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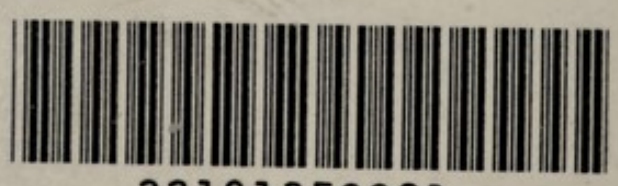

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GREEN'S
MANUAL OF PATHOLOGY
AND
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TWELFTH EDITION

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PREFACE TO THE TWELFTH EDITION

THE appearance of this, the twelfth edition of "Green's Manual of Pathology," has been somewhat delayed owing to the war. The book has been revised throughout, and some parts entirely re-cast. Thus, the chapter on Diseases of the Blood has been re-written, and the section on Immunity has been enlarged, and now occupies a separate chapter.

Ninety-eight new illustrations, including four plates in colour, have been inserted, and all but four of these have been specially drawn for this edition. Many of the older drawings have, in consequence, been omitted.

We wish to acknowledge our indebtedness to Messrs. Baillière, Tindall and Cox for the interest which they have taken in the preparation of this new edition, and for their ready acquiescence in the extensive alterations and additions which have been made, especially in regard to the illustrations. Our thanks are also due to certain authors for permission to reproduce figures from other works, or from original articles. These are acknowledged individually where they occur.

W. C. B.
W. W. C. T.

October, 1917.

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A MANUAL OF PATHOLOGY

PART I

GENERAL PATHOLOGY

CHAPTER I

INTRODUCTION

PATHOLOGY is the branch of science which deals with the Nature and Causation of Disease. Just as anatomy and histology investigate the naked-eye and microscopic structure of the healthy body, while physiology examines the functions of the parts revealed by them, and studies the chemical processes which constitute healthy life, so in the realm of disease we have corresponding divisions—morbid anatomy, morbid histology, and pathology. At post-mortem examinations we note all the naked-eye departures from normal anatomy; with the microscope we discover the finer changes to which these departures are due; and by experimental methods and bedside observations we investigate the causes of the abnormal structure and function, their mode of action, and the nature and sequence of the disturbances which they produce.

All complex organisms can be reduced to very simple elements—the *cells* and the *intercellular substances* to which they give origin. Among the latter we must include the fluids with which the cells are bathed, containing both the nutrient materials for the cells and the excretory products formed by the latter. It is now universally believed that the individual *cell* is the seat of nutrition and function.

NATURE OF DISEASE.

In pathology we have to deal not with new tissue-cells and functions, but simply with disturbances of those which normally exist. The cells met with in morbid formations can nearly always be shown to correspond with forms which occur in health at some stage of development; and even the products of morbid degeneration of cells seem, as a rule, to have physiological prototypes. In other words, pathological processes differ only quantitatively from allied physiological processes. New forms of cell-life, both animal and vegetable,

are frequently found within the body ; but these are parasitic, introduced from without, and are *causes*, not *products*, of disease.

In the study of living things we have to consider two factors—the living organism, and its surroundings or environment. The latter includes air to breathe, water to drink, food to assimilate, and warmth, light, and other physical conditions necessary to existence. An organism which is suited to its surroundings, and readily reacts to changes in the latter in such a manner as to prolong its own existence, is said to be *healthy*. By the study of many individuals we arrive at a general idea of the phenomena which constitute healthy life : this is not an exact standard, but admits of a certain range of variation in the directions both of excess and of defect. Any departure from the normal response to stimulus which goes beyond this range constitutes disease. A *definition of disease* is not easy to construct, but it may for practical purposes be roughly defined as any state of a living organism in which it fails to respond normally to the conditions of its environment ; or, in other words, in which there is a failure of some of its normal activities.

The existence of disease is manifested to outside observers by perceptible alterations in the condition of the sufferer, and to the consciousness of the latter himself, in the case of man, by disturbed sensations ; these objective and subjective phenomena constitute the signs and symptoms of disease. Disturbances which attract the attention of the sufferer himself are usually termed *symptoms ;* those which are discovered by the observation of others are called *signs*. As instances of the former we may mention pain, giddiness, and nausea ; of the latter, hardness or swelling of a part and abnormalities in the sounds which are heard on listening over the surface of the chest, or which are elicited by tapping upon it with the fingers. There is no essential difference between the two classes of phenomena ; many disturbances are perceptible to both sufferer and observer, such as palpitation of the heart, vomiting, or staggering gait.

Experience has shown that the signs of disease tend to occur in definite groups, or, in other words, that many different individuals suffer from similar combinations of perverted vital activities. These groups of symptoms come to form distinct ideas in the minds of observers, and each group is called a *disease*, and is labelled with a distinctive name. Thus, the sudden onset, in a previously healthy person, of pain in the side, shivering, rapid breathing, and fever forms a group of phenomena sufficiently characteristic, and recurring with sufficient frequency to attract attention. In course of time this group was recognised as " a disease " distinct from other groups of symptoms, and received the name of *pneumonia*. But further observation showed that, in persons who died after presenting such symptoms, some portion of one or both of the lungs was altered in structure, so as to appear solid instead of spongy, and this underlying physical condition came to form part of the idea of the disease. Indeed, in conditions in which well-marked structural alterations

are found to exist, these form a more important part of the connotation of the name applied to the condition than do the external manifestations, which are liable to vary considerably in individual instances.

As knowledge advanced still farther, constant precedent conditions or *causes* became recognised as associated with certain diseases; thus it was noted that exposure to cold often preceded an attack of pneumonia, while in recent years it has been discovered that many diseases are the effects produced upon the body by the invasion of minute vegetable or animal organisms, which grow in the fluids of the living tissues, and produce poisons capable of injuring the component cells. Different parasitic organisms are found to be responsible for different diseases. The question then arises, whether we are to include in the definition of a disease the cause which produces it—whether, for instance, the term "diphtheria" should be limited to cases of sore-throat in which a certain bacillus is found, or should continue to be applied to all cases of sore-throat in which there is formation of a false-membrane in the fauces. The tendency at the present day is in the direction of defining diseases according to their causes rather than according to their clinical features; but it is well to recognise that by so doing we are altering the connotation of well-established medical terms.

Varieties of Disease.

Distinguishing, as we have done, the living organism from its surroundings or environment, we see at once that causes of disease may be roughly classified into (*a*) those arising out of defects in the original constitution of the individual, or **hereditary** disease; and (*b*) those produced by abnormal or hurtful external circumstances, or **acquired** disease. Thus, on the one hand, a person may be born with gross or minute structural defects, rendering some organ incapable of performing its normal function; or certain of his tissues may be defective in that they rapidly degenerate or wear out. On the other hand, injury may be inflicted by external agents—by cold, heat, or mechanical violence, by poisons taken in with the food, or by the entrance of parasitic organisms. When, however, we look a little more closely into the matter, we find that no definite line can be drawn between these two classes of disease. Thus, a parasitic organism may be unable to establish itself in the body and induce disease except in the presence of some hereditary defect in resisting-power on the part of the individual; while those who are the subjects of manifest hereditary weakness may be able to survive if their surroundings are modified—as premature babies may be reared in artificial incubators, or "bleeders" may suffer no inconvenience if protected from all possible sources of mechanical injury—the congenital defect consisting in a failure of these organisms to adjust themselves to ordinary external conditions, which in these cases are actually injurious.

The two classes of diseases thus distinguished must be considered in rather more detail.

Inherited Disease.—The tendency to *inherited* disease either exists in the ovum at the commencement of development, or is acquired by the ovum in fertilisation ; tendencies formed later are obviously *acquired.* As in normal development certain organs manifest their inherited tendencies many years after birth—*e.g.*, the development of the female generative system at puberty and its atrophy at the menopause—so inherited tendencies to disease may not show themselves until late in life, as is the case in cancer of the breast or of the uterus. It is possible that in many cases the same unrecognised conditions which induced in a parent the morbid tendency handed down, continue to act on the offspring, until—with or without some obvious exciting cause—the disease becomes evident. We cannot say when this tendency to disease begins ; it may have been slowly gaining strength for generations. The fact that no progenitor had the disease in question, if he or she lived well past the age at which such disease usually manifests itself, shows simply that the causes had not acted long enough or with sufficient energy to produce it. It is important to recognise that even inherited disease has its starting-point in conditions external to the cells of the body.* We must also bear in mind that every individual is the offspring of two parents, from both of whom characters are inherited. Tendency to disease in one parent may either be neutralised by opposing characters in the other parent, or may be reinforced if identical peculiarities exist on both sides.

With regard to the actual mode in which disease is inherited, it is in some cases possible that the poison, the actual cause of the disease, is present in the ovum or spermatozoon, as has been shown to be the case in the silkworm disease (Pasteur). But how diseases and tendencies to disease which are not due to any specific poison are handed down, we know no more than how it is that children inherit the features of their parents.

Acquired Disease.—Diseases occurring in an organism or part possessed of normal vital energy must necessarily be the result of external conditions. The chief causes of acquired disease are: mechanical injuries, extremes of heat and cold, alterations in the pressure of the atmosphere, electrical shocks, defective food, lack of air and sunlight, mineral and vegetable poisons, and parasitic organisms. In pathology the distinction popularly drawn between " injury " and " disease " cannot be maintained.

Disease may be acquired during intra-uterine life—*e.g.*, variola, syphilis, tuberculosis, the infective agent passing from the mother to the fœtus by the blood-stream.

General and Local Disease.—The complete healthy life of a cell consists in the perfect performance of all its functions. For this it is necessary not only that its structure and vital energy should

* It is not at present clear whether any diseases constitute " variations " or " mutations," such as occur without ascertainable exciting causes as characteristics of living germinal matter.

be normal, but that the nutriment which it receives should be sufficient and suitable, and that its surrounding conditions—pressure, temperature, and connections with other tissues—should be normal. Failure in any one of these will lead to defective action or death of the cells with resulting disease of the organism as a whole.

Any change in external conditions acting upon a unicellular organism would probably affect every particle of its substance and modify all its functions; all its diseases would therefore be *general*. But multiplication of cells and specialisation of functions in the higher animals enable abnormal conditions to act upon certain groups of cells, and to disturb their functions without affecting—primarily, at least—those of other groups. We thus get *local* disease, and the great majority of diseases belong to this class.

Disease affecting *primarily* one part only may be followed by *secondary* affections of other organs; indeed, it is probably impossible for any "local" disease to exist without some disturbance of the general economy, though this may be so slight as to escape the notice of observers. As an instance of a primary local disease followed by secondary general disturbance, we may quote tuberculosis of the suprarenal bodies (Addison's disease); destruction of these glands is followed by pigmentation of the skin and vascular disturbance, with rapidly fatal result. Many diseases, apparently primary, are in reality secondary to other lesions due to ill-recognised causes. Thus, myxœdema, the condition arising from defect of thyroid secretion, is in reality a secondary affection, the primary disease being atrophy of the thyroid gland, arising from unknown causes; and paralysis caused by embolism of a cerebral artery is secondary to some affection of the heart.

Structural, Organic, and Functional Disease.—A disease is referred to an organ or tissue during life by its symptoms and by its physical signs; and, after death, the localisation is justified by the discovery, in that part, of corresponding structural changes. This is *organic* disease. Diseases in which no visible or chemical change has been found, are sometimes classed as *functional;* the belief being that in them the functions of certain cells are abnormally performed, without any structural change. Very brief reflection shows that this conception involves an impossibility, since the function of an organ or cell is merely alteration of its structure—gross or minute—in response to stimulus; consequently the same structure must, under identical conditions, always perform the same function. "Functional disease" is therefore a term which merely denotes morbid conditions of which the underlying structural (molecular) changes have not been discovered.

Ætiology of Disease.

The causes of disease are often divided into two classes—*Predisposing* and *Exciting*.

In so far as this division represents any useful distinction, and

is not a mere survival of scholastic logical subtleties, it serves to separate causes of disease into: (1) conditions which act upon the living organism so as to render it susceptible to outside agents, and (2) those agents themselves. Thus, starvation or overwork may render a person susceptible to attack by a parasitic organism which would otherwise be unable to settle in his tissues and cause disease. In discussing the subject of immunity, we shall have occasion to consider the mode of action of such predisposing causes. It is only in reference to diseases produced by the action of parasites that the distinction of "predisposing" and "exciting" causes appears to have much meaning. The term **predisposing** is, however, applied to certain natural conditions of the body which influence the occurrence of morbid processes. Chief among these are Age, Sex, and Heredity.

Age.—The special liabilities of *childhood* are to some extent explained by supposing that the power of resisting injury, which all cells possess, is not fully developed until adult age: a condition of stable equilibrium has not been attained. Further, growing tissues are liable to certain affections which do not occur in adult cells—*e.g.*, rickets. In *old age* the vital powers are wearing out and degeneration is occurring.

Sex.—The existence of organs peculiar to each of the two sexes renders each liable to special diseases. Women are also the special victims of hysteria and chlorosis. We cannot explain their greater liability to these conditions or to endemic and exophthalmic goitre and myxœdema, nor their comparative immunity from Addison's disease, locomotor ataxy, and progressive muscular atrophy.

Heredity.—Feeble vital power without actual disease may be the heritage of the body, or of one of its parts. It may further be noted that, like physiological and personal peculiarities, disease—*e.g.*, gout—sometimes skips one or more generations (*atavism*). In other cases, as in hæmophilia and pseudohypertrophic muscular paralysis, the disease appears generally in the males only, although the females may, without themselves manifesting it, transmit it to their offspring.

Other diseases which obviously "run in families" are functional nervous disorders, such as hysteria, epilepsy, and insanity, which are more or less interchangeable; Huntington's chorea; carcinoma, especially of the breast and uterus; some simple growths, especially if multiple (lipomata, osteomata, papillomata); gout and tubercular disease; retinitis pigmentosa and colour-blindness. The condition known as Friedreich's ataxy usually affects several children of the same family, but is not passed on from parent to child.

Exciting Causes.—We have already enumerated the principal external causes of disease (p. 4). Certain secondary causes acting locally upon the cells must, however, be mentioned.

Abnormal Blood-Supply.—Defects in the blood-supply may be due to errors in the circulation or in the composition of the blood. A defective blood-supply may result from hyperæmia or anæmia; and

from all abnormalities in the constitution of the blood, due either to faults in its formation or purification, or to the presence of poisons, whether formed by the cells of the body or by parasitic organisms, or introduced from without.

Abnormal Local Conditions.—In this group we may include the results of mechanical obstacles to discharge of function—*e.g.*, stricture of a duct or orifice, strangulation of gut, pressure arising from neighbouring structures, and the mechanical effects of parasites.

Altered Nervous Influence.—The nervous system apparently exerts a direct controlling influence over some, if not all, of the other tissues, and perversion or impairment of this influence causes disturbance of nutrition in the cells affected. Thus, in cases of injury to spinal motor nerves the muscles supplied by them rapidly degenerate, and in certain cases of affection of the posterior spinal root-ganglia, hyperæmia and exudation take place in the corresponding area of the skin (herpes zoster). In locomotor ataxy and syringomyelia a rapidly progressing disorganisation of some of the joints may occur; and perforating ulcers of the foot appear to be associated with similar defects of nerve-supply. Severe nervous shock may determine the onset of such affections as diabetes, chorea, or exophthalmic goitre. The extent of the "trophic" influence of the nervous system is not yet ascertained.

Effects of Previous Disease.

Some diseases, when they have occurred once, tend to recur again and again—*e.g.*, tonsillitis, rheumatism, erysipelas. In the case of others, to have suffered once is to have secured practical immunity against a second attack. (See Immunity, Chapter XII.)

Certain other diseases, again, seem to modify very deeply the functions of the body. Many years after these diseases, it is found that illnesses, which seem at first sight to have nothing to do with them, yield only to the treatment proper for the original malady. Such are malarial fever, syphilis, and gout. The causal agents of the first two are probably still latent in the body: as to gout, though its pathology is not yet fully made out, it is possible that all its manifestations are due to the deposition of biurate of sodium in the tissues concerned, which may be induced by injury or other disturbance in persons whose peculiar metabolism gives rise to a constant excess of this substance in the blood-stream.

Modes of Extension of Disease.

Extension of disease may be effected by spread of the causal agent to neighbouring parts; or by the gradual involvement of more and more tissues or organs in the ill effects of a stationary cause; while secondary lesions, as already mentioned, may be caused by failure of function in the part first affected. Extension thus takes place:

1. *By the carriage of the exciting agents of disease from a primary focus to neighbouring or distant parts.* Thus, the so-called "direct extension of inflammation" is due to carriage of infective organisms and their toxines by the *lymph-stream* to the tissues in continuity with the primary focus, and to the neighbouring lymphatic glands; and cells of malignant tumours are detached and deposited either in neighbouring glands or in distant organs, in which positions they give rise to other tumours. Pieces of clot may be conveyed by the *bloodvessels*, and produce embolism; and a renal calculus may be transferred through the ureter to the bladder.

2. The gradual extension of a single cause of disease is seen in successive involvement of successive nerves (palate, eyes, skeletal muscles) in diphtherial paralysis, and in the extension of such conditions as progressive muscular atrophy or Landry's paralysis.

3. *Mechanically*, by so-called "*back-telling.*" Thus, stricture of the urethra causes hypertrophy of the bladder, if the obstacle to the outflow of urine can thus be overcome; or simple dilatation of the bladder, if its efforts are futile. In either case, the difficulty of entry of urine into the bladder is increased, and the ureters, pelves, and kidneys dilate. Interstitial nephritis results from the pressure, the renal functions are imperfectly performed, and this is detrimental to the organism at large. The succession of changes which result from incompetence of the mitral valves is another familiar example of this mode of extension of disease. (See Passive Hyperæmia.)

4. *Failure of any part to do its share of work in the economy.* The result of such failure will depend upon the readiness and completeness with which its defects can be compensated. If the work can be readily taken over by other parts, as can that of a sweat or sebaceous gland, nothing is noticed; on the other hand, extirpation of a kidney which was doing work is followed by a time of danger from the consequent interference with the excretion of waste products, as the other kidney is at first unequal to the double duty. Absolute failure of the cardiac or of the respiratory function will cause death, there being no power of compensation. Allusion has already been made to secondary diseases such as myxœdema and Addison's disease.

Terminations of Disease.

The possible terminations of disease are *recovery*, or return of the part to the discharge of its normal functions; *partial recovery*; and *death*, or complete cessation of function. Certain diseases can scarcely be said to have a termination; when once established they remain stationary.

Tissues which are the seat of disease have a natural tendency to recover—*i.e.*, to return to their normal condition, when the morbid process has not been sufficient to cause grave structural damage. An experiment of Lister's illustrates this tendency: If a hot iron be brought near to normally-acting ciliated cells, detached from the

body, the first effect will be to increase or stimulate the movement of the cilia ; but if the hot iron be kept near them long, or brought closer, the movement becomes slower, and finally ceases. If the iron be then removed, the cilia will, after a period of quiescence, begin to work again. We may compare this property of living tissue with the behaviour of a body placed in stable equilibrium, which tends to return to its original position, if displaced.

The power of resisting injurious agencies varies not only in different individuals, but in different tissues. Not only does a "strong" man recover from a disease which would be fatal to a weaker one, but we find experimentally that a rabbit's ear will resist the effects of anæmia longer than will a knuckle of its intestine or the cells of its central nervous system. In the case of the intestine, the presence of micro-organisms capable of invading the damaged tissues must be borne in mind.

It will be useful here to give a **list of the morbid processes** to which all organs are more or less liable :

Developmental errors.

* * *

Results of mechanical injury.

Displacement.

Hæmorrhage.

* * *

Anæmia.

Hyperæmia.

Œdema.

Atrophy.

Degeneration.

Necrosis.

"Inflammation" (reaction to irritants).

[Regeneration and repair.]

Hypertrophy.

* * *

Tumour-formation.

* * *

Lodgment of parasites.

* *

Stricture and its consequences may occur in any duct or canal ; and calculi may develop in any of them.

Regeneration is included in the above list, since, although it is not itself a morbid process, it is the result of injury or disease, and is therefore intimately connected with pathology ; while the products of the reparative process often differ from the original tissue of the injured part.

CHAPTER II

MALFORMATIONS

THE term **malformation** is applied to structural defects of parts and organs, the result of errors or accidents in the process of development.

It is customary to classify malformations into three groups: (1) malformations by excess, (2) malformations by defect, and (3) malformations by perversion.

1. *Malformations by excess* include all double monsters; all repetition of parts or of structures—*e.g.*, supernumerary fingers and toes; and all giant-growth, whether general or local.

2. *Malformations by defect* comprise all those due to arrest of development. The large majority of these arise at an early period of embryonic life. In this group are included dwarfing and the absence or defective formation of parts, provided they are due exclusively to the *arrest* of normal processes, as in hare-lip, cleft palate, cleft sternum, and imperforate anus.

3. *Malformations by perversion* include those congenital errors in which the process of development is irregular and disorderly. In this group are placed, among others, the transposition of viscera and many forms of congenital heart-disease.

This classification is, however, not so useful as one based upon the normal order of events which occur in the course of development.

In the space available for this subject it is not proposed to deal with the formation of *double monsters*, whether derived from two ova or from a single ovum, nor with such grave disturbances of development as may lead to any of those abortive results of impregnation which are grouped together under the term *mole*. *Dermoid cysts* are considered along with other cysts at the end of the chapter on Tumours.

A very considerable number of the malformations commonly met with depend on imperfect union in the posterior or anterior median line of the body.

Defective Development in the Posterior Median Line.—It will be remembered that the whole of the central nervous system is developed from an invaginated fold of epiblast known as the *neural* or *medullary groove*, which subsequently becomes converted into a canal, and separated from the originally adjacent epiblast by a thin layer of mesoblast.

The grossest forms of malformation depend upon the failure of the neural groove to form the neural canal. Thus, both cranium and brain may be absent (*anencephalus*), or the spinal canal and spinal cord may remain an open groove (*open spina bifida*). These conditions, as well as many other malformations of the brain, are incompatible with life, and are, therefore, of little practical interest.

A minor degree of spina bifida often occurs, in which a hernial protrusion either from the central canal of the spinal cord or merely from the spinal canal, combined with defective formation of the arches of the vertebræ, forms a central tumour in the back—usually in the lumbar region. When the tumour consists of a protrusion from the *central canal of the spinal cord*, its wall is lined internally by nerve-roots and rudiments of the spinal cord (*syringo-myelocele*). When the protrusion only arises from the *spinal canal*, and not from the centre of the spinal cord, the latter generally runs across the cavity, and is attached to the middle of the projecting wall of the protrusion, giving rise to a central depression in the tumour when viewed from behind ; thence it turns back and, as the *filum terminale*, reaches the canal again. In such cases (*myelomeningocele*), as well as in those which only contain fluid (*meningocele*), the wall of the tumour is formed of the ordinary integuments lined by the rudimentary spinal meninges. Similar pouches may be formed in connection with defects in the cranium. They generally arise from the occipital region. They may contain brain-substance (*encephalocele*), or brain-substance and fluid (*encephalo-meningocle*), or fluid only (*meningocele*).

Malformations of both brain and spinal cord may also arise after the cranium and vertebral column are formed. These comprise (1) a uniform smallness of the brain (*micrencephalia*) or of the spinal cord (*micromyelia*), in which the former may be from two-thirds to one-sixth its natural size ; (2) irregular defects in the cortex of the brain, in which some of the convolutions are absent, and others small and thin ; and (3) more or less extensive depressions or clefts in the cortex due to defective development, and constituting the condition known as *porencephalia*. The cerebrum and cerebellum are more liable to malformations than the central parts of the brain. The spaces resulting from the defects in the cortical or central parts occurring after the formation of the cranium are filled up by cerebro-spinal fluid—in the ventricles or in the subarachnoid spaces, as the case may be. When the defects are marked and the quantity of fluid is large, the condition is known as *congenital hydrocephalus—internal*, if the fluid is in the ventricles, and *external*, if it is on the surface of the brain.

The majority of instances of malformation are probably due to primary developmental errors. Injury and circulatory disturbances may be the initial causes in the rest.

Defective Development in the Anterior Median Line.—Defective development and coalescence of the structures forming the anterior median line include a large number of common malformations,

The imperfect union is generally attributed to some primary germinal defect or regarded as the indirect result of amniotic bands and adhesions.

If the growth of the naso-frontal and both superior maxillary plates (Fig. 1) be defective, a large gap, involving upper lip, nose, and palate, will be left.

If the defect be confined to the failure of coalescence on the part of the naso-frontal and one maxillary plate, a cleft in the upper lip (*hare-lip*) will be produced on the corresponding side of the mid-line. If the coalescence of the maxillary plates and corresponding soft parts to form the palate be incomplete, a central cleft (*cleft palate*) will occur in the posterior part of the roof of the mouth. In extreme cases, when the cleft is wide and extends far forwards, the lower part of the naso-frontal process may be seen forming a narrow central

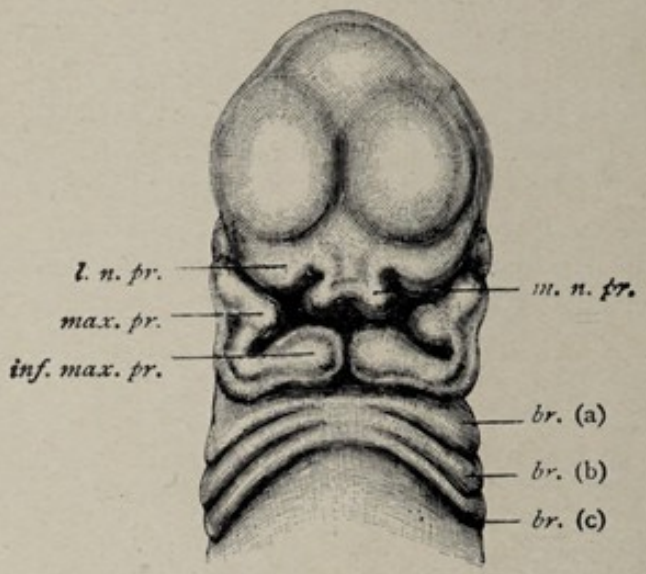


FIG. 1.—HEAD OF FŒTUS. (SEMI-DIAGRAMMATIC, AND MODIFIED FROM SEVERAL ILLUSTRATIONS FROM HIS.) (WATERHOUSE.)

l. n. pr., lateral nasal process; *m. n. pr.*, mesial nasal process; *max. pr.*, maxillary process; *inf. max. pr.*, inferior maxillary process; *br.* (a), *br.* (b), *br.* (c), the three lower branchial arches.

plate, partly filling up the cleft between the maxillary processes. In the majority of instances, both of hare-lip and of cleft palate, only the soft parts are defective. Very rarely, a median cleft in the lower lip and even in the lower jaw may arise from the defective union of the inferior maxillary processes.

Minute *fistulæ in the neck* connecting the surface of the skin in front of the sterno-mastoid with the pharynx, may result from imperfect closure of the branchial clefts (Fig. 1); and *cysts* may arise from unobliterated remnants of these openings. Fissures may also occur, from somewhat analogous causes, in the sternum, in the diaphragm, and in the sides of the thorax.

The parts concerned in the formation of the umbilical cord furnish many malformations. A persistent urachus may lead to a *vesical fistula*, and its imperfect obliteration to a *cyst* in the urachal cord

which then connects the umbilicus and bladder. In the same way a persistent omphalo-mesenteric duct, which connects the yolk-sac with the alimentary tract, may, in similar fashion, give rise to an *intestinal fistula.* In most cases, however, the persistent duct merely consists of a pouch arising from the ileum opposite the mesenteric attachment about three feet above the ileo-cæcal valve. This pouch is similar in structure to the rest of the adjacent intestine, and generally forms a simple cul-de-sac two or three inches long (*Meckel's Diverticulum*), constituting one of the commonest malformations in the body. More rarely it may attain a length of six inches or upwards, and be connected by a fibrous band with the umbilicus (Fig. 2) ; only in very exceptional cases does it extend to

FIG. 2.—MECKEL'S DIVERTICULUM.

a, umbilicus ; *b*, impervious fibrous cord ; *c*, diverticulum ; *d*, ileum below diverticulum.

the umbilicus as a patent tube and give rise to a fistula. A pouch of peritoneum may project into the umbilical cord, giving rise to a hernia.

Fissures in the abdominal wall are generally situated below the umbilicus. If the lateral plates are defective, amnion, peritoneum, and the anterior wall of the bladder may give way, and the mucous surface of the posterior wall of the bladder, with the openings of the ureters, project on the surface (*extroversio vesicæ*). The urethra may remain unclosed, appearing, in the male, as a groove along the dorsum of the penis (*epispadias*), and this condition may be associated with absence of the symphysis pubis and extroversion of the bladder. A commoner deformity is a defective development of the penis, in which that organ is small and grooved on its under surface.

The urethra may open at the root of the penis, at the base of the glans, or at any point between these. To these deficiencies are added undescended testicles and a cleft scrotum somewhat resembling the labia majora of the female. This general defective development of the generative organs is known as *hypospadias*, although, strictly speaking, the term should be limited to the urethral malformation.

When the ordinary invagination of the skin to form the anus does not occur, or more commonly when the hind-gut is too short to communicate with the more or less completely invaginated portion of the skin, an *imperforate anus* results. The walls of the hind-gut and of the invaginated anus may lie in close contact, or may be separated by an interval of several inches (Fig. 3).

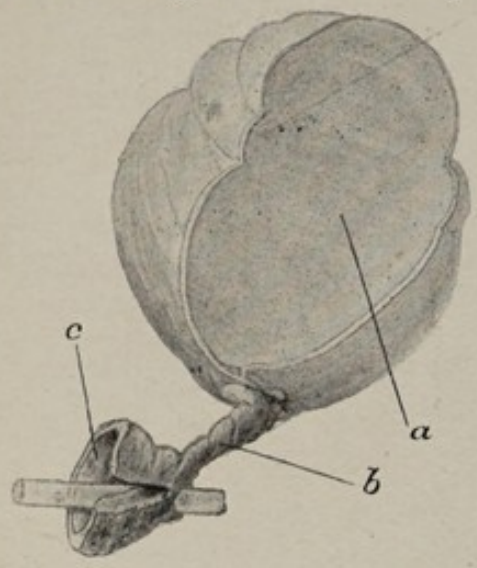


FIG. 3.—IMPERFORATE ANUS. (C. C. H. MUSEUM.)

a, rectum; *b*, fibrous cord connecting imperfectly developed rectum and invaginated skin; *c*, skin.

Occasionally the hind-gut may be incompletely differentiated from the genito-urinary apparatus owing to the imperfect involution of the allantois, but in such cases the fœtus rarely attains maturity.

Miscellaneous Defects.—The commonest and least important malformation of the **kidney** is an irregularity of the surface due to the persistence of the original lobulations, marking the position of the pyramids—a normal condition in the ox and many other mammals.

Occasionally the lower ends of the kidneys are found united across the bodies of the vertebræ so as to form a horseshoe-shaped organ. The connection may be effected either by fibrous tissue or by ordinary renal tissue. In nearly all cases of horseshoe kidneys the ureters pass downwards over the anterior surface, while the arrangement of the bloodvessels is generally somewhat unusual.

The pelvis of the kidney may be subdivided, and the ureter may be double at its upper part or even throughout its whole length.

On rare occasions the development of one kidney may be so far interfered with that it is represented at birth by a mere fibrous plate; while the opposite kidney is double, or nearly double, its normal size.

Neither **liver** nor **lungs** are liable to any important developmental errors, unless the dilatation of the neighbouring bronchial tubes which results from the inefficient expansion of any part of the lung at birth (*atelectasis*) be regarded as a malformation.

Malformations of the **limbs** are numerous and varied. Those due to excess take the form of giant-growth, in which all the tissues of a

limb may be concerned ; or of additional parts, as in supernumerary fingers or toes (Fig. 4), and " webbing " of fingers or toes. These two latter deformities are frequently found together, and are often hereditary, occurring in different members of a family.

The absence of limbs may be due to germinal defects, or to intra-uterine amputation by amniotic bands at an early period of development. When hands and feet, however imperfect, exist without the intermediate parts, the defect is always germinal.

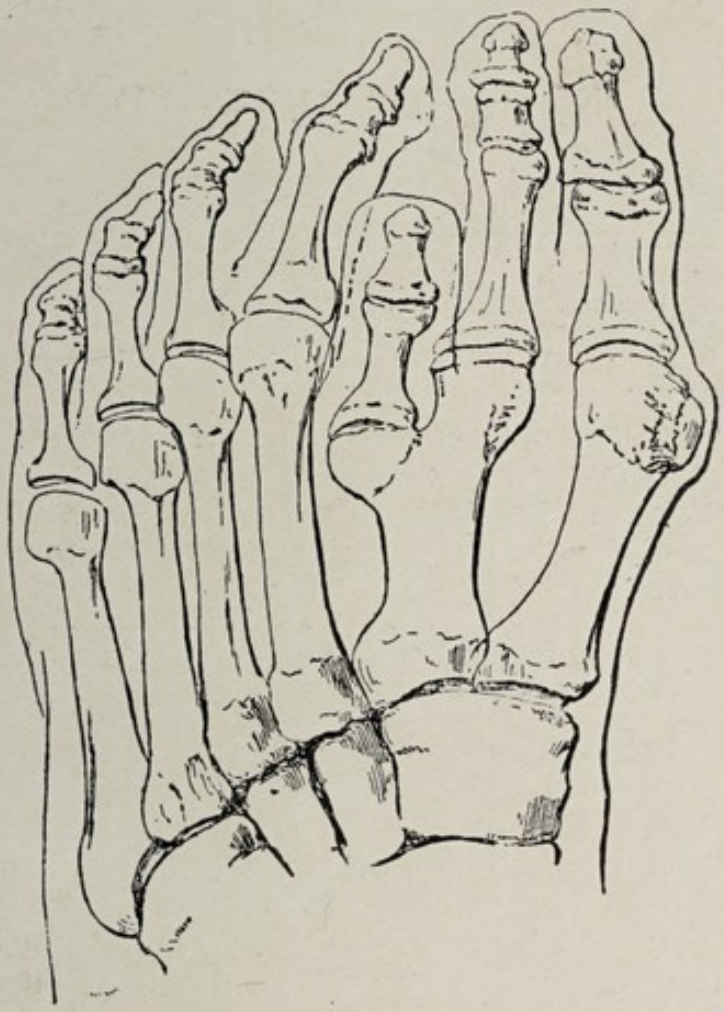


FIG. 4.—FOOT WITH SEVEN TOES. (MONTAGUE MURRAY.)

The first two metatarsal bones articulate with the internal cuneiform bone. The third toe has only two phalanges and arises from the second metatarsal bone, the distal end of which is bifurcated.

Congenital dislocations, especially of the hip-joint, are not infrequent, and are associated with defective formation of the joints concerned.

The various forms of congenital club-foot are accompanied by defects in the formation of the tarsal bones, especially of the astragalus, and are possibly due to the pressure exerted by the walls of a misshapen uterus. They are occasionally associated with corresponding cerebral defects.

Malformations of the **Heart** will be considered in the chapter dealing with diseases of that organ.

CHAPTER III

NUTRITION ARRESTED

NECROSIS.

THE complete and permanent arrest of nutrition in a part constitutes necrosis, gangrene, or local death.

ÆTIOLOGY.—Whatever interferes with the supply of nutritive material to a part, or destroys the vital activity of its cellular elements, may cause its death.

A. *Interference with the Supply of Nutritive Material.*—Such interference may be the result of:

1. **Obstruction in the Arteries.**—This is a common cause of necrosis. The obstruction may be caused by compression, by ligature, by rupture, by thrombosis, by embolism, or by disease producing thickening of the arterial coats, and consequent narrowing of the lumen of the vessel. Long-continued spasm of the vessel-wall may have the same effect (Raynaud's disease). If the obstruction be complete and a collateral circulation cannot be established, death of the part quickly ensues (Fig. 5).

2. **Obstruction in the Capillaries.**—Obstruction is often the result of pressure upon, or stretching of, these vessels. This may be due to exudation from the vessels, or to extravasated blood, or to the pressure exercised by new growths. The resulting obstruction to the capillary circulation causes the death of the immediately adjacent tissues. As examples of necrosis from this cause may be mentioned: necrosis of the superficial layers of a bone resulting from periostitis, and due to the compression of the capillaries between the bone and the periosteum; the sloughing of tendons in whitlows before the latter are opened; and the formation of ordinary bedsores. It has been suggested that the condition known as "gas gangrene" should be included in this category. The lesion is a spreading necrosis affecting the muscles and subcutaneous tissues, and is associated with the production of a varying amount of gas in the parts affected. It results from a gross infection with certain anaërobic organisms which are active gas producers. Some authorities consider that the main factor in the causation of the necrosis is the anæmia produced by the increased pressure resulting from the local gas-formation, but others would assign the most important rôle to the toxines produced by the bacilli, which are

present in enormous numbers. When an infective process causes gangrene, this result is aided by the stasis which occurs in the capillaries. Coagulation of blood takes place in the vessels of the necrosed tissue, and thus hæmorrhage from gangrenous parts is prevented.

3. **Obstruction in the Veins.**—Obstruction to the return of blood by the veins is seldom complete enough to arrest nutrition, and is therefore rarely a cause of necrosis. When, however, it is associated with cardiac weakness or obstruction in the arteries, it constitutes an important agent in producing this result; for then the force

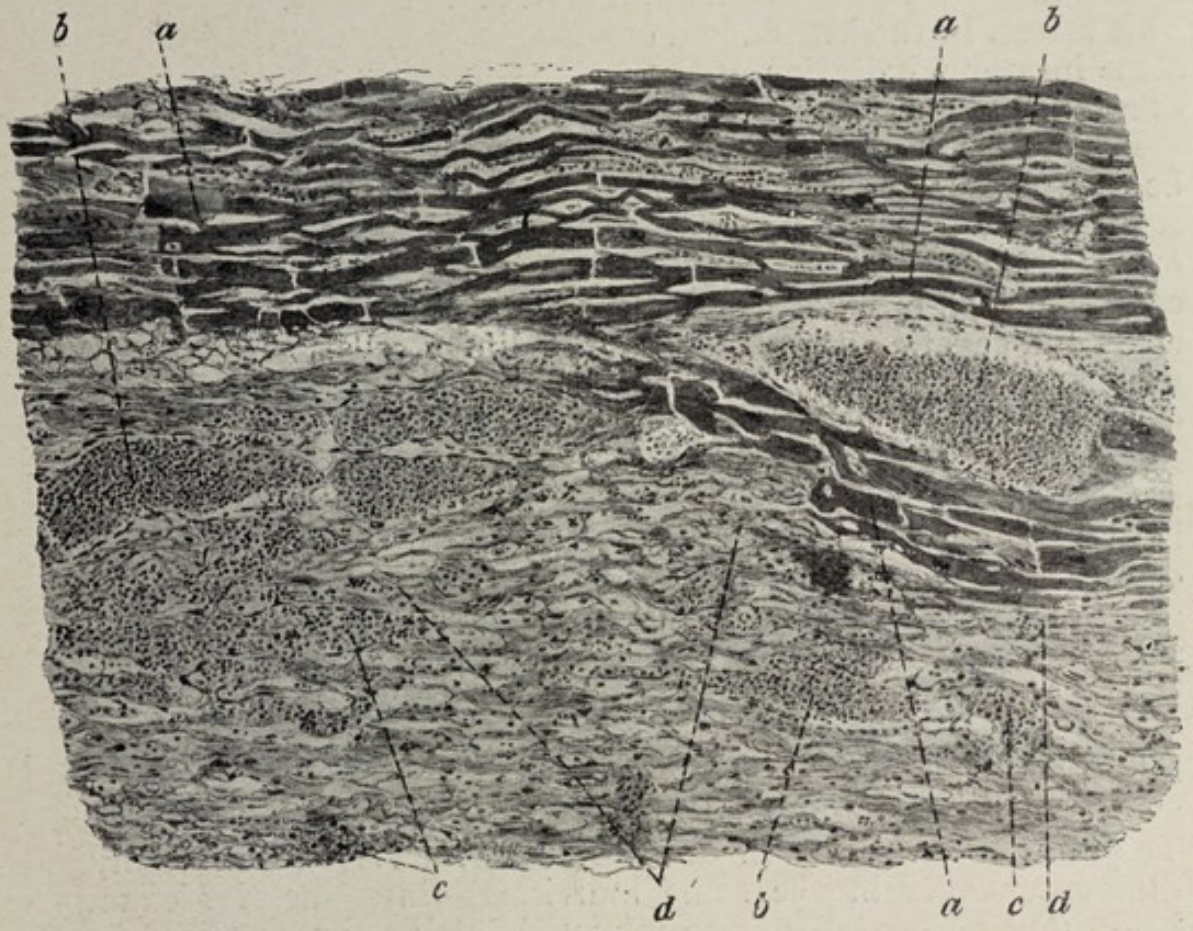


FIG. 5.—A NECROSED PATCH IN THE MYOCARDIUM. (× 150.)
At (*d*), where the muscle-fibres have disappeared, the structure consists of the connective-tissue stroma and the débris of necrosed muscle-fibres. At other places engorged bloodvessels and extravasated blood (*b*, *c*) are seen. The muscle-fibres remaining (*a*) have lost their striation.

necessary to drive the blood through the narrow venous channel is quite inadequate. Gangrene due to these combined causes occurs after ligature of a main artery and its vein, and may follow accidental injury of the vein during the operation of ligature of a large artery, especially in the thigh. It may also result from constriction of a part by a bandage not tight enough to occlude the arteries as well.

When a strangulated or invaginated piece of intestine is released and the circulation is re-established before gangrene has occurred, severe reaction, leading to gangrene, may ensue. In this way any much contused and lacerated part may ultimately be killed because

the pressure of the effusion from its injured vessels still further impedes the flow through them.

4. **Diminished Cardiac Power.**—This is never by itself a sufficient cause of necrosis. In cases, however, of excessive general debility, or of disease of the cardiac substance, the consequent diminution in the contractile power of the heart materially aids the foregoing causes in producing a fatal blood-stasis. The arrest of the circulation in senile gangrene (p. 22), and in that form which so often occurs in the tissues of the back (*bedsores*) in prolonged fever and in chronic exhausting diseases, is in part the result of diminished cardiac power. This arrest, in the last-named conditions, is usually determined by some injurious irritation of the tissue—in other words, it is a part of a toxic or infective process.

B. *Destruction of the Vital Activity* of the cellular elements may be caused by:

Physical and Chemical Agencies.—A part may be completely disorganised and lose its vitality as the result of external *violence*, excessive *heat*, or extreme *cold*. Many corrosive *chemicals*, such as acids and caustic alkalies, destroy the life of cells. Putrid urine or foul secretions from wounds will sometimes destroy the cells like a caustic. Certain diseases have a special tendency to cause necrosis—*e.g.*, diphtheria, carbuncle, noma, "hospital gangrene," and spreading traumatic gangrene: in these conditions the injury to the tissues is due to the chemical action of bacterial products. In infective conditions, such as pneumonia and enteric fever, small scattered areas of necrosis occur in the liver and spleen, due to the action of the toxines of the bacteria concerned (Fig. 6).

These are the several causes of necrosis; but it must be borne in mind that the process is often complex, and due to the combined influence of two or more of them. The liability to necrosis will greatly depend also upon *the power of the tissues to resist injury*. This varies, probably, in different individuals, and, certainly, in different tissues in the same individual—intestine, for example, being much less resistant to injury than skin, and glandular epithelium than connective tissue. Conditions which would lead to the death of a part in which the circulation was already impeded, or in which the vitality of the cellular elements was impaired, would produce no such effect where such local weakness did not obtain. This is well exemplified by senile gangrene; by the formation of ulcers in the skin drained by varicose veins in the legs; and by the necrosis of the tissues of the back (*bedsores*) from pressure, which so often occurs in conditions of debility, especially in persons who are lethargic, heavy, and imperfectly conscious. Diabetic, albuminuric, and intemperate persons are peculiarly liable to gangrene, owing to the weakened resistance of their tissues, produced by the poisonous bodies respectively present.

VARIETIES.—These generally follow one of two types known as *dry* and *moist* gangrene respectively. There are three conditions which mainly determine into which of these two varieties a given

instance will fall. These are (1) the amount of fluid which the tissues involved naturally contain; (2) the extent to which the vessels of the part affected are engorged with blood, and the amount of additional fluid which is therefore present at the time; and (3) the rapidity of the evaporation from the surface.

Dry Gangrene (*mummification*) will therefore occur in those parts in which the tissues naturally contain but little fluid, such as bone, cartilage, and tendon. It will also be frequently associated with such obstructions of the arteries as may occur without any corresponding interference with the circulation in the veins and lymphatics. Dry gangrene, therefore, may result from embolism, from slowly progressing arterial thrombosis, and from the prolonged administration of ergot. Again, free exposure to dry air, slow progress, and the destruction of the epidermis will all, by promoting or permitting evaporation, aid in producing dry gangrene. Under these circumstances, the part, which is pale from the first, gradually dries up and becomes converted into a dark, shrunken mass, undergoing but little further change. The conditions obtaining in dry

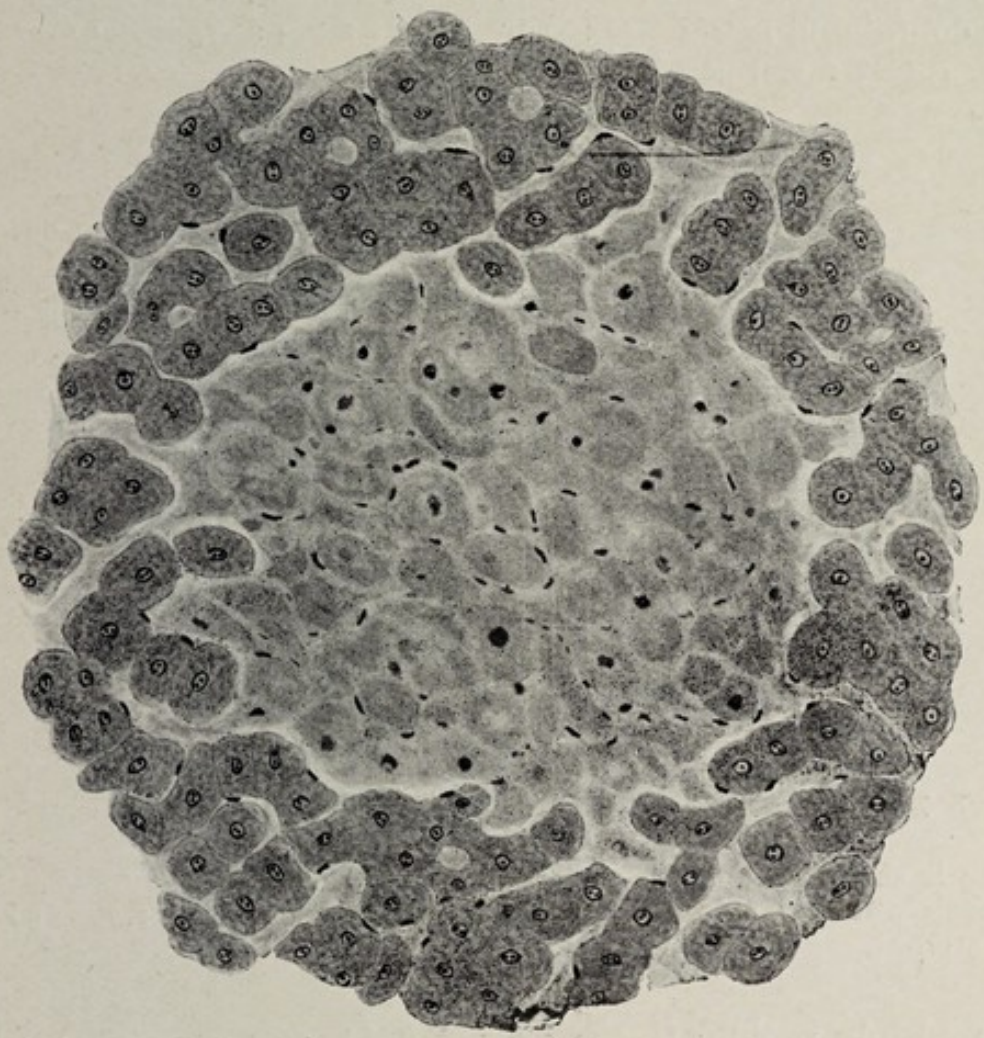


FIG. 6.—FOCAL NECROSIS OF LIVER-CELLS.
From a case of typhoid fever.

gangrene are precisely those which render the growth of organisms difficult or impossible (Fig. 7).

Moist Gangrene.—Under opposite circumstances, a part, consisting largely of muscle and other soft structures, may become rapidly gangrenous, either from an acute infective process, or from venous obstruction combined with a weak arterial supply. When this happens, its tissues are engorged with an albuminous fluid full of breaking-down red blood-corpuscles. The hæmoglobin of these forms a red solution, which soaks into and stains all the tissues. The part is much swollen, of purplish colour, and often studded with bullæ containing blood-stained fluid. If such a part is exposed to warm, moist air, putrefactive bacteria quickly grow through the

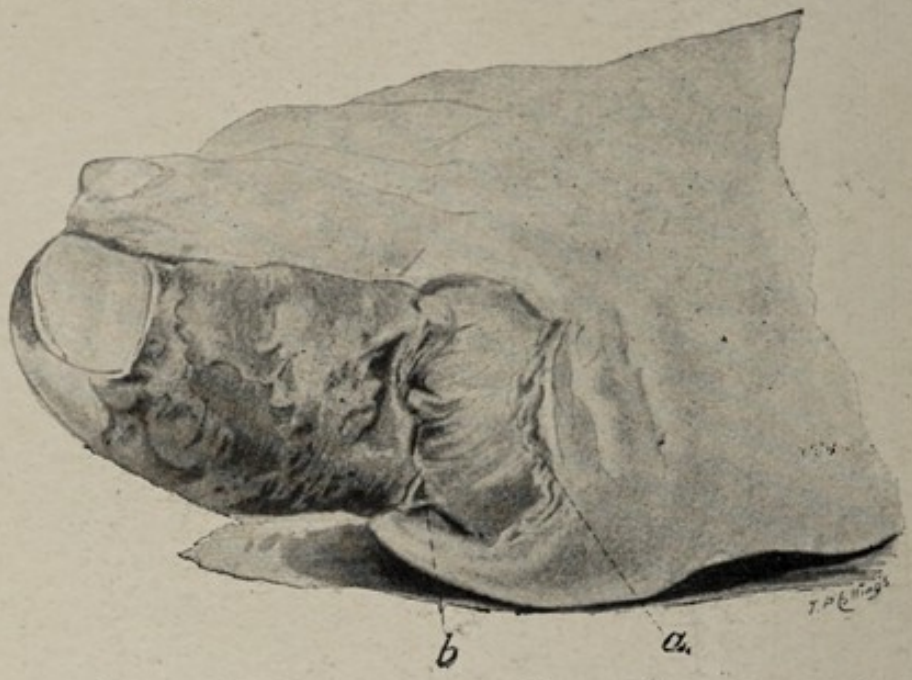


FIG. 7.—SENILE GANGRENE OF THE GREAT TOE FROM A CASE OF ARTERIAL THROMBOSIS. (C. C. H. MUSEUM.)

The toe is shrunken and its epidermis is being exfoliated. At the line of demarcation the skin has retracted (*a*) and the deeper parts are separating (*b*).

skin, multiply rapidly in the effused fluid, and generate by their action gases—chiefly hydrogen sulphide, ammonia, nitrogen, and carbon dioxide—which give rise to the emphysematous crackling so often associated with gangrene. The tissues soften and liquefy, the whole part becomes exceedingly offensive, and its tissues change in colour from red to brownish- or greenish-black. For putrefaction to occur it is absolutely essential that bacteria be admitted to the part; consequently such changes are met with chiefly in external parts or in those internal parts to which organisms have free access.

When the life of an internal organ or part is destroyed and bacteria are not admitted to it, as in simple infarction, its tissues subsequently undergo degenerative changes due to the action of natural enzymes, and are ultimately in great measure absorbed.

COURSE.—Gangrene may be circumscribed or spreading. *Circumscribed gangrene* implies a *circumscribed cause.* This form is exemplified by the death of tissue resulting from mechanical violence, the actual cautery, or complete stoppage of the local circulation. On the other hand, *spreading gangrene* implies a *spreading cause.* Gangrene from arterial thrombosis spreads slowly as the thrombus spreads and involves other vessels, and has a well-defined margin. The typical *spreading gangrenes* are produced by the action of living organisms, which continually multiply and provide fresh quantities of the irritant, while they are constantly being carried by the lymph-stream farther into the surrounding tissues.

When the process becomes circumscribed, the dead tissue—*sphacelus* or *slough*—acts as an irritant to the adjacent living structures, causing more or less inflammation in them. If the slough is aseptic, the inflammation is slight—leading merely to the formation of a layer of fibroid tissue round the dead mass. This occurs specially in internal parts, and is best illustrated by the usual fate of a small simple infarct. When thus encapsuled, the dead part ceases to irritate; it becomes decolourised, and infiltrated with phagocytes which absorb the fatty detritus; and is ultimately converted into a small fibrous scar, which may calcify.

When the slough is superficial it generally putrefies and becomes strongly irritant; but mummification will minimise this. Vascular reaction occurs freely in the narrow zone of living tissue (*line of demarcation*) surrounding the edges and base of the slough; fibres and all firm connections between the living and dead tissues are softened, and eaten through by leucocytes (suppuration); and, finally, when this process is complete, the slough is cast off. If the whole thickness of a limb die, the stump left by casting off the sphacelus will be conical; for the soft parts retract somewhat, and the bone separates lower down. The less vascular a tissue, the longer will be the time occupied in the separation—*e.g.*, fascia, tendon, bone. If the dead mass be deeply seated, and suppuration occur about it, *fistulæ*—tubular passages through the tissues—will form, leading from it to the surface. Through one or more of these it may ultimately be cast off, as in necrosis of bone. After removal of a superficial slough, an *ulcer* is left.

Chemical Changes in Dead Tissue.

The series of chemical changes which occur in dead tissues has been named "autolysis" or "self-disintegration." In this process, which is equivalent to digestion of the dead cells by their own enzymes, there first takes place a change resembling cloudy swelling (p. 32), the cell becoming acid in reaction instead of alkaline, owing to the formation of lactic, acetic, and butyric acids. Next, fat is split off from the protoplasmic molecule, and becomes visible in fine droplets; this is subsequently saponified and absorbed. The nuclei

break up at an early period, first failing to stain with the usual dyes, and then disappearing, with formation of purin-bodies (Chapter XXII.). The proteins undergo changes similar to those of pancreatic digestion, splitting into ammonia; amino-acids, such as glycocoll, alanin, and leucin; diamino-acids, as lysin, arginin, and histidin; and aromatic compounds, as tyrosin and tryptophane; while the sulphur-containing radicle splits off as cystin. Lecithin present in living cells is broken up after death into choline, glycerophosphoric acid, and some fatty acid, the last differing with the different lecithins. In some conditions special enzymes contained in the leucocytes assist in the process of disintegration of dead cells; this is the case in the absorption of the intra-alveolar products in acute pneumonia. In others micro-organisms take part in the peptonising process.

Senile Gangrene.

This is a form of necrosis which affects especially the lower extremities of old people, and is the result of several of those ætiological conditions which have already been enumerated.

The most important element in the production of senile gangrene is the presence of *atheromatous or calcareous changes in the arteries* of the limb, which greatly diminish the elasticity and calibre of these vessels, thus hindering the circulation in the part and impairing its nutrition. This is shown by the coldness of feet, cramps, and other abnormal sensations so often experienced by the patient for some time before the gangrene appears. The slowing of the circulation is usually increased by defective action of the heart, due to atrophy or degeneration of its muscular substance. Thus the contact of the blood with an abnormal vessel-wall is prolonged, and this is sometimes sufficient to cause the formation of a *thrombus* in the artery. (See Thrombosis.) The clot thus formed spreads slowly until it may extend from the foot to the groin. Dry gangrene gradually supervenes. This begins in one toe or in several simultaneously, and extends slowly. It is often surprisingly limited, and even where the thrombus extends into the popliteal artery, part of the foot may escape. In other cases, *embolism* with superadded thrombosis may be the starting-point—a chalky plate or a parietal thrombus being swept from a large into a smaller artery.

The determining cause of the gangrene is often some trivial injury, such as a slight abrasion of the foot, or the cutting of a corn—these slight wounds permitting the entrance of micro-organisms—or some excess of heat or cold, acting upon feebly-nourished tissues supplied by diseased vessels.

Coagulation-Necrosis.

This is a term applied to a peculiar form of sudden tissue-death. Coagulation of cell-proteins may be induced by the action of heat or of chemical substances (corrosive sublimate); also at times by

bacterial toxines. The cells in dying give rise to substances (*coagulins*), which unite with the lymph and cause it also to coagulate. Thus the process only occurs in parts freely supplied with lymph, and is never found in the brain. Microscopically, the nucleus disappears, and the contents of the cell are replaced by a structureless hyaline material. Fatty degeneration subsequently sets in. S. Martin would confine the term "coagulation-necrosis" to conditions in which cells are killed by sudden cutting-off of their blood-supply, as in cases of embolism of a terminal artery. Caseation is sometimes considered an example of coagulation necrosis.

Colliquative necrosis is the term employed when the dead tissues do not coagulate, but, as in the case of the brain, soften and liquefy. The cerebro-spinal fluid is non-coagulable, and necrosis in the brain is colliquative from the first: here the liquefaction may be connected with the presence of lipoid bodies. In acute pneumonia it follows coagulation, and is due to bacterial enzymes.

Fat-Necrosis.

Under the name of *fat-necrosis* a peculiar change occurring in fat has been described. It consists in the formation of opaque white areas, half an inch or less in diameter. These are of firm consistence, and are scattered through otherwise normal fat. They stain with osmic acid, and melt on the application of heat. Under the microscope the contents of the affected cells are either crystalline (fatty acids), or opaque and granular. The transition from diseased to healthy cells is abrupt. The surrounding parts are occasionally infiltrated with leucocytes. Fat-necrosis is probably always associated with disease of the pancreas, and is almost certainly due to absorption of pancreatic juice, which acts upon the fat and saponifies it. Lipase has been identified in the necrotic areas, and may also be found in the urine of such cases. Fat-necrosis is most frequently seen in the sub-peritoneal fat, but is occasionally found in distant parts, as in the pericardial fat or in the medulla of bone: in these situations it has been attributed to embolism of small masses of pancreatic cells.

POST-MORTEM CHANGES.

The changes which always occur in tissues after death must now be briefly considered. The blood undergoes the earliest and most rapid change. The hæmoglobin escapes from the red corpuscles, dissolves in the liquor sanguinis, and permeates the surrounding tissues. The corpuscles ultimately disappear, nothing remaining but a few minute granules. The staining of the tissues with hæmoglobin is commonly known as **post-mortem staining,** and the appearances it presents are very characteristic. The lining membrane of the heart and of the bloodvessels, being in immediate contact with the blood after death, is the part principally affected. The dissolved hæmoglobin also

soaks through the walls of the veins, thus giving rise, on the surface of the skin, to red lines which mark the position of the vessels lying beneath. The staining is of a uniform pinkish-red colour, thus differing from the punctiform and linear redness of hyperæmia, from which it must be carefully distinguished. The amount of staining is in proportion to the rapidity with which decomposition has taken place, and to the amount of blood contained in the part at the time of death. Marked staining of the endocardium and great vessels occurs very rapidly after death from septicæmia.

Post-mortem staining must be distinguished from **post-mortem discoloration.** The latter is a purplish colour seen in dependent parts which are not pressed upon, and is due to the gravitation of fluid blood into the vessels of these parts. It disappears after a time, if the body be turned over.

In muscle the arrest of nutrition is accompanied by a state of rigidity known as **rigor mortis.** This is a peculiar condition of the muscles, observed in almost all bodies after death, in which they become firm and somewhat shortened, as though in a state of permanent contraction. It comes on as soon as the muscles have lost their irritability—in other words, as soon as the nutritive processes have completely ceased.* The time of its appearance will therefore depend upon the state of nutrition of the muscles at the time of death ; the more healthy and vigorous this is, the longer will be the interval before nutritive processes completely cease, and consequently the longer before rigor mortis supervenes. Its duration and its intensity are in direct proportion to the lateness of its appearance. In people, for example, who are in perfect health and die suddenly, as from accident, the rigor mortis does not usually come on until from ten to twenty-four hours after death : it is very marked, and often lasts two or three days. In those, on the other hand, who die from some exhausting disease, as from chronic phthisis, in which the nutrition of the muscles has become much impaired, the rigor mortis appears very soon, sometimes as early as ten minutes after death ; it is very slight, and may pass off in less than an hour. It has been said that in cases of death from lightning, and from some of the severer forms of the adynamic fevers, the rigor mortis is entirely absent. It is doubtful, however, if this is the case : the rigor mortis has probably escaped observation, owing to its arly supervention and rapid disappearance.

With regard to the nature of the change, Kühne and others have shown that it is really owing to the coagulation of the muscle-globulin (myosinogen) and the formation of a proteid clot—myosin. The coagulation is attended by the liberation of free sarcolactic acid. Thus are produced the firmness, hardness, and opacity of the muscle which are together characteristic of rigor mortis. This change is not confined to voluntary muscle ; a similar coagulation of the protoplasm takes place after death in all involuntary muscle-fibres.

* It is said that slight degrees of rigor mortis may appear in living muscles, nd may pass off on irrigation with salt-solution.

As soon as **decomposition** commences, rigor mortis disappears. The transverse striation of the fibres then becomes indistinct, and gives place to irregular rows of granules and fat-molecules. In the meantime the muscle softens, its sarcolemma disappears, and ultimately nothing remains but a soft structureless débris. (See p. 21.) In adipose tissue, the cells diminish in size, owing to the escape of the fluid fat, which diffuses itself throughout the surrounding structures. The fibres of the connective tissue swell, become opaque, and ultimately liquefy. In nerve-fibres, the white substance of Schwann coagulates and collects into small drops within the neurilemma. Cartilage, bone, and hair resist the putrefactive process longer than any of the other tissues, and are the least altered by it.

CHAPTER IV

NUTRITION IMPAIRED

It has been shown in the preceding chapter that the complete and permanent arrest of nutrition in a part causes death, and, therefore, cessation of function. We have now to consider those morbid processes in which *nutrition* is more or less *impaired*, and in which, therefore, there is a proportionate *diminution* of function. Nutrition may be impaired in two ways : in *quantity*, so that waste comes to be in excess of assimilation ; or in *quality*, either the food or the metabolism of the cell being abnormal. Excess of waste over assimilation leads simply to **atrophy,** or simple diminution in the size of a part or of the whole body. On the other hand, alteration in the chemistry of the cell, or in the quality of the food supplied to it, may lead to **degeneration** of the cell-contents, some abnormal substance appearing in the tissues.

Such abnormal products may theoretically be formed, (1) *anabolically*, by the cell from its food-supply, (2) *catabolically*, by abnormal disintegration of the cell-protoplasm, and (3) by *ingestion* or *simple deposition* in the cell from the lymph.

There is a growing tendency among pathologists to regard degenerations as largely due to the action of bacterial products (*toxines*). In some forms this has been proved to be the case.

Degenerative processes are generally divided into two groups : the *degenerations* proper and the *infiltrations*. In the **degenerations,** the cell-protoplasm is gradually transformed into some new material. This process is often continued until complete destruction of the histological elements has taken place, and all trace of the original structure is lost. In the earlier stages of the process, function is impaired : in the later, it may be completely arrested. In the **infiltrations,** the new material is supposed to be passively deposited from the lymph (calcareous infiltration), or absorbed by the cells from their food-supply* (fatty accumulation). Infiltration is not necessarily followed by destruction of the histological elements, and function is but little interfered with.

The *degenerations* are: fatty, mucoid, and colloid. Cloudy swelling also comes under this heading. The *infiltrations* are: fatty, calcareous, pigmentary, and probably amyloid.

* The term "infiltration" is unsuitable for such an active process. Passive infiltration probably occurs only in dead or dying cells.

ATROPHY.

Atrophy must be carefully distinguished from arrested development. It is a *decrease* in the amount of a tissue, owing to a diminution either in *size* (*simple atrophy*) or *number* (*numerical atrophy*) of the histological elements of which it is composed. It is attended by loss of weight and impairment of function. The two varieties, simple and numerical, are often associated, the latter being an advanced stage of the former.

Simple atrophy is the commonest form, and may affect all tissues, as is well shown in ordinary emaciation.

The cells of all glands may undergo simple atrophy; they become smaller, and are often finely granular from the presence of molecular fat. Muscular tissue may also atrophy by simple diminution in the size of its primitive fasciculi.

Unless their *vital activity* is exhausted, the shrunken cells are capable of recovery; all that is necessary for their restitution is diminution of waste or increase of assimilation, according as the one or the other is faulty.

Numerical atrophy is often an advanced stage of *simple atrophy*. The elements not only diminish in size, but some actually perish, as is well seen in advanced atrophy of muscle; restitution is then possible only by the production of new elements. In certain tissues —as the spleen, lymphatic glands, and skin—atrophy is due mainly to numerical loss.

Although atrophy in its strict signification consists simply in a diminution in size or in number of the component elements of a tissue, it *is rarely a perfectly simple process*, but is usually associated with more or less *fatty degeneration*. This indicates some qualitative error in the metabolism of the cells. It will be seen subsequently that fatty degeneration arises from causes very similar to those which produce atrophy itself.

All the tissues of which an organ consists may waste, but the term " atrophy " implies, primarily and chiefly, wasting of its characteristic cells, as opposed to the stroma. The vessels and nerves also share in the wasting process. The fibrous constituents are the last to atrophy; indeed, as the higher cells shrink and disappear, the connective tissue of the organ tends to *increase* (*replacement-fibrosis*) —as in the secondary " scleroses " of the spinal cord. The overgrowth of connective tissue in such cases is probably due to the fact that, owing to the death of the higher cells, a larger blood-supply than before is available for the less specialised tissue. It is also possible that substances formed in the process of degeneration of the higher cells may act as irritants to the connective tissue and provoke its overgrowth.

The **naked-eye** recognition of atrophy is often difficult. Atrophied organs contain less blood, and are drier, paler, tougher, and more fibrous-looking than in health. An atrophied organ containing

pigment may, however, look unusually dark in colour—*e.g.*, the liver in starvation. The great criterion is the *diminution in weight and size* of an organ; these, however, vary considerably in health—proportionately to the weight and size of the whole body; moreover organs may be small from incomplete development. Again, accumulation of blood and other fluids in an atrophied organ, or overgrowth of its fibrous stroma, or accumulation of fat, may bring its weight and size up to or beyond the average, although its essential tissue is considerably diminished in amount.

ÆTIOLOGY.—Atrophy may be caused by (1) deficiency in the supply of nutriment, (2) by injurious pressure exercised by neighbouring parts or by external agents, (3) diminution of function, (4) exhaustion of inherited vital energy, or (5) removal of trophic nervous influence.

1. **Deficiency in the Supply of Nutriment.**—The effect of diminishing the blood-supply to a part will vary, according to the degree of the diminution, from slight atrophy to absolute necrosis.

This cause of atrophy may be brought about: (1) *By obstruction of the supplying vessels before they enter a part.* Thus pressure of an abdominal aneurysm on the spermatic artery may cause atrophy of the testis; and fracture of a long bone, above the point where its nutrient artery enters, may result in wasting of the upper fragment. (2) *By passive congestion.* The circulation is impeded, as the blood is not returned normally by the veins. Hence there is deficient arterial supply, and atrophy results. This is seen in the passively-congested liver of heart-disease.

2. **By Uniform and Continuous Pressure** which does not compress the veins disproportionately. Thus, atrophy, even of bones, results from pressure of aneurysms and tumours; deep fissures are formed in solid organs from pressure of band-like adhesions; atrophy of the kidneys will follow obstruction in the urinary passages; and, rarely, wasting of a testis may be due to pressure of an old hæmatocele or hydrocele. Pressure may also arise within an organ by the appearance of some new growth distending its capsule and pressing on the rest of its contents, or by the formation of bands of contracting cicatricial tissues traversing its interior. The effect of the latter process is seen in cirrhosis of the liver. In all " pressure-atrophies " the constant pressure also acts directly on the cells of the part and thus impairs their powers.

3. **Diminution of Function.**—Atrophy always causes diminished functional activity; but sometimes diminished functional activity seems to be itself the cause of atrophy (*disuse-atrophy*).

Probably exercise of the proper function of any tissue is a necessary condition of its maintenance in health. Further, this vital activity stimulates in some way the blood-flow to the part. The supply is, as a rule, speedily adapted to any variation in the demand, and may be stimulated by the presence in the blood of hormones derived from the activities of the cells in question. Consequently, tissues will, soon after they have ceased to perform their functions,

receive only sufficient material for those chemical processes which still go on in them. This is insufficient to maintain the mass of protoplasm required to do the full work of the tissue; hence some of it atrophies.

Muscles atrophy when they are rendered inactive by chronic disease of joints, by splints, or by paralysis from disease or injury of the nervous system *above* the anterior cornual cells with which they are connected—*i.e.*, by an "upper segment" lesion. When the muscles of a part waste, all its other tissues—nerves, vessels, bones, and skin—suffer ultimately from impaired blood-supply. Thus, in part at least, we may explain wasting of the bone in a stump or limb long kept at rest: the absence of that intermittent pressure, which it is the function of bones to bear, is probably a secondary cause; at all events, increased strain causes hypertrophy of a bone. After removal of the distal part of a limb, the main artery and branches supplying it become smaller and thinner. The rectum dwindles after colotomy to a scarcely pervious cord: in this case the passage of fæces over the mucous membrane no doubt acts as a stimulant to its vessels, as well as an excitant of muscular action; and as, after colotomy, the rectum is never distended, its tissues adapt themselves to the empty condition.

4. **Exhaustion of the Inherited Vital Energy.**—After birth, those parts which are no longer required in the altered circulation gradually atrophy. The umbilical arteries and vein become thrombosed up to their first branches, and shrink to a fibrous cord as the clots organise—just like any other vessel cut across or tied. But this does not explain the closure of the ductus venosus or ductus arteriosus, in which the conditions are not favourable to thrombosis. Obliteration of these vessels can at present be spoken of simply as a developmental fact, comparable with closure of the foramen ovale. The Wolffian body disappears as the kidneys develop, and the thymus wastes in the second year of life. These, perhaps, are examples of atrophy of organs following the development of others better fitted to do the work—illustrating, as it were, the converse of the law that when an organ atrophies or is removed, correlated organs hypertrophy and take on its function. (See Hypertrophy.)

The female generative organs atrophy at from forty-five to fifty years of age, the male considerably later; the spleen and whole lymphatic system waste after middle life; probably in these cases the vital energy of the cells of the parts concerned is exhausted about the times mentioned, and diminished function is the result, not the cause.

5. **Removal of Trophic Nervous Influence.**—When a muscle is cut off from its connection with the cells in the anterior cornu, or when these cells are destroyed or seriously injured ("lower segment" lesion), atrophy sets in. Examples of this are afforded by the acute bulbar and spinal paralyses of adults, infantile paralysis, some cases of progressive muscular atrophy, neuritis from any cause, and rupture, contusion, or section of a nerve. Langley maintains that

after nerve-section the muscle falls into a state of continuous fibrillary contraction, and that the wasting is due to overaction, not to disuse. Salivary glands waste on section of their nerves. Nerves cut off from their ganglion-cells (of which they are long processes) also degenerate rapidly and waste. In all these cases the interstitial connective tissue increases, and often becomes loaded with fat, as the higher tissue disappears. (See Diseases of Nervous System.)

General Atrophy.

The term **general atrophy** is sometimes employed as a synonym for general wasting of the whole body. In general wasting, the first tissue to atrophy is the subcutaneous adipose tissue; the fat around the viscera, in the omentum, and in other parts follows; then the muscles and glandular organs; and, last of all, the osseous and nervous tissues.

General atrophy may be caused by:

1. **Deficiency in the Supply of Nutriment.**—Thus the following conditions may all be causes of general atrophy: deficient supply of food; obstruction to the passage of food into the stomach or intestines, as in stricture of the œsophagus or pylorus; the defective assimilation which results from the various conditions giving rise to dyspepsia; interference with the absorption of the chyle, from obstruction of the thoracic duct.

2. **Excessive Waste.**—All conditions attended by the loss of large quantities of nutritive material may also be causes of general atrophy. Among these are: continuous hæmorrhages; profuse and long-continued suppuration from chronic bone-disease or empyema; diarrhœa; and the excretion of large quantities of albumen in Bright's disease, or of sugar in diabetes mellitus. The waste from increased tissue-change accompanying acute febrile diseases must also be included under this head.

3. **The Action of Poisons.**—In children who are the subjects of congenital syphilis very marked wasting of all the tissues may occur, apart from such causes as vomiting or diarrhœa. This wasting appears to be analogous to the local atrophies of the nervous system (tabes dorsalis, etc.), which are caused by syphilis, and to be due to the direct action of the virus of the disease.

Although general atrophy may occasionally be referred to one of the foregoing causes, it is usually due to the combined influence of two or more of them. The atrophy associated with pulmonary tuberculosis, for example, results partly from *loss of nutritive material* in profuse expectoration and diarrhœa, partly from *deficient supply* consequent upon imperfect oxidation of the blood and upon interference with assimilation which is so often caused by structural changes in the stomach and intestines, and partly from the *increased tissue-waste* of fever. In the wasting of old age, in addition to the general diminution of nutritive activity, there is frequently some condition of the digestive organs which interferes with assimilation;

this materially aids in producing the ultimate result. Increased tissue-waste, loss of appetite, and interference with assimilation, all help to produce the atrophy which accompanies fever.

Atrophy of Bone.

As in other tissues, atrophy of bone is usually accompanied by more or less fatty degeneration. *Old age, disuse,* and *constant pressure* are its most frequent causes.

When due to *old age,* there is diminution in weight, but no change in size. The loss of weight is the result of the gradual conversion of the compact tissue into one closely resembling the cancellous. The spaces become larger and their bony walls thinner; the bone is rendered thereby markedly brittle. This form, known as **eccentric atrophy,** occurs with other senile changes, and generally affects all bones, but is specially marked in the neck of the femur, rendering it liable to fracture from trivial injuries.

Atrophy from *disuse* or from *constant pressure* is accompanied by diminution in size as well as in weight. The bone beneath the periosteum is gradually absorbed, and the medullary canal shrinks proportionately. This variety is known as **concentric atrophy,** but the changes characteristic of the *eccentric* form are often present as well. It is a local alteration, and is met with especially in the long bones, in cases of long-standing ankylosis, dislocation, or paralysis. The effect of constant pressure in the production of atrophy is well shown in the enlargement of clefts and perforations of the hard palate which often results from the insertion of plugs. These interfere with the blood-supply and thus cause atrophy.

Atrophy of bone must not be confounded with *arrested development.* The latter is commonly met with in the later stages of infantile paralysis; and a very similar result may be produced by anything which causes premature ossification of an epiphysis, such as rickets, inflammation, or injury. These are the common causes of stunted limbs.

Brown Atrophy of the Heart.

This condition consists in a gradual atrophy of the muscular fibres, together with the formation of granules of brownish-yellow or blackish pigment. These granules of pigment, which are probably the colouring matter of the muscle, are usually grouped in clusters around the nuclei. This condition may be associated with a more or less marked degree of fatty degeneration, and usually occurs as a senile change, or as a part of general marasmus from other causes. It is also met with in some cases of cardiac atrophy. Its recognition is in most cases impossible without the aid of the microscope.

CHAPTER V

NUTRITION IMPAIRED—*Continued*

DEGENERATIONS.

THE exact nature of the changes which occur in so-called Degenerations is not yet fully understood, and any classification of these processes is necessarily tentative. They have been divided into *intracellular* and *extracellular*, the only instance of the latter change being amyloid degeneration. They have also (p. 26) been divided into *infiltrations* and *degenerations* proper. For practical purposes they may be conveniently arranged in two groups: (1) *Cloudy Swelling* and *Fatty Changes*, including fatty infiltration (accumulation) and fatty degeneration; (2) *Mucoid, Colloid, Hyaline*, and *Amyloid* Degenerations, resembling one another in the transparent structureless character of the degenerative product. *Calcareous Infiltration* and *Pigmentary Changes* will be considered at the end of this section.

CLOUDY SWELLING.

Cloudy swelling, sometimes known as *parenchymatous or granular degeneration, or albuminous infiltration*, is a frequent change, being found in all diseases attended by considerable pyrexia. Wickham Legg and Liebermeister produced it by subjecting animals to a high external temperature; they therefore regarded the change as due simply to the fever, which, in their opinion, caused increased destruction of protein. It has been shown by Halliburton and others that coagulation of cell-globulins may occur at a temperature of 47° C. On the other hand, it may be noted that the degeneration is specially pronounced in bad cases of diphtheria, in which disease the temperature is often low. Hence rise of temperature is not the sole cause of the condition. A more probable explanation is that the infective material in the blood—the cause of the fever—has a deleterious action on the tissues. This is supported by the observation that cloudy swelling is the first change noticeable in poisoning by phosphorus, arsenic, and the mineral acids, all of which lead ultimately to fatty degeneration of protoplasm. Again, cloudy swelling is found in inflamed parts, and we shall see later that inflammation is always due to the action of an irritant, which, if it were of

sufficient intensity, would produce death of the tissue. Cloudy swelling also occurs as the first change in dead cells, constituting the earliest stage of autolysis. It would appear, therefore, that *cloudy swelling is due to the action upon the tissues of some agency which tends to cause their death;* in the majority of instances poisons are at work, while elevation of the temperature of protoplasm above the normal may assist their action, or possibly be efficient by itself in causing the change in rare instances.

In considering the histology of this change, we shall find that advanced cloudy swelling passes insensibly into fatty degeneration: it is, therefore, to be regarded *as the first step towards fatty degeneration.*

APPEARANCES.—To the *Naked Eye,* when the change is well-marked, the affected organs are somewhat swollen, and may be either anæmic or slightly hyperæmic; the surface of a section bulges up a little; and the tissue is softer and more opaque than natural.

Microscopically, the cells in unstained specimens are swollen, and their protoplasm is finely granular; the nucleus and any cell-structure being obscure or even indistinguishable. The granules, which first appear like a precipitate in the cells, refarct light but feebly; they are unstained by osmic acid; they dissolve in dilute acetic acid, but not in ether, and are therefore albuminous. In advanced cases, larger, strongly refracting granules, blackening with osmic acid, and soluble in ether, but not in acetic acid—therefore fatty—are found associated with the albuminous granules. The granules have been variously regarded as an accumulation of albuminous material, not used up in the metabolism of the cell, and as lipoid and albuminous particles derived from breaking down or alteration of protoplasm. Their exact nature still remains uncertain. The affected organs recover in those cases in which the primary disease does not prove fatal, although many individual cells may die and disappear.

SEATS.—The liver, kidneys, heart, and voluntary muscles show the change most plainly; but probably all protoplasm suffers. The change may be much more advanced in some organs than in others, owing probably to some special stress to which the organs most affected have been subjected.

In the **Kidneys** the cortex is principally affected. The Malpighian bodies and the pyramids are usually hyperæmic, and contrast with the general pallor of the cortex. The tubal epithelium presents the appearances above described; they are well seen in the early stages of scarlatinal nephritis.

The walls of the **Heart** become pale and soft. The muscular fibres are finely granular, and tend to lose their distinct striation.

In the **Lungs** the change cannot be recognised by the naked eye. The epithelial cells, according to Buhl, are swollen and granular from the presence of albuminous and fatty particles, and are easily detached from the alveolar walls.

EFFECTS.—This change is a sign of the impaired health of the

cells: their vital activity will therefore be proportionately affected. Its most serious effect is upon the heart: the vigour of the muscular contraction is always much impaired.

FATTY CHANGES.

According to Cohnheim, all fat found in the body has the same chemical composition, being a mixture of glyceryl-esters of stearic, oleic, and palmitic acids. The mixture, however, seems to vary somewhat in different parts of the body, and according to age, there being more oleic acid in elderly persons. Further, the deposited fat alters with diet; thus, in dogs fed with colza oil, linseed oil, or mutton-fat, these substances may be found in the normal reservoirs of fat.

Abnormal appearance of fat in living cells may result (1) from increase in the normal process of storage (*accumulation*), the cells themselves remaining healthy; or (2) from defect in the cell-functions, by which either (*a*) fat or its components (glycerine, soaps) are not utilised normally, or (*b*) the actual protoplasm of the cell is decomposed into fat. This last process may be classed as "fatty *degeneration*." Normal protoplasm contains a certain quantity of fat in loose combination (lipoid)—a condition in which it is not stained by appropriate reagents. This fat may separate out and become visible, without the cell actually containing any larger amount of fat than before. We may thus explain the fact that organs which have apparently undergone fatty degeneration do not contain any real excess of fat (Leathes).

The formation of fat by breaking down of protoplasm has been much disputed. It occurs in dead cells (see p. 21, Autolysis), and may perhaps take place in a living but damaged cell. The possibility of the formation of fat from protein was formerly supported by the experiments of Voit and Bauer on the fatty change that accompanies poisoning by phosphorus. These experiments were made to determine the source of the fat in the acute fatty degeneration produced by poisoning with this drug. Dogs were starved for twelve days, so that all available fat, whether in the tissues or in the food, might be exhausted At this period the daily excretion of nitrogen (urea) averaged eight grammes. Small doses of phosphorus were then given. The average daily excretion of nitrogen at once rose to twenty-four grammes, while the amounts of oxygen taken up, and of carbon dioxide given off, were greatly diminished. The animals were then killed, and large quantities of fat were found throughout the body. The increase in the excretion of urea showed that the destruction of proteins was also increased; and the presence of the large quantities of fat found after death made it highly probable that it had been formed as part of the general protein destruction.

These experiments have been justly criticised on the ground that it was impossible to insure the complete disappearance of fat

from the tissues in the preliminary period of starvation. Similarly the arguments brought forward by Voit and Pettenkofer, to support the theory of formation of fat from protein, based on the results obtained by feeding dogs on lean meat, have been criticised by Pflüger. He showed that their contention, that the amount of carbon retained could only be explained by its storage as fat, was based on unjustifiable assumptions regarding the composition of lean meat.

As already noted under Cloudy Swelling, organs (kidney, heart) which have undergone fatty degeneration do not contain any marked excess of fat as compared with normal organs. A fatty liver does, however, contain excess, due to abnormal transport and storage.

On the other hand, experiments were made by Lebedeff, and later repeated and elaborated by Rosenfeld, tending to show that the fat found in liver-cells as a result of poisoning by phosphorus and phloridzin is taken up by these cells from the blood and is not formed by breaking-down of the cell-protoplasm itself. Rosenfeld starved dogs till all their fat had disappeared, and then by feeding them with tallow caused this abnormal form of fat to be stored up in the adipose tissue in the place of the normal kind. On administering phloridzin to dogs thus treated, it was found that the liver-cells contained tallow in place of the fat normally produced in dogs by the action of this poison: this tallow must have been taken by the liver-cells from other parts, being conveyed to them by the blood-stream. In other words, there is abnormal transport of fat rather than abnormal formation. It must therefore be admitted that our views on the subject of fatty degeneration may need revision; and up to the present the formation of fat by the breaking-down of protein—as distinct from the complex protoplasmic molecule—remains unproved.

I. FATTY ACCUMULATION.

In fatty accumulation, fat brought by the blood is taken up and deposited in the cells of certain tissues which serve physiologically as reservoirs of fat—viz., (1) *connective tissue*, (2) the *medulla* of limb-bones, and (3), to a less extent, the *liver*. It is impossible to draw any line between normal and pathological fatty accumulation so long as the process is confined to those cell-groups which are physiologically liable to this change. Thus the subcutaneous fat and the fat normally present on the surface of the heart, along the coronary vessels, in middle-aged adults, vary much in amount consistently with perfect health. But when the fat spreads widely over the surface of the heart, it is clearly abnormal; and the evidence of disease is still stronger when the fat appears between the muscular fibres, in cells which normally contain none.

The tendency to morbid fatty accumulation may be **general** (*obesity*) or **local.** In obesity the subperitoneal and subcutaneous

connective tissues suffer earliest and most, the accumulation spreading later to the interstitial connective tissue of organs in which metabolism is still apparently normal, as in the heart. The seats of local fatty accumulation have already been mentioned. It may be noted that the cells of the connective tissue of working organs (muscles, nerves, glands) are not usually affected; but they may be so, if the activity of the organ is in any way arrested.

CAUSES—1. **Excess of Food.**—Whenever nutritive material is present in the blood in excess of the amount required for the supply of force and maintenance of heat in the body, there is a tendency to the deposit (storage) of fat, first in regions in which it is normally present, and later in parts which usually contain none. For this, *fat* itself need not be present in excess in the food: the presence of *carbohydrates* in quantity sufficient to satisfy the wants of the organism will protect fat from oxidation and lead to its deposition. The *proteins* of the food may also be split into nitrogenous and non-nitrogenous factors, and from the latter of these fat may possibly be formed (but see pp. 34 and 35). Excess of fat may sometimes be present in the fluids around certain cells—*e.g.*, the liver-cells after a meal containing much fat, and the connective-tissue cells and wandering cells near a focus of fatty degeneration.

2. **Inherited Tendency.**—A tendency to obesity or to leanness runs in families; and it is notorious that some very stout people are small eaters and take active exercise, whilst many thin subjects are just the reverse.

3. **Disordered Metabolism.**—This may result from sedentary and luxurious habits, lassitude of mind and body, high external temperature, destruction of much lung-tissue by chronic disease, or reduction of the oxygen-carrying power of the blood owing to diminution of red corpuscles or of their hæmoglobin. Some suppose that the fat contained in a normal diet may, under such circumstances, be incompletely oxidised; and that oxidation may be diminished by slow circulation or by the circulation of de-oxidised blood through a part—conditions which normally obtain in the liver and in parts thrown out of work—as in a muscle kept at rest. There is, however, no adequate proof of this.

It is not unlikely that fat-metabolism may be controlled by some internal secretion, not yet identified. Certainly adiposity is found associated with disease of the pituitary body, and it is common in castrated animals.

APPEARANCES.—To the *naked eye* an organ in which fat has accumulated is more or less swollen. Any sharp edges it may possess tend to become thick and rounded. It is generally somewhat pale and yellowish on account of anæmia (from increased intracapsular pressure) and the presence of fat; it is doughy and inelastic, and both receives and retains an impression from the pressure of a finger; and it is softer than natural. The knife used to cut a fatty organ becomes greasy, and may show distinct drops of oil on the blade. Except mechanically, the fat need not appre-

ciably hinder the protoplasm of the organ from discharging its functions. Ultimately, however, pressure upon the cells proper may become so severe that they may fail to get sufficient nourishment; they will then undergo fatty degeneration, and atrophy.

Microscopically, cells in which fat is accumulating are seen to contain droplets of oil—very small at first, but still distinct droplets. These run together, push the cell-nucleus aside and distend the cell until its original contents seem to have become a mere capsule to the fat. As the fat is added to the previous cell-contents, the cell is enlarged in proportion to the amount of fat it contains.

II. FATTY DEGENERATION.

In this condition the fat present in the cells is either (1) formed by actual disintegration of the protoplasm of the cells, or (2) is taken up by the cells from the blood and remains unaltered, owing to defect in the vital power of the cell to assimilate it.

That fat may be formed by breaking down of *protoplasm* is proved by the phenomena of autolysis; and a similar process is seen physiologically in the formation of cerumen and sebum. Evidence of the same process is seen in the fatty degeneration of the muscular fibres of the uterus undergoing involution. It was formerly supposed that the transformation of entire bodies, which have lain for many weeks or months in water or damp soil, into *adipocere*—a soap formed by combination of fat with ammonia and lime—was an illustration of the same process, but this change is now generally believed to be due to the action of micro-organisms.

Stolnikow and Gaule have published experiments which seem to show that fat can be produced by the decomposition of *lecithin*, the phosphuretted fat of the nervous system, and a constituent of many other tissues. According to these observers, glycero-phosphoric acid, stearic acid, and cholin are formed in the process.

ÆTIOLOGY.—The presence of visible fat in a cell which does not normally contain this substance indicates some disturbance in its metabolism. This may be due either (1) to direct injury of the cell, the protoplasm of which consequently breaks down with liberation of fat (autolysis); or (2) to the inability of the cell to utilise the food placed at its disposal. A certain quantity of fat is normally contained in the protoplasmic molecule ("masked fat"). Certain poisons cause this to appear as visible droplets. Loraine Smith believes that they act by preventing the cell-protoplasm from taking up fat in a normal manner.

1. Injury may result from insufficient blood-supply or from an unusual increase in the demand for nutriment. (*a*) *The normal blood-supply may be actually diminished*, as occurs when chronic arterio-sclerotic changes in the coronary arteries cause narrowing of their lumen and consequent diminution of the supply of blood to the muscle-cells of the heart (p. 44). (*b*) *Increased work may*

fall upon the cells without any corresponding increase in their blood-supply. Thus the fibres of a much-hypertrophied heart may undergo fatty degeneration because the coronary arteries—themselves free from disease—are unable to furnish the additional supply of nutriment required. (*c*) *Actual deficiencies in the blood may impair its nutritive value,* as when there is a diminution in the corpuscles or in the hæmoglobin, and, therefore, in the oxygen-carrying power. Thus fatty degeneration occurs to a notable degree in pernicious anæmia, in which the total hæmoglobin is much diminished. In these cases there is but little tendency to fatty degeneration in those parts which can be kept in comparative rest; for anæmia, while seriously interfering with the reserve power, is rarely intense enough to diminish the respiratory exchange usual during rest. It is possible, however, that in this disease some poison is at work which acts injuriously on the cells (see below).

2. The failure of the cell to make use of the material placed at its disposal is probably the more important cause. (*a*) This may be the result of the action of *bacterial toxines,* such as that of diphtheria, which causes fatty degeneration of voluntary muscle-fibres, including those of the heart; or that of tubercle, which leads to a corresponding degeneration of the affected cells. (*b*) It may also depend upon the influence of *inorganic poisons,* such as phosphorus, arsenic, alcohol, and carbon monoxide, which act directly upon the protoplasm. (*c*) In many cases, the failure of the cell must be regarded as a *senile change* and dependent upon the exhaustion of the inherited vital capacities of the cell. This is possibly a factor in the fatty degeneration of cancer-cells, which may occur independently of any limitation of the blood-supply.

Appearances.—In advanced stages fatty degeneration produces characteristic alterations visible to the *naked eye.* These are (1) slight or moderate swelling—which, however, is often replaced by more or less shrinking of the organ when absorption of the fat is going on, as in advanced acute atrophy of the liver; (2) admixture of an opaque yellow colour with the normal tint of the tissue, often in the form of patches, spots, or streaks, as extreme degrees of the change are usually reached only in limited areas; and (3) loss of elasticity with diminished consistence—the organ being flabby and friable, and its capsule wrinkling easily. When a section is cut, fat may be found upon the knife, and the normal distinctness of the structure is obscured.

The *microscope* is, however, necessary for the recognition of the earliest stages of this degeneration. The fat appears as minute granules, first of all in the protoplasm of the affected cells, and later on in the nucleus. The granules—characterised by their sharp contour, strong refractive power, staining-reaction (black with osmic acid), insolubility in acetic acid, and solubility in ether—gradually increase in number, till the whole of the protoplasm may be transformed; some of them may coalesce and form distinct droplets of fat. As the process advances, the cells increase in size

and become more globular in shape. A little later, the nucleus is involved; the cell-wall, when this exists, is destroyed; and the cell is converted into a mass of fat-granules, known as a *granule-cell.*

Granule-cells may be of two kinds: (1) dead or dying cells converted into masses of cohering fat-granules, or (2) living leucocytes (*granule-carriers*) which have taken up fat-granules from a focus of degeneration—probably to convey them into the lymphatics and thus effect absorption. Connective-tissue and neuroglia cells near foci of degeneration similarly become charged with fat-granules. *Fatty granules* may be distinguished from the *albuminous granules* of cloudy swelling by their larger size, their higher refractive power, their insolubility in acetic acid, their solubility in ether, and their staining-reaction with osmic acid. The histological methods for the demonstration of fat in the tissues have been added to and elaborated during recent years. Thus Scharlach R and Sudan III. have largely replaced osmic acid as general fat-stains. They are chemically indifferent bodies which depend for their staining properties on their ready solubility in fat, to which they impart a red or orange colour. In Nile blue sulphate A we have a differential fat-stain. The base combines with fatty acids, forming a blue compound, and, in watery solutions of the stain, a chemically indifferent body is gradually formed which is of a red colour and very soluble in fats; hence neutral fats are stained red and fatty acids blue. Again, the staining reaction with osmic acid, which depends on the oxidation of unsaturated fats such as olein, has been elaborated by Marchi and others to give differential results with fats which are oxidised with greater or with less difficulty, and these and similar methods have formed the foundation for the histological study of nerve-degeneration.

TERMINATIONS—1. *Recovery.*—The degenerative process may cease and the fat be absorbed before the part has been dangerously involved. Such recovery probably occurs frequently—for example, in the kidneys and heart. When the elements are completely degenerated, the fatty débris is usually removed by leucocytes, or saponified and absorbed. This is seen in the fatty degeneration and absorption of the inflammatory products occurring in croupous pneumonia; in the degeneration and absorption of the cells of new-growths—leading to central "cupping" or "umbilication" of nodules, or to shrinking of the whole mass (atrophic scirrhus); and in the degeneration of small damaged areas, such as result from embolism, thrombosis, or hæmorrhage in the brain or other organ. As the result of such absorption there may be left a meshwork of vessels and connective tissue from which the essential cells have disappeared, as in the later (red) stage of acute yellow atrophy of the liver; or there may be an ordinary scar, from the development of fibrous tissue; or, lastly, a cavity containing clear fluid may remain. For absorption to occur, the tissues round the degenerated cells must be freely supplied with blood.

2. *Caseation.*—In this mode of termination the fatty products

are not absorbed, but are gradually converted into a yellowish friable material, which has been compared to soft cheese. It is generally said to result from disproportion between the degenerated mass and the vessels by which absorption might be effected—a disproportion which is, in the first instance, the principal cause of the degeneration. It is most frequent, therefore, in parts which contain but few vessels, or in which the vessels become obliterated by pressure from without, or by narrowing of their lumen by endarteritis. Caseation is, consequently, most often met with in tubercular and gummatous masses, and in rapidly-growing carcinomata and sarcomata.

