales, like herpes.

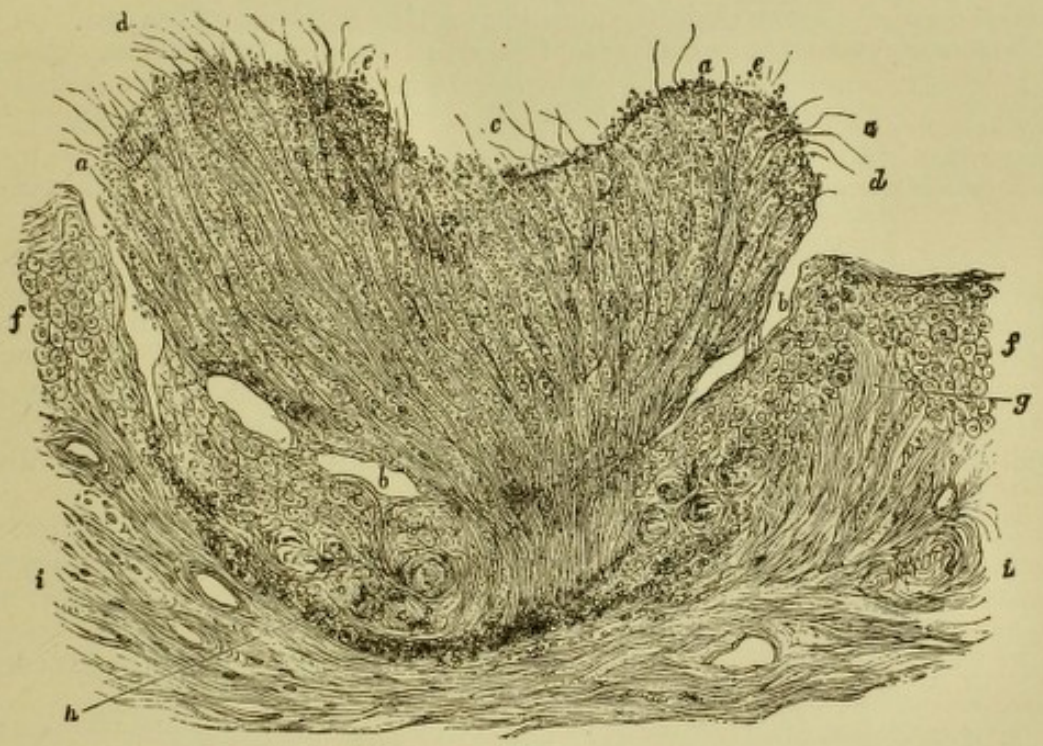


FIG. 476.—Favus scutulum. *a*, Free border of the scutulum; *b*, dead, horny layer; *c*, *d*, mycelial threads; *e*, conidia; *f*, epithelium; *g*, papilla of the skin; *h*, cellular infiltration at the basis of the scutulum; *i*, cutis. (After Neumann.)

According to Kaposi, the favus scutulum originates as a small punctiform yellow focus lying under the epidermis and penetrated by a hair. It grows to the size of a lentil, and forms then a sulphur-yellow, dimpled disc showing through the upper skin. The scutulum (Fig. 476) consists of fungus threads and conidia spores and lies in a shallow, funnel-shaped depression in the skin under the horny layer of the epidermis, which is drawn apart (this does not appear in the drawing). If the mass is removed during life the cavity shows a red watery surface. The

[1] *Gräfe's Archiv*, xxv.

[2] *Biol. Centralbl.*, ii., No. 8.

favus itself forms a white, only slightly coherent mass which can be easily disintegrated in water.

If the scutula are not removed they join together and form large masses. If the epidermis layer is desquamated the favus-mass becomes free and dries up to yellowish-white, mortar-like masses. The hairs appear lustreless, as if dusty, and are easy to pull out, since the fungus mycelia and conidia penetrate into the hair-shaft and into the bulb (Fig. 477, *a*), as well as into the follicle (*b*).

Not only can the hair be made to fall out by the growth of the mass of fungi, but the papilla may also undergo atrophy under the pressure of the accumulation of the mass of fungi. Simultaneously a more or less intense inflammation appears in the neighborhood of the hair-follicle, and this inflammation may assume the character of an eczema.

If achorion colonizes upon a nail (*onychomycosis favosa*) it forms sulphur-yellow deposits or uniform thickening, with simultaneous loosening and cheesy degeneration of the parenchyma of the nail.

Trichophyton tonsurans, the fungus of **herpes tonsurans,** consists of long, narrow threads, but little branching and with few conidia; it forms no scutulous nodules, but penetrates easily into the hair-shaft and makes the hair brittle. According to whether the herpes develops upon hairy surfaces or upon surfaces devoid of hair, it shows certain differences.

Herpes tonsurans capillitii forms bare discs which vary in size from that of a five-cent piece to that of a silver dollar. These spots, in which the hair is broken off short, look like places where the hair has been badly cut. The surface of the skin at these spots is smooth or covered with scales and reddened on the border of the disc. If the fungus threads penetrate into the hair-follicle, pustules and scales are formed. Such discs may appear at various places and constantly increase until finally a cure takes place.

On places devoid of hair herpes forms vesicles (*herpes tonsurans vesiculosus*), and red scaly spots, discs, and circles (*herpes tonsurans squamosus*). Occasionally there appear in a number of places, red spots which rapidly spread and just as rapidly heal up. The fungus will be found between the uppermost layers of the nucleated epidermis, immediately below the stratum of horny cells (Kaposi).

If trichophyton develops in the nails, the nail becomes cloudy, scales off, and becomes brittle—an affection designated as *onychomycosis trichophytina.*

Sycosis parasitaria results from the fact that the development of the fungus is accompanied by an inflammation of the hairy parts of the skin, which is more severe than usual, and which leads to infiltration and suppuration—that is to say, to the formation of pustules, abscesses, and papillary hyperplasia. According to Kaposi and others, *eczema marginatum* is also caused by the trichophyton tonsurans. It occurs especially in those places where two surfaces of skin come in contact and the skin is macerated by sweat. It is characterized by the formation of vesicles, pustules, and scabs situated on the periphery of a pigmented surface. According to others (Pick, von Hebra), the fungus elements contained in the efflorescences are smaller, and are therefore called *microsporon minutissimum.* On the other hand, according to H. von Hebra, *impetigo contagiosa*, an exanthem characterized by pustules, is caused by trichophyton tonsurans.

Microsporon furfur, the fungus of **pityriasis** or **mycosis versicolor**

or dermato-mycosis furfuracea, occurs likewise in the form of threads and conidia, which are somewhat smaller than those of other skin-fungi. The alterations caused by this fungus consist of discolorations of the skin of different sizes and shapes; some of the spots being mere points, while others may be as large as the palm of the hand. These spots, which sometimes are smooth and glistening, and at other times dull and

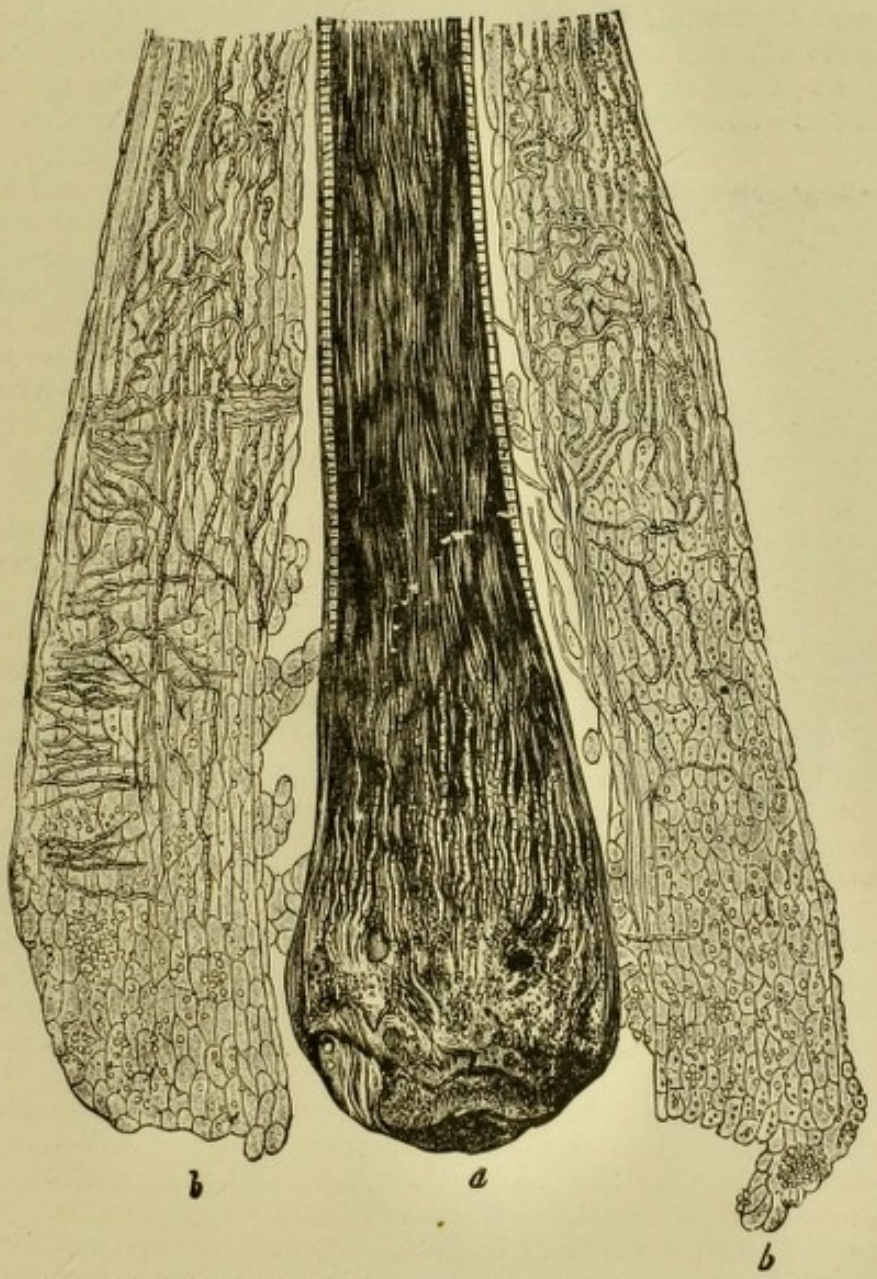


FIG. 477.—Hair affected with favus. (After Kaposi.) *a*, Bulb and shaft of the hair; *b*, sheath of the hair-root traversed in all directions by the mycelia and conidia.

desquamating, are spread uniformly over large areas of skin. Their color varies from a pale yellow to a dark brown or a brownish-red. They are found principally upon the trunk, neck, and flexor surfaces of the extremities, never on the hands, feet, or on the face.

Microsporon minutissimum is the name which has been given to a thread-fungus, which is found in the skin disease known as **erythrasma** (von Bärensprung). The disease is characterized by the formation of

brown or brownish-red, round patches, on the inner side of the thigh, which are only slightly scaly and may be as large as the palm of the hand. The fungi are found in the epidermis and are smaller than those of pityriasis.

The thread-fungi occurring in the diseased areas of the skin may be cultivated on suitable nutrient media (agar-agar, agar-glycerin, gelatin, potato, blood-serum, etc.), and from the conidia there then develop simple and branching threads, which become jointed (Fig. 478, *a*) and form chains of short cells (*b*). Club-like forms which frequently appear on the ends of the threads in cultures are looked upon by Quincke and Elsenberg as imperfect sporangia. The botanical position of these fungi is still undetermined. Nothing certain is known about their distribution outside the human body and the bodies of animals.

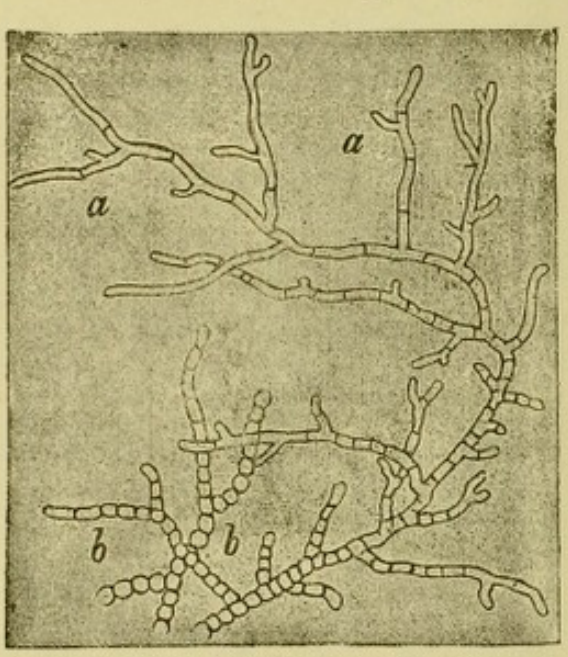


FIG. 478.—Culture of *trichophyton tonsurans*. *a*, Branching threads with long joints which have delicate walls; *b*, threads with thick-walled, short joints, some of them spherical. Magnified 300 diameters.

According to Quincke, three forms of fungus occur in favus-masses. Two of these represent varieties of one species of fungus. Elsenberg found only two forms, which he regards as varieties of one species. Pick, Plaut, and Biro hold fast to the etiological unity of the different forms of favus.

Sabouraud advocates the view that the fungi causing trichophytia represent entirely different varieties, which, however, all belong to the genus Botrytis. Krösing differentiates three groups of trichophyton-fungi, according to the different appearances of the cultures on potato, and he lays stress, among other things, upon the differences between their respective organs of generation and fructification. Rosenbach, who recently examined the mould-fungi occurring in deep suppurating inflammations of the skin, differentiates several trichophyton-fungi as the cause of this disease.

According to Spietschka the microsporon furfur from the dermal scales can be cultivated, and can be very well differentiated in cultures from other pathogenic thread-fungi. A typical mycosis may be produced in man by inoculation with the fungus.

From the large number of investigations of various authors carried out recently it is impossible to deduce anything with certainty about the number of kinds of favus- and trichophyton-fungi. Still this much is evident from the investigations: that the character of the nutrient medium has great influence on the kind of growth (Sabouraud, Waelsch), and that the difference in the results is to be attributed in large measure to the difference in the nutrient media on which the fungi were cultivated.

Inoculations with the fungi taken from cultures into the skin of human beings, rabbits, mice, etc., which were made by Grawitz, Boer, Munnich, and others, gave partly positive, partly negative results. Ac-

cording to Plaut, the inoculation never gives positive results when spore-formation has already taken place in the cultures.

A form of skin disease is described as *pityriasis rosea* (Gilbert) or *pityriasis maculata* and *circinata* (Bazin), which is very similar to herpes tonsurans, and, as it seems, is caused in part by a hyphomyceta. According to Behrend,[1] who suggests the name *roseola furfuracea herpetiformis*, the disease is characterized by the appearance of prominent spots of a rose-red color, which vary in size from that of a pin's head to that of a pea or bean, and which are covered with dust-like epidermis scales. They appear oftenest on the neck and spread thence quickly over the body, but leave the head, the hands, and the feet free. The spots vanish again in two or three days. In some cases the scales contain conidia and fine mycelia threads.

Von Hebra[2] described a peculiar itching dermatosis as *dermatomycosis diffusa flexorum*. It occurs on the elbow and bend of the knee, and is said to be caused by fungus elements which are like those of pityriasis versicolor.

Bizzozero[3] and Bordoni-Uffreduzzi[4] published a communication on microphyta which occur on the normal skin.

Favus and *herpes tonsurans* also occur in **domestic animals**,[5] the latter in cattle.

In **invertebrate animals** diseases occur not infrequently which are caused by mycelium-fungi. Thus *botrytis Bassiana* causes the so-called *muscardine* in silkworms. *Cordyceps militaris* destroys the injurious pine-spider *gastropacha pini*. *Tarichium megaspermum*, a black-colored fungus, kills the destructive earth-caterpillar *agrotis segetum*. Fungi belonging to the family *Empusa* attack especially the caterpillars of the cabbage-butterfly (*empusa radicans*) and the house-fly (*empusa muscæ*), and grow all through them and cause them to die. *Achyla prolifera*, according to Harz,[6] grows through the musculature of the crabs, and is the cause of crab-pest.

[1] *Berliner klin. Wochensch.*, 1881, Nos. 38 and 39.

[2] *Wiener med. Blätter*, 1881; and "Die krankh. Veränder. d. Haut," Braunschweig, 1881.

[3] *Virchow's Arch.*, 84 Bd.

[4] *Fortschritte d. Med.*, iv., 1886.

[5] Cf. Friedberger and Fröhner: "Lehbr. d. spec. Pathol. der Hausthiere."

[6] *Jahresber. der Münchener Thierarzneischule*, 1882–83.

CHAPTER XI.

The Animal Parasites.

I. Arthropoda.

1. *Arachnida.*

§ 190. The parasites included among the **Arachnida** are for the most part epizoa, which either temporarily or permanently inhabit the skin. But one species—the Pentastomata—occurs as larvæ within the tissues. Most of them belong to the group of *mites* (*Acaridæ*). The Pentastomata belong to the class *tongue-worms* (*Pentastomidæ* or *Linguatulidæ*).

1. **Acarus scabiei,** or **sarcoptes hominis,** the **itch-mite,** is a parasite the size of a pinhead, with a body shaped like a turtle's, provided on the ventral surface both anteriorly and posteriorly with two pairs of legs, each of which is furnished with bristles (Fig. 479). The foremost pair of legs extend out into stalk-like processes, ending in discs for clinging purposes. The same arrangement is found in the hindermost pair in the male, while the next to the last pair in the male and the last two pairs in the female end each in a long bristle. On the border of the hinder part of the body are located several bristles, while the back is covered with tooth-like knobs. The head is rather round and likewise covered with bristles. The female is almost twice as large as the male.

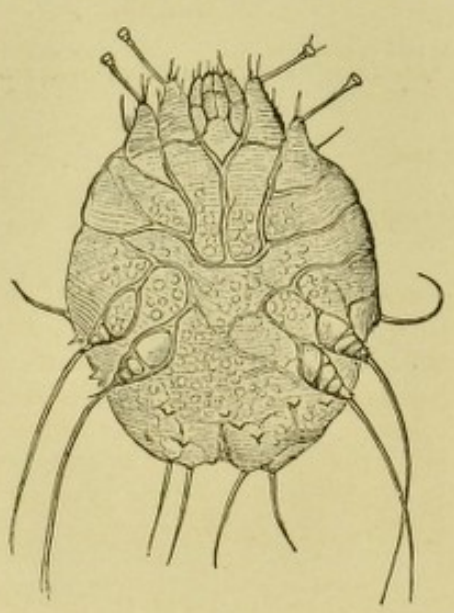


FIG. 479.—Female itch-mite, showing ventral surface. Magnified 40 diameters.

The mite dwells in the epidermal layer of the skin (Fig. 480, *a*, *d*), in which it digs burrows, some of which are 10 cm. in length. In these burrows the female (*d*) lays her eggs, which develop *in situ* into young itch-mites (*e*). These bury themselves still deeper in the epidermis, and after several times shedding their skins, develop into sexually mature individuals. The skin responds to the irritation which the presence of the mites occasions by increased epithelial cell-production (*a*) and by inflammation (*c*). The latter is considerably increased by scratching the spots which itch in consequence of the invasion.

2. **Leptus autumnalis,** the *harvest-mite* (Fig. 481), is the red-colored larva of a variety of Trombidæ, which lives upon grass and bushes and upon grain, and when opportunity offers alights upon the human skin; here it bores its way into the epithelium and occasions itching and inflammation.