Caseous masses are frequently met with in the lymphatic glands, the brain, the bones, and especially in the lungs. Considerable confusion has arisen as to their nature and origin. Formerly all caseous masses were regarded as essentially tubercular, and it is true that tubercular lesions have a greater tendency than any others to caseate fully, and to form *typical* cheesy collections. (See Tuberculosis.) But, as just stated, other formations may undergo a change which is practically indistinguishable; so caseation cannot be regarded as proving more than the previous occurrence of fatty degeneration. A caseous mass is tubercular only when it is due to the presence of the *Bacillus tuberculosis*.

The process consists in a gradual drying up of the degenerated elements; the fluids are absorbed, the cells—many of which are incompletely degenerated—shrivel and atrophy, the fat undergoes partial saponification, cholesterin forms, and the tissue thus becomes converted into a soft, yellowish-white cheesy substance, composed of atrophied cells, fatty débris, and cholesterin-crystals. This cheesy material may gradually dry up more and more, and ultimately become encapsuled by a layer of fibrous tissue, and even calcified. In other cases it may undergo a process of softening and liquefaction. (See Calcification and Chronic Abscess.)

Results.—The effect of fatty degeneration is to impair, and sometimes, as in the case of the heart, even to arrest function. Recovery is only possible in the earlier stages.

Fatty Liver.

In the liver fatty change is exceedingly frequent, constituting what is commonly known as the *fatty liver*. This is largely due (1) to the excess of fat and carbohydrates in the portal blood; (2) to the deposition of fat from the metabolism of proteins during the formation of urea; and (3) to the low pressure and slow circulation in the portal vessels—conditions least favourable to metabolism, and most favourable to deposition. An accumulation of fat in the liver may occur under two opposite conditions of nutrition. In the first of these there is *general obesity*, and the excess of fat accumulates in the liver as well as in other parts; in the second there are *general emaciation*, anæmia, and other conditions leading to diminution in the nutritive power of the blood and diminished vitality of

the liver-cells. The liver in phthisis is an example of the second of these conditions, the defect in the blood being, in this case, increased by the presence of bacterial products which affect the metabolism of the cells.

Whereas the healthy liver-cell constantly contains a small amount of fat, and may at times hold a considerable quantity, the *fatty liver* is one which constantly contains an abnormal quantity of fat. As the fat is usually deposited from the blood in the portal capillaries, the increase is first observable in the external zone of the hepatic lobules (Fig. 8). It accumulates within the cells as minute

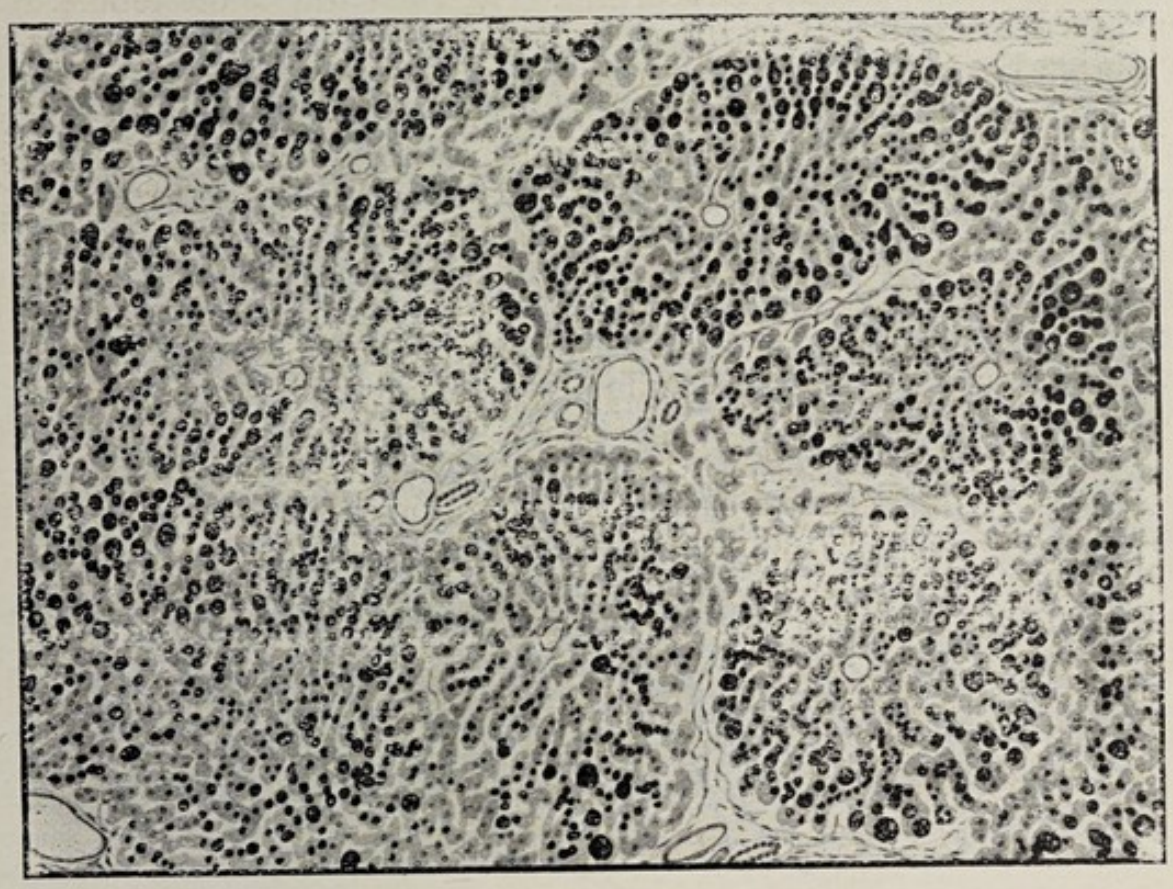


FIG. 8.—FATTY LIVER.

The globules of fat are darkly stained (with Scharlach R) and are situated mainly in the periphery of the lobules.

globules, which increase, coalesce, and form large drops of fat. These ultimately distend the cells, which become larger and more globular. As the process advances, the accumulation spreads from the periphery towards the centre of the lobule, until its whole mass may be involved, and all its cells distended with fat. The vitality of the cells is not materially impaired by the change, as is shown by the presence of bile in the intestine and in the gall-bladder. In some exceptional cases the accumulation of fat is most marked around the intralobular veins. Virchow suggested that in these instances the fat is becoming excreted, and that only the last cells retain a little of it.

To the *naked eye*, the fatty liver is generally increased in size—in advanced stages to perhaps twice the normal. The surface is smooth, the edges are thickened and rounded, and the specific gravity is diminished so that detached portions may float in water, although the absolute weight of the whole organ may be increased. If the accumulation of fat is slight, involving merely the portal zone of the lobules, the cut surface presents a mottled appearance, the external fatty zone being opaque yellowish-white, whilst the centre is unaltered, or is hyperæmic, and appears as a red spot (*fatty nutmeg liver*). The more extensive the accumulation, the larger is the pale zone; and ultimately, when the whole lobule is involved, there is left in the centre only a reddish-brown point—marking the position of the intralobular vein. In many cases even this point is lost: then the organ is of an almost uniform opaque, yellowish-white colour, and the boundary between the individual lobules may be completely obscured. In exceptional cases the accumulation of fat is much more abundant in some portions of the liver than in others, so that on section yellowish points and streaks are seen scattered over its surface. The consistence of the organ is much diminished; it feels doughy, and pits on pressure with the finger, while the knife used to cut it becomes coated with oil.

In cases of extreme fatty accumulation, such as sometimes occurs in persons dying of cancer or phthisis, a section of the liver may look exactly like ordinary adipose tissue, being distinguishable from it only by a faint appearance of a radiating structure here and there, and by the presence of the portal canals and their contained vessels.

The pressure exercised by the accumulated fat produces considerable anæmia of the organ, but the interference with the circulation is *never sufficient to cause ascites, hæmorrhage, or other evidences of portal congestion.*

Fatty Accumulation in Muscle.

1. **Fatty Accumulation in Voluntary Muscle.**—The *cells in the connective tissue* which surrounds the fasciculi of the muscle may become filled with fat. The interstitial fat thus produced varies in amount. In some cases single rows of fat-cells alternate with rows of muscular fasciculi; at other times the accumulation is less regular, more existing between some fibres than between others: in all but the most advanced cases, however, the muscular elements may, under the microscope, be discovered lying amongst the fat—even though, to the naked eye, the muscle appears to be entirely converted into fat. Ultimately the muscular fibres may undergo true fatty degeneration, and waste until they completely disappear.

This form of fatty accumulation is frequent in *animals* which have been *artificially fattened*—the fat being also increased in the usual situations. It may also occur in *muscles* which from any cause have

been *incapacitated* for some time, and in which, consequently, the circulation is reduced to a minimum. Thus it is found in long-standing paralyses from lesions of the brain or cord (upper segment), and in muscles which have been rendered useless by ankylosis of a joint. In progressive muscular atrophy, and in chronic lead-poisoning, the affected muscles exhibit this change, and an advanced condition of fatty accumulation is seen in pseudo-hypertrophic muscular atrophy.

2. **Fatty Accumulation in the Heart.**—This is not infrequent in general obesity, and after pericarditis followed by adhesion of the two contiguous surfaces of the pericardium. It must be carefully distinguished from the much graver condition of fatty degeneration. In health there is a varying amount of fat beneath the visceral pericardium; it is always most abundant around the vessels in the grooves between the auricles and ventricles. In fatty accumulation this may increase so as to cover the right ventricle, but the left is rarely, if ever, completely enveloped: at the same time, the fat may push in along the vessels between the muscular fibres, so that, on the right side, to the naked eye, all appearance of muscular structure may be lost, the walls looking like a layer of fat, perhaps half an inch thick. In hearts less affected, striæ of fat will be seen lying amongst the muscle. The fat is always most abundant near the surface, the muscular structure becoming more evident towards the endocardium; at the base of the ventricles thick villous processes may form.

The interstitial fat displaces and compresses the muscular fibres between which it lies, and diminishes the blood-supply and contractile power of the muscle, perhaps ultimately causing true fatty degeneration of the muscle. The two processes often coexist. Fatty accumulation is probably possible only as the functional activity of the muscle diminishes, and the continued action of the causes leading to this depression would ultimately cause degeneration of the fibres. Fatty degeneration and wasting of muscular fibres, on the other hand, are very likely to be followed by accumulation of fat in the interstitial tissue.

Fatty Degeneration of Muscle.

Both striated and non-striated muscle may be the seat of *fatty degeneration*. In both, the muscle-cells are the seat of the change; they become filled with fat-granules and are ultimately destroyed; the process thus differs essentially from *fatty accumulation*.

1. **Non-Striated Muscle.**—Fatty degeneration is frequently met with in the middle coat of arteries undergoing atheroma and in the muscular fibres of a uterus in process of involution.

2. **Striated Muscle.**—Both the voluntary muscles and the walls of the heart show identical changes. The earliest stage of the affection is characterised by an indistinctness in the transverse markings of the fibres, which in many parts become studded with

minute particles of fat. These gradually increase in number and size, but at first remain small, and are usually distributed somewhat irregularly within the sarcolemma. In some parts single or parallel rows of granules are found running along the length of the fibre; in others they are grouped around the nuclei, which they seem to lengthen, or arranged in transverse lines corresponding with the striæ of the muscle. The fibres become extremely friable, and are readily broken up into short fragments. As the process advances the transverse markings entirely disappear, and nothing but molecular fat and oil-globules are seen within the sarcolemma. It has, however, been affirmed that in some cases the striation is merely obscured by the fat-droplets, and that these are in the early stages confined to the interfibrillary sarcoplasm. The sarcolemma itself may ultimately be destroyed, and nothing remain of the original fibre but the fatty débris. This is true "fatty degeneration" of muscle.

This change is seen in diptheria, in certain blood diseases of a severe type, and in phosphorus poisoning.

It is in the **heart,** however, that fatty degeneration of muscle is most frequently met with, and here it assumes a most important aspect from the deleterious influence which it exercises upon the motor power of the organ. The degeneration may be *diffuse* or *circumscribed ; slight* or *advanced ; acute* or *chronic.* The wider the extent of tissue that is affected, the less advanced, as a rule, is the degree of the degeneration. It is in those cases in which small tracts of tissue only are involved that the process is met with in its most advanced stage.

When the change is slight, as in the **diffuse** form, the muscle is somewhat softer and more flabby than natural; it is more friable, and often breaks with a soft granular fracture; while its colour is rather paler and more opaque than that of healthy cardiac tissue. The microscope shows the muscular fibres to have lost to some extent their striation, and to contain granules of fat (Fig. 9). This form of degeneration often occurs rapidly, and is caused by these general disturbances of metabolism already alluded to (p. 37).

There is no clear line dividing the diffuse from the circumscribed form. Sometimes the degeneration, although more or less general and due to general causes, is much more advanced in some parts than in others.

The **circumscribed** form is generally due to *some interference with the circulation in the coronary arteries.* This occurs especially in connection with aortic incompetence, when the pressure of blood in the arteries is defectively maintained, and explains the early failure of cardiac power in this form of valvular disease. Atheromatous changes at the orifices of these arteries lead in the same way to diffuse fatty degeneration. Adhesive pericarditis and myocarditis act similarly; they hamper the heart mechanically, and the cause of the condition (rheumatism or other infection) acts injuriously on the muscle-cells.

In such cases the heart presents a mottled appearance; opaque, pale yellowish or brownish patches are seen irregularly distributed throughout its substance. These patches, which vary considerably in size and form, are met with especially in the papillary muscles, in the columnæ carneæ, and in the layers of fibres immediately beneath the endocardium. They may also occur beneath the pericardium, and in the deeper portions of the organ. They correspond with the most degenerated portions of the tissue. They are soft and flabby, and have a soft consistence, tearing readily under the finger. Under the microscope, the fibres are seen to be in an advanced stage of fatty degeneration, containing particles of fat and oil-globules, which in many parts have escaped and lie free

FIG. 9.—FATTY DEGENERATION OF THE HEART. FROM A CASE OF PERNICIOUS ANÆMIA. (× 400.)

From a case of pernicious anæmia. The protoplasm is replaced by globules of various sizes, stained black by osmic acid. The outlines of the fibres are irregular owing to inequality in their distension.

amongst the surrounding, but less degenerated, tissues. These more localised degenerations are most common in old people, and usually result from advanced disease of many of the *small* branches of the coronary bloodvessels, and not from conditions of general anæmia. The peripheral layers of the muscular walls also frequently undergo extensive fatty degeneration as the result of pericarditis. The connection between these localised degenerations and the occurrence of rupture or of aneurysm of the heart is described in the chapter on Diseases of the Heart.

Fatty Degeneration of Bloodvessels.

Primary fatty degeneration of bloodvessels is in most cases a senile change, but is not infrequently met with in young and apparently healthy persons. It is then, in all probability, due to

deleterious substances in the blood, or to some interference with the normal circulation.

Fatty Degeneration of Arteries.—This may be *primary*, or *secondary* to atheroma or to some infective condition of the vessels. (See Diseases of Bloodvessels.)

Primary fatty degeneration may affect any or all of the coats of the artery, but is most commonly met with in the *intima*. The change usually commences in the endothelial and sub-endothelial cells, small groups becoming affected in various parts of the vessel. It may gradually extend from within outwards, the intercellular substance softening, until, in exceptional cases, the whole thickness of the intima is destroyed.

In the earlier stages this condition is recognised by the existence of small, irregular, opaque, yellowish-white patches, projecting very slightly above the surface of the intima. These are often met with on the lining membrane of the aorta. They are in most cases readily distinguishable from atheromatous patches by their superficiality, and by the facility with which they can be stripped off from the subjacent layers, which present a natural appearance. In many cases the change is limited entirely to the innermost layers of the vessel. The more the subjacent tissues are involved, the greater is the irregularity in the shape of the patches, and the less readily can they be separated with the forceps.

The fatty patches may break down, if the cells are destroyed by the fatty change and the intercellular substance softened. The granular débris thus formed is carried away by the circulation, leaving small, irregular, superficial erosions upon the lining membrane of the vessel. These may eventually heal by proliferation of the marginal cells.

Fatty degeneration is also liable to affect the *media*—especially the muscle-cells—and in this situation its injurious influence is most marked. Here, by diminishing the elasticity and contractility of the vessel, it causes degenerative changes in the parts which it supplies, and may even lead to rupture of the affected vessel itself. This is exemplified by many cases of chronic cerebral softening and cerebral hæmorrhage, although in such instances atheroma is generally associated with the simple fatty changes. In the larger arteries, as the aorta, it is of much less importance than atheroma, which has a far more deleterious effect.

Fatty Degeneration of Capillaries.—Fatty changes are also found in the capillaries, especially in the nervous centres and the kidneys in Bright's disease. The process commences around the nuclei of the endothelial cells, and may involve considerable areas of the capillary wall, so that rupture is often the ultimate result. This is common in the smallest cerebral bloodvessels, where it is sometimes a cause of cerebral (capillary) hæmorrhage. It is said to be present in hæmophilia, and to assist in producing the tendency to hæmorrhage after slight injuries, which is characteristic of the malady.

Fatty Degeneration of the Kidneys.

Fatty degeneration of the kidneys frequently occurs as a result of disease of these organs, and accounts for the fatty casts met with in chronic tubal nephritis. It is also met with in acute yellow atrophy of the liver and in chronic wasting diseases, especially in chronic pulmonary tuberculosis. It is a result of phosphorus-poisoning and of pernicious anæmia, and accompanies amyloid degeneration.

For fatty changes in the tissues of the nervous system, see the chapter on Diseases of the Nervous System.

GLYCOGENIC ACCUMULATION.

Glycogen occurs in health, not only in the cells of the liver, but also in the muscles, in fœtal tissues, and elsewhere. Pathologically, it is found in the cells of tumours and in those at the edges of simple infarcts—both seats of fatty change; it may also be seen in the cells of inflamed tissues. Leucocytes containing granules of glycogen (*iodophilia*) are found in infective conditions (septicæmia, pneumonia, abscess-formation, etc.); it is not known whether they have simply taken up glycogen from the cells at a local focus of irritation, or acquire it at the time of their formation in the bone-marrow. The most notable accumulation of glycogen occurs, however, in *diabetes mellitus*, in which the cells of the renal tubules, of the heart-muscle, of the spleen, and of other parts, are found to contain marked quantities of glycogen. Here, as in the other cases mentioned, the accumulation of glycogen seems closely parallel to that of fat. The visible glycogen may either represent excess of saccharine matter taken up from the blood, where it exists in unusual amount, or may point to an injury to the cells arising from some form of poisoning, with consequent inability to utilise a normal kind of food.

Some authors deny that the substance stained brown by iodine in the above condition is in reality glycogen. Czerny, for example, believes it to be an albuminous material related to amyloid.

CHAPTER VI

NUTRITION IMPAIRED—*Continued*

MUCOID, COLLOID, AND HYALINE DEGENERATION.

Mucoid, Colloid, and Hyaline Degenerations resemble one another in the structureless appearance of the new material. The chemical composition of the degenerative product is not absolutely constant in any one of them. Chemically, *mucoid* and *colloid* changes seem to be identical. Probably they both include many complex proteid substances, resembling one another in their gelatinous consistence. Hyaline change is by some authors classed with these ; by others it is identified with amyloid degeneration, of which it may be an early stage.

Mucoid Degeneration.

In mucoid degeneration the affected tissues are transformed into a soft or semi-fluid substance, which, in its final stages, contains mucin. Chemically, the mucins are compounds, containing chondroitin-sulphuric acid, proteins of variable nature, and a reducing substance, glycosamin, which contains nitrogen. The substance formed under pathological conditions appears not to be absolutely identical with normal mucin. It is found in many cases to be soluble in water, and not to form a precipitate with acetic acid. It has been called " pseudo-mucin."

The *cause* of mucoid degeneration is unknown. Throughout life a mucoid change occurs physiologically in the cells of mucous membranes ; a clear drop of mucus appears in the protoplasm, and increases till the cell bursts and the mucus is evacuated—the cell, as a rule, not being destroyed, but remaining as a " goblet-cell."

In disease, mucoid degeneration may affect both cells and intercellular substance. It is met with (1) in *catarrh of mucous membranes*, the transformation occurring much more rapidly than under normal conditions, and the cells being often cast off ; and (2) as a gradual change in *connective tissue*, in *cartilage* (especially the intervertebral and costal cartilages of old people), in *bone*, and in many *new-growths*, including those of the connective-tissue type, as well as cancers, in which it may affect both cells and matrix. Ovarian tumours may also undergo mucoid degeneration.

To the naked eye, the affected parts are transformed into a homogeneous, colourless material, of a soft, mucilaginous, jelly-like consistence. When the change is limited to isolated portions of the tissue, the softened parts often present the appearance of cysts. These are most frequently met with in the costal cartilages and in new-growths. *Under the microscope*, the appearances are the same as in the physiological process, but the cells are more frequently destroyed.

Colloid Degeneration.

Colloid degeneration consists in the metamorphosis of cell-protoplasm into a gelatinous substance, which was formerly said to differ from mucin in containing sulphur, and in not being precipitated by acetic acid or alcohol; it may swell up when treated with acetic

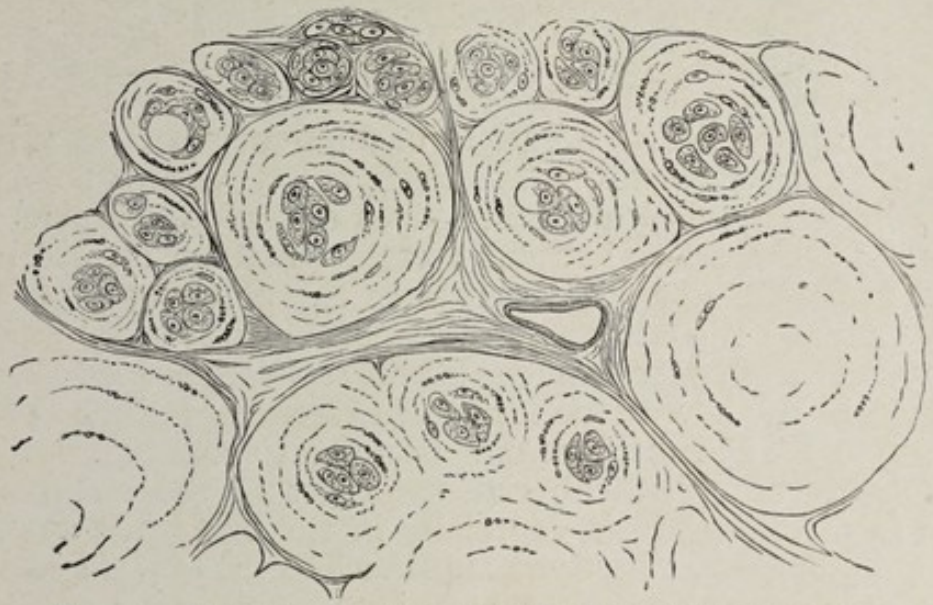


FIG. 10.—COLLOID CANCER, SHOWING THE LARGE ALVEOLI, WITHIN WHICH IS CONTAINED THE GELATINOUS COLLOID MATERIAL. (× 300.) (RINDFLEISCH.)

acid. In all probability the name is applied to different substances varying widely in composition, including mucin and pseudo-mucin. The degenerative product is quite distinct from the normal product of the thyroid gland.

The *cause* of this form of degeneration is unknown. It occurs in certain *new-growths*, both sarcomata and carcinomata (especially of the stomach), the secondary growths undergoing the same change ("colloid cancer"). Ovarian tumours often contain colloid.

To the *naked eye*, colloid is a colourless or pale yellow, glistening substance. It has the consistence of rather soft gelatine, which it much resembles, being thus rather more solid than the products to which the term "mucoid degeneration" is applied. Quite small points of colloid catch the eye; they do not stain brown with iodine, nor rose-red with methyl violet (p. 53). In advanced stages, colloid may soften; and the softened masses, separated by septa

of comparatively undegenerated tissue, give the appearance of cysts in the tumour.

Microscopically, the first change observed is the appearance of one or two small masses of colloid in a cell. These coalesce, enlarge, and push aside the nucleus until all the protoplasm is replaced and the cell is considerably swollen. The nucleus usually atrophies and disappears, but may become colloid. Neighbouring cells coalesce into small masses, and these again into larger, which not uncommonly look as if they were concentrically laminated (Fig. 10). Thus cavities full of colloid are formed. The intercellular substance atrophies rather than degenerates, whereas in mucoid degeneration it is frequently affected by the morbid process.

Change into true colloid material, such as is seen in the thyroid gland, does not occur, except in cysts of this gland and in metastatic tumours originating in this organ.

Hyaline Degeneration.

This term is applied to a variety of different conditions in which tissues are converted into a homogeneous transparent substance, which stains deeply with "acid" dyes (fuchsine, eosine). A distinction has been drawn between secretory hyaline, formed by cells, and exudative hyaline, deposited from the blood or some inflammatory exudate: the latter is the commoner source of the substance. The latter form of hyaline change affects *scar-tissue* especially, and is often seen in the new tissue formed in thickening of the pleura or pericardium. The substance may be allied to collagen. A similar, but probably not identical, change occurs in the *elastic coats of arteries* in arterio-sclerosis, especially in the brain, the spleen, and the lymphatic glands: here the substance formed is supposed to be a modification of elastin. In both these instances the alteration in structure may be rather physical than chemical.

Hyaline masses may occur in old *thrombi*, in which they arise apparently by transformation of red blood-corpuscles or fibrin; hyaline *renal casts* are probably formed of altered fibrin, but may be derived from degenerated tubular cells.

The former variety is seen in *epithelial cells*, when hyaline bodies may be formed by masses of keratin: such formations have frequently been mistaken for parasites.

The condition is only of importance as it affects the **bloodvessels,** and here rather as an index of disease than as itself constituting a morbid change. *Microscopically*, in the arterioles the intima is here and there converted into a shining thickened layer, giving rise to irregular spindle-shaped enlargements; in larger arteries becoming aneurysmal, the degenerative change follows the increased growth of connective tissue which occurs at the weakened spot.

A hyaline degeneration occurs in conjunction with amyloid change, and seems to be the immediate precursor of the latter.

Zenker's Degeneration of Muscle.

Two views are held concerning this change. According to some pathologists, it is a variety of degeneration or coagulation-necrosis in which the muscle-fibres become brittle, and generally rupture. Thus, Babes regards it as a coagulation-necrosis due to the action of the toxines of the typhoid bacillus. According to others, the muscle-fibres rupture from weakening due to granular degeneration or to damage; while the appearances just described are regarded as the ordinary manifestations of tissue-death, as they can be produced experimentally by rupturing the fibres.

In appearance it resembles hyaline degeneration. It was first found by Zenker in the muscles in typhoid fever—chiefly in the recti abdominis, the adductors of the thigh, the diaphragm, and the tongue-muscles. It occurs, though less often, in other infective febrile diseases, such as smallpox and cerebro-spinal meningitis; in trichinosis; in abscesses and tumours of muscle; and in the neighbourhood of burns and bruises—either before or after systemic death.

FIG. 11.—PORTION OF THE SOLEUS MUSCLE FROM A CASE OF TYPHOID FEVER, SHOWING ONE NORMAL AND TWO DEGENERATED MUSCLE-FIBRES. (× 150.)

Microscopically, the altered fibres are much swollen and the transverse striation is lost. The sarcolemma is occupied by a homogeneous, structureless material, which is exceedingly brittle, and usually presents a wrinkled appearance, or is broken up transversely into irregular fragments (Fig. 11).

The portions of muscle affected are, to the *naked eye*, semi-opaque, pale, slightly lustrous, of a reddish-grey or brownish-yellow colour, and abnormally friable. They appear somewhat like the muscles of frogs or of fish. In no part are all the fibres affected. The damaged fibres are regenerated in the usual way. Rupture of the fibres is often associated with hæmorrhage into the substance of the muscle.

Amyloid Degeneration.

Waxy, Albuminoid, or Lardaceous Degeneration.

This condition is usually classed among the degenerations (p. 32); recent authors, however, maintain that amyloid material is brought to the affected organs either in solution in the blood, or in the leucocytes, and is then deposited, constituting an infiltration with extraneous material. It is probable that the degeneration is always

due to the action of some ferment which affects the metabolism of the cells, and leads to the formation and deposition of unusual derivatives of albumen. It has been suggested that the enzyme at work is produced in the spleen, as this organ is the first to suffer, and amyloid change does not occur experimentally in animals which have been deprived of their spleens.

Amyloid degeneration is characterised by the appearance in the tissues of a firm, colourless, translucent substance, known as *amyloid* or *lardacein*. This substance offers an exceedingly prolonged resistance to gastric digestion—this procedure affording a method of obtaining it in almost a pure state—and exhibits characteristic staining-reactions. Chemically it was found by Krawkow to consist of some form of albumen in combination with chondroitin-sulphuric acid—a composition which brings it into relation with the mucins (nucleo-proteins), and with cartilage, in which a closely allied body is normally found.

ÆTIOLOGY.—Amyloid degeneration is said to be commoner in males than in females, and to originate below the age of thirty. It is almost always *secondary* to prolonged and profuse suppuration, and is commonly associated with chronic tubercular disease of lung, bone, joint, or kidney; with empyemata and septic compound fractures; and, less frequently, with dysentery, actinomycosis, and the cachexia of tertiary syphilis, especially when there is chronic bone-disease. Rarely it appears in the cachexiæ of severe malaria, of leucocythæmia, and of cancer; and very rarely, especially in children, the degeneration may seem to be *primary*.

The degeneration may appear in two to three months, or, under apparently similar circumstances, its onset may be long delayed, especially in young children. Like hectic fever, it occurs much more readily as a result of suppuration in an ill-drained cavity than from a cutaneous ulcer, upon which the pus cannot accumulate under pressure, and from which, therefore, toxines are not so likely to be absorbed.

Lubarsch produced the change experimentally in animals, by exciting and maintaining suppuration by means of cultures of the *Staphylococcus pyogenes aureus*, and proved its presence in a portion of the spleen which he excised. The animals were then allowed to recover from the suppuration and subsequently killed, when the remainder of the spleen was found free from any trace of amyloid degeneration.

The change may also follow suppuration induced by injections of turpentine, of rennin, or of the toxines of the *Bacillus pyocyaneus*. The variations in the chemical composition and in the staining-affinities of amyloid, and the varied conditions under which it occurs, certainly suggest the possibility of variety in its causation.

SEATS.—The change may be found in almost any organ; those most frequently affected are **spleen, liver, kidneys, intestines,** and **lymphatic glands.** Less frequently, and especially when the change in the organs just mentioned is advanced, minor degrees of it may

be found in the stomach, pancreas, suprarenal capsules, pharynx, œsophagus, bladder, prostate, generative organs, serous membranes, the membranes of the brain and cord, and muscle. There is no rule as to the order in which the organs are affected. As a **local change,** distinct from the above, it occasionally affects *pathological products,* as old thrombi, inflamed glands, scars (especially syphilitic), and tumours.

APPEARANCES.—*Microscopically,* the morbid substance usually appears first in the sub-endothelial connective tissue and media of the **arterioles** and around the **capillaries** (Figs. 12 and 14); the endothelium is unaffected, and the adventitia usually escapes. The change greatly diminishes the lumen of the vessel; it does not affect the walls of the latter uniformly, but frequently causes spindle-shaped enlargements. The vessels of many parts escape entirely, and the distribution of the change in an affected organ may be quite irregular, while the primary change may even occur in connective tissue apart from the vessels.

With regard to the further spread of the change, all authorities are agreed that the *connective tissue* in every affected organ suffers most, and swells into homogeneous waxy-looking masses which frequently coalesce. Between these the fatty and shrivelled cells of the organ may be seen. These rarely undergo amyloid degeneration, but it is difficult in degenerated tissues to be certain of the exact cells which have given rise to the new product. In a case of amyloid change in the liver, associated with gummata, the liver-cells appeared to be undergoing the degeneration (Daniel).

Organs in which amyloid degeneration is at all advanced present features so characteristic that its presence can be readily recognised by the *naked eye.* They are considerably and uniformly enlarged, any edges they may possess becoming more or less rounded. Their absolute weight is increased, and also their specific gravity; their surface is smooth, and the capsule tense and stretched; their consistence is firm and somewhat elastic. On section, they exhibit a peculiar homogeneous, glistening, translucent appearance, somewhat resembling white wax. Owing to the diminished calibre of their bloodvessels, and to the pressure exercised by the new material, they contain but little blood, and hence are always pale in colour. In slighter degrees of the change, spots and patches of the morbid material may be scattered, like grains of boiled sago, through the affected organs. Although the above characters are sufficiently distinctive in advanced stages, the colour-reactions mentioned below should always be used, for they will reveal altered patches—*e.g.,* in intestine—not obvious without them. For the recognition of the degeneration in its *earliest* stage the microscope is also necessary.

With regard to its **colour-reactions,** the best for *naked-eye* purposes is that with iodine. To obtain this, wash a thin slice of an affected organ, and pour over it a watery solution of iodine, made by diluting the tincture with three times its bulk of water. In this way the amyloid portions are at once stained dark mahogany-brown,

the healthy tissues assuming a bright yellow colour. If this surface be treated with a ten per cent. solution of sulphuric acid, the degenerated parts frequently, but by no means invariably, assume a dark greenish hue.

The iodine-reaction quickly fades, and, therefore, is useless for permanent preparations. It is occasionally given with other albuminous compounds, and cannot always be obtained in the earliest stages of amyloid degeneration. It is said to depend on a simple physical attraction of the amyloid substance for iodine.

For *microscopic* purposes, the most reliable reaction is that obtained by staining the sections with methyl violet (one per cent. watery solution.) After some hours, the amyloid parts are stained bright magenta, and the rest of the tissues blue. Sections must be mounted in glycerine or Farrant's solution, as the colour is destroyed by alcohol. This staining is more permanent than that by iodine. In advanced stages of the disease, a useful reaction may be obtained by staining sections with iodine, mounting them in glycerine, and placing at the edge of the cover-glass a very small quantity of strong sulphuric acid; in about twenty-four hours the amyloid tissues will be stained blue.

EFFECTS.—The diminution of the blood-supply, due to narrowing of the arterioles combined with the direct pressure of the new material, causes the atrophy and fatty degeneration of the essential cells which nearly always occur in organs undergoing amyloid degeneration. The change in the vessel-walls alters the quantity and quality of the transudation, as is shown by the changes in the urine (polyuria and albuminuria) when the kidneys are affected, and by the serous diarrhœa which accompanies amyloid change in the intestine.

Removal of the cause—*e.g.*, chronic suppuration—of amyloid degeneration may lead to arrest of the deposit, and to its disappearance from the diseased organs, even in marked cases; but in the great majority of instances the change is steadily progressive, and terminates fatally.

Amyloid Degeneration of the Liver.

Microscopically, the earliest changes are observed in the walls of the capillaries and arterioles of the hepatic artery; and, very rarely, in the capillaries of the portal vein. Thence the deposit spreads to the intralobular connective tissue round the affected vessels, ultimately reaching and affecting the tissue between the lobules and leading to confusion of their outlines. The connective tissue swells into homogeneous columns, which split readily into flakes, somewhat suggestive, under a low power, of masses of degenerated liver-cells or even of whole lobules. Careful examination, however, reveals, between the amyloid masses, the liver-cells more or less atrophied and pigmented, the peripheral cells especially being infiltrated with fat (Fig. 12).

To the *naked eye*, the amyloid liver possesses the typical characters already described (p. 53). If the change is very far advanced, the tissue may be perfectly homogeneous, all distinction between the individual lobules being lost. In other cases, the lobules are distinctly mapped out; they are enlarged, and the external zone may be of an opaque yellowish-white colour owing to the presence of fat. This association of the fatty and amyloid changes is exceed-

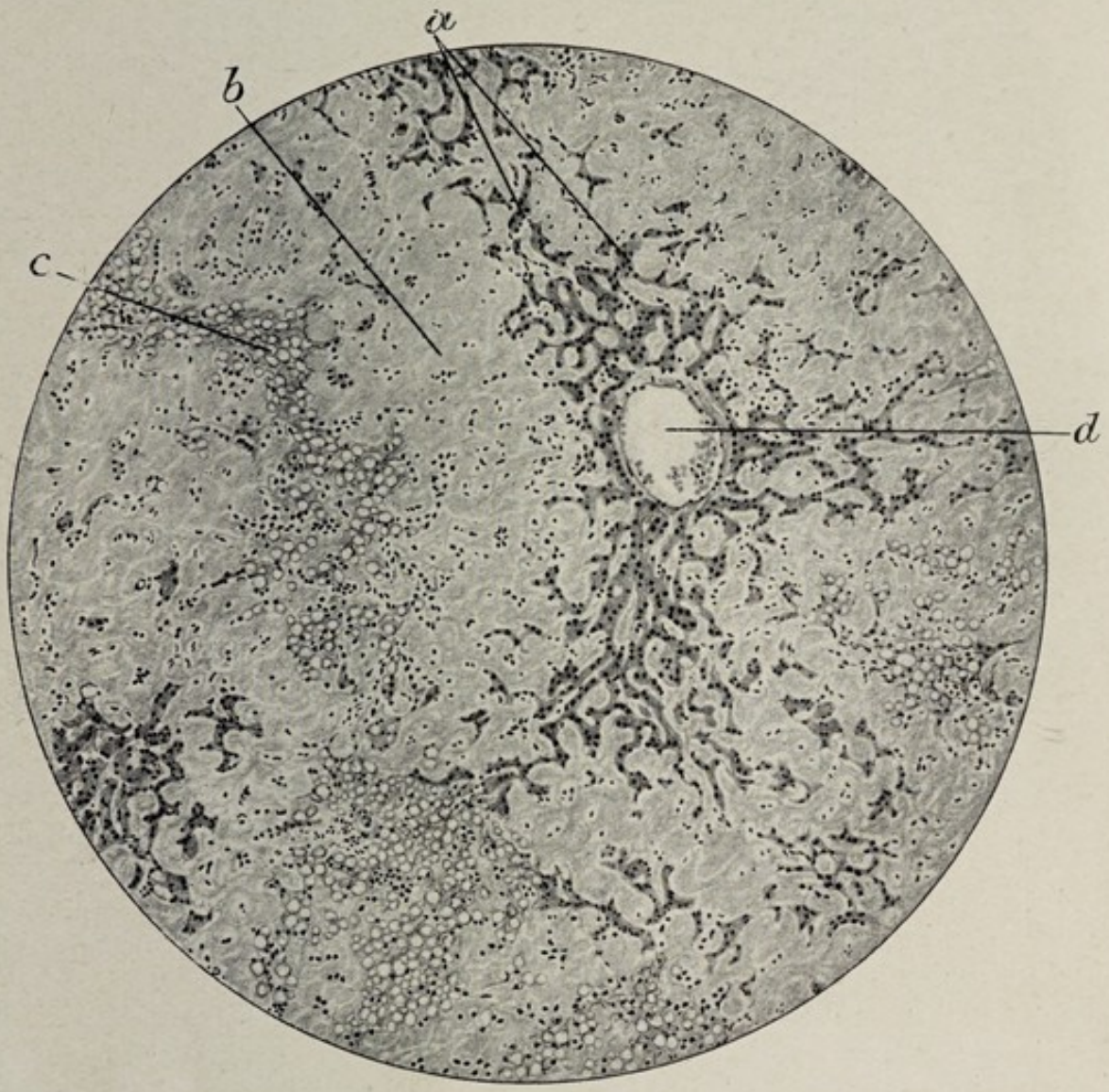


FIG. 12.—AMYLOID LIVER.

a, compressed liver-cells; *b*, masses of amyloid; *c*, fat-globules near periphery of lobule; *d*, intralobular vein.

ingly common. Amyloid degeneration does not obstruct the portal circulation, and hence does not cause ascites (see Cirrhosis of Liver), except in those rare cases in which the portal vessels are involved. It causes fatty degeneration and atrophy of the hepatic cells, and thus interferes with the functions of the organ.

If sections are stained with iodine, the mahogany colour will frequently be found limited to the so-called "intermediate zone" of

the lobules—the area of distribution of the hepatic artery. The appearance thus produced is that of a number of partially compressed rings with pale centres, and still paler intervening spaces (Fig. 13). Thus the earliest seat of amyloid degeneration differs from that of fatty infiltration, in which the fat first accumulates in the cells of the outer or portal zone, and from that of passive congestion, in which the changes begin in the central zone around the intralobular vein. All these changes not uncommonly occur together. As the amyloid change advances, first the central zone and, later on, the peripheral zone are affected, and even the interlobular connective tissue may ultimately become involved.

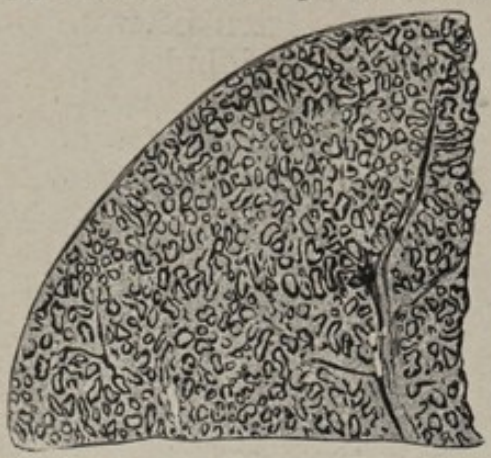


FIG. 13.—AMYLOID LIVER. Stained with iodine. The darkest portions represent the affected intermediate zones. (Natural size.)

Amyloid degeneration of the liver may be found as a local change in the neighbourhood of syphilitic gummata. (See p. 272, and Chapter XVII., Syphilis.)

Amyloid Degeneration of the Kidneys.

Microscopically, the degeneration is first observed in the Malpighian bodies (Fig. 14). At first only a few of the capillary loops in each tuft are affected, but all the loops gradually become involved. The whole coil then presents an ill-defined outline and glistening surface. The change extends to the afferent arteries, to the capillary network around the tubules, to the arteriolæ rectæ of the medulla, and, in advanced cases, to the intertubular tissue and to the tunica propria of the tubules. It is doubtful if the epithelium itself ever undergoes amyloid degeneration. The distribution of the change throughout the kidney may be very irregular.

At first the tubes and epithelium appear normal. Many of the former contain the pale hyaline casts which appear in the urine. These are probably simple exudation-products; but they occasionally stain brown with iodine, and have been supposed to consist of amyloid. According to Ziegler, however, these casts do not exhibit the other typical reactions of amyloid. As the change advances, the diminished blood-supply and the direct pressure of the new material may lead to atrophy and fatty degeneration of both glomerular and tubular epithelium; but more frequently these changes occur at an earlier stage, and are due to chronic parenchymatous nephritis. The tubes, in such cases, are distended with both cloudy and fatty cells, and the intertubular tissue is more or less infiltrated with round cells (*large white amyloid kidney*). In the later stages of the process there is almost always increase of the intertubular tissue,

which, together with the disappearance of tubes, leads to shrinking and toughening of the organ, to adhesion of the capsule, to irregularity of the surface, and to formation of small retention-cysts.

The *naked-eye* appearances vary with the extent of the degeneration, and may be modified by the presence of chronic nephritis.

If thin slices of a kidney in the earliest stages of amyloid degeneration be stained with iodine, a Malpighian body will here and there

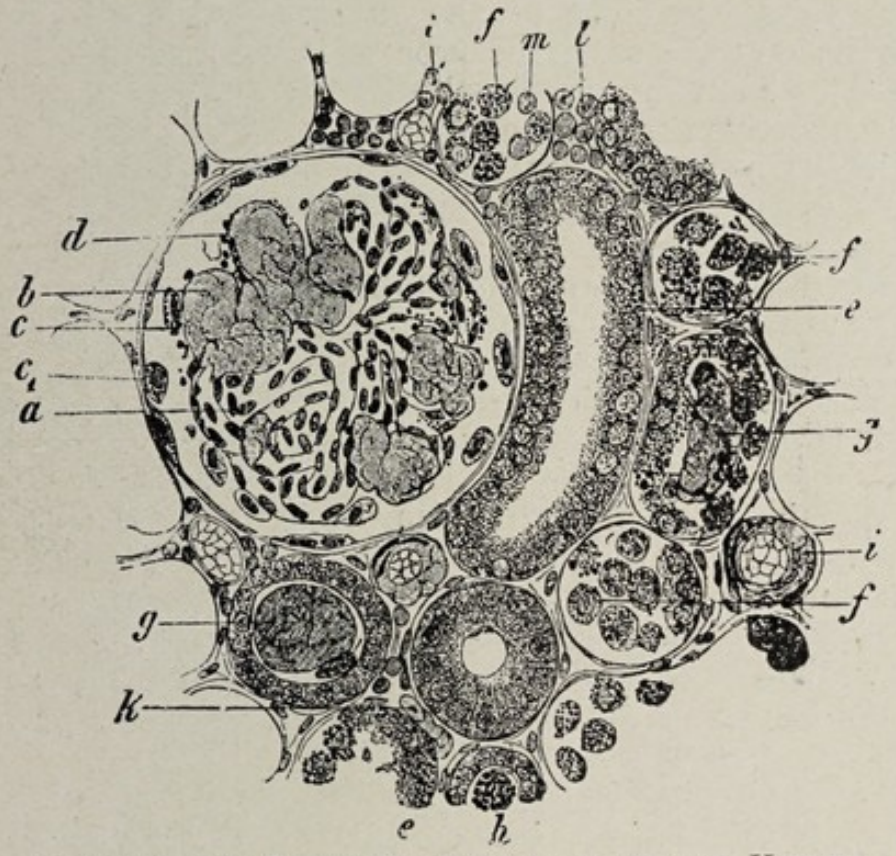


FIG. 14.—AMYLOID AND FATTY DEGENERATION OF THE KIDNEY. (× 300.) (ZIEGLER.)

a, normal capillary loop; *b*, amyloid capillary loop; *c*, fatty epithelium of the glomerulus; c_1, fatty epithelium of the capsule; *d*, oil-drops on the capillary walls; *e*, fatty epithelial cells *in situ*; *f*, loosened fatty epithelial cells; *g*, hyaline coagula (forming "casts"); *h*, fatty cast in section; *i*, amyloid artery; *k*, amyloid capillary; *l*, infiltration of connective tissue with leucocytes; *m*, round cells (leucocytes) inside a uriniferous tubule.

appear as a brown dot, and the straight arteries of the pyramids as brown lines, although the unstained kidney is still normal in appearance. As the disease advances, the organ enlarges, especially the cortex. The surface is smooth, and the capsule separates readily. The enlarged cortex is remarkably pale and anæmic, and has a peculiar translucent, homogeneous, wax-like appearance. Its consistence is hard and firm. A few scattered vessels may be seen on the surface, and the bases of the pyramids sometimes exhibit increased vascularity. If iodine be applied to the cut surface (p. 53), the Malpighian bodies and the arteries of the cortex become mapped

out as clearly as in an artificial injection (Fig. 15). The enlarged Malpighian bodies may, indeed, be seen as glistening semi-translucent points before the iodine is applied. Frequently, the homogeneous appearance of the cortex is interrupted by minute, opaque, yellowish-white lines and markings; these are produced by fatty changes in the epithelium of the tubes, due generally to concomitant nephritis. Ultimately the capsule becomes more or less adherent, and slight irregular depressions make their appearance upon the surface of the organ; the latter are due to atrophic changes in some of the tubes. If, as is usually the case, the process is associated with an increase in the intertubular connective tissue, the atrophy may render the organ even smaller than normal.

Sometimes the enlargement of the organs is very great. In these cases, the increase in size is mainly due to inflammatory changes, such as have been described. The frequency with which such combinations occur renders it advisable to examine all large pale kidneys for amyloid changes.

FIG. 15.—AMYLOID KIDNEY. (FROM A CHILD.) (NATURAL SIZE.)

Stained with iodine. The dark parts represent the Malpighian bodies and arterics which have undergone the amyloid change.

Effects.—The capillary walls in the Malpighian bodies are so altered that albumen and an increased quantity of fluid readily permeate them, and thus is produced the large amount of urine, sometimes loaded with albumen, which characterises the earlier stages of this affection; the polyuria is, however, not so great as in the granular contracted kidney, in which disease the general arterial tension is raised. If inflammatory changes supervene, the urine diminishes in quantity. The excretion of urea is less interfered with than in any form of nephritis; nor is the internal secretion of the kidney seriously affected, for uræmia seldom occurs in uncomplicated cases. Tube-casts are rarely numerous; they are for the most part hyaline or finely granular, though sometimes they are covered with fatty epithelium. In advanced cases there is marked dropsy.

The association of chronic tubal nephritis with amyloid change is so frequent as to suggest the possibility of a common cause for the two conditions.

Amyloid Degeneration of the Spleen.

Two forms are generally described: (1) the **sago** spleen, the commoner form, in which the disease commences in the Malpighian follicles; and (2) the **diffuse** form, in which the whole splenic pulp

is first implicated, and in which the Malpighian follicles often escape. The two forms are occasionally combined.

In the **sago** spleen the first *microscopical* changes are observed in the capillaries and arterioles of the Malpighian follicles. The reticulum, of which the follicle largely consists, is next involved, then the small vessels in the neighbourhood, and finally the pulp. In the early stages, the central artery of the corpuscle usually escapes. When it becomes affected, the change is first observed in its middle coat. In the **diffuse** form the degeneration begins in the neighbourhood of the capillary veins of the pulp, and spreads thence to the trabeculæ, arterial capillaries, and possibly—though this is very doubtful—to the cells. The Malpighian follicles often escape, but their central arteries are generally involved.

FIG. 16.—AMYLOID SAGO SPLEEN. (FROM A CHILD.) (NATURAL SIZE.)

Stained with iodine. The Malpighian follicles are darkly stained, and as a rule have unstained centres.

To the *naked eye*, the **sago** spleen is more or less enlarged; its weight and density are also increased. The cut surface is smooth, dry, and studded all over with small, glistening, sago-like bodies, varying in size from that of a pin's head to that of a hemp-seed. These are stained reddish-brown by the iodine-solution; but, as the central artery generally escapes, the mahogany-coloured nodules have pale centres. These nodules may enlarge until they occupy a considerable portion of the organ, although, in earlier stages of the affection, they are so minute that they can be seen only in thin sections of the tissue. In the later stages, therefore, there is a considerable resemblance between iodine-stained sections of liver and of spleen, as may be seen by comparing Figs. 13 and 16.

In the **diffuse form** the organ often attains a much larger size than is met with in the sago spleen. It is remarkably hard and firm, and the capsule is tense and transparent. On section, it presents a dry, homogeneous, translucent, bloodless surface; it is in some cases pale, in others of a mottled reddish-brown colour. Thin sections can be readily made with a knife, the organ cutting like soft wax. The corpuscles, if affected, are not visible as in the former variety, being obscured by the surrounding pulp.

Amyloid Degeneration of the Alimentary Canal.

The mucous, submucous, and muscular coats of the œsophagus, stomach, and intestines may be involved; but these organs are probably never affected alone. The change frequently coexists with tubercular ulceration. In the alimentary tract the disease is very apt to escape observation, as it usually produces little altera-

tion in the appearance of the parts. The mucous membrane may be pale, smooth, translucent, and œdematous ; in very advanced cases there may be some rigidity and thickening of the bowel-wall, and even ulcers—due, it has been suggested, to the snapping-off of the rigid villi. The effect of the application of iodine to the washed mucous surface is very characteristic. In the small intestine—perhaps the part most commonly affected—small, closely set, reddish-brown points appear over the whole surface of the membrane ; these correspond with the intestinal villi, the arteries and capillaries of which have undergone the amyloid change. In the stomach and œsophagus the vessels may be similarly mapped out by iodine

The change in the intestine gives rise to serous diarrhœa, probably due to increased permeability of the degenerated vessel-walls. Both absorption and secretion are much impaired, so that implication of the alimentary tract has a grave general effect.

Corpora Amylacea.

Corpora amylacea or "amyloid bodies" were formerly looked upon as consisting of amyloid substance ; there appears, however, with the exception of a certain similarity in their behaviour with iodine and sulphuric acid, to be no connection between them. They are said to consist largely of lecithin.

They are round or oval bodies, formed of a succession of concentric layers, and are often changed to a deep blue colour by iodine, thus bearing, both in structure and chemical properties, a strong resemblance to granules of vegetable starch (Fig. 17) ; but sometimes the blue is exhibited only after the subsequent addition of sulphuric acid, and thus a resemblance is shown to amyloid substance. Many of these bodies, however, are coloured green, or even brown, by these reagents. The green is due to their admixture with nitrogenous matters, which give a yellow colour with iodine, and hence the combination yields a green. The greater the amount of nitrogenous matter, the browner does the colour become. They vary in size from microscopic granules to bodies which are distinctly visible to the naked eye, sometimes being as much as a sixth of an inch in diameter. The larger are usually formed by the conglomeration of smaller granules, which are often enclosed by a common envelope.

FIG. 17.—CORPORA AMYLACEA FROM THE PROSTATE. (VIRCHOW.)

They especially occur in conditions of atrophy or softening of the nervous system. The ependyma of the ventricles, the white substances of the brain, the choroid plexus, the optic nerve and retina, and the spinal cord are their favourite seats. The larger forms are met with most frequently in the prostate. The prostate

of nearly every adult contains some of these bodies ; and they may accumulate in that organ to such an extent as to form large concretions. They are occasionally met with in the lungs, and in mucous and serous membranes.

The corpora amylacea, especially those occurring in the choroid plexus and in the lateral ventricles, are very liable to become calcified, and they then constitute one form of " brain-sand " which is so often met with in these situations.

The nature of these bodies is unknown : from their laminated structure they would appear to be formed, like renal and biliary calculi, by gradual deposition upon a central nucleus ; but in the prostate they are probably produced by degeneration of the glandular cells.

CHAPTER VII

CALCIFICATION AND PIGMENTATION

CALCAREOUS INFILTRATION.

Calcareous Infiltration, or *Calcification*, consists in the *infiltration* of tissues with calcareous particles. It is a purely *passive* process, the cells taking no part in it : the tissue is gradually petrified by the deposit of earthy salts from the blood. It is difficult to find a physiological type, but perhaps the deposit of earthy salts in the walls of the primary areolæ (see Rickets) in a growing bone may be regarded as such. *Calcification* is quite distinct from *ossification*, for in the latter everything points to life and growth ; the cells are undergoing *active* changes, and are obviously concerned in receiving the salts from the lymph and in combining them most intimately with the organic matrix.

Ætiology.—Earthy salts in solution, chiefly the *phosphates* and *carbonates of calcium and magnesium*, are brought to the part by the blood and lymph, carbon dioxide being probably the solvent. In inquiring why these salts should be permanently deposited in certain tissues, attention must be directed to the facts that, in the immense majority of cases, the tissues affected are dead or dying, and that calcification is a common senile change. It is probable, therefore, that feeble nutritive activity and a retarded blood-stream are together responsible for its occurrence. In scars and in epithelial cells calcification is preceded by hyaline change, and in other cases by fatty degeneration. Rindfleisch taught that carbon dioxide escaped from the stagnating lymph-stream, and that the earthy salts were consequently precipitated : more recently, others have held that calcification is due to a combination of these salts with certain albuminoid bodies and with fatty acids. Some authors attribute the calcification of arteries met with in old age to deficiency of sodium chloride in the blood and tissues, this defect permitting the deposition of calcium salts. It may be remembered that in degenerating tissues phosphoric acid and fatty acids may be formed, both of which have affinities for calcium ; while in tissues which have undergone fatty change, calcium soaps would easily be formed.

Sometimes calcareous infiltration appears to be due to an aboslute increase of calcareous salts in the blood, such as may be supposed to occur in extensive caries and in osteomalacia. A portion of the excess is then deposited more or less widely in the tissues—especially in the lymphatic glands and kidneys, and less frequently in the lungs, stomach, intestines, dura mater, and liver, without any signs of degeneration being found in the cells of these parts. The deposit takes place chiefly in the connective tissue, the least active constituent of the organ, which, moreover, immediately surrounds the vessel—*e.g.*, in the interlobular tissue of the lungs and in the stroma between the glands of the stomach; but, in the kidney, the epithelium is infiltrated as well as the intertubular tissue. Analogous to this form of calcification is the deposition of the biurate of sodium which takes place, especially in cartilage, fibrous tissue, and synovial membranes, and forms the commonest manifestation of gout. It is probable that, in this case also, the deposit occurs first in tissues in which the nutritive activity is most feeble. A certain amount of chalky—like fatty—infiltration may perhaps occur without marked impairment of function; but, as completely calcified parts are certainly dead, either the infiltration has the power to kill or it affects dying parts.

SEATS.—As a senile change, calcification affects most frequently the arteries and hyaline cartilages—excepting articular cartilages. It occurs similarly in pathological tissues of which the life is feeble—*e.g.*, in uterine myomata after the climacteric and in old scars. Dead tissues locked up in the body are also very likely to become calcified—*e.g.*, thrombi (*phleboliths*), infarcts, parasites, atheromatous patches in arteries, and the caseous masses so common in lungs and lymphatic glands which have undergone chronic tubercular changes. Calcification of ganglion-cells alone is not uncommon in degenerative processes in the brain. The best example of the process is the complete calcification of a dead fœtus (*lithopædion*), which sometimes occurs when this is retained in the abdomen, in a case of extra-uterine fœtation.

APPEARANCES.—*Microscopically*, the calcareous particles make their appearance both within the cells and in the intercellular substance; they are much more frequent, however, in the latter situation. They are seen at first as very fine dust scattered irregularly through the intercellular substance. They are characterised, when viewed by transmitted light, by their opacity, black colour, irregular outline, and solubility in dilute mineral acids, usually with evolution of bubbles of carbon dioxide. They gradually increase in number until ultimately large tracts of tissue may be converted into an opaque calcareous mass, in which the cells are enclosed and can no longer be recognised. These large masses have a sharp, black, irregular outline, and, as the calcification becomes complete. acquire a homogeneous, glistening, semi-transparent appearance, The cells themselves are much less frequently infiltrated, being merely enclosed and obscured by the calcified intercellular sub-

stance. Calcareous particles may, however, make their appearance in the protoplasm, and, gradually increasing, convert the cell into a homogeneous calcareous body.

If the saline matters are dissolved out with a little dilute mineral acid, the structure of the part may be again recognised, unless, indeed—as is so often the case—it has been destroyed by some antecedent change.

Apart from the microscope, calcification can be recognised more readily by touch than by sight. If the calcareous particles cohere in minute groups, as is common when the process succeeds that of caseation, a white mortar-like substance is produced. When the cohesion is more marked, the deposit resembles fine sand; and all stages between this and solid stony masses may be met with. The latter break with an irregular surface and present a yellowish or greyish aspect. A calcified part is dead and inert; it undergoes no further change.

Effects.—Calcification must be looked upon in many cases as a salutary process, the impregnation with calcareous matter preventing subsequent changes in the part. This is especially the case when it occurs in caseous *tubercular foci*, as it imprisons the cause of the disease. It is doubtful whether calcification of a *tumour* is of any benefit to the patient, for the infiltration is probably limited to the dead or dying parts, and does not hinder the spread of the actively growing portions. On the other hand, when it affects the arterial system, calcification may be attended by the most deleterious consequences, as will be seen in the following section.

Concretions of various kinds may be found in the gall-bladder, bile-ducts, pelves of the kidneys, ureters, urinary bladder, and other parts. They are commonly preceded by catarrh of the living membrane of the duct in which they are situated, due to bacterial infection. They will be referred to when diseases of the affected organs are discussed.

Calcification of Arteries.

Calcified plates are frequently met with in the intima of the aorta and other large arteries as part of the change known as *atheroma*.

Sometimes a more or less general calcification occurs, especially as a senile change, and is then frequently associated with other degenerative changes in the arterial walls. It is commonest in vessels of medium size, the arteries of the upper and lower extremities and of the brain being frequently affected. It may affect both internal and middle coats, often commencing in the muscle-cells of the latter. The calcareous particles, deposited from the vasa vasorum, make their appearance at first around and within the nucleus, and gradually accumulate until they fill the cell, which becomes converted into a small calcareous flake. The process may

go on until the muscular coat is completely calcified; or it may be limited to isolated portions of the coat, giving rise to numerous irregularly distributed calcareous rings and plates, somewhat suggestive of a piece of ipecacuanha root. These are best seen in vessels clarified and dried. From the muscular it may extend to the external and internal coats, until ultimately the vessel becomes calcified throughout.

The vessel thus calcified loses its elasticity and contractility; its lumen is diminished, and it is transformed into a hard, rigid, brittle tube, or "pipe-stem artery" (Fig. 18). Such an artery is partially protected against dilatation, but is predisposed to rupture: in amputations great difficulty may be found in securing such vessels, as ligatures cut through them at once. The nutrition of parts supplied by them is more or less impaired, and general calci-

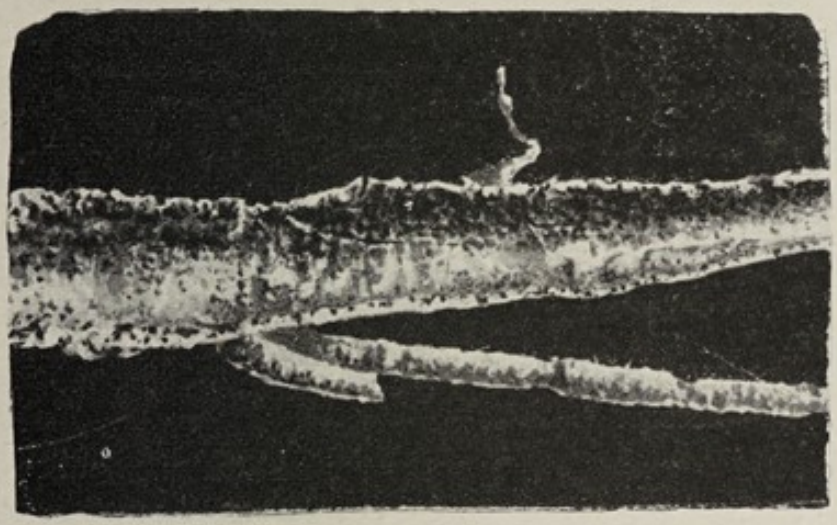


FIG. 18.—FEMORAL ARTERY, SHOWING EXTENSIVE SENILE CALCIFICATION, THE WHOLE VESSEL CONSISTING OF A MASS OF CALCAREOUS PLATES. (NATURAL SIZE.) (C. C. H. MUSEUM.)

fication of the arteries of the lower limb therefore predisposes to *senile gangrene* (p. 22), inasmuch as it renders the vessels less able to adapt themselves to the varying requirements of the circulation.

PIGMENTARY CHANGES.

Pathological pigmentation is a term used to imply the abnormal appearance of some kind of pigment in the tissues, and includes many conditions differing widely in their nature and origin.

The pigment may be derived: (1) directly from *hæmoglobin*; (2) from the blood by *cell-action*; (3) from *bile*; (4) from *extraneous substances* introduced into the body.

1. **Hæmatogenous Pigments,** derived directly from hæmoglobin, are the commonest. Red corpuscles break up, and their colouring

matter is set free. This occurs occasionally within the vessels, as in malaria and septicæmia, but more frequently after escape of the corpuscles into the tissues. The latter is due either to wounds or rupture of the vessels, or to congestion or inflammation without any visible breach in the vessel-wall. Such instances of pigmentation are common ; among them may be mentioned bruises of the skin, small hæmorrhages in the neighbourhood of varicose veins and passively congested parts, and stains after syphilitic and other inflammatory lesions.

The two principal pigments which form the final products of the breaking-up of red corpuscles in the tissues are *hæmosiderin* and *hæmatoidin*.

Hæmosiderin*—an iron-containing pigment—probably formed by the action of living cells, gives the ordinary reactions of iron, and is found in the liver, spleen, and other organs whenever excessive destruction of blood-corpuscles (*hæmolysis*) is present. It is also found mixed with hæmatoidin, which it closely resembles in appearance. It occurs as brownish or yellowish irregular granules, not in crystalline form. It is very insoluble.

Hæmatoidin—an iron-free pigment—is probably identical with bilirubin, which is also a derivative of hæmoglobin. It is insoluble in water, alcohol, ether, acetic acid, and in dilute mineral acids and alkalies ; it is soluble in concentrated acids, and in the caustic alkalies, giving, in the latter case, a red colour.

These final stages of extravasated blood occur in two forms—*granular* and *crystalline*. Both are of a very permanent nature, and may remain unaltered for years.

The *granules* of hæmatoidin vary in size from the smallest particles to masses as large as a red blood-corpuscle. The larger are commonly irregular in shape, sharply defined, and more or less glistening. Their colour varies from yellowish-red to brown or black ; the older they are, the darker they become. The smaller granules are usually dull and opaque.

The *crystals* of hæmatoidin are opaque rhombic prisms, usually of a yellowish-red or ruby-red colour, sometimes approaching to brown or black. They may also occur as little plates and fine needles, but these are less common forms. They are in most cases so small that considerable care is required to recognise their crystalline nature under the microscope, and they may easily be overlooked as merely irregular granular masses. In some cases, however, they attain a larger size.

Whether hæmoglobin is converted into granular or crystalline hæmatoidin appears to depend partly upon the tissue in which it is situated, and partly upon the amount of extravasation. Crystals are exceedingly common in some situations—*e.g.*, the brain and ovaries; whereas in others—*e.g.*, mucous membranes—only granules are met with.

According to Kunkel, some of the pigment left by hæmoglobin is

* Greek αἷμα, blood; σίδηρος, iron.

pure hydrated peroxide of iron. **Hæmatin** may also be found in old extravasations of blood, but is not permanent, breaking up readily into the two pigments just described.

The changes in colour which occur after a bruise—first purple, then green, and finally yellow—are due to corresponding changes in the extravasated blood. (1) Some of the fluid and cells are absorbed at once by the lymphatics, while the hæmoglobin is dissolved out of many of the red corpuscles, and the stromata disappear—no doubt after fatty degeneration. Thus there is formed a red fluid which infiltrates the tissues, and stains them yellow or brownish-red—the cells being coloured more deeply than the intercellular substance, or membranous or fibrous structures. The colour-changes on the surface are due to alterations in this dissolved hæmoglobin, which is soon decomposed into hæmatin or hæmochromogen, and an albuminous body. Part of the colouring matter is reabsorbed, and appears in the urine as urobilin; the rest undergoes a change, and is finally deposited as hæmosiderin or hæmatoidin. (2) Many corpuscles simply shrivel into brownish granular masses of pigment—said to occur chiefly in "hæmatomata," or tumour-like collections of blood. (3) Other red corpuscles, or the pigment-masses resulting from them, are taken up by leucocytes, which are attracted in large numbers into the extravasation. The pigment thus taken up may be deposited in the neighbourhood, or may be carried by the surviving leucocytes into the lymphatics, when it will probably be arrested in the nearest lymphatic glands, the lymph-paths being thus marked out by pigment; or it may pass through into the circulation and give rise to pigment-emboli of various organs.

The *ultimate fate* of extravasations is by no means uniform.

(1) Absorption may be, and in vascular parts often is, to the naked eye, complete; but even then crystals or granules of pigment may not infrequently be found by the aid of the microscope. (2) A scar—yellowish, brownish, or blackish, from granular or crystalline pigment—may mark the site of the destruction of tissue by hæmorrhage. (3) A collection of chocolate-coloured fluid may long remain surrounded by a capsule of inflammatory tissue, often lined by layers of clot, more or less decolourised and organised (*hæmatoma*): the fluid contains pigment and fat-granules along with cholesterin crystals. (4) A cavity, with more or less pigmented walls, containing clear fluid may be left—especially in the brain. (5) The fluid may be absorbed, and the clot become completely decolourised and organised—a good example of which is seen in the so-called "membranous pachymeningitis." The process can frequently be watched in aseptic wounds.

Hæmatogenous pigmentation is a very common occurrence, though one of little importance. The presence of pigment in or between the cells of a tissue can have little effect on the elements or their functions: any disturbance of these must be attributed rather to the conditions upon which the formation of the pigment depends.

The presence of this form of pigmentation may be the only evidence of antecedent disease, such as cerebral hæmorrhage, in which yellow staining may be left; or chronic catarrh of mucous membranes, in which a slate-coloured pigmentation marks the site of the inflammation. The pigmentation of the liver and spleen in malaria, and of the liver and other organs in the condition known as hæmochromatosis (*bronzed diabetes*), is of similar nature.

2. **Pigment derived from the Blood by Cell-action.**—The chief examples of this change are melanotic warts, nævi, sarcomata, carcinomata, and Addison's disease. The pigment, **melanin,** lies in the cells more often than between them, is granular, and varies from yellow to black in colour: it contains sulphur, but not iron. It differs spectroscopically from all known blood-pigments, and is probably derived from protein-radicals, such as tyrosin, phenyl-alanin, and tryptophane. An artificial melanin may be obtained by heating proteins with strong hydrochloric acid. Pigmented growths generally arise from pigmented tissues. (See Melanotic Sarcoma.)

The cause of the pigmentation of the skin in *Addison's disease* is not satisfactorily explained. Irritation of the abdominal sympathetic is believed to cause increased pigmentation, as in some cases of abdominal tumour, but of this there is no very certain proof. The pigmentation in Addison's disease is merely an exaggeration of the normal, but it is most marked at points of pressure (irritation). It has been suggested that the suprarenal glands normally eliminate waste products derived from breaking-up of hæmoglobin. On the other hand, they apparently contain a "chromogen," or substance capable of being converted into pigment; and a body of this nature, melanogen, is present in the urine in some cases of melanotic sarcoma.

Variations in the normal pigmentation of the skin occur during pregnancy and with various uterine troubles, as well as in melanodermia; but no certain explanation of these, or of blanching of the hair from neuralgia or fright, can be offered.

In the condition known as **ochronosis** a black pigment allied to melanin is deposited in the cartilages throughout the body, and sometimes in other parts. Alkapton (p. 387) has usually been present in the urine of patients thus affected. In two instances absorption of small amounts of carbolic acid from dressings applied to wounds was supposed to be connected with the onset of the pigmentation.

3. **Pigmentation from Bile.**—This form of pigmentation is known as **jaundice** (*icterus*), and is due to obstruction of the bile-passages. The obstruction may occur in the small ducts, in the hepatic duct, or in the common bile-duct. It is most frequently due to swelling of the walls from catarrhal inflammation, to blocking of the lumen by gall-stones, or to the pressure of a new growth outside the duct. The continued secretion of the bile behind the obstruction causes a rise in the pressure within the smaller ducts, with consequent

absorption of bile by the veins and lymphatics and its subsequent distribution throughout the body. It is first perceptible in the urine, soon after in the conjunctivæ and skin, and may ultimately stain all the tissues yellow or greenish-yellow. The staining of the skin persists some time after the bile has ceased to circulate in the blood. When the seat of obstruction is in the small bile-ducts, as in cirrhosis, the staining may be limited to small areas of the liver.

The pigmentation is due to diffuse staining ; but granules and even crystals of bilirubin are occasionally found, especially in *icterus neonatorum.*

With regard to the slight jaundice that occurs in septicæmia, the malignant forms of acute infective fevers, and some other diseases (*toxic jaundice*), no marked obstruction can be demonstrated in the ducts, and the exact cause is doubtful. It is probable that increased consistence of the bile, and diminished pressure in the bloodvessels, combined with catarrh of the smaller bile-ducts, cause the tension in the ducts to exceed that in the bloodvessels, or, at any rate, in the lymphatics, and thus induce a slight absorption of bile into the vessels, and a consequent mild degree of obstructive jaundice. It has also been suggested that the hepatic cells may in certain cases, by some perversion of function, discharge the bile into the lymphatics surrounding them, instead of into the bile-ducts. Injury to the walls of the small bile-ducts might of itself allow such escape of their contents.

4. **Pigmentation by Extraneous Substances.**—Examples of this form of pigmentation occur in the lungs, the skin, the lymphatic glands, and the mucous membranes. The substances accredited with its production are carbon, silver, lead, arsenic, and such pigments as may be used artificially ; to these may be added, in rare instances, mercury and picric acid.

The inhalation of fine particles of **carbon** and other substances produces pigmentation of the lungs and bronchial glands. This is of considerable importance, and will be described in detail later on. (See Pneumoconiosis.)

The prolonged administration of salts of **silver** leads to the development in the skin and adjacent mucous membranes of a peculiar brownish-grey colour. That portion of the metal which finds its way to these parts is, owing most probably to the action of light, deposited as minute particles of reduced silver. This condition is known as *argyriasis :* it is permanent.

The existence of **lead** in the tissues is often demonstrated by the presence of a thin, bluish, well-defined line *in* the gums where they are in contact with the teeth. It is due to the action of the sulphuretted hydrogen, given off by the decomposing matter which collects between the mucous membrane and the teeth, upon the lead in the adjacent tissue. The " lead-line " is, therefore, usually broken, and often absent in those whose teeth are kept thoroughly clean, even though other symptoms of lead-poisoning may be present. Pigmentation of the mucous membrane of the large in-

testine has been found associated with the presence of considerable quantities of lead and of **mercury** respectively in that part of the alimentary tract.

In **tattooing,** artificial pigments are placed in the deeper layers of the skin. Most of the pigment remains in its original position. Of the remainder, some is removed by the phagocytic leucocytes, and some is washed on into the lymphatics and filtered out by the glands, where it is retained.

Dead tissues in process of separation are frequently discoloured—black, greenish-black, or slate-grey—by the action of sulphuretted hydrogen upon the decomposed hæmoglobin; and *atrophied organs,* in which the pigment is concentrated, often appear darker than normal. Neither of these is an instance of true pigmentation.

CHAPTER VIII

HYPERTROPHY

THE morbid processes thus far described have been attended either by arrest or by impairment of nutrition ; there remain to be considered those in which the nutrition is so changed that formation exceeds waste, and increase of tissue results. They include hypertrophy and repair, and tumour-formation. Repair of tissue will be considered in Chapter XIII., as part of the reaction of the body to irritants ; and tumours in Chapters XVIII. to XX.

Hypertrophy may be defined as "*an increase in the size, weight, and functional activity of a part beyond the limit of health, due to an orderly enlargement or multiplication of all its normal constituents.*" From this definition it will be seen that the *nature* of the process is strictly physiological ; in *extent* only it is pathological. The weight of a hypertrophied organ, however, gives the most reliable indication of the extent of the change. Strictly proportional to the increase in size and weight is that in work done.

The terms "false hypertrophy" and "pseudo-hypertrophy" are used to indicate that the increase in size, while presenting a superficial resemblance to hypertrophy, is due either to the unequal overgrowth of the tissue-elements, or to the growth of only one of them—often at the expense of the rest ; and that there is no increase in work done. Thus *pseudo-hypertrophic muscular paralysis* is characterised by a marked enlargement of certain muscles, due to an increase in their connective tissue and fat, accompanied by atrophy of the muscular tissue, fatty accumulation, and diminished capacity for work.

Hypertrophy is said to be "simple" when due to an increase in the size of the tissue-elements of the affected part ; "numerical" when due to an increase in their number. The latter is also called *hyperplasia.* These terms are of little practical value ; for hypertrophy is in nearly all cases believed to be numerical ; and in many cases it is simple as well. In the great example of physiological hypertrophy—the gravid uterus—some of the muscular fibres may be ten times their normal size.

ÆTIOLOGY.—The principal factors in the production of hypertrophy appear to be (1) *increased functional activity,* and (2) *excessive*

nutritive supply. Other agents to which more or less importance is attached are (3) *diminished waste ;* (4) *removal of resistances to growth* offered by neighbouring or controlling tissues (*altered tissue-tension*) ; (5) *congenital conditions*, such as an increase in the embryonic rudiment or an excessive vital energy.

1. In a large number of cases hypertrophy seems to occur as a response to a demand which has arisen for **increased work.** An example of this occurs when a difficulty arises in the circulation. The difficulty may be due to a narrowing in the arterioles, to obstruction at one of the orifices of the heart, or to some interference with the movements of the heart-walls themselves, such as may be caused by the permanent adhesion of the visceral and parietal surfaces of the pericardium. Under the altered conditions the normal blood-flow can only be maintained by increased work on the part of the heart. In such circumstances it generally happens that in proportion as the difficulty gradually makes itself felt, so the part or parts of the heart, upon which the extra work required falls, gradually hypertrophy : thus the increased demand is permanently provided for. At the same time the supply of blood through the coronary arteries is also increased. It would seem, indeed, that this is the connecting link between the increased work and the production of the hypertrophy ; for, if through disease of the coronary arteries or other cause, the increase in the supply of blood to the heart cannot be affected, the requisite hypertrophy does not occur. When hypertrophy arises in this way it is termed *compensatory*.

In some instances a further explanation of the compensatory hypertrophy of the muscular walls of the heart seems possible. Regurgitation through the mitral orifice causes over-distension of the left auricle and stretching of its muscular walls, as well as overfulness of the supplying pulmonary vessels. The walls of the auricle being in the position of an overweighted muscle, will subsequently contract with proportionately increased vigour, and, if the increased work is accompanied by a proportionately increased blood-supply, will gradually hypertrophy. The increased amount of blood consequently discharged into the left ventricle, just before its contraction, will distend the latter cavity and stretch the muscular fibres in its walls during the period of their relaxation, and will lead, therefore, in a similar way to hypertrophy of the left ventricle. The right ventricle will also undergo hypertrophy, due to the increased work done in forcing the blood through the lungs into the left side of the heart.

The power of the heart thus to hypertrophy is by no means unlimited. One source of limitation is very clear : this is in the blood-supply. If in any way the quality of the blood deteriorates, or the coronary vessels become rigid or partly obstructed, not only is increased growth an impossibility, but, as has already been said, fatty degeneration will inevitably ensue (p. 37). The other chief source of limitation lies in the " growing-capacity " of the cells.

When the original disease is of a progressive character, or when its ravages are increased by the help of allied diseases, it is clear that there must come a time when, even though the coronary circulation be apparently adequate, the inherited capabilities of the cells will fail, and growth consequently cease. Little is known concerning this inherited growing-capacity, but it is a very important factor. Probably no increase of the blood-supply could save a thymus gland from atrophy or increase the number of adult ganglion-cells.

When muscle contracts frequently against a moderately increased load, it also hypertrophies, as is seen in training. Frequent contraction alone is insufficient, for the muscles of hands used actively, but not forcibly, do not enlarge, nor is frequent micturition in pyelitis followed by thickening of the muscular walls of the bladder. If, however, an obstruction occurs in the urinary passages, which the bladder can overcome by more powerful contraction, hypertrophy begins. Other examples of such *compensatory* hypertrophy may be seen in the walls of the intestine just above a permanent, but not impermeable, stricture ; or in those of a vein in aneurysmal varix ; or of any bloodvessel through which an abnormal quantity of blood is forced.

When any organ is removed, or prevented from fulfilling its ordinary functions, other organs, which take on its work, hypertrophy, receiving the blood which should have supplied the diseased organ as well as their own. This is best seen in the kidney ; rarely in the testis, and, perhaps, occasionally in the lung. The power of hypertrophy possessed by a glandular organ is only complete in fœtal life. If one kidney be destroyed before birth, the other will grow until it reaches double its normal weight ; but if the damage occur later, the increase in the surviving organ will not exceed one-third of the original, and the reserve power of the organ will accordingly be less. The kidneys seem to be excited to secrete by the presence in the blood of material suitable for their secretion, and hypertrophy naturally results from a continued and marked increase in the supply of blood containing such material—presumably the products of tissue-metabolism. Removal of one submaxillary gland is not necessarily followed by hypertrophy of other salivary glands ; this occurs from more frequent stimulation of their secretory nerves, which probably produces the large submaxillary glands seen in epithelioma of the tongue. Enlargement of lymphatic glands has been noted after removal of the spleen. Increased weight thrown on a bone causes thickening of it—*e.g.*, of the fibula in ununited fracture of the tibia.

2. **Increased nutritive supply** may be the primary cause of hypertrophy, as in those cases in which *continued hyperæmia* from hard use and slight injuries is followed by thickening of the epithelium, as in a labourer's hand. Under similar conditions a corn may arise. Increased blood-supply to a limb may cause lengthening of a bone, if the epiphysis be ununited, as is seen in connection with

large ulcers, caries, necrosis, and other conditions: the soft parts increase secondarily. Excessive growth of hair occurs in the hyperæmic zone of a chronic ulcer of the leg. In all probability, increased vascular supply cannot by itself give rise to hypertrophy of any but the least specialised tissues.

3. **Diminished waste** is not a common cause of hypertrophy. The sclerosis of bone produced by small doses of phosphorus, the increase in size and strength of animals treated with small doses of arsenic, and the invigorating effect of this drug upon Styrian mountaineers, may perhaps be explained by diminished waste.

An example often quoted is the sub-involuted uterus, the bulk of which is made up of hypertrophied muscle and connective tissue with thick-walled vessels, but it is doubtful whether chronic inflammation is not largely responsible in these cases.

4. **The removal of resistances to growth** is difficult to ascertain. It is sometimes mentioned as a factor in the production of such deformities as "knock-knee" (*genu valgum*): here excessive pressure is thrown on the outer articular surfaces of the femur and tibia, whilst the weight borne by the inner surfaces is less than normal, and they consequently grow excessively. This explanation is, however, incompatible with the occurrence of atrophy of the tibia in ununited fractures of that bone. Many *scleroses* or hypertrophies of connective tissue follow upon atrophy of the essential elements of an organ: the natural resistance between the two tissues (*tissue-tension*) has been removed.

Uncut hair and nails, and, in the case of many animals, unopposed teeth, grow till their vessels supply only nutriment enough to maintain them in their finally attained condition. These are, however, doubtful examples of hypertrophy: more probably they represent normal growth in the absence of normal attrition against opposing structures.

5. There remain certain cases in which the ætiology is even more doubtful than in the above. These are (1) cases of *true giant-growth—e.g.*, hypertrophy of the whole body (*giants*), of half the body, of whole limbs, or of parts of limbs, as fingers and toes: such parts are, on dissection, normal, except in size. A peculiar disease, acromegaly, characterised by enlargement of the extremities and of some of the cranial bones, is supposed to be due to disease of the pituitary body: and some cases of giant-growth are said to be examples of this condition. (2) Cases of *false giant-growth* occur in which the connective tissue alone is increased, the part being often misshapen: lymphatics are often dilated, and the bloodvessels may be nævoid. Examples are met with especially in the lip (*macrocheilia*), tongue (*macroglossia*), and lower extremity: these changes are by some authors classed as Lymphangiomata (Chapter XIX.). Hypertrophy of connective tissues and surface-epithelium may result from an excessive, though slow and impure, supply of blood. In some of the above, which are congenital or appear soon after birth, there may be **excessive vital energy** or **too large a number of the cells** forming the rudiment of the part or tissue.

Nothing is known of the causation of the enormous, but rare, enlargement of the female breast which may occur at puberty.

METAPLASIA.

The present may be a convenient place at which to allude to the change which epithelial cells at times undergo as the result of alteration in their surrounding conditions—an alteration of shape rather than of size. Thus columnar epithelium may be converted into squamous or into flattened pavement epithelium. An instance of the former may be seen in cases in which the uterus is inverted and prolapsed: the lining mucous membrane is thus exposed to the outer air and to irritation from contact with clothes, and under these conditions the columnar cells become squamous in type. The columnar cells lining ovarian and other cysts may, on the other hand, become flattened and thinned as the cysts enlarge, this alteration being produced by lateral stretching combined with direct pressure from the cyst-contents. An opposite change occurs in villous growths in the bladder, which often exhibit a columnar covering in place of the transitional epithelium from which they arise. The ciliated epithelial cells lining the nasal cavities become squamous in type as a result of infective or traumatic inflammation (ozæna, cautery). Change of type of the above nature is called *metaplasia*, or, when it occurs in malignant tumours, *anaplasia*. It is often seen in the secondary growths arising from carcinomata (see Chapter XX.).

CHAPTER IX

PARASITES

A PARASITE is an organism which obtains its food and lodging at another organism's expense, without necessarily destroying the latter and without rendering it service.

Human parasites may be classified according as their habitat is on the surface of the body (*external*) or in its interior (*internal*). Some parasites are *wholly* parasitic ; others only *partially* parasitic —*i.e.*, spend only a portion of their life's cycle in the parasitic state. Some parasites seem to possess a considerable degree of option as to their mode of life, remaining in an independent condition for irregular intervals without apparent detriment (*occasional parasites*). Some can exist in or on any one of many species of animal, others in or on only a few or even a single species ; while some are limited to one tissue of a single species.

Parasites generally obtain their nutriment easily, and tend to lose such parts as are not essential to life or for propagation. Thus, external parasites retain the organs of locomotion, for active movement is generally necessary to obtain food, to escape from danger, and to effect copulation. Internal parasites, on the other hand, generally lose these organs—teeth, suckers and cilia alone excepted. Moreover, internal parasites obtain food and oxygen by direct absorption, and tend to lose both alimentary tract and respiratory system. The power of reproduction which parasites possess is enormous. It has been estimated that the common intestinal round worm produces more than 60,000,000, ova per annum.

The effects of parasites may be either *chemical* or *mechanical*. The chemical effects are chiefly exerted by means of toxic products resulting from the growth and excretion of the parasitic organism. These products may lead (1) to general poisoning of the host ; (2) to local destruction of tissues ; (3) to inflammatory fibrosis ; and (4) to various reflex effects. The mechanical effects comprise (1) the blocking of tubes such as gland-ducts, intestine and blood-vessels ; (2) pressure upon and destruction of tissues by the mere presence of the growing parasites ; and (3) hæmorrhage from weakening and rupture, or from direct perforation, of the walls of the vessels.

There is a popular idea that some animal parasites can appropriate to themselves an amount of nourishment which seriously detracts from that usually at the disposal of the host. This effect, however, is at most unimportant.

It will be readily understood that in all local effects, either chemical or mechanical, the gravity of the results will depend largely upon the importance of the parts and tissues involved. The growth of a hydatid cyst in the liver may produce a tumour many inches in diameter, yet causing comparatively little inconvenience, while a much smaller growth occurring at the base of the brain may lead to a fatal result.

ANIMAL PARASITES.

Of the animal parasites which affect mankind some are *external* and some *internal*. The former belong to the classes *Insecta* and *Arachnida;* the latter include various forms collectively termed in popular language "worms" (*nematodes*, *trematodes*, and *cestodes*), and a variety of *protozoa* or unicellular organisms. Biting insects such as the *tsetse-flies*, and the various *ticks* (Arachnida) which may attack mankind, though often important as carriers of parasitic organisms, do not fall into the class of "parasites," as they do not live on the human body.

PEDICULI.

Pediculi and acari are the two principal *external pathogenic animal parasites* of importance in temperate zones. The former are wingless insects: the latter are members of the spider class (*Arachnida*).

Three varieties of pediculus are parasitic on man—*P. corporis*, *P. capitis*, and *P. pubis* (Fig. 19). The first two varieties are closely similar, and all three have many points in common. In length they vary from 1 mm. to 4 mm. The *head* is conical, constricted at its junction with the thorax, and provided with a proboscis, a pair of prominent jointed antennæ, and a compound lateral eye behind each antenna. The *thorax* in the *P. corporis* and *P. capitis* is marked off from the abdomen by a distinct constriction, and carries, in each of the three varieties, three pairs of jointed legs terminating in claws. The number of segments in the *abdomen* varies with the species. The surface of limbs, thorax and abdomen alike is provided with scattered hairs.

The sexes are distinguished from one another by their respective sizes and by their generative apparatus. The males are from half to two-thirds the size of the females. The penis is large and extends over the centre of the dorsal surface of the last three abdominal segments. The last of these segments is rounded. In addition to their larger size, the females are recognised by the notching of

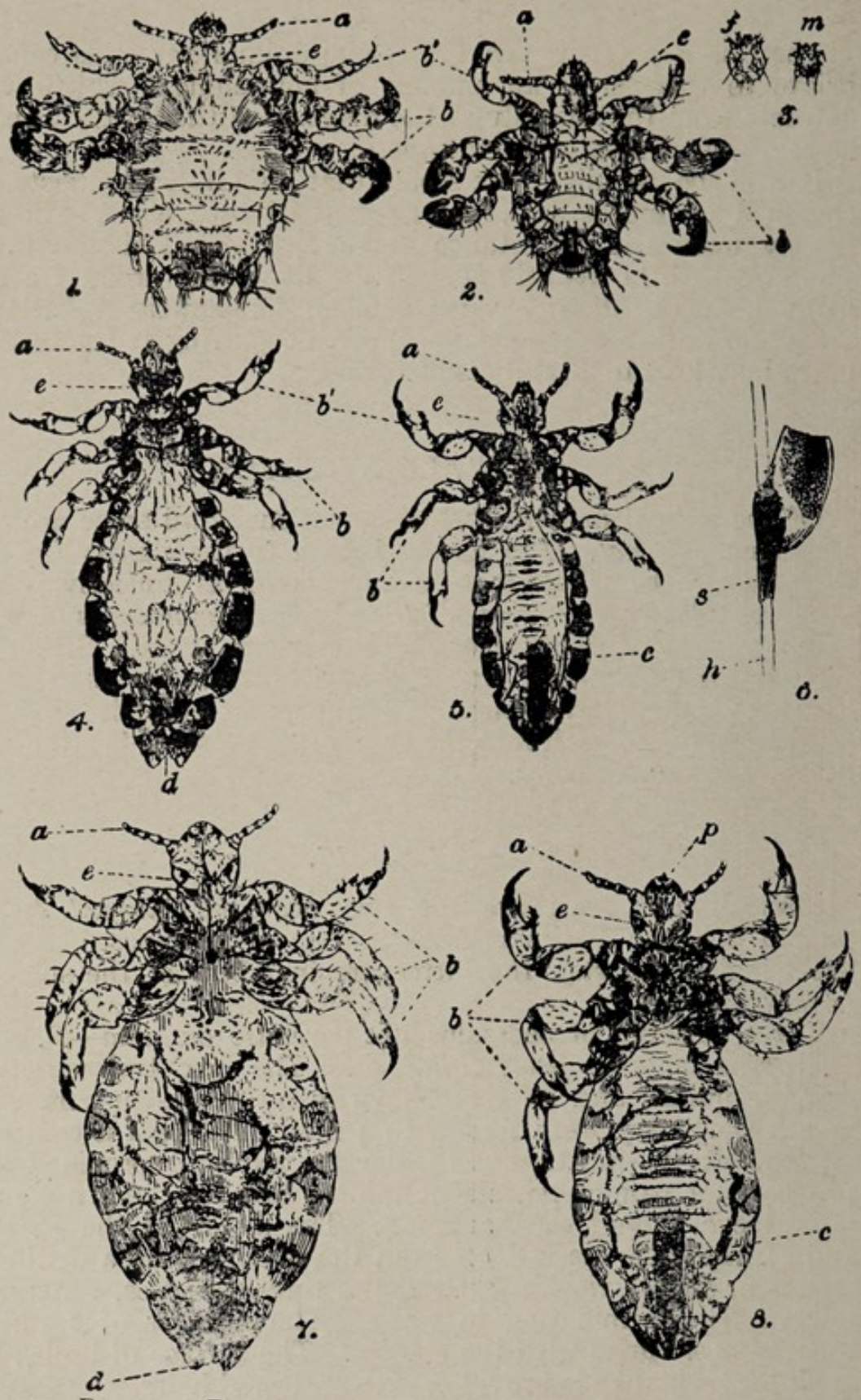


FIG. 19.—PEDICULI PARASITIC IN MAN. (× 15.) (MONTAGUE MURRAY.)

Fig. 1. *Pediculus pubis* (female). Fig. 2. *Pediculus pubis* (male). Fig. 3. *Acarus scabiei*—*f*, female; *m*, male—to show comparative size. Fig. 4. *Pediculus capitis* (female). Fig. 5. *Pediculus capitis* (male). Fig. 6. Ovum or nit of *Pediculus capitis*. Fig. 7. *Pediculus corporis* (female). Fig. 8. *Pediculus corporis* (male). These figures show the comparative size as well as the distinguishing features: *a*, antennæ; *b*, legs; *c*, penis; *d*, notched posterior segment; *e*, eyes; *p*, proboscis; *s*. glutinous sheath surrounding hair (*h*).

the last abdominal segment and by the possession of a ventral vagina. It follows, therefore, that the females are uppermost in copulation. The number of ova produced by a single specimen varies in the different species. The embryos emerge in from five to seven days, and mature in the course of the following fortnight.

The intolerable itching produced by the digging action of the parasites extends beyond the areas immediately affected, and leads to violent scratching of the parts involved, and this again to abrasions in the skin. Into these abrasions cocci grow rapidly, and in this way pustules and enlarged glands are produced.

1. The **Pediculus corporis** vel **vestimentorum** is the largest of the parasitic lice (3·5 mm. × 1·5 mm.). It is greyish and semi-transparent, and possesses well-developed legs which enable it to move rapidly. There are eight abdominal segments. This parasite inhabits the upper margin of the underclothing on the chest. Here it has easy access to the skin, whence it obtains its nutriment. Pushing its proboscis along some duct, it withdraws blood by suction, the point of entry being subsequently marked by a fine hæmorrhagic speck. The ova are generally deposited in the clothes, but may be occasionally seen fastened to the hairs growing on the skin of the thorax or abdomen.

2. The **Pediculus capitis** is smaller than the foregoing (2·5 mm. × 1 mm.). Its colour somewhat simulates that of the skin of its host, and thus may be pale, dark, or distinctly yellowish. In this country the sides of the abdominal segments are generally much darker than in the *P. corporis*, which in general appearance it closely resembles. The *P. capitis*, however, possesses only seven abdominal segments. This louse inhabits the occipital region of the scalp. Its legs are the least powerful of the three varieties, and its movements are correspondingly less active. The ova (fifty or thereabouts for each female) are fastened to the hairs of the scalp by a glutinous substance. They are flattened at the free end, and are provided with an operculum, which soon falls off and permits the escape of the embryos.

3. The **Pediculus pubis** ("crab-louse") is the shortest, and, proportionately to its length, the broadest of the three varieties. The antennæ are very prominent. The constriction at the base of the head is very slight, and the division between the thorax and the abdomen is marked only by the position of the legs. Of these the anterior pair are slight, and are used for walking, while the posterior two pairs are very powerful, and terminate in strong crab-like claws enabling the parasite to cling with great tenacity. This louse inhabits the pubic hair, rarely straying to more distant parts. It attaches its ova, ten or fifteen in number, to the base of the hair-shaft. These ova are difficult to see.

ACARI.

The only important parasite belonging to the class Arachnida is the **Acarus scabiei** (*Sarcoptes hominis*) or itch-mite. This minute tortoise-shaped mite is just visible to the naked eye as a white glistening speck : the female burrows in the epidermis, and the male roams over the surface of the skin (Fig. 20). Short hairs or setæ

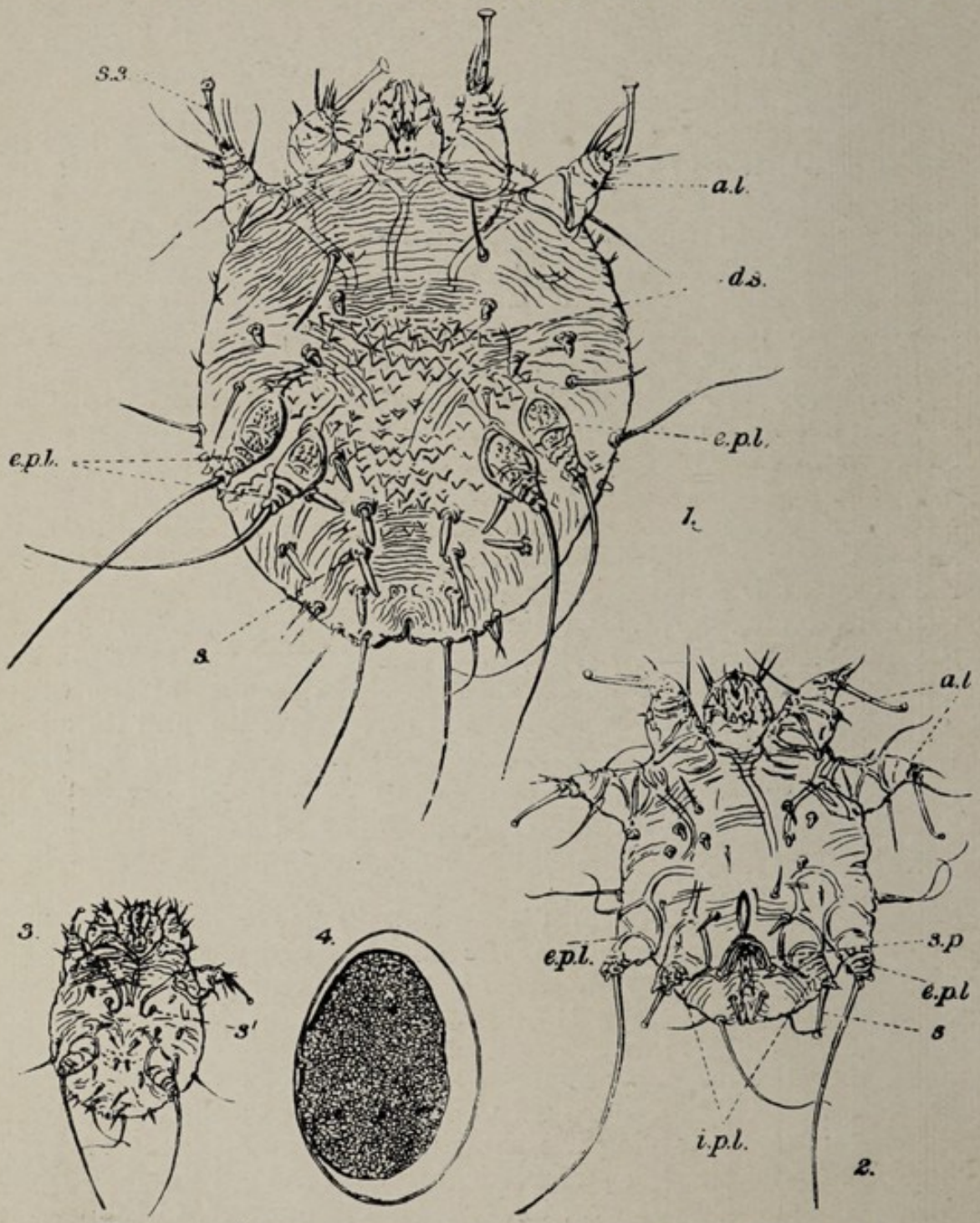


FIG. 20.—ACARUS SCABIEI. (× 150.) (MONTAGUE MURRAY.)

1. Female. 2. Male. 3. Larva. 4. Ovum. *a.l.*, anterior legs terminating in stalked suckers ; (*s.s.*) *e.p.l.*, posterior legs terminating in bristles ; *i.p.l.*, posterior median legs of male terminating in stalked suckers ; *d.s.*, dorsal spines ; *s*, setæ ; *s.p.*, support for penis.

are scattered over its body, which has, on its dorsal surface, rows of spines forming transverse, serrated lines ; and on its ventral, eight short conical legs, terminating in long bristles or long suckers.

Three features serve to distinguish the female from the male : (1) the size, (2) the distribution of bristles and suckers, and (3) the generative apparatus. (1) The female is rather less than 0·5 mm. long ($\frac{1}{50}$ in.), while the male is rather more than half the size of the female. (2) In both sexes the four anterior legs terminate in suckers. Of the posterior four in the female, all end in bristles ; while in the male, the two *external* end in *bristles*, and the two *medium* in *suckers*, an arrangement by which copulation is facilitated. (3) In the female, little evidence of generative organs can be seen beyond the occasional presence of an ovum on the ventral surface ; in the male, however, there is a penis, with a horny support, in shape not unlike a pitchfork.

The larval form is smaller than the male (Fig. 20), and possesses only six legs. Before reaching maturity it sheds its skin two or three times, and develops generative organs and eight new legs. The original six legs are not shed until the new ones are developed, so that in some specimens fourteen legs may be counted.

The female acarus burrows into the epidermis, depositing her eggs—about one a day—along the track. If undisturbed, she continues to do this for some weeks, and then dies. In the meantime, the ova gradually develop into the larval form, burrow a little, mature, become impregnated, and finally, in the case of females, start burrowing afresh. The male does not burrow, but, as the epithelium wears away, reaches the surface of the skin, over which it wanders.

Effects. — The presence of the parasite in the skin gives rise to intolerable itching, which is followed by violent scratching. Pyogenic cocci grow into the abrasions of the skin thus produced and give rise to a pustular eruption. The parasite seems to have a special preference for the hands, feet, and external generative organs. The disease arises from prolonged contact with infected skin, bedding, clothes, or tools.

A minute acarus, **Demodex folliculorum,** is found in the follicles of the skin. It is usually regarded as harmless, but Borrel, who finds that it exists in large numbers in some cases of epithelioma, suggests that it may have some causal connection with this disease—possibly by acting as carrier of an ultramicroscopic organism.

CESTODA.

The members of the *Cestoda,** indigenous in man, are long, flat, white, tape-like " worms " inhabiting, in their mature form, the intestinal canal. The mature " worm " consists of a minute head and neck with a longer or shorter row of attached segments. The

* Greek κεστός, a girdle. The Cestodes form a distinct zoological order, and are not in reality *worms* in the strict meaning of the term.

whole, known as a *strobilus*, is, in most cases, not a single individual, but a colony of individuals formed by continual budding from a single spot on a parent segment (Fig. 21). The "head" or parent-segment is generally 1 mm. to 2 mm. broad, and is provided with suckers which enable it to cling to the wall of the intestine. It is succeeded by a long narrow neck. At the farther end of this,

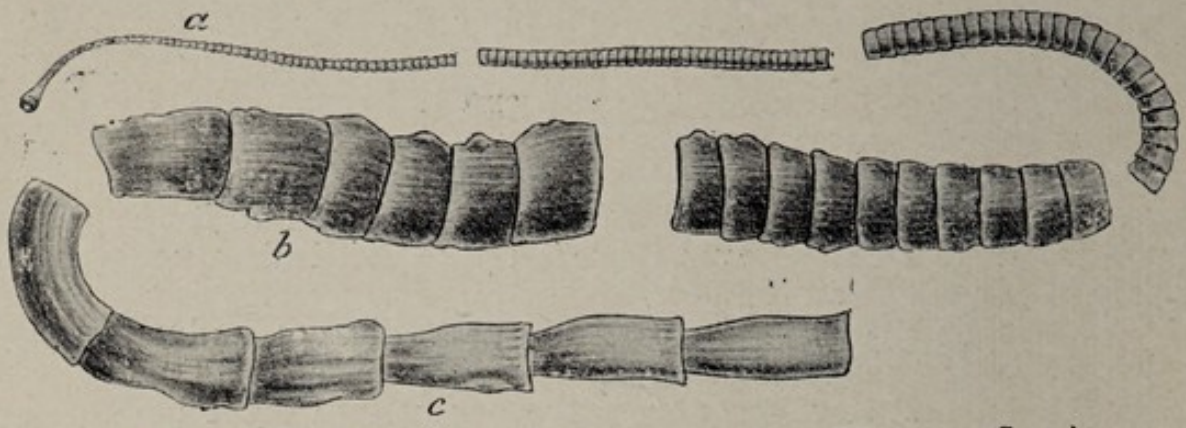


FIG. 21.—PORTIONS OF A TÆNIA SAGINATA. (NATURAL SIZE.) (MONTAGUE MURRAY.)

a, head, neck, and commencing segmentation; *b*, central; *c*, terminal proglottides.

in the large majority of instances, transverse lines become visible, indicating the divisions between the segments or *proglottides* of which the worm almost entirely consists. Those nearest to the neck are imperfectly developed and defined; those in the centre are distinctly marked off from their fellows and present well-developed generative organs; while those nearest the posterior end are crammed with ova. Each fully developed segment is hermaphrodite. These worms are destitute of digestive organs, and absorb their nutriment directly from the intestinal contents of the host. They possess a complete water-vascular system which takes the form of longitudinal tubes running down each side (Fig. 25).

FIG. 22.—TÆNIA SAGINATA. CYSTIC STAGE WITH HEAD EVERTED. (× 3.) (ZIEGLER, FROM LEUCKART.)

The life-history of a tape-worm includes residence in two hosts. The ripe proglottides are broken off, for the most part one by one, from the parent worm. Before they are discharged from the intestine, or even after they have been passed, the ova which they contain are set free. It is generally believed that the ova are expelled from the proglottides by the vermicular movements of the latter; in any case they retain their vitality for some days. If at this stage the ova are eaten by some animal capable of acting as the host of the intermediate form of the parasite, they continue their development until the shells are dissolved off in the alimentary tract, and an embryo with six hooklets is set free. By means of these hooklets the embryo is enabled to penetrate the wall of the

alimentary tract and, by way of the blood-stream or some other route, to reach some distant part. When the progress of the embryo is finally arrested, the hooklets disappear, and at the end of the embryo opposite to their attachment a cavity appears. From the wall of this cavity a fully formed head (*scolex**) develops, while the parasite gradually becomes enclosed in a fibrous capsule supplied by the surrounding tissues. In this *intermediate* or *cystic* stage the parasite, now known as the *cysticercus*† (Fig. 22),

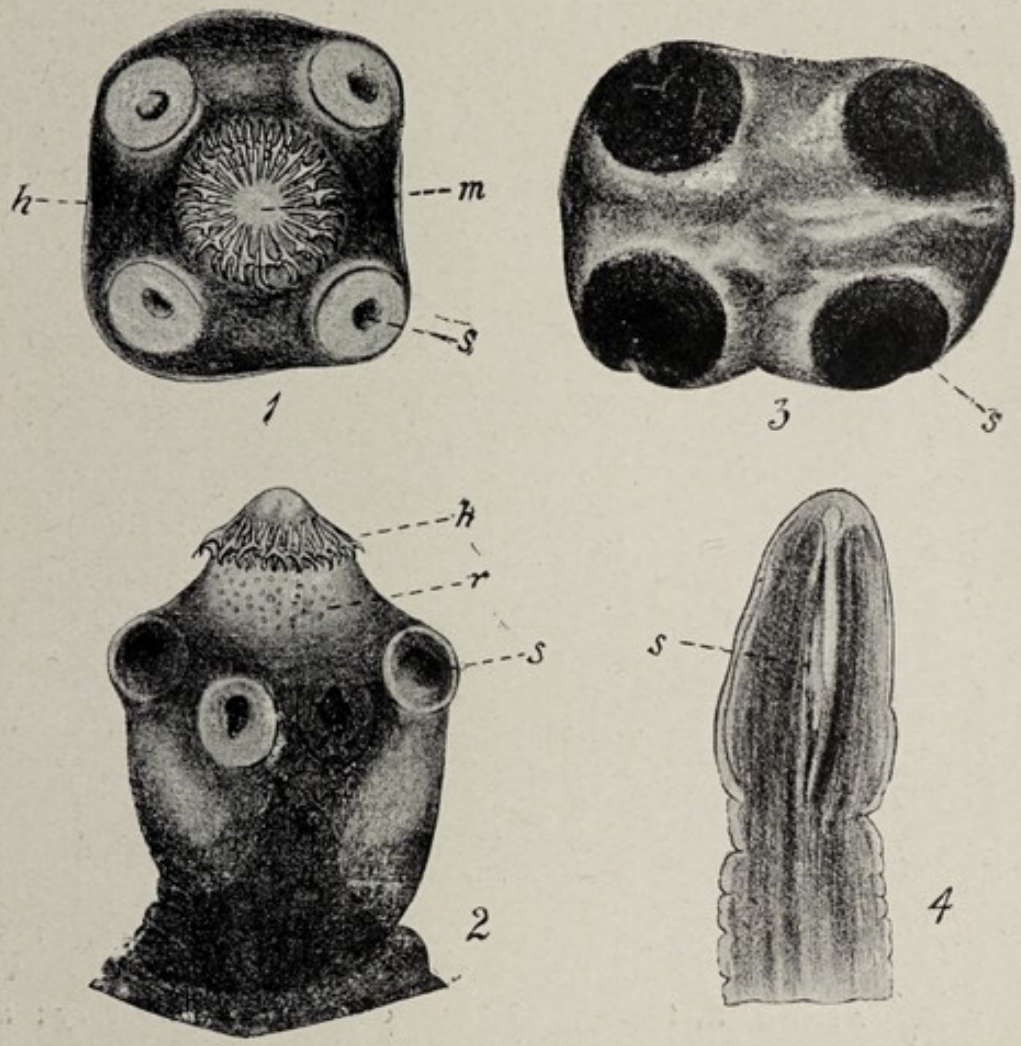


FIG. 23.—HEADS OF TAPE-WORMS. (× 20.) (MONTAGUE MURRAY.)

1. Head of *Tænia solium*, front view. 2. Head of *Tænia solium*, side view. 3. Head of *Tænia saginata*, front view. 4. Head of *Bothriocephalus latus*, side view. *h*, hooklets; *r*, rostellum; *s*, suckers; *m*, summit of rostellum.

may live for many months, or may soon die. When dead, it readily undergoes calcification. If, however, tissues containing living cysticerci be swallowed by an animal capable of acting as the host of the mature worm, the investing material is dissolved off, and the scolex is set free. By means of their suckers some of the heads will probably become attached to the wall of the intestine, and segments will quickly develop from the free ends. All new segments are formed at the neck, and the older ones are thus pushed farther

* σκώληξ, a worm. † κύστις, a bladder; κέρκος, a tail.

and farther from the head, at the same time gradually developing generative organs. Two months generally elapse between the swallowing of the cysticerci and the passage of the first proglottides from the rectum.

Four varieties of tape-worm are commonly parasitic in man. Three of these are found in the intestine, the *Tænia solium*, the *Tænia saginata* or *mediocanellata*, and the *Bothriocephalus latus*. The fourth, the *Tænia echinococcus*, does not infest the human intestine, but may be found, in its cystic or intermediate stage, in the liver and other parts. The characters of these four parasites are set forth in the table on p. 86, from which it will be seen that, except so far as the head is concerned, the *Tænia solium* and the *Tænia saginata* very closely resemble one another; while the

FIG. 24.—TÆNIA ECHINOCOCCUS. (× 12.) (ZIEGLER, AFTER LEUCKART.)

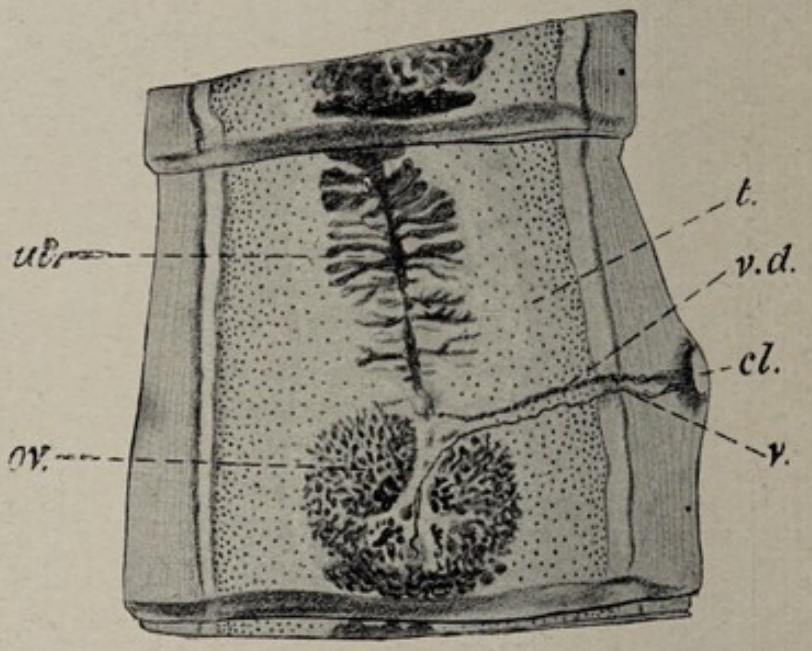


FIG. 25.—ONE OF THE MIDDLE SEGMENTS FROM A TÆNIA SAGINATA. (× 6.) (MONTAGUE MURRAY.)
t., testes; *v.d.*, vasa deferentia; *ov.*, ovary; *ut.*, uterus; *v.*, vagina; *cl.*, genital pore.

Bothriocephalus latus is easily distinguished by the shape of its head, by the breadth of its segments, and by the coil-like form of its uterus (Fig. 28).

Two other tape-worms are less commonly met with in the human intestine, the *Tænia nana* and the *Tænia canina* (*cucumerina*). Of these, the *Tænia nana* is from half an inch to one inch in length, and consists of head, neck, and about 150 broad segments. The head somewhat resembles that of the *Tænia solium*, but is more spherical; while the joints are broad, like those of the *Bothriocephalus latus;* but the genital pore is at the side. The *Tænia canina* is about one foot in length. The head has three or four rows of hooklets, which are twice as numerous as in the other varieties. The segments number about one hundred, of which

the last twenty-five are mature and rather more than a quarter of an inch in length. They have a genital pore on each side of every proglottis. This parasite is most frequently found in dogs and cats, and the intermediate host is supposed to be a tick or louse.

Effects. — These are generally so slight that the presence of the worm is unsuspected until detached proglottides are passed *per anum;*

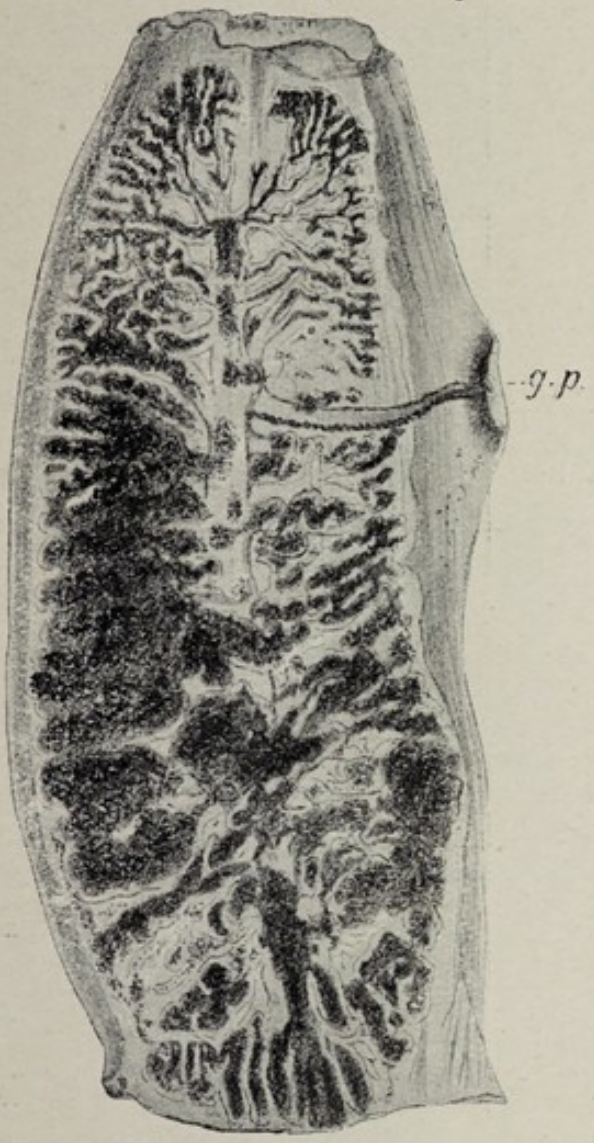


FIG. 26.—TÆNIA SAGINATA. (× 6.) (MONTAGUE MURRAY.)

A proglottis near the terminal end, showing the female generative organs crammed with ova. *g.p.*, genital pore.

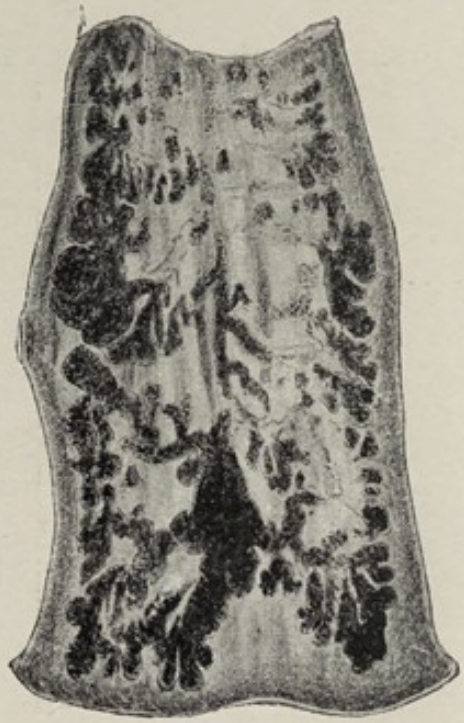


FIG. 27. — TÆNIA SOLIUM (× 6.) (MONTAGUE MURRAY.)

Mature proglottis, with ova. Branching of uterus less complex than in Fig. 26.

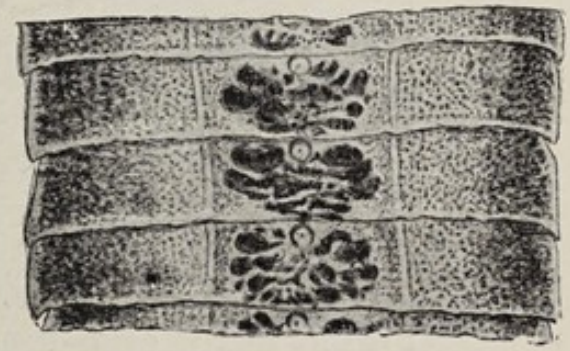


FIG. 28.—BOTHRIOCEPHALUS LATUS. (× 6.) (MONTAGUE MURRAY.)

Three mature segments with coiled rosette-like uterus and central genital pore.

but slight intestinal colic, and even convulsions and other nervous disorders, occasionally ensue, especially in children. These effects are due either to mechanical irritation or to the absorption of toxic substances formed by the parasites. In the case of *B. latus*, which may be associated with symptoms of profound anæmia, there is some evidence that the parasite secretes a hæmolytic poison.

COMPARATIVE TABLE OF PARASITIC TAPE-WORMS.

SEE FIGS. 21-30.

NAME:	Tænia solium.	Tænia saginata.	Tænia echinococcus.	Bothriocephalus latus.
LENGTH	7 to 10 feet	10 to 20 feet	½ inch	10 to 25 feet
SEGMENTS	700 to 1,000	1,000 to 2,000	4	3,000 to 4,000
HOST	Man	Man	Dog and Wolf	Man
SEAT	Intestine, often in numbers	Intestine, usually singly	Intestine, in numbers	Intestine, one or more
SOURCE	Infected insufficiently cooked pork	Infected insufficiently cooked beef	Infected viscera of sheep	Infected insufficiently cooked lake fish
INTERMEDIATE HOST	Pig: "measly pork"	Ox: "measly beef"	Man and Sheep	Pike and Trout, etc.
SEAT	Muscle and viscera	Muscle and viscera	Chiefly liver, less frequently muscle and viscera	Muscle and viscera
SOURCE	Food infected with dejecta containing ova	Food infected with dejecta containing ova	Food infected with dejecta containing ova	Food infected with dejecta containing ova
HEAD (FIG. 23)	Length, ¼ inch Rostellum, 26 or 28 hooklets, double row 4 suckers	Length, ¼ inch *No* rostellum, *no* hooklets 4 suckers	Length, ⅛ inch Same as *Tænia solium*, but smaller 4 suckers	Length, ⅛ inch Club-shaped oval, no hooklets 2 suckers
SEGMENTS	Mature segments, length greater than breadth	Mature segments, length greater than breadth	4 segments only	Breadth always greater than length
GENERATIVE APPARATUS	*Uterus*, a central canal with about 10 branches	*Uterus*, a central canal with between 20 and 30 branches	*Uterus*, a wide cavity in last segment	*Uterus*, tube arranged in loops giving appearance of rosette
	Papilla, with genital pore on side of segment: side alternating	*Papilla*, with genital pore on side of segment, alternation irregular	*Papilla*, with genital pore on side of last segment	Genital pore in centre (ventral)
OVA	Spherical Almost mature when discharged	Short oval Almost mature when discharged	Spherical	Oval, with operculum, immature, develop in water, where embryos swim about

Hydatid Cysts

Special reference must be made to the cystic stage of the *Tænia echinococcus*, owing to the frequency with which it is found in the viscera of man, especially in the liver—three-fifths of the total cases occurring in that organ.

The embryos derived from the ova of the adult worm (parasitic in the dog) are set free in the intestine, from which they escape, mainly by the veins, and thus reach the liver or other parts where they come to rest. Each embryo is capable of development through a long cycle of changes, the earliest of which consists in the formation of a spheroidal body which gradually develops into a cyst. The *cyst-wall* consists of two layers—an external, transparent more or less definitely *laminated ectocyst*, and an internal, granular *germinal* layer or *endocyst* (Fig. 29).

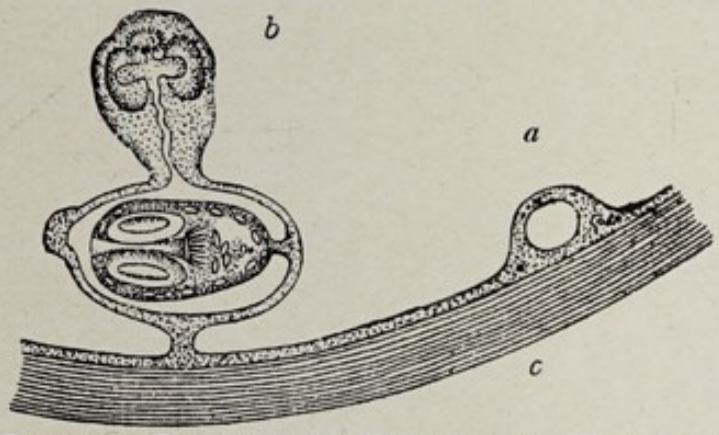


FIG. 29.—DIAGRAM OF PORTION OF WALL OF HYDATID CYST, TO SHOW DEVELOPMENT OF BROOD-CAPSULES AND SCOLICES. (× 50.) (MODIFIED FROM LEUCKART.)

a, germinal layer or endocyst showing commencement of brood-capsule; *b*, brood-capsule with two scolices, one inverted, the other everted; *c*, laminated layer or ectocyst.

The cyst contains (1) a varying amount of *fluid* which is clear, saline, and, in its primitive state, non-albuminous, with a specific gravity varying from 1,004 to 1,013; and (2) the *scolices* or immature heads of the adult parasite. The scolices differ from the heads of the adults only in the smaller size of the hooklets of the former and in the incomplete development of the roots of their hooklets. There is no complete agreement as to the exact procedure by which these scolices are formed. In all probability they may arise directly from the germinal layer of the original cyst-wall; but more usually they originate from secondary cysts known as "brood-capsules." These are formed as hollow elevations from the germinal layer, and gradually come to consist, as in the case of the original cyst-wall, of two definite layers—though their position is inverted—an outer germinal layer, and an inner imperfectly laminated layer. The outer layer is connected with the original cyst-wall by a stalk (Fig. 29). From the wall of the brood-capsule the scolices are formed, in some cases as invaginated depressions into the interior of the capsule, in others as external projections from the surface. If the wall of the brood-capsules is ruptured, the scolices may be scattered unattached through the contents of the cyst. According to Leuckart, all scolices are formed originally from the exterior as hollow buds which, later on, may become

invaginated, then appearing as internal projections into the cavity of the brood-capsule. However formed, they may remain quiescent for long periods, or may die and disintegrate (Fig. 30) and become calcified, the calcification of the cyst-walls preceding that of the scolices.

The brood-capsules do not always grow directly from the original cyst-wall, but on some occasions from secondary or daughter-cysts, which may arise as hernial protrusions from the original cysts, or as depressions into its interior. These daughter-cysts may by similar changes produce another generation of corresponding cysts, from any of which brood-capsules may be formed. Sterile cysts, containing neither daughter-cysts nor scolices, are sometimes found, the sterility apparently depending upon the lack of sufficient nourishment. It will thus be understood that the process of formation is very complex and that much room exists for difference of opinion.

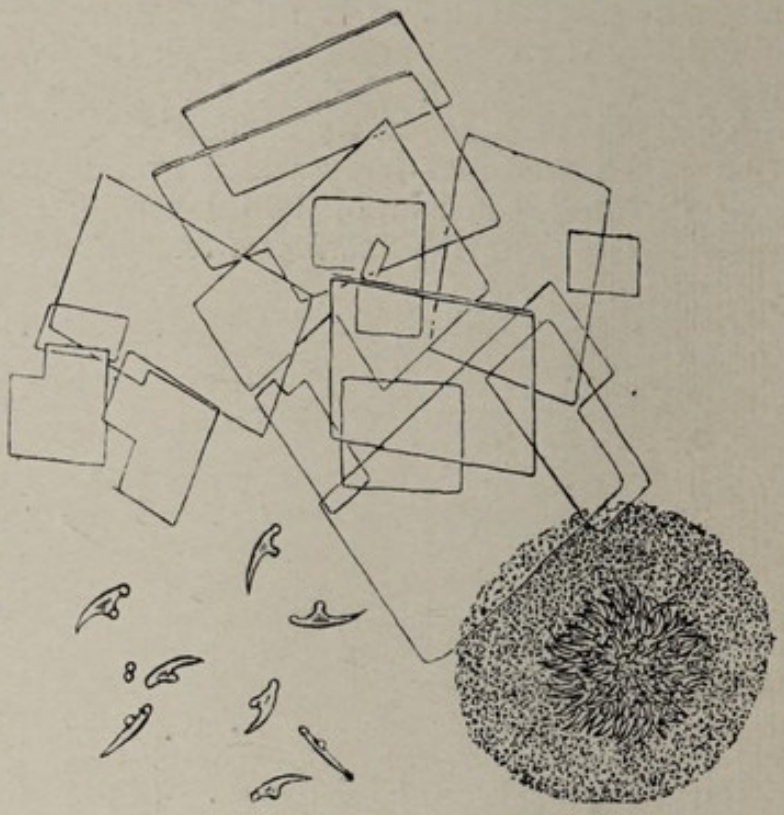


FIG. 30.—DEPOSIT FROM CONTENTS OF HYDATID CYST. (× 100.) (MONTAGUE MURRAY.)

a, scolex; *b*, scattered hooklets; *c*, cholesterin crystals.

The presence of the hydatid cyst leads to the proliferative reaction of the connective tissue in which it grows, and to the gradual development of an *external fibrous coat*.

Hydatid disease is generally derived from infection of the food or water-supply by contamination with the fæces of dogs, and is commonest, therefore, in those places in which dogs and men are close companions, and where insufficient care is taken to avoid infection. Iceland and Australia are the chief homes of the disease.

NEMATODA.

Nematoda,* or round worms, are long, slender and cylindrical, tapering at both ends. They possess a well-developed alimentary tract with a mouth at one end of the worm and an anus at the

* Greek νῆμα, a thread.

other. The sexes are distinct, the female being larger than the male. In the male, the genital pore is generally close to the anus, and therefore near the posterior end of the body. In the female, the vagina is near the middle of the abdominal surface. A short description will be given of the principal parasitic forms which are pathogenic in man.

1. **Ascaris lumbricoides.**—This is the common round worm of the intestine. During life it is of a pinkish-grey colour with a glistening surface ; after death, it loses its pinkish tint and becomes more opaque. The female averages about a foot long and the male six inches. The head has a central mouth provided with three lips. The ova are oval and generally surrounded with semi-transparent albuminous substance. When swallowed, they gradually find their way into the small intestine, developing into the adult form in the course of a month. As a rule, not more than five or six worms are found in the same host. They are especially common in lunatics, negroes, children, and other individuals of dirty habits. Occasionally, however, large numbers may be found in the intestine of a single individual—especially in tropical countries. Although the duration of their life is not accurately known, it is probably not more than a few months. Re-infection from swallowing the ova passed in the fæces may produce a supply lasting some years. The effects of the parasite are due (1) to *irritation*, which gives rise to slight colic and occasionally, in rickety children, to convulsions and other less important reflex effects ; (2) to their *wandering habits*, by which the worms may find their way into the bile-duct, stomach, larynx, middle ear, peritoneal cavity, vagina, or other places, and there give rise to symptoms of obstruction, or irritation ; and (3) to the *matting together*, in a few instances, of several worms, thus causing intestinal obstruction. In the majority of cases the presence of the parasites is unsuspected until they are expelled.

2. **Oxyuris vermicularis** (Fig. 31).—These are small round worms known as *thread-worms* (*seat-* or *maw-worms*), having the appearance of shreds of bent or twisted white cotton. The female is one-third to half an inch in length, the male is half this length. The head is pointed and furnished with two cuticular bags, one on the dorsal and one on the ventral surface. The posterior end of the female is long and tapering with a serrated edge ; that of the male is curved with a rounded extremity, furnished with a single projecting spike. The ova are of a peculiar and distinctive oval shape, being more convex on one side than on the other, thus taking the form of a bi-convex meniscus (Fig. 32). The ova of the *oxyuris* develop rather more rapidly than those of the *ascaris*, the process being completed in two or three weeks. The ova do not develop unless passed through the stomach. They must accordingly be passed *per anum* and the host re-infected by the mouth before a new generation can develop, in cases where any continuous infection is maintained. The oxyurides inhabit the large

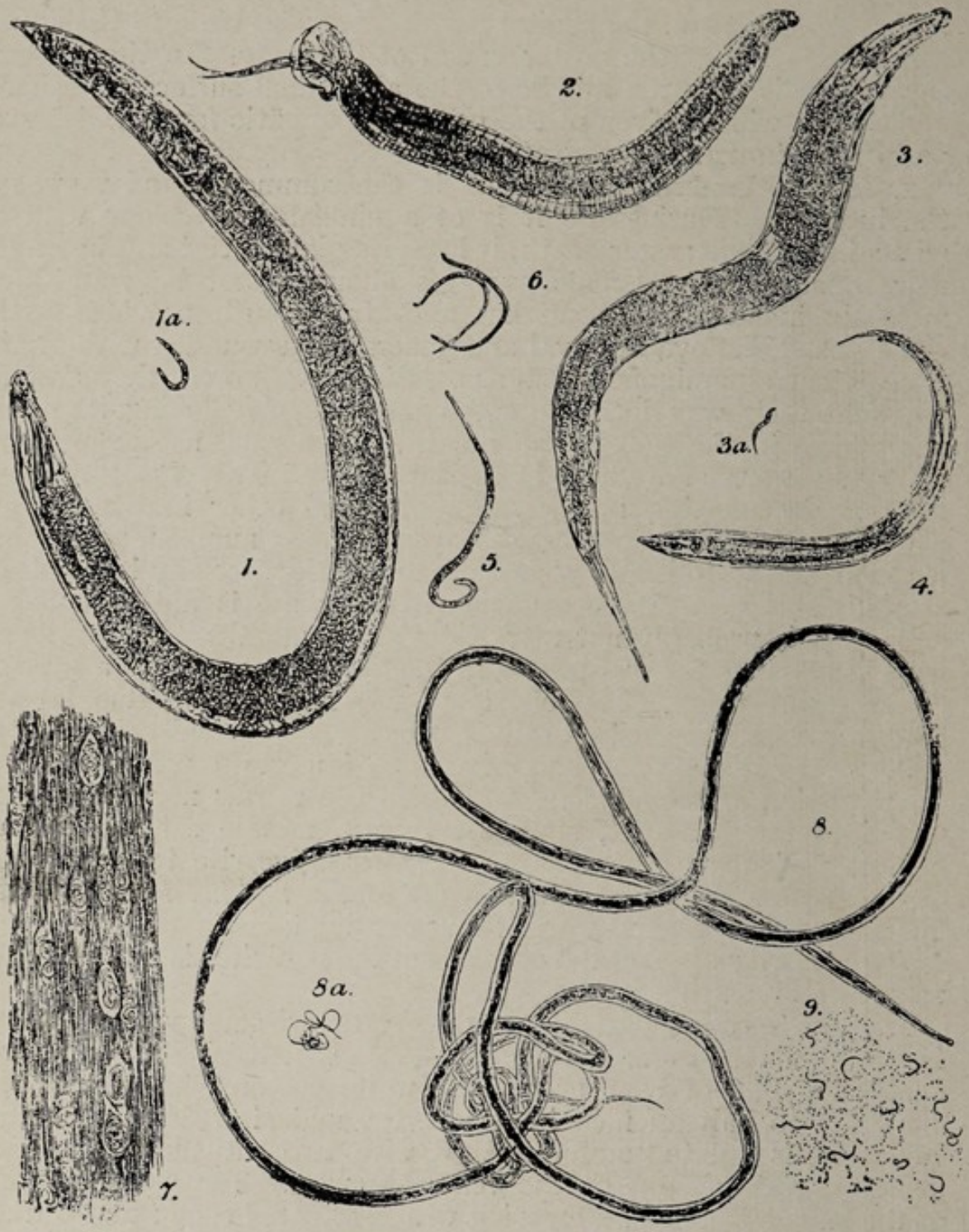


FIG. 31.—SHOWING COMPARATIVE SIZE OF VARIOUS NEMATODES. (× 14.)
(MONTAGUE MURRAY.)

1. *Ankylostoma duodenale* (female). 1*a*. *Ankylostoma duodenale* (female), natural size. 2. *Ankylostoma duodenale* (male). 3. *Oxyuris vermicularis* (female). 3*a*. *Oxyuris vermicularis* (female), natural size. 4. *Oxyuris vermicularis* (male). 5. *Trichina spiralis* (female). 6. *Trichina spiralis* (male). 7. *Trichina spiralis*, embryos in muscle. 8. *Filaria bancrofti* (female), parental form of *F. sanguinis hominis nocturna*. 8*a*. *Filaria bancrofti*, natural size. 9. *Filaria sanguinis hominis nocturna*, embryos in blood.

intestine, especially the cæcum, where they may exist in myriads. As the females become pregnant they generally pass into the sigmoid flexure and rectum.

These parasites are found mainly in children, and are probably derived from infected vegetables and fruit. Their principal effects are those of local irritation. They give rise to the formation of a large quantity of slimy mucus, some of which is passed with the stools. They may also lead to prolapse of the rectum and enuresis. Their reflex effects are somewhat indefinite. They are accredited with producing cough, restlessness, and even convulsions, though the last statement is probably erroneous. Their wandering habits are as marked as those of the ascarides, but the results are much less serious. The females make their way through the anus at night, causing intolerable itching, and may be found in the vagina, on the buttocks, and on the sheets. The itching at the anus leads to scratching and to the deposition of ova under the finger-nails. The additional itching at the mouth and nares, which is also a common effect, leads to the continual transit of the fingers between the mouth and anus during sleep, and accounts for the extreme frequency of auto-infection.

3. **Ankylostoma duodenale** (*Uncinaria duodenalis*, "*hook-worm*") (Fig. 31).—This parasite is not endemic in England, though it has been introduced into at least one mine in this country; but it is common in all tropical and sub-tropical countries. The females are rather more than half an inch, and the males rather less than half an inch in length, but the former are at least twice as thick as the latter. The head is provided with four hooks and two teeth. The posterior end is broad in both sexes, the male possessing an umbrella-like caudal expansion, fitted with ribs and two long projecting spicules. The ova are oval, segmented and enclosed in a thin transparent capsule. They develop rapidly in muddy water and in mould, especially if this is mixed with fæces. The embryos in this stage can exist for months. They are generally supposed to enter their host by the mouth, but it has recently been maintained that their point of entry is the skin, in which they give rise to a form of dermatitis. They take five or six weeks to form fully developed adults. They inhabit the jejunum and duodenum in large numbers, becoming attached to the mucous membrane by means of their hooks, and sucking the blood from the sub-mucous tissue. The results of their presence in the intestine are very variable. In some cases, even when large numbers are present, no symptoms occur: in other cases the parasites give rise to hæmorrhage and anæmia ("miner's anæmia"), as well as to colic and intestinal catarrh.

4. **Trichina spiralis** (Fig. 31).—In their fully developed form these minute round worms are, in the case of the female, about one-eighth of an inch long and in the case of the male about one-eighteenth. The head in both sexes is pointed: in the male the posterior extremity is furnished with two jaw-like appendages,

which probably serve to fix the female during copulation. The ova are hatched within the body of the female and escape from the vagina in the form of minute elongated embryos. The life-history of the parasites can be best understood by tracing the development of the embryos from the intermediate or encysted stage in which

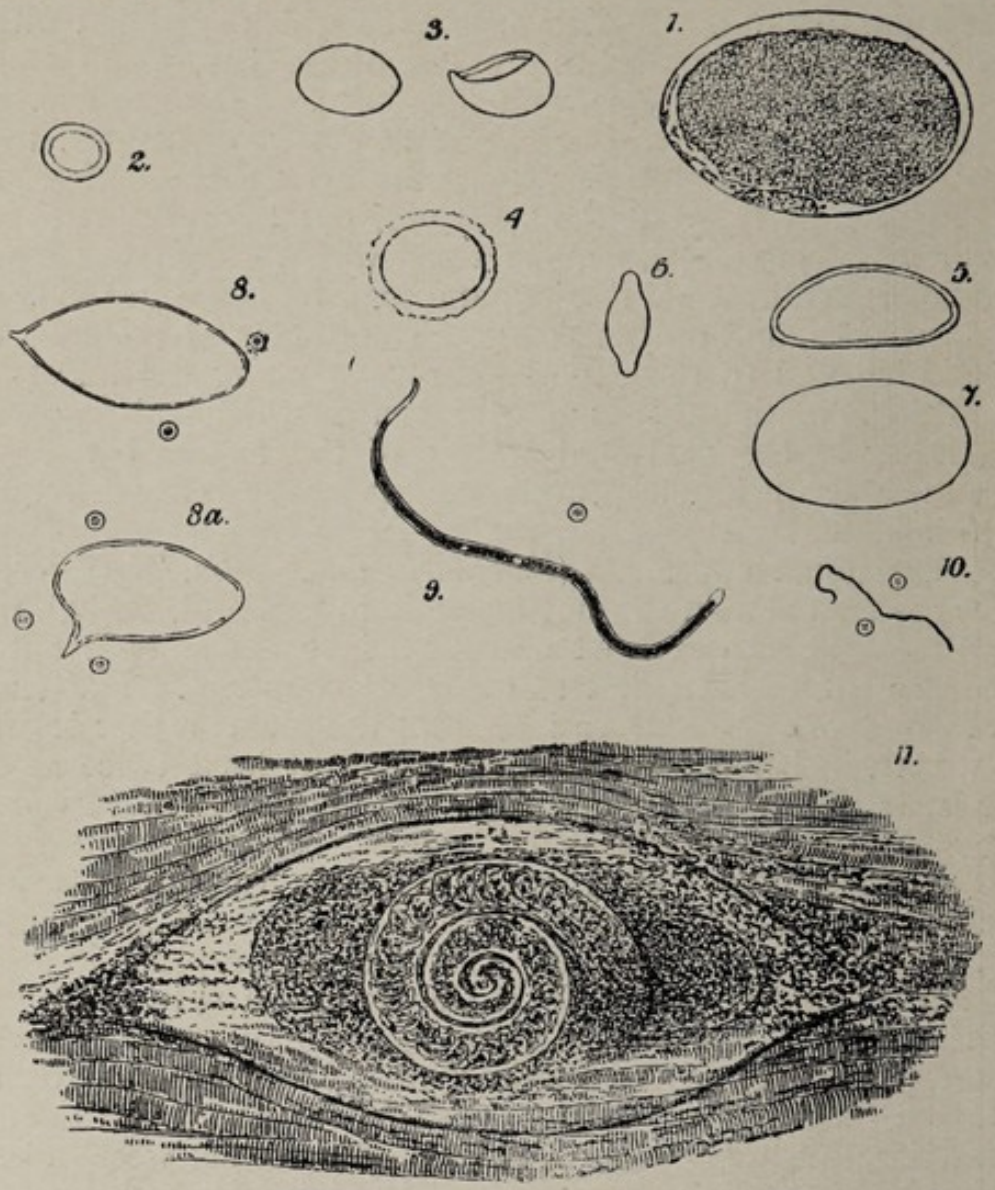


FIG. 32.—SHOWING COMPARATIVE SIZE OF VARIOUS OVA AND EMBRYOS. (× 150.) (MONTAGUE MURRAY.)

A few red blood-corpuscles have been drawn to serve as a standard of size. 1. *Acarus scabiei.* 2. *Tænia solium.* 3. *Bothriocephalus latus* (one without operculum). 4. *Ascaris lumbricoides.* 5. *Oxyuris vermicularis.* 6. *Trichocephalus dispar.* 7. *Ankylostoma duodenale.* 8, 8a. *Bilharzia hæmatobia.* 9. *Filaria nocturna* (with sheath). 10. *Filaria perstans.* 11. Trichina in muscle.

they lie encapsuled in the tissues. In this stage they may be found in the connective tissue between the individual muscle-fibres, in the subcutaneous fat, in the wall of the intestine, and in other places. If a portion of muscle infected with these embryos be examined, it will be found to contain a large number of minute

oval specks just visible to the naked eye. On microscopic examination each speck is seen to consist of a minute oval capsule with elongated ends, containing usually but one embryo (Fig. 32). These encapsuled trichinæ may live for years. After a time the cyst-wall may calcify: if the embryo within die, it also will undergo the same process. If a portion of a muscle containing living embryos be eaten by an organism capable of becoming the host, the capsules are dissolved off in the stomach and the embryos pass into the intestine, grow slightly ($\frac{1}{18}$ inch), mature and pair. The female grows rapidly to twice its former size, and develops ova and embryos as described. These are either discharged into the intestinal canal or, according to some observers, are deposited in the lymphatics of the intestinal walls. In any case they reach the muscle and become coiled up within a capsule as previously described. Their complete life-history can be accomplished in about eighteen days—two or three days occur between infection and the pairing of sexes, six or seven more before the embryos are set free, and another nine or ten before they become encysted in the tissues.

The principal hosts are man, the pig and the rat. The disease is probably conveyed to man in pork—the diaphragm, muscles of the neck, and intercostals being the muscles which contain the largest number of parasites and those which are principally used in the manufacture of sausages. It is obvious, however, that no animal can become infected which is not carnivorous, and it is therefore necessary to explain why the pig should so frequently become infected. The explanation probably lies in the fact that the rat, which is well known to eat its own kind, is very largely infected wherever the disease may be endemic. Thus, successive generations of the parasites are maintained, and pigs may at any time be accidentally infected by eating food containing portions of the diseased rats. With regard to the general subject of infection, it may be noted that, while the adult intestinal trichinæ probably only live for one or two months, the muscle-trichinæ not only live for years, but can resist the decomposition, pickling, and freezing of their environment, succumbing only to a temperature of 80° C., which is rarely reached in the interior of any large joint. The parasite is commonest in America and Germany. Its effects are so marked that they give rise to a definite disease known as *trichinosis*, consisting of two stages. The first stage is characterised by an acute gastro-enteric catarrh due to the presence of myriads of embryos in the intestine, and is sometimes mistaken for cholera or irritant poisoning. This is succeeded by a second stage, which develops when the embryos reach the muscles, and consists of intense muscular pain, swelling, rigidity, and tenderness, giving rise, in addition to a high temperature, to aphonia, dyspnœa, trismus, dysphagia, and other serious symptoms, according to the special muscles mainly involved.

5. **Filariæ.**—Filariæ are long thread-like worms. In tropical

countries many forms are parasitic in the human body. Thus, the *Filaria oculi* is found in the tissues of the eye; and the *Filaria medinensis* (guinea-worm) and the *Filaria loa* in the subcutaneous tissue. All these parasites may produce local irritant effects.

Of greater interest is a group of filariæ known as the *Filaria sanguinis hominis*, because the embryos of the parasites are found in the blood. Of this group, the *Filaria sanguinis hominis nocturna* is the best-known member.

The adult form of the *Filaria nocturna* is generally known as the *Filaria bancrofti* (Fig. 31). The female has the appearance of a white thread, about three and a half inches long and rather more than one-hundredth of an inch in diameter. The male is considerably smaller, and less frequently found. The posterior end in both sexes is blunt, and the head slightly bulbous with a central unprotected mouth. The vagina of the female is close to the head. After the death of the host these parasites are generally found in the retro-peritoneal lymph-channels, but may be lodged anywhere. The embryos found in the blood are about one-ninetieth of an inch long, and in breadth equal to the diameter of a red blood-corpuscle. The parasite is provided with a fine sheath which it does not completely fill, and in which it can move backwards and forwards (Fig. 32). It also exhibits lashing movements, but has no power of travelling from place to place. The embryos are only found in the blood during sleeping-hours; hence the name *nocturna*. They appear gradually at about six o'clock in the evening. At midnight they are present in greatest number, and Manson has estimated that there may be as many as 50,000,000 present in the blood of a single individual at that time. They then gradually diminish in number, and by six or seven o'clock in the morning have completely disappeared. During the night some of the parasites may be removed from the blood by mosquitoes. The embryos, which thus reach the stomach of the mosquito, pierce and escape from their sheaths and bore their way into the thoracic viscera, where they undergo further development. On the death of the mosquito they fall with the body of the insect into drinking-water, and thus are conveyed to the stomach of man. Here they develop into a larval form, which escapes from the alimentary tract into the lymph-channels and there develops into the adult form as described above. From this resting-place the female discharges her embryos into the blood-stream by way of the thoracic duct.

Effects.—In most instances of filariasis no effects are observed. In a few cases, however, there may be found associated with the existence of filariæ in the blood (1) an enormous overgrowth of the skin and subcutaneous tissue of the lower extremities, and occasionally of other parts (*elephantiasis arabum*). In these cases but few filariæ can be found in the blood. According to Manson the elephantoid condition is due to the premature discharge of the ova of the filaria. These ova are more than four times the breadth of the embryos, and broader, therefore, than the lymph-channels

in the glands, through which they cannot pass, and in which, therefore, they are likely to become embedded. Manson suggests that these ova block the lymph-channels in the lymphatic glands one after another, until the whole area drained by the connected lymphatics is engorged with lymph. Overgrowth of the superficial parts follows. The absence of embryos from the blood in these cases is readily explained by the blocking of the channels through which they would reach the blood-stream. (2) In other cases associated with the presence of filariæ, the abdominal, renal, scrotal, and pelvic lymphatics are intensely varicose and filled with chyle, which often finds its way into the urine as well, producing the condition known as "chyluria." The chyle found in these lymphatics can only reach them by regurgitation from the thoracic duct; and, on at least two occasions, the upper part of the thoracic duct has been found blocked. Manson has, therefore, suggested that the first step in the production of chyluria and lymph-scrotum is the plugging or inflammatory occlusion of the thoracic duct, and that the increased lymphatic pressure thus caused leads to a flow of the chyle back through the pelvic lymphatics to those on the abdominal wall, the lymph thus reaching the blood-stream through anastomoses between the lymphatics of the upper limbs and those of the lower. Thus, the presence of chyle in the pelvic lymphatics may be accounted for, while the rupture of varicose lymphatics thus produced suffices to explain the existence of the chyluria.

Several other varieties of the *Filaria sanguinis hominis* are described. The *Filaria diurna* in its embryonic form closely resembles the *nocturna*, differing from it only in the time at which it appears. The parental form of the *F. diurna* has not been described, but Manson suggests that the *Filaria loa* may really occupy this relationship. The embryos are not pathogenic.

The *Filaria perstans* is a thinner and shorter embryo than those before mentioned (Fig. 32). It has no sheath, possesses rapid movements by which it travels from place to place, and is never absent from the blood of an infected individual. The majority of the natives on the West Coast and in the central parts of Africa seem to be infected with it.

TREMATODA.*

Several members of this order are on rare occasions found as human parasites. Thus, the *Distoma hepaticum*, or parasite of sheep-rot, and the *Distoma lanceolatum* are occasionally found in the liver. The only species commonly parasitic in man are, however, *Distoma pulmonale*, which is the causative organism in Asiatic distomiasis, and the *Distoma hæmatobium* or *Bilharzia hæmatobia*. The female of the latter has the form of a thin thread an inch long;

* τρῆμα, an orifice.

the male is half an inch long, of milk-white colour, flat, and curved laterally so as to be slightly concave on the ventral side (Fig. 33). During sexual intercourse the curve increases so that the opposite sides meet to form a "gynæcophoric canal" in which the female is enclosed. At the anterior end of the male there are two suckers.

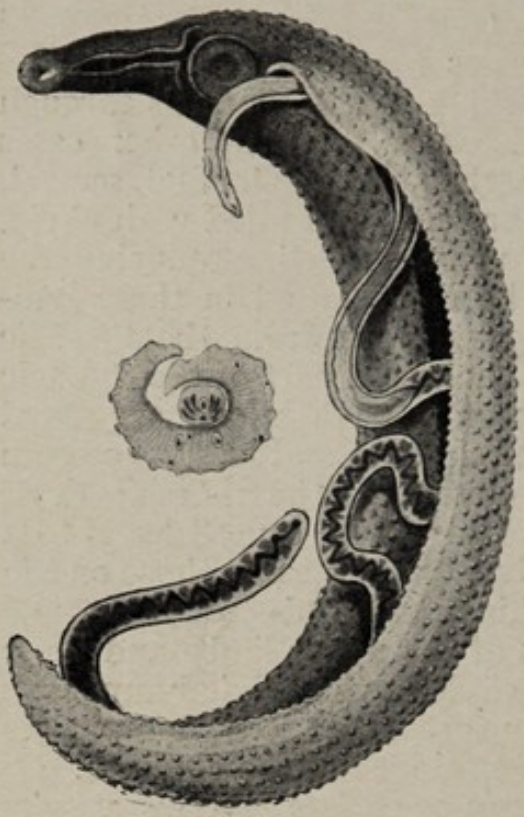


FIG. 33.—BILHARZIA HÆMATOBIA, MALE AND FEMALE. (×20.) (AFTER SANDWITH, FROM LOOSS.)

The small figure on the left shows a transverse section of the two worms *in situ*.

These parasites, especially the males, are found in large numbers in the genito-urinary and mesenteric veins of infected persons. After impregnation the females are believed to move into the smaller vessels, and there to discharge their ova. In shape these are generally compared to a melon-seed, being pointed at one end (spike), and enclosed in a transparent membrane (Fig. 32). Their contents often appear segmented, and occasionally the different parts of the future embryo can be clearly made out. They very rapidly mature in pure water, the membrane rupturing and setting free a somewhat elongated embryo (*myracidium*) provided with cilia. The eggs do not mature, and the embryos are never set free, either within the bloodvessels or in the urine. Sometimes the spike is placed on one side of the ovum (Fig. 32). The complete life-cycle of these organisms has recently been demonstrated for the Asiatic type by Miyairi and Suzuki, whose work has been confirmed by Leiper and Atkinson. The life-history of the *Bilharzia hæmatobia* has been also worked out by Leiper in Egypt. It has been shown by these observers that the myracidia enter the bodies of certain molluscs, which act as the intermediate host, and there, after making their way to the liver, go through a stage of development associated with cyst-formation. Eventually embryos known as cercariæ are liberated, and these are the infecting agents for man.

The period which may elapse between infection and the appearance of ova in the urine is variable, but never less than four months. The parasite is chiefly found in Egypt, Arabia, and South Africa. The path of infection in man is through the skin or by the mouth, but in the latter case the cercariæ perforate the buccal mucosa.

The effects of the parasite are to produce vesical and perineal pain with dysuria. Ova may be found in the urine, which frequently contains blood, especially towards the end of micturition. The ova

may lead to the formation of clots in the bladder, and subsequently to the formation of calculi; while in the tissues chronic inflammation may occur in the neighbourhood of both parasites and ova.

A trematode of an allied genus, *Paragonimus westermanni*, invades the lungs of persons living in tropical climates, and gives rise to attacks of hæmoptysis. It is said to pass one stage of its existence in certain crabs and other shellfish, and to enter the human host by the alimentary canal, either in drinking-water or uncooked food.

CHAPTER X

PARASITES—*Continued*

VEGETABLE PARASITES.

Fermentation and Infective Disease.—It has long been thought that the group of acute specific diseases must have a special cause. The characteristics of this group are: (1) that they occur in epidemics; (2) that they are obviously contagious and infectious; (3) that each member is absolutely distinct from its fellows, and runs a typical course; and (4)—the most important distinction of all—that the poison which gives rise to each of them multiplies in a marvellous manner. Thus the introduction into a community of a single case of one of these diseases may be followed by the death of thousands from the same malady. For a long time nothing could be discovered to account for the appearance of these diseases, though they were obviously produced by something which multiplied in the patient, which clung about his clothing, and which could be carried through the air for considerable distances. This "something" was, and still is, called the "*contagion*" of the disease. It was at the outset recognised that no gas could be a sufficient cause, for diffusion would soon put an end to its power for mischief. A fluid was still more out of the question. *Contagion* was, therefore, necessarily regarded as a solid in a state of very fine division—*particulate*. This view was confirmed by the discovery that it could be removed from fluids, both by subsidence (vaccine, Chauveau) and by filtration through porcelain—the poison not passing through the filter. These facts taken with its power of multiplication, seemed to show that the contagion was some living organism; hence the origin of the *contagium vivum* or *germ-theory* of disease.

In 1840, Henle clearly formulated the doctrine that living organisms, probably of a vegetable nature, were the causes of the acute specific fevers, and supported the view by arguments which have withstood all endeavours to refute them. Long before 1840, however, it had been noticed that a close parallel might be drawn between an infective disease and a fermentation. It may be presented thus:

Infection	Addition of ferment.
Incubation	Period during which nothing is noticed.
Fever, outbreak, and course of disease	Rise of temperature, and active fermentation.
Decline of disease	Gradual cessation.
Period of protection from same disease	Addition of more ferment has no effect.

The discovery by Pasteur of the fact that fermentation is due to the action of micro-organisms strengthened the evidence in favour of a parasitic cause of infectious disease.

The first organism identified as the exciting agent of a disease was the bacillus of anthrax or splenic fever, discovered by Davaine (1850). After this the progress of discovery was rapid; bacteria are now proved to be the causal agents in a large number of infectious diseases—anthrax, diphtheria, tetanus, tuberculosis, enteric fever, plague, cholera, influenza, Mediterranean fever, pneumonia, gonorrhœa, erysipelas, and suppurative conditions are examples—and in many others their causal connection is highly probable.

Certain other diseases have been shown to be caused by protozoal organisms (see Chapter XI.).

Proof of the Relation of Micro-Organisms to Disease.—To prove that a micro-organism is the cause of a disease, it is necessary that the following conditions should be fulfilled ("Koch's postulates"):

1. That the organism in question, as recognised by its form, mode of growth, or products, be found constantly associated with the disease, at least in its earlier stages.

2. That "pure" cultivations of this organism through several generations be made, until it may reasonably be supposed that everything, which could possibly have been taken from the animal that yielded the virus, has disappeared.

3. That other susceptible animals be inoculated with the cultivated organism, and that the disease be thus reproduced.

4. That the same organism be found in the tissues of the successfully inoculated animals, in such numbers and with such a distribution as to account for the disease.

To these may be added the fact that it is often possible to demonstrate a reaction occurring between the blood-serum of the patient suffering from the disease and the infecting organism.

Sidney Martin has suggested that the chemical products of the organism, obtained from the tissues of the animal or person dead of the disease, must correspond with those obtained from cultures of the organism in media resembling as nearly as possible in chemical composition those tissues in which the organisms are found in disease; but owing to the impossibility of insuring that artificial media shall at all closely resemble vital fluids, it is clear that it is impossible to insist upon such an identity of products.

The demonstration of a *well-characterised* organism in *constant*

association with a disease is now by many taken as almost equivalent to proof that it is the cause of the morbid process, for it is in most cases impossible to experiment on man, and frequently no animal can be found which suffers from the disease under investigation. In such cases the proof cannot be carried beyond the first stage.

The vegetable organisms, which have been found connected with the diseases of man (pathogenic) belong to the class of *Fungi*. The parasitic fungi are of three kinds—**Bacteria** or *Schizo-mycetes*, **Yeasts** or *Blasto-mycetes*, and **Moulds** or *Hypho-mycetes*.* The bacteria include the active factors in putrefaction and several of the "fermentations," as well as most of the organisms which are believed to produce the infective diseases. They are, therefore, by far the most important group.

Bacteria or Schizo-Mycetes.

Morphology and Life-History.—The Schizo-mycetes or Fission-fungi are, with very few exceptions, non-nucleated, unicellular organisms, which do not contain chlorophyll. Many of them approach the limits of microscopic visibility, whilst all are very minute, the smallest diameter of a pathogenic bacterium rarely exceeding 1 μ ($\frac{1}{25000}$ in.). It is highly probable that the causal agents of some diseases are so minute as to be invisible even with the highest powers of the microscope. It has been proved that the virus of certain infective diseases is capable of passing through the pores of a Chamberland porcelain filter.

Form.—In form they may be said to follow, more or less closely, one of two types—the *sphere* and the *rod*. The *spherical* bacteria comprise those of any shape between a sphere and a cube. The *rod-shaped* bacteria may be short and thick with rounded ends, so as closely to approach an oval; or they may be long and thin with square ends; or they may exhibit any possible combination of these features; they may be straight or show differing degrees of curvature; while some forms are twisted into *spirals*. Among the higher bacteria more complex forms obtain. Long septate and non-septate filaments are found. These may undergo false branching or true branching.

Structure.—Bacteria appear structureless. They consist of a peculiar form of protoplasm, known as *mycoprotein*, the composition of which varies in different species. It is probable, from their great resistance to alkalies and dilute acids, that bacteria possess a cell-membrane formed of some carbohydrate allied to cellulose. During the formation of spores, and after the action of tincture of iodine, which stains and causes shrinking of the protoplasm, a fine membrane may be actually seen. It is very elastic, and seems to form the inner layer of a gelatinous envelope, by more or less of which all bacteria are surrounded.

* Greek, σχίζω, I split; βλάστος, a sprout; ὕφη, a thread; μύκης, a fungus.

Colour.—Bacteria refract light strongly, and cause turbidity of any culture-fluid in which considerable numbers are present. Apart from artificial staining, a mass of organisms is usually colourless—*i.e.*, white or greyish. Some bacteria are brightly coloured, red, blue, yellow, etc., the tint being mainly in the envelope. Bacteria are stained with more or less facility by several aniline dyes, and many of them may be identified by their special staining-reactions. The substance of the bacterium does not always take the stain uniformly throughout.

Movement.—Some rod-forms are motile—*e.g.*, *B. typhosus*, *B. tetani*; some never move—*e.g.*, *B. anthracis*, *B. tuberculosis*. In most motile bacteria, when specially stained, one or more cilia-like filaments or *flagella* have been found. These seem to be connected not with the cell-membrane but with the protoplasm. In some organisms one or more flagella are found at one end only; in others they may grow from both ends; and in a few, among them the typhoid-bacillus, they are very fine and are attached all round. Some bacteria have a motile stage and a motionless stage. In these cases motility can often be induced by varying the medium and the temperature. In some, motility occurs just before division; in others, shortly afterwards.

A good supply of oxygen seems to be necessary for the active motion of some forms; others only exhibit motility in the absence of oxygen (*e.g.*, *B. tetani*).

Living bacteria are subject to attraction by certain substances, such as oxygen, solutions of peptone and dextrin (*positive chemiotaxis*); and may be repelled by others, such as acids and alkalies (*negative chemiotaxis*).

Reproduction by Fission.—All bacteria multiply by transverse division. In the rod-forms this occurs in a direction at right angles to the long axis. In the spherical forms it may take place in two or in three directions, at right angles to each other. Thus, one cell may divide by a single act of reproduction into two, four, or eight equal segments. If division occur in two or more parallel planes before the separation of the segments takes place, the number of these will be largely and proportionately increased. A cell, which divides in a single plane, elongates as it divides, so that the progeny retain the proportions of the original parent cell.

The new cells formed by fission may at once separate from the parent, or they may for a time remain united to each other, end to end. In this way pairs or chains of cocci and long filaments of rods are formed. The time occupied in division varies in different species from ten to thirty minutes; and, as the offspring proceed at once to divide like their parents, a single bacterium may, in twenty-four hours, give rise to more than 16,000,000.

A mass of organisms resulting from the multiplication of a single parent bacterium lying side by side in more or less spherical colonies, and bound together by a viscid substance formed of swollen cell-

membrane or of mycoprotein, is known as a *zoöglœa.** Zoöglœæ often combine to form constant characteristic appearances by which the organism may be recognised, even by the naked eye (Fig. 34).

Reproduction by Spores.—Another state of existence (*resting stage*) is met with among the fission-fungi—namely, the formation of spores. This process may take place in either of two ways, and spore-bearing organisms have accordingly been divided into two groups—*endosporous* and *arthrosporous*.

(1) The *endosporous group* consists of certain long rod-forms (*bacilli*) and some spiral forms. The spore first appears as a minute point in the cell, enlarging rapidly, and often attaining maturity in a few hours. It is then a clear, round or oval highly refracting body, which has evidently grown at the expense of the cell-contents: the latter gradually disappear. A spore consists of protoplasm and fat enclosed in a firm capsule; it is quite exceptional to find more than one spore in a single segment. Spores are extremely resistant

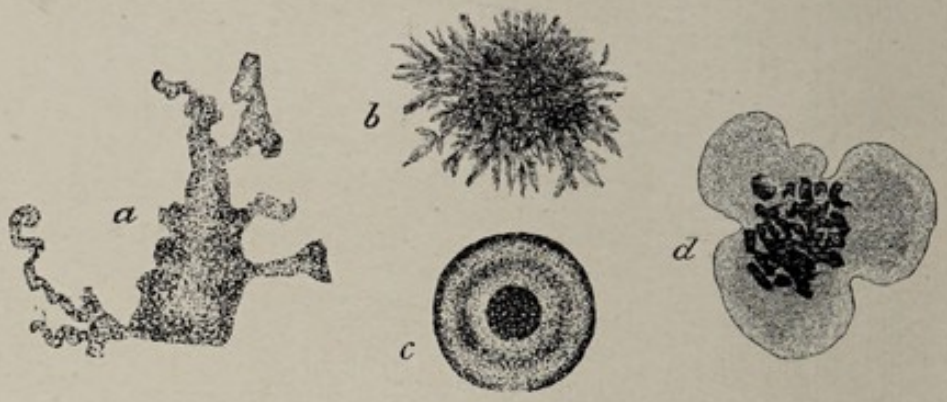


FIG. 34.—COLONIES OF BACTERIA. (AFTER STERNBERG.)
In this figure the enormous difference that may exist between the grouping of one mass of organisms and that of others is shown.

to unfavourable surroundings, owing, apparently, to the qualities of a fine limiting membrane. Spore-formation only takes place under special conditions, which are generally not those altogether favourable to growth and multiplication. But it can hardly be regarded as evidence of lowered vitality, for spore-formation in anthrax-bacilli can be arrested by reducing the temperature of the organisms below 20° C. or by introducing certain modifications into the culture-media. Fission and spore-formation may go on together.

(2) In the *arthrosporous group* no spores are found within the cells; but certain cells, during the process of division by fission, exhibit unusual powers of resistance, and are, therefore, regarded as spores. Sometimes these arthrospores are larger than the rest of the cells; in other instances no difference in appearance can be made out.

Some authorities hold that all micrococci are examples of the second variety. No distinction can, however, be drawn between the early and late stages of cocci, and it is better, therefore, not to include spherical forms among spore-bearing organisms. If after

* Greek, ζῶος, living; γλοῖα, glue.

even long periods of quiescence spores are placed in favourable conditions, their capsules burst and are shed; they lose their fine dark outline; and another method of reproduction is observed—viz., by *spore-germination—i.e.*, a new adult (*vegetative*) cell grows out—usually in the direction of the long axis of the spore, and in its turn multiplies by fission.

Variations in Form.—Many bacteria are *monomorphic*—that is, each individual organism, from the beginning of its existence to the end, preserves the same form. Slight inequality in the size and minor variations in the form of the cell are the only changes that such organisms present. Others are more or less *pleomorphic* —*i.e.*, in their life-history spores, rods, filaments, and other gross variations in shape can be traced, coexistent or succeeding each other.

CLASSIFICATION.—Until recently, the possibility of the variability of bacteria was much discussed. It was considered by some observers that many bacteria, differing in shape, characters and pathogenic effects, and hence regarded as belonging to different species, were really only modifications of a single form. It is, however, now generally agreed that no kind of bacterium, however nearly it may resemble another, ever becomes converted into it; *e g.*, the smegma-bacillus is never converted into the tubercle-bacillus, nor the *Bacillus coli* into the *Bacillus typhosus*, though certain characteristics may be for a time modified.

Notwithstanding the general agreement on the individuality of the various forms of bacteria, our knowledge is still too limited to enable us to classify them with any pretence to accuracy. The simpler forms are spoken of as (1) *cocci*, (2) *bacilli*, and (3) *spirilla*—the classification depending on their roughest morphological characters.* The more complex bacteria, which form the connecting link with the higher forms of fungi, are sometimes classified according to the structure of the filaments, the appearance of the protoplasm, and the existence of branching. Thus, Muir and Ritchie classify freely moving septate filaments containing sulphur-granules as members of the Beggiatoa group; similar filaments, fixed at one end and developing from the other, as members of the Thiothrix group; and filaments like thiothrix, but destitute of sulphur-granules, as members of the Leptothrix group. In the same way filaments that branch by the lateral displacement of a cell undergoing ordinary subdivision are classified as members

* The following terms are often used to describe varieties of bacteria:

Cocci and micrococci	Spherical or nearly spherical bacteria.
Diplococci	Cocci in pairs.
Streptococci	Cocci in chains.
Staphylococci	Cocci in groups like bunches of grapes.
Tetrads	Groups of four cocci produced by imperfect cleavage.
Sarcinæ	Groups of eight or more cocci, similarly produced.
Bacilli	Straight rod-shaped organisms.
Spirilla and vibrios	Curved rod-shaped organisms.

of the Cladothrix group, and non-septate filaments, undergoing true dichotomous branching, as members of the Streptothrix group. In several instances groups of organisms closely resembling one another are found to exist; examples are seen in the various acid-resisting organisms allied to the tubercle-bacillus (the grass-bacillus, the smegma-bacillus, etc.), in the group of bacteria resembling the cholera-vibrio, and in that containing the typhoid-bacillus, the colon-bacillus, and the paratyphoid-bacillus. We do not at present know enough about bacteria to decide whether these are true genera and species.

Conditions of Life and Growth.—There is often a marked contrast between the conditions essential to the mere existence of an organism and those which are necessary for its rapid growth.

Food.—Each variety of fungus seems to differ somewhat from all others in its food-requirements, though all must be supplied with the materials whence they can obtain the elements of which they uniformly consist. These are carbon, hydrogen, nitrogen, phosphorus, sulphur, calcium, magnesium, and potassium. The first four are generally provided by carbohydrates and proteins, the rest by inorganic salts present in animal and vegetable tissues. In general terms, bacteria thrive on the complex substances present in dead and dying organic tissues, converting them into simpler compounds. Certain bacteria, however, can assimilate nitrogen and carbon from much less complex substances than albumen and carbohydrates, when these are not available.

Environment.—The **reaction** of the fluid in which they are situated has a marked influence on the growth of bacteria. As a rule acidity is unfavourable to the development of bacteria, alkalinity favourable—the reverse usually holding for yeasts and moulds. Very slight differences may suffice to prevent the growth of a bacterium.

Many **chemical substances** are inimical not only to the growth but also to the very existence of organisms. It has been suggested that the term " antiseptic " should be reserved for those substances which *prevent* their *growth*, but which do not cause their destruction; while those which *actually kill* the germs should be called " germicides." But the distinction is not an absolute one. The difference in many cases depends on the degree of concentration. Thus most germicides can be so diluted that they act only as " antiseptics," though the converse is not equally true.

It will be readily understood that the germicidal power of any substance must to some extent depend—(1) on the nature of the organism; (2) on the vitality of the particular specimen in question; (3) on any physical conditions that may interfere with immediate contact; and (4) on the presence of any neutralising or incompatible substances. It must be remembered, too, that the rapidity and extent of the effect produced on organisms separated by cultivation from all the constituents of the exudations and secretions in which they are commonly found, as well as from other organisms that may usually coexist, is no *exact* measure of the effects that will

be produced when wounds, cavities, surfaces of the body, or excreta are concerned. Neither must it be forgotten that the very substances which are most efficacious in destroying organisms are generally those which interfere most readily with the nutrition of the tissue-cells.

Water.—The presence of *some* water is essential to the development of all fungi, for it acts as the medium for conveying oxygen and food-substances into the cell. It is easy to add too much or too little for a given species. *Desiccation* destroys some mature bacteria within a few days or hours, while others resist drying for months, and spores of the endosporous groups do so for years—it is impossible to say how long. Thus, dried cholera-spirilla die in three hours, whilst dried typhoid-bacilli survive more than as many months, and diphtheria-bacilli perhaps longer still.

Oxygen.—Pasteur has divided fungi into two varieties—aërobic and anaërobic. The presence of atmospheric oxygen is essential to the members of the first group, while it is fatal to those of the second. *Aspergillus niger*, *B. subtilis*, and *Mycoderma aceti* are examples of the first group (*obligatory aërobe*); the bacilli of tetanus and of malignant œdema belong to the second (*obligatory anaërobes*). By far the larger number of pathogenic organisms are able to live either with or without oxygen—at least for a considerable time. An organism which thrives *best* in the presence of oxygen, but which *can* grow in its absence, is said to be "aërobic and capably anaërobic" (*facultative anaërobes*); and *vice versâ*. The first of these groups is the most important, and includes the bacilli of anthrax, tuberculosis, typhoid fever, and diphtheria.

Oxygen under pressure may prevent the growth of even *aërobic* organisms, and, after months, kills them. Their spores also, according to Duclaux, retain their power of germinating much longer if oxygen is excluded; if true, this may partly explain the action of air as a disinfectant.

Temperature.—Each organism flourishes best at a particular temperature. All will grow, but less actively, at temperatures somewhat above or below this point. Now, no organism can become parasitic unless the temperature at which it grows corresponds with that of some part of the body to which it finds access. Hence it happens that *all pathogenic bacteria grow readily at about the temperature of the human body*. In some cases the range within which growth is possible is very limited. Thus the tubercle-bacillus only thrives at a temperature of 37° C., while its growth is absolutely confined within a range of from 28° C. to 42° C. Other organisms, such as those of cholera and typhoid fever, can, in suitable media, grow at a temperature as low as 16° C. These can therefore easily multiply apart from the body. The general statement may be made, with regard to bacteria, that reproduction ceases when the temperature is reduced to 5° C., and in the case of many organisms at a much higher point; but they do not necessarily die. Though rendered rigid and motionless, some can survive extreme cold. The

spore-bearing *B. anthracis* has been frozen in a fluid at – 110° C. without injury. The maximum temperature at which bacteria can grow is in most cases between 40° C. and 45° C. By further rise of temperature, rigidity and death are induced—more easily in moist than in dry conditions, and much more easily in the adult than in the spore-form. The reaction and nature of the medium in which the germs are heated has a decided influence. Boiling, and indeed a much lower temperature (60° C.) than 100° C., will kill the great majority of fungi; but solutions containing spores may need exposure to a temperature of 100° C. for many hours before they are completely sterilised. Thus Tyndall failed to sterilise a hay-infusion by eight hours' boiling. *Fluids containing spores may be readily sterilised if boiled, for a few minutes only, on four or five successive occasions at intervals of several hours;* possibly since the spores which can resist the heat develop in the intervals into adult organisms which are less resistant; possibly because of the deleterious effects of alternate heating and cooling. In like manner alternate freezing and thawing destroys organisms more rapidly than continuous freezing. Typhoid bacilli succumb to this treatment in a month, while they resist continuous freezing more than three times as long.

Some vegetative (adult) forms have been found which withstand temperatures higher than those named. Duclaux found some bacilli (*tyrothrix* in cheese) which, when suspended in slightly alkaline fluid, were not destroyed by 100° C.; but in an acid medium were killed in a minute: the spores were not destroyed by 115° C. Other species exist, the spores of which have withstood a moist heat of even 130° C. Streaming steam has a more powerful germicidal action than superheated steam. This is probably due to its greater degree of moisture, and its consequently greater penetrating power. The *dry* spores of the *B. anthracis* and of the *B. subtilis* may survive nearly three hours' exposure at 140° C.

Rest.—Most fungi flourish better in a still medium than in one whose particles are constantly moving.

Light.—Light, especially bright sunlight, has a destructive influence on organisms. The rays from the violet end of the spectrum and beyond are said to be the most powerful, those from the red end the least. All organisms do not suffer equally. Recorded experiments on this subject are contradictory. The contradiction may be due to the difficulty in excluding the influence of desiccation, oxidation and changes in the media in which the organisms are placed. Combined with these, light unquestionably forms a valuable means of disinfection.

Concurrent Growth of Bacteria.—Certain bacteria exhibit a marked preference for growing in company with one another. An example is the comparative ease with which the *B. influenzæ* will grow in conjunction with the *Staphylococcus aureus*. This phenomenon is known as *symbiosis*, and such concurrent growth may either increase or diminish pathogenic action.

Distribution of Bacteria in Nature.—Earth, air, or water may be the habitat of germs: these may also exist in and on the living body.

(*a*) **Earth.**—The soil is the principal storehouse of organisms. Portions of mould taken from the *surface*, and dropped into a sterilised culture-fluid, invariably infect it. Pyogenic cocci and the bacilli of tetanus and malignant œdema are among the forms usually found. In winter Koch failed to find any organisms at a depth of one metre in soil which had not been recently disturbed, which was not formed largely of decomposing material, and into which no unusual amount of water had penetrated.

All solids in contact with air, including the surfaces of animals, have organisms upon them.

(*b*) **Air.**—Spores of moulds are the commonest forms of aerial bacteria, then bacilli and their spores. Organisms of some kind exist in the air everywhere except away from all life—in mountains above the line of perpetual snow, or on the ocean far removed from land and ships. In such places a sterilised fluid would not decompose, even if left exposed till it dried. But wherever life is found germs are found. They increase in number as the population grows and as putrescible material becomes more plentiful. Hesse found that the air in a hospital-ward in Berlin contained thirty times as many bacteria as the air out of doors. Precautions against infection become more necessary as density of population and imperfect ventilation increase; and it is obvious that in the hospitals of large towns such measures, to be successful, must be most stringent, for here organisms will be comparatively numerous.

The air is kept supplied with organisms from the surfaces of objects over which it passes. The dust left as the final result of putrefactive processes is a fertile source of contamination. Perfectly still air becomes pure by subsidence of its germs.

(*c*) **Water.**—All water, except such as comes from a great depth (Artesian wells), contains organisms. Rain-water sweeps the air, and carries down with it floating germs. All surface-water is infected from the ground through which it soaks. River-water is exposed to all possible sources of pollution. It is scarcely necessary to add that, unless the water contains sufficient organic matter to serve as food for the fungi, no multiplication will take place, and that, sooner or later, the germs will die, though perhaps not for many weeks. Typhoid-bacilli in tap-water rarely survive for more than three weeks. The existence of many organisms in a sample of water points to the existence of much organic impurity, or to a continuous and plentiful supply of organisms.

(*d*) **In and on the Living Body.**—Bacteria exist in large numbers on the external (*skin*) and internal (*bronchial* and *alimentary*) surfaces, which are in contact with air. On the **skin** they are most numerous on the *hands*—beneath the nails, and in the folds of skin about the nails; and on *parts provided with hair and large*

glands—e.g., the scalp, axilla, and perinæum. Special care is therefore required to disinfect these parts. Inhaled with the breath, organisms are found in the **larger bronchi ;** but the smaller tubes and alveoli are probably free, for Tyndall has shown that the complemental air is pure, as it causes a non-luminous gap in an electric beam thrown across a dark room.

With food and drink many living germs are carried into the **alimentary canal.** All kinds of fungi swarm in the mouth. There are fewer in the stomach, for the acid gastric juice is unfavourable to the development of most of them. They become more plentiful in the duodenum even before the food has become alkaline ; and the food, when mixed with the pancreatic juice, swarms with organisms. Indeed, the products of normal pancreatic digestion and those of the ordinary putrefaction of albuminoids are practically the same. Throughout the whole intestine, but varying with the products and stages of digestion, and especially in the large bowel, enormous numbers of organisms occur. In abnormal states of the mucous membrane, or in too prolonged retention of intestinal contents, the fungi may multiply and excite irritation, and even poisoning, by the products of their action. Experience shows that after death putrefaction begins in the abdomen, spreading from the alimentary canal.

By obtaining pure urine directly from the urethra, Lister showed that a healthy urinary tract is free from organisms. The circulating blood, too, is " sterile."

Bacteria on the skin and mucous surfaces may fairly be regarded as *external* to the body proper—*i.e.*, to the tissues. Virulent organisms may be found in these situations, even in healthy persons.

Organisms are found in the tissues in many diseases. Organisms may reach the tissues either through the skin, or through the mucous membranes, especially the respiratory and the alimentary.

1. *Skin.*—As a general rule, uninjured epidermis is impervious to organisms ; and in practice nearly all organisms that gain access by this means enter through wounds or slight abrasions. Pustules have, however, been produced by rubbing into the skin a pure culture of the *Staphylococcus pyogenes aureus.* Inoculation in these cases seems to have occurred through the walls of the hair-follicles or the sweat-ducts, as it does in the case of acne-pustules.

In some cases infection through the skin is brought about by the agency of insect carriers of pathogenic organisms, Thus, it is established that the rat-flea is the guilty agent in the infection of man with plague bacilli from infected rats, while the case against the body-louse as the carrier of the organism of typhus fever is almost complete.

2. *Mucous Membranes.*—Entrance of organisms by the mucous membranes has been proved experimentally to occur. Thus animals were placed by Buchner in an atmosphere impregnated

with anthrax-spores; and out of sixty-six animals thus treated, fifty died from anthrax. In these cases it is almost certain that the bacilli entered through the pulmonary mucous membrane, and not by the alimentary canal; firstly, because, while large numbers were found in the lungs, few or none were present in the spleen; and secondly, because out of thirty-three animals *fed* on double the proportion of anthrax-spores only four succumbed. These experiments not only showed that in the case of anthrax the organisms can gain an entry through both these mucous membranes, but also that the entrance through the respiratory mucous membrane is the more readily effected. In the lung they are probably taken up like carbon-particles, carried to lymphatic glands, and thence perhaps to the blood. It is difficult to deny that in many cases there may have been some slight injury at the point of entry, but many later experiments have tended to support the view that infection may occur through an intact mucous membrane. Certainly organisms can pass through such a membrane without causing any discernible lesion.

In many diseases, such as typhoid fever and cholera, infection occurs via the alimentary tract. The mucous membrane of the naso-pharynx is a common and important portal through which infection occurs; while other mucous membranes, such as those of the urethra or vagina, serve as the site of entry in such infections as gonorrhœa.

Experiments have been made to determine *whether organisms are habitually present in healthy tissues*. Portions of healthy organs have been removed with aseptic precautions and placed under conditions best calculated to encourage the growth of any organisms that might be present, as well as to prevent their contamination from any extraneous source. Whilst the results have been contradictory, the balance of evidence seems to be distinctly in favour of the view that, *as a rule, living germs are not to be found in healthy tissues*. That *the blood* may sometimes contain living pyogenic cocci is probable from the frequency with which inflammation and abscess result from bruises occurring in depressed states of the system, without any break in the continuity of the epidermis. If, however, cocci could ordinarily obtain access to the tissues by means of the vessels, it would be impossible by antiseptic treatment (adapted to prevent the entry of living cocci *from without*) to prevent suppuration of wounds, for this would occur from causes reaching them *from within*.

Conclusions.—Organisms in great variety, but in very varying number, exist in air, water, earth, and on all objects exposed to air, on the skin and on those mucous surfaces which are in contact with air. Organisms can probably pass through the pulmonary and intestinal mucous membranes in small numbers, but the majority soon die if the tissues are healthy. It is a rare thing for such bacteria to reach the urine alive. Occasionally, however,

bacteria which can develop in living tissues gain entrance, and the individual invaded is then in more or less danger of disease. Organisms which can thus injure the tissues and produce diseases are termed *pathogenic*. The factors which regulate their growth in the tissues will be considered in a subsequent section.

In the meantime it may be concluded that organisms found in a wound have entered it *from without;* that fungi found in pathological lesions within the tissues have entered by a wound or through a mucous surface; that neither living organisms nor their spores exist normally in the tissues ; and that in health they are never eliminated alive by an excretory organ or by a wound.

This is of fundamental importance in surgery. If organisms could enter a wound from the side of the tissues, aseptic treatment would be impossible. As it is, we know that, if no loophole is allowed for the entry of germs from without, wounds will remain free from bacterial infection, and patients will be saved from pyæmia and septicæmia. If organisms once gain access to the tissues, it is extremely difficult to destroy the organisms without destroying the tissues as well.

Products of Bacteria.—The chemical products which result from the growth of bacteria are numerous and diverse. To a considerable extent they vary according to the conditions under which an organism is situated ; that is to say, upon the quantity and quality of the nutrient medium upon which it is living. The same organism may thus produce different substances according to alterations in its environment. For example, the cholera-vibrio, when grown in weak meat-juice, produces a peptonising ferment, but when supplied with a stronger solution forms a diastatic ferment.

Our knowledge of bacterial products is at present very limited, and recent researches have tended rather to establish the complexity of such substances than to define their exact chemical positions. Any classification of them can, therefore, be only provisional, and is liable to alteration with every advance of knowledge in this field. The following broad ground of division may be suggested :—(1) Bodies formed directly by the organisms themselves (primary products), analogous to the secretions of higher forms of life ; and (2) substances which result from the action of the bacteria and their secretions upon the medium in which they live (secondary products). Into the former group would fall the *ferments*, which play so important a part in the pathogenic action of micro-organisms, and perhaps, in some cases, the *pigments* with which they are coloured ; in the latter probably should be grouped the *albumoses, peptones, alkaloids, acids, gases,* and *pigments* produced by their activity.

In the great majority of instances the action of bacteria upon organic substances is in the direction of breaking up complex chemical bodies into simpler derivatives, as is seen in the putre-

factive decomposition of dead animals and plants—brought about very largely by various species of *Proteus*—and in the fermentation of sugar, which, by various kinds of yeast (*saccharomycetes*) is converted into alcohol and carbon dioxide. Some few bacteria, on the other hand, are capable of forming more complex substances from simple materials. An example of such chemical synthesis is seen in the process of nitrification, in which ammonium-salts are oxidised first to nitrites and then to nitrates by different varieties of organisms. Other bacteria found on the roots of leguminous plants have the power of forming nitrogenous compounds out of the nitrogen of the air. It is noteworthy that the products formed by micro-organisms in the course of their growth are generally, if allowed to accumulate in any quantity, poisonous to the organisms themselves, so that the growth of the latter is finally arrested in this way automatically. Thus, the yeast-fungus will not continue to grow in sugar solutions in presence of excess of the alcohol to which it has given rise, and other organisms similarly cease to multiply in artificial media before the nutrient capacities of the latter are actually exhausted.

The toxic bodies formed by some bacteria can be extracted from the media in which the organisms have been grown. Thus, the toxines of tetanus and diphtheria exist in a high concentration in filtered broth-cultures of these bacteria (*extracellular toxines*). On the other hand, in the case of the *Bacillus typhosus* and the cholera-vibrio, only feeble toxic substances can be extracted from such cultivations, whereas the bacteria themselves, if killed and injected into animals, are highly poisonous. It has, therefore, been inferred that the poisons of these latter organisms are integral parts of their body-substance (*intracellular toxines*).

It was long believed that each organism produced its own peculiar toxine, which was eventually set free by the death or destruction of the bacteria within the animal body. The results obtained during the extensive investigations which have been carried out in attempts to elucidate the phenomena of Anaphylaxis have, however, resulted in an entire revision of our ideas on this subject.

The different classes of products must be separately considered.

(1) *Ferments.*—By a ferment is meant a substance of which a very small quantity is able, under certain conditions, to produce an indefinite amount of chemical change in some other body. One such condition appears to be the sufficiently rapid removal of the products of its action. In the animal economy the digestive ferments, pepsin and trypsin, are perhaps the best-known examples of this class. The action of these is very closely imitated by certain substances formed by bacteria. Thus, a ferment produced by the anthrax-bacillus is capable of forming albumoses and peptone in nutrient media, these products being very closely analogous to those formed by the gastric or pancreatic juice. The following table shows this analogy more clearly:

TABLE COMPARING ACTION OF ANTHRAX AND DIPHTHERIA FERMENTS WITH THOSE OF PEPSIN AND TRYPSIN. (MARTIN.)

Primary Agent, or Primary Infective Agent.	Ferment or Secondary Infective Agent.	Digestive Products.
Living Cell.	Pepsin.	Syntonin. Albumose { Hetero-albumose. Proto-albumose. Deutero-albumose. Peptone.
Living Cell.	Trypsin.	Globulin-like body. Tryptone (peptone). Leucin and tyrosin. A bitter body.
Bacillus anthracis.	Anthrax-ferment	Albumose { Hetero-albumose. Proto-albumose. Deutero-albumose. Peptone. Leucin and tyrosin. Alkaloid (base).
Bacillus diphtheriæ.	Diphtheria-ferment in membrane.	Albumose { Hetero-, Proto-, Deutero- } in the membrane. in the body. Organic acid

The liquefaction of gelatine, so characteristic of many micro-organisms, is also due to the action of a ferment; since, if a small quantity of gelatine thus liquefied is freed from bacteria and added to a fresh tube of gelatine, the liquefying process is continued. The peptonising power of pyogenic cocci is likewise due to a special ferment secreted by them. It is probable that the true exotoxines fall into this group. It is impossible to separate them in a pure state by chemical methods; they are weakened by heat or sunlight; and they require an incubation-period for their action.

(2) *Albumoses.*—It is said that the poison contained in snake-venom is an albumose, and similarly some of the poisonous products of pathogenic bacteria have been assigned to this class. Such, for example, is perhaps the case in diphtheria; but the exact nature of the poison of this disease is not certain. The active principles of the poisonous fluid obtained from cultures of tubercle-bacilli (tuberculin) have been stated to be albumoses. Other substances of this class, such as those formed by the organisms of cholera and anthrax, are not apparently poisonous.

Recent investigations have so largely altered our whole conception of the nature of the toxic products of bacteria that little or no significance can now be attached to these earlier attempts to determine the chemical nature of toxines.

(3) *Alkaloids.*—Bodies much resembling the vegetable alkaloids are formed in the growth of many kinds of bacteria, and are collectively known as *ptomaines.* Many of them are poisonous, and such are probably the toxic agents by which decomposing meat and vegetables give rise, when eaten, to symptoms of irritant poisoning (*ptomaine-poisoning*). The resemblance borne by these bodies to the alkaloids derived from plants and used as drugs or poisons causes them to be of considerable medico-legal interest, since care is necessary to distinguish, in the dead body, between substances formed in the course of putrefaction and poisons administered during life.

(4) *Acids.*—The acid bodies formed by bacteria do not appear to be of much pathological importance. Instances are seen in the acetic and butyric acids formed in different varieties of fermentation.

(5) *Gases.*—Various gases are formed in the growth of different organisms, such as hydrogen, carbon dioxide, methane, and hydrogen sulphide.

(6) *Pigments.*—Many organisms in their growth give rise to different forms of pigment. This appears to be situated, in some cases, in the capsules of the bacteria. Examples of pigment are seen in the red coloration of growths of *B. ruber* and *B. prodigiosus,* the violet hue of colonies of *B. violaceus,* and the yellow of *Sarcina flava* and *Staphylococcus pyogenes aureus.* In most cases pigment is more readily produced at room-temperature than at body-heat. Potato is a favourite nutrient-medium for the display of colours. Pigments do not in themselves appear to be of any pathological importance. The pigment of *B. pyocyaneus,* which gives rise to *blue pus,* has been isolated as a body crystallising in the form of needles, and turning red on addition of acids like other vegetable blues.

Under the heading of " Pigments " may be noticed the substance *indol*—a chromogen rather than a true pigment—which is of some importance in the identification of certain forms of bacteria. It is one of the evil-smelling substances which normally occur in fæces, and is produced by many different organisms—the cholera-vibrio and the *B. coli communis* being well-known examples. The latter is distinguished from the typhoid-bacillus by this property among others.