3. **Demodex** or **acarus folliculorum hominis** (Fig. 482) occurs at times singly or in groups in the sebum of the hair-follicles and the ducts of the sebaceous glands. It is in the neighborhood of 0.3 mm. long, and has on its ante-

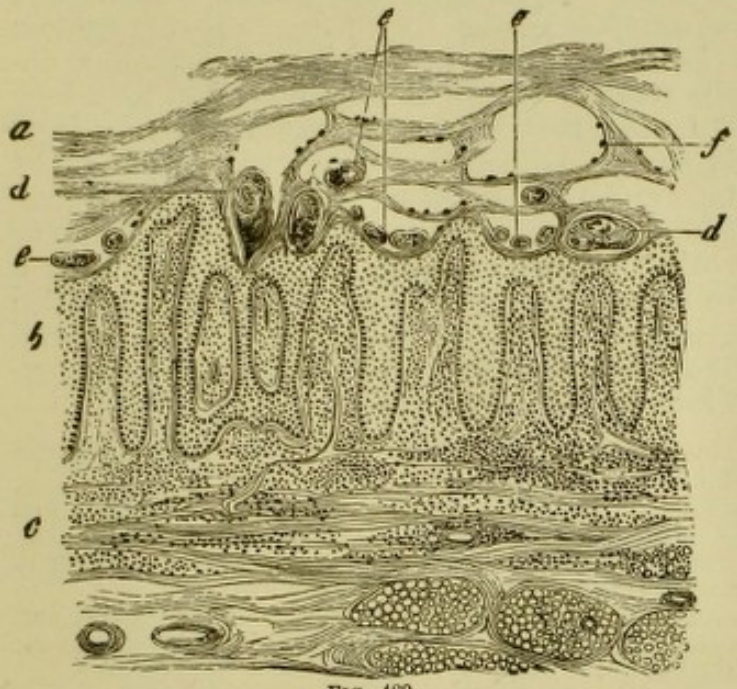


FIG. 480.

FIG. 481.

FIG. 480.—Scabies. (Alcohol; carmine.) *a*, Horny layer of the epidermis, perforated by numerous burrows of itch-mite; *b*, mucous layer and papillary body, the latter greatly enlarged and infiltrated with cells; *c*, cell-infiltrated cutis; *d*, section through a fully developed itch-mite; *e*, eggs and embryos of various sizes; *f*, fæces. Magnified 20 diameters.

FIG. 481.—*Leptus autumnalis*. (After Küchenmeister and Zürn.)

rior ventral surface four pairs of short, thick legs. The head is furnished with a snout and two feelers.

4. **Ixodes ricinus,** the *wood-jack* or *wood-tick* (Fig. 483), is a fairly large yellowish-brown member of the Arachnida, belonging to the group of ticks. It has a black head provided with a sucking apparatus, and a very distensible leathery body. It commonly occurs upon grass and bushes, and sometimes alights upon man or beast. By means of its sucking apparatus it draws blood from the skin, and in this way swells up to a very remarkable extent.

5. **Pentastoma denticulatum** is the larva of **penta-**

FIG. 482.—*Acarus folliculorum hominis*. (After Perls.) Magnified 300 diameters.

FIG. 483.—*Ixodes ricinus*, sucked half full of blood. Magnified 2 diameters.

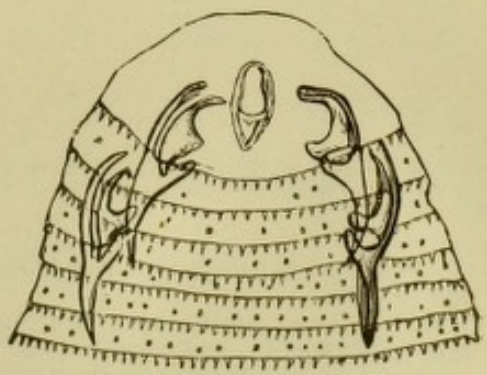


FIG. 484.—Head end of *pentastoma denticulatum*. (After Perls.) Magnified 40 diameters.

stoma tænioides, a lance-shaped organism belonging to the order of the tongue-worms or Pentastomidæ. It inhabits the nasal, frontal, and maxillary sinuses of various animals, especially the dog. It very seldom occurs in human beings (Laudon), and when it does it occasions inflammations. The sexually mature female is from 60 to 130 mm. long and anteriorly from 8 to 10 mm. broad, while the male measures from 16 to 20 mm. in length and anteriorly from 3 to 4 mm. in breadth. The larva is from 4 to 5 mm. long and 1.5 mm. wide; is plump, and of somewhat flattened, spherical shape. Its location is usually the liver or spleen, and, more rarely, other organs of men and herbivora. It is a quite common, though not a dangerous, parasite. Its body is divided off into some ninety ring-shaped segments, which are provided around the borders with thorn-like processes (Fig. 484), while the head extremity is furnished with four hook-shaped feet.

Living mites occur very frequently among the *domestic animals* as parasites on the skin, representing various species of different families.

Sarcoptes hominis, the burrow- or itch-mite of man, occurs also in horses and Neapolitan sheep. Not only this, but various kinds of sarcoptes are distinguishable, which infest the domestic animals—for instance, *sarcoptes squamiferus*, occurring in dogs, swine, sheep, and goats, and *sarcoptes minor*, in cats and rabbits.

Dermatophagus, the *biting-mite* (Fig. 485), with broad head, occurs in different animals, and various species of the same are distinguished. They live upon the cells of the epidermis and occasion desquamation of the skin.

Dermatocoptes, the *sucking-mite* (Fig. 486), with long slender head, robs the skin of blood and lymph, and produces inflammation. *Dermatocoptes communis* occurs in horses, cattle, and sheep. *Dermatocoptes cuniculi* is a parasite infesting the ears of rabbits.

Symbiotes equi of Gerlach is a mite occurring chiefly on the feet of heavy English and Scotch horses, where it excites a moist dermatitis, often incorrectly called *malanders*.

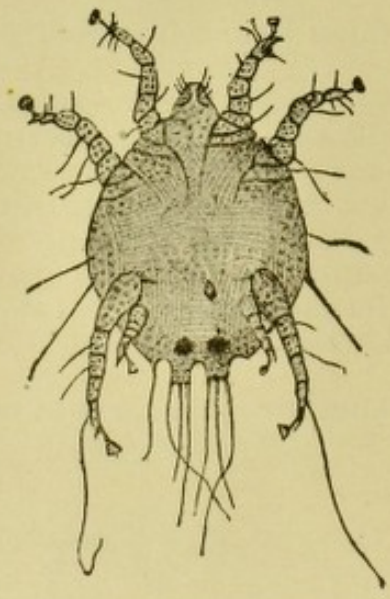


FIG. 485.—Male of the *dermatophagus communis*, showing ventral surface. (After Pütz.) Magnified 50 diameters.

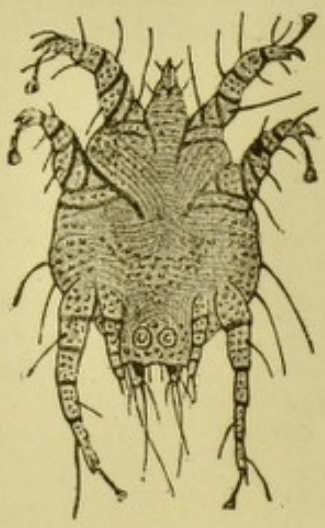


FIG. 486.—Male of the *dermatocoptes communis*, showing ventral surface. (After Pütz.) Magnified 50 diameters.

Dermanyssus avium is a red blood-sucking mite about 1 mm. long, which is seen often in birds.

Of the Tick family there occur in dogs, cattle, and sheep *various kinds of Ixodes*, while in pigeons the *argas reflexus* and others are found.

Leptus autumnalis occurs also in dogs and chickens.

Species of Demodex occur in dogs and swine, occasioning pustular eruptions.

Pentastomata are found also in cattle, sheep, and goats, and in certain regions are abundant in cattle.

2. *Insects.*

§ 191. Most of the parasitic insects are epizoa. Part of them remain only temporarily upon the skin, and from it derive their nourishment, while others remain there permanently and utilize the skin structures as a place in which to deposit their eggs. The following may be mentioned as belonging to the numerous species here included:

1. **Pediculus capitis,** the *head-louse* (Fig. 487), occupies the hairy scalp, and derives its nourishment (i.e., blood) from the skin by means

FIG. 487.—Female *pediculus capitis*, showing ventral surface. (Küchenmeister and Zürn.) Magnified 13 diameters.

FIG. 488.—Male *pediculus pubis*, showing ventral surface. (Küchenmeister and Zürn.) Magnified 13 diameters.

FIG. 489.—Female *pediculus vestimentorum*, showing ventral surface. (Küchenmeister and Zürn.) Magnified 9 diameters.

of its feeding apparatus. Its eggs or nits are barrel-shaped and white, and are fastened to the hairs by a coating of chitin. It takes the embryo only about eight days to hatch out. In consequence of the scratching induced by the itching there arise frequently quite severe dermatitides, especially eczema.

2. **Pediculus pubis,** the *felt-* or *crab-louse* (Fig. 488), dwells in the hairy parts of the trunk and extremities. Its habits are the same as those of the *pediculus capitis.*

3. **Pediculus vestimentorum,** the *clothing-* or *body-louse* (Fig. 489), lives in the wearing-apparel and deposits its eggs there as well. It gets upon man to obtain nourishment.

4. **Cimex lectuarius,** the *bedbug*, dwells in beds, floors, closets, etc., and gets upon people at night to suck blood. It causes wheals upon the skin.

5. **Pulex irritans,** the *common flea*, also draws blood from the skin. A little hemorrhagic dot may be found where it has sucked. Sometimes, also, there appear local swellings and wheals. It lays its eggs in the cracks of floors, in sawdust, etc.

6. **Pulex penetrans,** the *sand flea*, occurs in South Africa in the sand. The female lays her eggs in the skin and causes thereby intense inflammation

7. **Gnats,** having mouths provided with stinging and sucking apparatus (*Culicidæ* and *Tipulidæ*), **horse-flies** (*Tabanidæ*), and **common flies** (*Stomoxyidæ*) draw blood frequently from the human skin. Various **flies** (*Œstridæ* or biting flies, and *Muscidæ* or stinging flies) occasionally

lay their eggs in the skin, on wounds or ulcers, or in the cavities of the body accessible to them, after which the developing mites occasion local irritation of the tissues and inflammation (*Myiasis*). Under certain circumstances their larvæ may also get into the intestinal tract with the food, and here develop further. This happens especially when the stomach and bowels are the seat of abnormal conditions which interfere with digestion. The *eggs of the Muscidæ* (in Europe generally the Sarcophila Wohlfarti; in America chiefly the Compsomyia or Lucilia Macellaria and the Musca Anthropophaga), after being deposited upon the mucous membranes or upon wounds, hatch out within a few hours, and cause irritation of the neighboring soft parts by their efforts to obtain nourishment. They may even denude the bones in the canal of the ear, the nose, and the antrum of Highmore (myiasis muscosa). In the course of about a week the larvæ abandon the ulcers and in chrysalis-form remain buried in the earth. The *Œstridæ* (in Europe the hypoderma bovis and the hypoderma Diana; in America the dermatobia noxialis or cuterebra cyaniventris) lay their eggs on wounds or upon the intact skin; very soon the larva, hatching out, penetrates into the cutis by means of hooklets, and in the course of from one to six months, after repeatedly shedding its skin, grows to be some 2 cm. long; in the later stages it occasions in its vicinity a painful swelling (*myiasis œstrosa*).

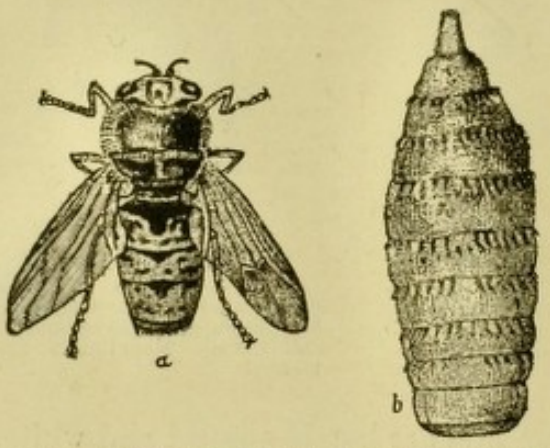


FIG. 490.—*Gastrophilus equi.* (After Brauer.) *a*, Male; *b*, larva.

The parasites belonging to the family of *Muscidæ* play a much more important rôle in the domestic animals than in man, and it is especially the *species of Œstrus* whose larvæ infest animals. Thus, for example, the larvæ of the *gastrophilus equi* (Fig. 490), *gastrophilus pecorum*, and *gastrophilus hæmorrhoidalis* live in the stomach and adjacent section of the intestine of the horse, and here they complete their development until they reach the chrysalis stage, upon which they depart.

Œstrus ovis lays its larvæ in the nasal cavities of the sheep, from whence they wander into the frontal, nasal, and maxillary cavities, and under certain circumstances also into the cranial cavity, and occasion inflammation.

The larva of the *œstrus bovis* bores into the skin of the cow, and here develops as far as the chrysalis stage, when it again leaves its host.

II. Vermes (Worms).

1. *Nematodes* (*Roundworms*).

§ 192. All the **roundworms** which occur as parasites belong to the **Nematodes.** They possess a slender, cylindrical, extended, and sometimes filiform body, with neither segments nor appendages. The cuticle is thick and elastic. The oral opening is found at one extremity, and is provided sometimes with soft and sometimes with horn-like lips. The elongated gut, together with the pharynx and chyle-stomach, extends through the entire body-cavity (Fig. 491), opening upon the ventral aspect a short distance from the usually awl-shaped posterior extremity. The sexual organs and their openings are also found on the ventral surface.

The female sexual orifice is located at about the middle of the body, less frequently near the anterior or posterior extremity (Fig. 491, A, *a*). In the male the sexual orifice and the anus are located together (B, *c*). The chitinous covering of the lower gut forms in the male the means of clinging in the act of copulation. The males are usually smaller than the females. The development is continuous, and the metamorphoses are not striking. The nematodes which occur in man are, some of them, harmless intestinal parasites, while others are very dangerous, sometimes even fatal, parasites of various organs.

§ 193. **Ascaris lumbricoides,** the *common spool* or *roundworm* (Fig. 491), is a light-brown or reddish-colored worm cylindrical in shape, and tapering generally to a point at the end. The female (A) is from 25 to 40 cm. long, the male (B) considerably smaller, and the posterior extremity of the latter is bent in the form of a hook and provided with two spicules (*c*) or chitin processes.

The mouth (*b*) is inclosed by three muscular lips, provided with very fine teeth. The sexual opening of the female (A, *a*) lies anterior to the middle of the body. The eggs, which the mature female contains in enormous numbers, possess in their fully developed condition a double shell (Fig. 492), and around this is an albuminous envelope. Their longest diameters amount to between 50 and 60 μ. The worm inhabits the entire intestinal canal, but most frequently the small intestine. It is the most common parasite in man, and frequently is found in great numbers. When mature females are present, the fæces contain numerous eggs. These are very resistant to external influences—for example, drying and freezing.

The eggs require no intermediate host (Lutz, Leuckart, Grassi, Epp-

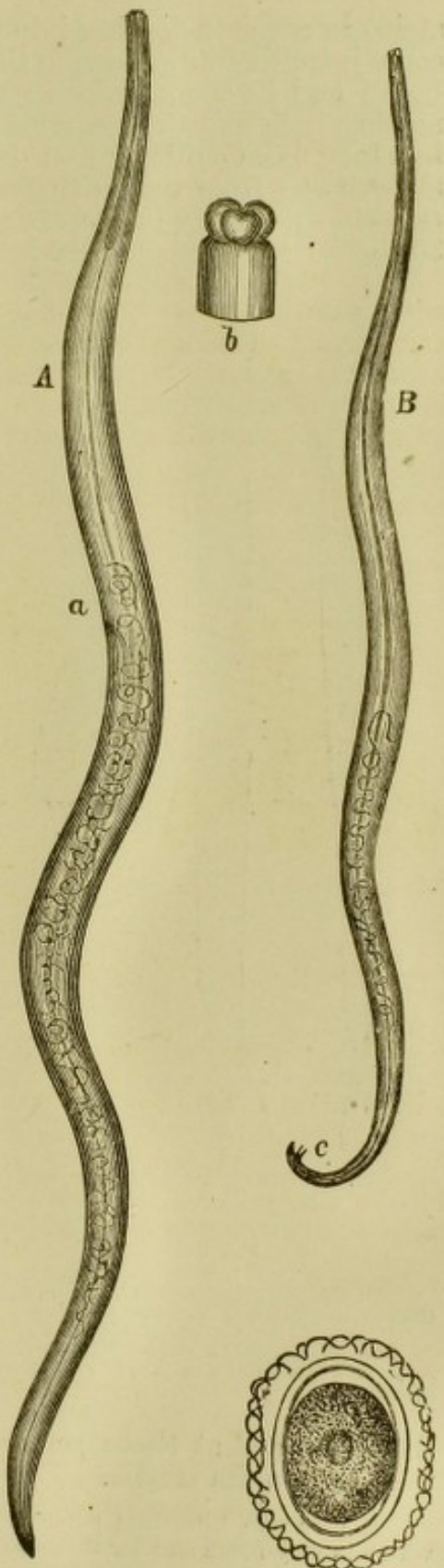


FIG. 491.

FIG. 492.

FIG. 491.—*Ascaris lumbricoides.* (After Perls.) *A*, Female; *B*, male. (Natural size.) At *a* is the female sexual orifice; *c*, the two spicules of the male; *b*, head extremity (magnified) of the worm, with the three lips.

FIG. 492.—Egg of *ascaris lumbricoides* (after Leuckart), with shell and albuminous envelope. Magnified 300 diameters.

stein) in order to develop into the roundworm, so that a person may become infected by swallowing the eggs which have been expelled from the bowel and have matured in the fæces. According to culture experiments which Eppstein carried out on human beings with eggs which had long been cultivated on damp fæces, the roundworm attains sexual maturity in from ten to twelve weeks after ingestion of the eggs. At this time the male is from 13 to 15 cm. long, and the female from 20 to 30 cm. Its presence in the intestine does not usually cause any noticeable disturbance. Only when present in large numbers does it sometimes, especially in children, cause intestinal catarrh, vomiting, nervous excitability, and convulsions. Occasionally it crawls into normal or pathological openings in the wall of the intestinal canal, and in this way causes trouble. Thus, when it gets into the ductus choledochus, it may produce bile-stasis. When it penetrates through an ulcer outward into the abdominal cavity or into a hernial sac, it may occasion inflammation of that particular tissue. By Leuckart it is also said to have the power of boring through the uninjured bowel-wall. Frequently the worm passes away *per anum* with the fæces, and at times *per os* in vomiting. From the pharynx it may wander into the larynx.

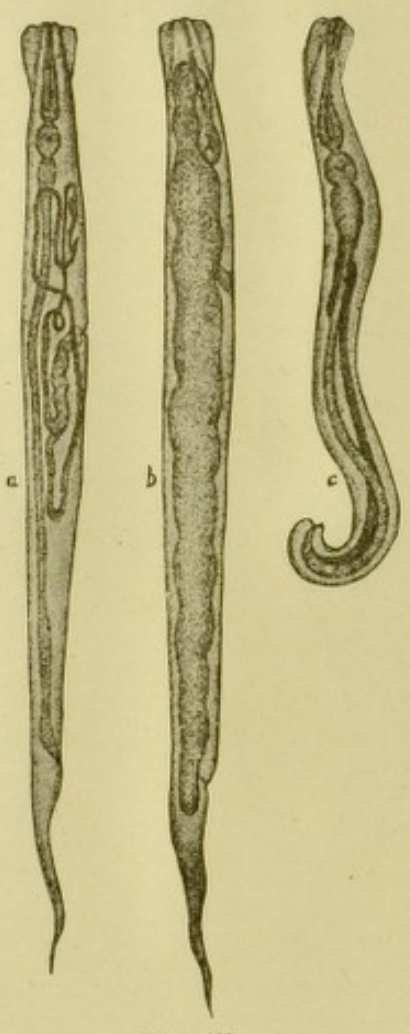


FIG. 493.