Fate of Organisms in Living Tissues.—It by no means follows that pathogenic organisms, which have actually entered the tissues, will always multiply and give rise to disease. Just as in the case of infective inflammations, so in all other infective diseases, *there are two factors in the production of disease*—the attack of the germs on the one hand, and the resistance of the tissues upon the other.

This question will be dealt with more fully in the chapter on Immunity, but in the meanwhile it may be noted that both factors concerned are liable to wide variation. Thus, all pathogenic bacteria are subject to increase or decrease in virulence. Some of the conditions which may initiate these changes are well known, and alterations in virulence can be brought about in the laboratory by certain definite procedures. The study of epidemiology, however, shows us that similar fluctuations may arise in circumstances which suggest seasonal or other influences; but the mechanism of the process in such cases remains largely unknown, and it is usually impossible to determine whether the main factor is a true alteration in virulence of the organism, or some change in social conditions which facilitates its spread.

Similarly, the resistance of the host may be either increased or lowered by general or local conditions. As regards the latter, there is strong clinical evidence to show that injury may often determine the site of an infective lesion, the infecting organism being apparently deposited in the injured part from the blood-stream.

METHODS OF STUDY OF BACTERIA.

In studying bacteria, and in describing those whose characteristics have been determined, attention is paid to the following points:

(*a*) The diseases and pathological conditions which the bacteria are known or believed to cause in the human subject or in animals.

(*b*) The results obtained by the experimental infection of laboratory animals.

(*c*) The morphology of the organism. Under this heading we may include its shape, size, and arrangement. At the same time certain other characteristics are observed, such as the presence or absence of a capsule, of spores and of flagellæ, and the motility or non-motility of the organism.

(*d*) *Staining Reactions.*—The morphology of a bacterium is largely studied by the observation of stained specimens; but, in addition to this, certain organisms show special staining reactions which are of great importance in their differentiation. Two of the more important of the staining reactions may here be mentioned:

(1) When an organism is stained with a strong solution of gentian violet and then treated with a solution of iodine in potassium iodide, it takes on a dark purplish-black colour. If the specimen be then treated with alcohol, the colour is removed from many bacteria, while others retain it. Such a specimen may then be counterstained with any red or brown dye, when the unstained organisms will take on this second stain. This staining method is known as *Gram's method,* and those organisms which retain the purple stain are said to be *Gram-positive;* those which lose it and take on the counterstain are said to be *Gram-negative.*

(2) If a given specimen containing bacteria be stained with a strong solution of carbol-fuchsin with the application of heat, all

the organisms are stained a bright red. The majority of bacteria lose this stain when treated with a strong solution of a mineral acid (such as 25 per cent. hydrochloric acid). A few organisms, however, retain the stain under these circumstances, and these are known as acid-fast organisms.

(*e*) *Cultural Characteristics.*—The size and form of the colonies which a given organism produces on the different laboratory media, its preference for aërobic or anaërobic conditions or for certain media, and its power of producing pigment, all serve as valuable aids in determining its identity.

(*f*) *Fermentation Reactions.*—These really form one aspect of the cultural characteristics. Bacteria differ greatly in their power of producing acid and gas in different carbohydrate media, in their ability to liquefy gelatine or to produce a clot in milk, and in their power of producing such substances as indol. These differences form one of our most important aids in the study and differentiation of bacteria.

(*g*) *Immunity Reactions.*—In the blood-serum of persons infected with a given micro-organism, or in that of animals which have been subjected to experimental inoculation, it is possible to demonstrate the presence of certain substances which react in various ways with the bacteria in question. These immunity reactions may be utilised either by testing human serum against various known bacteria, and thus arriving at a diagnosis of infection with any one of them, or, by using a known antiserum from an experimental animal, the reactions may be used to determine the identity of an unknown organism.

In the following brief descriptions of some of the more important bacteria, only their main characteristics will be described. The serum reactions are discussed more fully in the chapter on Immunity.

I. Micrococci.

These are round or oval cells, generally 0·5 μ to 0·2 in diameter. They are arranged (1) singly, (2) in pairs (*diplococci*), (3) in chains of varying number (*streptococci*), which may be straight or wavy, (4) in groups like bunches of grapes (*staphylococci*), or (5) in definite groups of four or eight (*sarcinæ*). The organisms belonging to this order differ among themselves in form, size, mode of grouping, and physiological action. Many varieties of cocci possess the power of producing pus. Amongst the most common of these are the *Staphylococcus pyogenes aureus*, the *Staphylococcus pyogenes citreus*, the *Staphylococcus pyogenes albus*, the *Streptococcus pyogenes*, the *Gonococcus*, and the *Pneumococcus*. Many other organisms may cause suppuration, such as the *Bacillus pyocyaneus*, the *Pneumobacillus*, and also organisms, such as the *Bacillus coli*, which are normal inhabitants of the body under ordinary conditions.

Staphylococcus pyogenes.—The various forms of this organism differ from one another in only one important particular—namely,

that, when cultivated on gelatine, agar-agar, or potato, in the presence of oxygen, they produce different pigments, the first a pale orange, the second lemon-coloured, and the third white (Fig. 35). They resemble one another in forming clusters (Fig. 36), in staining by Gram's method, and in liquefying gelatine.

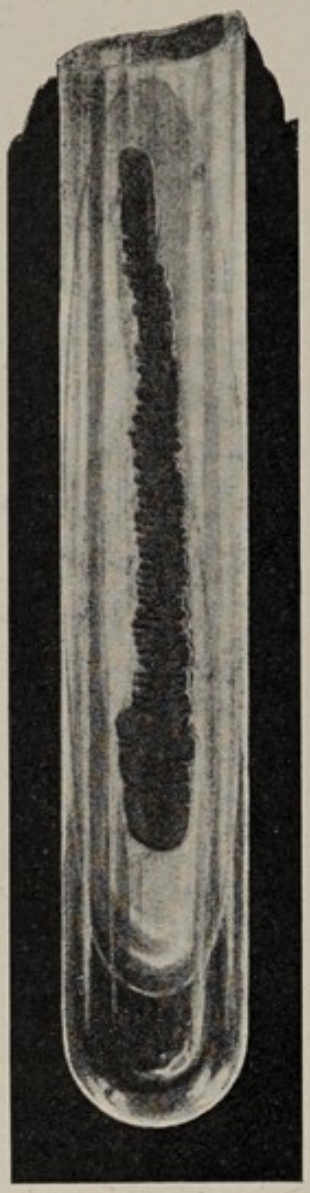


FIG. 35.—STAPHYLOCOCCUS PYOGENES AUREUS. (STREAK-CULTURE ON NUTRIENT AGAR-AGAR.)

The pyogenic staphylococci are the causative organisms in many forms of circumscribed suppuration, such as suppurative acne, furunculosis, boils, carbuncles, etc. In the more severe forms, such as boils and carbuncles, the *Staphylococcus aureus* is far more common than the white variety. The *Staphylococcus aureus* is also frequently found in suppuration affecting the nasal sinuses, and especially the frontal sinus. It is this organism which is almost constantly present in suppurative osteomyelitis. The staphylococci do not tend as a rule to produce rapidly spreading suppuration, though some cases of suppurative lymphangitis are due to infection with the *Staphylococcus aureus*. On the other hand, such lesions as suppurative osteomyelitis not infrequently lead to the formation of secondary pyæmic abscesses, and from these the *Staphylococcus aureus* may be recovered.

Streptococcus pyogenes. — This organism consists of cocci which grow in chains (Fig. 37), often of considerable length. Like the staphylococcus, it is Gram-positive, but it grows in much finer colonies (Fig. 38), does not liquefy gelatine, and does not form pigment. When introduced into the tissues, it tends to produce rapidly spreading inflammation. Sometimes this is confined to the true dermis, as in erysipelas; more commonly the lesion produced is a spreading cellulitis. The *Streptococcus pyogenes* is far more apt to produce a rapidly fatal septicæmia than is the staphylococcus. Different varieties of streptococci possess very different degrees of virulence. The classification of the streptococci is a matter of great difficulty, and we are still uncertain as to the relationship existing between the various members of this class. For instance, it was long maintained that erysipelas was due to infection with a distinct variety of streptococcus, but further investigations have failed to maintain this view.

Streptococcus lanceolatus (*Diplococcus pneumoniæ* or *Pneumo-*

coccus).—The production of acute pneumonia has been attributed to two distinct organisms. (1) The first known as *Friedländer's*

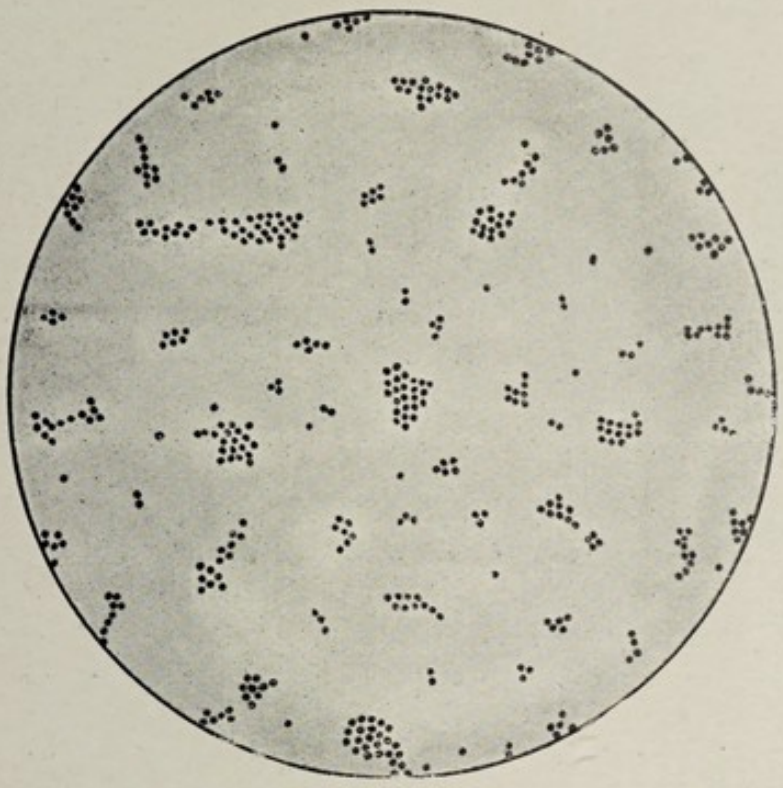


FIG. 36.—STAPHYLOCOCCUS PYOGENES, SHOWING ARRANGEMENT IN CLUSTERS. (× 1,000.)

pneumo-bacillus, was originally described by its discoverer as a coccus. He found great numbers of these capsulated organisms

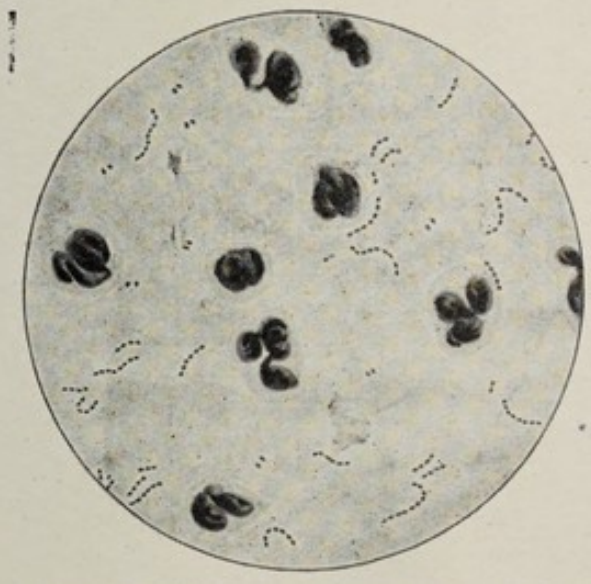


FIG. 37.—STREPTOCOCCUS PYOGENES IN PUS. (× 1,000.)

in the early stages of pneumonia, not only in the exudation, but also in the lymphatics of the lung, and in the fluid of any pleurisy or pericarditis which was present. Their importance in pneumonia,

however, is small, as they are only found in 5 per cent. of the cases of acute pneumonia.

(2) The second was independently demonstrated by Fränkel and Weichselbaum (*Fränkel's pneumococcus*, or the *Diplococcus pneumoniæ*), and can be found in nearly all cases of pneumonia, especially acute croupous pneumonia. In cultures these organisms occur as oval cells, usually in pairs, but often in chains of four to ten or even twenty to thirty. In the tissues, the microbes become lancet-shaped, with their pointed ends away from each other, and possess capsules which can be readily demonstrated (Fig. 39). They retain the aniline stain when treated by Gram's method. The pneumococcus is best grown on blood or serum agar at a temperature of 35° C. to 38° C., and the growth is scanty and produces small translucent colonies, similar to those produced by many forms of streptococci. The organism does not grow on gelatine. In many of its characters it resembles the *Streptococcus pyogenes*. Even when transferred daily from tube to tube the diplococcus rapidly loses its virulence. To preserve or to restore its pathogenic power, an occasional inoculation into a susceptible animal must be resorted to.

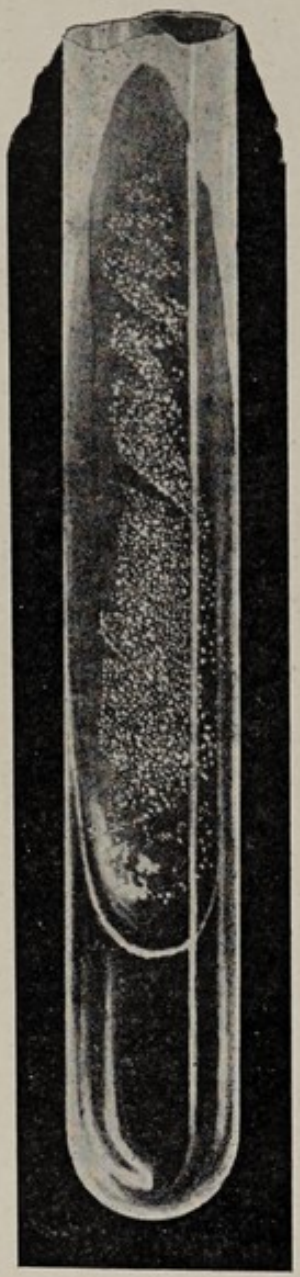


FIG. 38.—STREPTOCOCCUS PYOGENES. (STREAK-CULTURE ON NUTRIENT GELATINE.)

Subcutaneous injections of virus of full intensity into rabbits, mice, and guinea-pigs cause an acute, generally fatal, illness, like septicæmia, with characteristic post-mortem appearances; but there is no sign of pneumonia. Eyre and Washbourne produced lobar pneumonia by intratracheal injection of the cocci, and Salvioli similarly induced lobar pneumonia in guinea-pigs.

Besides being present in the lung, the cocci can usually be isolated from the blood, and have been shown to be the cause of inflammations arising during the course of pneumonia, or even independently, such as empyema, meningitis, endocarditis, peritonitis, otitis media, and suppurative arthritis. Moreover, it appears to be an *occasional* denizen of the mouth and nasal cavities, also occurring in the saliva and in the middle ear of healthy people. It would seem that the organism remains innocuous until some circumstance, such as chill, exhaustion, or intercurrent disease, enables it to gain a footing in the tissues. Pneumonia does not follow inoculation in the

lower animals unless the parasite is localised in the lung. It has frequently been cultivated direct from the blood-stream in cases of pneumonia, and in some cases from the heart valves in ulcerative endocarditis.

Gonococcus.—Neisser, in 1878, discovered in the urethral pus a micrococcus (*Micrococcus* or *Diplococcus gonorrhœæ* or *Gonococcus*, Fig. 40) peculiar to this disease. He recognised it by "facets," or flattenings, on the surfaces in contact, such as are now known to occur in other rapidly multiplying cocci. It is distinguished by its typical arrangement in pairs; by its inability to retain the principal stain when treated by Gram's method; and by the frequency of its occurrence within the pus-cells. Neisser considered its presence a means of diagnosing gonorrhœal from other discharges. It multiplies by fission in two planes alternately. In the first stage it is a diplococcus, each coccus having a bean-shaped outline. In the next stage each "bean" subdivides, and a tetracoccus is formed. The number of cells affected is always relatively small, and varies in different cases. The coccus is cultivated with much difficulty, and in the first instance only upon media containing blood or serum. Cultures were first carried out successfully by Bockhardt. This investigator injected a "fourth" cultivation into the urethra of a general paralytic, and produced a purulent discharge. The man died of pneumonia ten days later, and an examination of the urethra led Bockhardt to believe that the cocci probably pass through the epithelium into the lymphatics of the fossa navicularis, where they excite acute inflammation.

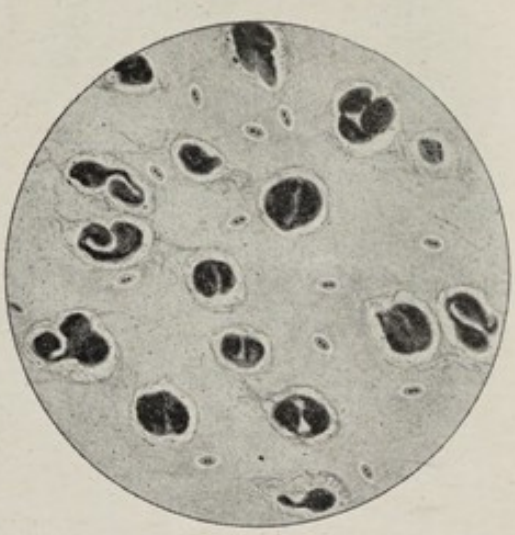


FIG. 39.—PNEUMOCOCCI IN SPUTUM, STAINED TO SHOW CAPSULES. (×1,000.)

Since then Bumm has succeeded in cultivating the gonococcus upon solidified blood-serum. He inoculated a second and a twentieth culture upon a female urethra, causing typical gonorrhœa in each of the two cases. The proof of causation, thus placed beyond doubt, was difficult to obtain, as no animal is susceptible to the disease.

With regard to complications, suppurative lymphadenitis (*bubo*), an occasional occurrence in gonorrhœa, is said to be due to infection of the glands by ordinary pyogenic organisms, the urethra in these cases being the seat of a mixed infection. The gonococcus, injected into subcutaneous tissue, does not cause suppuration, but disappears in twenty-four to thirty-six hours. It is, however, the only organism present in one-fifth of the cases of suppuration in the Fallopian tube (*pyosalpinx*), and is a frequent cause of pelvic peritonitis in the female.

The gonococcus may be present in joints, which are the seats of gonorrhœal arthritis. In some cases ordinary pyogenic organisms have been found, but in most cases none at all. It is quite unusual, but by no means unknown, for gonorrhœal joints to suppurate. Gonococci have been found on the valves of the heart in endocarditis, and have been cultivated. Inoculation of the resulting cultures has produced gonorrhœa. The organisms have also been found in, and cultivated from, the blood. It appears capable in susceptible persons of giving rise to a general septicæmia. Inoculated on the conjunctiva, it causes destructive inflammation (*gonorrhœal ophthalmia ; ophthalmia neonatorum*).

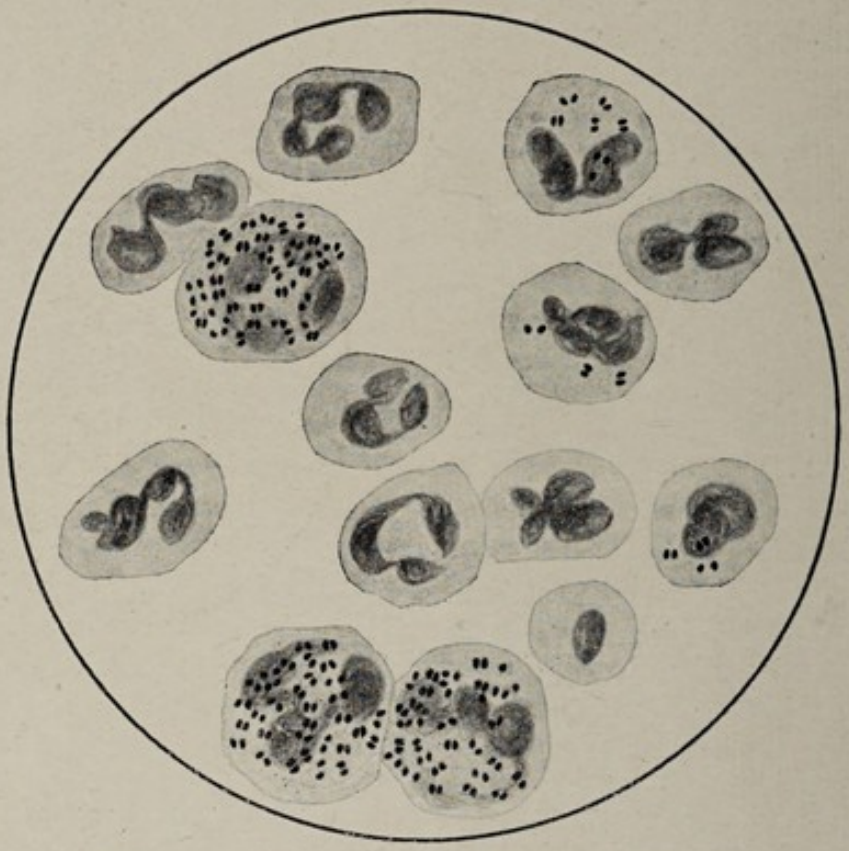


FIG. 40.—GONOCOCCI IN PUS. (× 1,000.)

The gonococcus is incapable of multiplying external to the body except under special artificial conditions, as in a culture. Its resisting power is feeble, and it soon perishes. If this were not so, considering the great frequency of the disease, infection otherwise than by contact would almost certainly occur.

Diplococcus intracellularis meningitidis.—This organism, also called the *Meningococcus*, was originally described by Weichselbaum, and is now generally recognised as the cause of epidemic cerebro-spinal meningitis. Still described a similar coccus in the posterior basic meningitis of infants, which is now generally regarded as being identical with the meningococcus. It is a diplococcus without a capsule, and is found principally within the multinuclear leucocytes of meningeal exudation, though some organisms lie free in the

fluid. The meningococcus is stained by the ordinary aniline dyes; it is decolorised by Gram's method. It grows well on blood-agar and on serum-agar when incubated at 37° C., forming round, whitish, viscid-looking colonies, clearly defined, and attaining a diameter of 1 to 1½ mm. in twenty-four hours (Councilman). It has been isolated from the naso-pharyngeal mucosa of patients suffering from the disease and of healthy contacts.

Micrococcus catarrhalis, an organism which is causally associated with acute and chronic coryza, very occasionally with lobar pneumonia, and more frequently with broncho-pneumonia and with certain chronic suppurative conditions, such as pyorrhœa alveolaris, is a coccus which closely resembles the meningococcus in morphological and staining (Gram-negative) characters, but is readily differentiated by reason of its luxuriant growth on artificial media at the body-temperature, and also by its ability to grow at the ordinary temperature of the air. The name is at present used to designate a group of micrococci having many features in common, but differing in minor details, rather than one sharply-defined species.

Micrococcus melitensis.—This minute oval coccus, discovered by Bruce, produces in tropical and sub-tropical countries an infection in man known as Mediterranean or Malta fever. This disease is propagated chiefly by the milk of infected goats, the micrococcus being present in enormous numbers in such fluid. The organism may occur singly, in pairs, or in bunches, but does not usually form chains. It is non-motile, and can be grown on slightly alkaline artificial media, either at room-temperature or at that of the body. It is decolorised by Gram's method. When inoculated into monkeys it gives rise to a disease identical with that observed in man. The serum of patients suffering from Malta fever agglutinates the cocci, even when it is considerably diluted (1 : 200, 1 : 2,000). (See Chapter XII.)

Streptococcus rheumaticus.—Many observers have found organisms in the blood of rheumatic patients, those most frequently noted being streptococci. These organisms were first described by Apert and Triboulet (1898), and their causal relation to rheumatic fever has been carefully investigated in this country by Poynton and Paine. Injections of these cocci into animals have produced articular lesions, endocarditis, and pericarditis, and in some cases spasmodic twitching of muscles, supposed to be analogous to chorea. The specific nature of these organisms and their relation to rheumatism are at present undecided ; but the work of many observers has strongly tended to confirm the conclusions of Poynton and Paine.

Micrococcus tetragenus is a pyogenic coccus which has on rare occasions been recorded as producing septicæmia in man. Usually it is responsible only for localised suppuration, and occurs most commonly in association with *Bacillus tuberculosis* in cavities in the lungs. It is a round or oval coccus, usually arranged in pairs and tetrads, and grows readily on all the ordinary media at 37° C. and

at room-temperature, forming raised, moist, shining white colonies. It does not produce any liquefaction of gelatine, and retains the stain after treatment by Gram's method.

II. Bacilli.

The members of this group are straight slender rods, the ends of which may be rounded, square, pointed, or slightly cupped. They multiply by transverse division, and often grow into long, jointed, but unbranched filaments, without constrictions at the joints. Formation of spores has been detected in some species.

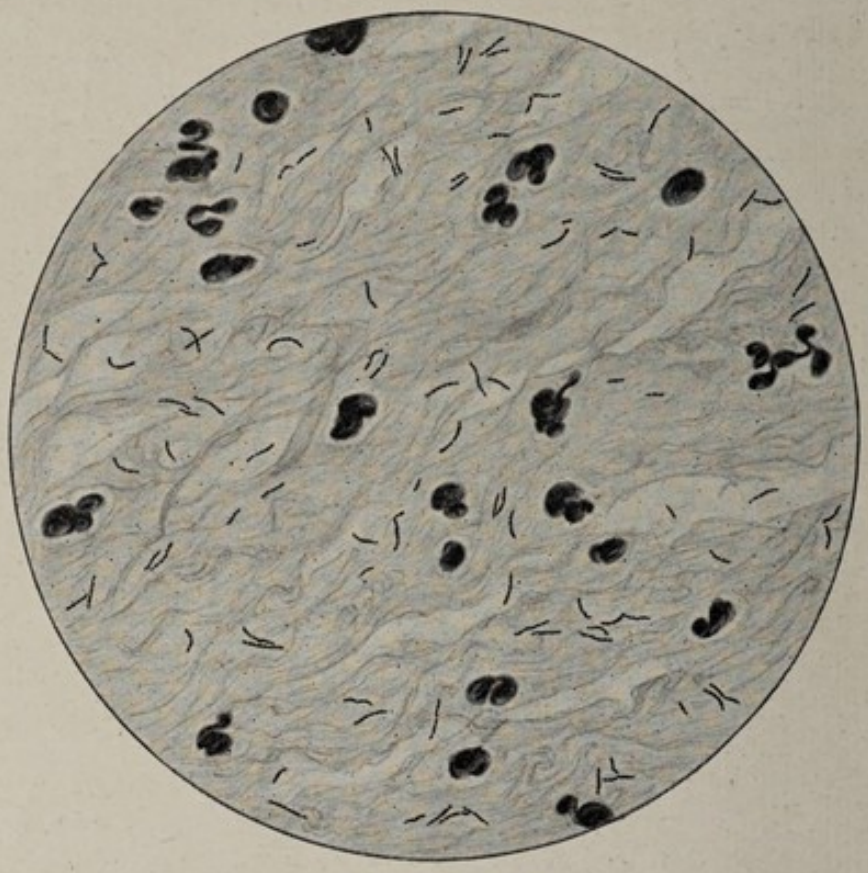


FIG. 41.—B. TUBERCULOSIS IN SPUTUM. (× 1,000.)

Bacillus tuberculosis.—This bacillus was discovered by Koch in the lesions of tuberculosis. It varies greatly in length, and in any one specimen or culture the long or short form usually predominates. It is usually long in relation to its breadth, and has often a beaded appearance (Fig. 41). The bacilli may be either straight or curved, and some observers have described branching forms, thus bringing this organism into close relationship with the streptothrix group. This bacillus is non-motile, does not form spores, is Gram-positive and acid-fast, and this last characteristic is utilised for its demonstration in sputum, etc.

The organisms can be cultivated on media containing glycerine, or blood-serum, or on Dorset's egg-medium. Their growth is slow, and it is only after some weeks that a culture presents its most

characteristic appearance. By that time the colonies have to the naked eye a heaped-up, scaly appearance, the older parts looking dry and shrivelled. When examined under the microscope the margins of the colonies show a peculiar wavy form, due to parallel chains of organisms following the same curve.

Tuberculosis occurs in other animals besides man, and some controversy has arisen as to the identity or diversity of the organisms at work. Koch maintains that the bacilli of human and bovine tuberculosis are distinct; the balance of opinion is, however, rather in favour of regarding them as identical, but modified by circumstances so as to differ in virulence. The guinea-pig is especially susceptible to infection with this organism, and the presence of tubercle bacilli in pathological material may often be demonstrated in this way when all other means have failed. The animal usually becomes seriously ill after the lapse of a few weeks, and dies in from one to three months.

Bacillus lepræ.—The bacilli found in leprosy closely resemble the bacilli of tuberculosis in morphology and staining reactions, but many variations occur in shape, size, and degree of acid-fastness. The bacilli may generally be distinguished from tubercle bacilli as seen in human tissues by the enormous numbers in which they occur. Up to the present no one has definitely succeeded in cultivating this organism on artificial media, though many claims to have done so have been made, and some of these are still awaiting further confirmation.

Bacillus mallei.—The bacillus of glanders was discovered by Loeffler and Schultz. It is a small non-motile, rod-shaped organism, usually straight, but sometimes slightly curved. It does not form spores. It does not stain by Gram's method, and when stained by ordinary dyes has a somewhat granular appearance, part of the organism remaining unstained. It grows well on ordinary laboratory media at the body-temperature. Its most characteristic growth occurs on potato, on which a thick yellowish film makes its appearance, gradually becoming brown, and eventually taking on a deep chocolate hue, while the potato in the neighbourhood of the growth becomes blackened. Equines are the animals which naturally suffer from glanders, and man only contracts the disease by contact with an infected horse, ass, or mule. Many laboratory animals are highly susceptible, and intraperitoneal inoculation gives rise in the guinea-pig to a typical suppurative orchitis.

Bacillus anthracis.—The bacillus of anthrax or splenic fever was the first bacterium to be discovered (Davaine, 1850), and was for a long time the best known of all the parasitic fungi. If the blood from the spleen of animals that have died from this disease be examined, enormous numbers of these organisms will be found. The bacilli are large rods averaging about 8 μ long by rather more than 1 μ broad. They are straight and motionless, and have slightly concave ends. In cultures the bacilli tend to form long filaments, and numerous spores are found occupying a central position

(Fig. 42). Later on the bacilli break up and the spores are set free. Under favourable circumstances these grow into bacilli. In living animals, where the supply of oxygen is not sufficiently plentiful, the long filaments and spores are not found, but the rods multiply rapidly by division.

While the bacteria are destroyed with comparative ease by the usual methods, the spores are extremely resistant. This bacillus is by preference an aërobic organism. When grown in a stab culture in gelatine, the growth takes the form of innumerable branched spikes jutting out transversely from the line of puncture (Fig. 43). These spikes are longer near the surface of the medium, where the supply of oxygen is more liberal; and the whole growth has for this reason been likened to an inverted fir-tree. The gelatine itself is

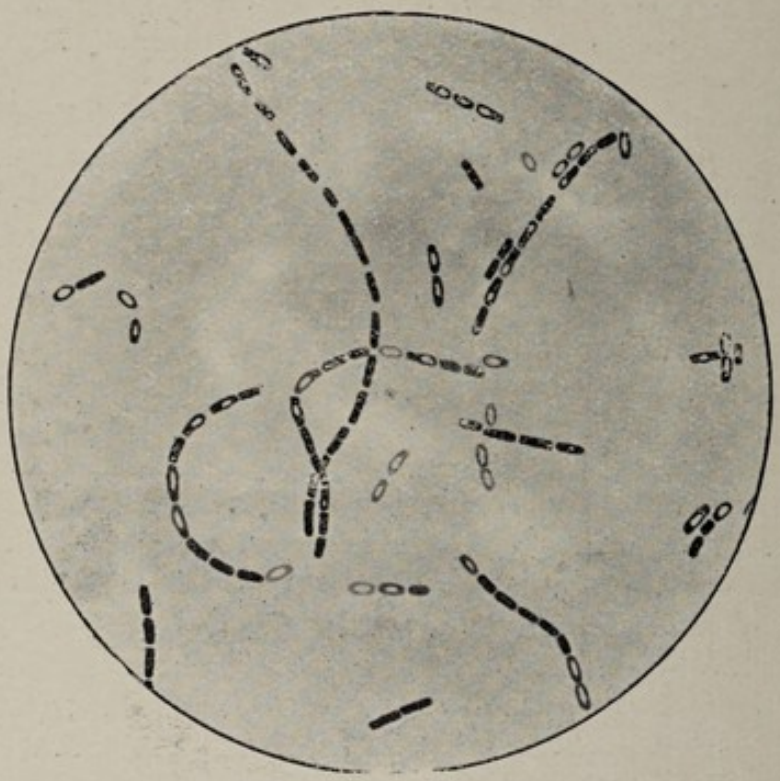


FIG. 42.—B. ANTHRACIS. (FILM FROM CULTURE.) (× 1,000.)

gradually liquefied. On a gelatine plate the colonies occur as granular spots with wavy margins, and examination with a low-power lens shows them to be made up of a tangled skein of filaments.

Anthrax is essentially a disease of sheep and bovines, but man may become infected through contact with these animals.

Animals vary enormously in their susceptibility to anthrax bacilli. Those most susceptible, such as white mice and guinea-pigs, die from splenic fever a few hours after inoculation; whilst those least susceptible, such as white rats and Algerian sheep, remain unaffected. In man, who is to a moderate extent susceptible, the disease is at first local, but soon becomes generalised.

In *animals* that have died of splenic fever, the spleen is much enlarged, the glands nearest the point of entry are swollen, and

cloudy swelling is universally present. The bacilli exist in enormous numbers in the capillaries of the spleen, and to a less extent in those of the lungs, liver, kidneys, and intestine. Numbers of bacilli are discharged from the body in the urine, fæces, and blood flowing from the nose and mouth of the animal before it dies. Thus, the ground in its neighbourhood becomes covered with the organisms, and is, therefore, highly infectious. In warm marshy districts the bacilli multiply and sporulate. The spores may be carried by water or other means to meadows where anthrax has not previously occurred. Sheep and cattle are infected while grazing. Pasteur considered that the mouths of the animals were wounded by siliceous grasses, and believed that the cuts thus made became inoculated with bacilli or spores. In favour of this view he quoted the frequent swelling of the cervical glands in sheep affected by this disease; but both animals and man may be infected by insects which bite them on the face. According to Koch, the intestine is the commonest seat of infection.

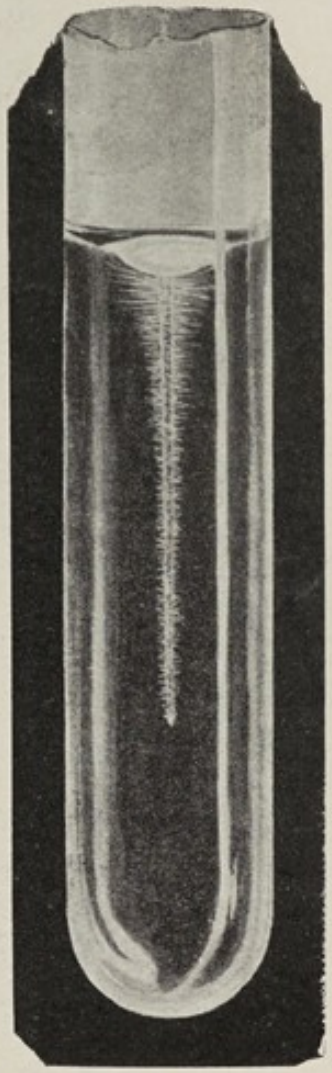


FIG. 43.—BACILLUS ANTHRACIS (STAB-CULTURE IN NUTRIENT AGAR-AGAR.)

If the bodies of the dead animals are buried at a depth of one metre or more, where there is neither oxygen nor a suitable temperature, no development of spores occurs, and the bacilli die.

In *man* infection may occur (1) through the skin, and (2) through the mucous membrane.

(1) Infection through the skin occurs especially in those who work with raw hides. The bacilli give rise to a characteristic local lesion (*malignant pustule*), consisting of a central, black, necrosed area surrounded by vesicles and a hyperæmic zone, the base of the whole mass being œdematous. If the pustule be excised at an early stage, the generalisation of the disease may be prevented, although there is a marked tendency to the production of a rapidly fatal septicæmia.

(2) Infection not infrequently occurs through the mucous membrane, especially the respiratory (*woolsorter's disease*), from inhalation of spores or bacilli with the dust from infected wool. In these cases the local lesions occur in the mucous membrane of the large bronchial tubes. Considerable swelling of the bronchial and mediastinal glands follows, and not infrequently effusion of fluid may occur into the pleura or pericardium. Such patients die more

apidly than in the case of malignant pustule, with symptoms of acute septic poisoning, though after death but few bacilli can be found in distant organs.

(3) Infection of the mucous membrane of the alimentary tract sometimes occurs as the result of the ingestion of the tissues of infected animals. The symptoms are then gastro-intestinal, and the disease is rapidly fatal.

Bacillus pestis.—Kitasato and Yersin discovered this bacillus during an epidemic of plague (*bubonic fever*) at Hong Kong in 1894. They succeeded in finding bacilli in the blood, buboes, and internal organs, especially the lungs, of the plague-stricken patients. The organisms stain readily with the usual reagents. They have rounded ends, which appear darker than the central parts; they are

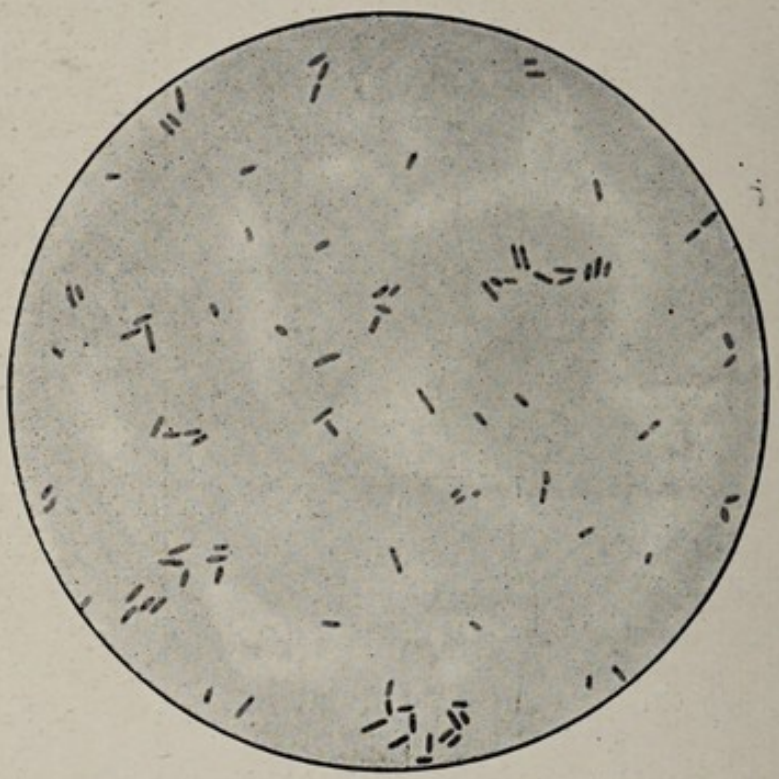


FIG. 44.—B. TYPHOSUS. (FILM FROM CULTURE.) (× 1,000.)

non-motile. No spores are formed. Similar organisms were never found in healthy persons, or in those suffering from any other disease.

Cultures may be obtained on blood-serum, glycerine-agar, and other media. The colonies are small whitish-grey, rounded patches, with uneven edges. In the cultures the bacilli often form long threads.

A cultural characteristic of great importance is the peculiar stallactite growth which these organisms form when grown in broth containing a little melted butter or other oily substance. The oil droplets float on the surface, and the bacilli form long hanging columns of growth, the upper ends of which are attached to these props. Mice, rats, guinea-pigs, rabbits, and monkeys, if inoculated

with pure cultures or with blood from patients, succumb to a general septicæmic infection, and the organism may be isolated, post mortem, from the blood or spleen.

It has now been conclusively shown that plague is a disease of rodents, especially rats, as well as of man, and that the disease is carried from rat to rat and from man to man by the bite of fleas; though whether these insects actually inoculate the bacilli at the time of biting, or whether the bacilli are deposited on the skin in the neighbourhood of the bite with the animals' dejecta, and subsequently inoculated by rubbing or scratching on the part of the patient, is not yet determined.

There are three main types of plague in the human subject: the bubonic, which is associated with swelling of the inguinal glands (the "buboes"); the pneumonic, where the primary infection seems to be localised in the lung; and the septicæmic. In the case of pneumonic plague, it seems probable that the infection may be carried from patient to patient by means of infected sputum.

Bacillus typhosus.—This organism, which was discovered by Eberth, is the causal organism in typhoid fever. It usually occurs as a short rod with rounded ends (Fig. 44), but, as in the case of so many other organisms, the length of individual bacteria varies greatly. The bacillus is actively motile, possesses numerous flagella which can be stained by appropriate methods, is non-capsulated, and does not form spores. It stains well with all the ordinary dyes, but does not retain the stain in Gram's method. It grows well on all ordinary laboratory media (Fig. 45). Its fermentation reactions in the various carbohydrate media are distinctive, and form an important means of differentiating it from the other members of this group.

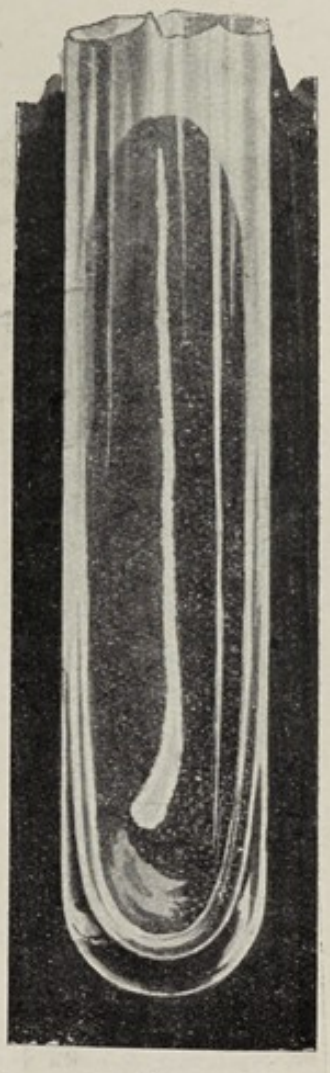


FIG. 45.—BACILLUS TYPHOSUS. (STREAK-CULTURE ON NUTRIENT GELATINE.)

The organism is easily isolated from a patient suffering from the disease. During the first week and the early part of the second it may readily be obtained direct from the blood-stream by suitable methods of culture. Later in the disease it tends to disappear from the general circulation, and must then be searched for in the fæces or urine, though it is by no means constantly present in the latter.

So far as is known, animals do not suffer from this disease, and attempts to reproduce it as it occurs in the human subject have

met with failure, though the animals readily succumb to an acute toxæmia.

The Paratyphoid Bacilli.—Two other organisms occur which produce in man a disease clinically indistinguishable from typhoid fever. These are known as *B. paratyphosus* A and *B. paratyphosus* B. In their morphology, staining reactions, and general cultural characteristics, they are indistinguishable from the *B. typhosus;* but they may be distinguished from this organism and from one another by their fermentation reactions and by various serological tests.

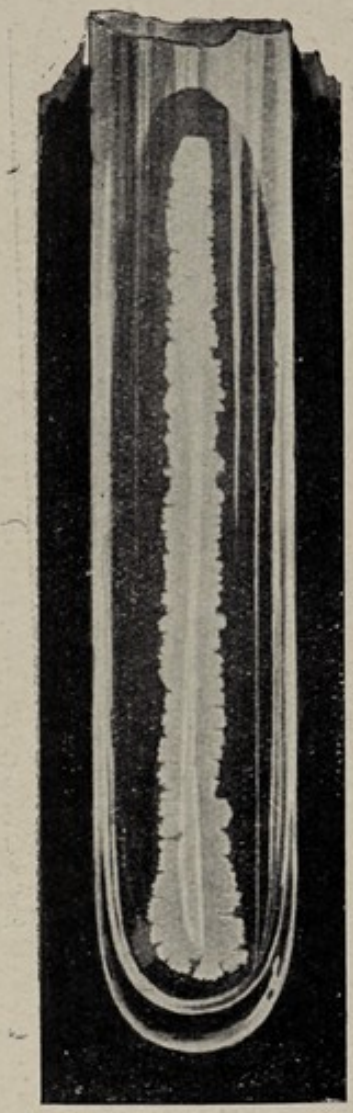


FIG. 46.—BACILLUS COLI COMMUNIS. (STREAK-CULTURE ON NUTRIENT GELATINE.)

Bacillus coli.—This organism is a normal inhabitant of the large intestine. In morphology and staining reactions it is identical with the *B. typhosus*. It is, however, almost, if not entirely, non-motile. It closely resembles this organism also in its cultural characteristics, but it tends to give a rather denser growth, and in streak cultures usually spreads farther from the inoculation tract (Fig. 46). It is readily distinguished from the *B. typhosus* and from the paratyphoid bacilli by its fermentation reactions.

Although this organism is a normal inhabitant of the large intestine, it very frequently assumes a pathogenic rôle, and gives rise to such conditions as cystitis, pyelo-nephritis, and is one of the most common organisms found in acute peritonitis.

Bacillus dysenteriæ.—There are several varieties of bacilli which cause the bacillary form of dysentery in man. One of these was first accurately described by Shiga in Japan, and later by Kruse in Germany; another type was isolated by Flexner in the Philippines, and slightly different varieties have been described by Hiss and others. The differences between these various types are slight, and depend on their fermentation and immunity reactions.

Morphologically and culturally the bacilli closely resemble those of the coli-typhoid group, but, unlike the *B. typhosus* and *B. paratyphosus*, they are non-motile.

Bacillus pyocyaneus.—This is a slender bacillus which occurs in forms of varying length, often in pairs and sometimes in filaments. It is non-sporing and actively motile. Its most distinctive characteristic is its power of forming a distinctive pigment, varying in tint from a bright blue to a greenish-brown. It is the cause of the "blue pus" which is sometimes met with in suppurating wounds,

and it has the same power of pigment formation when cultivated on ordinary laboratory media. It is under these conditions of artificial cultivation that the brownish tint sometimes occurs. It is doubtful whether this organism ever initiates suppuration—at all events in superficial wounds. In these lesions it seems almost always to be a secondary infection, and opinions differ as to the extent to which it retards healing, though in some cases it undoubtedly does so. It has also been met with in suppuration occurring in the pleural and pericardial cavities, in rare cases of appendicitis and otitis media, and it has been stated to be the causative organism in some cases of intestinal ulceration.

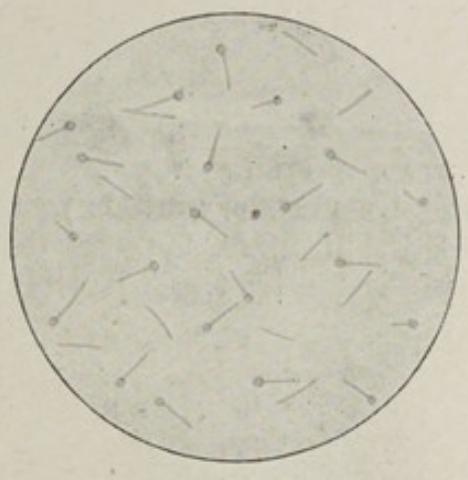


FIG. 47.—B. TETANI. (FILM FROM CULTURE.) (× 1 000.)

Bacillus tetani. — In 1884 it was shown that tetanus was an inoculable disease. In the same year a special bacillus was described, but it was not isolated and cultivated until 1889. Kitasato accomplished these results by heating the impure cultures of pus, obtained from the original wound, to a temperature of 80° C., and then incubating the residue in an atmosphere of hydrogen.

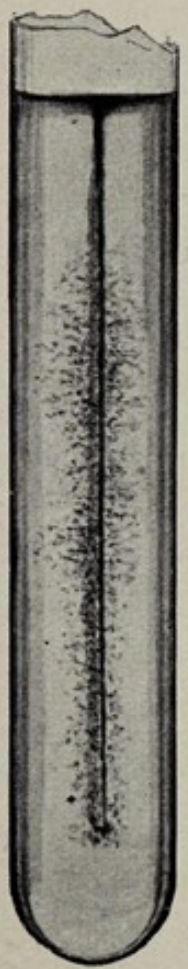


FIG. 48.—B. TETANI. (STAB-CULTURE IN NUTRIENT SUGAR-AGAR.)

The size of the bacillus is from 3 μ to 5 μ by 0·4 μ. Spore-bearing forms are nearly always present. The spore is situated at one end of the bacillus, and, being two to four times the diameter of the organism, gives it the appearance of a miniature drum-stick (Fig. 47). Flagella are attached to the ends and sides, but the organism is only slightly motile. The bacillus can be stained by the usual methods, and is Gram-positive. Its normal habitat seems to be the superficial soil, especially when mixed with manure, from which it can often be obtained.

The tetanus bacillus is a strict anaërobe—that is, it will only grow in the absence of oxygen. When grown in a stab culture of gelatine, growth occurs only well below the surface, and there forms thin lines radiating from the puncture tract (Fig. 48). The gelatine is slowly liquefied. The organism grows best at body-temperature.

The cultures have a characteristic odour and appearance. The spores are noted for the great resisting-power they show to the ordinary methods of

destruction. Thus, they have been known to resist successfully *boiling* for five minutes, *drying* for five minutes, and immersion in *carbolic acid* (1 : 20) for ten hours, and in *mercuric chloride* (1 : 1,000) for three hours. Fifteen minutes' boiling is invariably fatal.

In human patients suffering from clinical tetanus, the bacillus itself is situated only in the locality of the wound by which it gained entrance. The tetanic spasms and other symptoms of the disease are caused by a powerful exotoxine, which is absorbed along the motor nerves, and is apparently fixed by the nerve cells.

In animals, typical tetanic spasms resulting in death may be produced by the injection either of the bacillus or its exotoxine.

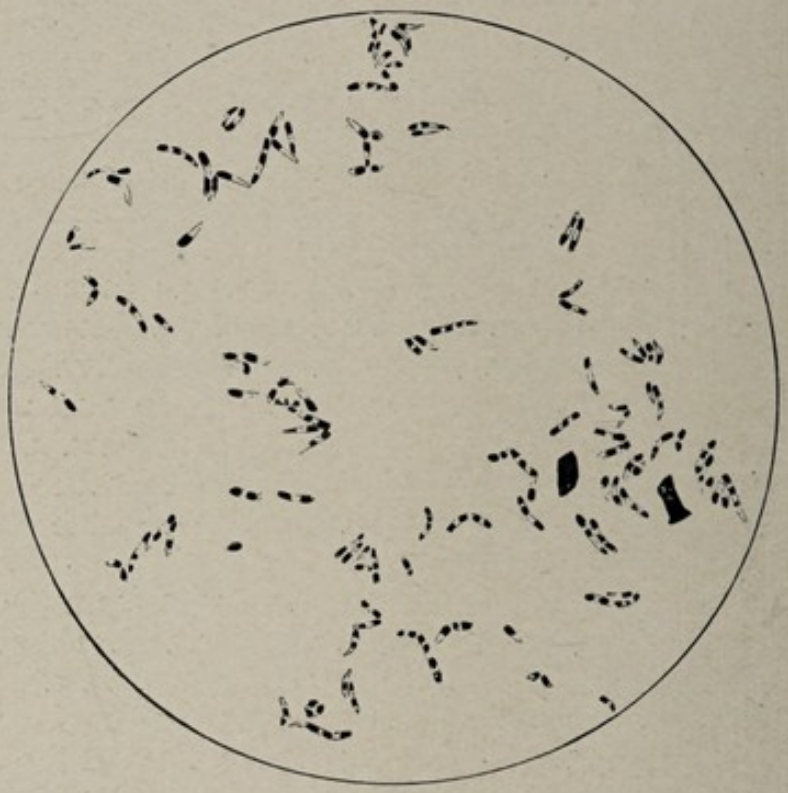


FIG. 49.—B. DIPHTHERIÆ. (FILM FROM CULTURE.) (× 1,000.)

Bacillus diphtheriæ.—This bacillus was described by Klebs in 1883, and more fully by Loeffler in the following year. It is hence known as the Klebs-Loeffler bacillus.

Different strains of this organism show marked morphological variations, which may affect the size, shape, and staining peculiarities. On the basis of these differences attempts at classification into different varieties have been made, but it is doubtful how far these are justified. All strains of the *B. diphtheriæ* have certain features in common. The bacilli tend to be arranged in small groups, the individual members of which lie either parallel with one another or may form angles of various degrees of acuteness. This peculiar grouping, which has been likened to Chinese letters, is due to the method in which the bacillus divides. When stained with a dilute solution of methylene blue, there is a marked tendency for the bacilli to stain irregularly, and both beaded and barred forms

occur, the former being by far the more common (Fig. 49). When stained by special methods, such as Neisser's stain, these deeply staining granules become specially distinct. The *B. diphtheriæ* is Gram-positive. It does not form spores, shows no capsule, and is non-motile.

Cultures can usually be obtained on the ordinary laboratory media, but blood-serum is much more satisfactory (Fig. 50). One of the most striking features of the diphtheria bacillus is its power of forming a powerful extracellular toxine in the fluid medium in which it is grown. Such toxines are known as exotoxines, and are to be sharply differentiated from the toxic bodies produced during the course of infection with the majority of bacteria. In man the organism is responsible for the various forms of diphtheria. The primary lesion usually involves the tonsil; but other forms, such as laryngeal or nasal diphtheria, are not rare, while other mucous surfaces have been affected. The local lesion consists simply of ulceration, which may be more or less severe in type; but the severity of the disease depends, not upon the degree of ulceration, but upon the secondary effects produced by the toxine which is absorbed, while the actual bacilli rarely, if ever, penetrate deeply into the tissue. Diphtheria toxine produces fatty degeneration of the heart, diaphragm, and voluntary muscles, and also degenerative changes in various nerves; and it is these secondary degenerative changes which are responsible for those symptoms of the disease other than those due to the local lesion.

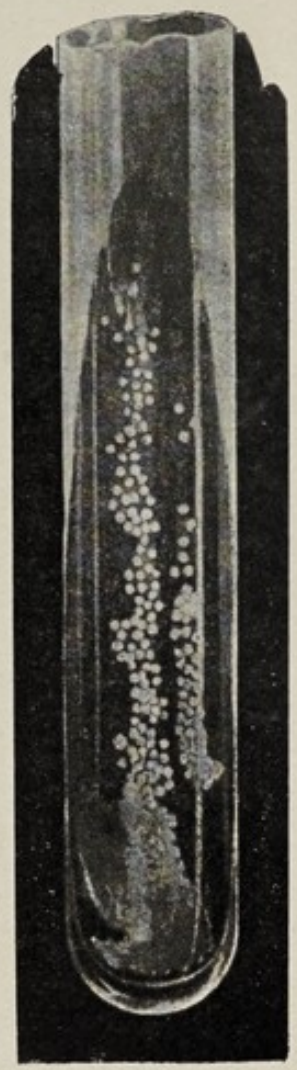


FIG. 50.—BACILLUS DIPHTHERIÆ. (STREAK-CULTURE ON BLOOD-SERUM.)

In certain laboratory animals, as, for instance, the guinea-pig, the various pathological changes can be accurately reproduced by the injection either of the bacillus or of its exotoxine.

Bacillus influenzæ.—In 1892, Pfeiffer, Kitasato, and Canon succeeded in finding a minute bacillus, which is now generally accepted as the cause of this disease. It is extremely minute, measuring 0·5–1·5 μ. It stains with the ordinary laboratory dyes. The ends take the stain best, and thus the organism often looks like a diplococcus. It does not retain the stain when treated by Gram's method. It occurs singly, in pairs, and in short chains. It is non-motile, and does not form spores.

This organism is very difficult to cultivate, and only grows on

certain special media. On blood-agar, colonies appear as small, discrete, transparent globules visible only with a lens. The bacillus is aërobic, and grows best at the body-temperature.

The *B. influenzæ* can be isolated from the sputum or naso-pharyngeal mucus in a proportion of the febrile conditions which are clinically grouped together as influenza. It has been also isolated from the sputum in cases of broncho-pneumonia, and much more rarely in lobar pneumonia. It can sometimes, though not often, be isolated directly from the blood-stream, and has been shown to be the causative organism in some cases of meningitis.

Monkeys are the only animals in which it is possible to produce a condition resembling the disease as seen in man. Most other

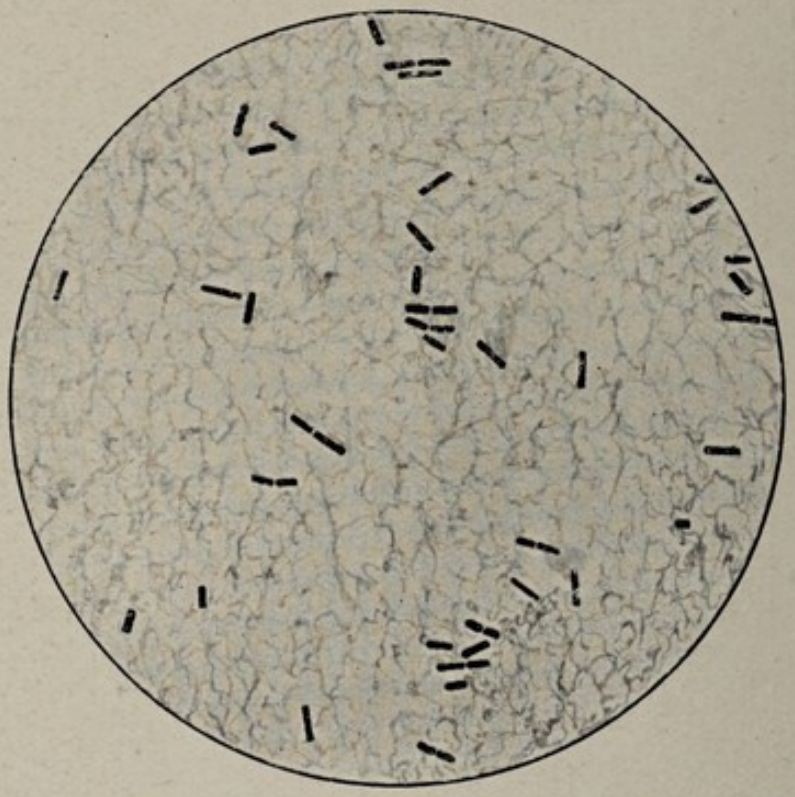


FIG. 51.—B. PERFRINGENS. (FILM FROM ŒDEMA FLUID.) (× 1,000.)

animals are almost insusceptible, but rabbits succumb to massive intravenous injections.

Bacillus perfringens.—This organism is also known as *B. wellchii*, *B. ærogenes capsulatus*, and by other names. It is a large, square-ended bacillus which may lie singly or in short chains (Fig. 51). It is non-motile, spore-bearing, and sometimes capsulated; but the last two characteristics are often difficult to make out in stained specimens, and sporing only occurs under certain conditions.

It is an anaërobe, and under this condition grows well on the ordinary laboratory media.

In man, under favourable conditions, the *B. perfringens* produces a spreading gangrenous inflammation with gas formation. Infection with this organism is liable to occur in lacerated and soiled wounds, especially when a massive mixed infection with other pyogenic

organisms occurs. It has been shown to be the main organism concerned in a production of the " gas-gangrene " which may follow severe gunshot wounds, and in this condition it has been shown that the infection affects mainly the large voluntary muscles themselves.

Bacillus œdematis maligni.—This bacillus is a long and slender rod. The organisms may lie singly, or are sometimes united end to end, forming a thread. It is a spore-bearing organism, the spores occupying a central position. The bacillus possesses flagella, and is motile. It is Gram-negative, and stains with the ordinary laboratory dyes.

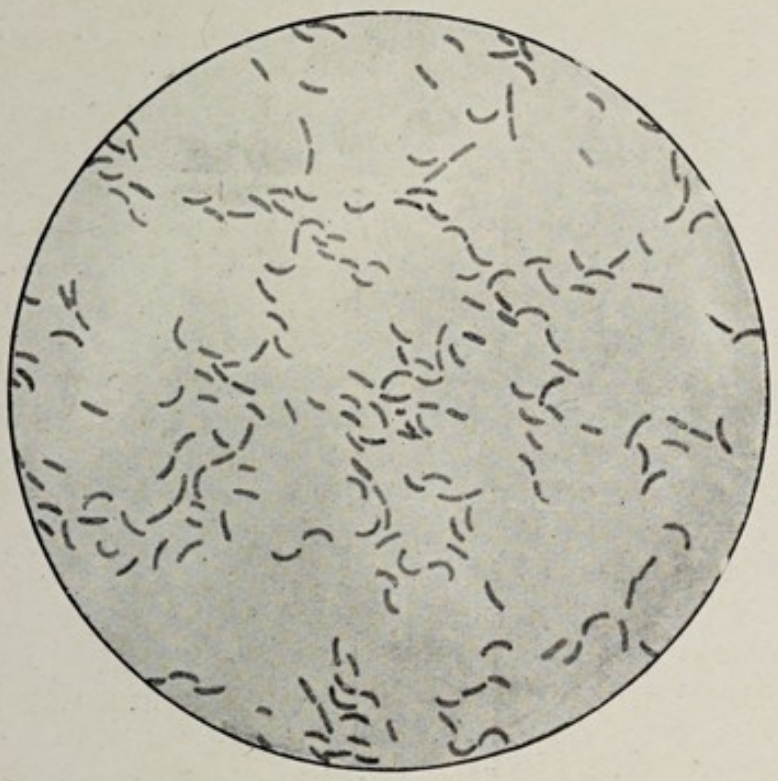


FIG. 52.—V. CHOLERÆ. (FILM FROM CULTURE.) (× 1,000.)

This organism is a strict anaërobe and an active gas-producer. Under anaërobic conditions it develops readily in the ordinary laboratory media.

The *B. œdematis maligni* causes a spreading gangrenous inflammation, with the production of subcutaneous emphysema in the human subject, and a similar lesion when inoculated into laboratory animals. It may occur in lacerated wounds, especially when soiled with earth.

The spirillum or vibrio of cholera is a short rod which, in its most typical form, is slightly curved like a comma (Fig. 52). The degree of curvature and the shape and size of the vibrio are, however, subject to wide variations, and the organism is essentially pleomorphic. The arrangement of the vibrios in any given preparation varies, but it is common to find two individuals united end to end and with their curves facing in opposite directions, thus forming an S-shaped figure. The vibrio is flagellated, the most typical form

possessing one flagellum at each end, and it is actively motile. It is not capsulated, and does not form spores.

The vibrio grows well on all neutral or slightly alkaline laboratory media, much better under aërobic than under anaërobic conditions. It liquefies gelatine, and a stab culture in this medium shows a line of growth along the inoculation stab with progressive liquefaction, commencing from above and leading at first to a funnel-shaped depression. The *V. choleræ* has the power of producing indol and a nitrite in peptone water, and hence the typical nitroso-indol reaction may be obtained by adding a little strong sulphuric or hydrochloric acid to such a culture after twenty-four hours or longer incubation. This is known as the *cholera red reaction.*

In man the vibrio is found in enormous numbers in the rice-water stools associated with the disease, and in the infected mucous membrane. It has little or no invasive power, and owes its high degree of pathogenicity to the acute toxæmia which results in an infected subject, and to some extent to the depletion of the body fluids resulting from the profuse diarrhœa. It was for long held that the organism was strictly localised to the intestinal mucosa, but more recent observations have shown that the vibrios may be isolated from the gall-bladder in a considerable proportion of cases.

The great majority of animals remain unaffected when attempts are made to infect them with this organism by feeding. The ground-squirrel is the only noteworthy exception. Koch, however, succeeded in producing cholera in guinea-pigs by feeding with a culture of vibrios after neutralising the acidity of the g stric juice and inhibiting the intestinal movements with injections of opium. Other observers have reproduced the disease in these animals by injecting the organism directly into the duodenum after performing laparotomy. Guinea-pigs and rabbits, but especially the former, are very susceptible to the toxic action of the *V. choleræ*, and rapid death may be brought about by the injection of living or dead cultures in suitable amounts.

The usual serological reactions employed for diagnostic purposes are of great importance in the study of this organism, since there are many closely allied species, and it is often necessary to employ all the serological tests at our command before we can be certain that we are dealing with a true cholera vibrio.

Streptothrix Organisms.

Streptothrix actinomyces.—The morphology of this organism differs accordingly as it is studied in the tissues or in culture. In the former it occurs in the form of small granules which consist of a central feltwork or mycelium of branching threads, surrounded by radiating club-shaped bodies from which its name is derived (Fig. 53). These clubs are much more marked in some lesions than in others, and are usually much less well seen in the human than in bovine lesions. In cultures these typical arrangements are not seen.

The organism occurs as branched filaments, rods, and coccal forms, but clubs are not seen. The filaments are Gram-positive, and to some extent acid-fast. The staining reaction of the clubs varies in the human and bovine lesions, the tendency in the latter being for these structures to retain the violet stain.

The descriptions of the cultural characteristics of this organism have varied considerably, and there seems little doubt that different workers have been dealing with different organisms, so that it is impossible to give a uniform description.

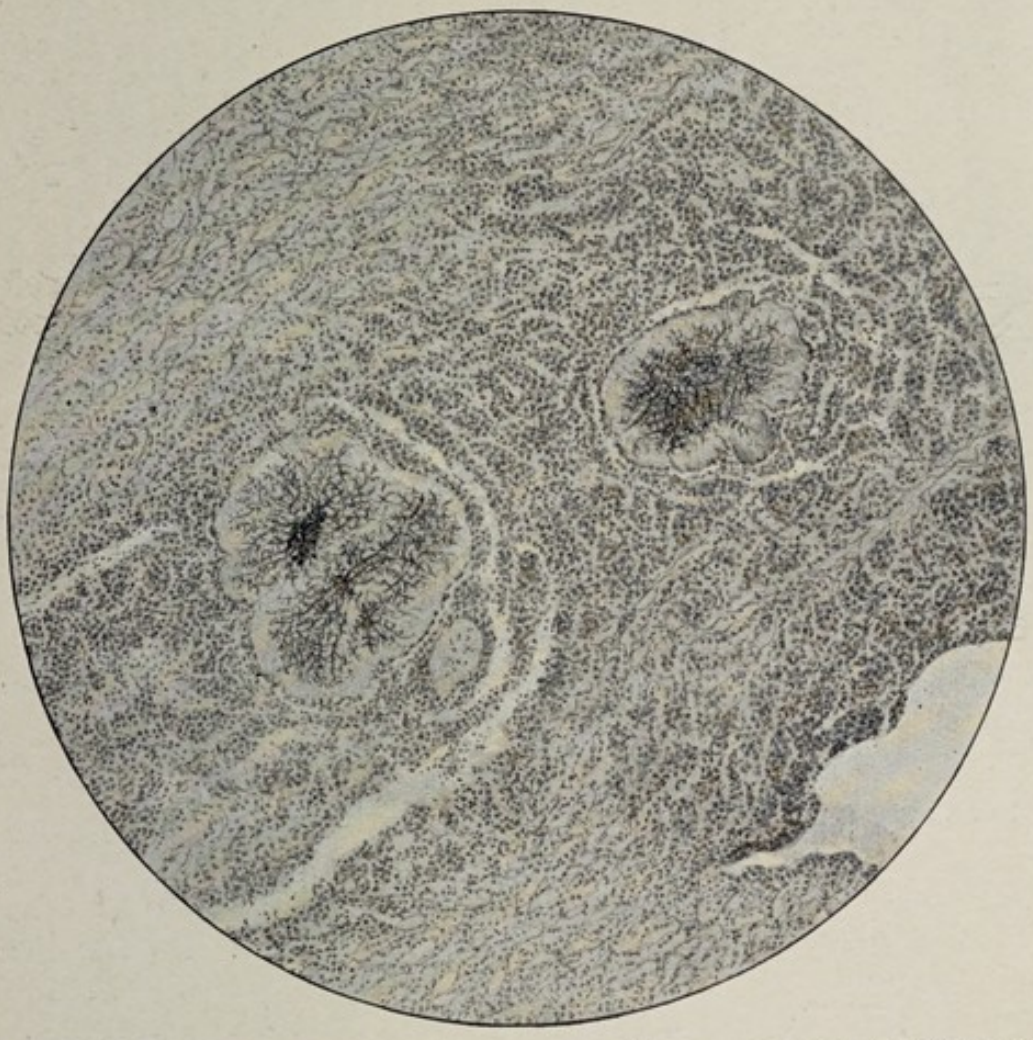


FIG. 53.—SECTION SHOWING COLONIES OF STREPTOTHRIX ACTINOMYCES IN GRANULATION TISSUE. (× 500.)

The *Streptothrix actinomyces* normally infects cattle, and man is only occasionally infected. The most usual lesion in the ox is the formation of large hard masses in the tongue, and sometimes in the bones of the jaw, which soon tend to break down and suppurate. In man the commonest lesion is situated in the region of the neck, but generalised infection is not uncommon. The internal organs which are most often affected are the liver and the lung.

The experimental infection of animals has, in many cases, given rise to typical lesions.

THE BLASTOMYCETES, OR YEASTS.

These are small, round or oval cells, which multiply by budding (*gemmation*). Sometimes the cells cohere and form branching chains. In some varieties, when food is not abundant, as in the case of potato cultivations, one to four spores may form in the interior of the yeast-cells; in others no spore-formation occurs. On this basis the blastomycetes are divided into two groups: (1) The *Saccharomycetes*, or true yeasts, which form spores; and (2) the *Torulæ*, which do not. The spores develop when placed in fermentable fluids. At other times, under unfavourable conditions, unjointed mycelium may be produced. When it is remembered that the growth of some higher fungi—*e.g.*, *Mucor mucedo*—under *exceptional* circumstances is the same as that of yeasts under *ordinary* circumstances—*i.e.*, by gemmation—it seems possible that yeasts may really be vegetative forms of higher fungi.

FIG. 54.—OIDIUM ALBICANS. (× 500.)
Cells and spores seen on the surface of epithelium, scraped from an "aphthous" patch on an infant's tongue.

Yeasts are of importance chiefly as causes of fermentation. Fungi referred to this group have also been isolated from certain tumours, and claimed as the cause of these formations. Certain blastomycetes also give rise to a form of dermatitis. Torulæ are common in the stomach either alone or in company with sarcinæ. They are frequently found in diabetic urine, but not at the time it is passed, being deposited from the air, and growing readily in the saccharine fluid.

Oïdium albicans is a parasite of which the botanical position is doubtful. It is generally regarded as a mould, but Grawitz states that, when cultivated, this fungus shows itself to be a yeast, and probably the *Mycoderma vini*, which he has proved capable of growing on mucous membranes. It is responsible for a disease characterised by pale grey patches adherent to the mucous membrane of the mouth, pharynx, and gullet. This occurs in children at the breast or adults exhausted by wasting diseases—*e.g.*, typhoid fever, phthisis. The patches consist of tortuous, often branched, filaments, formed of long cells united end to end, and distinctly constricted where they join. The filaments end in rounded cells, which produce one or more spores; these form heaps in the epithelium (Fig. 54).

THE HYPHOMYCETES, OR MOULDS.

These consist of filaments (*hyphæ*) formed by a single row of cells placed end to end, growing by means of an apical cell which elongates and divides transversely. Lateral offshoots are common, but dichotomous branching is rare. Hyphæ may occur singly, but

usually they are numerous, intertwining loosely or closely so as to form a feltwork (*mycelium*). All spring from an axis or *germinal tube* which grows directly from a germinating spore. Their growth is extremely slow compared with that of bacteria (p. 101).

In the adult plant the hyphæ are of two kinds: (1) The *nutritive*, which grow into, and extract nourishment from, the culture-soil, forming the mycelium; and (2) the *reproductive*, which spring from the mycelium, and stand up from the substance in which it lies. These are called aërial, or fruit-hyphæ. They are simple or branched,

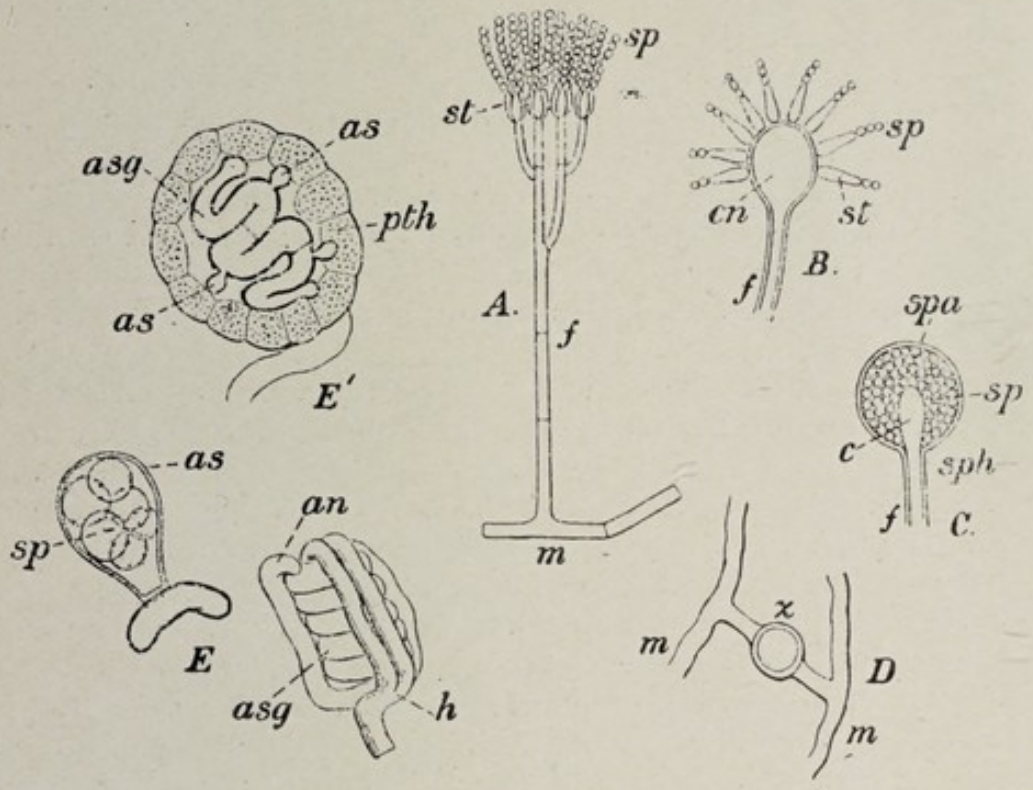


FIG. 55.—METHODS OF REPRODUCTION OF HYPHOMYCETES. DIAGRAMMATIC. (AFTER PRANTL AND VINES.)

A, *Penicillium glaucum*; *B*, *Eurotium repens*, *Aspergillus niger* (in section); *C*, *Mucor mucedo* (in section); *D*, Conjugation (Mucor); *E*, *E'*, sexual reproduction, fertilisation (Eurotium); *an*, antheridium; *as*, ascus; *asg*, ascogonium; *c*, columella; *cn*, conidiophore; *f*, fruit-bearing hypha; *h*, hyphæ covering ascogonium forming perithecium; *m*, mycelium; *pth*, perithecium; *sp*, spores; *spa*, sporangium; *sph*, sporangiophore; *st*, sterigmata; *z*, zygospore.

and bear at their ends spores or sexual organs. Reproduction is either asexual or sexual; the two methods may occur together on the same plant, or may alternate regularly or irregularly. In either case spores are formed—round, oval, or cylindrical, smooth or irregular, coloured or colourless. Most are motionless, but some "swarm." Each consists of a little mass of protoplasm, surrounded by an envelope which is made up of an outer (*exosporium*) and an inner (*endosporium*) layer; the exosporium is often pigmented. All spores have great power of resisting the action of physical and chemical agencies, and retain life for long peroids. Those formed

asexually are ready at once to germinate, but those due to a sexual process almost always require a resting period. The latter are the true *resting spores;* but this name is often applied to all spores capable of retaining life for long periods in spite of adverse conditions.

Asexual spore-formation occurs in three ways (Fig. 55)—

(1) Hyphæ spring from the mycelium, and perhaps branch. The terminal cells divide transversely into spores (*conidia*), which either fall away singly or form chains.

(2) A hypha (*sporangiophore*) stands up from the mycelium, and its end swells into a ball (*sporangium*) full of protoplasm, which segments and forms conidia.

(3) From the surface of a knob on the end of a hypha (*conidiophore*) peg-like processes (*sterigmata*) sprout, each sterigma, by growth and transverse division, forming a chain of spores.

Sexual reproduction occurs in the following ways :

(1) *Conjugation.*—The apical cells of two hyphæ meet end to end and blend into one cell (*zygospore*). From this, after a longer or shorter rest, a sporangiophore sprouts, and from its spores new plants grow, as in Mucor.

(2) *Fertilisation.*—The end of a hypha becomes twisted like a corkscrew, more and more closely, until the turns form a continuous tube—the *ascogonium.* From the lower turns spring fine branches, one of which (*antheridium*) conjugates by its apex with the ascogonium ; the others simply cover the ascogonium continuously, and are converted by division into polygonal cells, which form a capsule (*perithecium*) round it. Many transverse septa form in the tube of the ascogonium, and from the cells thus produced flask-shaped lateral projections (*asci*) develop ; in each of these, eight spores generally appear. The perithecium thins as the asci enlarge, the walls of the asci disappear, and an easily ruptured sphere of spores remains. When these germinate the endospore swells, splits the exospore, and throws out the germinal tube, whence springs the mycelium.

Conditions of Life—*Food.*—Possessed of no chlorophyll, moulds are unable to build up carbon compounds. They assimilate those built up by other plants or animals. They are, therefore, always either saprophytes or parasites ; in the latter case they may kill their host. They require a free supply of oxygen ; but some can obtain it, at least for a time, by decomposition of organic compounds like sugar. Thus, *Mucor racemosus,* cultivated on the surface of a saccharine liquid, absorbs oxygen, oxidises some of the sugar, forming carbon dioxide, and grows rapidly. If deprived of oxygen, as by immersion, only the mycelium grows, and this becomes broken up into short cells, which multiply by budding, and much resemble yeast-cells. The growth is then much slower, carbon dioxide escapes in bubbles, and alcohol appears in the liquid. These changes soon cease, and the process can only be started again by a fresh supply of oxygen (Duclaux). Some moulds, such as *Penicillium glaucum* and *Aspergillus niger,* have no power of thus obtain-

ing oxygen, and die if cut off from the free gas. The change in the character of growth above mentioned, accompanying changes in conditions of life, has been pointed to as evidence in favour of the mutability of bacteria.

Light.—Many moulds can develop completely without light; some require it for the formation of spores and other processes.

Temperature.—Ziegler states that moulds flourish best at temperatures *below* that of the body, and that some will not grow at all at so high a temperature. A few species of Aspergillus and Mucor grow well between 95° F. and 105° F. The spores are as resistant to external agencies as are those of bacteria.

Water, or at least dampness, is essential for the growth of moulds.

Moulds are associated with processes of *rotting* or *decay*. The peculiar smell and taste which they impart is well known. The products of their life-action have not been closely investigated, but they are neither very poisonous nor very irritating, so far as *human* tissues are concerned.

Distribution.—The spores of moulds are much more numerous in the air than are other organisms. They, therefore, constantly fall upon the skin and enter the air-passages with air and the food-passages with food. As a rule, they find no nidus suitable for their development; the supply of free oxygen is often insufficient, and the temperature too high. Certain of them, however, when brought into contact with accumulated inflammatory discharges, or with sloughs, take root and fructify. This is most likely to occur in the nose, mouth, and pharynx. They are here saprophytes, but the products to which they give rise may irritate the living tissues lying beneath the parts in which they grow. Species of Mucor and Aspergillus are those commonly found under these conditions.

Pathogenic Moulds.

Owing to the peculiarities mentioned in their life-history, these fungi have but little power of invading living tissues. Certain skin diseases are, however, due to the growth of species of this class in epidermic structures. They are: (1) *Favus;* (2) *Tinea tonsurans, Tinea kerion, Tinea circinata, Tinea sycosis, Tinea unguium;* (3) *Tinea versicolor;* and (4) *Erythrasma.* The fungi causing the diseases actinomycosis and mycetoma, or Madura foot, have been sometimes assigned to this class. Their exact position is still undecided, but they are generally regarded as forms of streptothrix. Instances of the invasion of living tissues by varieties of *Aspergillus* (*Aspergillus fumigatus, Aspergillus niger*) are occasionally met with. Thus, by the growth of the fungus in the lungs a disease is produced somewhat resembling tuberculosis in its symptoms (*Pneumomycosis*, or *Aspergillosis*). A form of *Mucor* has been described as giving rise to a dermatitis closely resembling scabies (Luck); the same fungus was also found in a case of intestinal ulceration complicated by cerebral abscess (Paltauf).

Achorion schönleinii forms almost the whole of the light yellow, mouldy-smelling crusts characteristic of Favus. On hairy parts—the usual seats of the disease—the hairs are always invaded, especially the roots. Here the parasite grows luxuriantly, but it does not extend far up the shaft; its primary seat is the epithelium of the hair-follicle. On other parts the mycelium invades the *deeper layers* of the *epidermis*, and may even penetrate to the corium; in this case the local irritation will be more marked. The mycelium consists of unjointed, branching, confusedly intercrossing tubes; in certain of them, which become divided into joints, oval spores form.

The nails are very rarely invaded, and then only by mycelium.

Trichophyton* tonsurans is generally assumed to be the one parasite common to *Tinea tonsurans*, *Tinea kerion*, *Tinea circinata*, *Tinea sycosis*, and *Tinea unguium*. Different varieties have been described. These are distinguished by the size of the spores (*Trich. megalosporon*, *Trich. microsporon*), their position, either within the hair-shaft (*endothrix*) or outside it (*ectothrix*), and their culture results (Sabouraud). These forms are not found growing together.

When the hair is affected, the root and the lower part of the shaft are crammed with spores, lying in rows between the fibrils of the degenerated hairs, which are opaque and brittle. It is doubtful how far the fungus makes its way down between the shaft and the wall of the follicle before it penetrates the former. The hair breaks just beyond the scalp, leaving a stubbly line of split or twisted ends. Epidermic scales from the surface of the scalp may contain the fungus, but the deeper living cells of the root-sheaths are always free from it (Thin and Taylor). Spores are abundant, and oval in shape; mycelial threads are rare. Points worth remembering in connection with the undoubted fungoid origin of the disease are: (1) Its usual limitation to children; (2) its tendency to fasten upon the weakly; (3) its great contagiousness when acute, diminishing as it becomes chronic; and (4) its greater severity when contracted from animals, as the horse (*Trichophyton megalosporon*). It may excite severe irritation, and even suppuration—*Tinea kerion*.

In *Tinea circinata* the parasite infests epidermic cells, always causing desquamation, sometimes vesiculation, or even more severe inflammation. It spreads uniformly from the point at which it first takes root, and consequently assumes the form of a gradually enlarging circle. The central parts of the fungus die, and the growing edge produces a ring of hyperæmia in its neighbourhood. Mycelium is present chiefly in the form of very long, jointed, and branched threads; the spores are scanty, single, or in short chains. The fungus altogether is often scanty, and is especially difficult to detect if it has excited inflammation.

When attacking the beard (*Tinea sycosis*), the fungus (*Trichophyton megalosporon*) is found chiefly in the hair, but also in the follicle; both mycelium and spores are seen, the latter in excess, but not so markedly as in *Tinea tonsurans*. The mycelium generally lies

* Greek θρίξ, a hair; φυτόν, a plant.

round the root of the hair, and is pulled out of the sheath with it. Severe inflammation is generally excited, upon which a secondary infection by *Staphylococcus pyogenes aureus* is frequently superposed.

Mycelial threads of trichophyton may occasionally invade a finger-nail (*Tinea unguium*), rendering it opaque, thick, and brittle. Unlike the effects of a general disease, these changes occur in two or three nails only, and the toe-nails are scarcely ever affected. In this situation it is extremely difficult to destroy.

The **Microsporon furfur** invades the horny layer of the epidermis of covered parts of the trunk, growing more superficially than any of the above, rarely causing irritation, and not attacking nails or hairs. It consists of jointed mycelial threads, which are always abundant ; and spores, which vary in form, lie in groups, and grow at the ends of the mycelial threads. On the skin it produces patches of brown discoloration (*Chloasma, Pityriasis versicolor*).

Microsporon minutissimum is a form of mould responsible for the rare disease *erythrasma*.

CHAPTER XI

PARASITES—*Continued*

PROTOZOA.

THE protozoa which are pathogenic to man belong to the classes Sarcodina, Flagellata, and Sporozoa. A few ciliated organisms—*e.g.*, *Balantidium coli* *—occur as accidental parasites, but do not seem to cause disease. The Sarcodina are represented by certain amœbæ, the Flagellata by the hæmoflagellates (*Trypanosoma* and *Leishmania*), and the Sporozoa by the malarial parasites (*Hæmamœbæ* or *plasmodia*). Spirochætes, which are believed by many writers to be protozoa, are described at the end of this chapter in a separate section, as their affinities appear to be rather with the bacteria than with the protozoa.

AMŒBÆ.

Amœbæ are found in the contents of the intestines both in health and in disease, and there is still some doubt as to the identity or diversity of the species present, and as to their pathogenic properties. It is usual to follow Schaudinn in distinguishing a harmless species, *Amœba* or *Entamœba coli*, and a pathogenic species, *Amœba dysenteriæ* or *Entamœba histolytica*, which is responsible for one form of tropical dysentery.

Entamœba coli† (Fig. 56).—This amœba is perhaps the commonest protozoal inhabitant of the human intestine, and is apparently non-pathogenic. It inhabits the large intestine and cæcum. The common form varies in size from 10 to 30 μ, and consists of a mass of protoplasm with a single nucleus, which possesses a nuclear membrane, on the surface of which are irregular masses of chromatin, while a central granule, or karyosome, is also present. The cytoplasm is granular and vacuolated, the vacuoles containing bacteria,

* This organism is found in large numbers in some cases of diarrhœa with ulceration of the colon (*Balantidic dysentery*), but its causal relation to the disease is not satisfactorily proved. In somewhat similar conditions a flagellate protozoon, *Cercomonas hominis*, has been found present.

† The descriptions here given of the *Entamœba coli* and the *Entamœba histolytica* follow those given by Wenyon in recent communications. The diagrams have been also adapted from his figures, and we should wish to express our thanks to him, for permitting us to reproduce them here.

yeasts, etc., which the amœba has ingested. There is as a rule no sharp differentiation into endoplasm and ectoplasm, either in the amœba itself or in the pseudopodia which it throws out in the course of movement.

Reproduction occurs by simple fission, the nucleus dividing first, and then the cytoplasmic body. The size of the amœbæ in any given specimen seems to depend largely on the rate of division, rapid fission leading to the predominance of small forms. During their sojourn in the large intestine certain individuals cease to multiply, become spherical, and secrete round themselves a protective covering or cyst-wall. The single nucleus divides into two; these again divide to produce four, and these again to produce eight. The

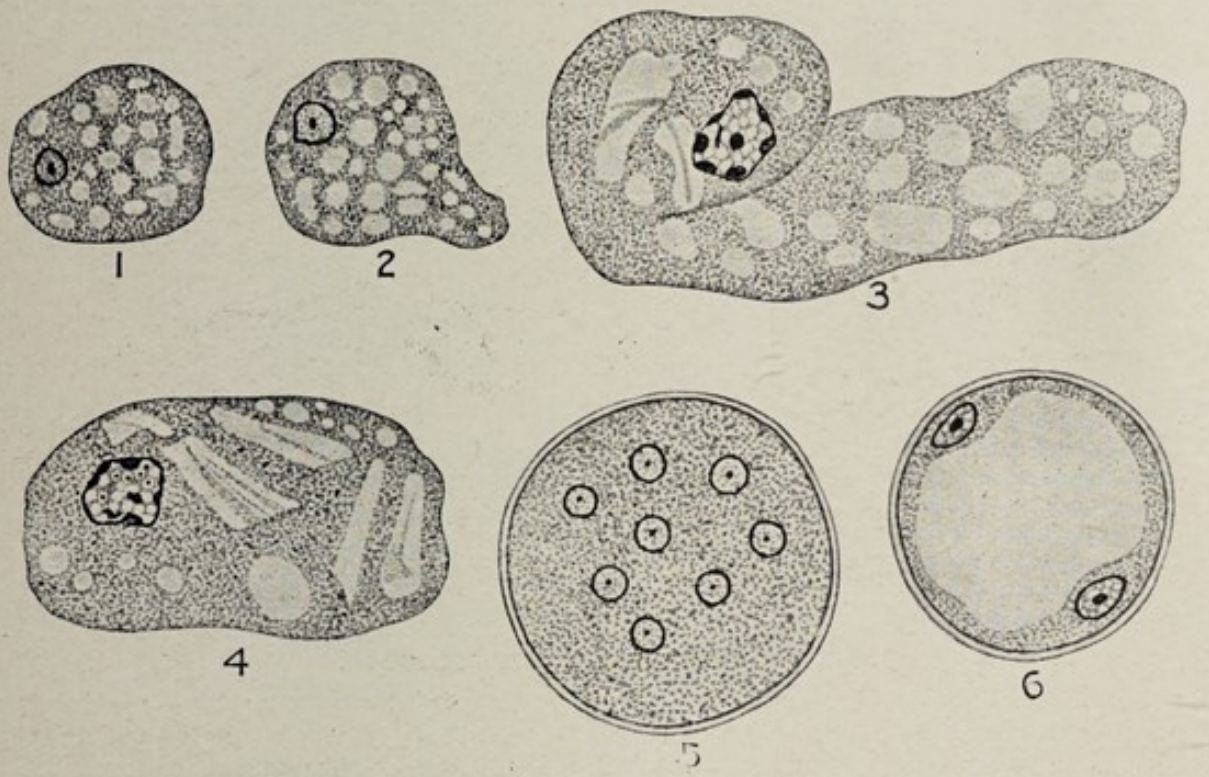


FIG. 56.—ENTAMŒBA COLI.

1, small entamœba; 2, small entamœba with pseudopodium; 3, large entamœba of irregular shape; 4, large entamœba with slit-like vacuoles; 5, encysted form of entamœba; 6, cyst with large central vacuole.

commonest form of cyst found is that containing eight nuclei embedded in a single mass of protoplasm, but cysts in all stages of development may of course be found. The size of the cysts of *E. coli* varies from 15 to 20 μ, but large forms having a diameter of 30 μ or over may be found. After escape from the body, these cysts apparently undergo no change till they are ingested by another host. Under the action of the digestive juices, the contents of the cysts divide into eight small amœbæ, which then escape into the intestine. It has been suggested that these small forms are really gametes which conjugate in pairs. Schaudinn described a complicated sexual process (autogamy) as taking place in the cysts, but this has not been confirmed.

Entamœba histolytica (Fig. 57).—This parasite is the cause of amœbic dysentery and of the liver abscess which occurs as a complication of this disease. The *E. histolytica* differs little in size from the *E. coli*, and, like it, inhabits the large intestine and cæcum, but it has the power of invading the tissues and multiplying in distant organs. The parasite occurs in two forms: the *tetragena* or tissue-invading form, and the minuter form. The former is found in cases of acute amœbic dysentery, while the latter increases in relative number during convalescence. The *E. histolytica* is more refractile than the *E. coli*, its nucleus is slightly smaller, and the granules of chromatin upon the nuclear membrane are much finer. The protoplasm is vacuolated, but the vacuoles tend to contain red

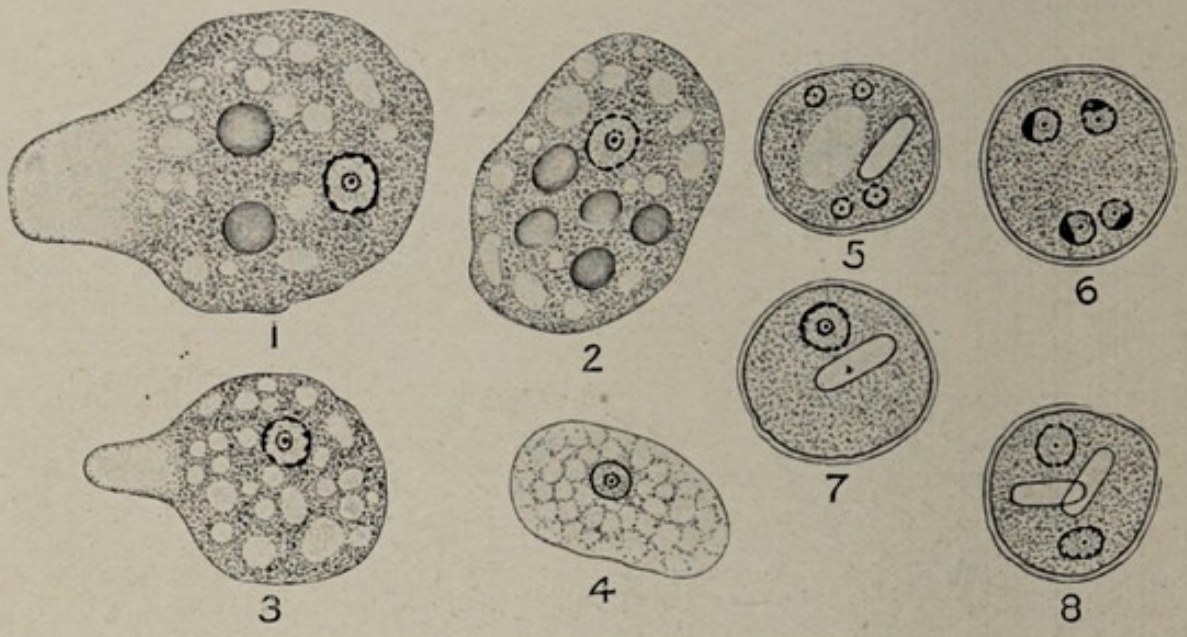


FIG. 57.—ENTAMŒBA HISTOLYTICA.