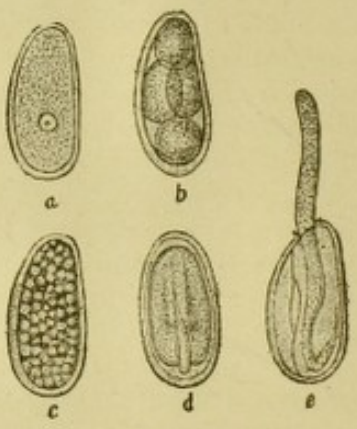


FIG. 494.

FIG. 493.—*Oxyuris vermicularis*. *a*, Sexually mature female; *b*, female full of eggs; *c*, male. (After Heller.) Magnified 10 diameters.

FIG. 494.—Eggs of *oxyuris vermicularis* in various stages of development. (After Zenker and Heller.) *a*, *b*, *c*, Segmentation of yolk; *d*, tadpole-shaped embryo; *e*, worm-shaped embryo. Magnified 250 diameters.

A very rare intestinal parasite is the *ascaris mystax*, the roundworm of the cat, which is very much smaller than the ordinary roundworm.

§ 194. **Oxyuris vermicularis**, the *awl-tail*, *maggot*, or *threadworm* (Fig. 493), is a small roundworm, the female being 10 mm. long (*a*, *b*) and pointed at the caudal end like an awl, while the male is 4 mm. long (*c*), with a blunt posterior ending provided with a spiculum.

The eggs (Fig. 494, *a*), which the belly of the female often lodges in immense numbers, are 50 μ long and 24 μ broad, have a flat and a curved surface, and a shell which is covered by a thin albuminous layer. The *oxyuris vermicularis* inhabits the large intestine and the lower part of the small intestine. According to Zenker and Heller, only the fructified mature female is found in the large intestine, while the younger individuals and the males occur in the small intestine. In greater or smaller numbers they are of very common occurrence. At night they are prone to wander outside the rectum into the anal region, and also enter the vagina, occasioning itching. The scratching thus produced sometimes leads to dermatitis, erections, masturbation, etc.

For the eggs to develop (Fig. 494, *a*, *b*, *c*, *d*, *e*) it is necessary after their expulsion with the fæces that they again make their way into the stomach of man or beast. It is very probable that the original possessor of the *oxyuris vermicularis* reinfects himself, the eggs which remained stuck to his fingers when he scratched himself later getting into his mouth.

The eggs are very resistant to drying, and when dry may be scattered from place to place.

§ 195. **Anchylostoma duodenale** (*dochmius duodenalis* or *strongylus duodenalis*) is a small palisade-worm which tenants the upper part of the small intestine (Fig. 495). The cylindrical body of the female possesses a length of from 5 to 18 mm., while that of the male is from 6 to 10 mm. long. The cephalic end (Fig. 496) is curved toward the dorsal surface, and is provided with a mouth-capsule located on the ventral side (*d*). It is almost completely divided dorsally, and the cleft is covered by two chitinous layers. On the ventral border are four incurving teeth (*b*), while on the dorsal border are two teeth perpendicularly arranged (*c*), both kinds being held together by chitinous bands. In addition the interior of the capsule contains a conical elevation beneath the cleft in the dorsal surface.

The male is provided at the caudal extremity with a threefold bursa (Fig. 495, *i*) and two thin bone-like spicules (*p*). In the female the caudal end is pointed and is armed with an awl-like prong; the vulva lies back of the centre of the body. The oval eggs (Fig. 497) are from 44 to 67 μ long and from 23 to 40 μ broad. They undergo the first stages of cleavage in the human intestine (*a*, *b*, *c*, *d*), develop still further in muddy water (*e*, *f*), and may then, if brought into the intestinal canal of man, immediately develop again into sexually mature individuals. Their presence in the intestinal tract is not without danger. With its teeth the worm works its way into the mucous membrane as far as the submucosa and sucks itself full of blood. Its point of attack is distinguishable later by a small ecchymosis, in the centre of which lies a white spot with a central perforation. Occasionally there are found in the mucous membrane of the bowel small blood-filled holes containing each a coiled-up worm. When present in large numbers they cause continuous and serious loss of blood, which produces a profound anæmia in the patient (*Egyptian chlorosis*). Perroncito, Graziadei, and Bäumler have ascertained the presence of anchylostomata in the intestine even several years after infection has taken place. The parasite is common in the tropics. According to Griesinger and Bilharz, something like a quarter of the population of Egypt suffer from this disease. A few years ago the parasite was very frequently observed among the laborers

in the St. Gothard Tunnel. Menche and Leichtenstern state that the brick-fields of the province of the Rhine are in great part infected with

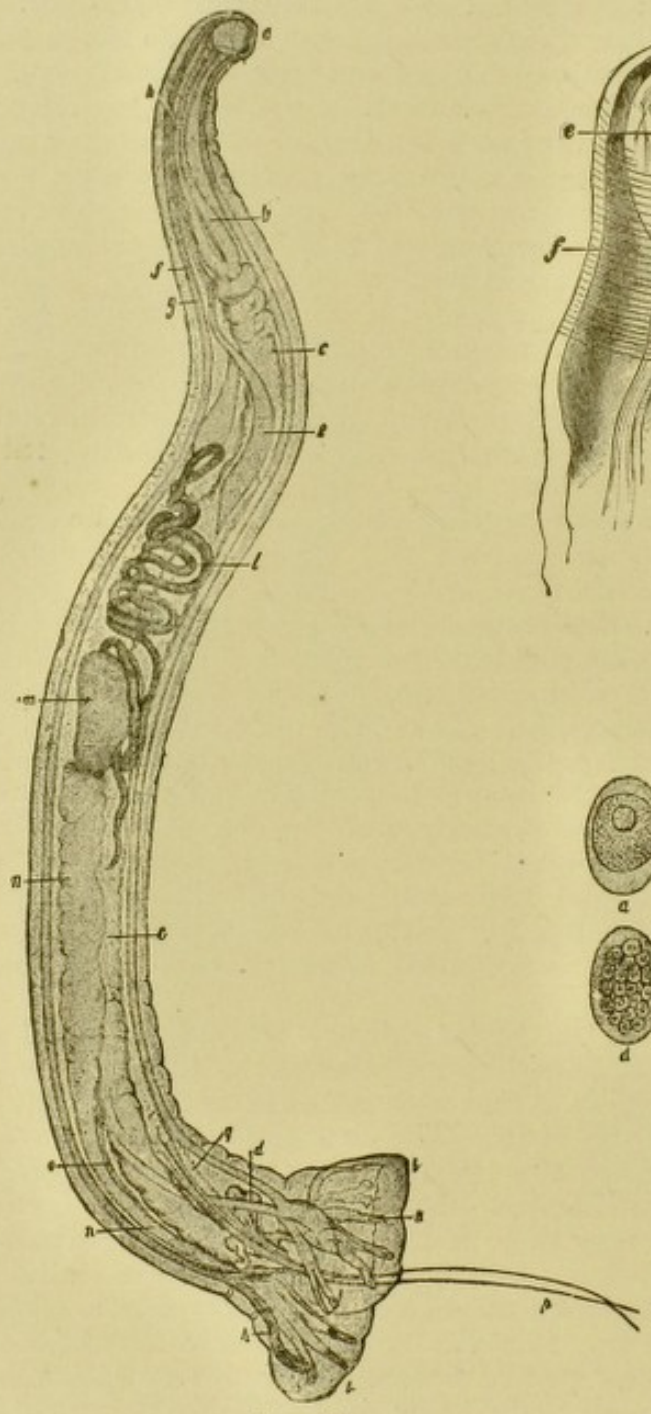


FIG. 495.

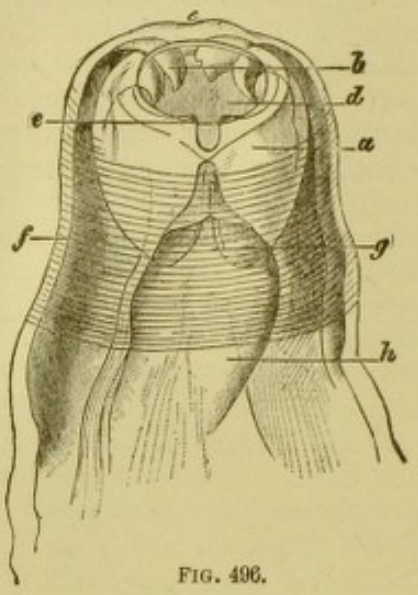


FIG. 496.

FIG. 497.

FIG. 495.—Male of *anchylostoma duodenale*. (After Schulthess.) *a*, Head with mouth-capsule; *b*, œsophagus; *c*, intestine; *d*, anal glands; *e*, cervical glands; *f*, skin; *g*, muscular layer; *h*, porus excretorius; *i*, triple bursa; *k*, ribs of the bursa; *l*, testicular canal; *m*, vesicula seminalis; *n*, ductus ejaculatorius; *o*, groove of latter; *p*, penis; *q*, sheath of penis. Magnified 20 diameters.

FIG. 496.—Cephalic end of *anchylostoma duodenale*. (After Schulthess.) *a*, Mouth-capsule; *b*, teeth of ventral border; *c*, teeth of dorsal border; *d*, buccal cavity; *e*, skin-sac on ventral side of head; *f*, muscular layer; *g*, dorsal groove; *h*, œsophagus.

FIG. 497.—Eggs of *anchylostoma duodenale*. (After Perroncito and Schulthess.) *a*, *b*, *c*, *d*, Different stages of cleavage; *e*, *f*, eggs with embryos. Magnified 200 diameters.

anchylostomata, and that the disease which was long considered in that region as brick-burner's anæmia is caused by the anchylostoma.

The **eustrongylus gigas**, a palisade-worm of red color, whose female reaches a length of a metre, is a very rare parasite, which has been observed but a few times in the pelvis of the human kidney. It possesses a buccal opening with six papillæ, and the male has at the caudal end a bursa with a single spiculum. The eggs are oval, 0.06 mm. long, and provided with an uneven albuminous envelope.

The **strongylus longevaginatus**, a white thread-like worm 26 mm. long, was observed in one instance in the lung of a boy.

Species of dochmius occur also in *dogs and cats*—not only the *dochmius duodenalis*, but also other varieties—and are said likewise to cause anæmia.

Varieties of strongylus occur very frequently in the domestic animals, sometimes as intestinal parasites, again as dwellers in the lungs.[1]

Strongylus armatus is a parasite of the horse, which enters the intestinal tract as an embryo, and thence bores into the mesenteric arteries, or even into a renal artery, where it develops to sexual maturity and then wanders back into the large intestine. The fully developed male worm is from 20 to 30 mm. long, the female from 20 to 55 mm. It causes clots to form in the arteries, and brings about aneurismal dilatations of the vessel-wall.

Strongylus filaria is a filiform worm some 25 to 84 mm. long, which occurs in the air-passages of sheep, goats, rabbits, and deer, and there occasions inflammations. *Strongylus rufescens* and *strongylus paradoxus*, *nematoidium ovis pulmonale* (Lydtin) or *pseudalius ovis pulmonalis* (Koch), are likewise occupants of sheep's lungs, *strongylus paradoxus* also of the lungs of swine. *Strongylus commutatus* occurs in the lungs of the hare and rabbit, while *strongylus syngamus* and *strongylus bronchialis* are found in the air-passages of birds, all three being productive of inflammation. *Strongylus micrurus* (Ströse[2]) occurs in cows and calves, not only in the air-passages, but also in arterial aneurisms.

§ 196. The **anguillula stercoralis** or *pseudorhabditis stercoralis* (Fig. 498) is a small nematode, the male possessing a length of 0.88 mm., the female 1.2 mm. The worm is indigenous to Cochin China and Italy, and in the latter country often occurs simultaneously with the anchylostoma. The fructified female contains both eggs and embryos (Fig. 498). The latter, which at birth spread through the whole intestinal tract, the gall-ducts, and the pancreatic duct, and even, according to Normand, occasion diarrhœa, may develop inside the intestine up to the point of formation of the sexual organs (Perroncito). In all probability some even attain complete sexual maturity, while others pass away earlier with the fæces. The larvæ at their departure are from 250 to 370 μ long.

FIG. 498.—Female of *anguillula stercoralis*, with eggs and embryos. (After Perroncito.) Magnified 85 diameters.

According to Golgi and Monti, the *anguillula stercoralis* penetrates into Lieberkühn's crypts, where it deposits its eggs and young; these cause sometimes epithelial degeneration, and at other times epithelial hypertrophy.

The **anguillula intestinalis** is a roundworm 2.25 mm. long, of which species the female alone is known. It has the same distribution as the

[1] A. Müller: "Die Nematoden der Säugethierlungen und die Lungenwurmkrankheit, eine zoologisch-patholog. Untersuchung," *Deutsche Zeit. f. Thiermed.*, xv., 1889.

[2] "Bau von *Strongylus micrurus*," *Deutsche Zeitschr. f. Thiermed.*, xviii., 1892.

anguillula stercoralis. The eggs do not develop in the intestinal canal, or, at any rate, exhibit only the first stages of segmentation at the time of their departure with the fæces. At a temperature of from 25° to 30° C. there sets in a very rapid segmentation of the eggs in the diluted fæces, and the development of the embryos commences, though the latter attain their complete development only in a new host.

§ 197. **Trichocephalus dispar**, the *whip-worm*, is indeed a common but comparatively harmless parasite, which is found in the cæcum and neighboring section of the intestine. According to Askanazy it draws blood from the intestinal mucous membrane. Both male and female are from 4 to 5 cm. long (Fig. 499). The anterior body-cavity (*a*, *b*) is very narrow and thread-like, while the posterior half of the body, which contains the sexual organs (*f*, *g*, *l*, *o*, *p*), is very much thicker, cylindrical in the female (B), and in the male (A) coiled up and provided with a spiculum (*g*).

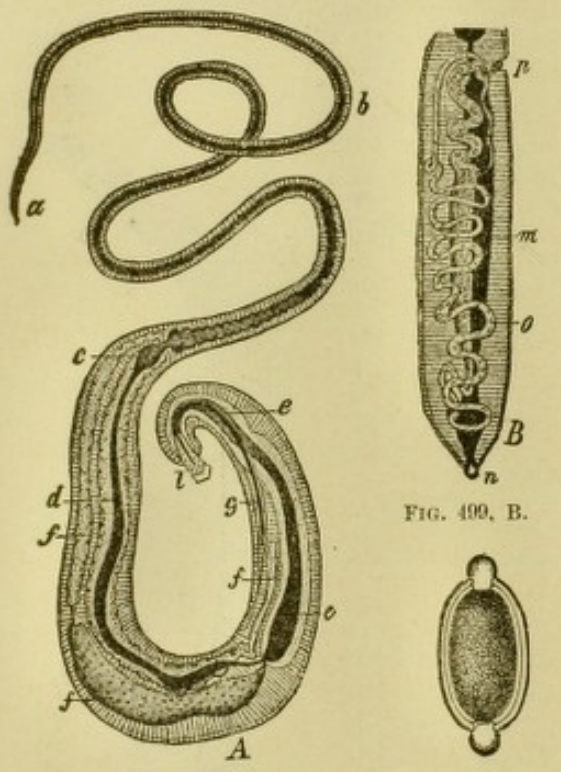


FIG. 499, A. FIG. 499, B.

FIG. 500.

FIG. 499.—*Trichocephalus dispar*. *A*, Male; *B*, caudal end of female; *a*, cephalic end; *b*, anterior belly with œsophagus; *c*, stomach; *d*, intestine; *e*, cloaca; *f*, seminal duct; *g*, penis; *l*, bell-shaped penis-sheath and end of penis; *m*, intestine of female; *n*, anus; *o*, uterus; *p*, vaginal orifice. (After Küchenmeister and Zürn.) Magnified 10 diameters.

FIG. 500.—Egg of *trichocephalus dispar*. (After Heller.) Magnified 350 diameters.

The eggs (Fig. 500) have an elongated oval shape, being 50 μ long. They possess a thick brown shell, which exhibits at each pole a peg-shaped swelling clear as crystal.

The first embryonal development takes place in water and damp earth. It progresses extremely slowly, requiring in the summer from four to five months, and in the colder periods of the year a much longer time. The eggs are very resistant to cold and dryness.[1]

Varieties of trichocephalus occur also in the *domestic animals*.

§ 198. The **trichina spiralis** is seen in two forms—namely, the trichina of the intestine and the trichina of the muscles.

It reaches sexual maturity as an intestinal parasite (Fig. 501)—the **intestinal trichina**—and then appears as a small, white, hair-like worm, visible even to the naked eye. The female (A) is 3 mm. long, the male (B) considerably smaller. The hinder part of the body is elongated in both sexes, and in the male (B) is provided on the dorsal half with two conical-shaped terminal pegs, which are directed toward the belly, and are separated from each other by four knob-like papillæ. Instead of a spiculum, the muscular cloaca is protruded outward in copulation.

[1] For the literature on this subject, consult Huber: "Bibliographie d. klin. Helminthologie," München, 1893, S. 213; and Askanazy: "Der Peitschenwurm," *Deutsches Archiv f. klin. Med.*, 57 Bd., 1896.

The intestinal canal begins with a muscular mouth, which has the functions and appearance of an intestine, and farther on, increasing in calibre, passes directly into the food-canal. This is surrounded throughout its entire length by so-called cell-bodies—that is, a row of large cells. The stomach, which is the continuation of the food-canal, is a flask-shaped dilatation of the intestine, and is covered with fine granular cells. The stomach passes, with no important change of structure, into the intestine, which in the male joins with the seminal duct at the caudal end to form a cloaca.

The testicle consists of a pouch, which commences near the caudal end of the body in a blind sac, proceeds forward as far as the cell-body, and bending there, passes over into the seminal duct.

The sexual organs of the female (A) consist of a single ovary, a uterus, and a vagina, which opens outward at the junction of the first and second quarters. The ovary likewise forms a pouch located close to the posterior extremity of the body, and in this develop the roundish eggs. The pouch passes anteriorly into the sac-shaped uterus.

The eggs develop within the uterus into embryos which are set free at birth.

The **muscle-trichina** (Fig. 502) is a worm from 0.7 to 1.0 mm. long which lives in the muscles of the body. It is generally coiled up in a spiral, and lies in a capsule, which occasionally contains lime-salts. Between the coils of the worm is a finely granular mass.

A single capsule may contain two, three, or even five trichinæ.

If a piece of muscle which contains living trichinæ finds its way into the stomach of a host —for example, man—the capsules are dissolved and the trichinæ liberated. Sexual maturity is attained in the intestinal canal in two and a half days, when copulation occurs. On the seventh day after the introduction of the muscle-trichinæ the birth of embryos begins, and continues quite a while, apparently for weeks. A single female trichina is said to bear from one thousand to thirteen hundred young. According to the investigations of Pagenstecher, Chatin, Cerfontaine, and Askanazy, the female trichinæ penetrate into the intestinal villi and deposit the embryos in the lymph-vessels, whence their migration begins. How far they are swept passively along with the lymph, how far active migration is concerned in their spreading, is a difficult matter to determine. Once in the muscles they penetrate the primitive fibres, bring the adjacent contents to degenera-

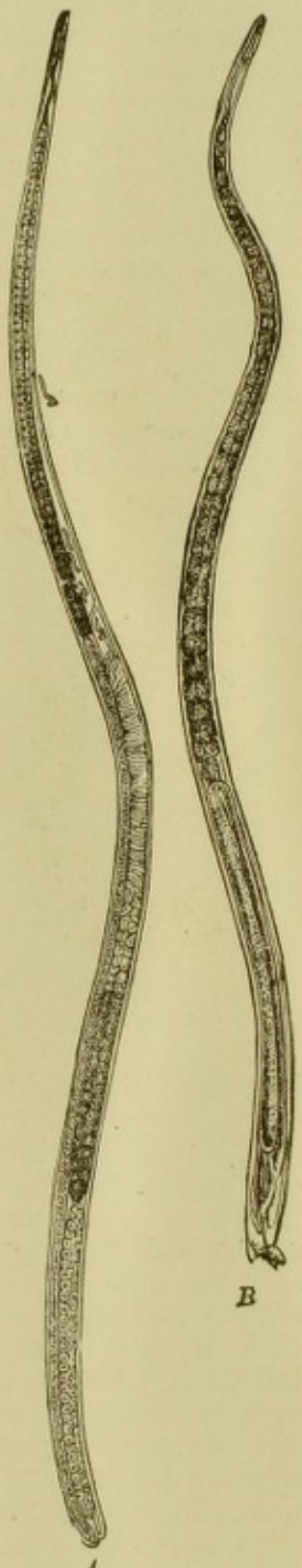


FIG. 501.—Sexually mature trichinæ. *A*, Female; *B*, male. (After Leuckart.) Magnified 120 diameters.

tion, and grow in about fourteen days to fully developed muscle-trichinæ. In the neighborhood of the muscle-fibres which contain trichinæ there sets in a growth of muscle-nuclei, while the invaded connective tissue becomes inflamed. At first the trichina is inclosed only by the sarcolemma, which shows hyaline thickening above it. But, later on, inflammatory granulation occurs in the neighborhood, producing connective tissue on the outer surface of the sarcolemma, and also penetrating into its interior, where the muscle nuclei in consequence perish. Fat cells may develop later in the connective tissue of the capsule, this tissue being especially well marked at the ends.

The intestinal trichinæ have a limited lifetime of from five to eight weeks. The muscle-trichinæ, on the other hand, may exist a very long, possibly an unlimited, time (that is, until the death of the affected individual), or at any rate for years; and yet, according to Ehrhardt, a few of them may die before the formation of the capsule is completed. After some time there takes place a deposition of lime-salts in the capsule, which causes it to appear glistening white by reflected light and

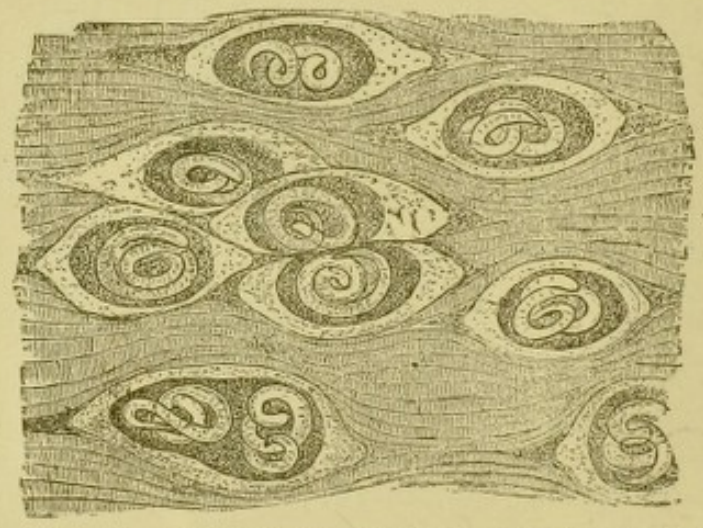


FIG. 502. Encapsulated muscle-trichinæ. (After Leuckart.) Magnified 60 diameters.

by transmitted light cloudy and dark. In rare cases the trichinæ themselves, after dying, undergo calcification.

The trichinæ have been observed not only in man, but in the swine, cat, rat, mouse, marmot, polecat, fox, martens, badger, hedgehog, and raccoon. Muscle-trichinæ are also produced in rabbits, guinea-pigs, sheep, and dogs by feeding on trichina-infected meat. Human beings are infected by the ingestion of uncooked pork. The invasion of trichinæ produces various phenomena in man. The symptoms of an intestinal catarrh follow the introduction of trichinous meat into the intestine. As the trichinæ wander into the muscles there arise pains, swellings, œdema, and paralyses, and not infrequently fever sets in. The symptoms are most severe in the fourth and fifth weeks. Not infrequently death follows. The intensity and severity of the symptoms are in general proportionate to the number of invading trichinæ in the muscles.

The trichinæ are found in greatest numbers in the diaphragm, the tongue, the intercostal muscles, the muscles of the neck and larynx, and the thighs, and are scattered most sparsely in the distant muscles of the extremities. The collection is usually greatest around the attachments of the tendons.

§ 199. **Filaria** or **dracunculus medinensis** (Fig. 503), the *guinea-worm*, is a thin, filiform worm from 60 to 100 cm. long. Up to the present the female alone is known. The cephalic end is rounded off, while the caudal end tapers into a pointed tail curved toward the belly. The external covering consists of a firm cuticle which becomes thickened at the cephalic end, taking the shape of a shield. The intestinal canal is narrow and possesses no anus. The uterus, filled with young, takes up the major part of the whole body-cavity. The embryos have no egg-shell, but possess a thick cuticle and an awl-shaped tail. As intermediate host, the embryos seek small crustacea, contained in which they reach the stomach in the drinking-water. In Africa and Asia the worm occurs very frequently. It develops in the skin to sexual maturity, and occasions cutaneous abscesses on the affected spots. Most usually it is found on the lower extremities, especially in the region of the heel.

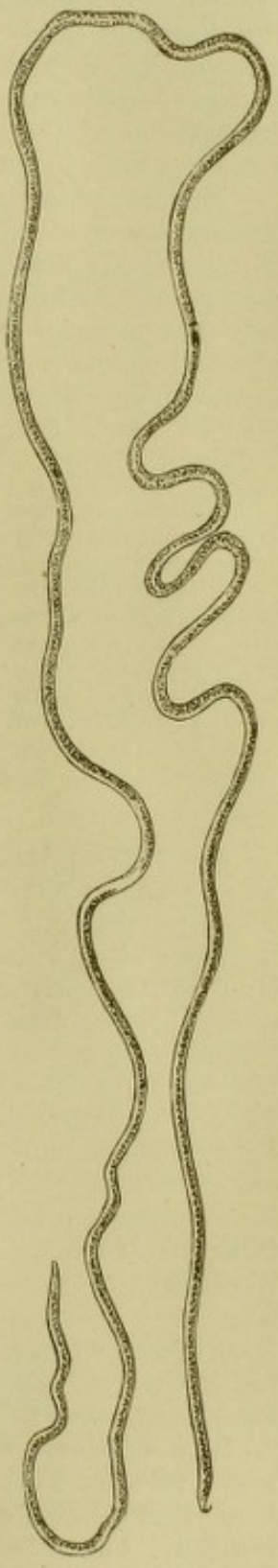


FIG. 503.—*Filaria* or *dracunculus medinensis*. (Leuckart.) Life size.

Filaria sanguinis hominis is the name applied to the larvæ (Fig. 504) of a worm which, when sexually mature, is filiform, and measures from 8 to 10 cm. in length. It is called after its discoverer **filaria Bancrofti.** The *larvæ* are 0.35 mm. long, and occur in the blood and lymph of man. The worm lives in the lymphatics, especially those of the scrotum and lower extremities. It causes lymph-stasis and inflammations, which in turn lead to *swelling of the lymphatic glands and elephantiasis-like thickening of the tissues*, combined with œdema and lymphangiectasia. Pustular inflammations, lymph-abscesses, buboes, chylous hydrocele, and ascites may also occur in consequence of its presence.

FIG. 504.—Embryo of *filaria Bancrofti*, known as *filaria sanguinis hominis*. (After Lewis.) Magnified 400 diameters.

From the lymphatics of the limbs and scrotum the eggs and embryos (0.35 mm. long) (Fig. 504) spread into other parts of the lymphatic system and into the blood, and cause hæmaturia, chyluria, and chylous diarrhœa. According to Manson and Scheube, the migration into the blood takes place chiefly at night—that is, while the patient is at rest. The hæmaturia is the result of a collection of embryos in the blood-vessels of

the urinary organs. The chyluria and the chylous diarrhœa, on the other hand, are said to come from the fact that the parasites obstruct the thoracic duct, so that lymph-stasis occurs; this affects also the lymphatics of the bladder and intestine and permits exudation of lymph in these localities. According to Scheube, the bursting of the lymphatics lacerates the blood-vessels also, so that blood is mixed with lymph. The embryos may leave the urinary organs by way of the urine.

The spreading of the embryos is effected, as Manson thinks, through the agency of mosquitos, which take them up in the act of sucking blood. The embryos attain a still higher stage of development inside the mosquitos, after which they make their way into water, and then once more into the human system. Probably their entrance into the latter is effected through the intestine. The correctness of Manson's views is, however, questioned by Leuckart.

The *filaria sanguinis* occurs, so far as is known, only in the tropics —Brazil, Egypt, southern China, Calcutta, Bahia, and Guadeloupe.

Mackenzie estimates the number of filaria embryos present in the blood of a case of hæmatochyluria carefully observed by him at from thirty-six to forty millions. The patient died of empyema, and the filariæ perished during this sickness.

Various species of filaria occur in the *domestic animals*, dwelling in various parts of the body. The *filaria papillosa* is quite a common parasite of the horse, ass, and cattle, living in the serous cavities and possessing a length of from 5 to 18 cm. *Filaria hæmatica*, a worm from 13 to 25 cm. long, occupies the right side of the heart and the pulmonary artery of the dog, and there surrenders its embryos to the blood. It occurs especially in America, China, and India.

2. *Trematodes* (*Sucking-worms*).

§ 200. The **trematodes** are sucking-worms of tongue or leaf shape. They possess a clinging apparatus in the form of ventrally placed sucking-cups varying in number; sometimes they are also provided with hook- or clasp-like horny projections for the same purpose. The intestinal canal is without an anus, and is split like a fork throughout most of its extent. They develop in two ways, either by the direct growth to maturity of the embryos (*miracidium*) which are hatched out of eggs, or by the method of alternate generation, *the germs developing inside of hosts*. The miracidium, or ciliated embryo, makes its way into a snail or mussel, and grows into a *germ-sac* (*sporocyst*) which later develops, either directly or by the formation of intermediary germ-sacs (*rediæ*), into *cercariæ*, a stage in which they swarm forth, provided with oar-like tails. Next they lose their tails, and make their way into a new host (molluscs, arthropods, fishes, amphibia), where they become encapsulated and develop sexually, as soon as they reach the final host. The sporocysts which produce cercariæ are classed as *primary germ sacs;* but if they produce cercariæ only after the formation of rediæ, then they are known as *secondary germ sacs*.

The **distoma hepaticum**, or liver-fluke, is a leaf-shaped sucking-worm 28 mm. long and 12 mm. wide (Fig. 505). The cephalic end projects like a beak, and bears a small sucking-cup, in which the mouth is located. Close behind this, on the ventral surface, is a second sucking-cup, and between the two lies the sexual orifice.

The uterus consists of a convoluted, bulb-shaped bag situated behind the posterior sucking-cup. On each side of the hinder part of the body lie the yolk-sacs, and between these the much-branched testicular canals. The forked intestinal canal also gives off numerous branches.

The eggs (Fig. 506) are oval, 0.13 mm. long and 0.08 mm. wide. A globular-shaped embryo—a *miracidium*—develops in water, and with the help of a finely ciliated arrangement swims about and looks up a new host (Limnæus minutus) of the Mollusk family. At the time of its

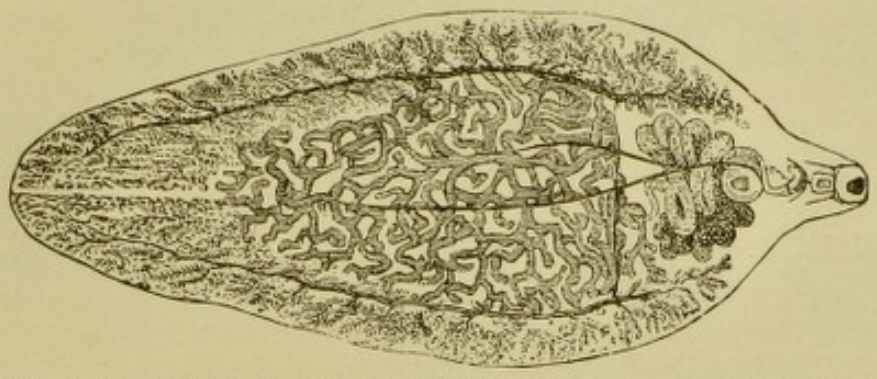


FIG. 505.—*Distoma hepaticum*, with male and female sexual apparatus. (After Leuckart.) Magnified 2.5 diameters.

penetration into the snail its envelope of skin is cast aside, and what was formerly a miracidium, possessing an intestine and excretory organ, as well as a brain ganglion, is transformed into a *sporocyst*. In this condition the intestine and nervous system atrophy, while collections of cells develop by cleavage out of the epithelium lining the abdominal cavity, giving rise to a *second generation of germ-sacs*, called *rediæ*. These rediæ (which are possessed of an intestine) next produce inside of the same host, out of cells which become separated from the collection, *the cercariæ* which desert the host and by the aid of an oar-shaped tail swim about in water. Finally they lose this tail and become encapsulated in almost any foreign body, and thence reach their final host (generally with the food), there to develop into sexually mature individuals. When sexually mature, they live in the biliary ducts, and are occasionally found in the intestine or the inferior vena cava. The liver-fluke is rare in man, though frequently found in ruminating animals. The consequences of its invasion, especially if it is present in large numbers, are occlusion and stricture of the biliary ducts from ulceration, then the formation of gall concretions, inflammation in the vicinity, and hyperplasia of the connective tissue of the liver, with atrophy of the glandular tissue.

The **distoma lanceolatum** is only 8 or 9 mm. long and from 2 to 2.5

FIG. 506.—Eggs of *distoma hepaticum*. (After Leuckart.) Magnified 200 diameters.

mm. wide, is lancet-shaped, and the head section is not specially marked off from the body (Fig. 507).

The skin of the body is smooth. Two irregularly shaped testicles lie close behind the ventral cup, in front of the ovary and uterus, the coils of which shine through the transparent body. The anterior coils,

which contain ripe eggs, are black, the rest being a rusty red. The yellowish-white yolk-sacs lie in the middle of the lateral margin.

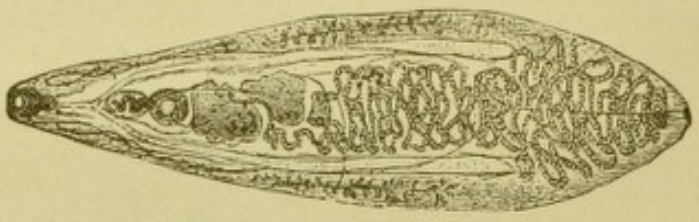


FIG. 507.—*Distoma lanceolatum* with its inner organs. (After Leuckart.) Magnified 10 diameters.

The eggs (Fig. 508) are 0.04 mm. long, and while still in the uterus contain an embryo, which does not escape, however, until several weeks after the eggs are cast off. Its metamorphoses are unknown.

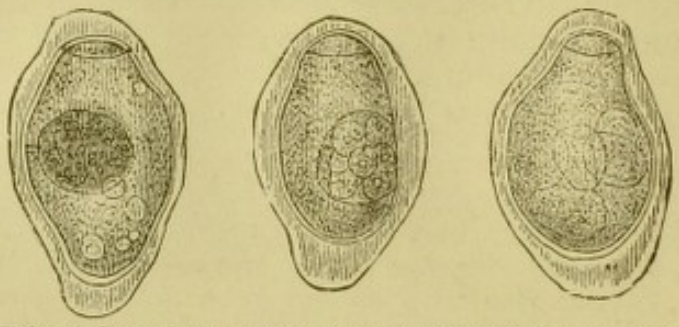


FIG. 508.—Eggs of *distoma lanceolatum* shortly after the formation of a shell. (After Leuckart.) Magnified 400 diameters.

The *distoma lanceolatum* likewise occupies the biliary passages, but is very rare in man. It occurs more frequently in sheep and cattle. It is present only in small numbers, and therefore occasions no important changes; when great numbers do occur, inflammation and proliferation of the peritoneal connective tissue may ensue.

Baelz has described three species of trematodes which occur in Japan, and which he calls *distoma hepatis endemicum perniciosum*, *distoma hepatis innocuum*, and *distoma pulmonale*.[1] The last-mentioned species is from 8 to 10 mm. long, dwells in the lungs, and causes hæmoptysis. The *distoma hepatis endemicum* is the size of a pea, and occupies the bile-passages, causing liver hypertrophies and diarrhœa. According to Winogradoff, there occurs not infrequently in Siberia a special kind of liver-fluke, the *distoma Sibiricum*, which, according to Brown, is possibly identical with the liver-fluke of the cat (*distoma felineum*).

§ 201. In the **distoma hæmatobium**, or Bilharzia hæmatobia (Fig. 509), the sexes are separate. The mouth and ventral cup lie only a short distance apart on the anterior extremity of the new-born individual. The sexual opening lies in both sexes close behind the ventral sucking-cup. The male is from 12 to 14 mm. long. Its body is smooth, but in its posterior portion is rolled up into a tube (Fig. 509) which serves for the reception of the female (canalis gynæcophorus).

The female is from 16 to 19 mm. long, and almost cylindrical. The eggs are an elongated oval (Fig. 510) measuring 0.12 mm. in length, and possess a terminal or lateral spine. According to Sonsino's observations, no alternate generation occurs in the development of the *distoma hæmatobium*. The part of intermediate host is taken by small crustacea,

[1] Cf. Manson: *Lancet*, 1883.

into which the ciliated embryo, swimming around in water, bores its way to become encapsulated in the former's tissues. In all probability, then, infection occurs by drinking water infected with the larvæ.

The worms are found in the trunk and branches of the portal vein, the splenic vein, the mesenteric veins, and also in the rectal and vesical blood-vessels. They get their nourishment from the blood, and occur in men and apes. Their eggs are distributed throughout the mucosa and submucosa of the ureters, bladder, and rectum, and at times they are found in the liver, lungs, kidneys, and prostate as well. They give rise to inflammation of the bladder and ureters, with the formation of papillary and polypoid growths, ulcerations, incrustations, and concretions. While still within the urinary passages, cylindrical embryos (miracidia) provided with fine cilia may develop. Their subsequent fate is uncertain. Sonsino states that the miracidium forces its way into crustacea and the larvæ of ephemerides, and there changes directly into a larva, which in turn develops directly into a sexually mature individual after its reception into a human body.

The parasite occurs through the entire eastern coast of Africa, and also in Zanzibar, Tunis, Lake Nyassa, in Beyrout, and in Sicily. It is

FIG. 509.

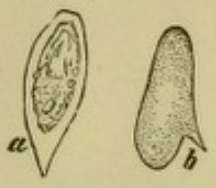


FIG. 510.

FIG. 509.—*Distoma hæmatobium*. (After Leuckart.) Male and female, the latter in the canalis gynæcophorus of the former. Magnified 10 diameters.

FIG. 510.—Eggs of *distoma hæmatobium*. (After Leuckart.) *a*, Egg with terminal spine; *b*, egg with lateral spine. Magnified 150 diameters.

most common in Egypt, where twenty-five per cent or thereabout of the native population suffer from this disease.

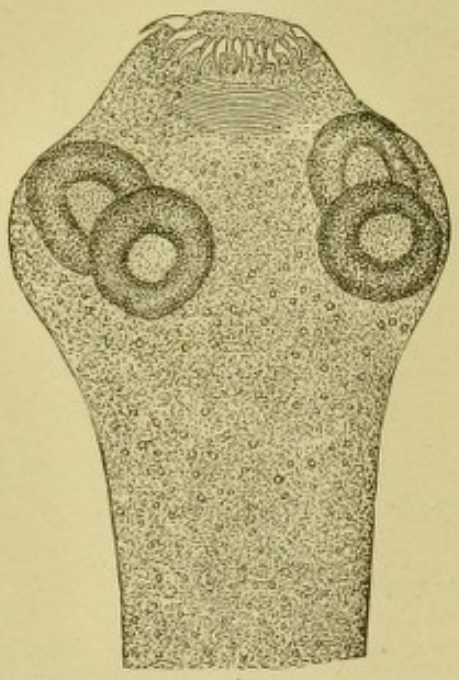
3. *Cestodes* (*Tapeworms*).