1, large tissue-invading form with ectoplasmic pseudopodium; 2, large form containing red blood-corpuscles; 3, small form with pseudopodium; 4, small (*minuta*) form; 5, encysted form with four nuclei, chromidial body, and vacuole; 6, encysted form with four nuclei; 7, encysted form with one nucleus and chromidial body; 8, encysted form with two nuclei and two chromidial bodies.

blood-corpuscles or leucocytes rather than bacteria or yeasts. The presence of red blood-corpuscles is, indeed, almost diagnostic, since *E. coli* does not ingest them. There is a clear distinction between endoplasm and ectoplasm, and the pseudopodia consist almost entirely of the latter element. The tissue-invading form of *E. histolytica* does not encyst, but the minuter form does so. The cysts are less accurately spherical than those of *E. coli*. They are usually smaller, 10 to 14 μ in diameter, but may vary up to 19 μ or down to 7 μ. In some types the cysts are uniformly small (7 to 10 μ). They are more refractile than the cysts of *E. coli*. Nuclear division leads to the formation of two, then four, but only very occasionally eight, nuclei. The cysts as they escape from the body may be in all stages of development, the four nuclear forms

predominating. They often contain one or more refractile rods, known as *chromidial bodies,* and a large vacuole may be present in the cytoplasm.

The pus from an amœbic abscess of the liver is usually reddish-brown in colour. It is sterile by the usual methods of cultivation, and the *E. histolytica* can seldom be demonstrated in it at the time of operation. In sections the amœbæ are found to be present in the wall of the abscess.

Intestinal Flagellates.—Certain flagellate protozoa are common inhabitants of the human intestine in many tropical countries, and are probably the cause of certain forms of acute diarrhœa. Among these are *Trichomonas intestinalis, Lamblia intestinalis, Tetramitus mesnili,* and *Cercomonas.*

Plasmodia.

Plasmodium malariæ.—*Malaria* is the name which for many years has been employed to denote the virus of a frequently fatal disease, occurring principally in tropical climates, and characterised by periodic attacks of fever. When these attacks recur *daily,* the disease is known as *quotidian* ague; when on *alternate* days, as *tertian* ague; when every *third* day, as *quartan* ague. The periodicity is not always so regular or so simple, nor are the intervals so short, as in these examples. When the individual febrile recurrences run into each other, so that there are no apyretic intervals, but only slight remissions, the term "remittent fever" is applied to the attack. The anatomical changes met with in the disease are great enlargement of the spleen and marked pigmentation of many parts—*e.g.*, spleen, liver, and brain. It is the type of an *endemic disease:* it is strictly limited to particular localities—that is to say, it can be acquired in these localities only, although its clinical manifestations may develop elsewhere. It is never communicated directly from person to person, except by the direct intravenous inoculation of blood taken from an individual in whose blood the germ is present.

Laveran first pointed out that if a careful examination be made of a drop of blood taken from a malarial patient during, shortly before, or, in certain types of the disease, some time after, one of these febrile attacks, certain characteristic appearances will be found. These are: (*a*) Circular or ring-shaped amœboid discs, pale and apparently structureless, lying on or in the red corpuscles, and not unlike vacuoles (Fig. 58, 2, 3); (*b*) pigmented amœboid bodies occupying from a sixth to almost the whole of the affected corpuscle, which usually contains only one such body (4, 5); (*c*) well-defined rosette-shaped or clustered bodies, the segments surrounding or radiating from a clump of pigment in or about the centre of the figure (7)—these may be free in the plasma, or may be encircled by the remnant of a red corpuscle; (*d*) pigmented crescentic bodies (10, 11); (*e*) flagellated organisms and free flagella (14*a*, 15); (*f*) leuco-

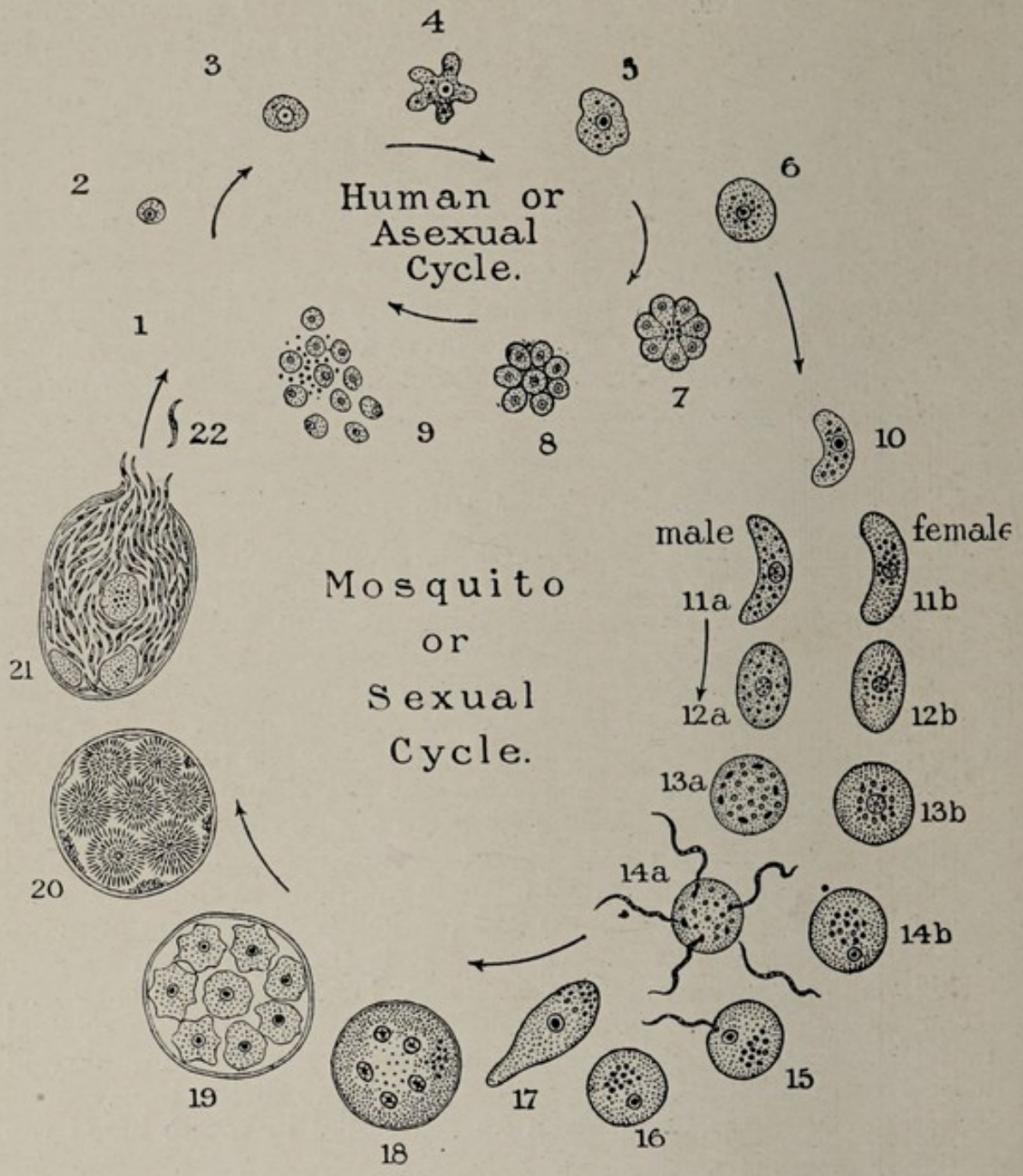


FIG. 58.—SCHEME OF LIFE-HISTORY OF MALARIAL PARASITES.

The upper circle (1 to 9) shows the development within the human body; the lower circle shows the changes which occur within the body of the mosquito (10 to 22). 1. Blood-corpuscles, ready to be infected by either merozoites (9) or sporozoites (22). 3-6. Development of amœbula within blood-corpuscle. 7, 8. Division of amœbula into merozoites, which are finally set free in the blood (9). 10. Crescentic body developed from parasite within blood-corpuscle, after this (6) is swallowed by mosquito. 11*a*, 11*b*. Male and female forms (crescents). 12*a*-14*a*. Development of male gametocyte. 12*b*-14*b*. Development of female gametocyte. 14*a*. Formation of flagella or male gametes. 14*b*. Female gamete after casting off polar body which is shown lying beside it. 15. Fertilization or conjugation. 16. Zygote. 17. Oökinete or travelling vermicule. 18, 19. Formation of sporoblasts. 20. Formation of spores or sporozoites. 21. Discharge of spores into body-cavity of mosquito. 22. Free spore leaving salivary gland to enter human host.

cytes containing black pigment. It is now proved that the appearances seen in the blood-corpuscles represent different stages in the life-history of parasitic organisms.

Three distinct parasites have been described as giving rise respectively to the quartan, the tertian, and the malignant form of malaria, and many different names have been applied to them. Adopting the rather unfortunate name plasmodium as the generic term, the quartan parasite may be called *Plasmodium malariæ*, the tertian, *Plasmodium vivax*, and the malignant form, *Plasmodium falciparum*, or *Plasmodium immaculatum*. This last is more often termed *Laverania malariæ*, but there seems scarcely enough divergency between it and the others to warrant the use of a separate generic name. Laveran, their discoverer, believes that they are all merely varieties of the same species. The life-history is practically the same in all of them, and they may conveniently be considered together.

The malarial organism passes through two phases or cycles of development—one, in which multiplication is by simultaneous multiple fission (sporulation) taking place within the body of the human host, and the other, in which sexual union (conjugation) occurs, within the body of the intermediate host, the mosquito. These cycles are diagrammatically represented in Fig. 58. It appears that, as is the case with other protozoa, multiplication by simple fission cannot continue indefinitely: hence the parasites tend to die out after a time within the human host, unless infection is renewed. In order that their vitality may be restored it is necessary that they should enter the body of a different animal—the mosquito—and therein carry out the process of conjugation, or union of two individuals representing respectively male and female elements. Infection of a second human being or re-infection of the original host is then effected by the bite of the mosquito.

Human Cycle.—If we start at the moment of infection by the bite of the mosquito, we see that a minute, rod-shaped body (Fig. 58, 22) is conveyed into the human blood from the insect's proboscis. This little rod or spore immediately proceeds to enter one of the blood-corpuscles of the new host, and within the corpuscle it goes through the following series of changes: It first enlarges until it may occupy the greater part of the corpuscle (2-6). Then segmentation takes place; the nucleus first divides, and its fragments take up positions at the periphery of the organism; then divisions appear in the protoplasmic substance between these daughter-nuclei, and the parasite divides into segments (7). Each of these segments now assumes a rounded form, so that the blood-corpuscle contains a number of small round bodies (*merozoites*) (8); and by the death and rupture of the corpuscle these are set free in the plasma (9), the shrivelled remains of the stroma of the corpuscle being sometimes visible in the blood as the "brassy bodies" of the Italian writers. Each spore next proceeds to invade a fresh blood-corpuscle; it there enlarges to adult size, and the process of segmentation begins again.

It is found that all of the parasites resulting from a single infection enter on the stage of segmentation at the same time, and that the simultaneous setting free of the merozoites into the blood-stream corresponds in point of time with the access of fever in the patient; taking place every third day in the case of the tertian parasite, every fourth day with the quartan parasite, and irregularly with the malignant organism. It must be assumed that on rupture of the blood-corpuscles some poison is liberated which is capable of exciting pyrexia.

By the destruction of the corpuscles a quantity of dark pigment is produced, and this is set free in the blood-stream. Some of it is deposited in the spleen and liver, which become deeply pigmented, while other granules are ingested by leucocytes. Pigmented leucocytes are very characteristic of the blood of malarious patients, and the discovery of them may aid in the diagnosis of the disease.

Mosquito Cycle.—When a mosquito, of the genus *Anopheles*, bites a human being who is the subject of malaria, it takes into its stomach some blood-corpuscles containing adult organisms (6, 10). These proceed to develop on lines differing from those pursued within the human host. The corpuscles are dissolved, and the organisms escape. These take on male and female characters (*gametocytes*). In the male (Fig. 58, 11*a*) the nucleus divides into a number of small fragments, arranged round the periphery of the protoplasm, and from each of these a long protoplasmic process or flagellum is extruded (*male gamete*, 14*a*), resembling in form and attributes a spermatozoön. These break off from the body of the parasite, and each proceeds to conjugate with a female organism, just as a spermatozoön unites with an ovum (15). Meanwhile the female organism (11*b*) has prepared for conjugation by throwing off a polar body, and forming a micropyle for the entrance of the head of the male element (14*b*). After conjugation has occurred, the nuclei of the male and female elements fuse, and the resulting organism becomes sharply pointed at one end. It is now called the "travelling vermicule" or "oökinete" (17), and proceeds to burrow through the wall of the mosquito's stomach (Fig. 59). Arrived within the tissues, it undergoes further changes: the nucleus divides into a number of fragments, and the protoplasm becomes arranged round these, forming rounded masses or sporoblasts (19). By fresh fragmentation of the nuclei and protoplasm of these sporoblasts a number of rod-shaped spores are formed, all adherent at first to a remnant of the sporoblast, which has not divided (20). These spores are finally set free in the tissues of the mosquito, enter its salivary gland, and are ready to be injected into a human host whenever the insect bites. When infec-

FIG. 59.—STOMACH OF MOSQUITO, SHOWING CYSTS OF MALARIAL ORGANISM IN THE WALL. (AFTER ROSS.)

tion is thus transmitted, the human cycle of the parasite takes place as already described.

The hypothesis originally framed by Manson as to the conveyance of the infection of malaria by means of mosquitoes has now been fully confirmed. In India, Ross fed certain species of mosquito on birds in whose blood an analogous parasite was present, and, on subsequently causing these mosquitoes to bite healthy birds, found that the latter became similarly infected, Bignami and Grassi obtained similar results with human malaria, while Ross demonstrated the existence of the parasite within the body of the mosquito.

The three species of malarial organisms already distinguished differ somewhat in appearance and life-history. The peculiar crescentic forms of gametocytes shown in Fig. 58, 10, are only met with in the case of *Laverania*, the intracorpuscular stage of which is often ring-shaped. *Plasmodium vivax* exhibits very active amœboid movements; the other forms move less rapidly. Corpuscles attacked by *Plasmodium malariæ* shrink in size, whereas those containing *Plasmodium vivax* become swollen and pale. In pernicious malaria the organisms may be found in large numbers in the cerebral capillaries, which they appear almost to block; the severe symptoms of this form of the disease may be associated with this localisation of the parasites.

The administration of quinine is followed by the disappearance of the intracorpuscular parasites; the crescentic bodies are the last to go. Leucocytes have been seen to approach and touch corpuscles containing the parasite, though they never *enclose* any but the extra-corpuscular forms. They also take up the particles of altered hæmoglobin set free on breaking up of corpuscles.

Hæmoflagellates.

Trypanosomes are elongated, flexible organisms, possessing a flagellum, which is attached to the body throughout the whole length of the latter by an undulating membrane, or thin fold of periplast (cuticle). They contain two separate nuclei—one large, known as the tropho-nucleus, and supposed to preside over the nutritive processes of the organism, and the other small, more deeply stained by dyes, and closely connected with the flagellum, the movements of which it may initiate (Fig. 62). Trypanosomes are found as parasites of many vertebrate animals, in which as a rule they give rise to no disease (*e.g.*, *Trypanosoma lewisi* in the rat, *Trypanosoma fringillarum* in small birds, *Trypanosoma raiæ* in fishes). A few species give rise to disease, such as *Trypanosoma equiperdum*, the cause of dourine in horses, *Trypanosoma brucei* of nagana in horses and cattle, and *Trypanosoma gambiense* of trypanosomiasis in man. Infection is always conveyed by the bite of some insect, the only exception being dourine, which is transmitted in coitus. Within the vertebrate host trypanosomes multiply by binary and multiple

fission (Fig. 60). Within the body of the intermediate host, the insect, a series of changes takes place in the trypanosome, which loses its flagellum, becomes rounded in form, and then multiplies by binary or multiple fission, with subsequent re-formation of typical trypanosome forms (Fig. 61). Conjugation is said to occur between the thin and stout forms of the parasites, representing apparently male and female elements (Prowazek).

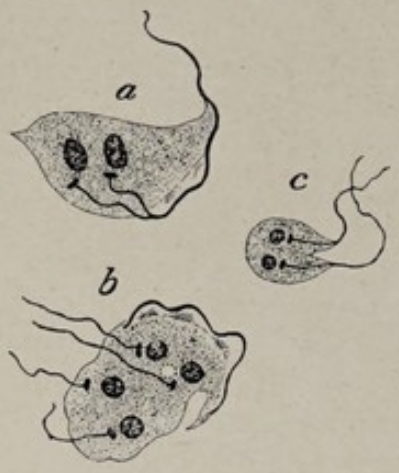


FIG. 60.—MULTIPLICATION OF TRYPANOSOMA LEWISI IN THE RAT.

a, binary fission of large individual; *b*, multiple fission; *c*, small form undergoing binary fission.

Trypanosoma gambiense.—This parasite (Fig. 62) is the cause of trypanosomiasis, or sleeping sickness, in mankind. It was discovered by Castellani in negroes suffering from the disease, and was established as the causal organism by Bruce and Nabarro. Individual trypanosomes differ considerably in shape and size, stout (female) forms, slender (male) forms, and intermediate (indifferent) forms being described. The indifferent forms are said to develop into males and females. This sexual differentiation is not certainly established, as the occurrence of conjugation is not beyond doubt. In the case of *Trypanosoma gambiense* the part of the life-cycle which occurs within the body of the invertebrate host is not known, but the process probably resembles that found in the case of *Trypanosoma lewisi* within the rat-flea, shown in Fig. 61.

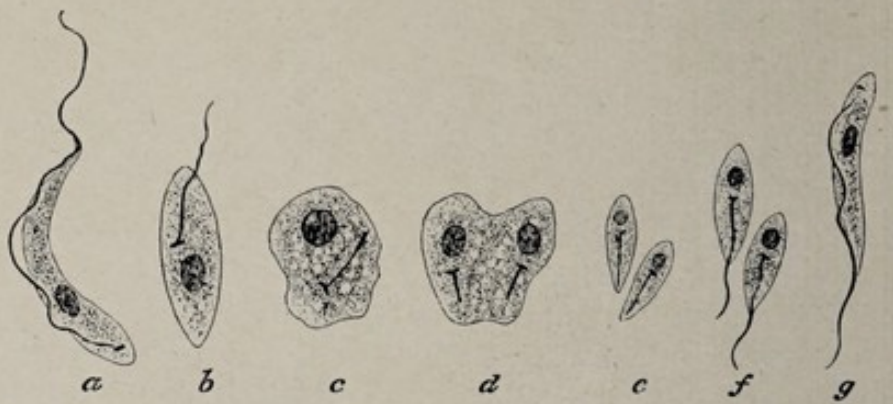


FIG. 61.—DEVELOPMENT OF TRYPANOSOMA LEWISI IN INSECT HOST. (MODIFIED FROM SCHWELLENGREBL AND STRICKLAND.)

Showing rounding off and loss of flagellum (*a-c*); fission and re-formation of elongated form (*d-g*).

Trypanosoma gambiense is transmitted to man by the tsetse-fly (*Glossina palpalis*). It has recently been affirmed that it may also be conveyed by *Glossina morsitans*, a closely allied species. The disease, trypanosomiasis, is endemic in West Africa, but has somewhat extended its range in recent years. The main symptoms are

gradually progressing somnolence and weakness, ultimately reaching a condition of complete lethargy. Enlargement of lymphatic glands usually occurs, and there is irregular pyrexia. Towards the

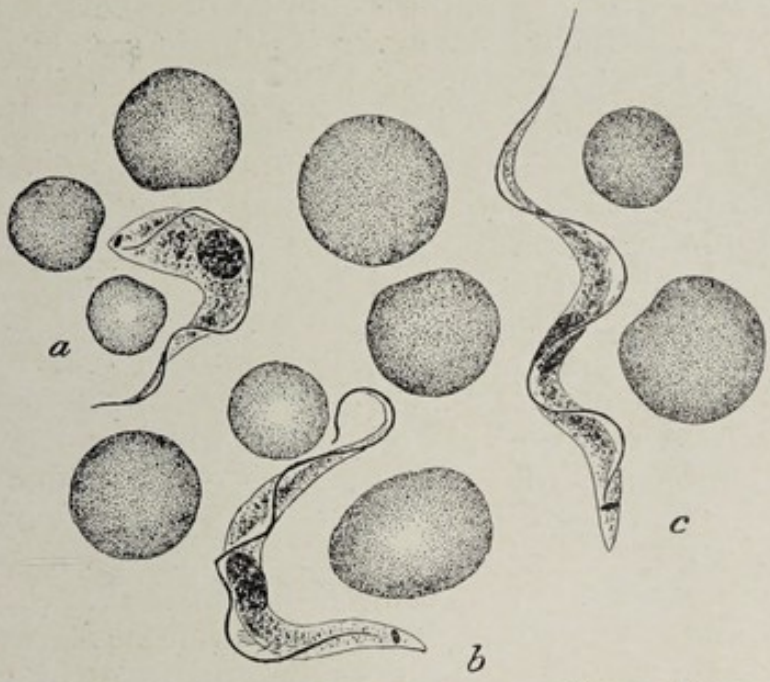


FIG. 62.—TRYPANOSOMA GAMBIENSE. (AFTER MINCHIN.)
a, stout form; *b*, intermediate form; *c*, slender form.

end tremors, choreïform movements, and actual convulsions may be seen. The disease appears to be invariably fatal. It is usually confined to the native population, but a few cases have occurred in Europeans. *Post mortem*, a condition of encephalitis, with accumulations of leucocytes around the cerebral vessels, is found.

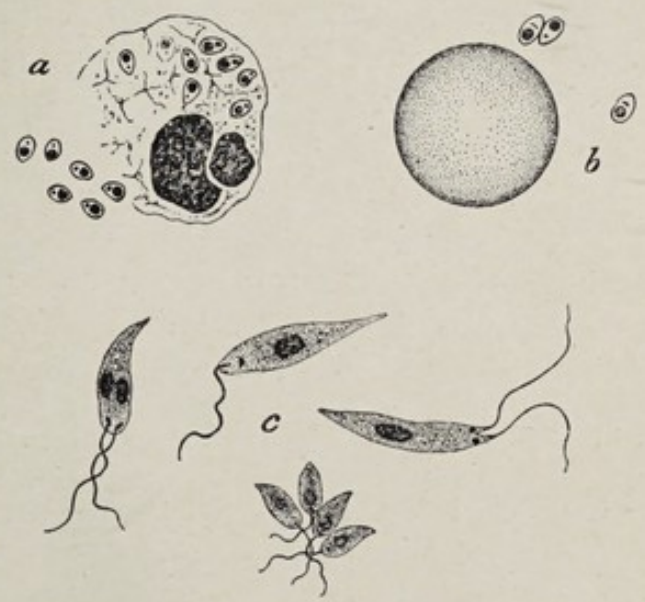


FIG. 63.—LEISHMANIA DONOVANI.
a, Leishman-Donovan bodies in leucocyte, some escaping; *b*, same bodies in blood; *c*, forms (resembling *Herpetomonas*) from a culture; two of these are dividing.

Leishmania donovani.—This parasite is found in the tropical disease, kala-azar, a form of continued fever, of remittent type, characterised by enlargement of the spleen, hæmorrhages, and dropsy. The organism can be cultivated outside the body in blood, prevented from clotting by addition of sodium citrate, and in its adult form, as seen in cultures, somewhat resembles a trypanosome, being elongated in shape, and possessing a tropho-nucleus and kineto-nucleus and a flagellum (Fig. 63, *c*). This last, however, does

not run along the whole length of the body, and is not attached by an undulating membrane, but is closely applied to a short portion of the organism, as in the genus *Herpetomonas*. Within the human body the parasite exists as minute oval bodies (Leishman-Donovan bodies), each possessing a large and a small nucleus ; these are found in immense numbers in the spleen of the patient, some free, but the majority enclosed within leucocytes or endothelial cells (Fig. 64, *a*, *b*). Multiplication takes place by binary or multiple fission. The mode of infection is unknown, but may possibly be by the bites of bugs (Rogers, Paton).

Closely allied parasites are found in the disease known as Oriental sore (Aleppo boil, Delhi sore, etc.), and are distinguished as *Leishmania tropica*, while a third variety found in children suffering from splenic enlargement is named *Leishmania infantum*.

Schizotrypanum cruzi.—This organism, which closely resembles the trypanosomes, but differs in its mode of reproduction (which gives it some resemblance to *Leishmania*), was found by Chagas in a fatal malady occurring in Brazil. The adult parasite resembles a small trypanosome, and may occur either in the erythrocytes or in the blood-plasma. Slender male and stout female forms occur, and conjugation takes place in the lungs, the organisms first uniting by their extremities to form a ring-shaped oökinete. The merozoites formed by its division enter the erythrocytes, and develop into adult forms. A form of multiplication of the parasites by schizogony (without conjugation) also takes place in the muscles, glands, bone-marrow, and central nervous system ; and by it enormous numbers of merozoites are formed, the masses of minute daughter-parasites resembling those of *Leishmania*. Infection with schizotrypanum is conveyed by the bite of the bug, *Conorrhinus* or *Lamus megistus*.

Other parasites belonging to the class Sporozoa have been described in man. Thus, Seidelin has found in patients suffering from **Yellow Fever** minute bodies situated in the red blood-corpuscles, somewhat resembling the organism *Piroplasma bigeminum*, which is responsible for the production of the disease of cattle known as red-water fever, and which is assigned to the Hæmosporidia. Yellow fever is conveyed by the bite of the mosquito (*Stegomyia fasciata*), and is not transmissible by direct infection from patient to patient. An incubation-period within the mosquito is necessary ; hence it would seem that a cycle of development takes place within the insect, as in the case of the malarial organism.

Bodies supposed to be parasites were found by Councilman and his assistants in the skin of patients suffering from **Smallpox,** and named *Cytoryctes variolæ*. A peculiar cycle of development is described, the organism being first extranuclear, and then entering the nucleus to undergo further changes. Somewhat similar parasites were described by Mallory in the skin of patients with **Scarlatina.**

A parasite, named by Minchin and Fantham *Rhinosporidium kinealyi*, is found in a peculiar affection of the nose, prevalent in India.

SPIROCHÆTES.

The exact biological position of these organisms is not yet determined. They were at first believed to be related to the hæmoflagellates (*trypanosomes*), and to possess an undulating membrane and blepharoblast. This relationship can hardly be maintained in view of later researches, and it becomes more probable that the spirochætes are closely allied to the bacteria. There is no evidence as yet that they are a stage in the development of a polymorphic organism, though this has been maintained by some observers.

Spirochætes are spiral thread-like organisms, which move chiefly by revolution on their long axis, like a corkscrew, but have also some flexibility and power of performing undulating and lashing movements. Considerable controversy has centred round their mode of multiplication—whether this is by transverse or longitudinal division. At present the view seems to prevail that both methods may be adopted, but the occurrence of transverse fission is best established in the case of the pathogenic varieties. In some of the larger forms, which are parasitic in mollusca, a complicated nuclear apparatus has been described, but it is doubtful whether this assertion is correct. In the small forms met with in disease dark granules may be seen in the substance of the organisms, which have been compared with nuclei. In other cases the whole body may appear broken up into a series of bead-like bodies. It is uncertain whether these last are involution-forms (degenerative), or point to a stage in development. Leishman has stated that *Spirochæta duttoni* breaks up into coccoid bodies within the body of its intermediate host, the tick, and it seems not unlikely that other spirochætes may break up into minute bodies resembling cocci or spores.

Conveyance of spirochætes from one patient to another by biting insects has been proved to occur in the case of *Sp. duttoni*, the parasite of African recurrent ("tick") fever, and in that of *Spirochæta gallinarum*, the infective agent in a disease of fowls. It is possible that *Spirochæta obermeieri*, the cause of relapsing fever, is conveyed by body-lice or bugs, but this is not satisfactorily proved.

The principal diseases of man associated with the presence of spirochætes are relapsing fever, a form of membranous sore-throat known as Vincent's angina, syphilis, and yaws. Spirochætes are also found in many gangrenous and ulcerative conditions, such as ulcerative granuloma of the pudenda, tropical ulcer of the leg, noma, and ulcerating tumours; in these maladies the organisms may be only accidentally present, living on the products of decomposition, and may have nothing to do with the original disease. All earlier attempts to cultivate spirochætes by the methods in common use yielded negative results. Noguchi, however, has recently succeeded in cultivating many varieties, including the *Spirochæta pallida*, by inoculating deep tubes of media containing ascitic fluid and a small

portion of sterile animal tissue, the whole being covered by a layer of sterile paraffin to insure anaërobic conditions.

Spirochætes appear to give rise in the patient's system to antibodies, like those by which bacteria are antagonised (*agglutinins, lysins,* etc.). They are very susceptible to the action of organic compounds of arsenic, especially dimethyl-diamido-arseno-benzol (Ehrlich-Hata).

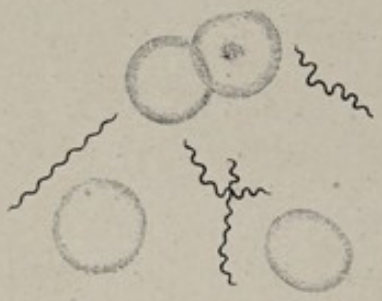


FIG. 64. — SPIRILLA OF RELAPSING FEVER WITH RED CORPUSCLES. (× 1,000.)

Spirochæta obermeieri (Fig. 64).—This organism, perhaps more correctly called *Spirochæta recurrentis,* was discovered by Obermeier in 1873. It is a sharply curved, corkscrew-shaped thread, 15 to 40 μ long, exhibiting quick gyratory or undulating movements. It is stained best by Giemsa's reagent, and does not retain the stain when treated by Gram's method. The organisms appear in the blood just before the commencement of an attack, and disappear with remarkable speed during the crisis. Metchnikoff states that during the apyrexial interval they accumulate in the spleen, where they are taken up by the multinucleated leucocytes. Soudakewitch has shown that the previous removal of the spleen enormously increases the mortality. Nothing is seen of the spirochætes till the relapse, when they return to the peripheral blood. All attempts to cultivate them have hitherto failed. The disease has been inoculated from man to man, and from man to apes (Carter, Koch). It is said that the blood is not infectious during the fever-free period, but that the splenic pulp is then capable of transmitting the disease. Possibly the usual mode of infection is by the bites of bugs or lice. The blood of convalescents has an agglutinative action on the spirochætes, and contains a body (copula or opsonin) capable of effecting the destruction of the organism in the presence of leucocytes.

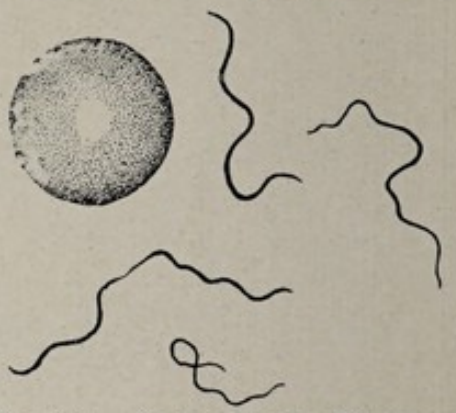


FIG. 65.—SPIROCHÆTA DUTTONI WITH BLOOD-CORPUSCLE FOR COMPARISON.

The spirochæte below to the left is dividing.

The organisms present in the forms of relapsing fever met with in America and in India closely resemble the *Spirochæta obermeieri,* but seem to be distinct species, since, while each produces immunity to a subsequent attack, they are not mutually protective.

Spirochæta duttoni.—This organism was found by Ross and Milne in the blood of patients suffering from so-called " tick fever " of Uganda. The disease is characterised by attacks of fever, with headache, pains in the limbs, vomiting, and prostration, separated by intervals of freedom from symptoms. Four or more of such

relapses may occur. The organism closely resembles *Spirochæta obermeieri*. Dividing forms may attain a considerable length, and show a thin uniting filament at the centre, where the division is about to occur (Fig. 65). The disease is conveyed by the bite of the tick, *Ornithodorus moubata*, which inhabits the huts of the natives. It would seem that the organism passes from the adult tick to its ova, and matures in the body of the second generation of these parasites, being then conveyed by their bite to another human host. Leishman has found coccoid bodies in the bodies of ticks, which he believes to be a stage in the life-history of the spirochæte. Presumably infection is conveyed by inoculation of this minute form of the spirochæte.

Spirochæta vincenti.—This organism is found in certain cases of membranous sore-throat along with an organism known as the *Bacillus fusiformis*. It is uncertain whether these spirochætes and bacteria are stages in the life-history of the same organism, or whether they are separate organisms living in a condition of symbiosis, though there is some evidence pointing in the former direction. Vincent's angina is a necrotic (ulcerative) process accompanied by formation of false membrane. The spirochætes and fusiform bacilli may also be found in abscesses secondary to the ulcers. Very similar spirochætes are found at times in ulcerative processes in other parts of the body, and many spirochætes exist in the mouth in conditions of gingivitis and stomatitis, as well as in carious teeth (*Spirochæta buccalis, Spirochæta dentium*). The relationship between the various forms is uncertain.

Spirochæta pallida.—The special attention paid to spirochætes in recent years dates from the discovery by Schaudinn and Hoffmann of a slender corkscrew-shaped organism in cases of syphilis. This spirochæte is some 20 μ in length by μ $\frac{1}{4}$ or less in breadth. It has even, closely-wound curls, and is furnished with terminal processes, which resemble flagella, but probably consist of prolongations of the outer sheath of the organism. Examined in the dark field of the microscope it is seen to be sluggishly motile, progressing with a twisting movement like a corkscrew.

*Spirochæta pallida** is found almost invariably in cases of syphilis, both in the secretion of the primary chancre (Fig. 66), in the enlarged glands in the groin, in the blood in the secondary stage, especially in the cutaneous lesions, and in congenital syphilis. In gummata only degenerative forms of the parasite are said to occur. The causal relation of the organism to syphilis is held to be proved by its constant presence in the disease, and in lesions produced by inoculation of syphilitic material in animals, and by its absence in all other conditions. A lesion resembling a syphilitic sore can be produced in apes by inoculation with material from a human

* Owing to the regular character of the spiral twist exhibited by *Spirochæta pallida*, the presence of terminal filaments and the absence of an undulating membrane, Schaudinn placed it in a separate genus, and called it *Treponema pallidum*. This distinction is of very doubtful validity.

patient, and the spirochæte is found in the tissues of the animals. It has also been found alive in rabbits, dogs, and other animals similarly inoculated, although no species except monkeys is supposed to be susceptible to true syphilis. The lesions produced by corneal or intratesticular inoculation in rabbits are, however, constant and typical in character.

FIG. 66.—SPIROCHÆTA PALLIDA (*a*) AND SPIROCHÆTA REFRINGENS (*b*), WITH LEUCOCYTE.

The *Sp. pallida* is best stained in smears from the primary sore with Giemsa's stain (azure and eosin); in the tissues it is demonstrated by Levaditi's method of impregnation with nitrate of silver, and subsequent reduction with pyrogallic acid. For diagnostic purposes the examination of unstained preparations by means of dark-ground illumination affords the readiest and most certain means of detecting this organism.

Spirochæta pertenuis.—An organism morphologically almost exactly resembling *Spirochæta pallida* was found by Castellani in cases of yaws (framboesia tropica). This malady is characterised by a primary lesion, followed by secondary symptoms in the form of fever and a generalised cutaneous eruption. Castellani also recognises a tertiary stage. Much controversy has taken place as to the identity or diversity of this disease and syphilis. The balance of evidence is in favour of regarding them as two distinct but closely allied affections. Inoculation of animals with either spirochæte produces immunity to further infection by this form, but not by the other.

Spirochæta balanitidis.—The disease of the external genitals known as balanitis or balano-posthitis is associated with the presence of spirochætes, and these are stated to be a distinct species, *Spirochæta balanitidis*. Some writers, however, regard these organisms as identical with *Spirochæta refringens*, a form usually found along with *Spirochæta pallida* in the primary lesion of syphilis, and regarded as saprophytic (Fig. 66).

Spirochæta ictero-hæmorrhagica.—A spirochæte has been recently described by Inada, Ido, Oki, Kaneko, and Ito, as occurring in the endemic and epidemic jaundice which prevails in the western part of Japan. The same organism has still more recently been demonstrated in cases of a similar type occurring among the troops in France by Martin and Pettit, and by Stokes, Ryle, and Tytler. The disease is characterised by fever, vomiting, headache, and pains in the back of the limbs, associated with varying degrees of jaundice

and petechial hæmorrhages. A hæmorrhagic form of herpes labialis seems to be especially common. The spirochæte has been found in the patient's blood, in the intestinal wall, in the adrenal glands (in one case), and in the kidney. The disease is transmissible to the guinea-pig, and in this animal the spirochætes may be demonstrated in the kidney and the liver, and sometimes in the adrenal glands, spleen, lymph nodes, and heart-muscle. In the blood of the guinea-pig they are often fairly numerous. The spirochæte is of about the same thickness as the *Spirochæta pallida*, and of about the same length. Its curves, however, are very irregular, some forms being nearly straight, or showing only wide undulations. With dark background illumination, they are less refractile than *S. pallida* or *S. refringens*. The typical corkscrew movement is rarely seen, the motion of the organisms being usually of a slow and undulating type. A definite cross-striation is usually seen.

CHAPTER XII

IMMUNITY

CERTAIN diseases which are common in some species of animals are practically unknown in others very closely allied to them. Thus, tuberculosis is common in pigs and cows, but excessively rare in sheep, goats, horses, and asses. Mice fall a ready prey to anthrax, while rats escape unharmed. Accordingly, pigs and cows are said to be susceptible to tuberculosis ; while sheep, goats, horses, and asses, are, on the contrary, said to be immune against it. The exact conditions on which this susceptibility or immunity depends are unknown. To distinguish it from the acquired form, it is known as natural or inherited immunity. When an animal is only slightly susceptible, it is often termed refractory or resistent.

Similarly, some human races are immune to diseases which readily affect others ; thus, negroes are to a great extent immune to yellow fever, while the white races are susceptible. Again, certain individuals escape a given disease, though repeatedly exposed to infection, while others contract it.

This inborn tendency to resist infection with a given organism may therefore be a characteristic of a species, a race, or an individual ; but it is very difficult to exclude the possibility that racial and individual immunity really belong, at least in many cases, to the acquired type. Natural immunity is seldom if ever absolute.

Some specific diseases tend to recur again and again in the same individual. Of these, pneumonia is a prominent example. Other diseases seem to show a precisely opposite tendency. To have suffered once from one of them is to have secured almost certain freedom from a second invasion. Freedom thus insured is known as acquired immunity. It is by no means certain how long such immunity lasts, and in man there are no means of definitely ascertaining its duration. Indeed, there is good reason for believing that pneumonia is as certainly followed by a period of immunity as is smallpox, but that the immunity lasts a much shorter time in the former disease than it does in the latter.

Just as an attack of a disease may protect against subsequent infection, so various methods of artificial inoculation may produce immunity. Two distinct methods of procedure may be adopted. In the first, the micro-organisms themselves, living or dead, or some

chemical product derived from them, form the material for inoculation. The result obtained in this case is comparable with that which follows actual infection with the organism in question. A series of changes are initiated in the body, which, in successful cases, result in an increased resistance to any subsequent invasion by that organism. This variety of immunity is usually of considerable though varying duration, and depends upon the activity of the tissues. It is known as active immunity. In the second method of conferring artificial immunity, the substance inoculated consists of the serum of an animal previously treated in the manner described above, or of a patient who has recovered from an actual infection. The increased resistance obtained in this case depends upon the presence in the tissues of the protective substances which existed in the serum inoculated, the tissues of the recipient playing a passive rôle. Hence the decreased susceptibility which results in this case is known as passive immunity. It is usually of short duration.

All varieties of immunity are specific. Thus, an attack of a given disease may greatly lessen the chances of a subsequent attack of that disease, but has little or no influence on other infections. Similarly, artificial immunity is strictly specific against the organism employed.

The study of immunity, then, resolves itself into an attempt to explain these various phenomena. In the course of the research which has been carried out along these lines, various other phenomena have been observed, which would appear to have little or no relation to actual disease, but which possess obvious points of similarity to processes which have been demonstrated to occur in actual infections. The detailed study of these reactions, in which it is often possible to control the experimental conditions far more strictly than can be done when dealing with changes occurring in the animal body, has yielded results of the greatest interest.

Our knowledge of this vitally important subject is as yet so incomplete, and the theories advanced to explain the phenomena observed are, in many cases, so tentative in character, that it must be realised at the outset that, while we are in possession of a large mass of accurate and repeatedly confirmed observations, their interpretation, and especially the application of such an interpretation to naturally occurring infection, is still a matter of active controversy.

It is, indeed, as the result of prolonged dispute that our knowledge of immunity has been acquired. Experiments, which were planned by their originators to demonstrate the truth of a particular theory, have often proved capable of an entirely different interpretation in the light of further knowledge; and the long series of accurate investigations which have been carried out to confirm or refute the statements of particular investigators have resulted in the acquisition of a foundation of unquestioned facts on which all future theories must be built.

As our knowledge of immunity has increased, so the facts which need explanation have multiplied, and the simple theories which

were advanced in early days to account for the phenomena of inherited and naturally acquired immunity could not survive the artificial production of a similar condition, and the extended knowledge which followed from it. Among such early theories may be included the " exhaustion theory " of Pasteur, who suggested that in the initial infection with a given organism the particular foodstuffs necessary for its growth were used up, and that, when subsequently introduced into the body, it was unable to multiply; and the " retention theory " of Nencki and others, who suggested that the organism during its initial attack produced substances which inhibited its further growth, as is indeed known to be the case in test-tube experiments, and that it was the retention of these inhibitory substances which conferred subsequent immunity. It will be noticed that a common feature of these two views is the passive rôle attributed to the tissues, and the same is true of the majority of the earlier theories.

Very soon, however, the active part played by the body tissues was recognised, and almost immediately two hostile schools came into existence. One, led by Metchnikoff and his co-workers, attributed the phenomena of immunity entirely to the activity of the body-cells, and especially of the leucocytes. The other, including Nuttall, Büchner, Flugge, and many others, held that increased resistance depended upon specific properties acquired by the body fluids, and especially by the blood-serum. Thus were founded the " cellular " and " humoral " doctrines of immunity, and for many years the activities of the great majority of investigators were devoted to upholding the observations or deductions of one or other school. It is only within recent years, and especially since the increase in our knowledge concerning the processes underlying the phenomenon of phagocytosis, that the two theories have been harmonised and the controversy has ceased to be of importance.

The cellular theory of immunity was advanced by Metchnikoff as the result of extensive observations on infection occurring in the lower forms of living animals. In these studies he was able to demonstrate that a phenomenon common to all such infections was the ingestion and subsequent destruction of the invading parasites by certain wandering cells present in the tissues, and he believed that this ingesting action, or phagocytosis, was the essential factor in combating the microbial attack.

The theories put forward by the humoral school were based on the observation made by Nuttall, that normal blood possessed the power of destroying bacteria, and that this power remained when the plasma or serum was freed from all cellular elements. The attitude adopted by Büchner, Flugge, Nuttall, and other exponents of the humoral school, was that Metchnikoff and his co-workers had never conclusively demonstrated the phagocytosis of living organisms, and they suggested that the essential nature of this process was the removal of bacteria which were already killed or injured by the body fluids. The reply of the upholders of the cellular doctrine was that, in so

far as the body fluids possessed antibacterial properties, they derived them from substances liberated by the phagocytes themselves.

It is impossible in a short summary such as the present to deal with the stages of this controversy on any historical basis, or to discuss at length the secondary dispute that arose, during the researches into the properties of the blood-serum and body fluids, between Ehrlich and his school on the one hand, and Bordet and his followers on the other. It may, however, be noted that the careful examination of the properties of normal and immune sera yielded results of such interest and importance that the majority of workers in this field of research were for many years occupied with this aspect of the subject, and the revival of general interest in the phenomenon of phagocytosis, as well as the realisation of the inadequacy of either the cellular or humoral theory taken alone, dates from the investigations into the rôle played by the blood and body fluids in this process, undertaken by Leishman, Wright and his co-workers, Neufeld, and others, in more recent years. No adequate comprehension of the subject of immunity is possible without some knowledge of the rival theories which have from time to time been advanced, and of the experimental evidence which has been put forward to uphold or refute them.

The various phenomena exhibited by the blood-serum and body fluids of normal and immunised animals will now be considered in more detail.

THE TOXINE-ANTITOXINE REACTION.

As mentioned above, certain micro-organisms—*e.g.*, the *B. diphtheriæ* and the *B. tetani*—possess the property of forming in suitable culture media very powerful exotoxines. These exhibit characteristics which differentiate them very sharply from the endotoxines which constitute the poisonous element in most bacterial infections. In the first place they are infinitely more powerful—at least, as found in cultures ; and in the second they give rise, when inoculated into animals, to the formation of neutralising substances, or antitoxines, the presence of which may be demonstrated in the blood-serum.

If an animal be inoculated with gradually increasing doses of one of these exotoxines, its serum gradually develops the following powers : (*a*) When mixed with the toxine outside the body, it will neutralise it, so that subsequent inoculation of the mixture into another susceptible animal will produce no ill effects. (*b*) When inoculated in sufficient amount into an animal previously injected with a dose of the corresponding toxine, or of the micro-organism which produces it, or into a human being infected with that micro-organism, it will counteract the toxic effects and thus cut short the disease, provided that too long an interval has not elapsed between the initial infection or inoculation and the administration of the antitoxic serum. (*c*) When an injection of the serum is followed by

an injection of the corresponding toxine, or when the serum is administered to a person who has been in a position to contract the disease, it acts prophylactically and prevents the appearance of the toxic symptoms.

The greater part of our knowledge concerning the mechanism of the toxine-antitoxine reaction has been acquired during the studies on diphtheria antitoxine which followed the discovery of this substance by von Behring. Attention has mainly been directed to the neutralisation of toxine by antitoxine *in vitro*, since the experimental condition can be much more accurately controlled under these circumstances. It was early shown that very definite quantitative relations exist between the amounts of toxine and antitoxine which just give complete neutralisation. At first it was believed that these relations resembled those existing between a strong acid and a strong base, so that a given amount of antitoxine always neutralised the same amount of toxine, and equal multiples of these amounts likewise produced neutralisation. This was, however, soon shown not to be the case. It was found that a considerable degree of dissociation of the toxine-antitoxine combination could be brought about by appropriate means for some time after the constituents had been brought together, and certain irregularities were observed in the quantitative relations existing when varying amounts of toxine were added to a constant amount of antitoxine. The great therapeutic success obtained by the use of antitoxic sera in the treatment of diphtheria led to an attempt to standardise the various sera produced, and in the course of these investigations certain definite standards of measurement came into use. Thus, the minimal lethal dose of toxine (M.L.D.) was defined as that amount of toxine which sufficed to kill a guinea-pig weighing 250 grammes in four days, and the unit of antitoxine was defined as that dose which would exactly neutralise 100 M.L.D. of toxine.

In standardising various toxines against antitoxine, mixtures were prepared which contained varying amounts of the toxine, together with one unit of antitoxine. Such a mixture which failed to produce any effect upon injection into a test guinea-pig was said to contain the *limes nul* (L 0) dose of toxine. The accurate determination of this limit was, however, found to present considerable difficulties, and hence another standard mixture was adopted—namely, that which, together with one unit of antitoxine, contained sufficient toxine to leave unneutralised sufficient of the latter to produce death of the test guinea-pig in four days (*i.e.*, to produce the same result as one minimal lethal dose of toxine). This amount of toxine was known as the *limes tod* (L+) dose. Now, from definition it should follow that, were the conditions similar to those existing between a strong acid and a strong base, for any given toxine L+ minus L 0 should equal 1 M.L.D. As a matter of fact, it was found that this never occurred. The actual difference between L+ and L 0 was always many multiples of the M.L.D., and the exact figure varied considerably.

In attempting to explain this phenomenon, Ehrlich was first led to assume the existence in the toxine molecule of two distinct groups: the toxophore group, which is the actively poisonous element; and the combining or haptophore group, which actually combines with the molecules of the cell protoplasm when the toxine gains entrance to the tissues, and which similarly unites with the antitoxine during neutralisation (Fig. 67). Now, it had been previously demonstrated that a toxine deteriorated more or less rapidly on storage, and that this deterioration could be brought about much more rapidly by subjecting it to moderate heat; but it was also found that, although the toxic effect had been considerably diminished or altogether eliminated under these conditions, the power of uniting with antitoxine remained unaltered. Ehrlich accounted for this by assuming that the toxine molecules had become converted into toxoids—that is, into molecules the toxophore groups of which had been altered or destroyed, while the haptophore groups had remained unchanged. He further assumed the existence of toxoids which possessed varying affinity for antitoxine, and which he designated as prototoxoids, syntoxoids, and epitoxoids, according as they possessed an affinity for antitoxine greater than, equal to, or less than, that possessed by the toxine itself. The existence of these hypothetical epitoxoids enabled him to offer an explanation of the phenomenon described above, by supposing that in such a toxine-antitoxine mixture the epitoxoids are left free because of their small affinity for antitoxine; and hence it is only after sufficient toxine has been added to replace the epitoxoids already in combination, and to leave one M.L.D. of true toxine free, that the standard result of death in four days can be produced. The peculiar symptoms which often followed the inoculation of these non-lethal mixtures led Ehrlich later to suggest the existence of substances which he called toxones, possessing the same diminished affinity for antitoxines as the epitoxoids, but in addition having a special or modified toxophore group.

Arrhenius and Madson offered an explanation of the toxine-antitoxine reaction based on the assumption that the neutralisation effected resembled that produced by the action of a weak acid on a weak base, and hence obeyed the laws of mass action, free toxine, free antitoxine, and toxine-antitoxine combination coexisting in any given mixture, the proportions of each depending on the concentration of the various constituents.

Although this explanation offers certain definite advantages over that which likens the interaction of toxine and antitoxine to that of strong acid and strong base, and over the purely hypothetical explanation of Ehrlich, both alike fail to explain certain phenomena which have been repeatedly demonstrated.

It was shown by Danyz that the toxicity of a toxine-antitoxine mixture varied not only with the amounts of the two constituents present, but with the manner in which they were brought together. Thus, if the toxine were added to the antitoxine in several fractions

at considerable intervals of time, the mixture was much more toxic than if all the toxine were added at once.

Similar peculiarities have been shown to occur in the interaction of certain colloids, and the suggestion brought forward by Bordet,

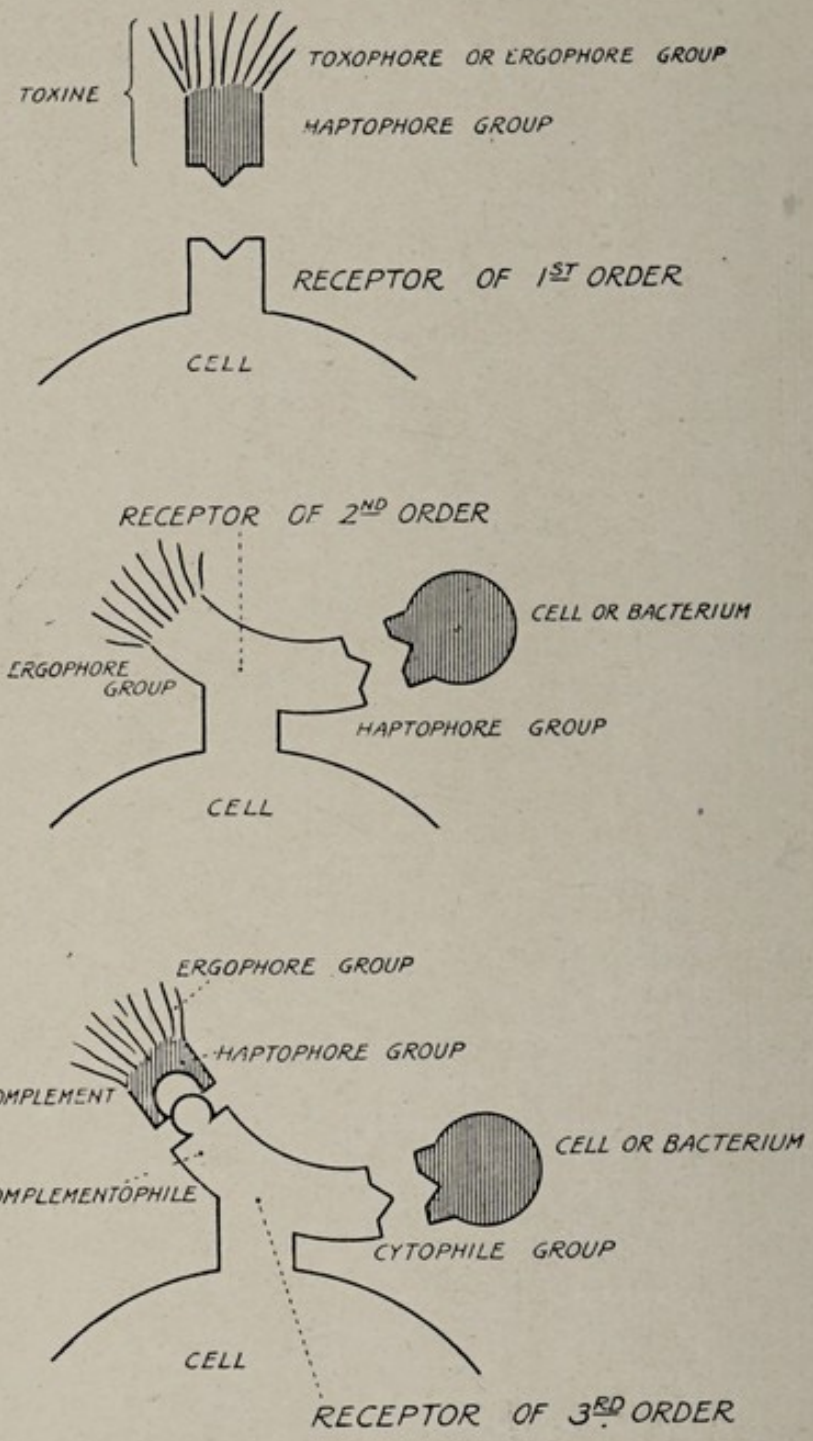


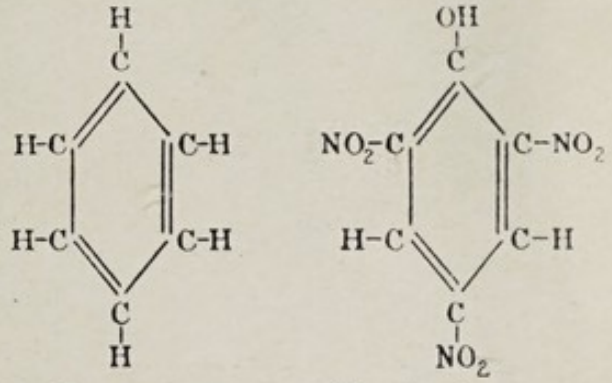
FIG. 67.—ILLUSTRATING EHRLICH'S SIDE-CHAIN THEORY.

Craw, and others, which would bring the toxine-antitoxine reaction into the group of colloidal phenomena, would seem to afford the best and least cumbersome explanation of the observed facts so far put forward. It is, moreover, supported by the growing tendency to accept similar explanations for other immunity reactions.

EHRLICH'S SIDE-CHAIN THEORY.

It was the study of diphtheria antitoxine which formed the foundation on which Ehrlich built his celebrated side-chain theory. The majority of the earlier theories of antitoxine formation regarded this body as being in some way produced from the toxine itself, but the enormous quantitative differences which could be shown to exist between the toxine injected and the antitoxine produced soon rendered this idea untenable. Many experiments pointed unmistakably to some activity of the body-cells as the underlying factor involved, and it was with this fact in view that Ehrlich elaborated his theory of immunity.

He started by assuming that the processes involved were probably similar in many ways to those which occurred during the normal metabolic activity of the cell, since we must suppose that the toxine enters into some form of chemical union with the cells before producing its harmful effects. We know that the protoplasmic molecule is extraordinarily complex, and Ehrlich suggested that it is essentially composed of a central mass or nucleus which remains stable throughout a series of combinations and resolutions, and gives its individual character to the cell or tissue of which it is a part, and of outlying atom-groups which enter into combination with other radicles. He found an analogy for this conception in many of the more complex organic compounds. Thus, the benzine ring remains intact throughout a series of compounds of which trinitro-benzine may serve as an example (Fig. 68). It is these outlying groups or " side-chains " which, according to Ehrlich, form the means by which nutritive substances become incorporated into the cell protoplasm, and he has hence named them " receptors." He believes that it must also be with these receptors that the toxine molecule unites, and he would explain certain instances of immunity to toxines by supposing an absence of suitable cell-receptors. When, however, side-chains of the necessary type are present, the toxine, by its haptophore group, unites with them. If the amount of toxine present be above a certain limit, the result is acute poisoning and death of the cell ; but if sublethal doses are administered the result is different. In this case certain of the cell-receptors are rendered useless for normal metabolic processes, since they are in combination with the toxine molecule, which, being of an abnormal nature, does not undergo the subsequent changes which would occur in the case of a molecule of suitable food material. The cell therefore



Benzene. Trinitro-benzene.

FIG. 68.—CHEMICAL FORMULÆ OF BENZENE AND TRINITRO-BENZENE, SHOWING CENTRAL RING AND SIDE CHAINS.

produces fresh receptors to take the place of those thrown out of action, and Ehrlich assumes that, if the stimulus is long continued or repeated, as by successive injections of toxine, the cell will produce fresh receptors greatly in excess of the number necessary for its actual use, thus obeying the law which Weigert has shown to hold for many physiological and pathological processes. This excess of receptors leads eventually to their being shed off from the cell and appearing free in the body fluids, and they constitute the antitoxine, which acts by uniting with the haptophore group of the toxine and so preventing its combination with the cell (Fig. 69).

This is the simplest example of the side-chain theory of immunity, which has been elaborated by Ehrlich and his co-workers, as need arose, to cover almost the whole field of observed phenomena. The receptors are in this case simply atom-groups which enable certain other molecules to enter into chemical union with the cell protoplasm, and they are called receptors of the first order (Fig. 67).

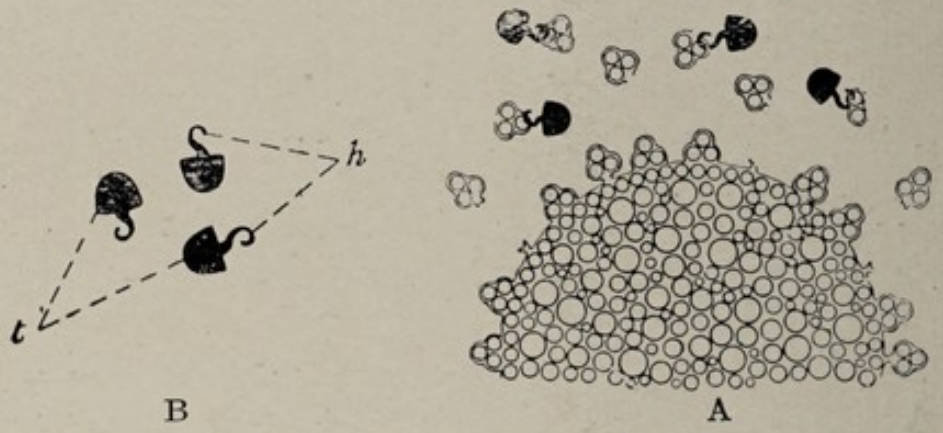


FIG. 69.*—DIAGRAM ILLUSTRATING FORMATION AND ACTION OF ANTITOXINE.

A, cell with receptors increased in number; some of these have been cast off into the circulation, and are uniting with molecules of toxine. B, toxine, showing (*h*) haptophore and (*t*) toxophore groups.

It would seem to follow naturally from these conceptions that the production of antitoxine should be a function of the actual cells which are attacked by the toxine. This has in no instance been conclusively proved to be the case, and it has been argued by certain members of the Ehrlich school that it is not an essential consequence of the side-chain theory.

The development of Ehrlich's extremely ingenious conception to meet the new experimental facts which have since been demonstrated will be considered when dealing with the particular phenomena concerned. It will be noted that the theory fails in some cases to explain the facts, and in many others it suffers from over-elaboration. There is, indeed, a growing tendency towards the acceptance of the ideas put forward by Bordet and his followers, at least in so far as the serum reactions are concerned. It should,

* Figs. 69, 70, 72 and 73, are taken, by kind permission of Messrs. Cassell and Co., the publishers, from the book on "Serums, Vaccines, and Toxines, in Treatment and Diagnosis," by Bosanquet and Eyre (1904).

however, be borne in mind that Ehrlich's theory possesses certain points of advantage, especially as an attempt at explaining the extreme specificity of immunity phenomena, nor should it be forgotten that it was on this foundation that Ehrlich based his researches on specific chemo-therapy, which have yielded such brilliant results.

BACTERIOLYSIS.

As mentioned above, the foundation of the humoral theory of immunity was the observation that blood-serum, freed from all cellular elements, had the power of destroying bacteria. The earlier experiments of Nuttall and of Büchner also established that this destructive power was unstable, tended to disappear on storage, and could be rapidly removed by moderate heat (50°-60° C.).

Pfeiffer, in his experiments on cholera immunity, provided the next important advance in our knowledge of this phenomenon. He showed that guinea-pigs which had recovered from an infection with the cholera vibrio could withstand a subsequent intraperitoneal injection of a living cholera culture in amounts which were fatal to normal control animals. By periodical examination of the peritoneal exudate, he was able to demonstrate that the actual changes which occurred consisted in the swelling, degeneration, and final solution, of the vibrios.

In further experiments he demonstrated that the immunity could be transferred from a treated to a normal guinea-pig by the intraperitoneal injection of serum taken from the immune animal, and that this serum was just as potent after being heated to 50°-60° C. for a period sufficient to destroy its bactericidal power. He was therefore inclined to assume the presence of some special cellular activities in the living tissues of the animal, since it seemed impossible to attribute the lysis entirely to the heated serum. He was, however, able to show that the immunity in the treated guinea-pigs and in those animals which had been rendered practically immune by the injection of their serum was strictly specific against the cholera vibrio. Moreover, he demonstrated that the lytic action was the essential factor in the immunity conferred, since the fact that there was no increased immunity to the toxic action of lethal doses of dead vibrios proved that no antitoxine was formed.

Bordet soon afterwards repeated Pfeiffer's experiments in the test-tube, and brought out the following fundamental points: Lysis occurred when fresh serum from an immunised animal was added to the bacterial suspension. It failed to take place if the serum was previously heated to 50°-60° C. for thirty minutes. It consistently occurred if to such a mixture of vibrios and heated immune serum a little fresh normal serum, from any source, was added. The reaction was specific, and the specificity rested in some substance present in the immune serum. Bordet, moreover, extended his researches to the lysis of red blood-corpuscles and of other cells by the sera of normal and of immune animals, and

showed that the same principles held good here also. Figs. 70, 71, and 72, illustrate diagrammatically the essential points involved, taking the case of the lysis of fowl corpuscles by the serum from an immunised rabbit.

These experiments were of the greatest importance, for they first clearly demonstrated that two substances were necessary to produce lysis: the first, heat-stable, specific, occasionally present in normal sera, but always produced or increased as the result of active immunisation; the second, thermolabile (*i.e.*, destroyed by moderate heat), non-specific, present in normal sera, and undergoing no in-

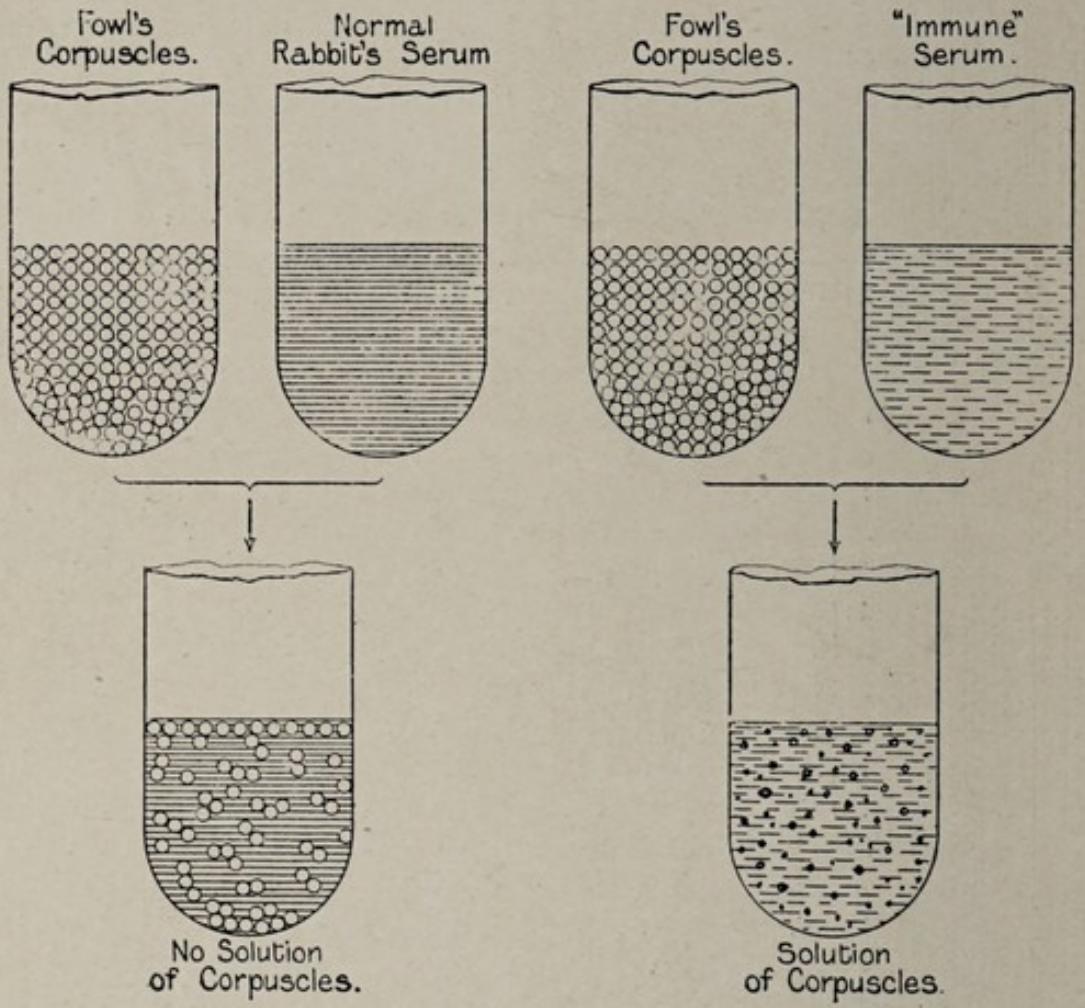


FIG. 70.—DIAGRAM ILLUSTRATING PHENOMENA OF HÆMOLYSIS.

crease in immunised animals. The first of these substances has received various names, such as sensitising substance, amboceptor, copula, immune body, and antibody. The second, active, thermolabile substance, present in normal serum, has been designated alexine or complement. The terms antibody or immune body, and complement, are those which are now most generally employed.

The demonstration by Bordet of the essential similarity of bacteriolysis and hæmolysis led to extensive investigation into the latter phenomenon, since the results were here much more easily observed.

Ehrlich and Morgenroth initiated a long series of experiments designed to interpret the observed results in terms of the side-chain theory. With this object in view, they elaborated the initial conception of the cell-receptors by introducing more complex types. One of these, referred to by them as a receptor of the third order (Fig. 67), was endowed with two groups of the haptophore type. One of these, the cytophile group, was supposed to combine with food substances, etc., during the normal life of the cell, and with foreign cells or invading bacteria during immunisation or infection. The other, the complementophile group, combined with the haptophore group of the complement, and hence linked this substance to the cell or bacterium to be acted upon (Figs. 67 and 73). The mechanism of excessive receptor production, and the eventual shedding of receptors into the blood-stream, was similar to that described above in the case of the production of antitoxine.

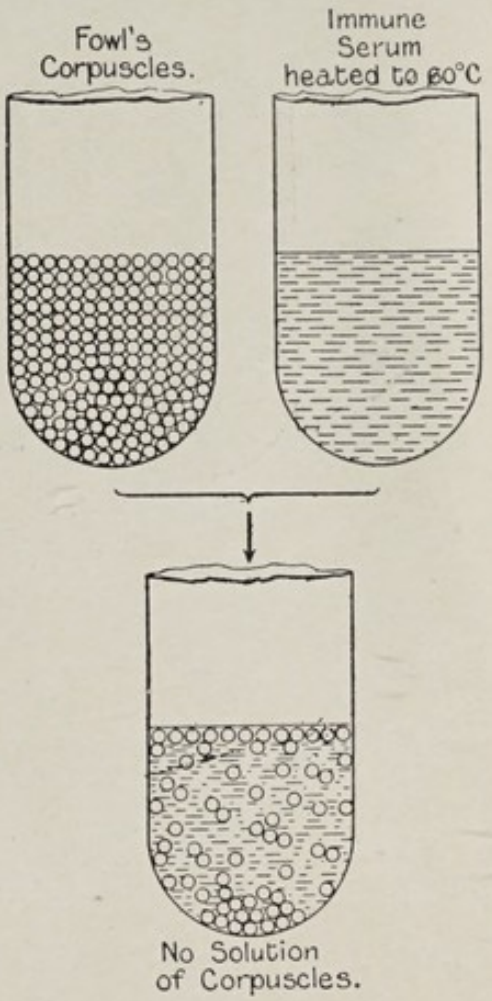


FIG. 71.—DIAGRAM ILLUSTRATING PHENOMENA OF HÆMOLYSIS.

The fundamental experiments upon which this conception was based were the following: To two tubes were added, in the one case a suspension of red cells and some heated immune serum; in the other, the red cell suspension and some fresh normal serum containing complement. These tubes were then incubated at 37° C., when no hæmolysis occurred. On centrifugalisation the corpuscles were sedimented, and a clear supernatant fluid remained. It was found that if the deposit from the tube containing the immune heated serum were resuspended in saline, and some fresh normal serum added, lysis occurred on further incubation. If to the supernatant fluid from this tube fresh red cells and some complement were added, no hæmolysis occurred when the tube was again incubated. It followed that the hæmolytic antibody had combined with the red cells and been removed with them. In the case of the tube which originally contained red cells and complement, it was found that the deposited corpuscles, on resuspension in saline, were not lysed by the addition of heated immune serum containing hæmolytic antibody; whereas, if further red cells and heated immune serum were added to the supernatant fluid from this tube, complete lysis resulted. It followed that the complement did not directly

combine with the red cells, but only after these had been sensitised by the hæmolytic antibody or copula.

Now, the main point of contention between the Ehrlich school on the one hand and Bordet and his supporters on the other has been the nature of this sensitisation. Ehrlich has consistently asserted that the hæmolytic antibody is an amboceptor—*i.e.*, it has two groups, one of which combines with the cell, the other with the complement. This view is diagrammatically represented in Figs. 67 and 73. Bordet has throughout favoured an explanation which

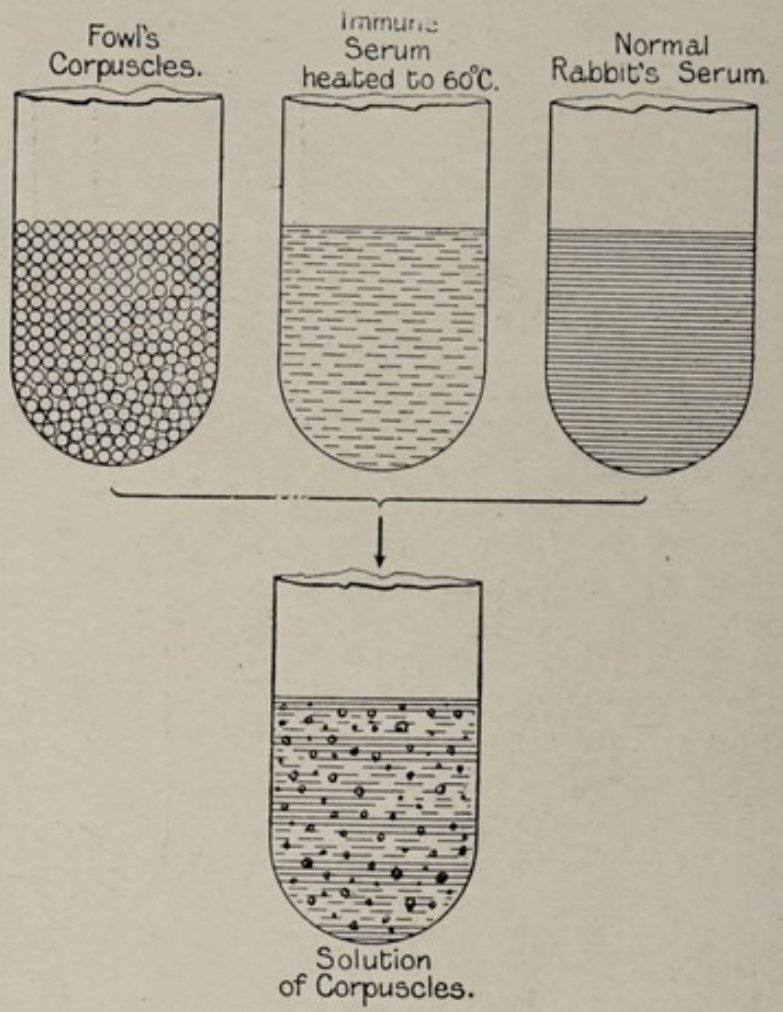


FIG. 72.—DIAGRAM OF HÆMOLYSIS.

brings the process more into line with adsorption phenomena. He regards the hæmolytic antibody as in some way sensitising the cell, so that the complement can combine with it. This view is diagrammatically represented in Fig. 74.*

The controversy hinges around the proof of the existence of the

* It will be noticed that, in the various diagrams used to illustrate the immunity reactions, uniform symbols have not been employed. The symbols in Fig. 67 are those adopted by Ehrlich and his school, and have become classical. Those employed in Figs. 69, 73, 74 and 79, differ from these, and in some cases from each other; but they all illustrate the essential points, and the lack of uniformity will help the student to realise that they are symbols only.

complementophile group of the amboceptor, and it has more than an academic interest; for, could Ehrlich's hypothesis be proved, many definite quantitative relationships would follow. It is impossible to discuss the evidence bearing on this point, but it may be stated that Ehrlich's hypothesis has never been satisfactorily proved, and that all the more recent studies have lent

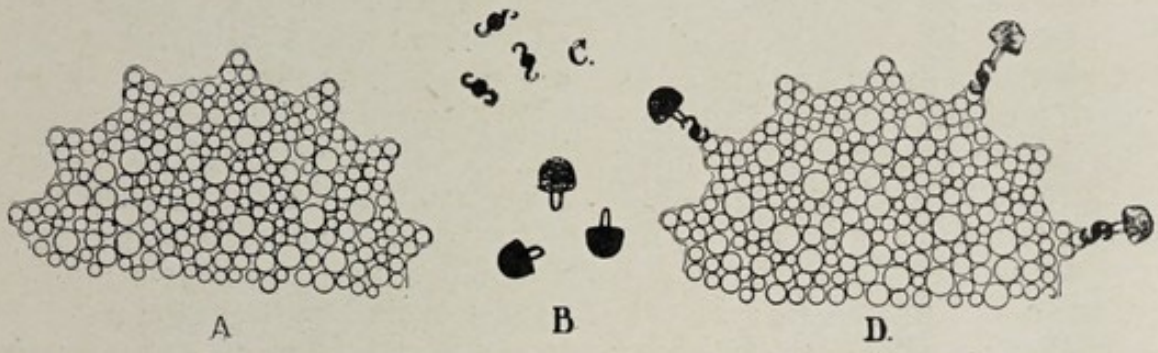


FIG. 73.—DIAGRAM ILLUSTRATING ACTION OF ALEXINE AND COPULA.
A, cell or corpuscle with side chains or receptors; B, complement; C, copula; D, cell with complement united by copula to its receptors.

support to the view that it is in the laws governing the interaction of colloids that we must seek for an explanation of this and other immunity reactions.

The Nature of Complement.—In the preceding paragraphs complement or alexine has been alluded to as the active substance present in normal serum, which is unstable, thermolabile, non-

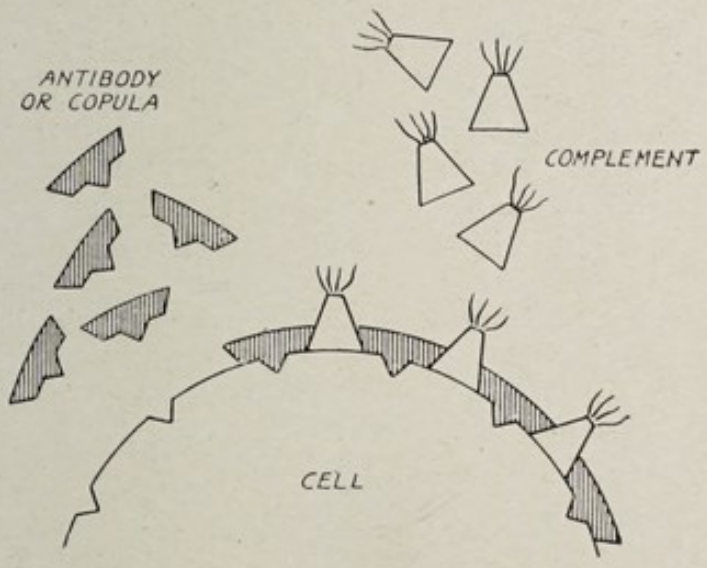


FIG. 74.—DIAGRAM ILLUSTRATING BORDET'S THEORY.

specific, and produces certain effects in the presence of a specific sensitiser or antibody. A large amount of work has been devoted to attempts to discover the actual nature of this important body. It may, however, be said at once that we know little or nothing as to its chemical nature, and can, indeed, only recognise its presence by its activity. In many ways it closely resembles a ferment, but

it shows one striking difference. It is used up in the course of the reaction in which it takes part, and apparently disappears. This fact is not admitted as strictly correct by all observers, although the actual experimental results are not disputed, and recent careful analysis of the processes in question have tended to give increased support to the view that complement is of the nature of a ferment.

Other recent experiments have resulted in the observation that it is possible, by dialysis and certain other means, to obtain a globulin precipitate from a complementary serum which apparently contains a portion of the complement itself. If this precipitate be separated from the supernatant fluid and redissolved in normal saline, while the isotonicity of the supernatant fluid be restored by the addition of sodium chloride, it is found that either portion alone has become inactive, while in combination they still produce hæmolysis under suitable conditions. As a result of a further elaboration of the side-chain theory, the precipitated portion has been named the mid-piece, and the portion which remains in solution the end-piece. It should, however, be noted that complete " complement-splitting " (as it is called) is very difficult to bring about, and the existence of the mid-piece in its original sense is now denied by several authorities.

Agglutination.—In many of the earlier experiments with immune sera it was observed that bacteria and cells, when mixed with a specific antiserum, tended to mass together into small clumps. It was not, however, until the publication of the researches of Grüber and Durham in 1896 that the reaction was recognised as distinct and specific. As the result of their findings, these observers suggested that the method might be employed as a means of identifying various bacteria, and a short time afterwards Grünbaum and Widal, independently of each other, suggested that the reaction might be applied by testing the action of a patient's serum on the organism with which he might be supposed, on clinical grounds, to be infected. This was the origin of the Widal reaction, which has since been so extensively used in the diagnosis of typhoid and paratyphoid infections.

The reaction may be observed either microscopically or macroscopically. In the former case the serum, suitably diluted with saline solution, is mixed with the bacterial suspension on a cover slip, and a " hanging drop " preparation is prepared. In a positive reaction the bacteria soon become massed together into tight clumps, until eventually few, if any, organisms are left free (Figs. 75 and 76). In the macroscopic method the bacterial suspension and serum dilution are mixed in suitable tubes, which are then incubated for a definite period. Agglutination is evident by the formation of flocculi, which gradually sink to the bottom of the tube, leaving a clear supernatant fluid. Fig. 77 shows the effect of adding an agglutinating serum, in gradually increasing dilutions, to a suspension of *B. typhosus*.

The agglutinins are relatively thermostable. They withstand heating to temperatures between 50° and 60° C. for half an hour

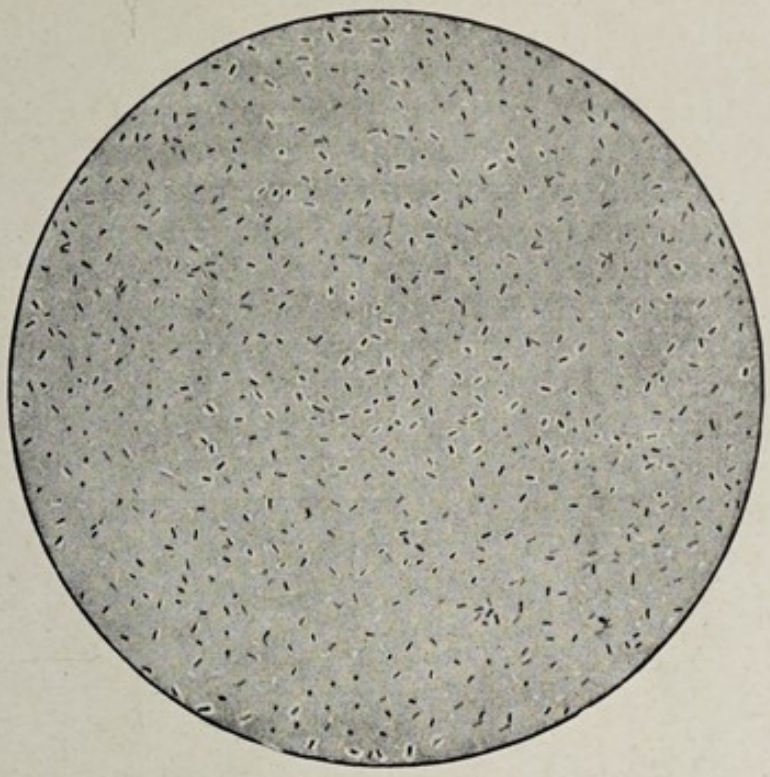


FIG. 75.—UNIFORM SUSPENSION OF BACTERIA. (HANGING-DROP PREPARATION.)

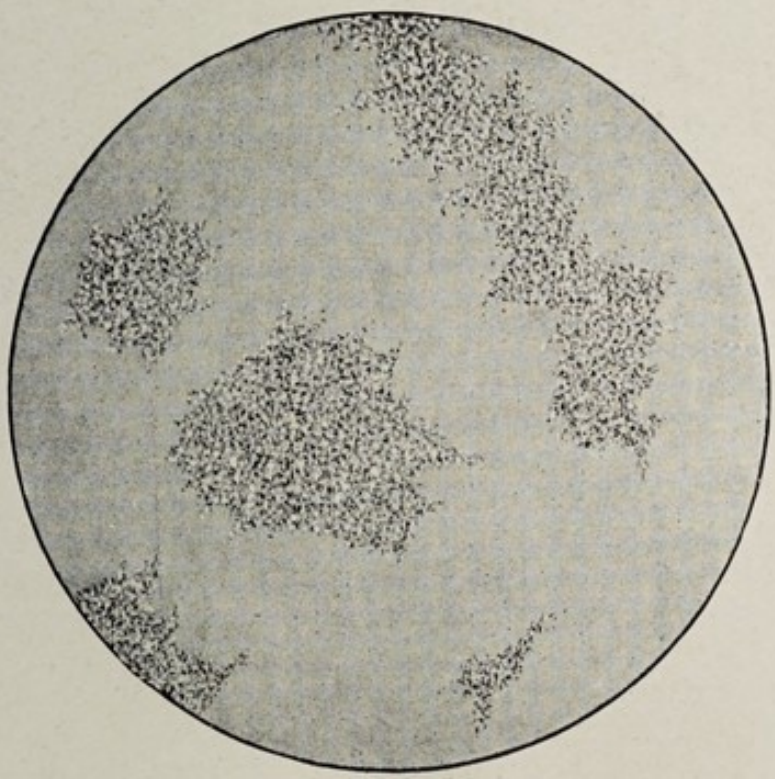


FIG. 76.—THE SAME SUSPENSION AGGLUTINATED BY THE ACTION OF AN IMMUNE SERUM.

or more, but they are rapidly destroyed when the temperature rises much above 70° C. An agglutinating serum inactivated by this means is not reactivated by the addition of fresh normal serum.

It was soon shown that the phenomenon was in no way dependent upon the activity of the bacteria themselves, since organisms killed by various methods were agglutinated as readily as living ones. The earliest theories suggested that changes in the flagella of the organisms were an essential part of the process, but it was soon found that non-flagellated bacteria were agglutinated as readily as the flagellated types. Another early suggestion was that the capsules, or external layers of the bacteria, became swollen, and in some way sticky, so that the individual organisms tended to adhere

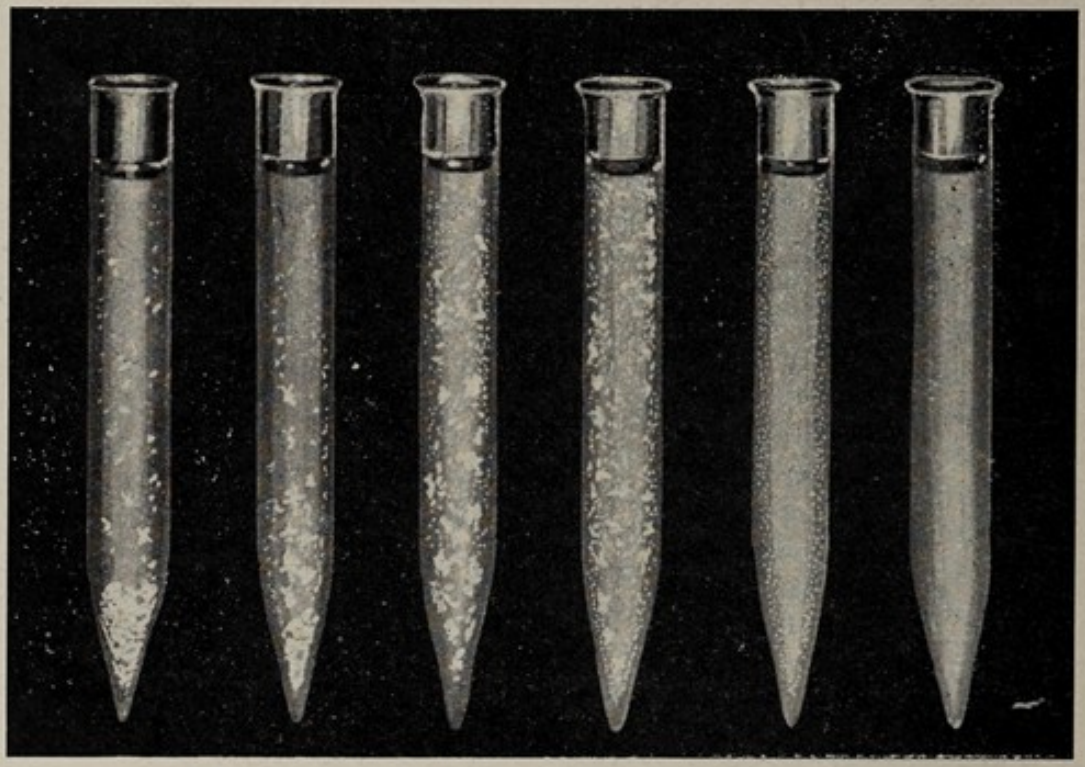


FIG. 77.—THE EFFECT OF ADDING GRADUALLY INCREASING DILUTIONS OF AN AGGLUTINATING SERUM TO A BACTERIAL SUSPENSION. (MACROSCOPIC METHOD.)

to each other. Further work, however, rendered such an hypothesis untenable. Bordet drew attention to the importance of the presence of salts in the solutions employed, and suggested that the flocculation of the bacteria was a secondary phenomenon, similar in character to the flocculation of colloids. To explain this reaction in conformity with the side-chain theory, Ehrlich and his school postulated the existence of a special side-chain group which was designated a receptor of the second order (Fig. 67). This possessed a haptophore group which combined with the bacterium or cell, and an ergophore group which was concerned in bringing about the essential change. On inactivation by heat this ergophore group was destroyed and an agglutinoid produced. Since there was no

complementophile group, no reactivation occurred upon the addition of fresh serum.

Bacteria are able to absorb the agglutinins from their corresponding antisera, a phenomenon which had already been demonstrated in the case of red blood-corpuscles and the hæmolytic antibodies. This fact may be utilised in differentiating the members of a closely allied group of bacteria, since in such cases it is frequently found that an agglutinating serum, produced by immunisation with one member of such a group, possesses a certain degree of agglutinating power against some or all of the other members.

In such a case it will be found that the homologous organism—that is, the one actually employed in immunisation—will remove all the agglutinins; while any one of the closely allied organisms will remove only those agglutinins which act on itself, leaving the agglutinating power of the serum for the homologous organism and for the other group organisms unaffected or but slightly decreased.

Precipitation.—The study of agglutination led to attempts to demonstrate similar phenomena, using bacterial extracts instead of the bacteria themselves. Experiments carried out on these lines showed that when such an extract, filtered through a porcelain candle to free it from all bacterial cells, is added to the serum of an immunised animal a definite precipitate results. More extensive research showed that not only bacterial extracts, but any foreign protein, such as the serum from an animal of another species, is capable of giving rise to the formation of precipitins when injected into the tissues. Like the agglutinins, the precipitins are relatively heat-stable, and when inactivated by subjection to high temperatures (70°-80° C.) they are not reactivated by the addition of fresh serum. Hence, Ehrlich applies to them the same explanation as in the case of the agglutinins, but postulates the existence of a special type of receptor of the second order.

The study of precipitins has, however, yielded results of considerable significance. Welsh and Chapman have shown, by careful quantitative experiments, that by far the greater part, if not the whole of the precipitate, is derived from the antiserum, and not from the antigen.* It follows that the result of immunising an animal against a foreign protein is that, when this protein and the immune serum are brought into contact, it is the protein which precipitates the serum, and not, as one might expect, the converse.

Like agglutination, the precipitin reaction is strictly specific if the correct dilutions are employed, but displays a well-marked group reaction when the reagents are present in higher concentrations. Thus, under these conditions an antihuman precipitating serum will react with the sera of many of the anthropoid apes. This reaction has received a practical application in medico-legal practice for the determination of the human or other origin of

* The term " antigen " is used to denote any foreign substance, bacteria, cells, or other protein material, which when introduced into the animal tissues lead to the formation of specific antibodies.

blood-stains, etc., and for this purpose it is necessary to carefully exclude any possibility of a misleading group reaction by the use of correct dilutions and full controls.

In precipitation and in agglutination tests the occurrence of so-called "zone phenomena" is frequently encountered. These consist in the failure of the reaction in a given dilution of one of the reagents, while with progressive dilution the reaction becomes well marked, only to fade away again as the dilution increases beyond a certain limit. The explanation of such phenomena on the lines of the side-chain theory, or, indeed, any other theory which involves chemical combination in definite multiple proportions, offers very great difficulty, and the attempts to meet these have consisted, for the most part, in assuming the existence of modifications of the agglutinins or precipitins, as the case might be, which possessed modified or inactivated ergophore groups, and haptophore groups of diminished or increased chemical affinity. These zone-phenomena have, however, their exact counterpart in the observed reactions between mutually flocculating colloids, where the occurrence of the reaction depends entirely on the relative proportions existing between the reagents present in a given mixture.

Complement Fixation.—It was originally demonstrated by Bordet and Gengou that, when a bacterial antigen is allowed to react with its specific antiserum in the presence of complement, this complement is in some way fixed, and is no longer present in the mixture in the free state. The absence of free complement is demonstrated by the addition of red cells sensitised by an inactivated hæmolytic serum, when, on further incubation, there is no hæmolysis, whereas in control tubes containing in the one case antigen and complement, but no antibody, and in the other antibody and complement, but no antigen, free complement is present and hæmolysis occurs (Fig. 78). It should be noted that the lysis of the sensitised blood-corpuscles is simply used as a test for the presence of free complement, which can be recognised only by its activity.

This reaction has been largely utilised both for testing a patient's serum against a known organism to determine the presence or absence of a particular infection, and also for the identification of a given organism by testing it against a series of immune sera. It should be noted that complement fixation can be demonstrated with all known types of antigens, and not only with bacteria and their extracts.