§ 202. The **tapeworms** are *flat worms devoid of mouth or intestine*, which increase after the method of alternate generation, through the germination of a pear-shaped primary host (head or scolex), and remain united to the latter for a considerable time as a (usually) long, band-shaped colony. The single members of this colony, the sexually active individuals, or **proglottides**, increase in size the more widely they become separated from their place of origin by the formation of new members, but outside of this are devoid of any outward peculiarity. The pear-shaped primary **host**, on the other hand, known as the *scolex* or **head**, is provided with from two to four suckers, and usually also with curved, claw-like hooks. With the help of these adhering organs the tapeworms fasten themselves to the intestinal wall of their intermediate host, which invariably seems to be one of the vertebrate animals. The scolices develop out of a round embryo with from four to six hooks, and

are found as so-called "measles" in the most diverse organs, chiefly the parenchymatous ones; later, they move out of these organs by a passive migration into the intestine of their future host.

The *tapeworms which occur as parasites in man* belong to different families—the *Tæniæ* and the *Bothriocephali*. The former live in man either as "measles" or as tapeworms. The latter occur in human beings as tapeworms only.

§ 203. The **tænia solium** in its fully developed condition possesses usually a length of from 2 to 3 metres. Its *head* (Fig. 511) is as large as a small pinhead, and is spherical in shape; it has quite prominent sucking-cups. The crown of its head is not infrequently pigmented, and is the bearer of a fairly large rostellum with some twenty-six coarse, closely aggregated hooks, with short rootlets (Fig. 511). Following the head comes a filiform *neck* almost an inch long. A certain distance from the head there commences a division into segments. The first *segments* are very short, but their length increases from before backward (Fig. 512). They become first square and finally longer than they are wide. About 130 cm. behind the head the mature segments begin, though the sexual organs were fully developed in the earlier segments. The mature segments (Fig. 513) are, when stretched out, 9 or 10 mm.



A.

FIG. 511.

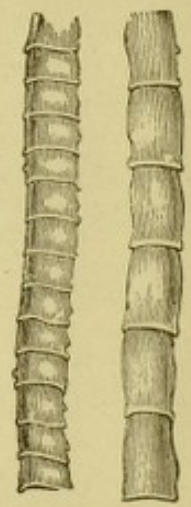


FIG. 512.

FIG. 513.

FIG. 511.—Head of *tænia solium* with protruding rostellum. (Preparation stained with carmine and mounted in Canada balsam.) Magnified 50 diameters.

FIG. 512.—Half-developed and fully matured segments. Natural size. (After Leuckart.)

FIG. 513.—Two proglottides with uterus. Magnified 2 diameters. (After Leuckart.)

long and 6 or 7 mm. wide, and have their corners rounded off. The sexual orifice is situated laterally in the posterior half of the body. The uterus possesses from seven to ten lateral branches, which are separated from one another by a considerable distance, and end in a variable number of boughs branched like a tree. The uterus is filled with eggs.

The parenchyma of the body of mature as well as of immature *proglottides* (or tapeworm segments) (Fig. 514) is divided into two chief layers, of which the central is known as the middle layer, the peripheral as the cortical layer. The middle layer includes the sexual organs (Fig. 514, *c*, *d*, *e*, *f*, *g*, *h*, *i*, *k*, *l*, *m*, *n*), and also the water vascular sys-

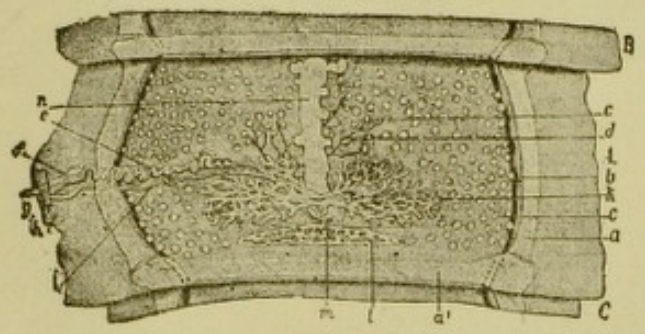


FIG. 514.—Segment of *tænia solium* with fully developed sexual apparatus. (After Sommer.) *A*, Surface view of segment; *B*, border of adjacent anterior segment; *C*, that of adjacent posterior segment. *a*, Longitudinal excretory trunk; a^1, transverse anastomosis; *b*, longitudinal plasma-vessel; *c*, testicular vesicles; *d*, seminal ducts; *e*, vas deferens; *f*, cirrus-bag with cirrus (or penis); *g*, porus genitalis; *h*, border papilla; *i*, vagina; *k*, ovary; *l*, albumin gland; *m*, shell-gland, and oviduct in front of same; *n*, uterus. Magnified 30 diameters.

tem (*a*), an excretory apparatus which traverses the whole tapeworm from head to last segment in the form of two canals located in the lateral border of the middle layer. The canals are connected with each other at the posterior end of each segment (a^1) and also send subdividing branches to the parenchyma of the body.

The *sexual apparatus* consists of male and female sexual organs lying close together. A number of clear, small vesicles serve as testicles (*c*), lying chiefly in the anterior part of the middle layer. The vas deferens (*e*), which is connected with the testicles by the seminal ducts (*d*), opens into an umbilicated papilla located on the lateral border (*h*). The coiled end (*f*, *g*) lies in a muscular bag and may be protruded through the sexual orifice (*cirrus*). The female sexual orifice is located just back of the male orifice in the same sexual cloaca. The vagina (*i*) leads thence to the posterior border of the segment. Before reaching the latter it widens into the seminal vesicle, and behind this into the fructifying canal and the so-called "globular body." The germ-preparing organs, which are to be sought in the immature segments, consist of a double ovary (*k*) and a single albuminous gland (*l*); these are sac-like or tubular organs which lie in the posterior part of the segments and are connected with the globular body. The latter is joined to the anteriorly located uterus (*n*), which at the time of sexual maturity forms a straight canal. When the eggs enter the uterus from the globular body, in which they attain their first stage of development, the above-mentioned lateral branches sprout forth and become filled with eggs. While this is going on the remaining sexual organs disappear.

The *cortical layer of the proglottides* is essentially muscular in character, but in addition contains a large or smaller collection of so-called calcareous bodies, which are not entirely wanting in the middle layer as well. The muscular supply consists of smooth fibres, which form special groups on the suckers of the head. The surface of the tapeworm is covered with a clear cuticle, which forms the hooks on the head.

The *eggs in the ovary* are thin-skinned, pale and yellow, almost globular cells. In the uterus they change into yellowish balls with a

thicker, more or less opaque shell, which is covered with closely placed spicules (Fig. 515, *a*). This shell is frequently surrounded by a second envelope, an albuminous layer (*b*), limited by a membrane, and in it are embedded nuclei (primitive yolk-skin, or vitelline membrane). The diameter of the eggs, not including the vitelline membrane, amounts to 0.03 mm.

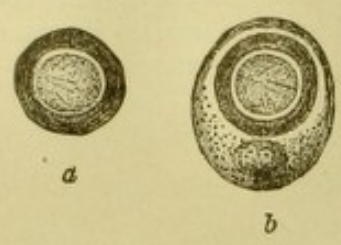


FIG. 515.

FIG. 516.

The thick-shelled balls are no longer undeveloped eggs, but contain an *embryo* with six hooklets. There takes place, then, while it is still in the uterus, a development of the embryo, and the fully developed segments are here impregnated.

The *further development of the embryos*, which are now inclosed in a brownish shell, does not take place in the same host which shelters the tapeworm, but in another. If the embryos reach the stomach of a pig the egg-shell becomes dissolved, and the embryos, thus liberated, bore their way into the wall of the stomach or intestine. Thence they proceed, either by way of the blood or by means of active migration, through the tissues into this organ or that. Having reached a resting-place the embryo undergoes various metamorphoses, and changes inside of two or three months into a *cyst* filled with serum (Fig. 516), from whose wall there shoots forth like a bud, toward the interior, a *scolex;* from this a new tapeworm head develops, as does also a sac enveloping the same (*receptaculum scolicis*).

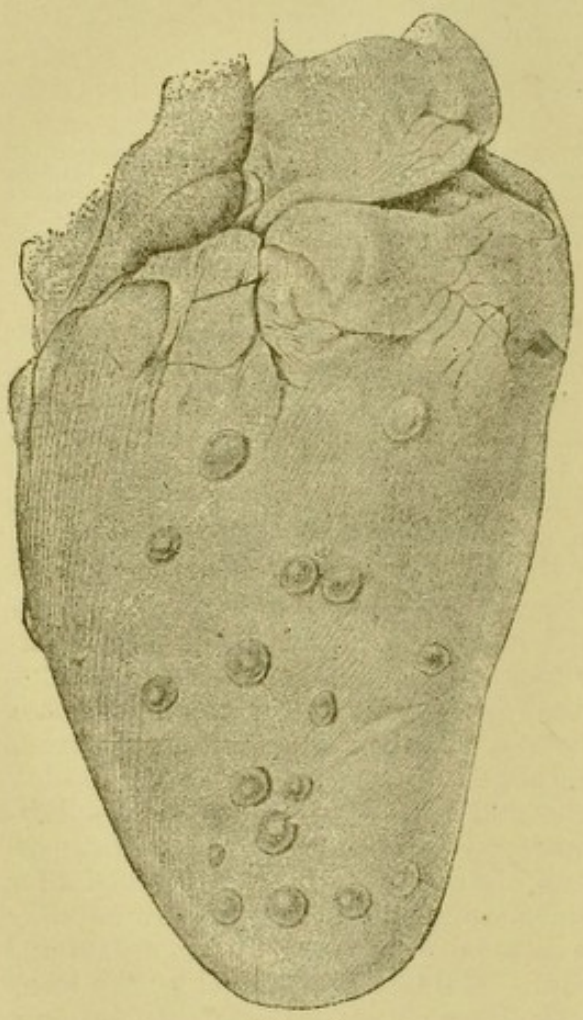


FIG. 517.

FIG. 515.—Eggs of *tænia solium*. *b*, With vitelline membrane; *a*, without latter. (After Leuckart.) Magnified 300 diameters.

FIG. 516.—*Cysticercus cellulosæ* with fully developed head *in situ*. (After Leuckart.) Magnified 4 diameters.

FIG. 517.—Cysticerci of the *tænia solium* in the epicardium and muscular tissue of the heart of a pig.

The cyst provided with a tapeworm head is known as a "**measle**" or **cysticercus cellulosæ**. The scolices, when fully developed, possess a circle of hooks, suckers, a water vascular system, and numerous calcareous bodies in their body parenchyma. If they get into a human stomach the cyst dissolves, and there develops, through formation of segments from this primary host (*Amme*), a new chain of proglottides, a new *tænia solium*.

The *tænia solium* occupies the small intestine in man, and is acquired by the consumption of uncooked pork, since the "measles" belonging to this parasite occur almost solely in human beings and swine. Generally there is only a single parasite present in the intestine, though the simultaneous occurrence of several is not rare. Occasionally as many as thirty or forty are observed in one individual. They occasion irritation of the intestinal mucous membrane, colic, and reflex disturbances in the central nervous system.

The "measles" in the tissues of the swine are sometimes single, sometimes numerous (Fig. 517), and it can happen that single organs—as, for example, a muscle or the heart—may be thickly sprinkled with them.

In man the cysticerci occur in the most varied tissues—the muscles, brain, eyes, skin, etc. In the brain membranes and the brain itself the "measles" may appear in the form of collections of cysts bunched like mulberries or grapes, and called *cysticercus racemosus* (Zenker). The cysts are mostly sterile, though some of them may contain a scolex. Their importance depends upon their location, but is generally slight; their presence in the brain often gives rise to serious disturbances, and yet in other cases all morbid symptoms may be lacking. Locally their presence excites a slight inflammation, which leads to a thickening of the connective tissue in the immediate vicinity of the cyst. The latter retains its vitality for years. After the death of the scolex the cyst shrivels up, and within it there accumulates a chalk-like mass. In this mass the hooks remain a long time. Infection with the "measles" follows the presence of eggs or proglottides in the human stomach.

§ 204. The **tænia mediocanellata** (or **saginata**) surpasses the *tænia solium* not only in length (it measures from 4 to 7 metres in length and even longer), but also breadth and thickness, as well as in the size of the proglottides (Fig. 518).

The *head* is devoid of rostellum and a circle of hooks (Fig. 519), but is provided with a flat crown and four large and powerful suckers, which are generally surrounded by a black fringe of pigment.

The *eggs* are similar to those of the *tænia solium*. The fully developed, pregnant *uterus* (Fig. 520) has a great number of lateral branches which run close together and, instead of branching like a tree, divide only dichotomously. The sexual orifice lies posteriorly to the centre of the lateral border. The eggs are for the most part already discharged from those segments which become spontaneously separated from the rest.

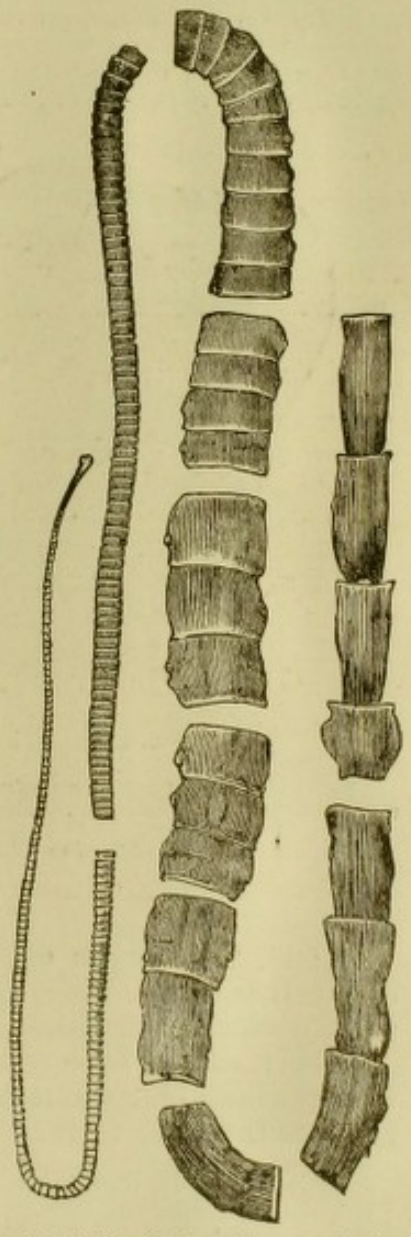


FIG. 518.—Portions from a *tænia saginata*. Natural size. (After Leuckart.)

The "*measles*" are found in the cow chiefly in the muscles and heart, more rarely in other organs, and are somewhat smaller than in swine.

The *development* follows a course similar to that of the *tænia solium*. Irregularities of formation are very common in the tapeworm.

Human beings acquire tapeworms by the consumption of raw beef. This worm is more widespread than the *tænia solium*. It has not been definitely settled whether the "measles" occur in the human being or not, although some authors (e.g., Arndt and Heller) insist that they do.

The *tænia cucumerina* (or *elliptica*) is from 15 to 20 cm. long, and possesses a head with a rostellum and a circle of hooks. It occurs very frequently in dogs and cats, but more seldom in man. Its cysticercoid infests the louse and flea of the dog, and more rarely the flea of human beings (Grassi [1]).

Tænia nana, a small tapeworm from 8 to 15 mm. long, has a head with four suckers and a circle of hooks. It has been observed in Egypt and Italy. B. Grassi [2] was able to obtain several thousand specimens from two Sicilians who had suffered from severe nervous disturbances. According to his investigations,[3] the tænia passes its whole period of development, from the embryonal stage onward, in the interior of one host. Visconti [4] found, in an autopsy on a young man from northern Italy, *tænia nana* in great numbers in the lower part of the ileum. According to Grassi, the *tænia leptocephala*, which is common in mice, occurs also in man.

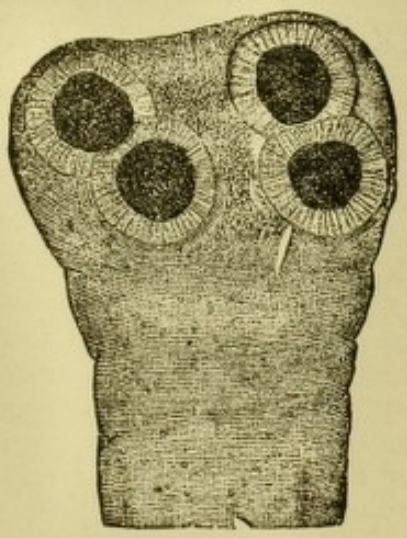


FIG. 519.

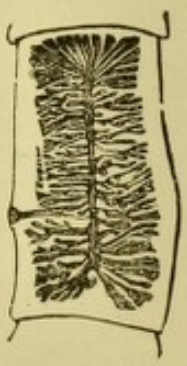


FIG. 520.

FIG. 521.

FIG. 519.—Head of a *tænia saginata*, retracted. Black pigmentation in and between the suckers. (Unstained glycerin preparation.) Magnified 30 diameters.

FIG. 520.—Segment of *tænia saginata*. Magnified 1½ diameters. (After Leuckart.)

FIG. 521.—Full-grown tænia echinococcus. (After Leuckart.) Magnified 12 diameters.

§ 205. The **tænia echinococcus** lives in the intestinal canal of the dog. It is 4 mm. long, and possesses only four segments, of which the most posterior surpasses in length all the rest put together (Fig. 521).

The hooklets have coarse root processes and are implanted on a rostellum which bulges out considerably. The number of hooklets amounts to some thirty or forty.

[1] "Beiträge zur Kenntniss des Entwickelungscyclus von fünf Parasiten des Hundes," *Centralbl. f. Bakt.*, iv., 1888.

[2] *Centralbl. f. Bakt.*, i., 1887.

[3] *Centralbl. f. Bakt.*, ii., 1887.

[4] *Rendiconti R. Instituto Lombardo*, xviii., 1886.

Only the *cyst-worm* occurs in man. It follows the introduction of the tænia eggs into the intestinal canal.