The reaction has obtained its most widely used application in the form of the Wassermann reaction. This test has proved of the greatest possible utility in the diagnosis of syphilitic infection, but extended knowledge of the factors involved has shown that it is not a true immunity reaction. Wassermann, Neisser, and Brück, in their original work, utilised a saline extract of the liver of a syphilitic fœtus as their antigen, and believed that the undoubtedly specific results which they obtained were due to the presence of the spiro-

chætes in the liver tissue. It was, however, soon demonstrated that normal liver tissue gave equally good results, and later that any substance of a lipoid nature would serve as an efficient antigen for the reaction, and almost all workers now employ some form of lipoid extract obtained from normal organs or tissues. Thus, the Wassermann reaction depends on the presence, in the serum of a syphilitic patient, of some substance which, acting together with certain lipoid extracts, fixes complement. Fig. 79 illustrates diagrammatically the stages of such a reaction and the effects produced. It must, however, be remembered that it represents

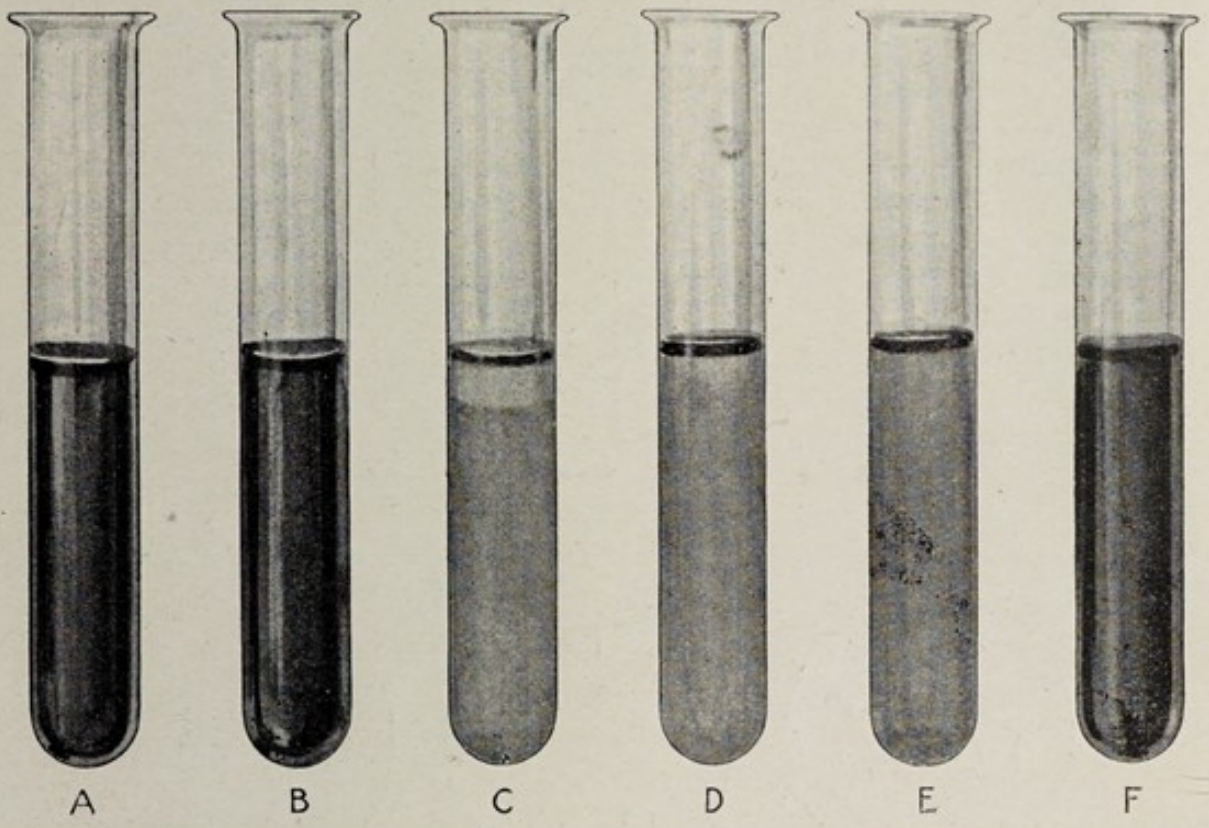


FIG. 78.—ILLUSTRATING THE RESULT OF A COMPLEMENT-FIXATION TEST.

A originally contained antigen and complement without antiserum, and now shows complete hæmolysis; B contained antiserum and complement without antigen, and here, too, hæmolysis is complete; C contained antigen, antiserum, and complement, in suitable dilutions; the complement has been fixed, and no hæmolysis has occurred. D, E, and F, show the effect of gradually decreasing the amount of antiserum, the amount of antigen remaining constant.

the reaction in the terms of a true immunity phenomenon, and, moreover, uses the symbols of a true amboceptor action, which probably does not occur. It serves, however, to afford an accurate mental picture of the essential points of this very important reaction.

The mechanism of complement fixation has formed the subject of much careful inquiry, and results have been obtained which possess considerable significance in regard to the relation of the various immunity reactions to each other. The upholders of the

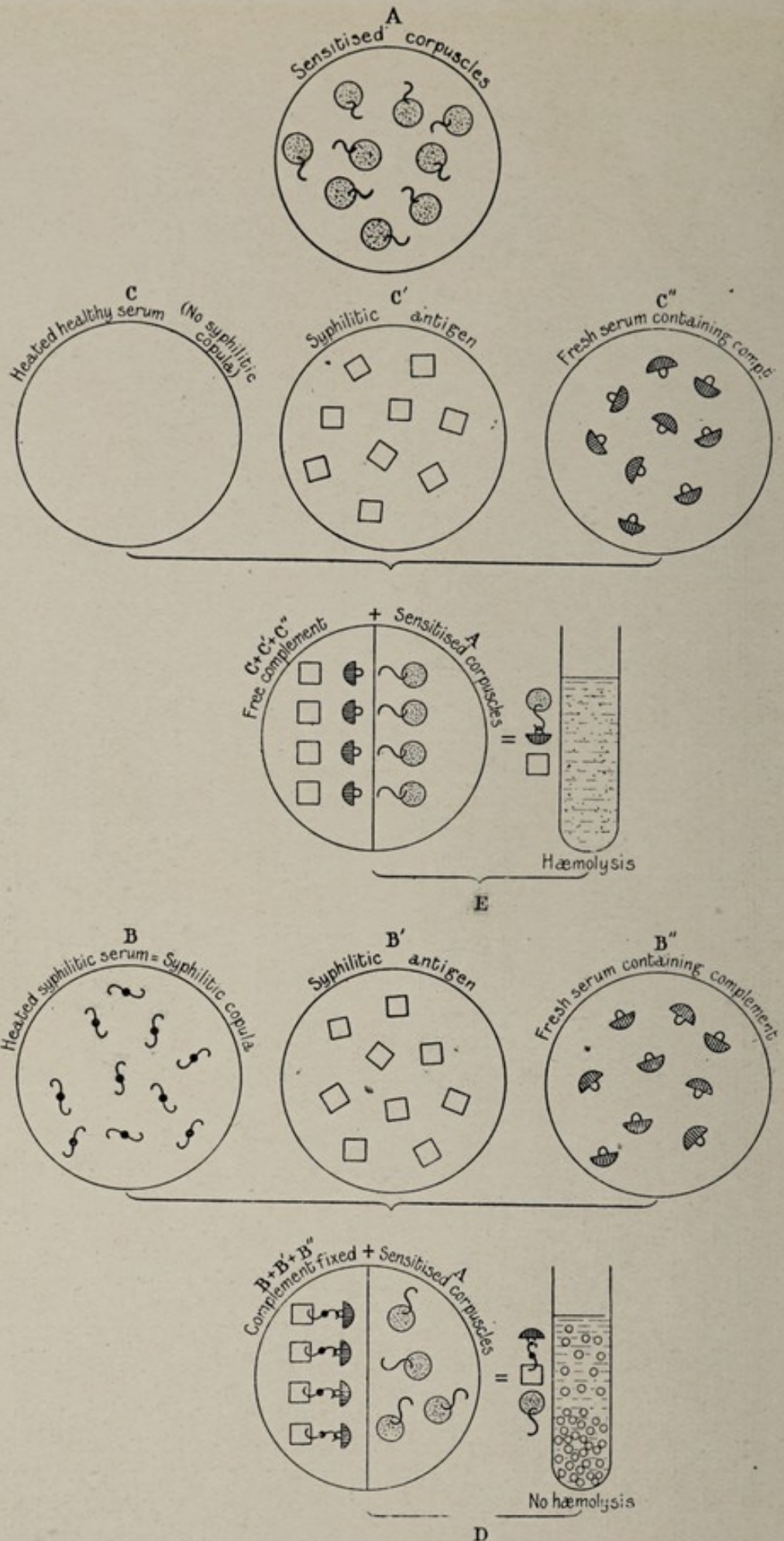


FIG. 79.—DIAGRAMMATIC REPRESENTATION OF WASSERMANN'S REACTION AS TEST FOR SYPHILIS.

A, sensitised corpuscles, needing only complement to produce hæmolysis. C, C', C", system containing only syphilitic antigen and complement. The latter remains free; therefore, when this system is added to A, hæmolysis occurs (E). B, B', B", system containing syphilitic antigen, syphilitic copula and complement. This last is "fixed"; therefore, when this system is mixed with A, no hæmolysis results (D).

side-chain theory sought to explain the phenomenon as due to a special amboceptor which linked the complement to the antigen. Further researches, however, have yielded results which offer a simpler explanation. The work of Gay and others has shown that an antigen-antibody mixture which forms a precipitate tends also to fix complement, and *vice versa*. It has been objected to this that such mixtures can be prepared which form a precipitate without fixing complement, or fix complement without forming a precipitate. The careful quantitative experiments of Dean have, however, clearly demonstrated that this discrepancy is due to the fact that, for a given antigen-antibody mixture, the relative proportions of the two reagents which tend to rapid precipitation are not those which lead to complement fixation, but that in every case there is an optimal proportion for the exhibition of each of the two phenomena. Complement fixation seems to be greatest when the precipitate is slight and develops slowly, which is to be expected if the result be due to adsorption of the complement by the particles of the precipitate, since it is in this early stage that the total surface area presented will be greatest. There seems, therefore, to be very considerable evidence in favour of the view that precipitation and complement fixation are two phases of one and the same phenomenon.

Phagocytosis.—The phenomenon of phagocytosis, upon which so much stress was laid by Metchnikoff and his school, has more recently been extensively studied from a new aspect—*i.e.*, that of the rôle played in the process by the body fluids.

The studies of Wright, Neufeld, Hektoen, and others, have demonstrated that the blood-serum and tissue fluids are intimately concerned in phagocytosis. The main facts which have been demonstrated up to the present time are as follows: Normal leucocytes, when mixed with a bacterial suspension and normal serum, actively ingest the bacteria under suitable conditions as regards temperature, etc. The same leucocytes, acting in the absence of serum, fail to ingest the bacteria, except in insignificant numbers (Figs. 80 and 81). The action of the serum is exerted upon the bacteria, not upon the leucocytes. The latter view was held by certain early investigators, and the substances present in the serum were hence named stimulins. Wright, to indicate that they in some way prepared the bacteria for ingestion by the leucocytes, coined the name opsonins.

The opsonins present in normal sera which act non-specifically on all bacteria, and also on particles of inert matter, are thermolabile. Following the immunisation of any animal with a given bacterium, opsonins develop in that animal's serum which are heat-stable and specific.

Considerable controversy has arisen as to whether the opsonins are special immune substances, or whether they are identical with complement or with the specific sensitiser or copula. As regards the normal opsonins, it appears that any method of treatment which removes complement from a serum removes normal opsonin

as well, but certain experimental facts would seem to indicate that a non-specific sensitiser is also involved. As regards the immune opsonins, it seems clear that they can produce their result in the absence of complement. The experimental arguments for and against their separate identity cannot be entered into here; but it may be stated that, while many workers of great authority regard the opsonins as a distinct class, there is a growing tendency to identify them with complement and sensitiser.

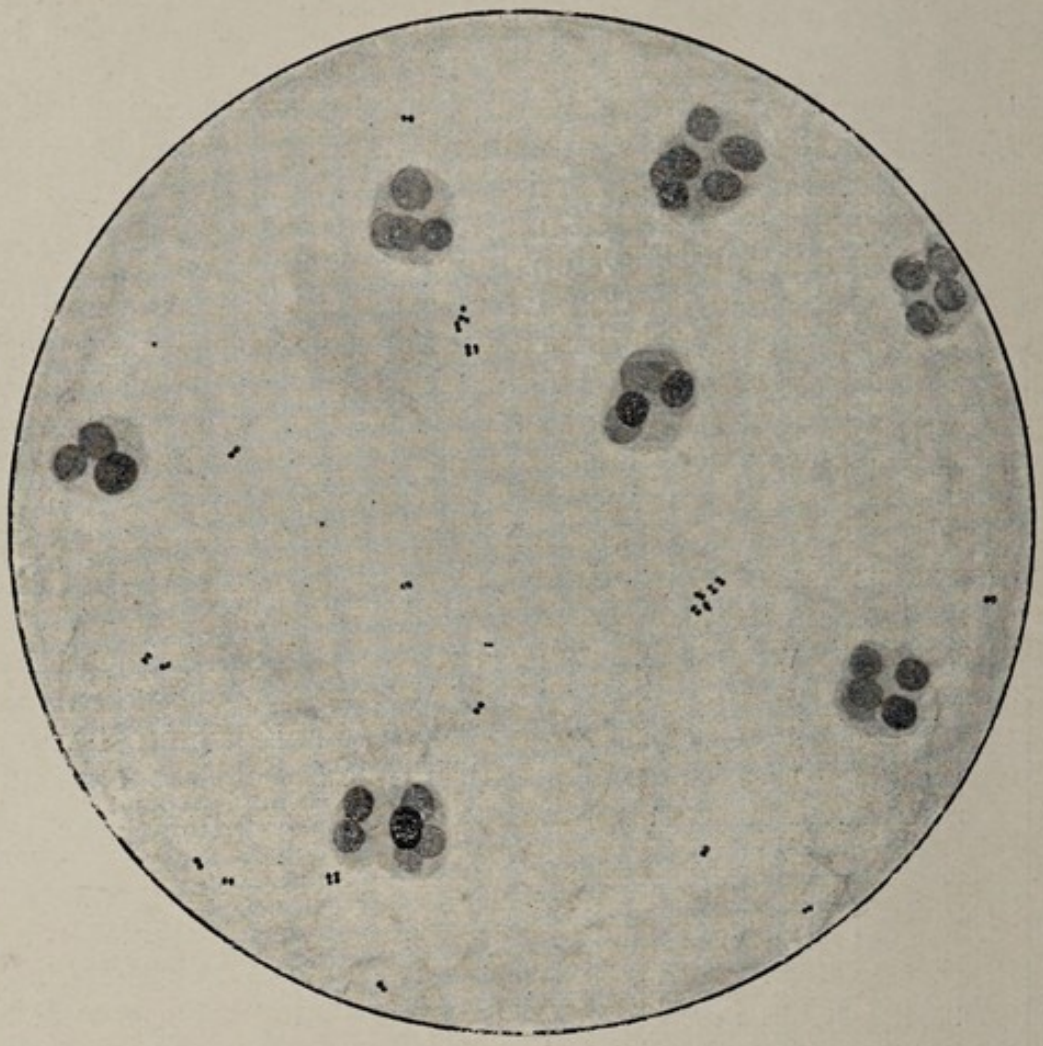


FIG. 80.—SHOWING THE RESULT OF INCUBATING A MIXTURE OF LEUCOCYTES AND BACTERIA IN THE ABSENCE OF SERUM.

Experiments have shown that the phagocytic powers of the leucocytes themselves cannot be altogether disregarded, since variations in the number of bacteria injected have been noted when leucocytes obtained from various sources have been allowed to act in the presence of the same serum.

The Question of the Multiplicity of Antibodies.

It will be seen, from the above brief description of the more important serum reactions, that, as this branch of knowledge has developed, fresh phenomena have from time to time been observed

when an antigen has been allowed to react with its specific antiserum.

As each of these new reactions has been noted, a fresh name has been coined to denote the particular immune substance which brings it about. Thus, we speak of lysins, agglutinins, precipitins, opsonins, etc., with a more or less implicit understanding that such substances actually exist. Ehrlich and other supporters of the side-chain theory do indeed strenuously support the separate identity

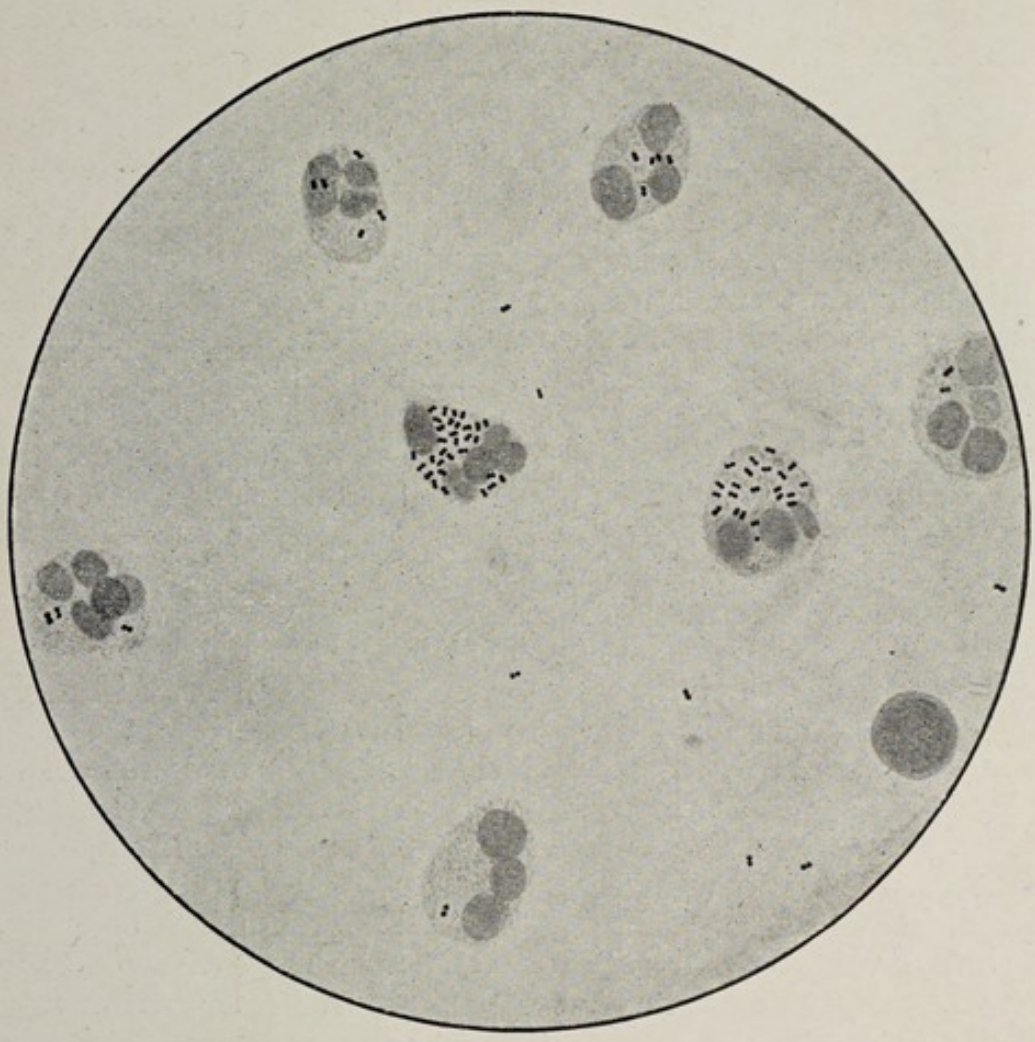


FIG. 81.—SHOWING THE RESULT OF INCUBATING A MIXTURE OF LEUCOCYTES AND BACTERIA IN THE PRESENCE OF SERUM.

of these bodies, and have, moreover, as occasion has arisen, assumed the existence of various complicated modifications of them to account for discrepancies in the phenomena observed.

Those workers, however, who prefer to regard the serum reactions as belonging to the class of colloidal phenomena, have in many cases begun to doubt the necessity for assuming such a multiplicity of antibodies. Very recently Dean has clearly formulated the unitarian view, and has suggested that the various serum reactions are simply different methods of observing and measuring one single reaction, and that the different attendant phenomena—

precipitation, agglutination, lysis, etc.—depend on the nature of the antigen, the relative proportions existing between the antigin and the antibody, and the presence or absence of normal serum containing complement. It must be remembered that Ehrlich's theory has still many eminent supporters, and the questions involved cannot by any means be regarded as settled; but the adsorption theory of Bordet, and the possible unification of the various phenomena observed, tend to simplification and not to increased complexity, and, moreover, avoid the necessity of assuming the existence of many complex substances in order to explain away a conflict of experimental facts.

The Site of Formation of Antibodies and Complement.

It is obvious that ignorance as to the seat of origin of complement and of sensitiser leaves a very unfortunate hiatus in our knowledge of the mechanism of immunity, but in spite of extensive research we possess as yet no definite information on this important matter.

The origin of complement or alexine has been attributed by many observers to the leucocytes, and especially to the polymorphonuclear cells. This was the view persistently maintained by Metchnikoff and his school. The majority of the earlier work on this subject, which consisted in the extraction of lytic substances from leucocytes and from various tissues, must be disregarded; since it was performed before much of our present knowledge was obtained, and the substances in question have been shown to be relatively heat-stable, and to belong to a class entirely different from either complement or the lytic antibodies. In general it may be said that all attempts to demonstrate the formation of complement by the leucocytes have failed, though no evidence excluding the possibility of such an origin has been produced. This problem is intimately bound up with that of the presence or absence of free complement in the circulating blood. Metchnikoff consistently held that it was normally absent, only appearing after cell-injury, and certain experiments have yielded support for this view, notably those of Gengou, who found an absence of complement in the serum obtained from clotted plasma which had been rapidly freed from cells before coagulation occurred. Later workers have, however, obtained diametrically opposite results, and the question cannot be regarded as settled; but other considerations, including the phenomena which we know to result from the inoculation into living animals of cells or bacteria on the one hand, and of hæmolytic or other sera on the other, render it unlikely that complement is absent from the circulating blood.

Other possible sites of formation of complement include the thyroid (Fassin) and the liver (Nolf). The experimental results obtained have been very suggestive, but the difficulties in technique, especially in the case of the liver, are so great that disturbing factors cannot be satisfactorily excluded.

As regards the specific antibodies or sensitisers the same ignorance prevails. Many workers have upheld the view that any cell or tissue can form antibodies. Others would limit this function to some special organ or type of cell. The hæmopoietic organs, and especially the spleen, have been frequently suggested as a probable source. A careful study of the literature shows that the theory of the universal origin of sensitising substances obtains its support mainly from a few isolated but classical experiments, which are constantly quoted, but which have never been satisfactorily confirmed. Much careful work has been done on this subject, especially by Hektoen, Carlson, and other American workers; but, although their results have demonstrated that the spleen is apparently concerned in some way in the formation of antibodies, they showed quite clearly that its presence is not essential, and here, again, the introduction of disturbing factors as the result of severe operative procedure cannot be disregarded. It has been suggested by Teal and Embleton that immune body is itself derived from complement.

ANTIBACTERIAL SUBSTANCES DERIVED FROM LEUCOCYTES.

As has been already stated, many of the earlier investigators believed that the bactericidal and other antibodies found in the blood-serum, and also complement itself, were derived from the leucocytes. Substances possessing definite lytic action have undoubtedly been extracted from tissues rich in these cells, but more careful studies by Schattenfroh, and later by Petterson, showed that these lysins differ fundamentally from the serum lysins, in that they are relatively thermostable. These results have been recently confirmed, as regards leucocytic extracts, by Zinnser, who has also shown that, after inactivation of such extracts at a suitable temperature (70°-75° C.), there is no reactivation on the addition of fresh extract. Moreover, the bacteriolytic power of these extracts is insignificant when compared with that of the blood-serum, and no increase in its activity can be obtained by immunisation.

In addition to these lysins, various true ferments, and in particular proteases, have been extracted from leucocytes; and these would seem, from the investigations of Jochmann, to be quite distinct from the antibacterial substances, their rôle being probably confined to the liquefaction of necrotic tissue.

The earlier experiments of Petterson, the later work of Opie, and especially the extensive investigations of Hiss and Zinnser, have shown that leucocytic extracts appear in many cases to exert a favourable influence on the course of experimental and naturally occurring infections. But the mechanism underlying the results obtained has never been satisfactorily explained, and the results themselves have not met with uniform acceptance. The whole matter is still awaiting further investigation, but it may be broadly stated that up to the present no evidence has been acquired to

prove the elaboration by any form of leucocyte of antibacterial substances at all comparable in their potency to those found in the body-fluids, and that all attempts to demonstrate the derivation of these serum antibodies from the leucocytes have failed. The essential rôle of the leucocytes in immunity remains that of phagocytosis.

ANAPHYLAXIS.

Although isolated references to phenomena which were certainly examples of anaphylaxis are found scattered throughout the literature of immunity, it is only comparatively recently that we have acquired any real knowledge of the factors involved. It is to the work of Richet, and to the later observations of Arthus, of Rosenau and Anderson, and of Friedberger and others, that we owe the greater part of our present knowledge.

The fundamental facts are as follows : If an animal receive intravenously, hypodermically, or intraperitoneally, a small dose of some foreign protein, such as horse serum or egg albumen, it usually suffers no harm ; but if, after an interval of some twelve or fourteen days, a second injection of the same substance be administered, severe and even fatal symptoms may ensue. The most susceptible animal is the guinea-pig, and in such an animal death may occur within a few minutes with convulsions and collapse, or in less fulminating cases there may be vomiting, with passage of bloody urine and fæces, severe dyspnœa, and paralysis of the limbs. In all cases there is marked restlessness and irritation. The blood-pressure falls to a low point, and there is a definite fall in temperature. There is a marked leucopenia, and a decrease or total disappearance of complement from the blood-serum. After death the whole alimentary tract is found congested ; there is blood in the lymphatics of the mesentery, and hæmorrhage into the lungs and beneath the pleura and pericardium. The most constant and striking feature is, however, a marked emphysema. The studies of Auer and Lewis have shown that this is due to a tetanic contraction of the small bronchioles which is of peripheral origin, and is apparently the actual cause of death.

More rarely a condition of chronic cachexia occurs : the animal becomes dull and listless, the coat is rough and staring, and emaciation and exhaustion lead to final death. Since it is only after a second injection that these severe symptoms occur, it would seem that the first injection in some way renders the animal unduly sensitive to the protein in question, and this condition of supersensibility was named by Richet " anaphylaxis," and the illness itself " anaphylactic shock." It is noteworthy that there is a definite incubation period after the first injection, no ill effects being manifested as a rule if the second injection be given before the twelfth day. Indeed, a second injection during this period seems to prevent the appearance of anaphylaxis (anti-anaphylaxis).

The nature of anaphylaxis is not well understood. The most generally accepted explanation is that put forward by Friedberger. He believes that anaphylactic shock is the result of an acute intoxication due to toxic products produced by the splitting up of the proteid molecule by the combined action of a specific sensitiser and complement. When foreign serum or albumen is injected into an animal, a sensitiser is produced, which in the presence of complement is capable of breaking up the proteid molecule into its constituent polypeptides, amino-acids, and so forth. When the first dose of foreign protein is administered, the sensitiser is formed slowly in response to the stimulus, and the toxic bodies are formed gradually in small quantities; but when the second dose is given there is a large amount of the sensitiser available, and an overwhelming amount of the toxic cleavage-products is immediately formed. Hence arise the dangerous symptoms. An animal may be passively sensitised by the injection of serum taken from an actively sensitised animal, and the production of the toxic substance or anaphylatoxine can be actually demonstrated *in vitro* by making a mixture of the blood-serum of a sensitised animal with a little of the appropriate antigen, and injecting this mixture into a normal animal after a suitable incubation period. Symptoms of anaphylaxis ensue, whereas no ill effects follow the injection of either antigen or the blood-serum of the sensitised animal alone.

While these facts, which have been repeatedly confirmed, leave no doubt that the body fluids, and especially the blood-serum, play an important rôle in anaphylaxis, and might be considered to account for all the phenomena observed, yet certain experiments seem to indicate equally definitely that the cells and tissues themselves are in some way sensitised. Thus, Dale has shown that the uterus of a sensitised guinea-pig, freed from all blood by perfusion, is specifically stimulated to contraction by the appropriate antigen.

The importance of the study of the phenomena of anaphylaxis from the point of view of human pathology is increased in view of the administration of serum as a remedy. It was soon discovered that, while a single dose of serum was occasionally followed by an urticarial rash or other slight disturbance, a second injection might give rise to severe symptoms, such as fever, pains and swellings of the joints, marked eruption, and rarely sudden death, the patient dying with dyspnœa, convulsions, and coma. The study of anaphylaxis in animals has now thrown some light on the cause of these phenomena.

It has also been suggested that certain obscure diseases, such as asthma and hay fever, as well as the disturbances which in some persons follow on the consumption of shellfish, eggs, or strawberries, are instances of anaphylaxis. The urticarial rash, which often follows the escape of hydatid fluid into the tissues of the person who harbours this parasite, is similarly explained.

Bacterial Anaphylaxis.

As a natural consequence of the studies described above, attempts were made to demonstrate the anaphylactic reaction, employing bacteria as the antigen. Although many difficulties presented themselves, successful results were obtained, and have since been repeatedly confirmed and greatly extended.

It is obvious how far-reaching these new facts and theories may prove to be. It is impossible to consider at any length the lines of reasoning which have arisen from them, but it is clear that they may lead to entirely new conceptions of the very nature of the bacterial endotoxines. Already certain observers have put forward the view that all bacterial disease is essentially an intoxication with proteid split products, the individual phenomena displayed depending rather on the localisation and mode of entry of the organisms than on any differences in the toxines. According to this view, the bacteria do not themselves contain any true toxine, the toxic substance being produced by the action of the body fluids and cells on the bacterial protein. While all such theories leave very many clinical and experimental facts unexplained, they have provided a fresh stimulus to the study of the essential nature of infection and immunity.

VIRULENCE AND PATHOGENICITY.

In the preceding pages we have studied the problems of immunity from the point of view of the host. But to obtain a complete picture it is necessary to examine the phenomena of infection from the point of view of the invading parasites. Reference has already been made to the fact that differences in virulence and pathogenicity are observed, not only in different bacteria, but in one and the same organism at different times and under varying conditions. Thus, it has been shown to be a general rule that bacteria decrease in virulence on prolonged artificial cultivation outside the body. Again, if a given organism be injected into an animal of a particular species, and be then passed from this animal to another of the same kind, and so on through a series, there will usually result a definite increase in virulence towards this species, associated in many cases with decreased virulence towards animals of other species. We must conclude, therefore, that the bacteria gradually adapt themselves to the tissues of the host—partly, at any rate, by certain alterations which tend to overcome the resisting powers opposed to them. Of the factors involved we know little, but the work of Bail, and later the extensive studies of Dudgeon, have thrown considerable light upon one aspect of the problem. As the result of the work of these and of other investigators, it has been shown that in the exudates from many inflammatory foci substances are present which inhibit phagocytosis, and which may possess certain other properties, such as the power of binding complement. It

has been suggested that these substances, which have been named "aggressins," are identical with the endotoxines, but, as we have seen, the nature of the endotoxines themselves has lately been the subject of active controversy.

There seems little doubt that in some cases an increase in virulence is associated with the acquisition of a capsule by the organism concerned, which very probably serves to protect the bacteria against the action of the body-fluids.

It will be seen that our conceptions of the factors involved in infection and resistance are incomplete, and in many cases inconclusive. We are in possession of a large number of facts concerning the action of the cells and body-fluids of immune patients and experimentally immunised animals on the bacteria concerned; but we do not yet know how far any or all of these reactions contribute towards immunity. It is clear, however, that the eventual conquest and prevention of bacterial disease depend on the elucidation of the problems involved, and we have at least a large mass of ascertained facts upon which to base further experiment and theory.

CHAPTER XIII

INJURY AND REPAIR

A LIVING tissue has the property of reacting in a peculiar manner to injurious stimulation (irritation), and in the most favourable instances the series of changes which ensues ends in repair of the injury, cells destroyed being either re-formed (epithelium) or replaced by connective tissue (scars), and solution of continuity or loss of substance being thus made good. In the great majority of cases the reaction takes the form clinically termed "inflammation." The causes of injury have already been briefly enumerated (p. 4), but must now be considered in greater detail.

SOURCES OF LOCAL INJURY.—Injury may result from the action of chemical, mechanical, or other physical causes, and these may act either directly from without (traumatism) or through the medium of the blood or lymph with which the cell is surrounded. Thus, deprivation of blood-supply may, as has been already shown, cause death of certain cells, and the poisonous products resulting from their disintegration may act injuriously on other cells, especially those in their immediate neighbourhood, to which they are carried by the circulation or by the lymph. An area of necrosis is thus almost always surrounded by a zone of hyperæmia and cellular proliferation in the living tissue at its margin.

In many cases it is difficult or even impossible to discover the actual cause of local irritation, and this can only be hypothetically assigned to some poison formed in the body by disordered metabolism (auto-intoxication). It is well to bear in mind that a spreading process of disease must be produced by a spreading cause, and that chronic irritation must be due to a continuing source of injury.

Finally, since different individuals react differently to similar stimuli, it is found that the degree of disturbance produced by an irritant varies widely in different subjects, a degree of cold which would cause frost-bite in one person inducing merely numbness in another, and an infective organism which causes serious disease in one subject failing entirely to establish a footing in a more "resistant" individual. Hence it is customary to speak of *predisposing* and *exciting* causes of injury, the former word denoting a condition of the living tissues which causes them to suffer readily from a particular source of injury.

1. **Simple or Traumatic Causes.**—These include any very evident injurious agencies, such as mechanical violence, caustic and irritating chemicals, excessive heat or cold, electricity of sufficient strength, and prolonged local anæmia with consequent privation of nutriment. It is characteristic of the reaction excited by such causes alone that it has *no tendency to spread beyond the part originally injured, or to pass on to more advanced stages after the causes have ceased to act.* It is well known how slight are the inflammatory changes induced by very severe *subcutaneous* injuries, even though bones be broken and the capsules of joints torn; and how limited is the inflammation when similar injuries, *communicating with the atmosphere—e.g.,* compound fractures—are treated in such a way (antiseptically) as to counteract all infective agents. In animals, the effects of each of these irritants can be accurately studied. Hüter injected a 5 per cent. solution of nitrate of silver, or a similar solution of chloride of zinc, into the muscles and other tissues of animals, and thus killed the part acted on. In a large number of the cases the inflammation was practically limited to the zone immediately surrounding the dead tissue. Other experiments were made by plunging a cautery into a muscle (Hallbauer) and bringing the previously divided skin together over the injured part, antiseptics being used. Only such changes occurred round the eschar as take place in the absorption of a simple infarct and its replacement by fibrous tissue. In these instances, although the most severe mechanical, chemical, and physical agents were employed, killing considerable masses of tissue, yet the action of the irritant, though intense, was localised and of short duration. Certain parts were killed absolutely, and inflammation was limited to a narrow area surrounding these. So soon as the irritant had ceased acting, the tissues tended to recover. Hence the reaction excited by such causes as the above reaches its height very soon after the introduction of the irritant, and soon subsides unless some other cause of irritation is superadded. A similar sequence of events is frequently seen after the infliction and proper treatment of a clean-cut wound by a sharp knife.

A chemical irritant may enter the body at a distance from the part at which its chief action takes place. Thus, turpentine or cantharides may cause inflammation of the kidneys, and iodide of potassium may produce a pustular eruption on the skin.

Lesions which are referred to cold and wet—"rheumatic" and "reflex" inflammations—are difficult to explain. When conjunctivitis occurs from the action of a draught upon the eye, the relation between cause and effect is easily comprehensible; but, except on the hypothesis of greater delicacy of nerve-tissue, it is not so easy to understand why inflammation of the facial nerve should ensue from exposure to cold, whilst a great thickness of superficial tissue seems uninjured. This difficulty becomes even greater when internal organs (lungs, kidneys) are affected, apparently in consequence of cold acting upon the surface, or of wet feet.

In these cases any effect produced by cold may perhaps be regarded as predisposing to the action of other causes, usually infective organisms. We know, however, that surface-cold drives the blood to internal organs, and raises the blood-pressure, and experiments suggest that direct injury may result. Thus, Lassar plunged rabbits, shorn of fur, into iced water, and thoroughly chilled them. On subsequent examination he found changes in all the organs, especially the lungs and liver, the vessels being often greatly dilated, the arteries thrombosed, and the veins surrounded by patches of round cells. When the animals were pregnant, the same changes were noted in the organs of the fœtus. He believed the changes to be due to the irritant action of cooled blood upon the vessels of internal parts. Perhaps something of the same kind may occur in man, as the result of a chill, although individual difference of resistance or the presence of organisms must be assumed to explain why the kidney in one case, and the lung in another, is affected. In the light of this experience, frequent exposure to cold may be regarded as a cause of chronic nephritis; for the temporary albuminuria induced in some people by a cold bath shows that in them the kidneys are easily damaged.

It is held by some that *excessive functional activity* may in itself act as an irritant, conjunctivitis from overwork being quoted as an example. This sequence may appear doubtful, but it is not difficult to conceive that overwork might cause in some organs—*e.g.*, muscles—an excess of waste products which might act injuriously on the cells, or diminish their resistance to infection.

Nervous influence, called into action by irritative lesions of nerve-trunks, appears capable of directly producing a local condition resembling that induced by an irritant. The most striking instance of this is seen in herpes zoster, in which an erythematous and vesicular eruption on the skin is associated with neuralgic pain and with changes in the cells of the posterior root-ganglia corresponding with the nerves going to the affected area. The action of superficial cold on internal parts may be due to reflex circulatory changes.

2. **Infective Causes.**—A very important cause of local injury is the lodgment and growth of parasitic organisms in the tissues. These organisms, in their growth, give rise to chemical irritants, producing inflammation in the same way as do the agents which have just been mentioned. But, as long as the bacteria grow in the body, a continuous supply of the products of their life-action is kept up. These products, continuously spreading through the tissue, will accordingly give rise to an extending zone of reaction. The products of different bacteria vary enormously in their power of injuring the tissues, some producing actual necrosis, others varied degrees of inflammation. If the irritant be sufficiently intense, some variety of fibrinous inflammation is induced, just as by chloride of zinc; when a strong irritant exerts positive chemiotaxis on the leucocytes, and proteolytic ferments are formed either by the leucocytes or the irritant or by the tissue-cells, suppuration results.

In clinical medicine and surgery, suppuration is invariably due to the action of bacteria, but there is reason to believe that suppuration is possible in experimental pathology without the action of organisms. If glass capsules, containing croton-oil or turpentine, are placed aseptically in the subcutaneous tissue, and the capsules broken when the wound is soundly healed, suppuration results, and no organisms are found in the pus (Cheyne, Councilman). Grawitz and Scheuerlen have produced acute aseptic (free from organisms) suppuration by the injection of cadaverine and putrescine—alkaloids separated by Brieger from putrid flesh. These substances are not only irritants, but also possess proteolytic (peptonising) powers. If the irritant is less intense, marked cellular proliferation may result, as in tuberculosis and leprosy.

The *presence of organisms* capable of producing irritant products is not necessarily sufficient in itself to cause inflammation. The *resistance of the tissues* must always be taken into account. Moreover, the degree of irritation caused by organisms will be influenced by their detention in the tissues, by any local lesion or predisposition in the part, by its anatomical characters, and by other conditions.

REACTION OF TISSUES TO INJURY.

I. Injury and Repair of a Non-Vascular Tissue.—To a minute spot in the centre of the anterior surface of the cornea, Senftleben applied a solution of chloride of zinc, which soaked through the dense anterior corneal lamina without destroying it. By this method he found it possible to kill the corpuscles immediately underneath the affected area of the cornea without influencing the marginal vessels. The cornea remained quite clear, showing no naked-eye change ; but, on the third day, microscopic examination showed that the swollen corneal corpuscles round the damaged area were shooting processes into it. By normal karyokinesis, these cells gradually replaced those destroyed, until the corneal corpuscles were completely restored. In this instance of tissue-reaction we have simple destruction on the one hand, and simple regeneration on the other.

II. Injury and Repair of a Vascular Tissue (" Inflammation ").—If the web of a frog's foot, or some other piece of thin transparent tissue, be placed under a microscope, and the part under observation be touched with a drop of chloroform or other volatile irritant, a definite series of changes can be observed. The first of these is a distinct *dilatation* of the arterioles ; then of the veins ; and, about an hour afterwards, of the capillaries. The dilatation progresses steadily, and is accompanied by some increase in the length of the vessels, so that they become slightly tortuous. The arterioles are affected most, then the veins, and, least of all, the capillaries. This enlargement of the bloodvessels is at the onset accompanied by a temporary *acceleration* in the flow of the blood. If the injury has been extremely slight, the vessels and circulation may at this point

gradually return to the normal; but, in the large majority of cases, by the time the dilatation is complete, this acceleration begins to give place to progressive *retardation*, the vessels still remaining dilated. Pulsation can now be observed in the smallest arteries, and the blood-stream is slow enough for the observer to distinguish the individual corpuscles in the capillaries and smaller veins, and sometimes even in the arterioles. The retardation of the blood-current may take place rapidly, and is always first observable in the veins.

As the blood-current becomes slower, the axial stream becomes broader, and white corpuscles, in increasing numbers, fall into the

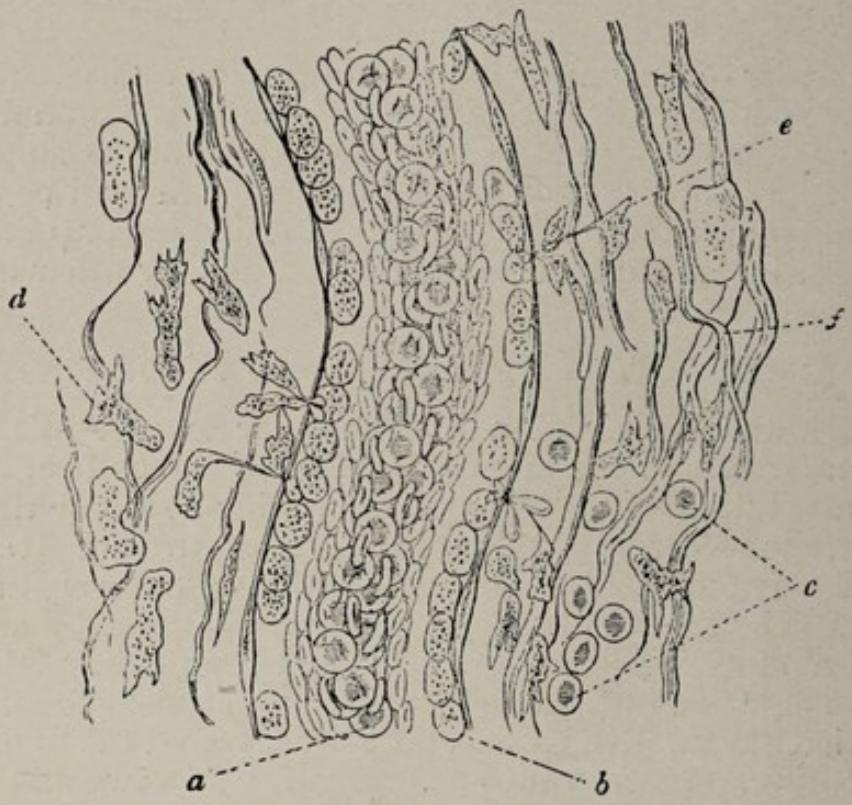


FIG. 82.—SMALL VEIN IN MESENTERY OF DOG, AFTER EXPOSURE FOR HALF AN HOUR AND IRRIGATION WITH SALT-SOLUTION. (× 340.) (MODIFIED FROM THOMA.)

a, red corpuscles; *b*, leucocytes adhering to wall of vein; *c*, red corpuscles; *d*, leucocytes which have escaped from vessel; *e*, leucocyte in act of escaping; *f*, fibrous tissue.

marginal stream, rolling slowly along, stopping here and there, and finally coming to a standstill (Fig. 82). Thus the smaller veins become lined with leucocytes. Somewhat similar, but less complete, changes occur in the capillaries. In the meantime the distinction between axial and marginal streams completely disappears, and the vessels become filled with both red and white corpuscles. Actual measurement shows that the vessels may be at least one-fourth larger than natural. After a time all onward movement ceases in the capillaries, and their contents sway to and fro with the pulse. This is known as the stage of *oscillation*, and is succeeded by that of *stasis*, in which no movement of any kind occurs. In

the severest cases, thrombosis may take place; this always occurs when the capillary walls are dead.

If a small vein lined by leucocytes be carefully watched, some of the leucocytes immediately adjacent to the wall can be seen gradually sinking into and passing through it into the surrounding tissues. The actual passage of the leucocytes through the wall cannot ordinarily be observed. Small button-shaped elevations appear on the outer side of the wall of the vessel. These gradually enlarge, assuming the form of irregular, pear-shaped bodies adherent by their small ends to the vessel-wall, and often send out processes whilst so attached (Fig. 82). Ultimately, the small pedicles of protoplasm give way, and the corpuscles are free outside the vessel. A similar escape takes place, but to a less extent, from the capillaries (*diapedesis*).

As a rule, in inflammation the escape of white corpuscles greatly exceeds that of the red; but in some cases, in which almost complete stagnation is induced in a large number of capillaries, the usual state of affairs may be reversed. From such capillaries the red corpuscles pass out in great numbers—probably between the endothelial cells—occupy the interstices of the tissues, and give the exudation a hæmorrhagic character. Several may escape in quick succession from one place, giving rise to a red spot, visible to the naked eye as a punctiform hæmorrhage. No gross rupture of the vessel-wall occurs, as may be shown by injecting the vessels. On the other hand, when *retardation has not culminated in stasis*, most red corpuscles remain within the vessels, and pass along through the inflamed area, whilst the leucocytes adhere to the walls and some pass through them into the tissues.

Both red and white corpuscles at first remain near the vessels whence they have escaped, but they are soon pushed away by other corpuscles, or washed on by the escaping fluid. The white corpuscles have, in addition, some power of amœboid movement, stimulated and directed by the chemical products in the neighbourhood of the irritation (*chemiotaxis*, p. 207); for this reason they may ultimately be found far from their place of egress. When absolute stasis occurs, the emigration of corpuscles ceases.

While these visible changes are in progress, a much larger amount of fluid than naturally escapes from the vessels passes into the surrounding tissues. Moreover, the exuded fluid differs in composition from the normal lymph. The greater the damage to the vessels, the more nearly the exudation approximates to the liquor sanguinis, and the greater the number of corpuscles it contains.

By the time all these events have occurred, the irritant may have disappeared, and the consequent vascular changes just described may have begun to subside. If the extreme periphery of the inflamed area be closely watched, the corpuscles of the stagnant blood will be seen to move off one after another, until a slow stream is re-established through the inflamed area. This stream quickens as resistance diminishes, and contraction of the vessels follows the

gradual recovery of power by their muscular coats. Exudation, first of corpuscles, then of fluid, ceases, and the circulation again becomes normal.

The cells are removed mainly by the lymphatics; the exuded fluid also escapes by the lymphatics and, after restoration of the circulation, by the veins as well. In the later stages any unremoved blood-corpuscles or fibrin undergo autolysis, and thus the complete removal of the inflammatory products is much facilitated. Any endothelial or connective-tissue cells, which may have been destroyed by the irritant, are replaced by multiplication of the surviving cells, and the recovery of the inflamed tissue is complete.

The changes which occur in the *healing of wounds* furnish good illustrations of the phenomena of "inflammation" just described.

1. **Healing by First Intention.**—If an incision through the skin and underlying structures be made by a sharp aseptic instrument, and no subsequent infection of the wound be permitted, the following changes can be observed. The incision through the capillaries, arterioles, and venules will be followed by a small amount of hæmorrhage, and the damaged vessels will dilate. If no large bloodvessel has been injured, the hæmorrhage will quickly cease, as the divided vessels become plugged by thrombi, the thrombosis extending in each vessel to the nearest collateral branch. If the cut surfaces remain apart, and such blood as may have collected on them be removed, they will gradually acquire a shiny or glazed appearance. This glaze is formed by exudation of fluid and cells from the neighbouring vessels, in the manner just described as occurring in the web of the frog's foot. At first there will be a large proportion of red corpuscles in the exudation, but this proportion will rapidly diminish, and the coagulating fluid will then become clear and yellow. If the cut surfaces be now brought into exact apposition throughout their whole extent, they will become glued together by the exudation, some of which will infiltrate the tissues in the immediate neighbourhood, and some escape between the edges of the wound, thus reaching the surface of the skin. If the wound be large and deep, and the exudation considerable, it is necessary to provide channels to facilitate the escape of the exudation. The same events will occur if the cut surfaces be brought together directly the bleeding has ceased.

Microscopic examination, on the second day after the injury, shows the cut surfaces of the wound connected by a narrow layer of coagulated exudation and leucocytes; while the tissues in the immediate neighbourhood of the incision are swollen and granular, and much infiltrated with leucocytes. These are apparently instrumental in removing such minute portions of the original tissue as may have been killed by the injury. As the leucocytes disappear, they are gradually succeeded by cells derived from the neighbouring uninjured connective tissue; while, on the external surface of the wound, the epithelium multiplies and covers the edges of the wound. In the meantime connections are also established between

the cut vessels in a manner that will subsequently be described. All these changes may be complete in a few days—less than a week—though they often take longer (Figs. 83 and 84); but if the cells of any more specialised tissues have been destroyed, their regenera-

FIG. 83.—HEALING OF AN INCISED WOUND OF THE SKIN UNITED BY SUTURE—SIXTH DAY. (× 75.) (ZIEGLER.)

a, epidermis; *b*, corium; *c*, fibrinous and hæmorrhagic exudate; *d*, newly-formed epithelium, containing numerous karyokinetic figures, and showing epithelial plug projecting into exudate lying beneath; *e*, karyokinetic figures at some distance from line of incision; *f*, new connective tissue growing from connective-tissue spaces, and containing cells with karyokinetic figures and bloodvessels with growing walls; *g*, developing connective tissue with leucocytes; *h*, collection of leucocytes at the lower angle of the wound; *i*, fibroblasts lying inside the exudate; *k*, sebaceous gland; *l*, sweat-gland.

tion, if it occur at all, will not begin until the repair of the connective tissue is complete.

This form of healing will not occur if the surfaces of the wound are left gaping superficially, or are separated in their deeper parts by foreign bodies, blood, or any considerable quantity of exudation; nor will it occur if the surfaces are allowed to move one on the other;

nor if any considerable portion of the tissues has been destroyed; nor if pyogenic organisms or any other source of irritation are admitted.

It often happens that in an extensive wound, however accurately adjusted, small collections of blood-clot will be found here and there in the course of the incision, wherever hæmorrhage from an imperfectly plugged vessel has caused separation of the surfaces. At such places the healing process is somewhat different. The vascular changes already described will occur, and the clot will thus become

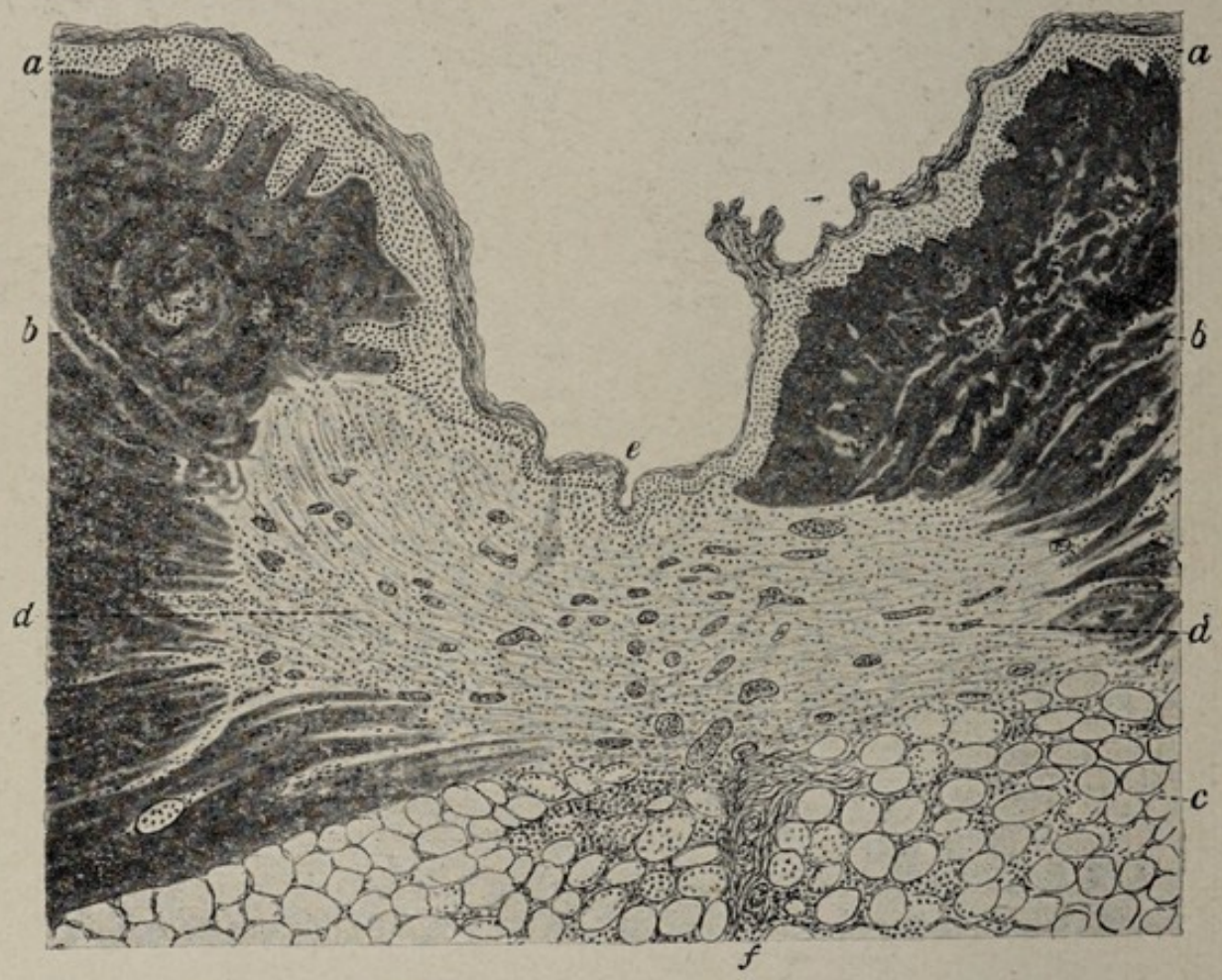


FIG. 84.—LAPAROTOMY WOUND—SIXTEENTH DAY. (× 40.) (MODIFIED FROM ZEIGLER.)

a, epithelium; *b*, corium; *c*, subcutaneous fat; *d*, vessels in scar-tissue of corium; *e*, newly-formed epithelial layer; *f*, vessels in subcutaneous scar-tissue.

surrounded by the exuded fluid and leucocytes; the latter will gradually penetrate the clot and destroy the red corpuscles. The leucocytes will be followed by cells derived from the fixed cells and plasma-cells (p. 209) of the surrounding connective tissue, and the organisation of the mass—*i.e.*, its replacement by scar-tissue—will gradually follow.

2. **Healing by Granulation.**—If the cut surfaces of the original wound are permitted to remain apart, so as to form a large and open cleft, the healing process is much slower. The *glaze* on the surface

of the wound liquefies and disappears; a larger amount of the damaged tissue dies; a greater number of leucocytes make their way from the vessels to the surface; and the vascular phenomena extend over a somewhat larger area.

The uninjured connective-tissue cells situated immediately below the wound gradually multiply, and at the same time new capillaries develop from the endothelium of the nearest surviving vessels, and form loops which penetrate into the layer of leucocytes now closely aggregated in the most superficial stratum of the wound (Figs. 85, 86). On section, a few days after the injury, there may be seen, immediately above the undamaged tissue at the base of the wound, numbers of fibroblasts in various stages, supplied with developing vessels; and, superficial to this, leucocytes, plasma cells, and fibroblasts arranged round the summits of the capillary loops, so as to form a number of small red points or granulations, from which this method of healing takes its name. Thus the wound is gradually and permanently filled up by the multiplication of the surviving connective-tissue elements—plasma-cells and fixed cells. As the granulation-tissue reaches the level of the skin, the epithelium at the surrounding edge multiplies, and, gradually extending, covers the intervening space. Many of the new bloodvessels subsequently become obliterated, and the new tissue, known as *scar-tissue*, though for a time pinker in appearance than the surrounding parts, becomes subsequently whiter and denser than the tissues around it. Healing by granulation is necessarily a much slower process than healing by first intention; while infection by micro-organisms almost invariably occurs. The presence of organisms on the surface of a granulating wound will lead to the death of many of the leucocytes, and newly formed connective-tissue cells, and, in most cases, to the formation of pus.

FIG. 85.—A GRANULATING SURFACE. DIAGRAMMATIC. (RINDFLEISCH.)

a, layer of pus-cells; *b*, granulation-tissue with loops of bloodvessels; *c*, commencing development of the granulation-tissue into a fibrillated structure.

3. **Union of Two Granulating Surfaces.**—When two surfaces have granulated as above described, they may sometimes be caused to unite if brought together, thus saving much of the time which would be required for filling up from below. The presence of micro-organisms and imperfect drainage will prevent such union. This is the way in which abscesses should heal when their walls are allowed to fall together by evacuation of the pus.

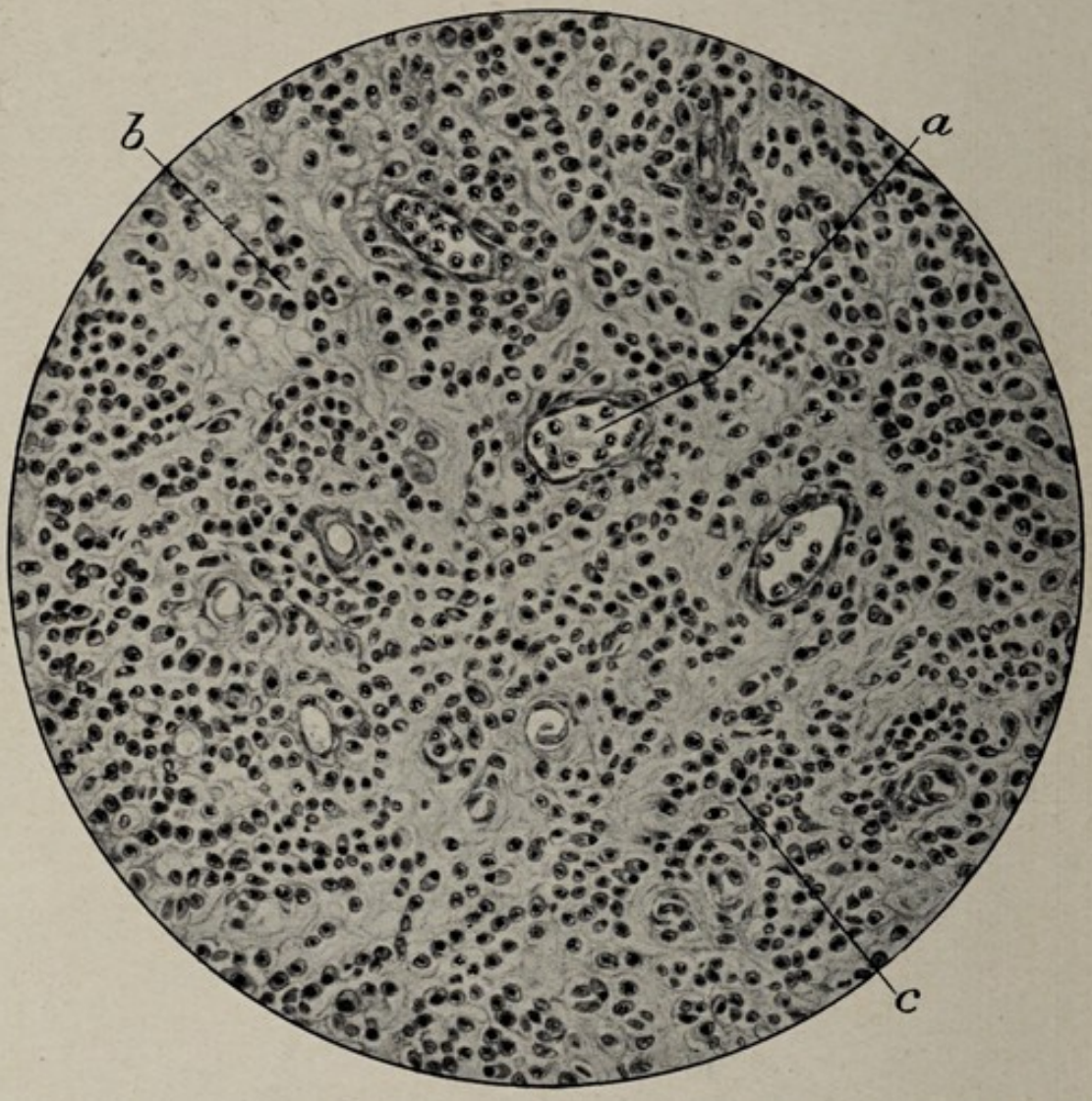


FIG. 86.—SECTION OF GRANULATION-TISSUE SHOWING THE NEWLY-FORMED LOOSE CONNECTIVE-TISSUE WITH BLOODVESSELS.

a, containing red corpuscles and numerous polymorphonuclear cells. The tissue-spaces are infiltrated with polymorphonuclear and mononuclear cells. At *b* and *c* are groups of plasma cells. (× 325.)

4. **Healing under a Scab.**—This form of healing is possible when the wound is small and the exudation forms a scab as it dries on the surface. It is not common in man, except in superficial abrasions. The formation of granulation and scar-tissue takes place beneath the scab, as also does the inward growth of epithelium. When the surface beneath the scab is completely covered with epithelium, the scab drops off. The dry scab is but slightly irritant in itself,

and does not putrefy. An attempt is made to imitate this process when wounds, such as those leading to cavities, are closed with collodion. Such treatment is, however, not free from risk; for if septic or infective organisms have entered the wound, they will probably excite inflammation, and the absence of drainage will be most prejudicial.

III. Suppuration.—In naturally occurring or experimental infection with pyogenic organisms, such as the *Staphylococcus pyogenes*, the inflammatory reaction usually proceeds to suppuration.

In the course of a few hours vascular changes, precisely similar to those described in the preceding section, can be observed in full progress. Considerable numbers of leucocytes, mainly of the polymorphonuclear variety, make their appearance in the affected area. Cocci may be found, not only at the point of inoculation, but at some little distance from it. Some will be lying free in the tissue, while many may have been taken up by the cells of the part—whether leucocytes, fixed connective-tissue corpuscles, or endothelial cells of the capillaries.

During the next twenty-four hours the cocci, on the one hand, multiply rapidly and pass into the adjoining lymph-spaces, while the polymorphonuclear leucocytes, on the other hand, collect in increasing numbers until they have completely surrounded the cocci.

By the end of the second day there are generally several central masses of cocci imbedded in, and surrounded by, a well-defined zone of leucocytes. The portions of the original tissue in which the masses of cocci lie do not stain, for, owing to the proteolytic action of the products of the cocci and leucocytes, all vessels and other evidences of structure have disappeared, except the leucocytes with which the area has become more or less crowded. Many of these show degenerative changes (fragmentation of nuclei). In the outer part of this zone the tissue is also crowded with leucocytes. In the extreme periphery, persistent remnants of the original tissue-cells may be seen. Beyond the actual limits of this mass of cocci and leucocytes (*abscess*) the vessels are dilated, and present the vascular changes previously described; while here and there cocci may be found in the lymph-spaces, in the endothelial cells of the capillaries, or in the interior of the leucocytes.

If the affected area be examined a few days later, further changes will be seen to have taken place. The centre of the abscess consists of cocci, leucocytes, and fatty débris in an albuminous fluid (*pus*). Around the pus a barricade of new cells consisting mainly of *fibroblasts* has appeared, and in it a series of new capillary loops in connection with the neighbouring and pre-existing vessels.

If the pus be removed, and the entrance and growth of other organisms prevented, the cavity will disappear by the gradual extension inwards of the granulation-tissue, until the walls meet, assisted in some cases by the collapse of its sides. The permanent obliteration of the abscess-cavity is insured by the union of the walls

and by the development of the constituent fibroblasts into cicatricial fibrous tissue.

If left unopened, an abscess generally extends or shifts its position. Its advance is due to the growth of the cocci and the action of their products: the extension is marked by thrombosis in the dilated vessels and necrosis of the cells they supply, as well as by emigration of leucocytes and exudation of fluid into the newly affected area just beyond, followed by a progressive repetition of the changes just described. The former site and track of the abscess are marked by the formation of granulation-tissue, and, later on, of cicatricial fibrous tissue. The progress of an abscess is rarely arrested until it reaches some free surface or open cavity, upon or into which it bursts. On section of the wall of a spreading abscess all the stages of inflammation can be seen—in the centre, necrosis; in the vessels, as we pass outwards from the centre, thrombosis, dilatation, and emigration of leucocytes.

Diffuse suppuration is a similar process going on over a wide area. The damage to the tissues is often more intense than when the phenomena are circumscribed, and the effect of the irritant on some portions of tissue may be so intense as to cause death of large masses of cells simultaneously. Diffuse suppuration is often due to the *Streptococcus pyogenes*, an organism which may attain a high degree of virulence.

Pus, from a simple abscess occurring in an otherwise healthy person, is a thick, creamy, opaque, yellowish-white, slightly viscid fluid, having an alkaline reaction, and a specific gravity of 1030 to 1033. It contains 10 to 15 per cent. of solids, among which are lecithin, cholesterin, fatty acids, purin bodies, nucleo-protein, albumoses, and peptones. On standing, pus separates into a dense yellow layer (*pus-corpuscles*) and a clear supernatant fluid (*liquor puris*). Pus-corpuscles are for the most part dead leucocytes of the polymorphonuclear variety. They are more or less granular and motionless: they usually contain a tripartite nucleus, which has not infrequently undergone degenerative fragmentation. A small minority of the cells may be still living and retain their amœboid movements. These are the more recently migrated leucocytes.

Chronic Abscess.—On rare occasions, if all the bacteria be destroyed, a collection of pus may become encapsuled by the uniform development, round the fluid, of granulation-tissue and its subsequent change into fibrous tissue. Such pus may long remain encapsuled, its corpuscles breaking down into fatty débris; but, as a rule, the fluid part is absorbed, and a more or less dry, cheesy-looking mass, consisting of cell-débris and cholesterin crystals, is left in the capsule.

Ulceration.—When a granulating wound is infected with pyogenic organisms, the superficial cells of the granulation-tissue will be killed, the tissues liquefied, and pus formed on its surface, while the healing process will be consequently delayed. If the growth of the organisms be very abundant and extend into the underlying tissues,

the same phenomena will occur as in the spread of an abscess, and the wound will consequently become larger. This process is known as ulceration, which may be defined as progressive *molecular destruction of tissue by irritant substances.*

Formation of Scar-Tissue (Fibrosis).—In many cases, when the injury to the tissue has been slight, but long continued, a considerable formation of granulation-tissue takes place, and a large amount of new fibrous tissue finally results. Spindle-cells develop around, and form the walls of, the capillary loops in the granulation-tissue, and from these points they gradually extend through the new tissue. Fibres seem to grow from the periphery of these cells, while the cells themselves shrink until little of them remains besides their nuclei. The new fibres also contract, and many of the capillaries become obliterated. The condition is sometimes termed *productive* or *proliferative inflammation.*

The formation of this tissue is, as a rule, preceded by the usual vascular changes and by a slight emigration of leucocytes ; and one of the most difficult problems in morbid histology has been, and still is, to discover how far the succeeding fibrous tissue is formed from the migrated leucocytes, and how far from the pre-existing connective-tissue corpuscles.

Among many important experiments which have been devised to solve this doubt, those of Sherrington and Ballance may be quoted. These observers constructed chambers, formed of two slightly separated circular cover-glasses with their edges cemented except at one spot, so that nothing could enter the space between the two cover-glasses except by the one small aperture which remained. These glass chambers were, with strictly aseptic precautions, placed in the subcutaneous tissue of dogs, and were removed at varying periods. In some cases, in less than twenty-four hours after the cover-glasses were placed in position, leucocytes had entered in considerable numbers, and had distributed themselves all over the enclosure. Only at the point of entry were there other cells. These cells differed from the "pioneer" leucocytes in that they were larger, more coarsely granular, and possessed a single clear oval nucleus. In no case were transitional forms seen. The original leucocytes were never observed to undergo any but degenerative changes. The large mononuclear cells, on the other hand, showed greater power of amœboid movement and of enclosing corpuscles than the original leucocytes. It seemed evident that they were the *successors, but not the progeny,* of the leucocytes found in the earliest stages of inflammation. Sherrington and Ballance considered that these cells were one of the normal constituents of connective tissue. Metchnikoff maintains that fixed connective-tissue cells, endothelial cells, and the large uninucleated hyaline variety of leucocytes have alike the power of giving origin to fibroblasts, and, therefore, of developing into fibrous tissue. At the present time it is generally conceded that the fixed cells of the part—connective-tissue corpuscles and endothelial cells—take

the principal share in the formation of cicatricial fibrous tissue, though it is possible that the large hyaline leucocytes also take some part in the process. In the tadpole, the formation of fibrous tissue from leucocytes has been observed. Recent studies on the healing of wounds of connective tissue in the frog have apparently demonstrated the formation, in this animal, of definite fibres of this type, which are not derived from any of the cellular elements.

The newly-formed **scar-tissue** is precisely similar to that formed during healing by granulation. At first it is highly vascular, so that a recent scar is redder than the surrounding parts. It is also characterised by a tendency to contract. This property is useful as tending to draw the edges of wounds together, and thus diminishing the area which has finally to be covered by fresh epithelium. As this process of shrinking continues, the vessels disappear, and the scar, in the course of some months or years, becomes white as compared with the surrounding parts. This *contraction* of scar-tissue appears to be essential to the process of healing, for a callous ulcer of the leg will cease to heal if contraction of the new tissue be prevented by the infiltration of the surrounding tissues and their adhesion to deeper parts. It may, however, produce the gravest deformities, as after severe burns ; or may, by pressure, cause atrophy of gland-cells and other parts, as in syphilitic cirrhosis of the liver. The contraction is most marked where the tissues are loose, as about the scrotum. A scar, and especially a tight scar, is always liable to secondary changes, such as *ulceration*, or *overgrowth* ("*Cheloid*," Chapter XIX.).

Defective Development of Granulation-Tissue.—Granulation-tissue does not always develop directly into scar-tissue. If some source of continued irritation be present, or if the vascular supply be deficient, the process may be arrested or delayed.

The normal healing process is dependent both upon the general health of the person affected and upon the local blood-supply ; in some cases the granulation-tissue, owing apparently to defective nutrition of its cells, may fail to be converted into fibrous tissue, remaining soft, pale, and gelatinous, and secreting thin sero-purulent fluid. Owing to the failure of the normal process of contraction, such "weak" granulation-tissue may grow above the level of the surrounding parts, constituting "exuberant granulations"—the "proud flesh" of popular parlance.

Deficient blood-supply may be due to insufficient development of vessels, to diminution of their lumina (as occurs in gummata), or to pressure from too dense packing of the cells.

Giant-Cell Formation.—Certain forms of inflammation are characterised by the presence of giant-cells of various types. The most prominent example is tuberculosis, in which the large multinucleated giant-cell with numerous nuclei situated round the periphery is a feature of diagnostic importance (Chapter XIV.). Large cells closely resembling these tend to form round any small foreign

bodies which gain entrance to the tissues, such as silk or catgut sutures, etc. (Fig. 87).

The giant-cells which occur in leprosy and syphilis are smaller and less distinctive than the tuberculous giant-cell, and also less numerous, especially in the case of syphilitic lesions, in which they are often entirely absent.

If we include lymph-adenoma as an infective disease, and regard the new formation of lymphoid tissue as inflammatory in nature, we have another example of the inflammatory giant-cell in the large cell described by Virchow, which is of the endothelial type, but possesses two or more nuclei which are centrally situated.

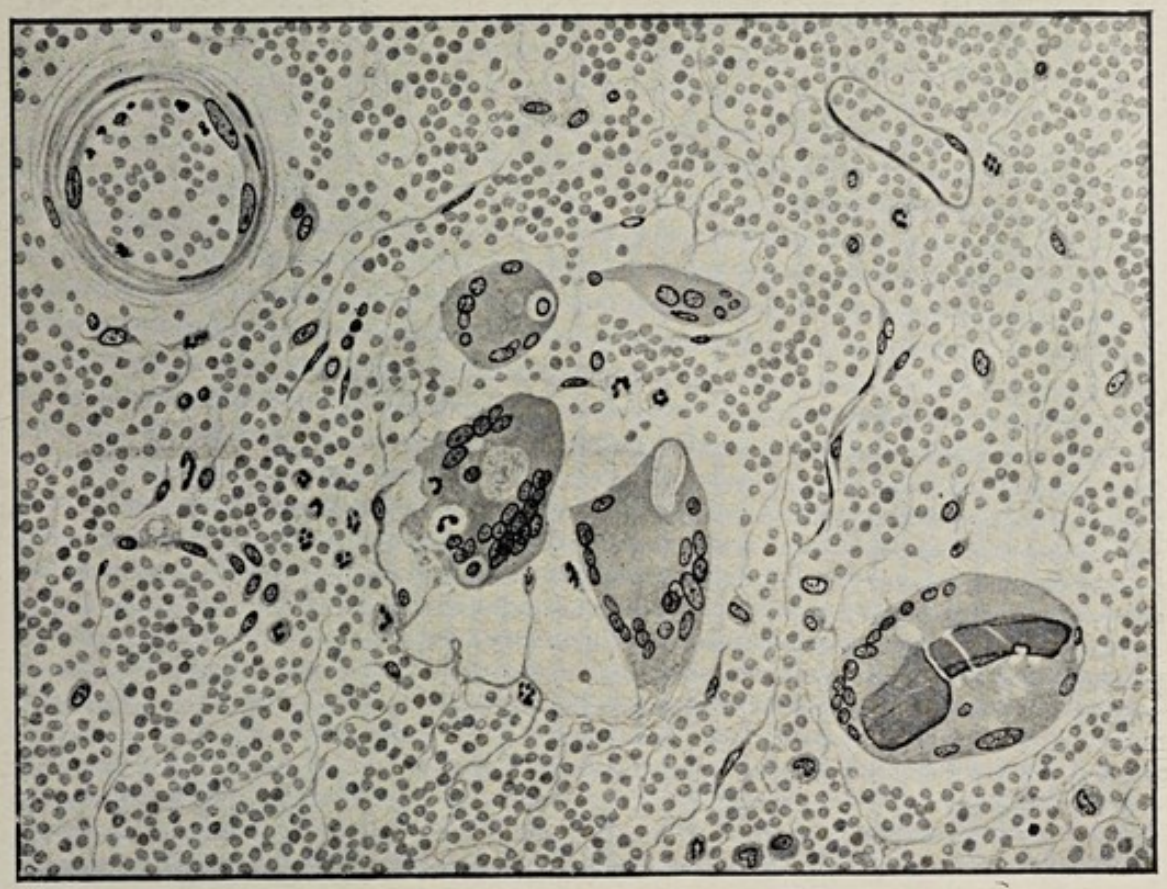


FIG. 87.—SECTION OF GRANULATION-TISSUE SHOWING THE FORMATION OF "FOREIGN BODY" GIANT-CELLS ROUND PIECES OF LIGATURE. (× 325.)

In inflammatory reactions involving voluntary muscles the fibres usually become swollen and degenerate, and this is associated in some cases with an increase in the number of the nuclei, so that structures, closely simulating multi-nucleating giant-cells, may be found in sections.

The origin of the tuberculous and other types of giant-cell has been ascribed by some to the fusion of several cells of the endothelial type, and by others to repeated division of the nucleus of a single cell, the cell itself failing to divide. The balance of available evidence is strongly in favour of the former explanation.

Fibrosis of Uncertain Origin.—Reference may conveniently be made at this place to the origin of the fibrous overgrowth which is

frequently met with in the many organs of the body, as in "sclerosis" of the central nervous system, "cirrhosis" of the liver, "myomalacia cordis," "granular" kidneys, chronic interstitial mastitis (Fig. 88), etc.

In the great majority of cases such fibrosis is associated with degenerative or atrophic changes in the more highly organised cells of the tissue affected, and with a varying degree of infiltrations with mononuclear cells.

It was formerly assumed that all such fibrous tissue was inflammatory in origin—the result of long-continued slight irritation—and

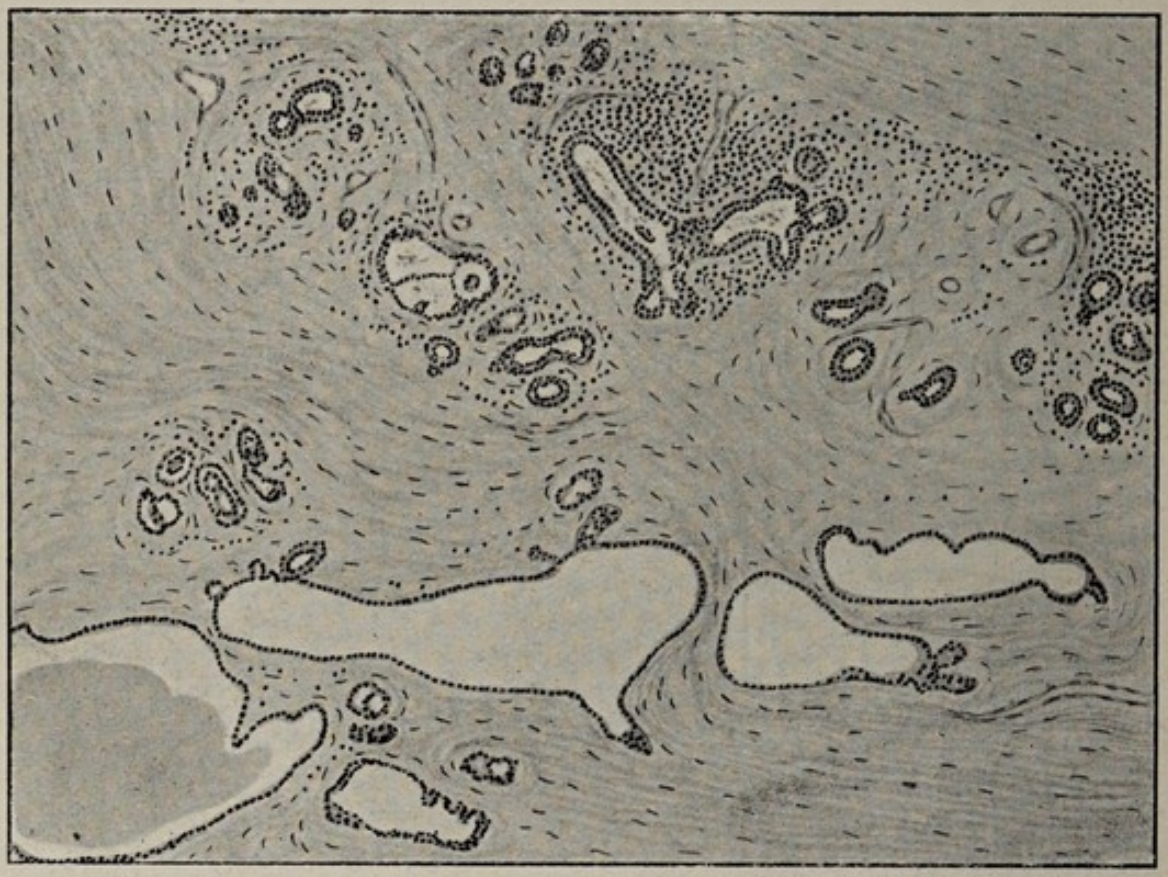


FIG. 88.—CHRONIC INTERSTITIAL MASTITIS, SHOWING THE GREAT INCREASE IN FIBROUS TISSUE, AND AREAS OF INFILTRATION WITH SMALL MONONUCLEAR CELLS. (× 79.)

that the atrophy of the glands, muscles, and nerve-cells, respectively associated with it, was due to the contraction of the cicatricial tissue thus formed. But in the case of the nervous system there are strong reasons for believing that the atrophy of the nerve-elements precedes the development of the fibrous tissue, and is due to either defects in the blood-supply, or to the direct action of such causes as syphilis and alcoholism. That in many cases the fibrous growth is not inflammatory in its origin is clear from the facts (1) that it is exactly limited to the definite nerve-tracts, and shows no tendency to spread beyond them or to follow the distribution of the bloodvessels or lymphatics; (2) that it is extremely gradual in its growth; and

(3) that it follows the experimental destruction of the higher parts of the central nervous system. The fibrous overgrowth in such cases is probably due to the increased vascular supply available for the skeletal tissue after atrophy of the nerve-elements, though it is possible that the products of the degeneration of these cells act as irritants to the connective-tissue cells, and stimulate their growth; but to some extent it is more apparent than real, being due to the increased concentration and visibility of the pre-existing connective tissue, which necessarily follows the shrinking of the atrophied parts. The position of the fibrosis occurring in the liver (cirrhosis) and in the kidney (granular contracted) is still disputed, and will be referred to when these diseases are described. The fibrosis which is associated with myocardial and vascular degeneration is, in many cases at least, of syphilitic origin.

Adami considers that non-inflammatory fibroses are due to the effect on pre-existing fibrous tissue of (1) increased arterial supply, (2) venous congestion, and (3) lymphatic obstruction.

EXPLANATION OF THE PHENOMENA.—We have now to seek the explanation of the various phenomena which constitute the reaction of living tissues to injury.

Dilatation *of the bloodvessels with* **acceleration** *of the blood-current* may probably occur in two ways: (1) Irritation of a sensory nerve is well known to cause dilatation of the arterioles in its own area of distribution. The action of an irritant not sufficiently intense to paralyse the vessels at once will stimulate the sensory nerves and cause this *reflex local dilatation* over a larger area than that mechanically damaged. The arterioles dilate, and, the blood-pressure being maintained, a larger quantity of blood is admitted to their capillaries, which cannot dilate proportionately. The blood-pressure in the capillary areas is, *ceteris paribus*, raised in proportion to the increase in the cross-section of the supplying arterioles. Under these circumstances, acceleration of stream will accompany dilatation of vessels. The walls of the latter, being uninjured, may contract after such dilatation. (2) Cohnheim found that dilatation of the vessels in the frog's tongue followed irritation, even after section of all the nerves—indeed, of everything except the lingual arteries and veins. The dilatation may then be due to *direct action of the irritant upon the local vascular nervous system*, which maintains a certain "tone" in the vessels, even after section of the sympathetic. Dilatation of arteries diminishes the resistance to the flow of blood, injury of endothelium increases it. If the former is in excess of the latter, acceleration of the blood-flow will occur. The acceleration is not seen in a part severely injured, nor as the result of the slow action of croton-oil on a part. The acceleration is most marked in the outlying parts of the inflamed area.

Dilatation *of the bloodvessels with* **retardation** *of the blood-current.*—Retardation soon follows upon acceleration, though the driving force continues unaltered and no contraction of vessels has occurred.

That this retardation is not due to any change in the blood is

absolutely certain, for (1) not only do the corpuscles behave in a perfectly normal manner just before they reach, and directly after they leave, the affected area; but, further (2), if the blood be replaced by milk or other fluid, before the inflammation is induced, precisely the same dilatation and retardation will occur. Almost the only conceivable cause of slowing is, therefore, increased local resistance, due to *alterations in the vessel-wall.* We know that in inflammation the endothelial cells swell, throw out processes and exhibit phagocytic powers. Owing to the necessary molecular changes, the cells may possibly become more sticky, or may present a rougher surface, and may thus give rise to increased friction. The rapid passage of fluid out of the vessels may also assist in delaying the blood-stream. Our knowledge concerning the cause of dilatation and retardation is, however, still very imperfect.

Exudation of Fluid.—To show this, Lassar tied a cannula into a large lymphatic of each hind-leg of a dog. He then stopped the circulation in *one* leg, and dipped this into hot water (130° F.), thereby exciting acute inflammation. On removing the obstruction the lymph-stream from the cannula at once exceeded the normal, and soon reached *eight times* that on the sound side. At first the fluid was clear, but after a time increasing numbers of white corpuscles made it cloudy, and red corpuscles were also found in small numbers. Swelling of the foot began, while the flow of lymph was free, evidently because the exudation was too rapid to be conveyed away by the lymph-channels alone, even when fully dilated. Later in the experiment the flow diminished, partly because exudation diminished as pressure on the vessels (from effusion beneath the skin) rose, and partly from coagulation in the lymphatics, and consequent blocking of these channels. The lymph collected in this experiment differed from the exudation-fluid in passive hyperæmia in that it contained a much larger proportion of protein, and exhibited a much greater tendency to coagulation. This latter property varied with the number of white corpuscles which it contained. On the other hand, it differed from liquor sanguinis in containing less protein and having a slighter tendency to coagulate. *The composition of inflammatory effusion, however, is not constant.* In the most acute inflammations it contains a large number of red corpuscles; in less severe forms white corpuscles are greatly in excess. In the more acute inflammations the fluid approaches plasma in its composition and tendencies; whilst in the less severe it becomes very like the fluid which exudes in passive hyperæmia. It also varies according to the part from which it comes: a mild degree of peritoneal inflammation will produce an effusion containing a larger proportion of protein than a far more severe inflammation limited to the leg. Inflammatory exudation is generally coagulable. Absence of coagulation may depend on the action of some restraining substances such as albumoses, or on the solution of the fibrin by some ferment.

The increased exudation is attributed to an increased permeability

of the vessel-wall, and, to a less extent, to changes in the capillary pressure : the latter is a doubtful factor.

Exudation in an internal organ gives rise to distension ; in the subcutaneous tissue, to œdema ; on a mucous surface, to a sticky fluid containing mucin, or to a firm fibrinous layer on and sometimes in the lining membrane ; on a serous surface, to a thin serous fluid, a fibrinous deposit, or a purulent accumulation.

The result of the exudation is to flush the part, thereby diluting the irritant and thus weakening its action. The exudation has also an antagonistic chemical effect on bacteria.

Emigration of Corpuscles.—It has already been pointed out that the escape of *red corpuscles* is a purely passive process, and is practically of the same nature as an ordinary hæmorrhage. With regard to the *leucocytes*, the process is more complicated.

The power of amœboid movement ordinarily possessed by these cells is sufficient to enable them to leave the blood-stream and to find their way into the tissues in inflammation. That the process of emigration is not a passive one is shown by the facts (1) that these corpuscles pass out long before any others ; (2) that their amœboid movements may be observed both before and after they leave the vessels ; (3) that, although absolute cessation of the circulation generally causes arrest of diapedesis, in some cases (tadpole) this is not so.

We have, however, still to inquire (1) why leucocytes collect in the vessels of an inflamed area ; (2) why they tend specially to pass out at that place ; and (3) what is the result of their emigration.

1. It has been proved experimentally that, if the velocity of the circulation be gradually reduced, the leucocytes and the blood-platelets are the first constituents of the axial stream which tend to fall into the peripheral. It is uncertain why this occurs. That it is not due to the low specific gravity of the leucocytes seems clear ; for if their specific gravity be artificially increased, by the ingestion of particles of vermilion, the tendency to margination is in no way affected. Once in the peripheral stream, itself moving at a slower rate than the axial, the leucocytes, rolling along the side of the presumably roughened wall of the vessel, will naturally tend to lag behind. Probably the principal force causing their detention in the peripheral stream is the same as that which attracts them through the walls of the vessel.

2. It is well known that the mere presence of particles of metallic copper in the tissues of a part (anterior chamber of the eye) will cause leucocytes to collect in the neighbouring vessels, to pass through the vessel-walls, and to approach the seat of the metallic particles. This attractive power is known as *chemiotaxis*. It seems to be possessed by the diffusible substances produced by most pathogenic bacteria during their growth in the tissues.

There are two groups of experiments which are capable of explanation on this hypothesis. In the *first*, various organisms and chemical substances have been introduced into the tissues—generally in glass

tubes which are subsequently broken *in situ*. As a result, various degrees of irritation, followed by diapedesis, have occurred, certain organisms leading to the aggregation of special kinds of leucocytes. In some instances the subsequent introduction of some other substance has, by its repellent action, arrested the emigration already in progress (*negative chemiotaxis*). Thus, Metchnikoff has shown that if a frog's mesentery be moistened with a solution of quinine, no diapedesis will occur. By the *second* group of experiments it has been shown that, if substances possessing a positive chemiotactic influence be introduced into the circulation and subsequently into the tissues, their usual effect will by this means be neutralised and no emigration result. It seems to follow, therefore, that the aggregation and emigration of leucocytes at an inflamed spot are due to the attractive influences of certain substances existing in greatest quantity in the part to which the corpuscles make their way; while the vascular changes, including the dilatation of the vessels, the lowered rate of the blood-stream, the margination of the leucocytes, and the changes in the vascular endothelium, are mainly due to the action of the same substances, and are valuable accessories in the process of diapedesis.

The action of the leucocytes on bacteria, which are the cause of practically every case of naturally occurring acute inflammation, has already been discussed in the chapter on immunity. We may, however, recall a few of the more important points.

The essential action involved is phagocytosis, and it is the polymorphonuclear cell which is the principal agent in the ingestion of most micro-organisms. Phagocytosis is itself dependent on the presence in the body-fluid of certain substances which are known as opsonins, while the accumulation of certain other substances (aggressins) derived in some way from the bacteria themselves are able to inhibit this process. The importance of substances derived from the leucocytes themselves either as the result of secretion or cytolysis is not fully understood, but the body-fluids, and especially the blood-serum, possess markedly antibacterial and, in particular, bactericidal properties.

Phagocytosis of cellular elements and débris is carried out mainly by cells of the large mononuclear type.

If the leucocytes are not attracted to the seat of the bacteria, neither their chemical nor their phagocytic action will come into play; and, unless some germicidal influence is exerted by the tissues, the bacteria will multiply and become disseminated, giving rise to generalised disease.

Tissue-Cells in Foci of Irritation.—In addition to the leucocytes just enumerated, other cells are found in inflammatory foci, the origin of which is not determined with absolute certitude. It is not even possible to distinguish the true leucocytes from some forms of cells derived from the tissue-elements. Thus, embryonic cells derived from connective tissue, as in irritation of the cornea, are practically indistinguishable microscopically from lymphocytes.

A larger form of cell possessing a single nucleus is the so-called "plasma cell," which may perhaps originate in the elements of the perivascular lymphatic sheath (Adami). This is an elongated, somewhat pear-shaped cell with a single nucleus which is situated excentrically towards the rounded end of the cell. The nucleus usually shows a deeply staining chromatin network. The most distinctive picture is obtained in preparations stained by the Unna-Pappenheim method, by which the cell protoplasm is stained a brilliant red. An unstained area of varying size is usually present, situated close to the nucleus and between it and the pointed end of the cell. The plasma cell is found in many acute and chronic inflammatory foci, often in very large numbers.

The well-known large cells of epithelial type seen in foci of tuberculosis, and called "epithelioid cells," probably originate in the endothelial cells of the capillaries and lymphatics. In bronchopneumonia the cells of the pulmonary alveoli multiply, and are shed into the air-chambers; the epithelioid cells of this condition are therefore truly epithelial in origin. In the exudates met with in affections of serous membranes many cells are present, large and small, with single nuclei, derived from proliferation of the lining cells.

Influence of the Nervous System.—All the phenomena collectively termed "inflammation" may occur in a tissue, the nervous supply to which has been completely severed. The part played by local ganglia in such a case is uncertain. The central nervous system is not, however, without influence in ordinary cases. A remarkable experiment by Samuel shows this. He took a rabbit, and divided on one side the branches of the sympathetic supplying the ear, and on the other side the auricular branches going to the other ear. As a result, the vessels were dilated on the former side, contracted on the latter. On irritating the two ears with hot water, it was found that on the side where the vessels were dilated the congestion became more pronounced, but recovery finally ensued; on the side where the vessels were contracted no such congestion resulted, but there was stasis, and finally gangrene of the ear. The same results follow inoculation of irritant bacteria. Hence it appears that the vascular phenomena are facilitated by the action of the central nervous system, but that the integrity of the latter is not indispensable to their appearance.

Clinical Signs of Simple Inflammation.—These are: *redness, heat, swelling, pain, tenderness, and impaired function.*

Redness and *heat* may be considered together, as they both depend upon *the quantity of blood passing through the part* in a unit of time. As a rule, this quantity of blood is increased, the excess being most marked in the early stage of the process, when the part is bright red and hot. While most of its vessels are dilated, the velocity of the blood-stream through them is not appreciably delayed; but as retardation supervenes, the quantity of blood passing through the part is diminished. Cohnheim excited inflammation in one foot

of a dog, and then measured the blood returning through both femoral veins. At first the delivery from the injured side was excessive, sometimes more than twice the normal; but when diffuse suppuration or sloughing was induced, and the circulation in a large area consequently delayed, the delivery became markedly less than normal. *Such a part is colder than normal,* and *bluish* if its vessels are dilated and full, but *mottled* or *pale* if they are compressed by exudation. In most inflammations the increased circulation in the outlying vessels is more than sufficient to compensate for the retardation and stasis in the most injured parts; consequently, the delivery from the veins remains excessive throughout, and the part is red and hot. Both redness and heat may be concealed if normal tissues cover the inflamed part. The skin of an inflamed foot may appear to be several degrees hotter than that of its fellow, but its temperature will never equal that in the rectum. An inflamed pleura is never any hotter than its fellow, and may be colder. The local rise of surface-temperature is due merely to more rapid circulation of arterial blood; *excess of heat is not produced in an inflamed part.*

Swelling, beyond the most trivial, which may be due to dilated vessels, is the result of *exudation of fluid and corpuscles.* It varies in amount with the distensibility of the part, being most marked in such tissues as the scrotum and eyelids, and least marked in bone. When due to fluid (*inflammatory œdema*) the affected part "pits" on pressure, unless it is very tensely stretched. In cases of slight inflammation, in which the lymphatics suffice to carry away the increased exudation, there may be no perceptible swelling.

Pain and *tenderness* are due to *pressure* of the exudation *on nerve-endings,* perhaps also to *chemical irritation* of them. They vary directly with the sensitiveness and the tension of the part, as well as with the rapidity of the effusion into it, as is seen in acute suppuration in a digital tendon-sheath. Pain is often throbbing from the increase of tension produced by each heart-stroke. The influence of increase of pressure in producing pain is well shown by allowing an inflamed part (*e.g.,* a finger which is the seat of a whitlow) to hang down.

Impaired function is due to the fact that every inflamed tissue is injured. The degree of impairment is proportional to *the amount of damage done to the essential cells* of the affected part.

Application of the Term "Inflammation."—Inflammation is a clinical term of great age, and suffers from the same disadvantage as other clinical terms adopted by pathologists, inasmuch as each successive discovery concerning its nature necessitates a wider divergence between its clinical and pathological connotations. For centuries, inflammation was known as the condition characterised by the presence of *redness, swelling, heat,* and *pain*—the cardinal signs of inflammation. Later on, two others were added—*tenderness* and *impaired function.* It was next gradually recognised that inflammation is a process rather than a condition; and it was

accordingly defined as the " succession of changes which takes place in a living tissue as the result of some kind of injury, provided that this injury be insufficient immediately to destroy its vitality " (Sanderson) : in other words, the processes comprised in inflammation represent, and can best be described as, *the reaction of the tissues to irritation.* The reaction of the tissues under such circumstances is very complex, and varies both with the irritant and with the tissue.