If the embryo chances to wander from the intestinal canal into some organ, it changes into a *cyst* which is incapable of active motion. It consists of an external, very elastic *cuticle divided into layers* (Fig. 522,

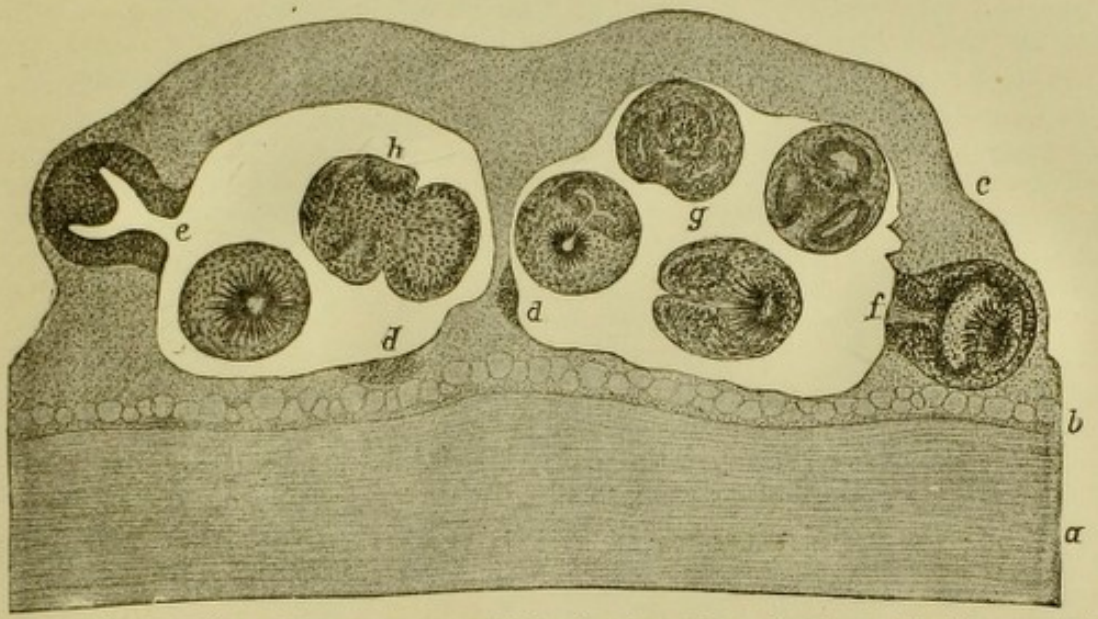


FIG. 522.—Wall of an echinococcus-cyst containing brood-capsules and scolices. (Alcohol; carmine.) *a*, Chitinous membrane; *b*, parenchymatous layer with distended cells; *c*, brood-capsules, *d*, *e*, *f*, *g*, *h*, scolices in different stages of development. Magnified 100 diameters.

a), and a parenchymatous layer lying internal to this, consisting of granular matter and cells, and containing muscle-bundles and a circulatory system (*b*). When the cyst has reached the size of a walnut approximately (sometimes earlier), there are formed from the parenchymatous layer small *brood-capsules* (*c*) which produce a still greater number of *scolices*. The first stage of this tapeworm head consists of a granular mass of protoplasm (*d*) lying in the wall of the brood-capsule; this develops further, and shows a cavity (*e*) which communicates with the cavity of the brood-capsule, and later on becomes differentiated into a tapeworm head (*f*) provided with a circlet of hooks. By this time the head (*h*) protrudes into the lumen of the brood-capsule (*g*, *h*), and measures some 0.3 mm. in length. It possesses a rostellum with coarse hooklets, four suckers, a water vascular system, and numerous chalk-like bodies in its parenchyma. Frequently the anterior part of the body is telescoped into the posterior part (*g*).

In many cases the **echinococcus cyst remains single.** The only possible variation consists in an enlargement to the size of an orange or fist, through the development of new brood-capsules and heads. The surrounding tissue forms a connective-tissue capsule, in which the cuticular cyst lies inclosed. The cavity of the cyst is filled with a clear fluid, which does not precipitate on boiling or on the addition of acid. The brood-capsules are always fastened to the inner surface, unless mechanically dislodged, and are visible as small white points through the translucent cyst-parenchyma. Occasionally the cyst remains sterile.

In some cases **daughter-cysts** develop (Fig. 522, *c*). Their development proceeds independently of the real parenchymatous layer in the depth of the cuticle. Between two lamellæ of the cuticle there is formed

a collection of granules, which become surrounded by a new cuticle and in this way become the centre of a fresh set of layers. As the number of layers increases the cavity grows larger and its contents become clear. When the daughter-cysts grow they bulge out the wall of the parent-

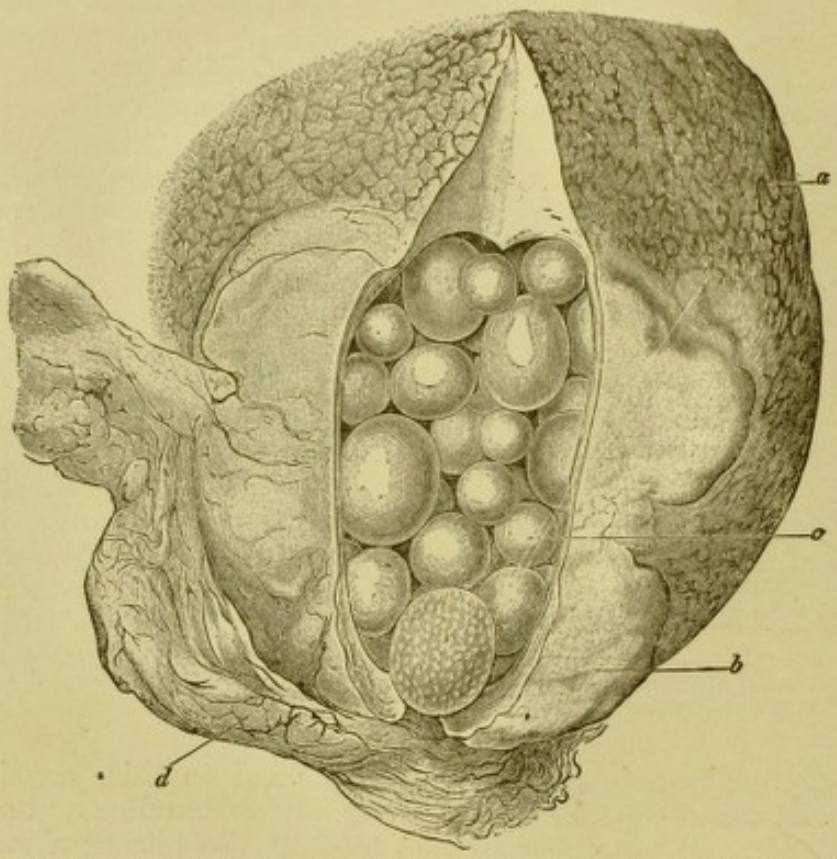


FIG. 523.—Echinococcus hydatidosus. *a*, Surface of the liver; *b*, indurated connective tissue; *c*, daughter-cysts within a parent-cyst which has been opened by an incision; *d*, membrane which has become adherent to the cyst. Five-sixths natural size.

cyst like a hernial sac until it finally gives way and liberates its contents. If these travel outward beside the parent-cyst they derive from the parenchyma in which they lie an external connective-tissue capsule, and then proceed to generate brood-capsules in the same way as do the primary cysts which grow from six-hooked embryos.

An echinococcus with an *exogenous proliferation* is called **echinococcus granulosus** (*scoleciparíens* of Küchenmeister), or sometimes **echinococcus veterinorum**, because it occurs commonly in the domestic animals.

A second, compound form of the echinococcus is the **echinococcus hydatidosus.** It is characterized by the presence of *inner daughter-cysts* (Fig. 522, *c*). According to statements made by Naunyn and confirmed by Leuckart, the scolices and brood-capsules may undergo a cystic metamorphosis and in this way become daughter-cysts. The daughter-cysts occasionally, in a later stage of their existence, give origin to a third generation of cysts. All cysts occurring in the forms of echinococci thus far considered may attain a very considerable size.

The third form of echinococcus, the **echinococcus multilocularis,** never develops any but small cysts which vary in size from that of a millet-seed to that of a pea, but these cysts are invariably present in larger numbers. This echinococcus presents itself as a firm tumor, lo-

cated usually in the liver, very rarely in other organs, and possessing an alveolar structure (Fig. 524)—that is, a thick, compact connective-tissue mass inclosing numerous cavities. Its contents are gelatinous and translucent, or else consist of a fluid and a gelatinous mass. The shape of the cavities is somewhat globular at times, at others irregular. Usually through softening and destruction of the parenchyma ulcerous cavities (*c*) are formed here and there. In other places the cysts are shrivelled up and calcified, or the tissues are infiltrated with bile. Where the development of the colonies has progressed further there appear in the tissues yellow nodules (*d*) in which a dark centre soon forms, later becoming liquid. The exquisite alveolar structure has given rise to the theory that echinococcus is an alveolar tumor with colloid contents. Virchow was the first to recognize the real nature of the process and to demonstrate that the so-called colloid masses are echinococcus cysts. The contents of the smallest cysts are granular masses; in larger ones the contents have become liquefied. The granular coating of the cuticle only rarely contains scolices, the cysts being for the most part sterile.

Whether the multilocular echinococcus is a modification of the exogenous proliferating echinococcus or a separate species is as yet undetermined. Mangold and Müller consider it a distinct species.

The *infection of human beings* follows the chance ingestion of eggs of the tænia which occurs in dogs. The liver is the most frequent site of the cysts, but the echinococcus occasionally occurs in the most diverse organs—e.g., the lungs, spleen, intestine, bones, or heart. Apart from

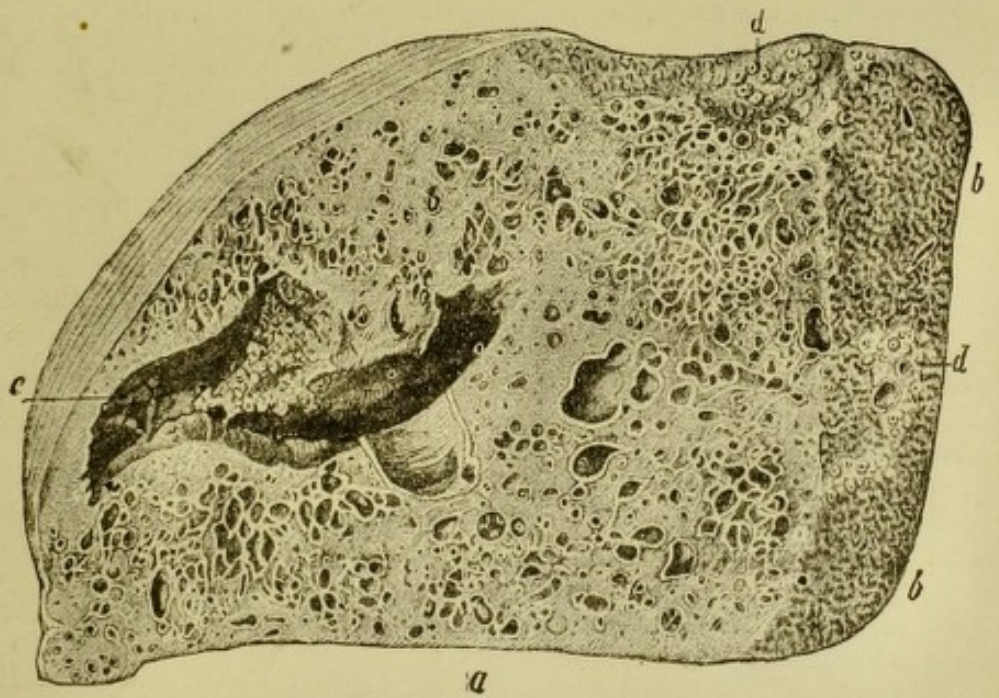


FIG. 524.—Transverse section of an *echinococcus multilocularis*. *a*, Alveolar structure of the echinococcus tissue; *b*, liver-tissue; *c*, cavity produced by softening; *d*, fresh nodules. Natural size.

the disturbance of the tissues and the local inflammation which it excites (the latter cause leading in some organs to the formation of a connective-tissue capsule), it frequently has no harmful effect whatever on the patient. It often dies on attaining a certain size (from the dimensions of a walnut to those of an apple), the liquid becomes absorbed, the cyst shrivels up, and there remains within only a fatty, caseous detritus,

which often calcifies to a mortar-like mass. The hooks may be found in this mass for a very long time.

In other cases the echinococcus enlarges, especially if endogenous or exogenous daughter-cysts develop. Under these circumstances it may become dangerous on account of its size. Occasionally, especially following traumata or rupture of the cysts into one of the body-cavities, severe inflammations ensue. Rupture into the blood circulatory system also occurs, and may lead to a transplantation of the cysts and to a plugging of the vessels. In more favorable cases the rupture points outwardly or into the intestine.

The echinococcus is very widespread, though not very common. It occurs most frequently in Iceland, where the inhabitants live in close contact with dogs. It is a striking fact that the multilocular form is chiefly observed in Switzerland and in southern Germany.

Tæniæ, exclusive of the kinds shared in common with man, occur very frequently in the *domestic animals*, and not only in the Carnivora and in birds, but also in the Herbivora.

The *tænia marginata* of the dog is a tapeworm from 1 to 5 metres long, provided with a double circlet of hooks, living as a cyst-worm in and beneath the serous membranes of sheep, cattle, goats, and swine, and forming cysts of various sizes.

The *tænia serrata*, a tænia of the dog, some 50 to 100 cm. long, armed with hooks, is the developed state of certain cysticercæ occurring in rabbits and hares.

The *tænia cœnurus*, a tapeworm of the dog, some 40 to 100 cm. in length and provided with hooks, passes its cystic stage most frequently in sheep. Here it seeks out the central nervous system and forms cysts which vary in size from that of a millet-seed to that of a hen's egg, and which produce great numbers of scolices. Their presence in the brain causes the so-called "staggers."

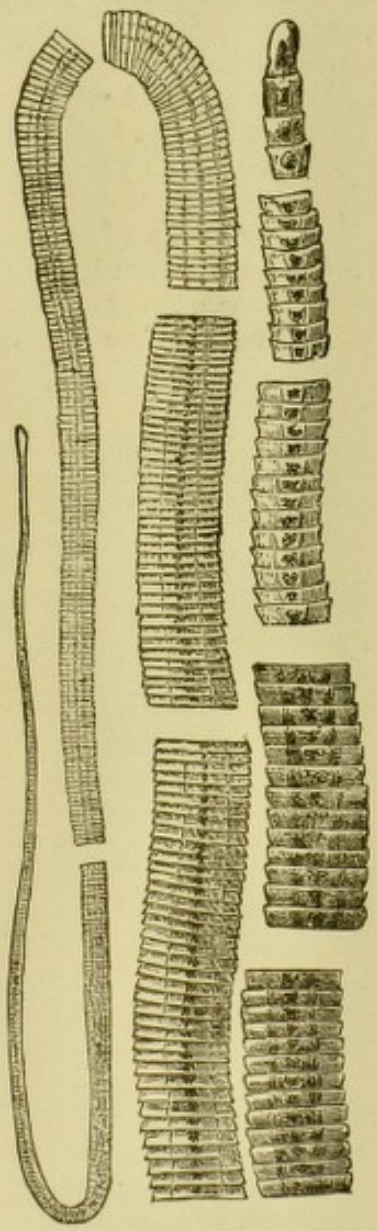


FIG. 525.

FIG. 525.—*Bothriocephalus latus.* (After Leuckart.) Natural size.

§ 206. The **bothriocephalus latus,** or **pithead,** is the most formidable tapeworm of man, measuring, as a rule, from 5 to 8 metres in length, and being made up of from three to four thousand short but broad segments (Fig. 525); these are broadest in the middle region and get narrower at the end. The length of the largest segments amounts to 3.5 mm.; the width from 10 to 12 mm.

FIG. 526.

FIG. 526.—Head of *bothriocephalus latus* of Bremser. Magnified. (After Heller.)

The *head* (Fig. 526) has an elongated oval or club shape, is 2.5 mm. long and 1 mm. wide, and is somewhat flattened down. It possesses on each lateral border a slit-like depression, and is mounted on a filiform neck.

The *body* is thin and flat like a ribbon, except the central parts of the segments, which project somewhat outward. At this spot the uterus is

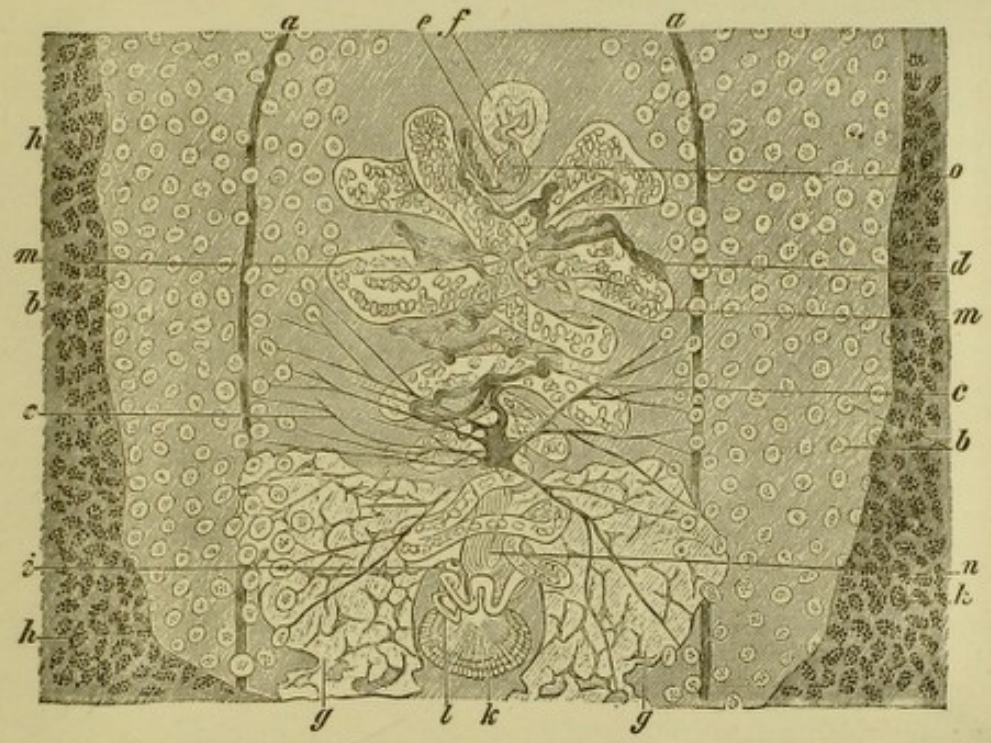


FIG. 527.—Median portion of a proglottis of the *bothriocephalus latus*, showing dorsal surface. The cortical layer of the segment has been removed, except a border on each side, and the middle layer thus exposed. (After Sommer.) *a*, Lateral vessels; *b*, testicular vesicles; *c*, testicular canaliculi; *d*, vas deferens; *e*, posterior, *f*, anterior hollow muscle arrangement (cirrus-sac of vas deferens); *g*, ovary; *h*, yolk-chambers, situated in cortical layer; *i*, collecting-tube of yolk-mass, branches of which lead ventrally to the yolk-chambers; *k*, shell-gland; *l*, beginning of uterus; *m*, knot of uterus filled with eggs, with orifice opening on the anterior surface; *n*, vagina; *o*, vaginal orifice. Magnified 35 diameters.

found, in the shape of a simple canal, which forms a number of coils (Fig. 527, *m*). When the eggs collect here in great numbers the lateral coils of the uterus arrange themselves in knots, so that a remarkable rosette-like appearance is produced. The sexual orifices lie in the median line of the ventral surface, near the anterior border of the segment, the female orifice (*o*) being close behind the male (*f*).

The ovary (*g*) is a double organ which lies in the middle layer. The yolk-chambers (*h*), on the other hand, are located in the cortical layer. Back of the collecting-tube (*i*) of the yolk-chambers lies the shell gland (*k*). The testicles consist of clear vesicles (*b*) lying in the lateral part of the middle layer and connected by means of fine canaliculi (*c*) with the vas deferens (*d*), which terminates in the cirrus-sac (*e*, *f*).

The *eggs* (Fig. 528) are oval, and have a length of 0.07 mm. and a breadth of 0.045 mm. They are surrounded by a thin brown shell, the anterior pole of which is formed by a sharply limited cap-like cover.

The *bothriocephalus latus* occurs especially in Switzerland, northeastern Europe, Holland, and Japan, and lives, like the Tænia, in the small intestine of man. According to Bollinger, it is also quite common in Munich. The first development of the eggs takes place in water. Months afterward there develops an embryo (*Oncosphæra*), armed with six hooklets (Fig. 529) and covered with minute cilia. This develops in an intermediate host (as yet unknown) to a "measle" (*Plerocercoid*), which, according to the investigations of Braun in the Russian Baltic Sea provinces, seeks out as second host the pike or tadpole, and either

in the muscles or in the intestines of these fish develops to a sexless tapeworm. According to Grassi and Parona, the "measle" of the *bothriocephalus latus* occurs in Italy both in the pike and in the river-perch; in Japan it is found most often (Ijima, Leuckart) in the *oncorhynchus Perryi*. Zschokke found it in the following fishes of the Lake of Geneva: *Lota vulgaris, perca fluviatilis, salmo umbla, esox lucius, trutta vulgaris*, and

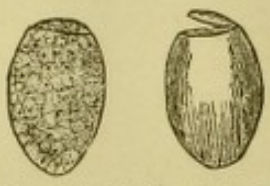


FIG. 528.—Eggs of *bothriocephalus latus*, the one to the right having been emptied of its yolk-contents. (After Leuckart.)