Further consideration shows that this reaction tends in favourable instances to counteract the irritant, and to produce repair of the injury caused by it ; and Adami consequently proposes to define inflammation as " the series of changes constituting the local manifestation of the attempt at repair of actual or referred injury to a part, or, briefly, as the local attempt at repair of actual or referred injury." It has been rightly objected by Ainley Walker that this is not a legitimate definition, since a thing or process cannot be defined in terms of its object or sequel. Indeed, the expression " attempt " is clearly inadmissible, as suggesting conscious volition on the part of the tissues. A result diametrically opposed to ordinary conceptions of inflammation also follows from accepting the view, since, according to the definition, the overgrowth of epithelium by which a wound is finally covered over is inflammatory, whereas the destruction of tissue by which, for example, a phagedænic ulcer spreads is not so, since it is not a process of repair.

It seems clear that the process of inflammation does not differ, except in degree, from response to ordinary stimuli. The repair of an injury is brought about by the same process of cell-division which effects the repair of cells which perish in the normal wear and tear of life ; and the vascular dilatation is similar to that by which increased nutriment is brought to a muscle in action. Escape of leucocytes into the spaces of the tissues probably occurs to a small extent under normal conditions, and escape of plasma certainly does so, as by this means lymph is formed. There is thus no essential difference between the replacement of cells worn out in ordinary processes of life and the replacement of corneal cells killed by a caustic. Again, the phenomena seen after simple destruction of such cells, and those resulting from injury to a portion of the skin, differ from one another merely owing to the presence of bloodvessels in the latter part : all the special features of the cutaneous lesion—hyperæmia, exudation, and the rest—result from the action of the irritant on the vessels and their contents. Finally, it is clear that the phenomena occurring after a simple aseptic incision into the skin are essentially the same as those which are present when " inflammation " of such a wound occurs. Thus, the phenomena of what is clinically called " inflammation " differ only in degree and duration from those of conditions in which there is no such occurrence. In view of this series of gradations, no point can be fixed, on pathological principles, at which " inflammation " begins ; and it is easy to account for the failure of all pathologists so

far to coin a definition of the process which shall be generally acceptable.

If, however, attention be paid only to the phenomena which are to be defined—the heat, redness, and swelling of the clinical condition—it is not difficult to explain what is meant by the term, and to define it—*i.e.*, to limit it to the state of things which is involved. In this limited sense inflammation is the series of processes which occur in a living vascular tissue in response to irritation. By "irritation" is implied the action of an injurious degree of stimulus which yet does not produce immediate death *en masse* of the tissue concerned.

Since in the course of evolution living organisms are exposed to injury and react to it, those forms which react in such a way as to effect repair of the injury tend to survive. Hence in existing forms of life reaction to injury, including inflammation, tends to result in repair. In this sense there is an "attempt" at repair, as stated by Adami. The vascular reaction leads to effusion of fluid, which dilutes the poisons responsible for most instances of inflammation and also facilitates the assemblage of leucocytes at the point of injury, carrying with them substances antagonistic to invading bacteria, and ready to devour the germs themselves; later, the connective-tissue cells multiply and fill the gap left by the death of those who have been killed by the irritant, and thus repair is effected. These cells are partly stimulated to multiply by the action of the original irritant; partly, in all probability, they increase through diminished surrounding resistance, owing to the death of neighbouring cells, and partly as a result of the increased blood-supply which exists in an inflamed part.

Varieties of Inflammation.—It has been shown that necrosis and degeneration form the earliest changes produced by irritants in the tissues, and that repair and regeneration, always more marked in the connective and least organised tissues, form the final stage. Between these, in point of time, when vascular tissues are involved, are the series of changes in the vessels and surrounding tissues, involving various disorders in the circulation, but especially a marked emigration of leucocytes and still more marked exudation of fluid. These various phenomena—damage, exudation, repair—do not exist in the same proportion in every instance of inflammation. Sometimes the necrosis and degeneration are very marked, while the vascular changes and the subsequent repair are comparatively slight. In other cases, particularly where surfaces of tissue are affected, the exudation of fluid and the escape of leucocytes are the principal changes. In other examples, especially where the connective tissues are involved, the proliferation of existing tissues is more marked than the degenerative or the vascular phenomena. For these reasons Leber has suggested a classification of inflammation into three varieties: (1) *Degenerative*, as in acute parenchymatous nephritis; (2) *Exudative* or *Infiltrative*, of which suppuration is the best example, but which also includes catarrhal,

croupous, diphtheritic, serous, fibrinous, and all acute forms of "surface" inflammations (see Diseases of Mucous and Serous Membranes); and (3) *Proliferative*, of which verrucose endocarditis may be, according to Leber, taken as the type. The difference in the character of the inflammation depends partly on the tissue affected, and partly on the nature of the irritant at work. Examples of the different forms will be found in the sections dealing with the diseases of special organs.

MODES OF SPREAD OF INFLAMMATION.—An inflammation which is characterised by a tendency to spread will always be found to be of parasitic origin. Clinically, inflammations spread by continuity of tissue, by the lymphatics, or by the blood-path. *Micro-organisms*, having settled at a spot, can spread thence in different ways. (1) They may push their way along the paths of least resistance as they grow, or be carried for short distances by the exudation from the vessels, by the ordinary lymph-streams, or by leucocytes which have taken them up—spread of the inflammation by "continuity of tissue" resulting in each case. (2) They may be carried by the lymph-stream long distances from the primary focus. Conveyed in this way, they are usually arrested in the first lymphatic gland they reach. Here they often excite a secondary inflammation without having caused any trace of disturbance between the primary focus and the gland—the organisms passing easily through the lymphatic vessels, but becoming arrested in the sinuous channels of the gland, precisely like the particles of pigment which may be found, upon microscopic examination of a gland, on the "central" side of any extravasation of blood. (3) The organisms may enter the bloodvessels, and be carried about by the blood-stream until arrested, when, under suitable conditions, they will multiply and give rise to a secondary (metastatic) inflammation, such as occurs in pyæmia in almost all organs or parts, and in mumps when the testis or ovary becomes inflamed.

MODES OF ARREST OF INFLAMMATION.—The cessation of inflammation excited by one of the *simple* causes is brought about by *removal* or *encapsulation* of the cause. (1) *As soon as the causes are removed, the cells of the damaged tissues begin to exert their inherent tendency to recover from injury.* Dead and dying cells are, in most cases, removed by leucocytes, or washed on by the exudation from the vessels; later on, their places are taken by new cells springing from the normal tissue-elements. (2) When the irritant cannot be removed, as in the case of some foreign bodies and animal parasites, it may become enclosed by a firm envelope of cicatricial fibrous tissue, and its effects thus neutralised. This process is known as *encapsulation*.

REPAIR OF SPECIAL TISSUES.

The power which most tissues possess of repairing losses of substance has been alluded to. We must now briefly state how such losses are repaired.

There are certain general statements that may be affirmed of the process of regeneration.

1. A tissue can only be regenerated by the growth of a tissue of the same kind. It is well known that the cells of one embryonic layer never produce tissues other than those which normally develop from this layer; and it is also true, with few exceptions, that regeneration of a tissue occurs only from cells of that tissue — *e.g.*, muscle from muscle, epithelium from epithelium.

The regenerative processes which ordinarily go on in adult mesoblastic tissues are still imperfectly known. Their reproductive energy has been supposed to be limited to molecular repair. Nevertheless, it is certain that the cells of most adult tissues retain the power of multiplication. That this is not manifest under normal conditions is possibly because the blood-supply received by the tissues is only sufficient to maintain the existing condition, while the resistances opposing growth, such as mutual pressure of cells, are equal to the force with which they tend to multiply. If, however, the intercellular pressure be lessened by a wound or by destruction of tissue, absorption of the damaged elements and multiplication of the cells round about will begin. Such injuries are usually followed by increased blood-supply.

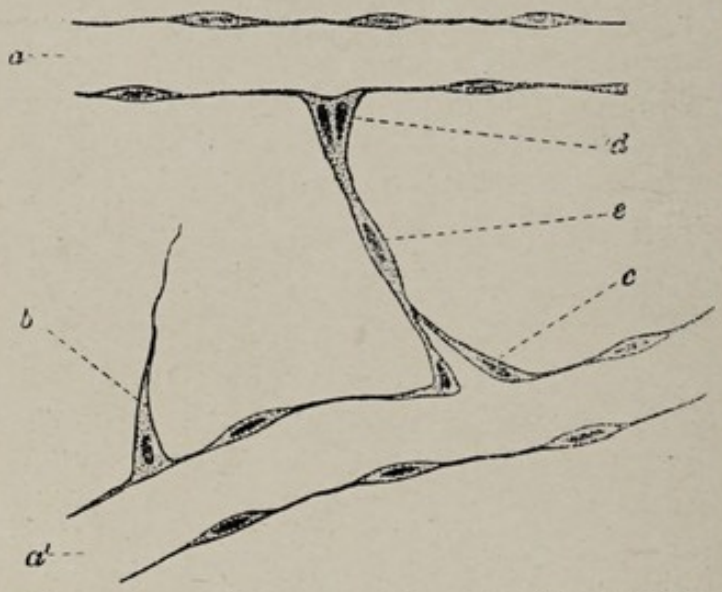


FIG. 89.—REGENERATION OF CAPILLARY BLOODVESSELS. DIAGRAMMATIC.

a, normal capillaries; *b*, capillary process; *c*, new capillary appearing in divided process; *d*, process undergoing division; *e*, connecting cell in which no sign of division has yet appeared.

2. The tendency of a tissue to regenerate varies with (1) the age of the tissue, all tissues being more easily regenerated in fœtal and early life than later on; (2) with the blood-supply; and (3) with the kind of tissue; the more highly specialised the tissue, the less readily does regeneration take place. Complex tissues are often temporarily repaired by an overgrowth of their connective-tissue stroma.

The multiplication of cells in repair, as in normal development, generally takes place by the division of one cell into two, the nucleus first dividing by the process known as karyokinesis or mitosis. This process in no way differs from that described in normal histology. On rare occasions mitotic division of the nucleus into three or more segments may occur, or direct division of the nucleus and cell take

place without the nuclear changes just described (*amitotic division*). In other cases, so-called fragmentation of the nucleus may occur, in which the nucleus alone subdivides with or without any increase in the chromatin.

Connective Tissue and Bloodvessels.

Connective tissue may be derived (1) from the fixed connective-tissue cells ; (2) from the wandering uninucleated plasma-cells ; and (3) from the endothelial cells of the vessel.

The repair of connective tissue has, however, already been discussed : it is here only necessary to describe the formation of blood-vessels in detail. In post-embryonic life capillaries develop by budding. By the end of the second day after the infliction of a wound, solid, pointed processes begin to project from some of the cells forming the walls of the capillaries : they increase in length and unite with similar processes from other capillaries, or, occasionally, with processes of branched connective-tissue corpuscles. The processes are at first very fine, but gradually widen, especially at the place where they join the fully formed vessels. Nuclei appear in the processes, and then divide, complete cell-division following a little later. The lines of union of the individual endothelial cells, as shown by nitrate of silver, appear subsequently. In the meantime, channels are formed as the cells divide. These channels open into the original capillaries, and thus the blood-cavity becomes extended (Fig. 89).

The new vessels increase in size with the new demands made upon them. According to Thoma, the increase in the size of the vessels is in proportion to the rapidity of the blood-flow through them ; while the thickness of the vessel-wall depends upon the tension of the wall—that is, upon the diameter of the lumen and upon the blood-pressure.

Muscular and fibrous coats are developed by direct extension from similar cells on the original vessels.

Epithelium.

Epithelium is always derived from pre-existing epithelium by mitotic division of the cells. This is shown by the fact that it always spreads in from the edge of an ulcer, unless islets of the rete have been left undestroyed in the midst of the granulation-tissue, or unless accidental transplantation has occurred.

The *epithelium of the skin* and mucous membranes is readily destroyed and replaced throughout life—sometimes very rapidly, as in catarrh of mucous membranes.

Glandular epithelium regenerates less readily. If all the cells in an acinus or in a tubule be destroyed, there is no reproduction of the epithelium therein. A wound of a gland, with or without loss of substance, heals by scar-tissue, which is permanent. Regeneration of *liver-cells* is known to take place in the dog, cat, and rabbit.

Mitosis has also been observed in the *renal epithelium* of man. The regeneration of epithelium furnishes many illustrations of the rule that, the more highly specialised the function of a tissue, the less likely is that tissue to be capable of regeneration.

Regeneration of *nails* and *hair* is frequent. These structures are continually being formed (" growing ") by groups of cells situated at their bases: destruction of these cells prevent further growth or regeneration of the hair or nail.

Muscle.

A *wound* in a **voluntary muscle** is temporarily repaired by fibrous tissue. As a rule, such a wound gapes widely and heals by granulation; but in some parts—*e.g.*, the tongue—retraction is prevented, and then union by first intention occurs readily.

When a muscle is incised, the protoplasm escapes through the opened sarcolemma, and leucocytes penetrate for some distance between the fibres. Granulation-tissue, followed by ordinary scar-tissue, is formed from the endomysium, and unites the ends of the muscle. New muscle-cells may then be produced by mitotic division of those on each side of the scar, and, later on, these may invade and eventually replace the cicatricial tissue. According to some observers, the surviving nuclei of the damaged fibres are sometimes able to multiply and form new fibres. In some cases, no regeneration of the muscle-cells occurs, and it is very rarely complete.

Degenerated fibres may be similarly replaced. This is seen in acute febrile diseases, especially typhoid fever.

Involuntary muscle-cells also multiply by division.

Cartilage.

A wound or breach in cartilage is generally repaired in the first instance by scar-tissue. This may be replaced later by hyaline cartilage formed from the perichondrium, and by proliferation of neighbouring cartilage-cells. The matrix is formed, according to Strasser, from the protoplasm of the cells. Often the replacement of the scar-tissue by cartilage does not occur. In cases of fractured rib-cartilages the fibrous tissue may ossify into a clasp of bone round the broken ends.

Bone.

When a bone is broken, it generally happens that the encircling periosteum is partly, or completely, torn across, as well as separated from the broken ends for some distance above and below the fracture. The damage to the surrounding tissues is liable to greater variation. In any case, many bloodvessels will be ruptured, while the interval between the ends of the bone will be filled, and the rent in the soft tissues distended, by the resulting hæmorrhage, which is finally arrested by the pressure of the extravasation and by the occurrence of thrombosis, as in healing by *first intention*. If bacterial infection

be prevented and the parts kept at rest, reparative changes commence in a few hours. The vessels undergo the usual changes characteristic of simple inflammation, and large numbers of leucocytes infiltrate the damaged tissue and invade the blood-clot. The exact intervals between the appearance of the different changes, which next follow, vary with the size of the bone and the extent of the damage.

In general terms, the damage outside the periosteum is repaired by formation of granulation-tissue and by regeneration, as in the case of any aseptic wound ; while, inside the periosteum, new tissue of a somewhat similar type is developed, mainly from the periosteum itself, forming a spindle-shaped swelling in which the broken ends of the bone are embedded (Fig. 90). This tissue also grows between and connects these ends, forming the basis of the final repair. To a less extent, similar tissue is formed in the medulla. The new tissue thus formed round the bone and in the medulla is known as the *provisional callus*.

In the case of a bone like the fibula (Fig. 90), the cells of the separated periosteum and of the medulla begin to proliferate two or three days after the injury. By the latter half of the first week the innermost (osteoblastic) layer of the periosteum has produced a large amount of new tissue consisting of broad spindle-shaped cells, plentifully supplied with bloodvessels derived from the proliferating endothelium of those in the neighbourhood.

Trabeculæ of osteoid tissue, and occasionally of cartilage, next appear in the new tissue in immediate contact with the stripped bone, and gradually spread until they occupy the whole space between the separated periosteum and the bone. By the end of the second week the extravasated blood and emigrated leucocytes have disappeared, and the space between the fractured ends is bridged by osteoid trabeculæ with osteoblasts, fragments of cartilage, and strands of connective tissue. These are gradually transformed into bone, while the remnants of vascular granulation-tissue lying between the osseous trabeculæ come to resemble ordinary bone-marrow. The growth of the trabeculæ is more extensive between the periosteum and the bone than it is in the medulla. In the meantime the dead tissues, including the sharp and jagged ends of the bones, have been absorbed.

The new tissue which actually connects the broken ends is derived from the vascular, spindle-celled tissue developed from the periosteum ; it is the last of the permanent tissue to appear, and the last to undergo final and complete ossification (*permanent* or *definitive callus*).

The first sign of involution is the removal of the jagged ends already referred to, and the absorption of any detached fragments of bone that may have died. When the ends of the bone are thoroughly united by firm compact tissue, resorption of the callus begins. This generally commences in the third month after the injury. The more accurate the apposition of the ends, and the more correct the general position, the more complete will be the

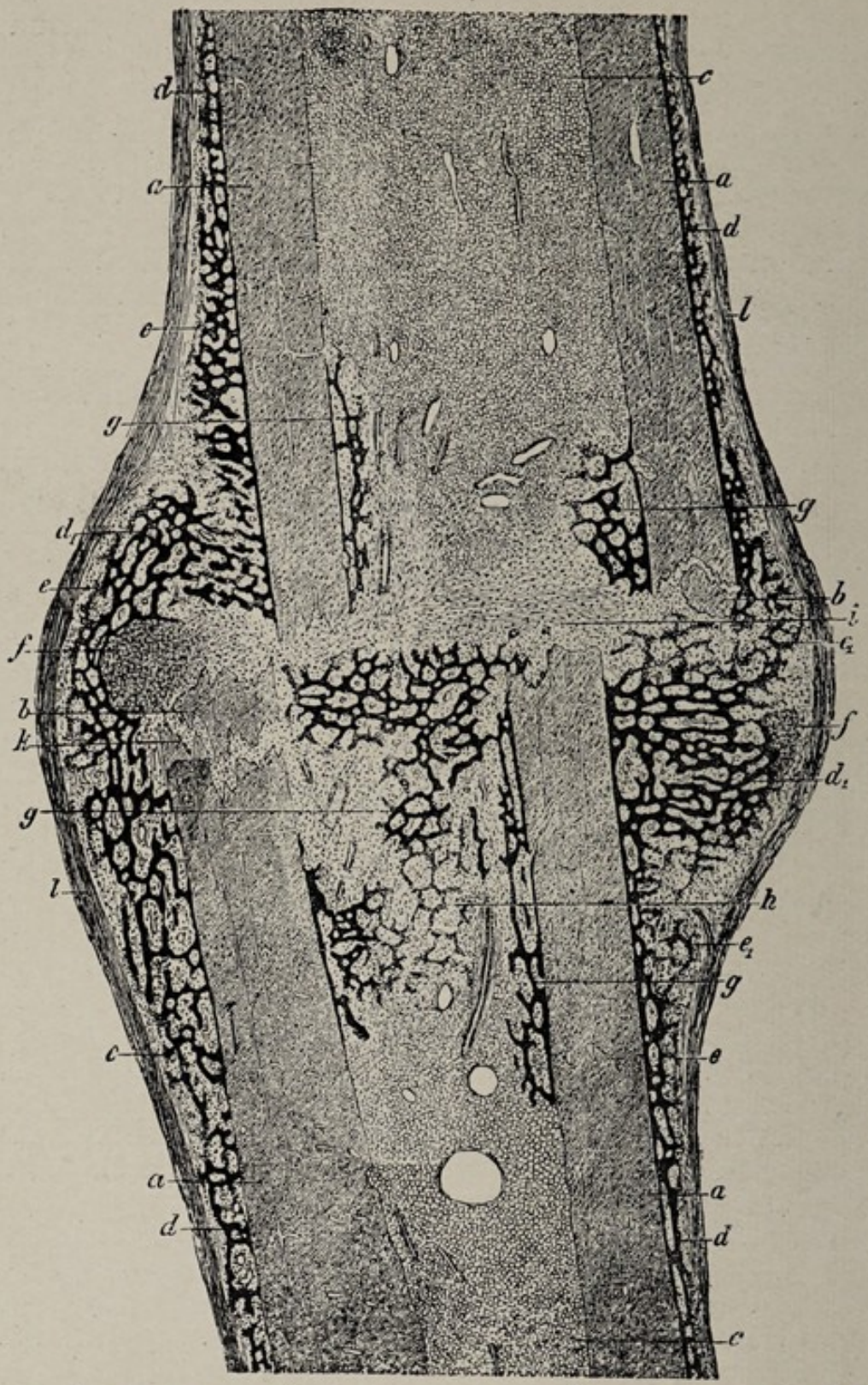


FIG. 90.—LONGITUDINAL SECTION THROUGH A FRACTURE OF THE FIBULA, FOURTEEN DAYS OLD. (FROM A MAN AGED TWENTY-FIVE; PREPARATION HARDENED IN MÜLLER'S FLUID, DECALCIFIED WITH PICRIC ACID, STAINED WITH HÆMATOXYLIN AND CARMINE, AND MOUNTED IN CANADA BALSAM.) (×6.) (ZIEGLER.)

a, compact tissue of the fibula; *b*, small splinters; *c*, fatty marrow; *d*, d_1, periosteal osteophytes; *e*, e_1, trabeculæ of osteoblasts and osteoid tissue; *f*, newly-formed cartilage; *g*, myelogenous osseous trabeculæ; *h*, myelogenous trabeculæ of osteoblasts and osteoid tissue; *i*, connective tissue covering the fractured ends; *k*, osteoblasts; *l*, external fibrous layer of the periosteum.

disappearance of the callus. So completely may it disappear that in a few months or years it may be extremely difficult to localise the exact position of an old fracture.

Repair of a fracture may be impeded by anything that causes undue movement of the fragments, by strands of muscle or other foreign tissue lying between the ends of the fragments, or by constitutional diseases which reduce the regenerative power of the tissues. If the fracture cause laceration of the nutrient artery leading to either fragment, the latter may undergo atrophy and exhibit no tendency to repair.

Nerve-Cells and their Processes.—These will be referred to in the chapters on the Pathology of the Nervous System.

Transplantation of Tissues.

Even before John Hunter's success in transplanting a cock's spur into its comb, it was believed that pieces of the body, like the tip of the nose or finger, might reunite if fixed in position soon after complete separation from the body; but accurate knowledge on this subject has been acquired only since Reverdin's discovery of "skin-grafting."

The tissues, as is well known, may survive systemic death for a short time. Portions of almost all tissues may be removed from one part or animal and successfully transplanted to another part or animal, if the conditions are suitable. These are: transference of the portion of tissue with sufficient gentleness and quickness to insure that it is alive when transferred; close contact with the raw surface prepared for it; maintenance of its temperature; and the avoidance of all bacterial contamination. The piece of tissue will, under these circumstances, become united by "first intention" to its bed, and will be nourished by lymph transuding from this surface until vessels shoot across into it. Those tissues which are least highly organised, and which require least nutriment, bear transplantation best.

Epithelium is the tissue which can most easily be transplanted. Use is made of this fact in the operation of grafting, in which small bits of *the superficial part* of the *rete* are placed upon a healthy granulating surface. Nourished at first by the exudation, these fragments grow, adhere, and form centres whence epithelium spreads over the surface. Granulation-tissue may be covered with new skin in this way; but unless scar-contraction accompanies the skinning-over, the cicatrix is liable to break down.

A piece of *skin*, an inch square, freed from all fat, may be transplanted, and thus ectropion and similar deformities may be remedied.

Similarly, a bit of *mucous membrane*, usually obtained from a rabbit's conjunctiva, is transplanted in cases of entropion.

Cartilage and *periosteum*, especially when young, bear transplantation well. So also do small pieces of *bone*. Macewen built up the shaft of a humerus with bits removed from deformed tibiæ

and introduced the practice of replacing, in the opening made in the skull by a trephine, chips of the bone removed.

Pieces of *muscle* have been successfully transplanted, and part of the sciatic *nerve* of a bird has been substituted for a corresponding piece excised from another bird. In *man* transplantation of nerve-lengths, taken from man and other animals, has been several times successful in restoring the function of divided nerves, even when months have elapsed between the injury and the operation. In all probability, however, these nerve-lengths merely act as guides along which the regenerated axis-cylinders can grow.

CHAPTER XIV

FEVER

By the term "fever" is meant an abnormal rise in the temperature of the body, together with other changes due to increased combustion of the tissues and abnormal exchange in material.

Temperature in Health.—It is usually stated that the mean daily temperature of the body is 98·4° F. This statement is only approximately correct, for the temperature varies (1) in different parts of the body, (2) with the time of day, and (3) according to the age of the patient. The variations due to these factors are greater in disease than in health. (1) The normal temperature of the *surface* of the body is always lower than that of the *internal parts*. Moreover, it is lower in proportion as we pass from the trunk towards the periphery, as well as more liable to variation from change in external conditions. In the *mouth* it is about 98·3° F.; in the *axilla*, 98·4° F. (36·9° C.); and in the *rectum*, 98·9° F. (37·2° C.). It is essential, therefore, if results are to be compared, that all observations be made in the same place. Accurate results are most readily obtained in the *rectum*. The *axilla* is less liable to variations in temperature than the *mouth*. (2) The time of the observation must always be stated, for the temperature rises during the day, reaching its maximum between five and eight o'clock in the evening, and falls during the night to its minimum between two and six o'clock in the morning. (3) The average temperature of an infant or young child is slightly *higher* than that of an adult: in the aged it may be slightly *below* the average in the adult. The full range between all these extremes is from 97° F. to 100° F.; though the average range is rather less (97° F. to 99·2° F.).

The regulating (thermotactic) mechanism is less easily disturbed as age advances. The temperature of young children is easily raised or depressed; an attack of crying may cause a distinct rise. In old age, on the other hand, when the exchange of material is small, the temperature is more easily depressed than raised. For this reason a slight rise of temperature in the aged is of much graver significance than in the average adult, and in the former even acute forms of infection may be present without any accompanying rise of temperature. The effect of food is to excite metabolism in the large mass of gland-tissue connected with the alimentary tract, and to cause a slight

rise of temperature; the taking of food may therefore quicken a rise or retard a fall. The effect of ordinary exercise is to produce a rise: severe exercise, such as prolonged running, may cause a rise of one or two degrees, or even more. Mental exertion, unless accompanied by excitement and muscular activity, has little effect upon the temperature. The greater activity of the tissues and the combustion of the ingesta are the most obvious reasons for the higher temperature during the day. A similar daily variation is observed in the respiration and pulse, in the discharge of urea and carbon dioxide, and in the intake of oxygen. The diurnal variation, however, occurs in persons confined to bed and deprived of food, so that the explanation may lie in the diminution of tissue-activities during sleep. In those people who are in active work during the night, and are asleep during the day, the normal course of the temperature is reversed.

Symptoms of Fever.—Since the introduction of the clinical thermometer the term "fever" has come to be almost synonymous with that of "rise of temperature." This latter condition is certainly the most easily ascertained, the most readily recorded, and, on the whole, the most reliable symptom of fever. The course of the temperature in all febrile attacks is divisible into three stages: (1) the *onset*, or period of rise; (2) the *acme*, fastigium, or stationary period, during which the temperature is more or less at its height; and (3) the *fall*, decline, or period of defervescence.

The **onset** may be *sudden*, the temperature rising three to seven degrees before the end of the second day; or it may be *gradual*, rising every evening, and falling slightly every morning, until the full height is reached, as in typhoid fever. The sudden onset is frequently accompanied by an intense sensation of cold and a violent attack of shivering, known as a *rigor*. The arterioles of the skin are contracted, and though the internal temperature is rising rapidly, the skin is cooler than normal, and the ordinary loss of heat from this source is diminished. In children, in whom the controlling power of the nervous system is less developed than in later life, a *convulsion* often takes the place of the rigor. The gradual onset may be marked by slight chilliness, but very rarely by rigors.

The **fastigium,** or second stage, may be over in a few hours, or may last for weeks. The temperature may remain at a fairly constant level, or it may oscillate several degrees each day.

The **final stage** of fever, like the onset, may be sudden or gradual. When sudden, it is said to end by *crisis*. The drop is often accompanied by "critical" sweating, or diarrhœa; and even when the internal temperature is normal, the patient, guided by the sensations usual in sweating, may feel uncomfortably hot. Sometimes the fall is so rapid and so marked that the patient may be in danger of dying, and may actually die, of collapse. When the fall is gradual, it is said to end by *lysis*. This is analogous to the corresponding form of onset, as the temperature falls by a series of morning drops, broken by slight rises in the evening. The special types of fever

characteristic of some diseases are in all probability dependent on peculiarities connected with the growth of special parasites. When fever ends in death, the temperature often rises just before this occurs, and may occasionally go on rising for a short time afterwards.

The **extent** of the rise of temperature varies greatly. Above 107° F. the fever is called *hyperpyrexia*, and a temperature at or above this point, enduring for any length of time, is usually fraught with the greatest danger to life. In such cases prompt measures are necessary to prevent death.

Types of Fever.—A febrile temperature almost always exhibits a tendency to rhythmic daily **variation** like the normal temperature —being higher in the evening than in the morning. Sometimes the opposite is the case, and the temperature is then said to be of the *inverted* type. When the daily variation does not amount to much more than two degrees, the fever is termed *continued*. When the variation is greater than this, the fever is *remittent;* of this type *hectic fever*, which accompanies chronic suppuration, is a good example. When the drop between two maximum points reaches or falls below normal—so that there is a fever-free period—the fever is said to be *intermittent;* of this variety malaria is the type. In many instances the course of the temperature is quite irregular.

Effects of Fever.—High temperature is generally accompanied by cloudy swelling of the tissues, and, if prolonged, by fatty degeneration.

Apart from rigors and chilliness, which are usually associated with the onset of fever, the earliest symptoms, as regards the **nervous system,** are headache, incapacity for self-application, general sluggishness of mind, loss of self-control, and hyperæsthesia of the special senses. Delirium is frequent—at first at night, and for short periods only, but later on more marked, and even constant. Vague muscular pains are common in early stages; even in their absence, unwillingness for exertion is marked. The muscles waste rapidly, and their movements become weak and tremulous. The nervous system has a large share in producing tremor and prostration, and is responsible for such a symptom as constant picking at the bed-clothes (*carphology*); general convulsions, as already mentioned, may occur in children. In fever the frequency of the **heart-beats** is increased. This result can be obtained experimentally by the application of heat. Yet the rapidity of the pulse bears no exact proportion to the height of the temperature. It is much greater in some diseases than in others; for example, in scarlatina than in typhoid fever. The heart, among other muscles, fails progressively in quality and power; and as it does so, its beat becomes more frequent and less effective. Here, again, the nervous system may be partly at fault, the inhibitory influence of the vagus being impaired; but direct damage to the cardiac muscle is probably the most important cause. Similarly arterial tone is progressively lost. The result of the progressive failure of the heart-force and

arterial tone is that the pulse, which in a healthy individual at the commencement of a long fever is quick, full, strong, and often inclined to hardness from high arterial tension, becomes, as the disease progresses, quicker, softer, and fuller, though no further rise of temperature has occurred. The softness and fulness of the pulse are due to loss of arterial tone while the heart-beat is still strong; the softness increases as the arterial tone yields, and actual *dicrotism* of the pulse may result. Later on, the size diminishes as the still more rapidly beating heart fails to fill the vessels. Ultimately the pulse is very small, soft, and frequent, or, as it is termed, *thready*. Increasing frequency of pulse, with a steady or falling temperature, is often regarded as the characteristic sign of a failing heart; though the "quality" of the first sound really affords an earlier indication of this occurrence.

Respiration is quickened. This change, like the increased frequency of the pulse, is possibly due in some measure to the effect of the rapidly-heated blood—in this case, on the respiratory centre—as it can be induced experimentally by similar means. The oxygen absorbed and the carbon dioxide exhaled are increased during the initial rise in temperature, but both fall to their normal level if the fever is prolonged.

Digestion is impaired, for the secretions from the glands discharging into the alimentary tract are diminished. Appetite is lost (*anorexia*), and its place is taken by thirst. The tongue is dry and often furred. There is usually constipation, due probably to sluggishness of the intestinal muscle, to lack of secretion, and perhaps to absence of some of the normal stimuli to contraction. **Excretion,** as tested by the rapidity with which certain ingesta appear in the urine, is said to be slow in fever. Although the amount of fluid taken is larger than in health, the urine is small in quantity, has a high specific gravity, yields a copious precipitate of urates, and contains an excess of urea, uric acid, potassium salts, and pigment (*pathological urobilin*). The chlorides are diminished; a trace of albumen is often present, and occasionally hyaline casts. The amount of acetone is increased, and diacetic acid and other organic acids may appear in some instances.

The increase of *urea* excreted is one of the earliest changes, and may even precede the rise of temperature. The excess is generally absolute: sometimes it is only relative; that is, more is passed than would be excreted by a healthy man confined to bed on a similar diet. There is usually a marked increase at the commencement of defervescence: this is most likely due to an accumulation of its precursors in the blood or tissues.

Post-Mortem Rise of Temperature.—A slight rise of temperature often occurs after death, especially in those dying suddenly or of acute diseases. It is most marked in cases of fever due to the presence of bacterial products in the blood, and in cases where death occurs with a high and rising temperature. Tetanus is probably the best example. The explanation is, that cessation of the action

of the heart is not accompanied by immediate extinction of tissue-change. Thermogenic processes continue for a longer or shorter time; and thus, while the production of heat ceases gradually, the loss of heat, being largely dependent on the respiration and circulation, is cut down so suddenly that the rectal temperature rises for a brief interval, and then falls gradually, as in other cases.

PATHOLOGY OF FEVER.—The foregoing account has shown that the essential condition in fever is increased *thermogenesis* combined with a disturbance of the heat-regulating process, or *thermotaxis*, whereby the normal balance between heat-production and heat-loss is upset. The thermogenesis is due to increased breaking-down of the tissues, especially of the muscles and the glands. As has been already indicated, by increased thermogenesis is meant that a febrile patient will produce more heat in a given time than a healthy person upon the same diet and under similar circumstances; not necessarily more than a healthy person on ordinary diet, though even this may be the case. The febrile patient takes less food, and the increased heat which he produces is due to the excessive combustion of his tissues. Traube held that diminished loss of heat was the principal cause of the raised temperature in the body of a febrile patient, and that this was brought about by an energetic contraction of the vessels of the skin. But such a contraction of vessels is by no means constant, and when it occurs is not of long persistence. Moreover, a high temperature and a freely sweating skin often occur together, and calorimetric observations have actually demonstrated the increased thermogenesis. If support be required for the view that fever is dependent on increased destruction of tissues, it is found in the proportionately increased discharge of urea.

Thermogenesis is under the control of the central nervous system, but in the present state of knowledge it is impossible to speak certainly of the position of the controlling centre, of its function, or of the paths of its afferent and efferent fibres. It is evident that the causes of fever may induce the increased thermogenesis, either by acting *directly* upon the tissues or by acting on them *indirectly through the nervous system*. In certain cases—*e.g.*, nervous or hysterical fever—it seems impossible that the cause can act upon the tissues otherwise than through the nervous system, but in the majority of cases it may act either way.

It has been shown that thermogenesis may be increased enormously in health without any rise of temperature, and it is therefore believed that fever involves a disturbance of **thermotaxis,** whereby the balance between heat-production and heat-loss is disturbed. If this balance were maintained, as in health, a stable temperature at a higher level than the normal would result. But the chief characteristic of the temperature in fever is its variability. Cold, food, excitement, effort, antipyretic drugs, all affect the temperature in fever much more markedly than they affect the temperature in health. As MacAlister says, the usual daily fluctuation of the temperature in fever shows merely that *all* the thermal processes

are not utterly deranged, some which are rhythmic in health remaining so in disease.

CAUSATION.—Fever may be due to *infective* or to *non-infective* causes. The **infective** causes are living organisms, animal or vegetable, which multiply within the body.

The **non-infective group** includes: (1) *simple traumatic fever*, which ensues upon aseptic injuries (contusions and fractures). It is generally slight, and is most probably due to the absorption of fibrin-ferment (and very likely other pyrogenic bodies) from the seat of injury: possibly irritation of nerves—by the original injury or by fragments of bone or tissue—may have some effect in causing the fever, though *strong* irritation of a sensory nerve causes depression of temperature. The fever which occurs in aseptic wounds is probably due to the same causes as the simple traumatic. (2) Rise of temperature and symptoms of fever may be caused by *injuries to the central nervous system—e.g.*, hæmorrhage into the pons Varolii. (3) *Nervous* (*hysterical*) *fever* is supposed to be due to the defective control of the central nervous system over the regulation of temperature. The rises of temperature which, in children, puerperal women, and other weakly adults, occur from various emotions and other slight causes—*e.g.*, the rise which is so commonly found after an entertainment has been held in a hospital-ward—seem to be examples of nervous fever. This form is unaccompanied by the other phenomena of fever (p. 223).

CHAPTER XV

CERTAIN INFECTIVE DISEASES

SEPTICÆMIA AND PYÆMIA.

THE diseases known as *Sapræmia*, *Septicæmia*, and *Pyæmia* result from the absorption and dissemination throughout the body of organisms—mainly, but by no means solely, pyogenic cocci—and their products.

Under *Sapræmia* (*Septic Intoxication*) are sometimes included those forms of "septic" absorption which are due to the introduction of the chemical products of the organisms without the organisms themselves; and under *Septicæmia* (*Septic Infection*) those due to the introduction and multiplication of the organisms within the body. Neither of these diseases is accompanied by secondary suppuration. *Pyæmia*, on the other hand, is a term used to denote those cases of pyogenic infection which are characterised by the occurrence of embolism and abscesses. The three conditions are frequently associated, and the distinction between them is based on clinical and not on pathological grounds, and has little to recommend it.

1. **Sapræmia.**—The constitutional effects produced by the absorption of pathogenic organisms are always due to the toxic action of their products. It is theoretically conceivable (1) that in some cases these products may be absorbed without any of the organisms which gave rise to them; and (2) that, even if any organisms be simultaneously introduced, they may be accompanied by so large a quantity of the poisonous products that death will follow before the organisms have time to multiply and afford proof of their presence. In both these instances symptoms will rapidly follow infection—as in any other case of chemical poisoning.

The word sapræmia* literally means the entrance of *putrefactive* products into the blood-stream. Such products are poisonous, but they are only exceptionally formed within the body, as in instances of decomposition of pleural effusions, owing to admission of putrefactive organisms from without. Sapræmia is generally due to poisoning with the toxines of pyogenic cocci, which have developed

* Greek σαπρός, putrid. The term "sepsis" as used in surgery is applied to invasion by pyogenic cocci, rather than to putrefaction.

in blood-clot or other discharges connected with wounds. This form of septic poisoning can occur only where extensive surfaces are open to the absorption of large quantities of toxic products under considerable pressure. Such conditions may exist in bad compound fractures, in wounds of large joints or of serous cavities, and in the uterus immediately after parturition. Any of these may form an extensive culture-ground for organisms, the products of which may be rapidly absorbed. It is worthy of note that absorption takes place with comparative difficulty from a granulating surface; hence septic intoxication is commoner as an immediate result of an operation or injury than at later stages, when granulation-tissue has had time to form. Pure *sapræmia* without any *septicæmia* rarely, if ever, occurs, and the term has little real significance, in a pathological sense.

Diphtheria and tetanus may be regarded as instances of sapræmic diseases, inasmuch as the bacilli in both instances remain localised, and do not, apart from exceptional cases, enter the blood-stream.

2. **Septicæmia.**—All diseases in which living organisms multiply in the blood-stream are technically instances of septicæmia: examples are seen in plague and Mediterranean fever. Surgically the term is usually limited to cases of infection with pyogenic organisms, especially streptococci. Infection may occur from the smallest prick; no large wound is necessary. The organisms grow in the blood, and may be isolated from it by suitable methods. Many adhere to the endothelium of the capillaries, and by their growth and "clumping" form plugs which block the vessels, in some cases giving rise to minute hæmorrhages, and occasionally to miliary abscesses.

The blood in cases of septicæmia generally contains an increased number of leucocytes of the polymorphonuclear type. In severe and rapidly fatal cases the number of leucocytes may be diminished from the outset, and such a diminution usually occurs during the last stages of any fatal case. There is usually a secondary anæmia of varying severity (Chapter XXVII.) and there may be a certain degree of jaundice. The petechial hæmorrhages that occur may be due to an action of the toxines upon the walls of the capillaries, similar to that which takes place in snake-poisoning.

The *post-mortem changes* in *Sapræmia* and *Septicæmia* are indefinite, but practically identical. Decomposition sets in early, owing to the organisms present. The lining membrane of vessels and heart is often blood-stained from the rapid disintegration of the red corpuscles. Minute hæmorrhages may be found anywhere, especially beneath serous membranes, and the spleen is enlarged. The bases of the lungs are congested, partly because of the changes in the vessels, and partly because of the heart-failure which precedes death.

3. **Pyæmia.**—Pyæmia differs from septicæmia in that the absorption and dissemination of the bacteria give rise, not only to a general infective disease, but also to scattered abscesses. This is the

distinctive pathological characteristic of the disease. It is always accompanied by some septicæmia.

The source of infection is usually some suppurating wound; but cases may arise independently of any wound, as is seen in acute osteo-myelitis, infective endocarditis, and those rare cases of "spontaneous" pyæmia in which no primary lesion can be found. In these cases the bacteria have probably entered through some trivial, unobserved lesion in the skin or mucous membrane. As in septicæmia, they gain access to the blood, and are thus distributed. Clinically, the disease is generally signalised by an intermittent form of pyrexia, rigors often occurring with each rise of temperature. The other features are those of septicæmia.

Pyæmic abscesses are most frequent in the *lungs*, but may be found in the liver, spleen, kidneys, and brain. They may occur in any vascular part. They lie generally upon the surface of organs immediately beneath the capsule, possibly owing to the arrest of the organisms taking place most readily in the smallest vessels. They vary in size from minute, scarcely visible points of suppuration to cavities an inch or more in diameter; they are usually multiple, and may be very numerous. They are surrounded by a hyperæmic zone. Often more than one organ is affected, and these abscesses may occur with others of the second kind. Sometimes the lungs escape, while other organs, lying beyond them on the blood-path, are affected.

Suppurative pylephlebitis, or portal pyæmia, is a local variety occurring as a rare complication of chronic ulceration in any part of the gastro-intestinal tract, of suppuration of the gall-bladder or in the neighbourhood of the portal fissure, or of inflammation of the umbilical vein in newly-born infants. It gives rise to small multiple abscesses, often scattered throughout the liver, but always in connection with branches of the portal vein.

A disease somewhat similar to pyæmia has been experimentally produced in animals by the introduction of pyogenic cocci into the blood.

Besides the abscesses, the following *post-mortem changes* may be found. As in all septic diseases, rigor mortis is feeble and decomposition sets in early. Emaciation is generally marked, and the skin yellow or jaundiced. Petechiæ may be present. The wound, if there be one, is sloughy, offensive, and perhaps surrounded by diffuse inflammation. Thrombi are present in one or more inflamed veins leading from the foci of infection, and are undergoing infective puriform softening (see Phlebitis); the ends of one or more thrombi perhaps project into a large vein in which the circulation is not arrested. Hypostatic congestion of the lungs is generally present; the spleen is large and pulpy; and the heart, liver, and kidneys show cloudy swelling.

Infective Granulomata.

The diseases included in the group now to be described are collectively known as the "Infective Granulomata," since the

characteristic lesions produced by the organisms respectively present take the form of small nodular masses of granulation-tissue.

GLANDERS.

Glanders (*Equinia*), an infective disease, due to the growth of the *Bacillus mallei*, is, like all the members of this group, distinguished by the presence of characteristic local lesions.

In *animals* two varieties of the disease are described. In (1) *Glanders*, the nasal mucous membrane and its prolongations are the seat of the earliest lesions; in (2) *Farcy*, the skin and subcutaneous tissue. Each form may run a rapid or a slow course. Both varieties of the disease are common among equine animals, especially horses, and are communicable from them to other animals, including man. The disease is also transferable from man to man.

In *Man* the distinction between the two varieties does not obtain, as the lesions of the one form nearly always supervene upon those of the other.

Appearances.—The characteristic lesions resemble acute abscesses in some particulars, and typical tubercles in others. They are best seen in the more **chronic** varieties. A circumscribed nodule (*farcy-bud*) appears, varying in size from a mere point to that of a pea or bean. On section, this is found to consist of a mass of leucocytes in the centre, and a zone of epithelioid cells around it, while an additional external zone of red blood-corpuscles is not uncommon; vascularisation of the bud is at best very imperfect. Necrosis occurs in the centre, and more or less suppuration follows. When a farcy-bud forms near a free surface, an ulcer, with a sharply-cut indurated margin and a very foul base, usually results. Such ulcers may heal, but their course is generally very chronic.

In the more **acute** forms of the disease the poison sets up ordinary suppuration at the spot where it develops. The inflammation is not always circumscribed: sometimes it is diffuse, giving rise to infiltration of muscles, of subcutaneous tissue, and of the connective tissue of the orbit. This is succeeded by suppuration at several points, or throughout the infiltrated tissue.

Course.—A wound is a common place of entry; mucous membranes, especially the conjunctival and nasal, are also seats of primary affection. In many cases there is no evidence to show how the poison has entered.

In **acute glanders,** after a variable period of incubation, inflammatory nodules appear in the mucous membrane of the nose, frontal sinuses, or other places, and run on more or less rapidly to suppuration and ulceration. The fever and muco-purulent or bloody discharge from the nostrils are thus explained. The submaxillary and cervical glands swell—from infection through the lymphatics. The bacteria then enter the blood-stream, and are carried to distant parts, giving rise to metastatic abscesses in the lungs and other internal organs, in the skin, and in the mucous membranes of the

respiratory and alimentary tracts. Abscesses in the subcutaneous and intermuscular tissues are common, and suppuration in joints occurs. In fact, the disease resembles pyæmia in many respects, being, like it, due to the dissemination by the blood of an organism capable of exciting suppuration. The abscesses in organs are generally small, but may reach a large size. The respiratory and alimentary mucous membranes are probably infected from the nose. On the skin, red papules and larger patches of inflammation appear. On these, vesicles and then pustules—often with hæmorrhagic contents—quickly develop. These constitute the *rash* of the disease. The earliest stage is a collection of round cells in the superficial part of a papilla; a little later a pustule is found to have developed under the rete. The fever is high throughout the disease, symptoms of prostration appear early, and death occurs with all the signs of septic poisoning.

In **chronic glanders** large "buds" appear in the subcutaneous, submucous, and intermuscular tissues. Those near the surface break down slowly, and form foul ulcers; the lymphatics become much swollen, hard, and knotted, and the glands are greatly enlarged. The general symptoms are much milder. This form often ends in recovery. In fatal cases the symptoms of acute glanders frequently supervene before death.

RHINOSCLEROMA.

This rare disease, which presents some points of resemblance to glanders, is due, in all probability, to infection with *B. rhinoscleromatis* of Frisch. It consists in the formation of hard, sharply-defined masses in the skin or mucous membrane near the anterior nares, the process subsequently spreading to the lips, gums, and nasal cavities, and thence to the palate. Later on, the pharynx and glottis may be involved, thus becoming both rigid and narrowed. Similar changes have been described in the external auditory canals. The growth has never been known to generalise, and for years the health remains unaffected. When the disease is not interfered with, extension is slow, but continuous. Recurrence has invariably and rapidly followed even apparently complete removal.

The masses round the nostril are like cheloid or hypertrophic scars. They are light or dark brownish-red in colour, and here and there smooth and fissured. The skin around is quite normal. There is little or no tendency to ulceration.

Microscopically, there is found dense infiltration of the corium, with small round cells lying in a fibrillated stroma. Many of the cells are spindle-shaped, and a few may be epithelioid, but large cell-forms are the exception. The growth is moderately vascular, and presents no tendency to fatty degeneration. Cornil describes some of the cells as containing "hyaline masses," which may also be present in the tissue.

ACTINOMYCOSIS.

This disease consists in the formation of small tumours or abscesses, due to the growth of the *Streptothrix actinomyces* (p. 135). The commonest seats are the lungs and liver, but the fungus may be found in any part. It is more commonly met with in the lower animals than in man. In cattle the disease most often affects the jaws.

APPEARANCES.—On section, the tumours have an open spongy appearance (Fig. 91), and a puriform or caseous fluid can be squeezed

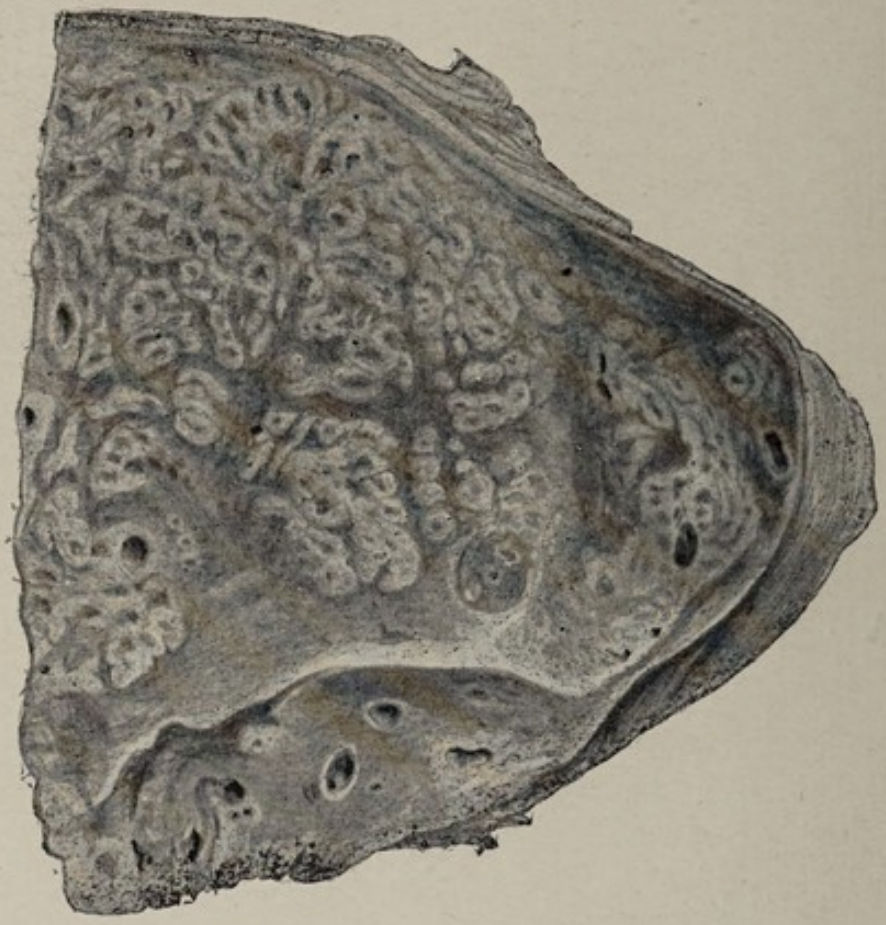


FIG. 91.—ACTINOMYCOSIS OF THE LIVER. (C. C. H. MUSEUM.)
The sponge-like areas are made up of fibrous trabeculæ enclosing spaces filled with granulation-tissue and pus.

from them. Besides fatty cells, this fluid contains many pale yellow granules, just large enough to be visible to the naked eye. These, when gently squeezed and cleared up by potash, are seen to consist of filaments radiating from a common centre, and bearing at their free ends club-shaped swellings (Fig. 53). The filaments are often branched. Threads and spherical bodies are found less frequently. The nodules and abscesses also contain granulation-tissue, intersected here and there by bands of fibrous tissue. In the older specimens there are found, round each fungus, the usual signs of a chronic inflammation caused by a slight, constant irritant.

ÆTIOLOGY.—The fungus may enter by one of three channels.

1. **The Mouth.**—Through a carious tooth or extraction-wound the fungus reaches the interior of the jaw. It then grows and bursts through the outer plate, and gives rise to an abscess in the glands or in the connective tissue of the neck. It is probable that infection may also take place through the follicles of the tonsil in tonsillitis, or of the pharynx in pharyngitis (*prævertebral abscess*).

2. **The Respiratory Passages.**—When the fungus is inhaled, bronchial catarrh is set up, and the parasite may be found in the sputum. It next gains access to the alveolar walls and there gives rise to nodular foci. These develop into suppurating or caseous centres, which bear a superficial resemblance to the caseous broncho-pneumonia of phthisis. The cavities may rapidly coalesce, with symptoms like those of phthisis, though marked hæmoptysis is uncommon. Some of these abscesses, after much burrowing, may find their way into the chest-walls, involving the breast or even the subcutaneous tissue and skin. It is noteworthy that, though the actinomyces affects the lungs from above downwards like the tubercle bacillus, it leaves the apex—above the clavicle—uninvolved. The pleura and lung may occasionally be infected secondarily from the posterior mediastinum: in these cases the œsophagus is probably the source of infection. This disease, in its progress, may give rise to ordinary serous or purulent inflammations in which no trace of the actinomyces can be discovered.

3. **The Intestine.**—The intestine may be affected primarily from within, or, secondarily, by embolism or by extension from other organs. The primary form generally gives rise to nodular foci in the mucous and submucous tissues, which break down into ulcers with undermined edges. Actual actinomycotic lesions of the intestine are very uncommon, though several cases of appendicular actinomycosis have now been recorded. The comparative frequency of hepatic lesions, however, suggests that infection via the alimentary tract is not uncommon.

In some cases actinomycotic embolism may lead to scattered abscesses accompanied by symptoms of pyæmia. Secondary foci may occur anywhere. Ponfick has seen a granulation-mass growing into the jugular vein in a case in which there were growths in the right auricle and ventricle.

There is no reliable evidence that the disease can be acquired by direct infection from diseased meat. The history of an epidemic in Iceland suggests that the bristles from ears of barley and other cereals, in penetrating the mucous membrane of the mouth and pharynx, may give rise to the disease, though it is not yet proved that the parasite can flourish in the ears of cereals.

Madura Foot or Mycetoma.

In certain parts of India the feet of the natives are liable to a peculiar swelling; "tubercles" form beneath the skin, burst, and leave sinuses from which bodies, like those constituting the roe

of a fish, are discharged, or, more rarely, bodies like grains of gunpowder. In the latter, fungous elements have been recognised, and were originally called *Chionyphe carteri;* they are now recognised as a form of Streptothrix (*Str. maduræ*). These are believed by some to be the cause of both classes of the disease. On section through a diseased part, masses of the above bodies are seen, especially in the fatty subcutaneous tissue; the masses may have no obvious communication with each other or with the surface. Kanthack considered the disease a form of actinomycosis: Boyce and Surveyor acknowledge the similarity, but not the identity, of the two, and this view at present prevails.

CHAPTER XVI

CERTAIN INFECTIVE DISEASES—*Continued*

TUBERCULOSIS.

TUBERCULOSIS is an infective disease due to infection with the *Bacillus tuberculosis*. The characteristic naked-eye lesion produced by the growth of this organism is the formation of small circumscribed inflammatory lesions known as " tubercles."

Tuberculosis occurs in two distinct forms—*the acute generalised* and the *chronic localised* disease. *Acute generalised tuberculosis* is a rapidly spreading infection, in which the bacilli are carried to all parts of the body by the blood-stream, and establish themselves in many organs simultaneously, giving rise to symptoms of fever and general toxæmia, closely resembling those of enteric fever or any other specific infection. After death the lungs, meninges, liver, spleen, and other parts, are found studded with miliary tubercles. A primary focus can usually be identified, in a caseous bronchial or mesenteric gland, from which infection has been carried in the form of a massive dose of tubercle bacilli to all parts, by rupture of the caseous focus into a bloodvessel.

In the *chronic localised* form of the disease some organ, usually the lungs, but in other instances the kidney, synovial membrane, bone, or other part, is the seat of an infection which spreads gradually by local extension, producing a destructive lesion confined at first to the organ originally affected, which is gradually destroyed by caseation and fibrosis.

The cause of this difference is to be sought for in varying degrees of resistance to the bacilli. The acute generalised disease is usually met with in children and young adults, and is analogous to the condition induced in rodents by intravenous injection of a large dose of organisms. It indicates a very deficient degree of resistance to the infection. This susceptibility of children to tuberculosis is similar to their susceptibility to other infections, such as scarlet fever or measles. In them the localised form of tuberculosis of the lungs which constitutes the " consumption " of adults is rare, this localisation of the infection pointing to an increase in resisting power acquired with advancing age. It is probable that this increase in resistance is dependent on accidental inoculation from time to time

with minute quantities of bacilli, too few to induce disease, but capable of exerting a " vaccinating " influence. Post-mortem and other evidence (v. Pirquet's reaction) shows that as age advances an increasing number of children and adults give signs of tubercular infection, although the individuals do not exhibit symptoms of disease: they have been attacked by the tubercle bacillus and have overcome it, thus acquiring increased immunity. Evidences of this past infection are seen in calcified tubercular glands or scars in the lungs found at necropsies on those who have died from other diseases; these are said to occur in over 90 per cent. of the inhabitants of certain towns who have reached the age of forty years.

A noteworthy decline in the mortality due to tuberculosis has taken place in Great Britain, and also in other European countries, within the last seventy years. It is probable that just before the period at which health statistics were first regularly compiled, owing to the migration of masses of the population from the country into towns, a considerable rise in the tuberculosis death-rate had occurred. As the people gradually accustomed themselves to the new conditions, and as sanitary improvements were effected, a fall in the death-rate due to tuberculosis occurred. At the same time, owing to the widespread distribution of the infection, the more susceptible individuals and families tended to die out, while a general rise in resistance was brought about by transmission of acquired immunity by those who had been brought into contact with the bacilli in non-lethal quantities and who had overcome the infection. It is apparently a law of general application that as a disease becomes more widely spread among a population, so it tends to become less virulent and fatal. This is probably the case with syphilis at the present day, as well as with scarlet fever, diphtheria, and other infective diseases.

Sources of Infection.—In every case of tubercular disease the bacilli are introduced from without, and are derived directly or indirectly from some previous case of the disease in man or animals. The two principal sources of bacilli are (1) *the sputum of persons with tuberculous lungs*, and (2) *the milk of cows with tuberculous udders*.

1. **Sputum.**—When it is remembered that about one-seventh of mankind die of pulmonary tuberculosis, and that, in the majority of cases, the patients, for weeks or months, expectorate large quantities of bacilli, without any precautions being taken against infection, it is clear that there is an ample supply. The bacilli, with small particles of mucus, expelled by coughing, may be inhaled directly by the healthy; but the sputum which dries upon handkerchiefs, bedding, garments, furniture, and the walls and floors of workshops and other rooms, thence to be detached as dust, appears to be the most fertile source of infection.

2. **Milk.**—When the disease of the udders is extreme, tubercle bacilli can be found in the milk; but when the disease is less marked, its infective quality can only be shown by inoculation, and, less certainly, by feeding. Butter made from infected milk is itself

infective. It is probable that tuberculosis in children is often due to infection with bovine bacilli.

Other sources of tubercle bacilli exist, but they are rare:

3. The **fæces** and the **urine,** in cases of tuberculosis of the intestine and the genito-urinary tract respectively, and the discharges from **tubercular abscesses and ulcers,** are infective.

4. Tubercle bacilli may be occasionally conveyed in **tuberculous meat.** The muscles themselves are rarely involved, but infected glands may be left, or the meat during its removal may be smeared with tuberculous material. The surface of meat, however, is generally raised to a temperature over 100° C. in the process of cooking; and this source of infection is, therefore, practically confined to those cases in which glands are eaten, or in which raw meat is prescribed in the treatment of disease.

5. **Tuberculous mothers** may conceivably infect their offspring during intra-uterine development (see below).

Modes of Entry.—There are four possible ways in which tubercle bacilli may enter the body: (1) *inhalation,* (2) *feeding,* (3) *inoculation,* and (4) *in utero from the mother.*

1. **Inhalation.**—The inhalation of tubercle bacilli is usually regarded as the most frequent cause of the disease, especially in adults. In favour of this view are quoted the frequency with which the lungs, or the bronchial glands, are alone involved; the readiness with which animals can be similarly infected; and the accidental death, in one case, from pulmonary tuberculosis, of an assistant engaged in such an experiment. In ordinary respiration the inhaled bacilli are not carried beyond the smaller bronchi, where they may be deposited; and as they multiply but slowly, many are expelled by ciliary action and coughing before they can seriously injure any spot and effect an entrance. In the deep inspiration through the open mouth which follows the expulsion of the reserve air in coughing, the bacilli may be carried almost to the infundibula, if not to the air-cells, while the existence of pleural adhesions, or of a badly-formed thorax, by limiting the movements of the lung, will lead to the retention of local secretions.

Having no power of locomotion, the bacilli must be carried through the mucous membrane like the particles of carbon in anthracosis. The leucocytes, reaching the surface, may there meet and enclose the bacilli, and in many cases carry them back into the tissues. If the cells degenerate while the bacilli survive, the latter may find themselves in some place where they can thrive, multiply, and produce their characteristic lesions. In catarrhal states many phagocytes reach the inflamed surface, and any bacilli that may be present are therefore more likely to be introduced into the tissues. Not infrequently the bacilli may lodge and multiply in the mucous membrane, and the disease commence as a local tubercular bronchitis.

In children, and less frequently in adults—especially in those who, because of nasal obstruction or habit, breathe through the

mouth—the bacilli may reach the cervical glands and distant organs through the mucous membrane of the mouth and fauces. Not improbably this is the route by which inhaled bacilli usually reach the tissues.

2. **Feeding.**—Tubercle bacilli may also enter through the alimentary tract from infected food. Possibly, in some cases where they pass through the mucous membrane of mouth and fauces, as has just been stated, they may be derived from the food. In the large majority of cases, however, bacilli derived from food enter by the intestine.

It is often found, especially in children, that no lesion is produced by the bacilli at the point of entry, but that marked changes may occur in the lymphatic glands or in distant parts; it is also well known that marked local changes in the walls of the intestine are more often due to secondary infection from swallowed sputum in the case of persons suffering from advanced pulmonary tuberculosis, than to primary infection from contaminated food. An explanation of these facts is afforded by experiments on animals, for it is found that if *virulent infective material,* containing large numbers of bacilli, be used, marked local lesions occur at the seat of invasion, but that if *less virulent material,* containing only small numbers of bacilli, is employed, the seat of invasion presents no local lesion, while the neighbouring lymphatic glands may be largely infected, and the bacilli be carried thence to distant parts. Now it is quite certain that the swallowed sputum in most cases of advanced pulmonary tuberculosis will contain a far larger proportion of bacilli than infected food, and the presence, or absence, of local changes at the seat of invasion seems, therefore, to depend upon the virulence of the infecting material.

There is some difference of opinion as to the principal seat of invasion in instances of tuberculosis occurring in young children. It is often stated that the lungs are not affected in the same proportion as they are in later life; that the disease is not so localised, general miliary tuberculosis being common; that the bones are frequently the seat of the disease; and that the lymphatic glands are more universally affected. It is also maintained that the intestine is the part most often attacked primarily, even in those cases in which the patients ultimately succumb from disease of the lung. It is certainly sometimes possible to trace the infection from an old calcified gland in the mesentery, to the retroperitoneal, posterior mediastinal, and bronchial glands, and thence to the lungs. On the other hand, observers generally agree that, in the large majority of cases of tuberculosis in children, the bronchial or cervical glands alone are caseous—an indication that infection has occurred by inhalation, or through the mucous membrane of the mouth.

3. **Inoculation.**—It occasionally happens that a wound, in an otherwise healthy person, becomes inoculated with tubercle bacilli. Nurses have been thus infected by broken vessels containing tuber-

culous sputum; and persons taking part in autopsies on cases of tuberculosis, human and bovine, have also contracted the disease by the introduction of tuberculous material. In such cases the organisms may produce catarrhal inflammations of the skin; or they may cause delay in the natural healing of the wound, and, later on, give rise to progressive infection of lymphatics, glands, and distant parts. Sometimes, as in the case of the lungs and alimentary tract, the bacilli may cause changes in the glands and distant parts without producing any visible lesion at the point of entry.

4. **Infection in Utero.**—This may occur in cases of tuberculosis of the placenta. The possibility of latent tubercular disease being conveyed through the medium of the ovum or of the spermatozoon will be referred to when the influence of heredity is considered.

Effects of the Bacillus in the Tissues.—Once deposited in the tissues, the bacillus proceeds to multiply, and to produce a special lesion which for a long time was considered characteristic, and is known as **a tubercle** (Fig. 92). Each tubercle, as a rule, contains the following elements: (1) centrally, either one or more multinucleated *giant-cells*, or some granular débris surrounded by giant-cells; (2) outside the giant cells, in most cases, large cells with big nuclei and granular protoplasm, called *epithelioid cells;* and (3) outside these again, a zone of small mononuclear cells, which has no definite external or internal limit. The giant-cells in slowly developing lesions often send off processes which anastomose and help to form an open network in the periphery.

A *non-vascular* nodule of the above structure is the anatomical characteristic of tuberculosis, but it is not microscopically distinguishable from the products of other very local chronic inflammations. Baumgarten produced typical "tubercles" in a rabbit's cornea, by sticking fine hairs into it. Laulanie states that, in the lung disease caused in dogs by the *Strongylus vasorum*, the ova and embryos may be seen in giant-cells surrounded by zones of epithelioid cells and leucocytes. More recently Flexner has described similar lesions produced in man by a form of *streptothrix;* and so-called *pseudo-tuberculosis* in rodents has been traced by A. Pfeiffer to a short thick bacillus differing in its characters from the tubercle bacillus.

Nor can the above structure be said to be constant; for, especially in acute cases, some of the tubercles seem to consist entirely of small round cells—no epithelioid or giant-cells being visible.

Each of the smallest tubercles visible to the naked eye consists of a group of three or four giant-cell systems of the above structure (Fig. 92). Foci thus formed are known as **grey,** or **miliary tubercles.** They are greyish, semi-translucent, rounded bodies, varying from just-visible points to nodules the size of a pin's head, or larger. They are firm and shot-like, distinctly circumscribed, and project above the surface of the tissue when it is cut. The term **"yellow tubercles"** is applied to foci which are rather larger, less regular, less closely defined, and softer than those just described, owing to

the process of caseation. A large mass of yellow tubercle (*conglomerate tubercle*) is formed, not by the continued growth of a single grey tubercle, but by the blending of several arising close together and by the caseation of the participating grey tubercles and of the intervening inflamed tissue. It is often possible to recognise, round a yellow caseous mass, a narrow gelatinous zone, consisting of grey tubercles. Grey tubercles may also be seen radiating from the caseous focus into the surrounding tissues, thus indicating that infection from the central focus leads to the formation in its immediate neighbourhood of fresh tubercles which, as they enlarge and degenerate, become part of the central mass.

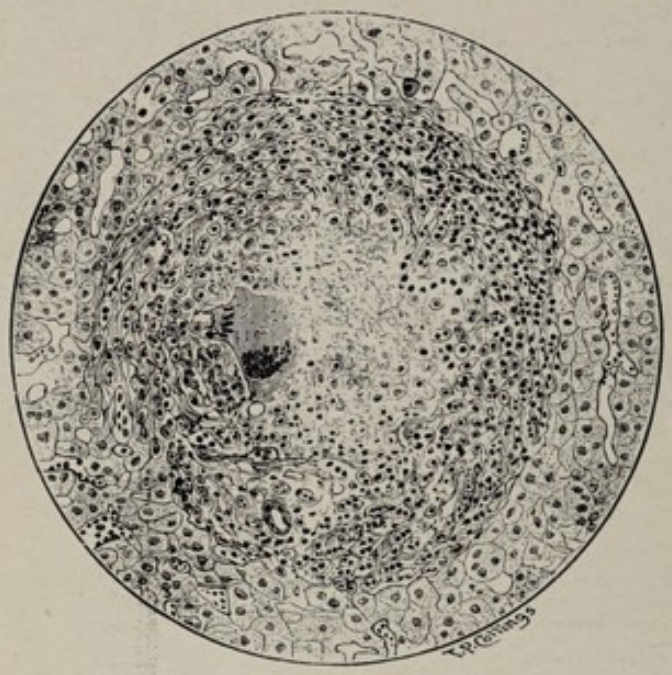


FIG. 92.—A GIANT-CELL SYSTEM, INVISIBLE TO THE NAKED EYE. (× 250.) (MONTAGUE MURRAY.)

From the liver of a child, aged five, who died from acute tuberculosis. A giant-cell with two groups of nuclei is seen near the centre. Surrounding it is an area of commencing caseation in which the cells are becoming indistinct. Enveloping this is a zone consisting of epithelioid cells and leucocytes. The leucocytes are most numerous on the side where the caseation is most advanced. The whole mass is imbedded among granular liver cells in the interlobular area.

Sometimes, especially in the lungs, the formation of giant-cell systems is followed by more or less acute inflammation in the surrounding tissues. (See Broncho-Pneumonia, Chapter XXX.) Multiplication and desquamation of the alveolar cells and escape of leucocytes together produce consolidation of the lung-substance, and the solid mass may undergo caseation, blending thus with the original tubercular masses.

SOURCE OF THE CELLS IN TUBERCLES.—According to Baumgarten *the giant-cells and epithelioid cells are derived from the local tissue-cells*, including both epithelial and connective tissue. He introduced pure cultures of tubercle bacilli into the anterior chamber of the eye in albino rabbits. In a few days mitotic changes appeared in the connective tissue and endothelial cells of the iris. These changes were limited to the cells in which bacilli were present. They were followed by proliferation of the cells themselves, which gradually assumed an epithelioid type. The proliferating patch was then gradually invaded by leucocytes, until they quite obscured the epithelioid cells. Giant cells were occasionally present, but only in the later stages; when present, they showed no sign of division, but only of degeneration.

Metchnikoff, on the contrary, maintains that the cells believed by Baumgarten to be the progeny of connective tissue are uninuclear leucocytes. In the case of the lung he admits that the endothelial cells of the bloodvessels take a share in the process, and also attributes to them a phagocytic function. In his opinion, a tubercle is formed by the *accumulation* of phagocytes and *not* by the *proliferation* of any form of cell. Giant-cells, according to his view, are phagocytes that have combined to form a "plasmodium"; while to Baumgarten and Koch they are single epithelioid cells that have begun to multiply, but, though their nuclei have divided and their size has increased, have failed at the final stage of cell-division. In parts in which epithelium is present, as in the lung, liver, kidney, or testicle, there can be no question but that the epithelial cells multiply freely.

The *giant-cells* in tuberculosis usually have their nuclei arranged round the periphery: it has been suggested that the outer zone of the cell is the part which is best nourished, and that the nuclei lie there for this reason. The central part of a giant-cell is often necrotic.

Secondary Changes in Tubercles.—The following changes may occur in tubercular foci—(1) *fatty degeneration* and *caseation*, (2) *fibrosis*, (3) *calcification*, and (4) *softening*.

1. **Fatty Degeneration and Caseation.**—These changes commence in the centre of the nodule. The central portion of a tubercle, in which caseation is commencing, consists of finely granular amorphous débris, containing, towards its periphery, shrunken nuclei—the relics of its original cells; not infrequently a more or less degenerate giant-cell may be seen within the caseated area or in its immediate neighbourhood. The process of caseation varies much in rapidity. It is usually most marked in the larger and more diffuse lesions, and these are, therefore, as a rule, of a yellow colour and soft consistence. This process often terminates in the formation of the so-called tuberculous abscess, containing "pus," which is usually curdy in consistency and, on microscopical examination, shows the presence of granular and fatty débris and scanty degenerate leucocytes.

2. **Fibrosis.**—In other cases the central portion, which has undergone fatty degeneration, is more or less completely absorbed, whilst the cells of the connective tissue at the periphery gradually form a dense, contracting fibrous capsule. This replacement of the tuberculous tissue by scar-tissue occurs in the smaller lesions, and in many of larger size which open upon the inner or outer surface of the body, and from which the infective material can be thus discharged. Ultimately a mere scar may remain, but small caseous areas are frequently present in the midst of the fibrous tissue.

This "fibroid change" is simply the encapsulation of a slightly irritant foreign body, and occurs as readily round a bullet or piece of wire lying in the tissues as round tubercular organisms in fatty detritus. It differs in no way from the formation of an ordinary

scar. The change obviously tends to protect the organism against general infection from the focus in which it occurs, and indicates that the tissues have gained the upper hand and have imprisoned the bacilli. When complete, it is the most favourable termination that can possibly occur.

Sometimes, in cases which have run a chronic course, hard, glassy bodies, often specked with black pigment, are found after death in the lung-tissue, and more rarely in the lymphatic glands. There is no caseation, and the microscope shows the masses to consist of almost hyaline fibrous tissue.

3. **Calcification** may follow caseation, if the cheesy products become encapsuled and almost all the fluid is absorbed: deposition of lime-salts takes place in this cheese-like material, and converts it either into a gritty mass or into an irregular stony body. Caseous mesenteric glands are especially prone to this change. Calcification principally affects very old limited lesions.

Sections of the small calcareous particles, when decalcified and examined under the microscope, are seen to consist of a series of concentric layers. These layers are composed of a substance which, according to Metchnikoff, gives the same reactions as that forming the envelopes of the tubercle bacilli. Arguing from his experiments on Algerian rats, he maintains that these layers are formed by degenerative changes in the bacilli within the giant-cells, and that they subsequently become infiltrated with phosphate of calcium.

Spread of Infection.—1. **By Lymphatics.**—In this way masses of *conglomerate tubercle* and patches of infiltrating tubercle, such as those of the skin (*scrofulodermia*), are formed. It is supposed that leucocytes enter the primary focus, take up bacilli, and wander out again along fine lymphatics into the surrounding tissues, there to degenerate and die not far from the parent mass. A fresh tubercle thus forms and caseates, and its margin coalesces with that of the parent mass, which in this way gradually enlarges. The young tubercles form the greyish translucent ring, with here and there an offshoot, seen round the conglomerate mass. Leucocytes containing bacilli, and free organisms, are also carried by the lymph-stream to the nearest *glands*. Thus, the process of infection of mesenteric glands from an intestinal ulcer may sometimes be traced by the presence of tubercles along the track of the lymphatics. Infection by lymphatics is most frequent when there is a marked lesion at the point of entry—*e.g.*, in tubercular ulceration of the intestine—and from time to time a spreading tubercular lymphangitis and lymphadenitis is seen in the limbs originating in an infected wound. Tubercles have been found in the thoracic duct in cases of acute tuberculosis: this is evidence that the bacilli passed by this channel to the blood.

2. **By Some Natural Passage.**—A sudden inspiration following the bursting of a tuberculous focus into a bronchus may draw the infective material into many of the smaller bronchi, with the result that a caseous broncho-pneumonia develops simultaneously in many

parts of the lung. In the same way the palate may be infected from the tongue, the intestine from swallowed sputum, and the lower urinary tract from the kidney.

3. **By Bloodvessels.**—The walls of bloodvessels, especially in the lung, may be affected by tuberculosis. The caseating foci may then rupture into the lumen and the bacilli be carried in the blood-stream to distant parts.

In one or more of these different ways the organisms reach the blood and are carried all over the body, developing when and where the conditions are suitable—in the lungs, meninges, joints, or other parts.

General Infection.—An acute miliary tuberculosis of the meninges, lungs, peritoneum, and various abdominal viscera plainly implies that a large number of bacilli have found their way within a short space of time into the blood: the result is similar to that following the intravenous injection, in rodents, of a pure culture of the bacilli. To provide the large number of organisms necessary to produce this general infection, multiplication must have first occurred in some part of the body. The focus, in which this multiplication most often takes place, and whence general infection usually starts, is a caseous bronchial gland. The caseous matter probably enters directly into the blood-stream, by means of an opening formed by ulceration into a small vein or artery. Acute miliary tuberculosis may, however, originate in any localised focus containing living bacilli. Extension by means of a lymphatic vessel leads to the formation of tubercles along this vessel, or in glands through which the lymph passes. If the thoracic, or right lymphatic, duct be affected, the organisms find their way into the systemic veins.

Limitations of General Infection.—The term *acute general miliary tuberculosis* has hitherto been used in contradistinction to *localised tuberculosis*—*e.g.*, a mass of conglomerate tubercle in the brain, or a caseous gland. But even a "general" tuberculosis, due apparently to the rapid entrance of numbers of organisms into the blood, is far from being really general; for while the lungs, spleen, liver, kidneys, testes, and meninges, are very frequently affected, the voluntary muscles, mammæ, ovaries, and thyroid gland nearly always escape. Thus, a series of regular gradations occur, commencing with (1) the most widespread miliary tuberculosis, and including successively (2) cases of miliary tuberculosis limited to the meninges or peritoneum; (3) cases of multiple infiltrating tuberculosis—*i.e.*, tubercle limited to glands, skin, or bones and joints; and finally (4) cases in which a single spot of skin, a single joint, or a single gland is affected.

The selection of special organs in "general" tuberculosis seems to indicate **local predisposition** on the part of these organs. In this way the limitation of the infection to the meninges can be explained. There is no reason for assuming that the bacilli are arrested in them rather than in other parts. The same explanation appears applicable to cases of limited miliary tuberculosis,

and may possibly be the reason why tubercular meningitis affects the base rather than the convexity of the brain.

Next, with regard to the *dose of organisms :* this may be large or small. It may be single, or it may be repeated at longer or shorter intervals. The different doses may come from the same or from different foci, giving rise to successive " crops " of tubercles, distinguishable after death—the more recent being small and grey, and the older large and yellow. When only a few bacilli enter the circulation at one time,the infiltrations which they excite reach a far larger size than they could possibly attain in the speedily fatal cases of general tuberculosis.

The *seat of infection* may assist in explaining some peculiarities of the disease, and should be borne in mind. The *different strains of the bacilli* also seem to possess somewhat different qualities, the bovine type occurring often in children, and producing lesions of bones, joints, and glands, and also a generalised tuberculosis ; whereas the human type is found most often in adults, and is specially responsible for the chronic affection of the lungs.

It is impossible to explain why some tubercular processes remain local, whilst others generalise. Blocking of lymphatics, exemption of the walls of bloodvessels, feeble local growth of the bacillus, healthy resistance on the part of the tissues in general, may afford hypothetical explanations.

Predisposing Causes—**Age and Sex.**—The disease is very prevalent during the first two years of life. The death-rate then falls, and remains low until about the tenth year, when it begins to rise again. The rise begins some years earlier in the case of girls than in that of boys, though, when all ages are considered together, the sexes are found to be equally affected. Tubercular disease is often apparently quiescent during pregnancy, but is frequently fatal soon after parturition ; and death from phthisis is often attributed to " childbirth."

Heredity.—There is a firm belief in the hereditary nature of tuberculosis, and especially of pulmonary tuberculosis. From the statistical point of view the belief probably rests on stronger evidence than has yet been adduced, for many cases of tuberculosis die unrecognised, and in many others the disease is arrested—neither of these classes appearing in the statistics.

Three explanations of the influence of heredity in tuberculosis have been put forward :

1. It is suggested that all cases are due to infection from the outside alone, and that heredity acts either (*a*) by subjecting the individual to more than the average *chances of infection,* and causing him to live in infected rooms with infected persons, and to use infected articles ; or (*b*) by aiding in the development of *habits* (for example, alcoholism), which render him less resistant to invasion There can be but little doubt that this explanation is, in a large number of cases, correct, but it certainly is not universally applicable ; for, in many instances, long intervals elapse between the

death of a parent from phthisis and the outbreak of the disease in the children; while the locality, house, and general surroundings are all different. Furthermore, it has frequently been noted that, even when the children of a phthisical parent are widely separated and living average healthy lives under diverse conditions, they still seem especially liable to infection.

2. According to Baumgarten, the solution of this question lies in the actual *transmission of the bacillus from parent to embryo*, and in its latent existence in the tissues for many years. According to him, infection may occur before or about the time of fertilisation; the bacilli reaching the uterus from the peritoneum through the Fallopian tube, or gaining access with the spermatozoa. The evidence in support of this view is derived almost exclusively from experiments on animals. Thus, fertilised hens' eggs were inoculated with tubercle bacilli; the chicks were hatched at the ordinary time, and were normal in appearance, but three weeks later tuberculosis rapidly developed. There is some reason to believe that tubercle bacilli may exist for a time in tissues without producing tubercles. They have been found in the apparently healthy testes and prostate in cases of tuberculosis of other organs; while the fœtus of a tuberculous mother has served to infect animals, though itself apparently free from disease. But if these organisms often exist in seminal discharge and thus affect the ovum, it is at least curious that tuberculosis of the female generative organs is so rare. Furthermore, this theory in no way explains the peculiarities of the disease as regards age or sex, which have been already alluded to. The possibility of this form of hereditary influence must be decided by further investigations, but it is not now usually believed to occur.

3. The least definite, but the most probable, explanation is that of some special *predisposition of the tissues to tuberculosis*, such as is now generally recognised to exist, in a less degree, in the case of such diseases as typhoid fever and diphtheria. In no other way can the objections to the other explanations be met. We have no knowledge of the physical factors in which this predisposition consists. A small flat chest and a tendency to catarrh are often present in people who ultimately develop tuberculosis of the lungs; and the absence of free respiratory movements is held to favour the development of the bacilli. The recovery of certain cases is explained on the assumption that the soil which was at one time favourable to the growth of the bacillus became at a subsequent period unfavourable; and as tuberculosis is readily arrested in some individuals, it is not unreasonable to suppose that in others the bacilli are not even able to multiply and give rise to their characteristic lesions. It is quite certain that some animals are far more susceptible than others to the disease.

Immunity to tuberculosis may be produced in animals by inoculation with attenuated bacilli, or with bacilli belonging to a different strain. Koch has endeavoured to raise the resistance of persons already infected with tuberculosis, by injecting them with a solution

of the bodies of the bacilli (*new tuberculin*) or with the actual bacilli suspended in an emulsion. The serum of healthy persons possesses some power of neutralising the toxines of the tubercle bacillus, while that of tuberculous patients is said not to have this power (Mircoli). Destruction of the bacilli is probably effected by leucocytes, aided by some special substance developed in the serum.

Tuberculosis of the Larynx.

Tuberculosis of the Larynx (*Laryngeal Phthisis*) is generally secondary to tuberculosis of the lungs, and is then due to infection from the sputum. It commences as subepithelial tubercles, situated chiefly in the arytæno-epiglottic folds, on the cords, and on the under surface of the epiglottis. These may be few or numerous, and may ulcerate early—especially on the cords—or may multiply and form a diffuse infiltration, which in the arytæno-epiglottic fold produces a pear-shaped swelling with its large end towards its fellow in the mid-line. The caseous masses rupture and ulcerate. In this way considerable masses of tubercular granulation-tissue may be formed above the vocal cords. Later on, secondary infection with pyogenic cocci may lead to abscesses and necrosis of cartilage, with hectic fever, exhaustion, and death.

Tubercular ulcers in the trachea are usually small and superficial, and also arise from the breaking-down of subepithelial tubercles. Occasionally they are both deep and extensive, and may be followed by abscesses and necrosis of the cartilages.

Pulmonary Tuberculosis (Phthisis).

The lungs form one of the commonest sites of tuberculosis in the human subject, and phthisis is one of the most important diseases contributing to the annual death-roll; moreover, those affected are largely young adults or those in early middle life.

The pulmonary lesions produced by the tubercle bacillus are of very varying type, when regarded from the point of view of morbid anatomy, though the essential cellular reactions involved do not differ from those occurring in any tuberculous focus.

The various forms assumed may be conveniently classified as follows, though the dividing lines are not definite nor rigid, and individual cases present different forms of lesion at different stages of the disease:

1. **Acute Pulmonary Tuberculosis**—(*a*) *Acute Miliary Tuberculosis.*—Infection by blood-stream.

(*b*) *Acute Pneumonic Tuberculosis.*—Infection by blood-stream.

(*c*) *Acute Broncho-Pneumonic Tuberculosis.*—Infection by respiratory tract or lymphatics.

2. **Chronic Pulmonary Tuberculosis**—(*a*) *Chronic Caseating or Ulcerative Phthisis.*—Infection by lymphatics or respiratory tract.

(*b*) *Chronic Fibroid Phthisis.*—Infection by lymphatics or respiratory tract.

The pulmonary lesions in *acute miliary tuberculosis* do not differ from those in other parts of the body. The same minute grey nodules make their appearance, scattered through the lung substance, but especially numerous immediately beneath the pleura. These nodules show the typical giant-cell systems, with a surrounding area of infiltration with small mononuclear cells. There is often a small central area of caseation and a localised breaking-down of the alveolar walls in the immediate neighbourhood (Fig. 93); but the progress of the disease is so rapid that there is seldom time

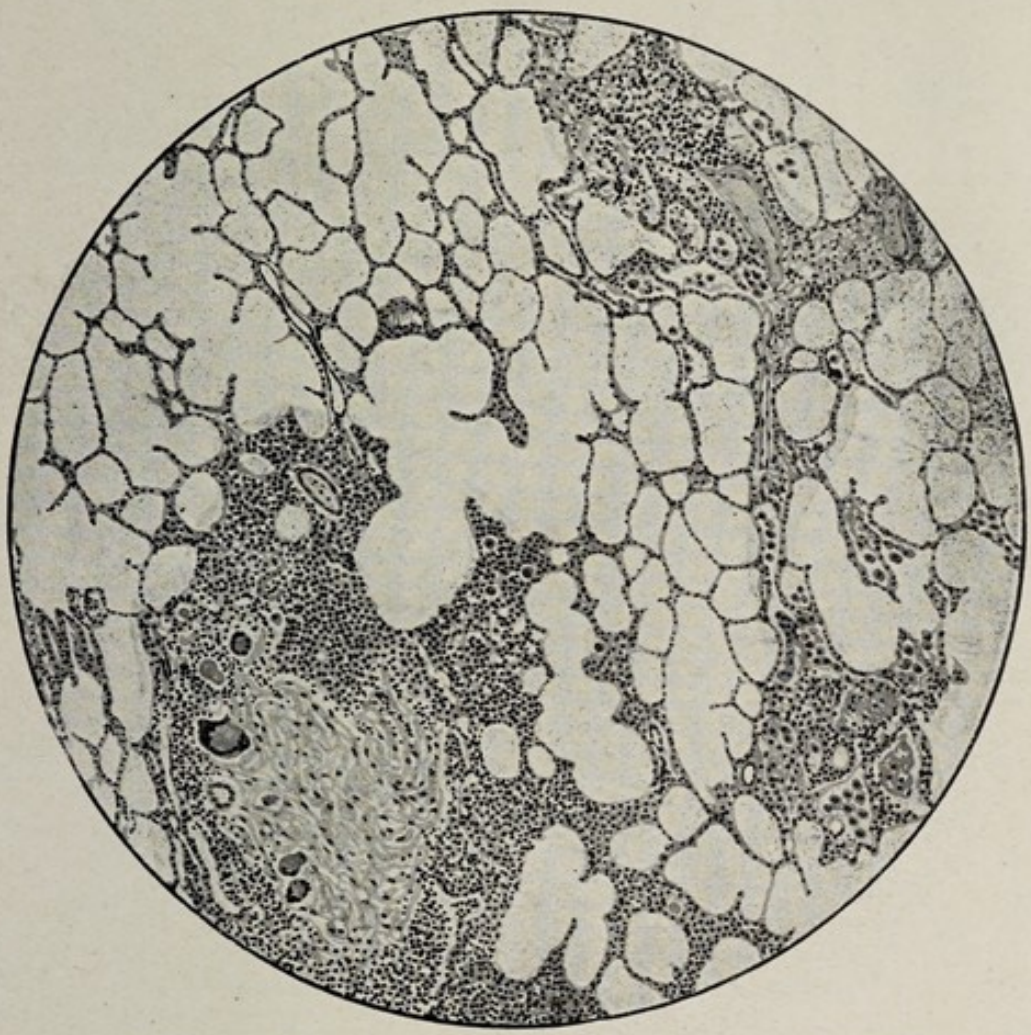


FIG. 93.—MILIARY TUBERCULOSIS OF LUNG, SHOWING SMALL TUBERCLE CONTAINING GIANT-CELLS. (× 79.)

for any extensive caseation to occur, and fibrosis is never present. It must be remembered that many cases of chronic pulmonary tuberculosis terminate by miliary dissemination, so that while one part of a lung may show the appearances described above, another part may show the disease in its chronic stage.

Acute pneumonic tuberculosis is a very rare form of the disease. As in the miliary type, dissemination occurs by the blood-stream, but the lung tissue shows areas of consolidation similar to those found in lobar pneumonia (Chapter XXX.). The non-consolidated portions of the lung usually show miliary tubercles. The disease

is rapidly fatal, and for this reason extensive caseation does not occur.

Acute broncho-pneumonic tuberculosis is most commonly encountered in children and young adults. The distribution is similar to that of the lesions in broncho-pneumonia due to pyogenic organisms, and each tuberculosis focus is surrounded by an area of hyperæmic and of localised consolidation of lung tissue, partly as the result of plugging of the alveoli by cellular proliferation and infiltration, partly from localised collapse of the alveolar walls.

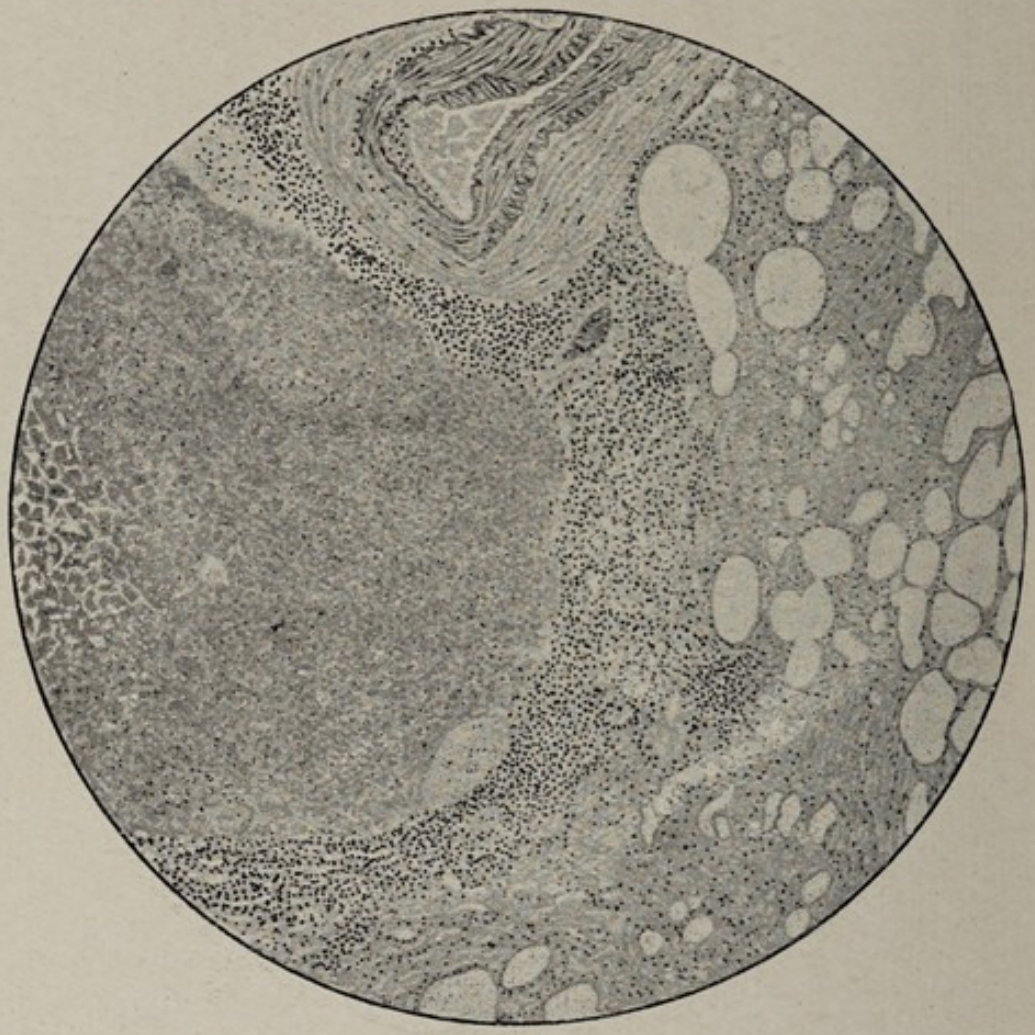


FIG. 94.—CHRONIC CASEATIVE PULMONARY TUBERCULOSIS, SHOWING CASEATION, A ZONE OF INFILTRATION WITH MONONUCLEAR CELLS, AND A SINGLE GIANT-CELL SYSTEM. (× 79.)

The lesions centre round the smaller bronchi and bronchioles, and infection is either respiratory or lymphatic in origin, or both factors may be involved. This form of the disease usually terminates fatally within a few months, so that there is seldom time for extensive areas of caseation to occur, while fibrosis is always at a minimum. Small areas of caseation, usually a few millimetres in diameter, are, however, scattered irregularly throughout the lung substance.

Chronic caseative pulmonary tuberculosis is the commonest type of the disease met with in adults. The lesion is at first localised

to some one particular spot, a point just below the apex of either lung being for some reason, not yet satisfactorily explained, the commonest site. From this initial focus the process gradually spreads, involving more and more lung tissue, while other small foci appear at other parts of the same or of the opposite lung, and, in their turn, pass through the same stages. It is needless to recapitulate the cellular reactions involved. The destruction of lung tissue occurs as the result of extending caseation (Fig. 94), and hence ragged, irregular cavities are formed (Fig. 95). The process involves all the tissues in the immediate neighbourhood, and hence an artery which crosses or lies in the wall of a tuberculous cavity gradually becomes involved in a tuberculous arteritis. The wall of the vessel softens and a small saccular aneurysm forms, and may eventually rupture, thus giving rise to hæmorrhage of varying severity, according to the size of the vessel involved.