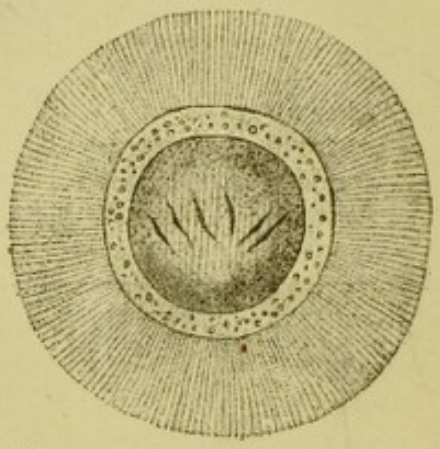


FIG. 529.—Free embryo of *bothriocephalus latus*, with ciliated envelope. (After Leuckart.)

trutta lacustris. It is most frequent in the tadpole (*lota vulgaris*) and the perch (*perca fluviatilis*). If it reaches the intestinal canal of man by ingestion of the afore-mentioned fishes it again attains sexual maturity. According to Braun and Parona, the "measle" may also be brought to development in the dog and cat. The presence of bothriocephali in the intestine may give rise to a gradually progressing *anæmia*, which resembles pernicious anæmia. How the presence of the bothriocephalus causes a diminution in the red blood-corpuscles and the percentage of hæmoglobin in the blood is unknown.

In Greenland there occurs in dogs and man another bothriocephalus, which grows only 1 metre long, and possesses a heart-shaped head. It is known as the *bothriocephalus cordatus*.

III. Protozoa.

§ 207. Of the **Protozoa** occurring as parasites in man, but a small number were recognized up to a few years ago, and even the recognized forms were of but slight importance, since there could be ascribed to them no particular influence on the tissues. Following the investigations of the last few years, however, various species have become known which must be regarded as the cause of morbid processes, and it is quite possible that there exist still other protozoa besides those already described which can bring about pathological changes in the human body. Representatives of all four classes of the Protozoa have already been observed.

Of the **Rhizopoda** there occur in the intestine three amœbæ, known as the *amœba coli vulgaris, amœba coli mitis* (Roos, Quincke), and *amœba dysenteriæ* (Kartulis, Osler, Councilman, Lafleur, Kruse, Pasquale). The amœba dysenteriæ is certainly distinguishable from the other two forms, while the amœba coli vulgaris and the amœba coli mitis resemble each other very closely and may possibly be identical.

The **amœba coli vulgaris** is a harmless intestinal parasite occurring (according to Roos, Kruse, and Pasquale) not infrequently in the bowel.

Roos observed the *amœba coli mitis* in a case of chronic enteritis, the patient having always lived in North Germany.

The amœba coli mitis consists, according to Roos, in a protoplasmic cell-body 25 to 35 μ in diameter in its globular form, exhibiting slow motion and very frequently assimilating foreign bodies (Fig. 530, *a*)—for example, bacteria and crumbs of food. Besides the movable form there occur (according to Roos) also encysted globular forms, surrounded by a membrane with a double outline, and inclosing clear round vesicles in their interior (Fig. 530, *b*). No pathogenic properties are disclosed if they are fed to animals (cats).

The **amœba dysenteriæ** (identical with the amœba coli described by Loesch) measures in diameter, according to Roos, from 15 to 25 μ, but according to Kruse and Pasquale, from 10 to 50 μ. On the cell-body are recognizable a homogeneous ectoplasm and a changeable granular entoplasm, the arrangement of which varies with the form of the amœba (Fig. 531, *a*). On staining, a nucleus in the interior becomes visible. The cells are capable of active motion, and assume thereby the most varied forms (*d*). Very frequently they contain foreign bodies in their interior, especially red blood-corpuscles or fragments of them (*b*), or else several clear vacuoles (*c*). Roos says they may also become encysted (*e*).

According to the investigations of Koch, Kartulis, Kruse, and Pasquale, they are invariably present in the dysentery prevailing in Egypt, and are usually also demonstrable in the fæces. They have also been observed in cases of dysentery in Russia (Loesch, Massiutin), in America (Osler, Councilman, Lafleur, Lutz, Dock), in Germany (Roos), and in Austria (Kovács). According to the investigations of Kartulis, Councilman, Lafleur, Kovács, Roos, Kruse, Pasquale, and others, there is probably no reason to doubt that they are of some significance in the origin of certain forms of dysentery. But even then it is a question whether they are able to bring about morbid changes of themselves or only when acting in conjunction with bacteria; the fact that when occur-

FIG. 530.

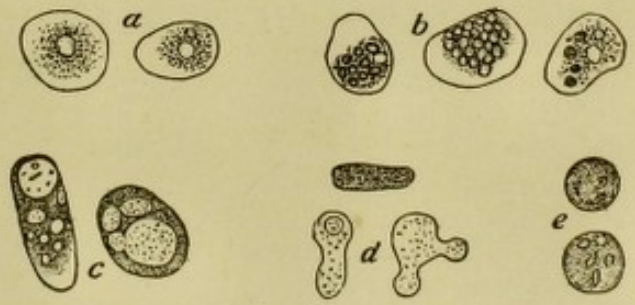


FIG. 531.

FIG. 530.—*Amœba coli mitis.* (After Roos.) *a*, Freely movable amœbæ; *b*, encysted amœbæ. Magnified 665 diameters.

FIG. 531.—*Amœba dysenteriæ* or *amœba coli felis.* (After Roos.) *a*, Amœbæ without any foreign contents; *b*, amœbæ containing blood; *c*, amœbæ with large vacuoles in their protoplasm; *d*, young forms; *e*, encysted forms. Magnified 665 diameters.

ring in the tissues they are invariably accompanied by bacteria may be considered as confirmatory of the latter theory.

The **dysentery due to amœbæ** is characterized by the occurrence of a hemorrhagic catarrh and the development of circumscribed ulcers with undermined borders. The amœbæ not only multiply in the intestinal mucous membrane, but, according to Councilman, Lafleur, Roos,

Kruse, and Pasquale, penetrate in even greater numbers into the mucosa and submucosa, and develop here great colonies, in the neighborhood of which the tissues become necrotic, even without any considerable quantity of exudation having collected. Following the perforation of the submucous centres of disease through the mucosa, there ensue ulcers with undermined edges, which, gradually enlarging, may attain a very considerable size.

If *abscesses of the liver* arise in the course of amœbic dysentery they contain not only bacteria, but also amœbæ, and it is to be considered that

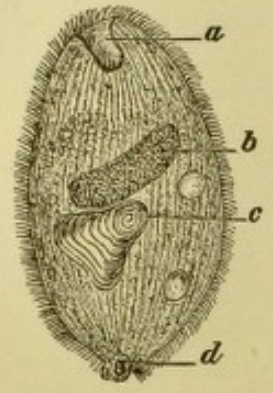


FIG. 532.

FIG. 533.

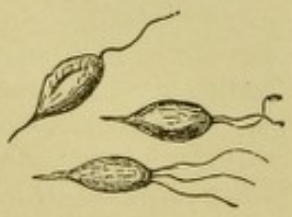


FIG. 534.

FIG. 535.

FIG. 532.—*Balantidium (Paramœcium) coli.* (After Claus.) *a*, Mouth; *b*, nucleus; *c*, a granule of starch which has been digested; *d*, a foreign body in the process of being expelled. Highly magnified.

FIG. 533.—*Cercomonas intestinalis.* (After Davaine.)

FIG. 534.—*Trichomonas vaginalis.* (After Kölliker.)

FIG. 535.—*Trichomonas intestinalis.* (After Zenker.)

the latter as well as the former are concerned in the disturbance of the liver-tissues.

The *amœba dysenteriæ is also pathogenic in cats*, causing, after being fed to them or introduced into the rectum, a rapidly progressing and frequently fatal dysentery which resembles exactly the amœbic dysentery occurring in man; in them, also, the amœbæ penetrate into the mucosa and submucosa.

Of the class **Infusoria** there occur both the flagellate and the ciliated varieties. Of the latter the best known is the **paramæcium** or **balantidium coli** (Fig. 532). This is a large infusorium, which is thickly covered with cilia; it occurs occasionally in the large intestine and the fæces. Of the flagellate Infusoria, the first to be mentioned is the **cercomonas intestinalis** (Fig. 533), a pear-shaped creature with a spinous process at the pointed end and a flagellum at the blunt end. It is found likewise in the intestine in catarrhal conditions, as in typhus and cholera cases. According to Bütschli and Perroncito, it is identical with the **megastoma entericum** of Grassi and the *megastoma intestinale* of Blanchard, and partially passes off in the fæces in an encysted condition (Perroncito), especially if there is no diarrhœa present. It also occurs in mice, rats, cats, dogs, sheep, and rabbits (Grassi), and fastens itself to the surface of the intestinal epithelia.

Kannenberg found cercomonas in the sputum in gangrene of the lung. There occurred in conjunction with the foregoing the **monas lens**, a globular infusorium with a flagellum. Streng communicates a similar observation.

Of the **Trichomonas**, an oval infusorium with several flagella and a comb-like, undulating fringe mounting its full length, there occurs one species in the vagina—the **trichomonas vaginalis** (Fig. 534)—and one in the intestine—the **trichomonas intestinalis** (Fig. 535).

Marchand found trichomonadidæ with four filiform flagella and an undulating fringe in the urine of a man. These are probably identical with the *trichomonas vaginalis*, in which four filiform flagella also occur. Miura also furnishes a similar observation. Grimm saw whip-infusoria in a liver-abscess and an abscess of the lung. Lindner found infusoria belonging to the ciliated class in the crusts of an itching eczema of the scalp.

Von Leyden and Schandinn[1] found in the fluid of two cases of ascites, which developed as a consequence of a malignant abdominal tumor, an amœba composed of colorless, gelatinous cells, which stretched out pseudopods, exhibited a hyaline entoplasm and a granular ectoplasm, and as a rule lay together in nests.

§ 208. Of the **Sporozoa** or **Gregarinæ** which occur as parasites in man, the **Coccidia** must first be mentioned. In the young state they exist as non-capsulated occupants of epithelia. After their growth has ceased they become inclosed in a shell. In this condition they abandon their resting-place, and generally their host, and develop from their contents spores containing granular masses and remarkable rod-like embryonal forms. The spores are spherical or ovoid.

The **coccidium oviforme** (Fig. 537) is a parasite of the intestine and bile-ducts, occurring especially in rabbits. In some cases they have been observed in man. Künstler and Pitres found coccidia in man in the exudation in a case of pleuritis, and Podwyssozki found them in the liver.

In the liver of rabbits the invasion of coccidia leads to the formation of white nodules, which may reach the size of a hazelnut, and are known as *coccidia nodules*. The nodules contain a white or yellowish-white mass, and consist principally of dilated bile-passages, the inner wall of

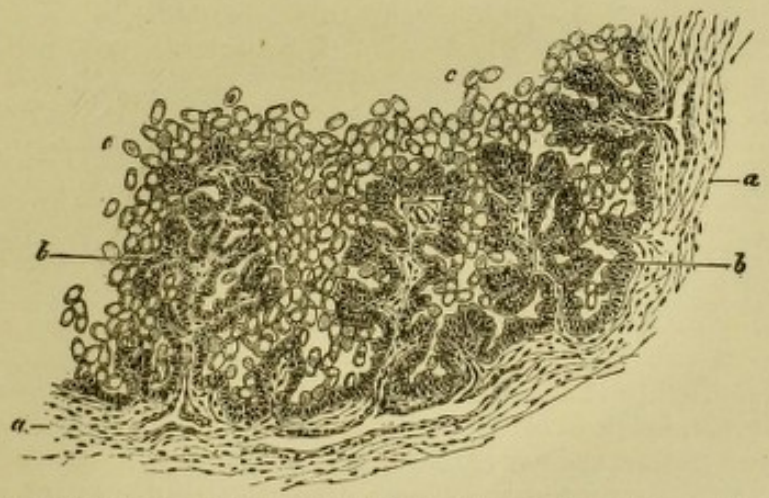


FIG. 536.—Section through the wall of a dilated bile-duct, filled with coccidia and the seat of papillary growths. This condition was found in a rabbit's liver that was studded with coccidia-nodules. (Müller's fluid; hæmatoxylin; eosin.) *a*, Connective tissue; *b*, branched papillary growths filled with epithelium; *c*, coccidia. Magnified 25 diameters.

which is more or less richly furnished with papillary growths (Fig. 536), and the lumen of which is filled with immense numbers of coccidia.

The coccidia exist in the bile-ducts partly in the form of a shellless protoplasmic structure, partly in the form of encapsulated bodies. The smallest coccidia (presumably to be regarded as early forms) exhibit a

[1] Leydenia gemmipara, *Sitzungsbericht d. k. Akad. d. Wiss.*, Berlin, 1896.

coarsely granular protoplasmic formation (Fig. 537 *a*, *b*), in the interior of which now and then a nuclear appearance (*a*) is recognizable. The larger forms exhibit on their outer surface regularly arranged granules (*c*, *d*), which stain deeply with hæmatoxylin. The encapsulated forms occur as oval, double-contoured, clear-looking bodies (*e*, *f*, *g*, *h*), in the interior of which lies a variously shaped mass with a variable amount of granular matter, the latter never taking up but a portion of the space in the capsule. According to R. Pfeiffer, the granular coccidia which are not encapsulated may split up in the animal body into a great number of *sickle-shaped germs*, and in this manner increase in number. There appear at one pole, whose position is indicated by a round mass (the nucleus), radiating septa, which wedge their way through the plasma. Probably the sickle-shaped germs become transformed into small amœboid masses of protoplasm.

Provided the encysted coccidia reach the outer world, there may arise, under suitable conditions, inside the protoplasm (which has drawn itself together like a ball) (Fig. 538, *b*) four *sporocysts* or *sporoblasts*

Fig. 537

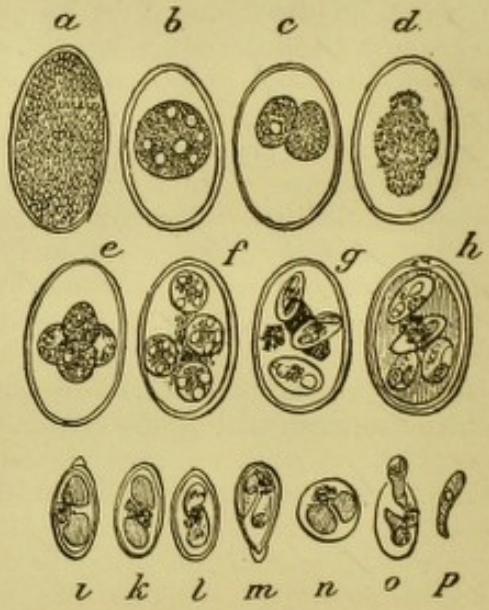


Fig. 538.

Fig. 537.—Coccidia from the bile-ducts of the rabbit's liver shown in Fig. 536, in various stages of their development. (Müller's fluid, hæmatoxylin.) *a*, *b*, Small, coarsely granular early forms; *c*, *d*, larger forms with darkly stained peripheral granules. *e*, *f*, *g* *h*, oval encapsulated forms, the granular protoplasm of which—partly coarse and partly fine—fills out only a part of the capsule. Magnified 400 diameters.

Fig. 538.—Development of spores in encysted coccidia. (After L. Pfeiffer.) *a*, Mature encapsulated parasite with evenly distributed protoplasm; *b*, protoplasm collected together into a ball; *c*, *d*, *e*, *f*, development of four sporocysts, a protoplasmic residue remaining; *g*, *h*, developing, *i*, *k*, *l*, *m*, *n*, fully developed sickle-germs inside the sporocysts; *o*, sickle-germ leaving sporocyst; *p*, free sickle-germ. Magnified 750 diameters.

(*c*, *d*, *e*, *f*). Inside these sporocysts develop formations which are primarily globular, later oval, and which at a still later date produce two sickle-shaped germs apiece (*g*, *h*, *i*, *k*, *l*, *m*, *n*, *o*, *p*).

To the *coccidia* probably belong also certain **parasites** which occur in the epidermis in man, and here produce peculiar growths known as **epithelioma contagiosum** (Fig. 539). In its fully developed condition the growth consists of a nodule the size of a small pea or larger, which projects above the surface of the skin, shows a small depression in the centre, and possesses a waxy lustre.

In the section there may be recognized an irregular epithelial growth (Fig. 539, *d*) with a central orifice opening outward (*g*)—that is to say, a formation which recalls a gland, and, indeed, is frequently considered as a hypertrophic sebaceous gland, but which is only an independent new growth of epithelium brought about by the parasites. These

develop inside the epithelial cells of the irregular growth (*e*), but are pushed toward the central orifice of the new growth by the epithelial

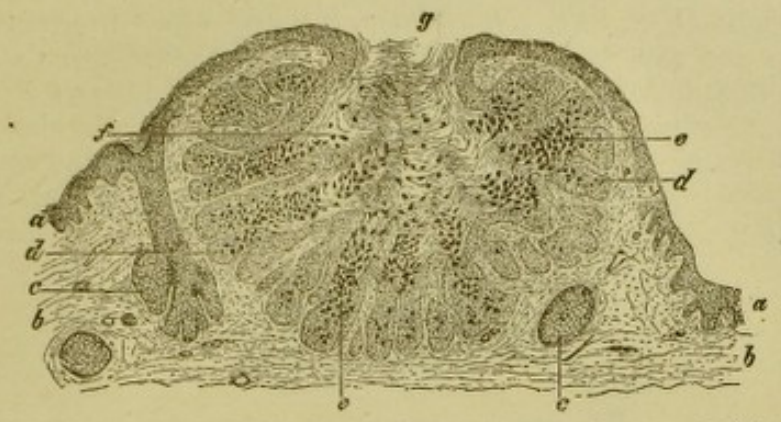


FIG. 539.—*Epithelioma contagiosum*. Section through greatest diameter. (Müller's fluid; hæmatoxylin.) *a*, Epidermis; *b*, connective tissue; *c*, sebaceous gland; *d*, gland-like epithelial growths; *e*, parasites; *f*, horny cells mingled with parasites; *g*, duct filled with horny epithelium and parasites. Magnified 15 diameters.

cells behind (*f*), and here they lie in a meshwork of cast-off and horny epithelial cells.

Representing the earliest stage of development of the parasites, there arise in the epithelial cells small protoplasmic bodies (Fig. 540, *a*, *b*), the borders of which are only with difficulty to be distinguished from the cell-protoplasm; occasionally, however, they contain in their interior small distinct granules, and become through them more distinct. Later on, their size increases, until finally they completely fill up the epithelial cells (*c*, *d*, *e*), so that the nucleus is pushed aside. At the same time the granules on the inside increase in number (*c*) and grow into larger bodies, so that the parasite finally becomes divided into a greater or less number of finely granular structures (*d*, *e*, *f*) lying in a finely granular network. During this time the cell-nucleus is destroyed.

The epithelial cells which inclose parasites early develop a distinct membrane, which grows more and more distinct and surrounds the parasites. Those parasites which have been expelled from the cells form oval bodies which appear to be inclosed in a capsule and present a homogeneous appearance. They stain deeply with hæmatoxylin.

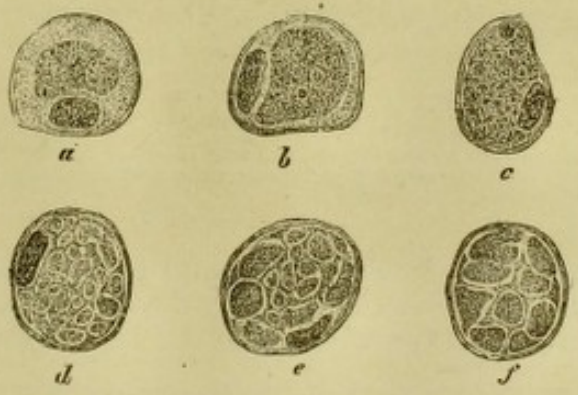


FIG. 540.—Parasites of *epithelioma contagiosum* in various stages of development, lying inside epithelial cells. (Müller's fluid; hæmatoxylin.) *a*, *b*, Epithelial cells inclosing a protoplasmic body inside of which lie single large granules; *c*, an epithelial cell almost completely filled with parasites; *d*, *e*, *f*, parasites which completely fill the cell they occupy, and which have become divided into numerous separate bodies lying in a granular network; the cell-nucleus has been destroyed in *f*. Magnified about 500 diameters.

The contagious epitheliomata may appear in great numbers in one and the same individual, and several persons living together may be either simultaneously or successively attacked. The spread of the disease may then be referred to contagion.

Our knowledge of the significance of the so-called "**sacs of Miescher**"

is still scanty. They are sac-shaped structures which occur not infrequently in the muscles of swine, cattle, sheep (especially in the œsophagus), and in mice. They differ in size (Fig. 541, *A*, *B*) and lie inside the muscle-cells (Fig. 541, *B*). In the fully developed parasite the contents of the sac are differentiated into single segments defined by a membrane (Fig. 541), and these in turn inclose globular (*A*, *C*) or kidney- and sickle-shaped bodies (*D*, *E*). The parasite is classed among the *Sarcosporidia*. The separate segments are known as *sporocysts* or *sporoblasts*, since in their interior the kidney- or sickle-shaped *spores*

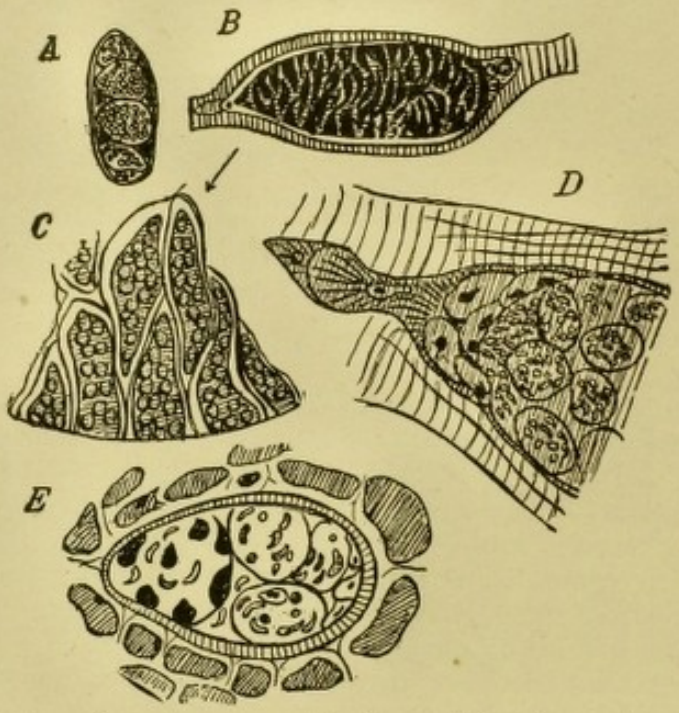


FIG. 541.—Miescher's sacs in various phases of development, taken from swine and sheep. (After L. Pfeiffer.)

A, Sarcospore with four sporocyst globules, taken from the cardiac muscle of a sheep. Magnified 120 diameters.

B, Sarcosporidia-sac in a striped muscle of the swine. Magnified 120 diameters.

C, Terminus of a sac with sporocysts, the latter containing round spore-cells. Magnified 500 diameters.

D, Terminus of a sac containing both undeveloped and mature sporocysts. At the left end, a pseudopod shaped like a cloak and covered with hairs. Magnified 500 diameters.

E, Transverse section through a sac with sporocysts, containing sickle-shaped spore-cells. Magnified 500 diameters.

arise (*Rainey's bodies*), and from these latter, under suitable conditions, new Miescher's sacs may develop (Pfeiffer). Ingestion of meat containing sarcosporidia is not dangerous for human beings.

The last few years have produced a very unusual number of reports of *parasites said to belong to the Sporozoa or Gregarinæ*, and numerous authors have considered that they were justified in ascribing various morbid processes, chiefly pathological epithelial formations, and of these more especially cancer, to the presence of gregarinæ. It may, however, be remarked that only a very small part of what have been described as parasites are really to be looked upon as such; so that, so far as man is concerned, the occurrence of parasitic gregarinæ is restricted to a few distinct diseases.

So far as *carcinoma* is concerned, notwithstanding the great number of works on the subject (so numerous that they can scarcely all be perused—compare § 128), the proof is by no means forthcoming that protozoa, especially gregarinæ, are present inside the epithelial growths, or are to be considered as the cause of the latter. All the appearances described, even the sickle-shaped formations and those provided with a sort of capsule, which have been seen in cancer-cells and considered convincing, permit of another explanation, and, in my opinion, are to be interpreted partly as changed nuclei, partly as altered protoplasm of the cancer-cells, partly as products excreted by the cells, and,

finally, partly as a product of cell-fusion, or of the assimilation of leucocytes by the cancer-cells.

The disease described by Darier as *psorospermose folliculaire végétante*, and referred by him to the presence of sporozoa, is very probably only a skin affection characterized by a pathological keratosis (keratosis follicularis of White), in which little horny plugs and pegs are developed one by one in the epithelium of the skin of some part of the body, the cutis exhibiting mild inflammatory symptoms. According to Buzzi, Miethke, Rieck, Krösing, Petersen, and others, the *corps ronds*, described by Darier as parasites, contain keratohyalin and eleidin—that is to say, substances which occur in horny cells, but not in gregarinæ.

Paget's disease is a process which spreads from the nipple, commencing with an inflammation resembling eczema and leading to superficial ulceration, said to finally end in a cancerous infiltration of the skin. It has been referred by Darier, Wickham, Malassez, and others to a parasite—a sporozoön which multiplies in the epithelial cells. It is, however, an eczema arising from other causes, and finally leading to cancer, or else a primary cancer accompanied by inflammatory changes, in which characteristic alterations occur in the epidermis—namely, swelling up of the protoplasm and nuclei, and development of vacuoles; there also develop some new growths, which present appearances that remind one strongly of parasites.

I consider the bodies found in molluscum as parasites (as already appears from the main text), though this opinion is opposed by various authors (Kromayer, Hansemann, Török, and others). The growths have totally different characteristics from those which are described as having been found in cancer.

Rosenberg reports the discovery of sarcosporidia in the muscle of the human heart. Kartulis made a similar discovery in an abscess of the liver and in the abdominal muscles of a Sudanese.

Pisenti, Silcock, Eve, Bland Sutton, and Jackson Clarke have pointed out the possibility that the cysts occurring in the descending urinary passages, in *ureteritis cystica*, may be of parasitic origin. Lubarsch and Aschhoff have expressed themselves as opposed to this theory. From the investigations of von Kahlden, it has nevertheless been made very probable that the ureteritis cystica is really caused by sporozoa.

According to Hess and Guillebeau, coccidia may occasion diarrhœal diseases of the intestine in young cattle.

Guarneri,[1] L. Pfeiffer,[2] E. Pfeiffer,[3] and others[4] consider the small, easily stained bodies, surrounded by a border of transparent substance, which are found in the epithelium in variola and vaccinia at the beginning of the disease, to be protozoa, and Guarneri has named the supposed parasites cytoryctes vaccinæ. Nevertheless, the parasitic nature of these organisms is not wholly proven. They may be merely products of the generation of epithelial nuclei, or wandering leucocytes (Salmon[5]).

According to Lindner, the organisms discovered by Rainey represent stages of dedevelopment of stemless vorticellæ.

§ 209. Through the investigations of Laveran, Marchiafava, Celli, Golgi, and others, it may be considered proved that the *cause of malaria* is a parasite belonging to the Protistæ, which has been named by Marchiafava and Celli the **plasmodium malariæ**, and which at the present time is commonly known by this name. The parasite exists in the blood of malaria patients in various forms, chiefly inclosed in cells; and, according to the observations of Golgi, Celli, Marchiafava, and others, a certain connection may be traced between the number and stage of development of the plasmodia and the attacks of fever. The parasites run through many stages of development in the interval between the separate attacks of fever, the stages (according to the authors mentioned) being different in the febris quartana, the febris tertiana, and the febris quotidiana; at the same time the parasites of the various

[1] "Ric. sulla patogenesi ed etiol. dell' infez. vaccinica e variolosa," *Arch. per le Sc. Med.*, xvi., 1892; and "Ulter. ric. sulla etiol. dell' infez. vaccinica," Pisa, 1896.

[2] "Die Protozoen als Krankheitserreger," Jena, 1895; "Vaccinecontagium," *Zeitsch. f. Hyg.*, 23. Bd., 1896.

[3] "Züchtung des Vaccineerregers," *Centralbl. f. Bakter.*, xviii., 1895.

[4] Compare Wasielewski: "Zelleinschlüsse bei Vaccineimpfungen," *Centralbl. f. Bakt.*, xxi., 1897.

[5] "Parasites de la vaccine et de la variole," *Annales de l'Institut Pasteur*, 1897.

forms of fever exhibit certain differences in their physiological characteristics.

The development and increase of the plasmodia take place in the interior of the red blood-corpuscles, where, first of all, small, colorless amœboid bodies appear (Fig. 542, *a*). In the *febris quartana* the further development is inaugurated by an enlargement of the small amœboid beginning forms (Fig. 542, *a*, *b*, *c*, *d*, *e*,) so that the red blood-corpuscles become more and more filled with them. Simultaneously pigment granules, which are derived from the coloring-matter of the blood, make their appearance in the interior of the plasmodia. When the plasmodia attain a certain size the pigment granules collect in the centre, while at the same time a radiating cleavage sets in, so that daisy-like figures are produced (*f*, *g*). These consist of a pigmented centre and radiating petals devoid of pigment. Later on, the petals become detached from the central pigmented portion and assume a circular shape (*h*).

According to Golgi, this development and segmentation of the plasmodia in febris quartana are completed in three days, and the attacks

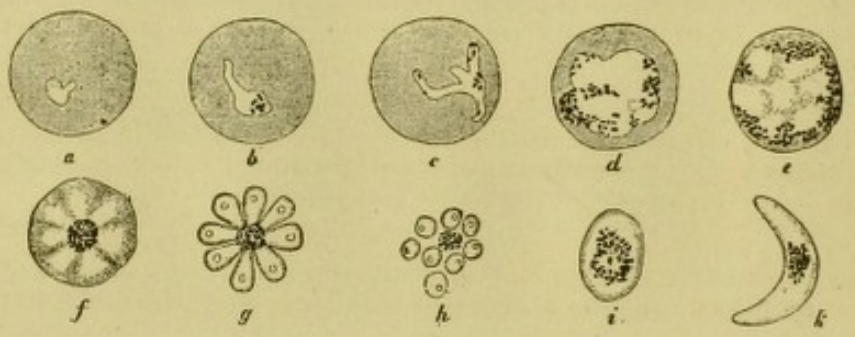


FIG. 542.—*Plasmodium malariæ* of a febris quartana in various stages of development. (After Golgi.) *a*, Red blood-corpuscles with a small, non-pigmented plasmodium; *b*, *c*, *d*, *e*, pigmented, variously sized plasmodia inside of red blood-corpuscles; *f*, plasmodium at the commencement of segmentation, with pigment collected in centre; *g*, segmented plasmodium; *h*, plasmodium divided into separate globules; *i*, *k*, two differently shaped, free plasmodia.

of fever set in at the time when the plasmodia are dividing. The red blood-corpuscles which are occupied by the plasmodia perish; the young plasmodia just formed by cleavage again penetrate the blood-corpuscles, whereupon their further development begins anew. The pigment granules formed by the plasmodia, some free, others inclosed in cells, are carried out of the circulating blood into various organs, especially the spleen, liver, and marrow of the bones.

In *febris tertiana* the cycle of development is complete in two days (Golgi). The plasmodia developing within the red blood-corpuscles (Fig. 543, *a*, *b*, *c*, *d*) show much livelier motion and at the same time lead very much more rapidly to a decoloration of the red blood-corpuscles than in the febris quartana, so that the latter are already decolorized on the first day of intermission of the fever, while the plasmodia are still small. The protoplasm of the plasmodia of the febris tertiana is, furthermore, more delicate and less sharply defined, and their pigment granules are also smaller. In its division each plasmodium splits up into from fifteen to twenty new cells (*e*), while in the quartan fever only from six to twelve develop. Finally, the red blood-corpuscles in the febris quartana are mostly crenated, while in the tertian form they retain their shape. According to Celli and Marchiafava, the formation of spores not infrequently occurs prematurely, from five to ten spores de-

veloping inside a red blood-corpuscle. According to Ziemann, the parasite of tropical fevers is smaller than that of European tertian fevers.

In *febris quotidiana* (late-summer and fall fever, febris subcontinua, perniciosa) the parasite (Fig. 544) consists, according to Celli and San-

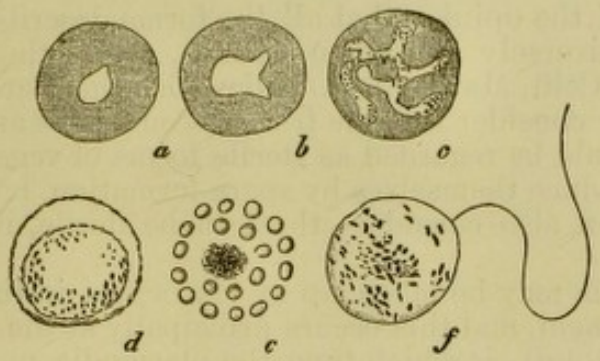


FIG. 543.—*Plasmodium malariæ* of a febris tertiana in various developmental stages. (After Golgi.) *a*, First step in development; *b*, *c*, enlarged plasmodia with pseudopods; *d*, plasmodia before the formation of spores—blood-corpuscle decolorized; *e*, formation of spores; *f*, free parasite with flagellum.

felice, of small structures exhibiting lively amœboid movements inside the red blood-corpuscles (*a*, *b*); shortly before each new febrile attack they become pigmented and round (*c*), and then divide into spores (*d*).

According to Celli and Marchiafava, nuclear bodies may be demonstrated in the protoplasm in all endoglobular hæmatozoa of malaria, in certain stages of their development. According to Ziemann, the first change which occurs in sporulation is a splitting-up of the chromatin into small masses, and then this is followed by a subdivision of the cell-body. As a result of these changes each small mass of chromatin is surrounded by a zone of protoplasm.

Besides the forms already described, which are considered by Italian authors as typical, there occur in the different malarial diseases in addition both endoglobular and free parasites, either oval or sickle-shaped (Fig. 542, *i*, *k*, and Fig. 544, *e*, *f*), sometimes provided with flagella

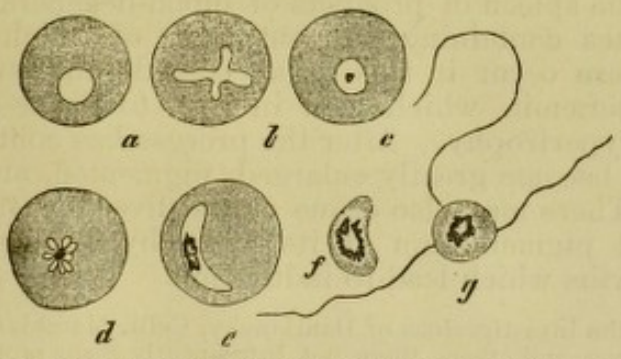


FIG. 544.—*Plasmodium malariæ* of a febris quotidiana in various stages of development. (After Celli and Sanfelice.) *a*, First step in the development; *b*, plasmodia with pseudopods; *c*, plasmodium which has become round and provided with pigment before segmentation; *d*, formation of spores; *e*, intraglobular crescent form; *f*, *g*, free plasmodia.

(Fig. 543, *f*, and Fig. 544, *g*), at other times having cast these off; and all these forms, especially described by Laveran, have been since confirmed by the Italian authors.

The significance of all the various forms of parasites which have been observed in malaria has not yet been fully solved; nevertheless, from

the preceding statements it may be considered settled that the endoglobular hæmatozoa destroy the red blood-corpuscles and thus manufacture pigment out of the coloring-matter of the blood; and it may also be assumed that their presence gives rise to the morbid symptoms of malaria.

Laveran is of the opinion that all the forms described belong to one and the same diversely shaped sporozoön, while the Italian authors (Golgi, Canalis, Celli, Marchiafava) believe that there are various malaria parasites. They consider that the free crescent forms and the plasmodia with flagella should be regarded as sterile forms of vegetation which are not able to reproduce themselves by spore-formation, but sooner or later perish. Ziemann also considers them to be sterile, inasmuch as they lack chromatin.

The plasmodia may be taken up by leucocytes in the various stages of their development, and this occurs principally at the beginning of the febrile attack (Golgi), at which time the plasmodia undergo segmentation. The leucocytes may contain plasmodia, accordingly, either entire or segmented, or indeed only the pigment masses.

The particular varieties of plasmodia correspond, according to the reports, to particular forms of fever, but yet it must be noticed that the febrile forms designated as febris quotidiana, subcontinua, and comitata may also be caused by the existence, in the blood, of plasmodia of the tertian or quartan form in various generations, so that part of the parasites reach spore-formation each day. In this way arise quotidian forms of fever which are to be considered as double tertian (quotidiana triquartanaria).

According to Golgi, there is also a malarial fever (summer and fall fever) the parasites of which develop not in the blood, but in the internal organs, especially in the marrow of the bones.

Within the organs of patients who have died of malaria there are found, first of all, the malaria parasites containing pigment, and lying more or less intravascularly. If the blood has undergone great destruction there will also be found pathological deposits of iron in the spleen, liver, medulla of the bones, and the kidneys. In consequence of the deposition in the spleen of products of blood-degeneration, and also of malaria parasites containing pigment (part of which are inclosed in leucocytes), there occur in this organ considerable swellings, accompanied by hyperæmia, which lead in part to tissue-degeneration, in part to tissue-hypertrophy. After the process has continued some time the spleen may become greatly enlarged, pigmented, and much changed in structure. There may also ensue in the liver, on the one hand, degeneration and pigmentation of its parenchyma, and, on the other hand, new growths which lead to induration.

According to the investigations of Danilewsky, Celli, Marchiafava, Grassi, Feletti, Crookshank, Laveran, and others, there not infrequently occur protistæ in the blood of mammalians and birds, as well as in that of cold-blooded animals, and among them some which resemble the *plasmodium malariæ* very closely and undergo a similar cycle of development inside the red blood-corpuscles. The closest resemblance of characteristics is seen in the hæmatozoa of birds (pigeons, owls, magpies, and larks); but even these show some variation, so that they are not the same form of parasite as is observed in man.

According to Celli, only the spores can live in the blood-plasma in man, while the other grades of development, in case they leave the blood-corpuscles for the plasma, are destroyed, forming flagella, swelling up, and becoming vacuolated. On the other hand, the hæmatozoa of birds can exist in the plasma for a certain length of time, and the hæmatozoa of the cold-blooded animals, whose development progresses very slowly, live

for a considerable period of time free in the blood ; and these forms which exist free in the blood are the ones which have been described as special parasites (drepanidium).

The systematic classification of the plasmodia of malaria, and the protozoa which are nearly related to them, is not yet arranged. Most probably they are to be classified with the Sporozoa ; and since the forms which occur in the muscles have received the name of sarcosporidia, the parasites of blood-corpuscles, belonging to the class last considered, might be called hæmosporidia (Danilewsky).

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