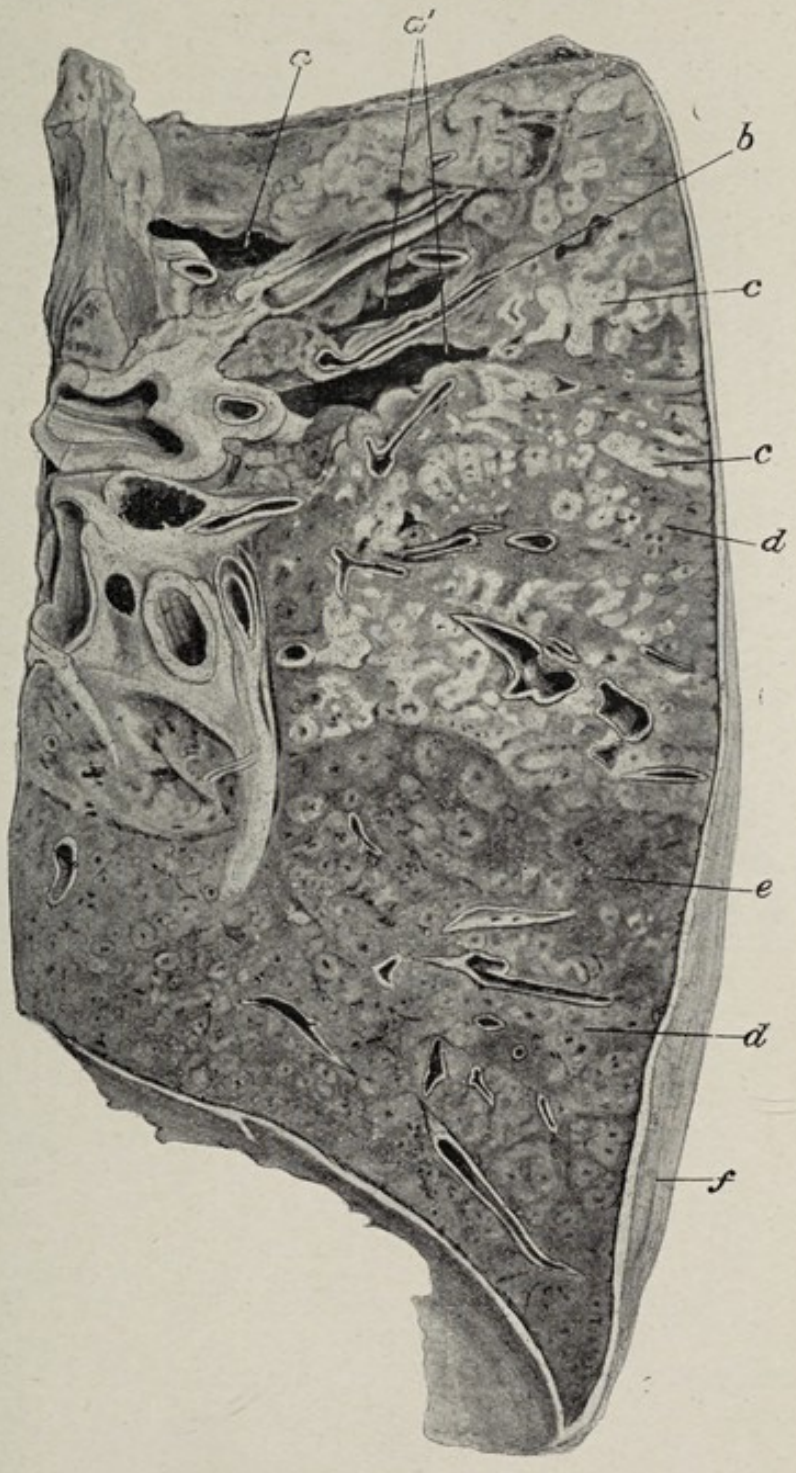


FIG. 95.—CHRONIC CASEATIVE TUBERCULOSIS OF LUNG. (FROM A SPECIMEN IN C. C. H. MUSEUM.)

a, *a'*, cavities; *b*, strand of tissue containing patent bloodvessel, crossing cavity; *c*, caseous masses; *d*, consolidated (broncho-pneumonic) areas; *e*, congested lung-tissue; *f*, thickened pleura.

When the pleura is reached the endothelial cells rapidly proliferate, and a progressive thickening sets in. The thickened pleura soon becomes infiltrated with mononuclear cells, giant-cell systems

form, and caseation occurs. Later, the visceral and parietal layers coalesce in many cases, and the lung becomes firmly bound to the chest wall. In other cases, a tuberculous cavity lying just beneath the pleura may rupture through it, and a pneumothorax will then result.

Thus it will be seen that in the chronic caseative type of pulmonary tuberculosis the tendency is towards a progressive destruction of lung tissue ; but though caseation may greatly predominate, fibrosis is never entirely absent, and round many of the caseous foci, and especially round any cavity, areas of fibrous tissue will always be found. The healing of these lesions, as has been described above, always occurs by a process of fibrosis ; and it is the relation of fibrosis to caseation which largely determines the prognosis in any case. Any isolated tuberculous focus may also undergo calcification.

The infection in this and the succeeding type of the disease occurs either by the respiratory tract or by the lymphatics, or by a combination of both channels. Probably the bacilli seldom gain access to the alveoli directly by the air-passages. If the main avenue is by the respiratory tract, the organisms are probably held up in the smaller bronchi or in the bronchioles, and from thence onwards are spread by the lymphatic route. In many cases, however, it seems probable that the actual primary focus may be in one of the mediastinal lymphatic glands, itself infected via the tonsils, the upper respiratory tract, or possibly via the alimentary tract, and that the lung itself may be secondarily infected from this source.

In *chronic fibroid pulmonary tuberculosis* it is unnecessary to detail the changes present, since the only outstanding feature is the marked predominance of fibrosis over caseation. The caseous areas are small, and rapidly become surrounded by fibrous tissue, the caseous material being ultimately absorbed or calcified. The pleura is usually greatly thickened and often adherent to the chest wall over large areas, while strands of fibrous tissue pass throughout the lung substance.

Secondary Infections.—The essential changes described above tend to be modified in the chronic form of the disease by the fact that the lesions are extremely liable to become secondarily infected with various pyogenic and other organisms via the respiratory tract, and it is often impossible to decide how far many of the various manifestations of the disease in its more chronic stages are due to the action of the tubercle bacillus itself or to these secondary infections.

Tuberculosis of the Kidney.

In acute generalised tuberculosis, miliary tubercles may often be found in the cortex of the kidney, and more rarely in the medulla. In other cases masses of caseating tubercle occur in one or both kidneys. The disease may extend and produce almost entire destruction of the organ affected, the kidney being converted into little more than a shell containing breaking-down caseous material.

The genito-urinary tract in the male is a common site of tuberculosis. The initial lesion is sometimes in the kidney, and then tends to spread down the corresponding ureter, which becomes greatly thickened. In other cases the initial lesion is in the epididymis, and extension takes place upwards, involving the prostate, bladder, ureter, and eventually the kidney on one or both sides.

Tuberculosis of the Pia Mater and Brain.

In the pia mater the tubercular process is associated with inflammation of the meninges and superficial parts of the brain, and is known as **tubercular meningitis,** or, more accurately, *meningo-*

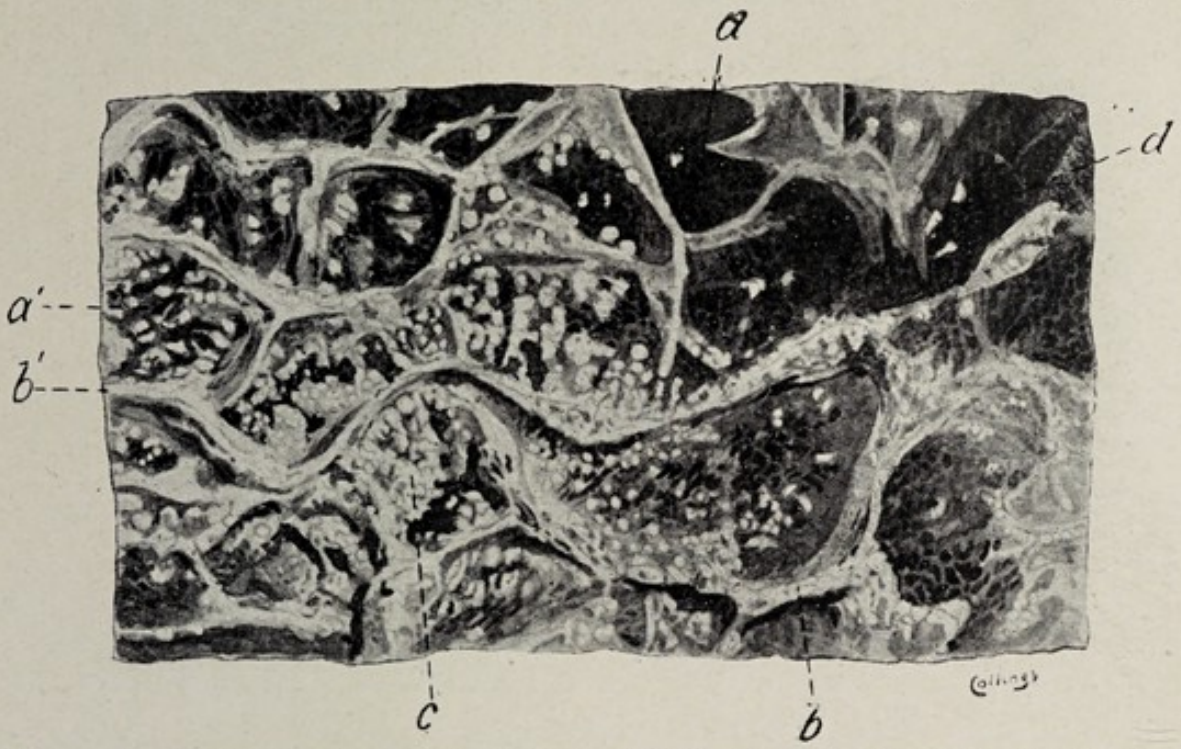


FIG. 96.—TUBERCULAR MENINGITIS: VIEW OF PIA MATER FROM THE VISCERAL SIDE. (NATURAL SIZE.) (MONTAGUE MURRAY.)

a, *a'*, tubercles, single and aggregated; *b*, *b'*, folds of pia mater dipping between convolutions; *b'* to *d*, line of Sylvian fissure; *c*, dense mass of tubercles; *d*, single tubercles—many of these can be seen situated on the vessels which form a network over the individual convolutions.

encephalitis. This is almost invariably the result of infection from a distant focus, though it may occasionally be due to extension from some tuberculous bone of the cranium.

The process is most marked at the base of the brain, and the *grey tubercles*—which may easily escape observation—are seen in connection with the small arteries in the Sylvian and longitudinal fissures, and are for the most part deeply seated between the convolutions. A few scattered grey granulations are frequently visible on the upper surface of the hemispheres. The tubercles may be best seen by stripping off a piece of membrane containing a middle cerebral artery and its branches, spreading it out in water on a glass plate, and then examining it over a dark background (Fig. 96). The

tubercles originate at those points in the walls of the small arteries of the pia mater where the bacilli conveyed in the circulation happen to be arrested (Fig. 97). Thus, by the usual process of proliferation and infiltration, commencing at several centres, numerous small grey nodules are produced around the vessels and in the adjacent and surrounding lymphatics. The tubercles thus formed rapidly caseate, though death usually occurs before this process is very advanced.

A *fibrinous inflammatory exudation* takes place, and the meshes of the pia mater become infiltrated with a sero-fibrinous or puriform liquid, which tends to collect in the grooves between the convolu-

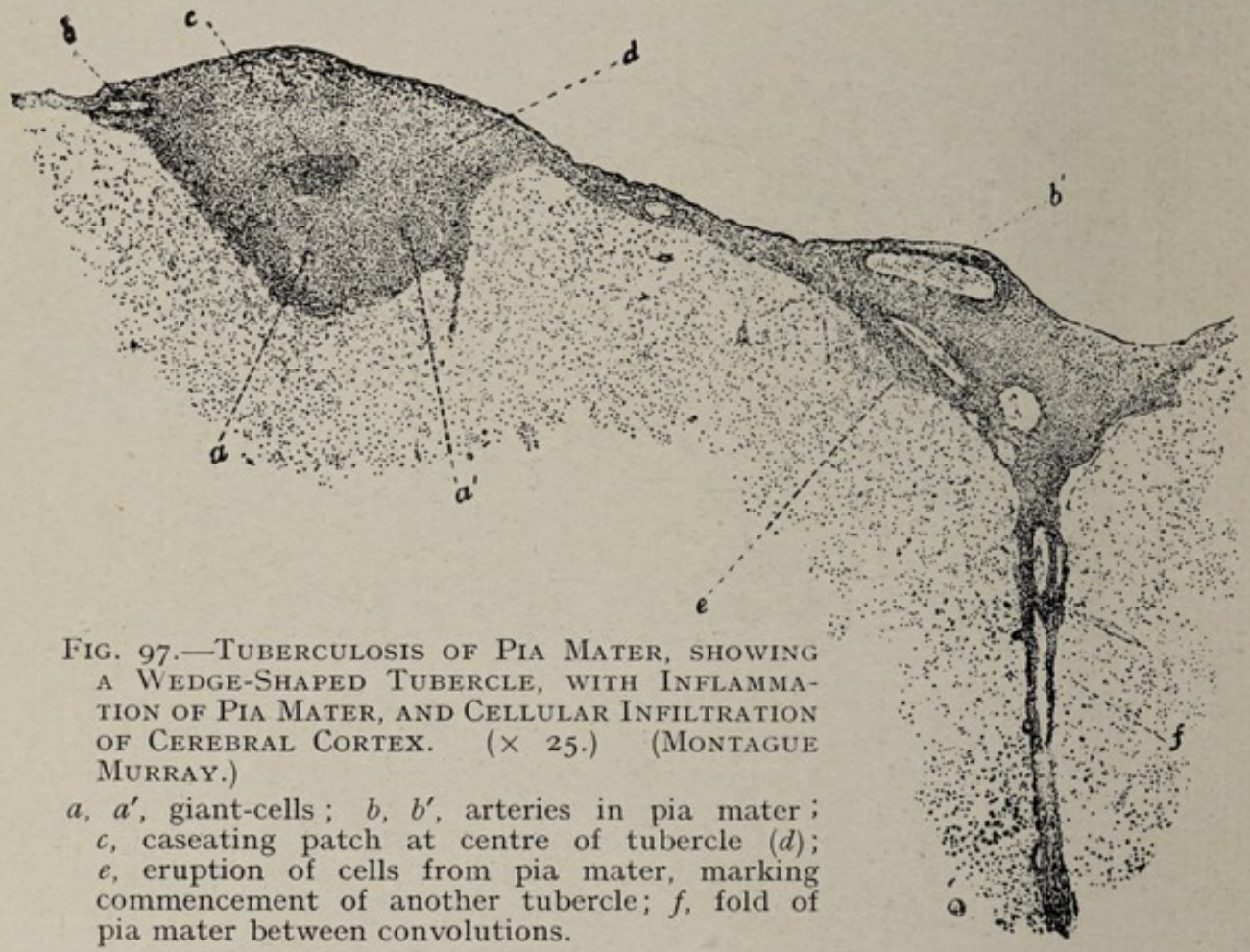


FIG. 97.—TUBERCULOSIS OF PIA MATER, SHOWING A WEDGE-SHAPED TUBERCLE, WITH INFLAMMATION OF PIA MATER, AND CELLULAR INFILTRATION OF CEREBRAL CORTEX. (× 25.) (MONTAGUE MURRAY.)

a, *a'*, giant-cells; *b*, *b'*, arteries in pia mater; *c*, caseating patch at centre of tubercle (*d*); *e*, eruption of cells from pia mater, marking commencement of another tubercle; *f*, fold of pia mater between convolutions.

tions, especially at the base of the brain. The subarachnoid fluid is turbid and increased in quantity, while the pressure within the dura mater rises steadily. Thrombosis may occur in the vessels, or these may rupture, causing minute extravasations of blood.

These changes in the pia mater at the base of the brain are attended by hyperæmia, infiltration with leucocytes and fluid, and slight softening of the subjacent cortical substance, accounting for the early delirium and the hyperæsthesia of the special senses. The ependyma and choroid plexus also become hyperæmic, and may be covered with inflammatory exudation; while the walls of the ventricles, the fornix, and the central commissure, soften. The

lateral ventricles become progressively distended with fluid (acute hydrocephalus), so that the convolutions on the surface of the hemispheres are found pressed against the skull and *flattened*. It is uncertain how far this fluid is due to local inflammatory exudation, and how far to dropsy, since the exudation generally causes marked pressure upon the veins of Galen near their entry into the straight sinus. All trace of fluid is driven from the subdural space, and the arachnoid is dry and sticky.

In the early stages of the disease the symptoms are those of cerebral *irritation* (stiffness of the muscles of the neck, squint, convulsions). Later, signs of *compression* ensue, and insensibility deepening into coma precedes death.

Tuberculous Masses in the Brain.—Large masses of conglomerate tubercle are occasionally met with in the brain, unassociated at first with any general tubercular process. The masses, which vary in size from that of a pea to that of a hazel-nut, or even to that of a hen's egg, commonly occur in the cerebral substance, especially in the cerebellum and at the base of the brain. They are of a pale yellow colour and firm consistence, and usually form round globular tumours. Their surface is often seen to be covered with minute grey nodules, which extend into the surrounding tissue ; and, on section, similar nodules are sometimes visible, scattered through the substance of the tumour. In most cases only one or two such masses are found, but occasionally they are more numerous. They occur especially in childhood. Near the edge, where the structure of the tubercles is recognisable and typical, compressed or obliterated bloodvessels may be seen. These masses not infrequently lead, after an interval of some months or years, to tubercular meningitis or to general miliary tuberculosis.

Tuberculosis of Lymphatic Glands.

In the lymphatic glands, tubercular processes first give rise to changes in the cortical portions, inasmuch as it is to these that the infective material, brought by the lymphatic vessels, is first conveyed (Fig. 98). In the earlier stage of the process small pale grey nodules are often visible scattered through the cortex. They gradually increase in size and become caseous. The gland meanwhile enlarges from the addition to its substance of these "tubercles," which gradually spread in along the lymph-sinuses to the medullary portion.

By this time the distinction between the medullary and cortical portions is lost, in consequence of the infiltration and filling up of the lymph-sinuses. A section at this stage presents a greyish homogeneous surface, on which are patches of caseous material. Fibroid changes frequently follow, and the capsule thickens, so that the caseous masses may become surrounded by dense fibrous tissue. The whole gland, especially in children, may be rapidly converted into a caseous mass. The caseous portions may subsequently

soften, and form tubercular abscesses; or they may dry up or calcify.

Sometimes no "tubercles" are visible to the naked eye, though a gland, when cut into, in the early stage has a pulpy, swollen

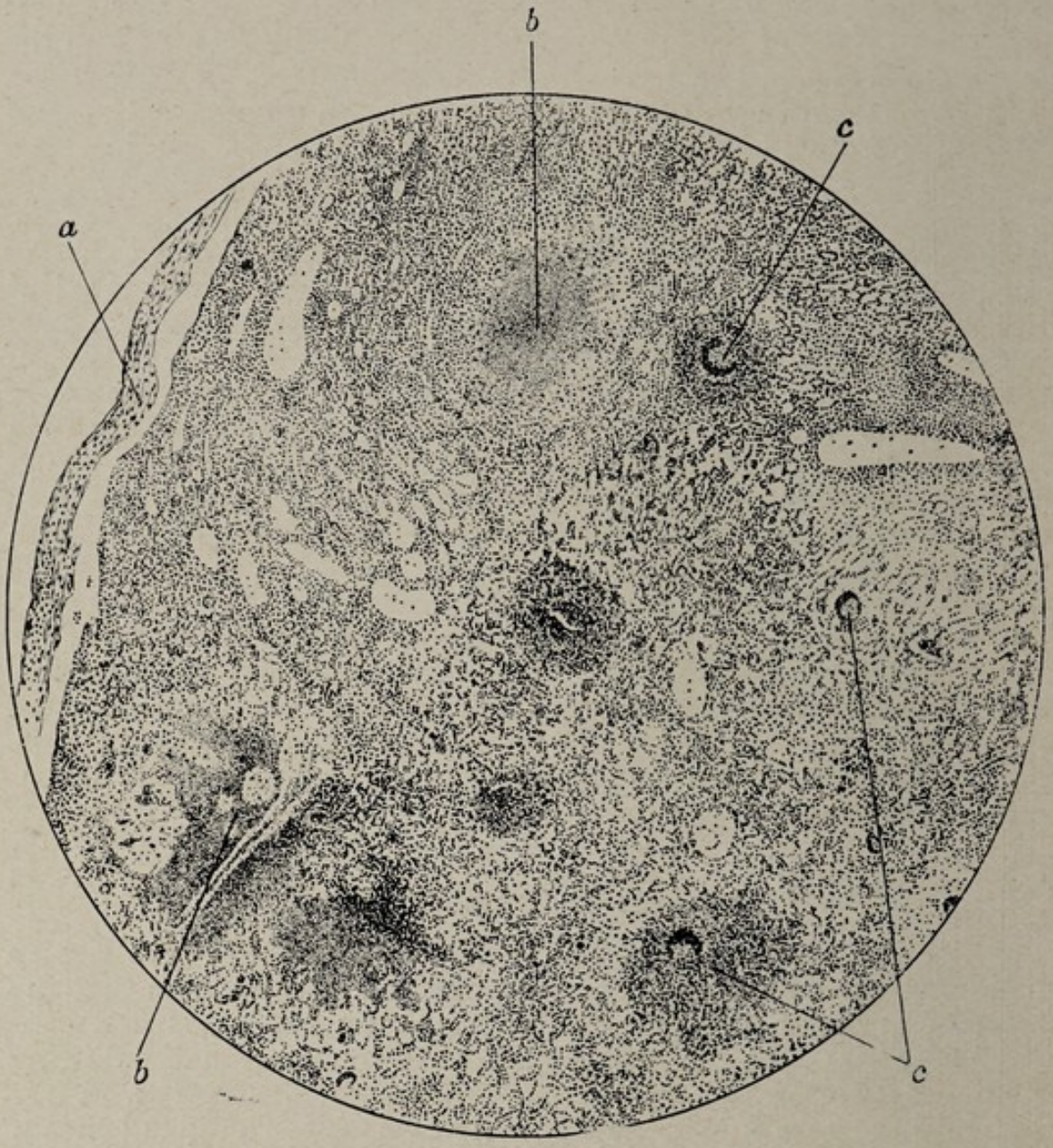


FIG. 98.—TUBERCULOUS LYMPHATIC GLAND.

a, thickened capsule of gland; *b*, *b*, caseous areas; *c*, *c*, giant-cells surrounded by inflammatory zone.

appearance, and may be distinctly more vascular than normal. Microscopically, small foci consisting of more or less well-defined giant-cell systems are found. Such enlarged glands may persist unchanged for some years, and then disappear; or caseation and fibroid changes may ultimately supervene.

Tuberculosis of Mucous Membranes.

The alimentary tract is a common seat of tuberculosis; it is, moreover, extremely probable that some catarrhal affections of the tonsils and pharynx, of the Eustachian tube and middle ear, as well as of the intestine, are due to infection with the tubercle bacillus.

Tubercular ulceration or fissure of the lip, usually with marked thickening, is not uncommon in children and young adults. On the tongue and pharynx tubercular ulceration is rare, and is usually secondary—at least, in point of time—to pulmonary tuberculosis. The occurrence of tubercular disease in the œsophagus and stomach is very rare, but cases have been described. The course and appearances (microscopic and naked-eye) of all these ulcers are the same. They will be described in the next section, as the intestine is the part of the alimentary tract in which they are most frequently found.

Tuberculosis of the Intestine.—Primary tuberculosis of the intestine may occur in children, but is rare in adults. It is probably caused by infection from tuberculous milk or meat. Secondary infection of the intestine occurs in from half to two-thirds of the fatal cases of phthisis, and is caused by swallowed tuberculous sputum. The morbid process begins in the solitary (Fig. 99) and agminated follicles (Fig. 100), and is most marked where these are most numerous—namely, at the lower end of the ileum and in the cæcum—but any part may be affected.

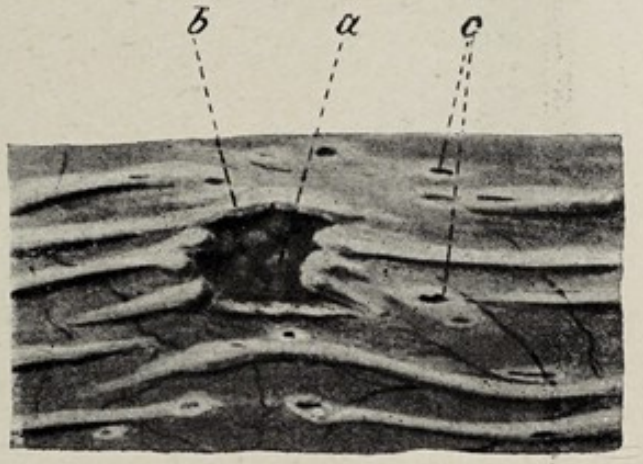


FIG. 99.—TUBERCULOSIS OF INTESTINE. (NATURAL SIZE.)

a, tubercles projecting from the floor of a tubercular ulcer; *b*, slightly thickened edge of ulcer; *c*, ulceration of solitary lymphoid follicles.

The first stage of the process consists in the appearance of tubercles in some solitary glands and in certain follicles (not all) of some Peyer-patches. The affected lymphoid-tissue swells, and therefore projects above the surface. The new elements, consisting mainly of small and large mononuclear cells, with occasional multinucleated giant-cells (Fig. 101), then undergo fatty changes and soften. The degeneration in Peyer's patches, commencing at a number of separate centres, is followed by a patchy ulceration of the mucous membrane; and the process extends by the development and subsequent breaking-down of fresh tubercles at the margin, until a considerable part of the patch is destroyed. As the result of these changes, an ulcerated surface is produced, the

floor and edges of which are more or less thickened, owing to the production of tubercles in the surrounding tissues (Fig. 100). In the floor of the ulcer—formed usually by the submucous, sometimes by the muscular, and rarely by the peritoneal coat—small tubercles are developed, principally in connection with the blood-vessels and lymphatics; and as these are arranged transversely around the intestine, the infiltration proceeds in the same direction, the submucosa always being first and principally affected. These nodules also soften and become caseous, and thus the process of ulceration gradually extends transversely until a complete ring of

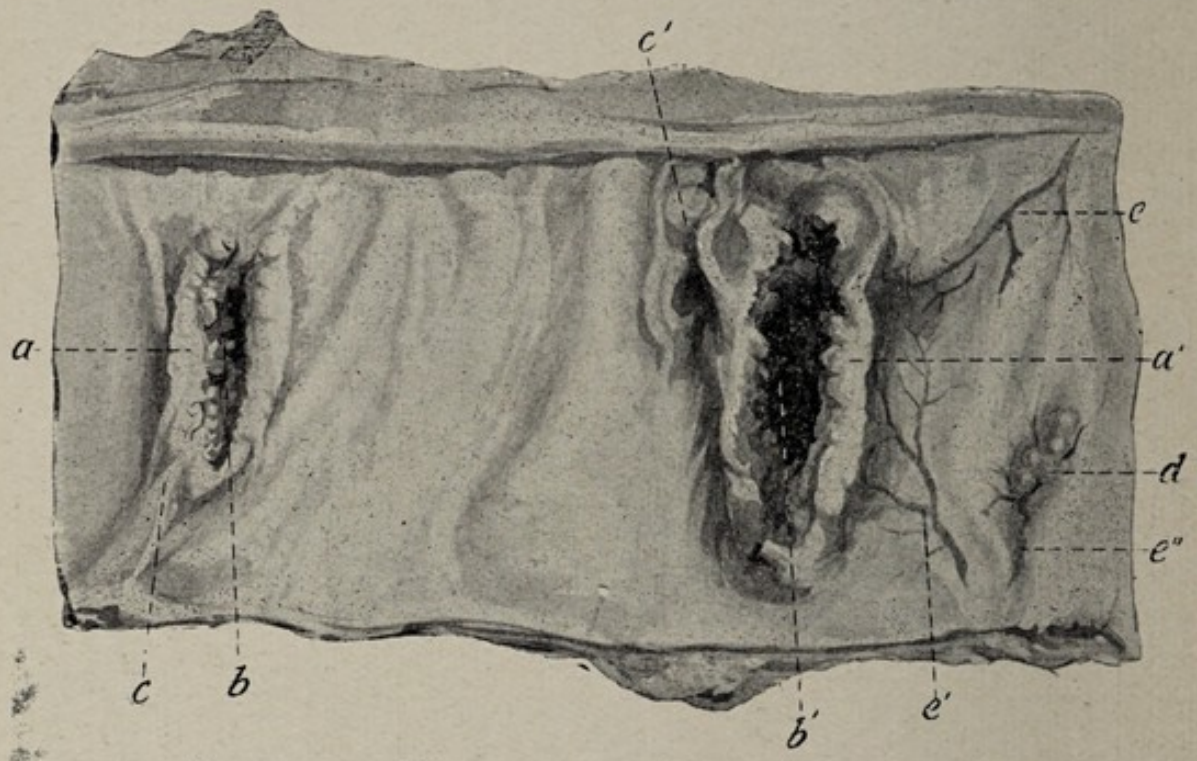


FIG. 100.—TUBERCULAR ULCERATION OF ILEUM (INTERIOR): TWO ULCERS WITH THEIR LONG AXES AT RIGHT ANGLES TO THAT OF INTESTINE. (NATURAL SIZE.) (C. C. H. MUSEUM.)

a, *a'*, thickened shelving walls of ulcers, containing tubercles; *b*, *b'*, roughened floor, with tubercular nodules and small sloughs; *c*, *c'*, outlying thickening due to tubercular infiltration; *d*, a mass of recent grey tubercles around a vessel (*e''*); *e*, *e'*, *e''*, dilated vessels in neighbourhood of large ulcer.

the mucous membrane may be destroyed (*annular ulcer*). The presence of tubercles on the peritoneal surface, together with the dilatation of the neighbouring vessels, may reveal the position of the ulcers before the bowel is opened (Fig. 102). By the blending of adjacent ulcers the mucous membrane is cut up into irregular patches, and, in extensive cases, only a few islets and bands are left in wide areas of the bowel. The ulcers thus produced (Fig. 103) present in advanced cases a strong contrast to those of typhoid fever (Fig. 104), but early ulcers of acute formation closely resemble the latter, and can only be distinguished, microscopically, by the presence of " tubercles " in the peritoneum over the ulcer.

Tubercular ulcers rarely, if ever, heal; but an ulcer *may* heal at one place, while it spreads to another, and the contraction of any resulting scar-tissue leads to marked stricture of the gut, and occasionally to complete obstruction. Owing to the thickening of the

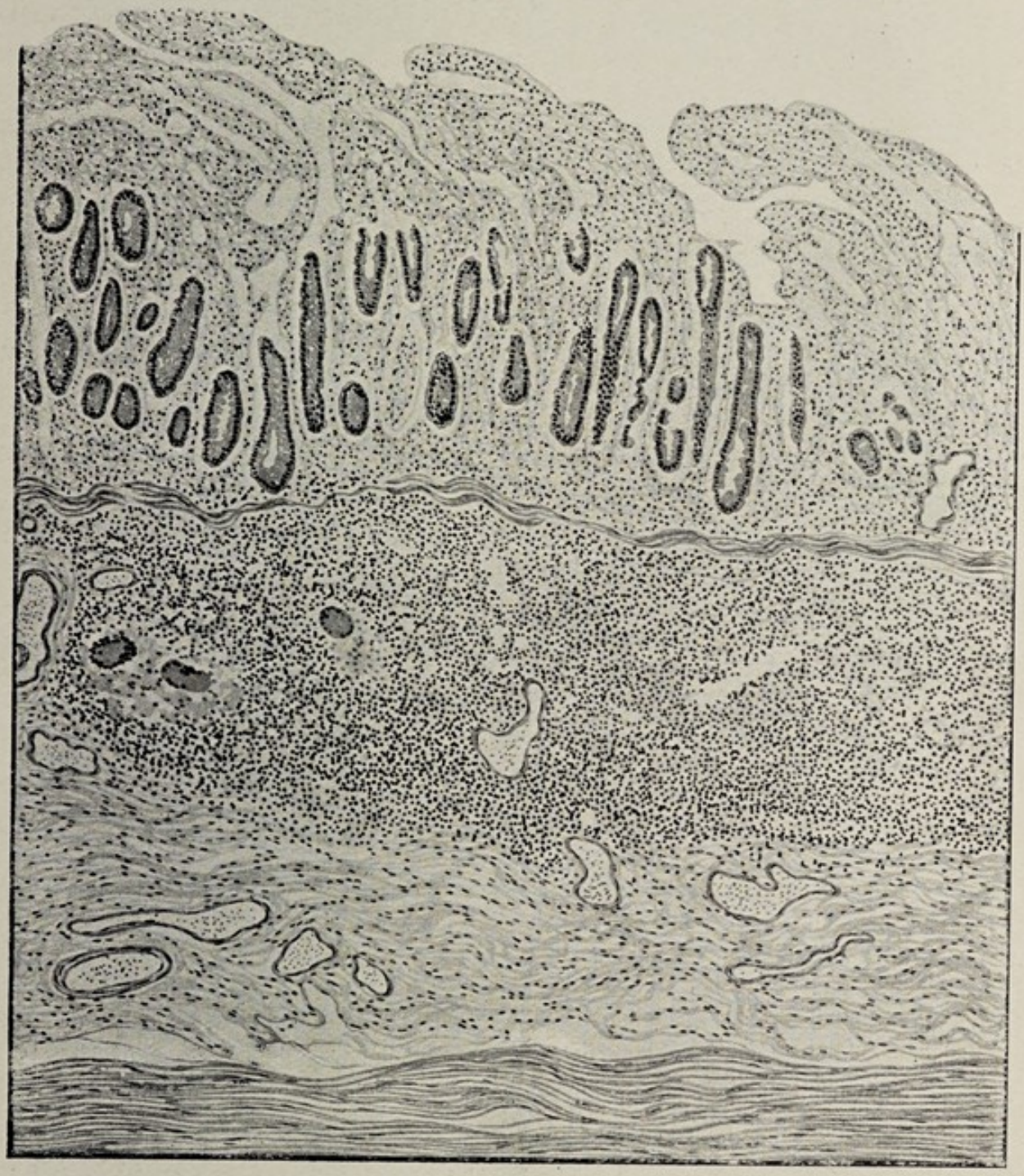


FIG. 101.—SECTION OF A PORTION OF THE EDGE OF A TUBERCULOUS ULCER OF THE SMALL INTESTINE, SHOWING INFILTRATION OF THE SUBMUCOSA, AND THE FORMATION OF GIANT-CELL SYSTEMS. (× 79.)

tissues at its base, perforation is an exceptional occurrence. It may take place into a neighbouring viscus to which the ulcer has become adherent, or into the peritoneal cavity.

The lymphatic glands in connection with tubercular ulcers are

generally affected. The lacteals leading from the ulcers, and even the thoracic duct itself, may be irregularly swollen by tubercles in their walls.

A peculiar form of chronic tuberculosis (*hypertrophic tuberculosis*) may occur—usually in the large intestine—in which there is great thickening of the wall of the bowel, which is converted into soft and gelatinous tissue, or occasionally into tougher and more fibrous

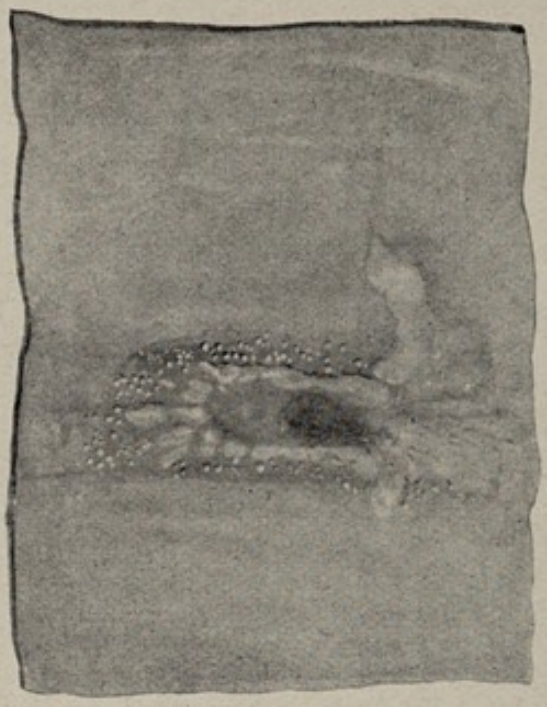


FIG. 102.—TUBERCULOUS ULCERATION OF SERUM, VIEWED FROM THE PERITONEAL ASPECT, SHOWING NUMEROUS SUBPERITONEAL TUBERCULES SURROUNDING THE FLOOR OF THE ULCER

FIG. 103.—A TUBERCULAR ULCER OF THE INTESTINE. (DIAGRAMMATIC.)

a, mucous membrane; *b*, submucous tissue; *c*, muscular coat; *d*, peritoneum.

FIG. 104.—A TYPHOID ULCER OF THE INTESTINE, SHOWING THE UNDERMINED EDGES OF THE ULCER AND THE SLOUGH STILL ADHERENT. (DIAGRAMMATIC.)

a, mucous membrane; *b*, submucous tissue; *c*, muscular coat; *d*, peritoneum.

material, which may reach an inch in thickness. Such cases have been mistaken for cancer of the bowel, but can usually be recognised, even apart from the microscope, by the presence of caseous or calcified mesenteric glands.

Tubercular disease of the peritoneum is considered in the section dealing with Inflammation of Serous Membranes.

Tuberculosis of Bones and Joints.

These parts may be conveniently taken together, as tubercular disease of a joint is frequently secondary to similar disease of a bone, and *vice versa*. The primary disease is, of course, due to infection through the blood; the secondary, to extension from the primary focus.

In cases of acute general tuberculosis, both bones and joints may be the seats of *miliary tubercles*. In *bones*, the tubercles are found chiefly in cancellous parts; in *joints*, in the synovial and sub-

synovial tissues. They present no peculiarities, and cause no local symptoms.

Tubercular Periostitis and Osteomyelitis.—Tuberculous periostitis and osteomyelitis often coexist. *Periostitis* cannot exist without a superficial *osteitis*; but the converse is not true, for a deep bony focus of tubercular inflammation may be present without any obvious involvement of the periosteum.

Seats.—Among the bones which are affected primarily are the bodies of the vertebræ, the ends of the long bones, the bones of the carpus and tarsus, the phalanges, and less often the metacarpal and metatarsal bones and the ribs. The shafts of the typical long bones are rarely affected by tubercular processes. The same may be said of the cranial bones, but certain bones of the face not uncommonly suffer.

The tubercular process more often starts in the bone than in the periosteum. Periosteal changes occasionally predominate in the case of the ribs, phalanges, and bodies of the vertebræ; when this is the case, early abscess almost always leads to their recognition. But in the vertebræ, and probably in the phalanges, primary central changes are much the commoner.

Morbid Changes.—Bacilli are deposited at a certain spot—*e.g.*, in an epiphysis. Miliary tubercles next develop; a group of these becomes surrounded by a mass of granulation-tissue, and this again, in cases which are not progressing rapidly, and where irritation is not intense, by a zone of fibrous tissue. In this outer zone it is common to find the bony trabeculæ becoming thicker at the expense of the spaces—*i.e.*, the bone becoming sclerosed; more centrally, in the area of greater irritation, the trabeculæ are undergoing absorption.

Bacilli carried from the primary focus cause infection of the surrounding tissue and the formation of tubercles in the granulation-tissue zone. As these increase in number, they gradually blend with the parent mass, which meanwhile has probably undergone caseation. The granulation-zone in the meantime extends into and replaces the zone of fibrous tissue and of bony sclerosis, which in its turn reappears still farther from the centre. Thus the process spreads—now quickly, now slowly. Cure may be effected by the encapsulation of the caseous masses in fibrous tissue. This is sometimes followed by their calcification. On the other hand, the disease may spread till the surface of the bone is reached and the soft parts have become infected. Any portion of bone separated entire by surrounding caseation forms a *sequestrum*. Usually only small fragments of trabeculæ are thus separated, but sometimes caseation follows infiltration so rapidly that masses of bone as large as a filbert, or even larger, are detached. A whole epiphysis, such as the head of the femur, may thus die. As Cheyne has stated, the trabeculæ of the sequestra are often thickened, showing that a chronic inflammation preceded the change which caused the necrosis. Sometimes the sequestra are soft and crumbling, consisting of

rarefied bone; sometimes the contents of the spaces, thus enlarged by rarefying osteitis, are calcified. An abscess often forms, with or without necrosis.

When the periosteum is primarily affected, the enlargement of the bone soon becomes apparent, owing to the growth of tubercles imbedded in inflammatory tissue in the deeper layers of the periosteum and in the superficial Haversian canals. This growth may extend over a wide area of bone, or may penetrate deeply at one or more spots, eroding the bone as it grows, even after causing a preliminary sclerosis. Commonly an abscess forms, and bursts if not opened. The rough surface of the infiltrated bone is then exposed. The resulting space is filled with a milk-like fluid, often containing caseating masses and bits of bone. The wall of such an abscess is formed of dense fibrous tissue lined by a layer of granulation-tissue which can be easily detached.

On section, this wall shows, from without inwards, œdematous fibroid tissue, probably containing tubercles with central giant-cells; then granulation-tissue with numerous, but less typical, tubercles; and, lastly, a layer, chiefly of epithelioid cells, which becomes more and more caseous as the cavity is approached.

Tuberculosis of Cartilage.—Hyaline cartilage, being a non-vascular tissue, is never attacked primarily. Destruction of cartilage is sometimes due to the *spread inwards*, over the surface of the cartilage, of tuberculous outgrowths from the synovial membrane. These processes adhere like ivy, and gradually erode the cartilage, producing a cribriform appearance. Similar destruction may also be due to the *perforation* of the cartilage by a mass of tuberculous tissue sprouting through it from a focus in the subjacent bone, or to the *spreading beneath* the cartilage of similar tissue from a bony source. Large pieces of cartilage may be thus loosened from the bone, while still retaining a normal appearance on the side towards the joint. In one or other of the above ways tubercular caries of the surfaces of a joint is established.

Tuberculosis of Synovial Membranes.—The tubercular changes met within the synovial membrane are the following: (1) *acute miliary tuberculosis*, as mentioned above; (2) *diffuse thickening* (*tumor albus*)—by far the most frequent and important condition; (3) *nodular thickening* (*synovitis tuberosa*); and (4) *serous effusion, or hydrops*.

Diffuse thickening may be primary or secondary. When *primary* it is due to the settlement of bacilli at one or more spots in the synovial or subsynovial tissue. Tubercular masses grow and spread, while the surrounding tissues become more or less swollen and gelatinous-looking from œdema and cell-infiltration. Clear or puriform fluid may be effused into the joint. The tubercular foci may soften and open either into the joint or into the periarticular tissues, or may form an abscess in the thickened synovial membrane. When *secondary*, the diffuse thickening may be due to bursting of a focus from the bone into the joint, and infection of

the whole synovial membrane from within. Soon afterwards this membrane presents the structure of the wall of a chronic abscess, and its cavity contains turbid or puriform fluid. In other cases the thickening may be due chiefly to œdema of the synovial membrane, excited by the presence of a focus in the bone, which has reached the surface at the reflection of the synovial membrane, and has thus been shut off from the cavity of the joint. At this point of reflection the membrane becomes infected, and the tubercular process leads to much œdema of the neighbouring parts.

In *synovitis tuberosa*, fungous masses of tubercular structure, from the size of a chestnut downwards, hang in greater or smaller numbers from the synovial membrane into the joint, which almost always contains fluid; this is often blood-stained. The membrane may be thick and deeply blood-stained towards the joint. The disease is due to infection conveyed by the blood.

Effusion may take place before thickening of the synovial membrane begins (*tubercular hydrops*), and is indistinguishable at this stage from simple synovial effusion. König states that in early stages a thin layer of tuberculous tissue can be found on the surface towards the joint.

Tuberculosis of the Skin.

Tuberculosis of the skin gives rise to many varieties of inflammation, of which some tend to suppurate. These are generally grouped under the term **Scrofulodermia** (*tuberculides*).

Lupus vulgaris is a form of tuberculosis characterised by the appearance of reddish-brown nodules of granulation-tissue upon the *skin* (chiefly of the face), and much less commonly upon the *mucous membranes* of the conjunctiva, tendon-sheaths, pharynx, vulva, and vagina. The nodules are situated primarily in the corium, and at first are smaller than a pin's head, though they may reach the size of a pea. These blend to form a more or less diffuse mass, while fresh foci appear at the periphery. The disease generally *appears* between the age of two years and puberty. *Recurrences* may take place again and again, and the disease may thus last, off and on, throughout a lifetime.

Microscopically, the nodules consist of granulation-tissue containing epithelioid cells and often a good many giant-cells. Many of them differ from true tubercles in being *rather richly vascular*. The intercellular substance is scanty and homogeneous. It is not uncommon to find that long anastomosing processes of epithelium have grown down into the round-celled growth. There is almost invariably increase in the size of the interpapillary down-growths of epithelium (Fig. 105).

The disease spreads by the production of fresh nodules at the margin of the primary focus. Its course is always chronic, and when the patch has reached a certain size it may remain quiescent.

The nodules and infiltration may end in degeneration and *absorption*—a white scar being left—or in *ulceration*. After eating away the tissues to varying depths, sometimes destroying large portions

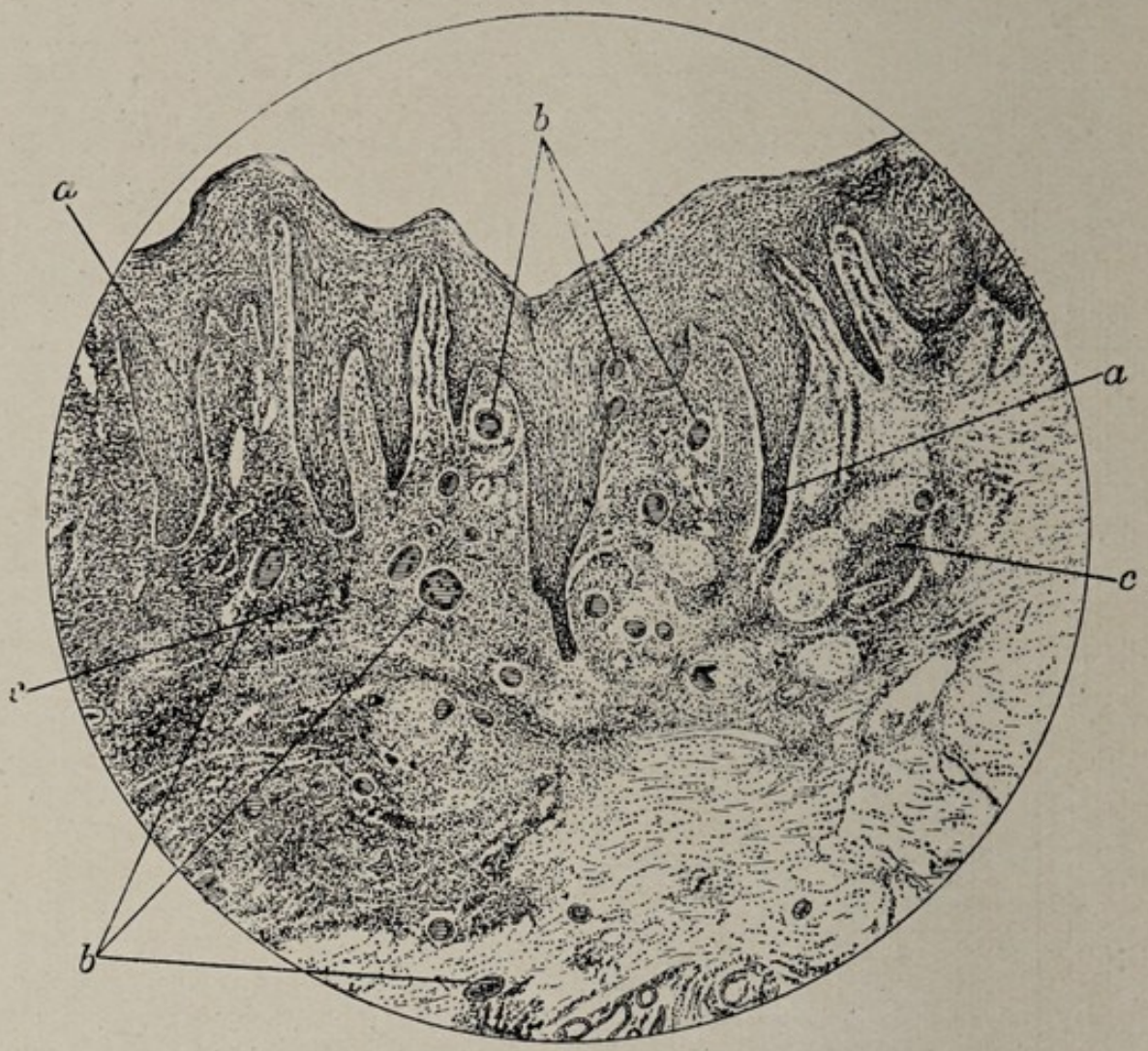


FIG. 105.—LUPUS VULGARIS. (× 200.) (FROM A SPECIMEN BY DR. J. M. H. MACLEOD.)

a, *a*, epithelial down-growths; *b*, *b*, giant-cells; *c*, *c*, inflammatory infiltration.

of the nose, lip, or eyelid, the ulcers may heal, or healing may go on at one point and destruction at another. There is little or no tendency to caseation, and glands rarely become affected. Most of those suffering from lupus die of tuberculosis of some other part.

CHAPTER XVII

CERTAIN INFECTIVE DISEASES—*Continued*

LEPROSY.

LEPROSY is a chronic, progressive, infective disease due to the introduction of the *Bacillus lepræ*, and its growth in the tissues.

There are two chief varieties—*nodular** and *anæsthetic*. In the former, the lesions affect chiefly the skin; in the latter, chiefly the nerves. The appearance of these changes is preceded by an incubation and a prodromal period. These together extend over nearly five years, and are often followed by a series of successive skin-eruptions.

In **nodular** leprosy, patches of hyperæmia are followed by thickening of the skin with the formation of small flat nodules, which grow very gradually and often run together, until, in some cases, they reach the size of walnuts. These changes are especially developed on parts exposed to the air—face, hands, and feet—and appear sometimes singly, sometimes in groups. The affected skin is at first firm and red or brownish; later on, it becomes soft and pale. Unless injured, it rarely ulcerates until some years have elapsed. When ulcers form, they cause great destruction of features and other parts (*lepra mutilans*). Healing may occur here and there. The nodules may affect other parts of the body, especially the extensor aspects of the limbs, and the mucous membranes of the eye, nose, mouth, and larynx.

In **anæsthetic** leprosy, cylindrical or fusiform swellings occur upon nerves, especially the ulnar and external popliteal, and the usual results of neuritis follow. These swellings surround long portions of the nerves, affecting primarily the cutaneous and, later, the muscular branches. At first the skin is often painful and hyperæsthetic; later on, it becomes thin, pale, and insensitive, while the paralysed muscles waste. A bullous eruption (*pemphigus leprosus*) in the area of an affected nerve may be the first sign of the disease. These bullæ may either dry up, leaving pale insensitive patches with a pigmented border, or they may be followed at once by ulcers. Sooner or later ulcers form upon the anæsthetic parts, leading to

* This variety is often called "tubercular." The term is objectionable, as it suggests an association with the tubercle-bacillus.

extensive destruction and even to dropping off of fingers, toes, or of large portions of limbs (*lepra mutilans*).

The two forms may run their course separately, but often occur together. The anæsthetic variety occurs chiefly in hot climates. In each form the glands receiving lymph from the diseased parts enlarge—first the superficial ones, then the deeper. Viscera—especially the liver, spleen, and testes—may also be enlarged. In

FIG. 106.—LEPROUS NODULE: SECTION THROUGH THE SKIN. (× 120.)
(FROM A SPECIMEN BY DR. J. M. H. MACLEOD.)
The dark masses consist of bacilli closely packed together.

the nodular form death results from exhaustion or some intercurrent disease, after a course of eight or ten years; in the anæsthetic form the duration is about twice as long.

HISTOLOGY.—To the *naked eye* the new tissue, wherever situated, has a greyish or yellowish semi-transparent, homogeneous appearance. The loose areolar tissues are chiefly affected, and, in a less degree, lymphoid tissue. *Microscopically*, the nodules consist of granulation-tissue, with large numbers of bacilli (Fig. 106).

Prominent in the new tissue are numerous large, granular, vacuolated, cell-like masses known as *lepra-cells* (Fig. 107); the vacuoles contain masses of bacilli. These cells are frequently found in the lymph-spaces. According to the old view, lepra-cells are epithelioid cells, possibly derived from the endothelium lining the lymph-spaces; while the vacuoles are the intracellular excretory products of the enclosed bacilli. According to Bergengrün and other recent observers, a lepra-cell is a transverse section of a lymphatic stuffed with bacilli which have led to coagulation of the contained lymph—a lymphatic thrombus. The irritation caused by these thrombi gives rise to proliferation of the lining endothelium, and from this are formed the giant-cells, which in leprosy do not commonly contain bacilli.

FIG. 107.—LEPROUS NODULE. PORTION OF PRECEDING FIGURE HIGHLY MAGNIFIED, SHOWING BACILLI LYING IN "LEPRA-CELLS" AND IN LYMPHATIC CHANNELS. (× 750.)

The fusiform swellings on the *nerves* consist of degenerated nerve-fibres and proliferated connective tissue, with numerous bacilli contained within the cells or lying free in the new tissue.

The new tissue in the *skin* very gradually undergoes fatty degeneration and is absorbed, or breaks down. The foci run together, and the diseased part appears, on section, to be divided into nodular masses by fibrous bands. Other tissues may, on account of the interference with their nutrition, necrose or atrophy.

The *lymphatic glands* contain small fibrous patches. As Delépine points out, the *liver*, *spleen*, and *nerves* all show signs of chronic interstitial inflammation. The *lungs* are often said to be tuberculous. They certainly have the appearances of organs undergoing caseous broncho-pneumonia, but it is doubtful whether this condition is not frequently due to the leprosy bacillus, although tuberculosis is unquestionably common in lepers.

ÆTIOLOGY.—This disease is endemic in many parts of the world, especially in the East and West Indies, China, South America, and Equatorial and Southern Africa. From the fourth to the fourteenth century it was widely spread over Europe, but began to die away at the beginning of the fifteenth, and was nearly extinct by the end of that century, when syphilis first became prominent. Leprosy still lingers in many places in Europe, particularly in Norway, Sweden, and Iceland.

From time immemorial leprosy has been looked upon as a contagious disease, and lepers have been rigorously excluded from social communities. In many cases, however, lepers have been known to live in the closest association with healthy people without communicating the disease. On the other hand, no one ever contracts

the disease without having been brought into contact with the contagion, which may in all probability remain latent for years. The extremely gradual development of the disease renders its contagiousness difficult to prove.

It may be noted that leprosy flourishes in all climates and upon all soils. There is no evidence that poor diet and salt fish take any prominent part in its causation, as some have thought, or that the disease is hereditary, although Hirsch strongly maintained that it was. Possibly there may be some hereditary predisposition analogous to that believed to exist in the case of phthisis.

Attempts to cultivate the organism have so generally failed that the few recorded exceptions are of little value until more fully confirmed. Amid conditions under which the tubercle bacillus will flourish, the leprosy bacillus will not grow at all.

Nor do inoculation-experiments give decisive results. In the case of a criminal, to whom inoculation had been offered as an alternative to execution, the disease followed the inoculation; but the result was inconclusive, as the man had up to that time been in frequent contact with lepers. Whether the affected tissues be introduced into other parts of leprous patients, or into animals, the results are uniformly unsuccessful, though the bacilli themselves are not destroyed, for they can be found months afterwards in the tissues.

SYPHILIS.

Syphilis is a chronic general infective disease, due to invasion by the *Spirochæta pallida*, and characterised by the presence of inflammatory lesions occurring in foci, some of which are infective. The primary lesion occurring at the point of inoculation is followed by enlargement of the neighbouring lymphatic glands, and, later on, when the virus becomes generalised, by a series of changes in the skin and mucous membranes along with fever and constitutional disturbance. At a still later period these may be succeeded by changes in the nervous system, bones, and internal organs—most of them the results of inflammatory processes induced by the syphilitic poison.

I. Primary Lesion.—In all probability there is always a local lesion at the point of inoculation, though it may be exceedingly minute and not infrequently escape observation, especially in women. This primary lesion is a small hard nodule (*hard chancre*) in the skin or mucous membrane, and consists of ordinary chronic inflammatory tissue, being made up of epithelioid cells, a large proportion of mononuclear leucocytes, and occasionally a few small giant-cells. There may also be some epithelial proliferation on its surface which is often eroded, a small ulcer with a hard base resulting. This ulcer may become infected with pyogenic cocci.

Spirochætes are recognisable in the discharge from the ulcer after the surface is cleaned. When the virus is introduced by absorption through a slight abrasion the infection spreads rapidly, by means of

the connective-tissue spaces and lymphatics, to the glands, which are thus quickly involved, though no evidence of the generalisation of the poison occurs for a period of time varying from two to six weeks. Spirochætes are obtainable by puncture and aspiration of the affected glands. When accidentally inoculated, as in the course of an operation, the virus may gain direct entrance to the blood-stream, and the evidence of general infection may thus occur much earlier, without any previous infection of the glands.

II. Secondary Lesions.—Two or three weeks after inoculation, lesions appear in many parts of the body as a result of the generalisation of the virus. These are characterised by inflammation of the perivascular sheaths and adventitia of the smallest vessels, and by the presence of epithelioid cells and leucocytes. Many of the lesions are anatomically indistinguishable from simple inflammations of the same parts. The rashes, for example, are due to inflammatory hyperæmia with more or less infiltration of the superficial layer of the skin, enlargement of the papillæ, and, often, excessive epithelial multiplication (*mucous tubercles*). As a rule these inflammations end naturally in resolution ; but, in tissues of feeble resisting-power, ulceration may follow. Early syphilitic periostitis (*nodes*) is indistinguishable from traumatic inflammation, and syphilitic iritis is diagnosed from rheumatic iritis only by concomitant circumstances.

III. Tertiary Lesions.—Other lesions, sometimes known as *tertiary*, occur later. The most characteristic of these are *gummata*, but the most frequent is simple *fibroid induration*.

Fibroid Induration.—Anatomically, this is ordinary proliferative inflammation, ending in scar-tissue. When the fibrous tissue is gradually developed without evidence of any change, except such degeneration and atrophy as may depend on or precede the subsequent contraction of this tissue, it is sometimes spoken of as an overgrowth of connective tissue. The density of the new tissue varies in different cases and in different parts of the same organ. The infiltration may be general, but much more commonly the fibroid areas are separated by comparatively healthy portions of the organ. It is the *irregular distribution* of these lesions which makes them so *characteristic of syphilis*.

The *capsules* of organs are *irregularly thickened ;* any serous coverings they may possess are involved, and more or less general adhesion to surrounding parts occurs. As the fibrous tissue contracts the organ shrinks and often becomes of stony hardness ; but the irregular distribution of the exudation often causes unequal contraction and puckering of the surface, amounting in some cases to the formation of deep fissures which almost divide the organ into lobes. In these cases the diffuse growth has probably been combined with the gummatous, and the thickened capsule is connected with fibrous strands which extend deeply into the surrounding tissue.

The naked-eye examination of a testis which has undergone these changes shows adhesions between the layers of the tunica vaginalis,

and intervening spaces containing fluid, as well as marked thickening of the tunica albuginea, with dense bands of fibrous tissue extending from it towards the mediastinum. The natural reddish-brown colour of the tubules is replaced by a much paler whitish-yellow tint, in which islands of normal tissue may remain. The consistence of the gland is greatly increased. One or two gummata may also be present. In syphilitic orchitis the affection of the tunica vaginalis is often manifested during life by the presence of hydrocele.

When occurring in bone, this fibroid induration may ossify. Under the periosteum, it causes thickening of the bone. In the Haversian canals and cancellous spaces it leads to increase in density.

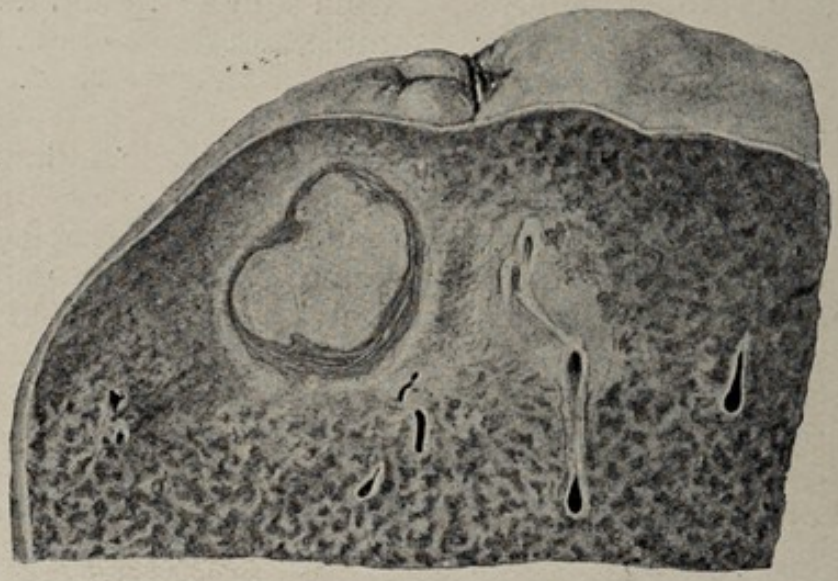


FIG. 108.—GUMMA OF LIVER.

Note the presence of a fibrous capsule round the caseous nodule, and the depressed scar on the surface of the organ.

No definite distinction exists between fibroid induration and gummata. The former is practically a diffuse form of gummatous inflammation, and may perhaps be invariably preceded by the formation of gummata, of which it represents a final stage after all caseous matter has been absorbed.

Gummata (*Syphilitic Tumours, Syphilomata*).—As usually met with, these are moderately firm, yellowish-white nodules (Fig. 108). They vary in size from that of a hemp-seed to that of a walnut, and are surrounded by a zone of translucent, fibrous-looking tissue, which sometimes has the appearance of a capsule, and which is so intimately associated with the surrounding structures that enucleation of the mass is impossible. The outline of the growth is generally irregular, owing to the number of fibrous processes which radiate from it along the natural septa of the organ (Fig. 109). In the *earlier* stages of their development, as seen in the liver in cases of congenital syphilis, where they occur as early secondary lesions,

gummata are much softer in consistence, more vascular, and of a reddish-white colour ; whilst in their most *advanced* stages, owing to extensive degenerative changes, they may be opaque, yellow, and fatty. The subsequent absorption and fibrosis often lead to marked scarring of the organ involved.

Examined *microscopically*, gummata are found to vary in their minute structure according to their age. When **recent** they are divisible into three zones. The *central* portions are composed of

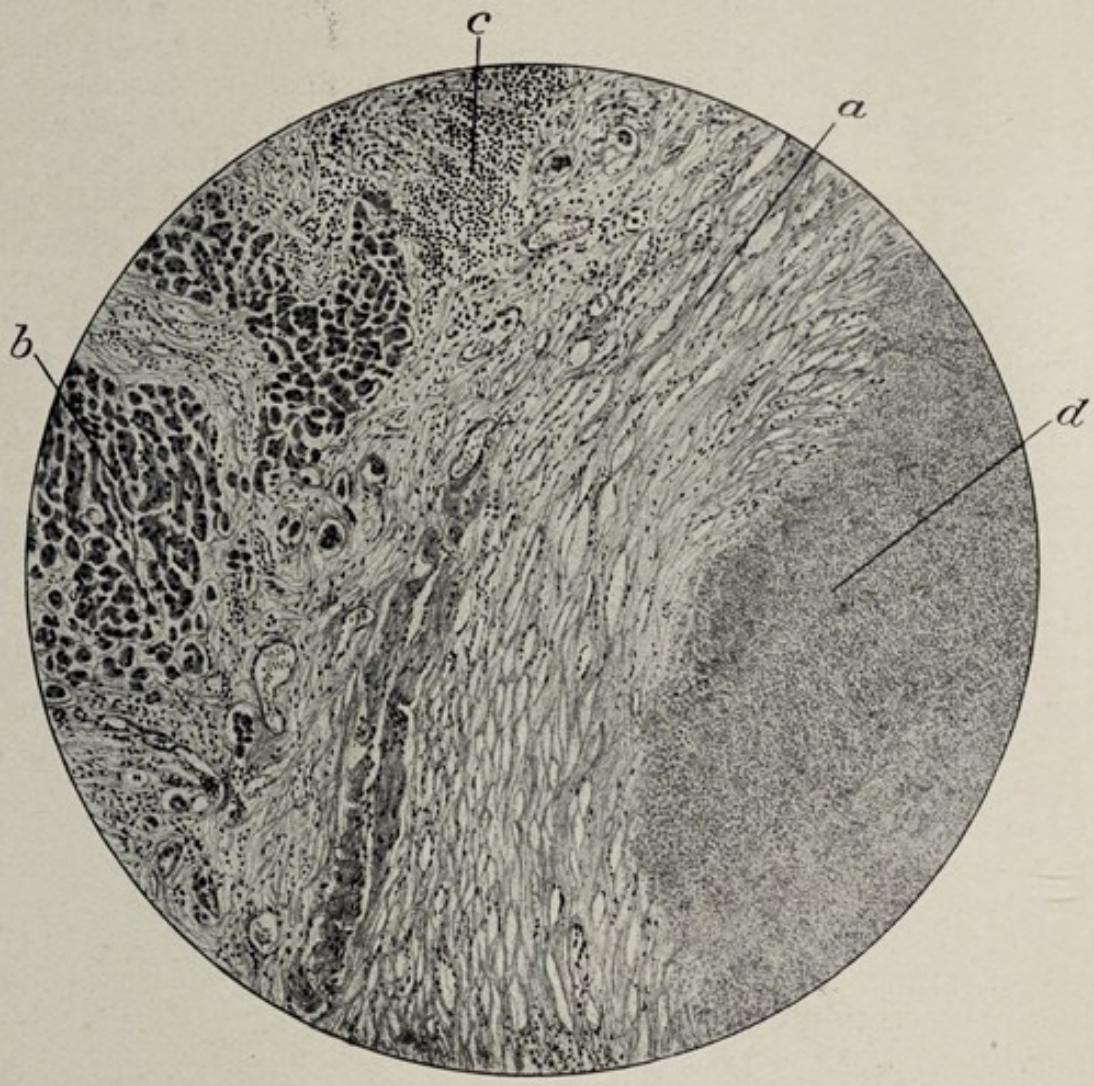


FIG. 109.—EDGE OF GUMMA OF LIVER.

a, Fibrous tissue; *b*, liver cells; *c*, area of infiltration with mononuclear cells; *d*, central caseous portion. (× 79.)

closely packed shrunken cells and nuclei, fat-granules, and cholesterin, amongst which is generally a little fibrillated tissue. Surrounding this and directly continuous with it is the *intermediate* zone, consisting of epithelioid cells in a distinctly fibrillated matrix. The *peripheral* portion of the growth, which is in direct histological continuity with the surrounding structures, consists mainly of leucocytes, though epithelioid cells and even giant-cells are also found. Giant-cells are much rarer than in tuberculosis. The cells are separated by a scanty, homogeneous, intercellular material, and

numerous new bloodvessels. In **older** gummata, only two zones may be apparent, an *inner caseous* zone and an *outer fibrous* zone. Spirochætes have been demonstrated in gummata by Levaditi and others.

The origin of the cells in gummata is most likely the same as in tubercles. It seems probable, however, that the chemical effects of the syphilitic virus are less toxic than are the corresponding effects of the tubercular. The further development of the new tissue therefore proceeds, and vessels are formed. The caseation which next occurs is, in all probability, not so much due to the direct action of the virus as to the subsequent shutting off of the blood-supply. By means of changes, presently to be described, the walls of the bloodvessels in the centre of a gumma become thickened, and in thickening, encroach upon and nearly obliterate the lumen. Subsequent thrombosis in the affected vessels completes the interference with the blood-stream. To these changes must also be added the strangulating effect on the bloodvessels, produced by the contraction of the new fibrous tissue. The parts thus gradually deprived of blood degenerate, and this occurs at a comparatively early stage, although not so early as in tuberculosis.

In *early* stages, before they have produced marked destruction of tissue, gummata may disappear under treatment. In *later* stages their *central* fatty portions are frequently absorbed, leaving a radiating puckered scar ; calcification is rare. If gummata become infected with pyogenic cocci, they soften, and suppuration occurs around them, the abscess bursts, and a yellow slough is exposed. This has a very characteristic appearance, resembling a piece of wet wash-leather ; it is tough and coherent, unlike the dead tissue from the caseous centre of a tubercular focus. It gradually becomes detached, leaving a larger or smaller cavity with soft ragged margins. These changes can often be seen in the tongue. Gummata of the *skin* and *mucous membranes* are the most prone to take this course. These ulcerations must be distinguished from the superficial ulcerations connected with the early rashes. It seems probable that gummata may sometimes soften, just as tubercular nodules do, without the action of pyogenic cocci.

Gummata are met with in the skin and subcutaneous cellular tissue ; in the submucous tissue, especially of the pharynx, soft palate, tongue, and larynx ; in muscle, fasciæ, and bone ; and in the connective tissue of organs—especially of the liver, brain, testicle, and kidney. Gummata also occur, but much less frequently, in the lungs, especially in *congenital* syphilis ; simple localised fibroid indurations are found under the same circumstances.

No definite line can be drawn *clinically* or *pathologically* between secondary and tertiary lesions. In congenital syphilis, gummata and pericellular cirrhosis of the liver are among the earliest manifestations of the disease.

Parasyphilitic Lesions.—The name *parasyphilis* has been applied to certain affections of a degenerative nature, due to the action of the syphilitic poison, which generally appear some years after the

primary affection. The best known of these are tabes dorsalis (locomotor ataxy) and general paralysis of the insane. (See Diseases of the Nervous System.) The syphilitic nature of these diseases has been proved by the discovery of the *Sp. pallida* in the central nervous system, and as the result of this demonstration the usefulness of the term itself has largely disappeared.

Syphilitic Disease of Bloodvessels.

Certain changes in the arteries, known as *Endarteritis obliterans*, occur in syphilis, either as a distinct local lesion—especially in the brain—or in conjunction with other syphilitic changes, as in gummata.

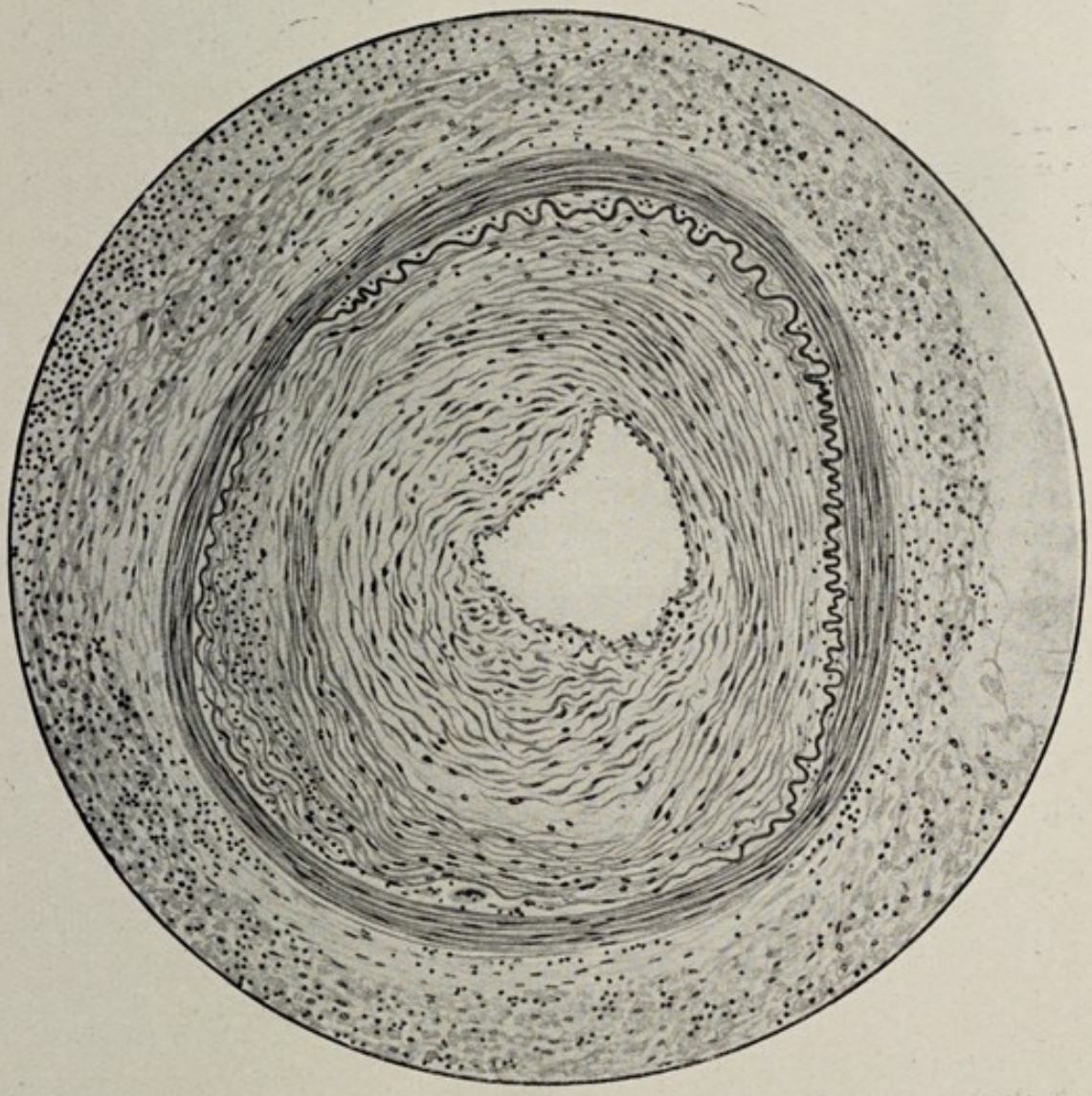


FIG. 110.—SYPHILITIC ENDARTERITIS OF A CEREBRAL VESSEL, SHOWING IRREGULAR THICKENING OF THE INTIMA. (× 175.)

In the cerebral arteries the changes produce opacity and marked thickening of the vessel, with considerable diminution in its calibre. It is this diminution of the lumen of the vessel which is especially

characteristic. The smaller vessels, arteries, and veins, are chiefly affected, and their lumina may be quite obliterated.

When transverse sections of the vessels are examined microscopically, the changes are seen to be situated in the *inner* coat (Fig. 110). The intima is considerably thickened by a cellular proliferation. The thickening, which is limited internally by the endothelium of the vessel, and externally by the membrana fenestrata, is very irregular, the lumen of the vessel being no longer circular on section. Sometimes the elastic layer is split into several strands.

In addition to the change in the intima, the outer coat is abnormally vascular, and is infiltrated with small mononuclear cells, and to a less extent this cellular infiltration usually invades the muscular layer as well. The marked diminution of the lumen of the vessel, and the consequent interference with the circulation, coupled with the changes in the endothelium, frequently lead to thrombosis, and, consequently, when the cerebral vessels are affected, to *cerebral softening*.

Syphilis is one of the factors in the production of arterio-sclerosis and of aneurysm. It also leads to amyloid degeneration of the walls of the vessels and of other parts.

Syphilitic Diseases of the Liver.

The liver is one of the most frequent seats of syphilitic lesions.

In **adult life** the commonest change is the occurrence of caseous foci (gummata) imbedded in localised tracts of dense fibrous tissue, with processes radiating into the surrounding lobules of the liver. These changes are generally connected with fibroid thickening of the capsule and adjacent peritoneum. The softening of gummatous masses may give rise to large abscess-cavities with thick fibrous walls. Sometimes no caseous masses may be found, and the change is limited to scar-like depressions on the surface of the liver, which is irregularly and deeply puckered. In these cases it is possible that there may have been gummata which have since been absorbed. In other cases, as Adami points out, a more uniform pericellular cirrhosis occurs and persists. This involves the central portions of the lobules quite as much as the peripheral.

In **congenital** syphilis two changes are common: (1) Recent gummata, consisting of small, pale, somewhat ill-defined patches of granulation-tissue, are not infrequently met with. (2) More often, diffuse changes, resulting in pericellular cirrhosis, are found. (See Pericellular Cirrhosis of Liver.) According to Hecker, the cellular accumulations causing the enlargement of the liver so common in children born with syphilis, are made up partly of proliferated liver-cells and partly of cells suggestive of newly-formed red corpuscles. By suitable methods of staining numerous spirochætes may be demonstrated in such organs.

Amyloid disease may be found in the liver as a local change in

the neighbourhood of gummata; it may also result from syphilis apart from any of the above changes.

It is unnecessary to describe the syphilitic lesions which occur in other organs, as they all present the same general characters—viz., cell-infiltrations, scars, fibroid indurations, and gummata, singly or in combination. The late syphilitic affections of the central nervous system have already been alluded to, and are more fully discussed in Chapter XXXIV.

CHAPTER XVIII

TUMOURS

In pathology the term *tumour* denotes certain *local growths of new tissue,* which appear to be excrescences upon the general plan of the organism. Tumours possess certain common characters which serve to distinguish them from other pathological formations, such as the masses of new cells which arise in conditions of chronic irritation and represent attempts at repair of injury ("inflammatory" swellings, granulomata). The chief of these *distinguishing features* are: (1) an unusual independence of growth (*autonomy*); (2) a varied degree of similarity of structure to that of the part from which the growth springs; (3) an extreme tendency of the component tissue-elements to undergo degeneration; and (4) an almost complete absence of all function, or, in other words, the uselessness of the mass of new tissue. These characters must be considered in detail.

1. **Independence of Growth.**—A tumour is at first a local growth of new tissue, which enlarges by multiplication of its component cells. Subsequently, by means that will presently be described, some forms of new-growth possess the power of reproducing themselves in other parts (p. 276). Two striking differences between the growth of ordinary tissues and that of tumours must be mentioned: (1) *The nutrition of a tumour is disproportionate to the nutrition of the tissues in its immediate neighbourhood, and often to that of the body taken as a whole.* Thus, in the case of fatty tumour in the subcutaneous tissue, the body may become thin and the subcutaneous fat disappear, while the fatty tumour wastes but little, if at all. Moreover, malignant growths often enlarge rapidly, while all the other tissues are as quickly emaciating. (2) *The nutrition of a tumour is often disproportionate to the age of the individual* in whom it occurs. This is seen in the growth of cancers which arise and grow rapidly in old people, while the rest of the tissues are gradually undergoing atrophy; usually, however, they grow more rapidly when they appear in young persons. The growth of a tumour often seems to continue indefinitely; it does not reach a definite size and remain at that.

2. **Peculiarities of Structure.**—In structure, tumours more or less resemble normal tissues in some stage of their growth—every morbid new-growth having its prototype among the normal tissues.

The resemblance, however, is at best incomplete, the tissue-elements often differing in form, arrangement, or some other detail; and tumours are thus always more or less atypical in their structure. As a rule, the difference between the normal and the abnormal tissue is so great that by means of the naked eye alone one can tell roughly where the one begins and the other ends.

Tumours are generally supplied with bloodvessels and lymphatics, but not with nerves. The bloodvessels often become much enlarged, pointing to some special stimulus or demand on the part of the newly-formed cells for blood.

The terms *homologous* and *heterologous* are sometimes applied to tumours. When the tumour resembles the tissue from which it originates, it is said to be homologous; when it differs from this, it is said to be heterologous. A cartilaginous tumour arising from cartilage is, therefore, homologous, but occurring in any other than connective tissue, as, for example, in the parotid gland, is heterologous. The distinction is unimportant, for, in the example just given, the cartilage does not actually arise from the gland-cells of the parotid, but, in all probability, from the connective tissue or from a misplaced remnant of Meckel's cartilage. Heterologous tumours are generally secondary to some primary growth occurring in a distant part.

Somewhat on the same lines is the division of tumours into *typical* and *atypical*, the former being formed of cells resembling those of adult tissues, the latter of embryonic or otherwise abnormal cells.

The relation of the tumour to the surrounding parts varies. Sometimes the tumour is *circumscribed*, merely displacing them and stretching and irritating their connective tissue, so that the latter comes to form a fibrous capsule around the tumour, which thus generally forms a spheroidal or lobulated mass. Lipomata, fibromata, and chondromata, are usually thus encapsuled. In other cases the growth *invades* the adjacent structures. There is then no real line of demarcation between the tumour and the surrounding parts; and, although to the naked eye there may seem to be one, the microscope will show that the apparently healthy tissues are more or less infiltrated with cells from the parent growth. In such a case, while the main body of the tumour may assume a roughly spheroidal shape, outlying discontinuous nodules may also be visible to the naked eye. The difference seems to depend on the rapidity of growth of the tumour, and on the varying degrees of mutual adhesion between the cells. Two or more tumours of a different structure may coexist in the same patient, and it is not necessarily the case that two tumours of the same structure need be derived from the same rudiment.

3. **Retrogressive Changes.**—A tumour very rarely disappears, thus differing from an inflammatory growth—*e.g.*, a gumma. It may either remain stationary, or grow—slowly or rapidly. Sooner or later it usually becomes the seat of necrosis or degeneration. The

time at which these commence varies. The more rapid the growth, and the less specialised the new tissue, the less is its durability and the sooner do retrogressive changes occur. Many carcinomata and sarcomata develop rapidly, and degenerate quickly. Osseous tumours, on the other hand, develop slowly; they consist of a more highly organised tissue, and have much greater stability.

The retrogressive changes are similar to those met with in the normal tissues. Thus, *fatty, pigmentary, calcareous, colloid,* and *mucoid degenerations* may occur. Tumours may also become the seats of *inflammation, ulceration, necrosis,* and *hæmorrhage.*

4. **Absence of Function.**—The origin of a tumour has no connection with the satisfaction of any need in the economy of the body. Some adenomata are said to have ducts and some secretory power, but their secretions are not available for use. Tumours derived from the thyroid gland often contain colloid, and adenomata of mucous membranes may form mucus.

Recurrence and Generalisation.—A tumour may recur locally after removal; and, independently of removal, growths similar to the primary tumour may form (1) in the neighbourhood of the parent growth, (2) in the nearest lymphatic glands, or (3) in more distant tissues or organs. Sometimes all these occur. Each must be considered separately.

1. **Reproduction in Adjacent Structures.**—The recurrence of a tumour *in loco* after operative removal is due to some of its cells having been left behind—and is therefore much more likely to occur in those growths which infiltrate the surrounding tissues, and really extend beyond their apparent limits, than in those which are encapsuled. The cells left behind continue to grow, and thus the tumour recurs. Apart from removal, cells may be carried to some little distance from the primary growth by currents of lymph or blood, and, on becoming impacted, may form the nuclei of secondary nodules springing up around the original tumour. In some tumours local recurrence may take place many times, and lead to the death of the patient without any infection of glands or distant tissues.

2. **Reproduction in the Nearest Lymphatic Glands.**—This is owing to the entry into the lymph-stream of cells from the primary growth. The cells are carried to the nearest lymphatic glands, and there are arrested and develop into secondary tumours of the same nature. When the lymphatic glands have themselves become the seat of secondary growths, they in their turn constitute new centres of infection, and may thus infect the more distant glands or the immediately adjacent tissues. When the lymph-sinuses of a gland are so blocked by new-growth that lymph cannot pass, a regurgitant flow is the natural result, and the lymph, bearing tumour-cells, has to find a new course and pass through other vessels and glands. In this way we can account for infection of the abdominal glands by a tumour of the lungs, and for the numerous nodules in the skin which sometimes occur all round an atrophied scirrhus of the mamma. The tendency of new-growths to reproduce themselves in the

lymphatic glands varies very much. The reasons for these differences will be seen in subsequent chapters.

3. **Reproduction in Distant Tissues.**—This is usually the final stage in the history of malignant growths, and is known as their "generalisation." The reproduction of the primary growth in distant tissues is, in the great majority of cases, owing to the entry of some of its elements into the lymph-stream; more rarely it may be effected through the bloodvessels. The secondary tumours are, therefore, the result of embolism of tumour-cells; and are of the same nature as the primary one, although they may be larger and are often softer, more vascular, and more active in growth. They may themselves become secondary centres of infection, and in the same way cause tertiary growths in parts beyond.

Although the general dissemination of a malignant growth is thus in most cases due to the transmission of its elements by the blood-stream, this is not the only way in which it may be brought about. Exceptional cases have been described in which the elements of a tumour have been distributed and have caused secondary growths in other ways, as by passing down the trachea, between the layers of the peritoneum, or from the kidneys down the ureters to the bladder.

A peculiar process of selection seems to occur in regard to the sites of metastatic growths; thus secondary growths are found especially in the bones in cases of cancer of the prostate, while bilateral affection of the suprarenal glands, kidneys, or ovaries is sometimes observed, with few scattered growths elsewhere. It appears that certain organs afford specially favourable soil for metatases in these cases, but the reasons for the selection are obscure.

Lastly, it must be borne in mind that growths may be secondary to each other only *in time*; that is, they may originate, independently of each other, from different primary foci.

We have spoken of generalisation and lymphatic infection as being due to the transference of tumour-cells from the primary growth. That the primary growth is the real source of the secondary growths is shown by their similarity in structure; by their time-relationship; by their demonstrable connection by means of lymphatics or bloodvessels; by the occasional discovery of tumour-cells impacted in the bloodvessels as emboli; by the invariable absence of secondary growths from non-vascular tissues, such as cartilage and cornea; and by the occurrence of secondary growths in tissues in which primary tumours of the structure in question are never found.

Clinical Course.—Tumours are divided clinically into two great types, the *simple* and the *malignant*.

A **simple** or **innocent tumour** is one which grows slowly and steadily, or, having attained a certain size, remains stationary. It usually consists of tissue closely resembling some normal adult tissue, and is generally surrounded by a distinct capsule, out of which it can be completely shelled—for there is no infiltration of surrounding parts. Consequently, it seldom recurs locally after

removal, and secondary growths in glands or elsewhere do not result from it. Its interference with health is only mechanical, unless some accident—such as infection or hæmorrhage—occur in it. Tumours of the fully developed connective-tissue type generally pursue this course, and may grow to a huge size.

A **malignant tumour,** on the other hand, grows rapidly and tends to enlarge continuously. It consists of tissue which is markedly atypical, and is, as a rule, unencapsuled, progressively infiltrating the surrounding tissues, and presenting no clear line of demarcation as a guide to removal. Complete removal is, therefore, very difficult, and subsequent recurrence, locally and in distant parts, is probable. Though the patient is often in excellent health when the tumour first appears, its effects soon give rise to the cachexia just described. The more rapidly and the more completely a tumour produces these results, the greater is said to be its *malignancy*. Growths vary much in these respects, and a sharp dividing line between innocent and malignant growths cannot always be drawn. Some unencapsuled growths are innocent (gliomata); some having the structure of malignant growths enlarge continuously, but do not invade glands or distant parts (rodent ulcer); while others recur in neighbouring glands, but not in distant parts (epithelioma of tongue). Some growths, at first innocent, occasionally become malignant (papillomata, adenomata). Sarcomata and carcinomata furnish the best examples of malignant tumours.

Effects.—A tumour, by its growth, position, generalisation and secondary changes, may, in many ways, produce marked effects on local and general nutrition. (1) The local growth may lead, mechanically, to the destruction of parts essential to life, as in the case of an otherwise innocent tumour in the pons or medulla; or it may similarly impair the action of important organs such as the lungs or stomach, and thus lessen the exchange of gases in the former or interfere with the digestive changes in the latter, or passage of food through it. (2) The rapidity and extent of the growth may lead to the abstraction of the nutriment needed for the maintenance of the normal tissues. (3) Hæmorrhage may occur into, or from, a tumour and give rise to secondary anæmia, as in the marked hæmaturia which sometimes characterises growths in the kidney. (4) Infection, ulceration, and septic absorption may occur, as in epithelioma of the tongue. (5) Pain and anxiety may cause anorexia and sleeplessness. (6) Some abnormal and deleterious substances may possibly be discharged into the blood-stream by the tumour-cells, although this is at present a purely hypothetical occurrence. (7) Many of these effects may be increased by similar action on the part of secondary growths. In these ways tumours may lead to wasting, loss of strength, and anæmia—in other words, to the condition known as the *cachexia of malignant disease.*

Locally, a tumour acts as a foreign body, irritating the cells which come in contact with it at its periphery, and causing proliferation of the connective-tissue elements. A zone of small mononuclear cells

of an "inflammatory" nature is therefore seen surrounding a rapidly-growing tumour, and these may become organised into the fibrous capsule which usually surrounds benignant growths.

ÆTIOLOGY.—Of the ætiology of tumours, as a class, nothing certain is at present known. A few scattered facts have, however, been ascertained, throwing light on the causation of certain divisions of the group. Recent research has been devoted almost entirely to the study of the malignant tumours, especially carcinomata, while simple growths have been comparatively neglected, and little attempt has been made to treat the question from a general point of view.

It is, indeed, possible that it may be necessary, in the light of additional knowledge, to subdivide the group, and to separate different varieties of tumour one from another, just as certain processes formerly looked upon as new growths have now been removed from this class and recognised as inflammatory: of such, tubercular and syphilitic granulomata afford instances. In the same way future analysis may carry the process further, and resolve the present apparently homogeneous group of tumours into a variety of separate formations due to entirely different causes. At present, however, there is no sign of any probable line of cleavage. Tumours form a group characterised by well-defined peculiarities which differentiate them from other pathological conditions; and, while they continue to form a class by themselves, it is necessary that any cause suggested to account for their production should apply to the whole group and not merely to isolated fractions of it.

Certain facts in relation to the formation of tumours appear to be firmly established, and must form the foundation of any theory of their causation.

1. **Statistical Data.**—*Heredity* appears to play some part in the causation of certain growths, especially those of the uterus and mamma, but it is difficult to estimate the exact weight that should be attached to this cause.

Age.—In general the liability to tumour-formation increases with age, but the influence of this factor is not the same with all forms of tumour. Carcinoma is especially a disease of late life, but sarcoma not infrequently attacks young persons and even children, and chondromata also occur frequently in the young.

Race.—The incidence of malignant tumours, which have been most carefully studied, varies in different countries, but little is known of the racial incidence of other forms of the disease.

An *endemic* prevalence of cancer in certain houses and localities has been recorded, but is not satisfactorily proved to occur.

2. **Clinical and Anatomical Data.**—The influence of **Chronic Irritation** in the production of certain forms of new growth is well established. Thus, the edges of long-standing ulcers are favourite positions for the development of epithelioma, and the points at which this disease most frequently affects the alimentary canal are

those at which the lumen is narrowed, and which are, therefore, specially liable to traumatism from the contents of the tube. Such localities are (1) the two orifices of the stomach, (2) the point where the œsophagus is crossed by the left bronchus, and (3) that where it joins the pharynx, opposite the cricoid cartilage. The large intestine is much more frequently the seat of tumours than the small, possibly owing to the solid nature of the contained fæces, their longer contact with the intestinal wall, and their consequent liability to irritate the mucous membrane: the rectum and anus, where this cause would be most at work, are specially frequent seats of tumour-formation. Cancer may develop in the lesions of chronic lupus, and a peculiar form of this disease may be the last phase of the dermatitis resulting from continued exposure to the X rays. Various chemical irritants, such as tar and paraffin, may give rise to epithelioma in the skin of workers engaged in handling them; and soot is apparently the exciting cause of cancer of the scrotum in chimney-sweeps.

On the other hand, the frequency with which instances of chronic irritation occur, and the relative rarity of the appearance of tumours in connection with them, render it certain that irritation alone cannot be a sufficient cause of tumour-formation. The number of ulcers of the leg, which may be seen every day at a surgical out-patient department, with a history of several years' duration, is alone sufficient proof of the inadequacy of this theory by itself to account for the phenomena. Further, in many instances of tumour-formation no source of irritation is discoverable.

Closely allied to the question of chronic irritation in relation to tumours is that of the influence of general *poisons*. Thus, long-continued administration of arsenic is said to lead to the appearance of epithelial growths, just as it may cause hypertrophy of the horny layer of the skin; and workers in copper and cobalt appear to be specially liable to suffer from malignant tumours.

In rare instances conveyance of *infection* from one individual to another is stated to occur, as in the case of communication of cancer of the genitals from husband to wife; but here again the evidence is not quite conclusive. In one curious variety of new growth, however, *syncytioma* or *deciduoma malignum*, a form of rapidly-growing tumour results apparently from development of portions of the chorionic tissue left imbedded in the substance of the uterus. The cells thus left multiply as independent organisms in the body of the mother, giving rise to secondary deposits in the lungs and other organs. The fertilised ovum with its covering membranes being practically a separate organism, this form of tumour seems to be constituted by a growth of parasitic cells, and is suggestive of a similar explanation of other new growths.

Simple tumours present little difference in *anatomical structure* from the normal tissues of the body; but the cells of a malignant growth tend to assume a simple, undifferentiated, or embryonic character.

Certain special forms of multiplication of the cells of tumours have been described. Thus the nucleus in malignant growths may undergo peculiar phases of mitosis, dividing into three daughter-nuclei instead of into two ; while the mitotic threads are reduced in number owing to failure of the original chromatin-filaments to undergo the usual longitudinal division (*heterotype mitosis*). This latter peculiarity resembles the behaviour of the cells of reproductive organs. Some observers have claimed to find evidence of conjugation taking place between the cells of malignant tumours, but this statement demands much fuller proof than has yet been adduced.

3. **Experimental Data.**—Attempts have been made to cause formation of tumours by injecting or otherwise inoculating living cells into animals. Thus Birsch-Hirschfeld and Garten injected emulsions of living embryonic cells into the livers of adult animals, and found that in some cases definite tumour-like growths resulted. These, however, did not persist, but were ultimately absorbed. Further, Lack has described an experiment by which cells from the ovary of a rabbit were set free, by scraping the surface of the gland, in its peritoneal cavity, and as the result of this, a definite carcinomatous mass with secondary growths developed. Attempts to repeat this experiment have so far been unsuccessful.

Recent work has been confined almost entirely to the investigation of the tumours which occur in mice, since these growths appear to be similar in nature to human cancer, and the animals breed rapidly, so that many generations are produced in a short period of time. Jensen first showed that a form of adeno-carcinoma occurring in these animals could be transplanted from one individual to another, and studied the resulting tumours ; and his experiments have been repeated and extended by other observers. It has been shown that if a minute portion of such a tumour is implanted aseptically under the skin of a healthy mouse, growth of the cells forming the graft may take place ; and if they can thus establish themselves, a typical tumour results. The connective tissue of the graft degenerates and is absorbed, but new stroma and bloodvessels are formed from the cells of the new host (the animal which receives the injection) and the nutrition of the tumour-cells is thus maintained.

Only a certain proportion of the mice thus inoculated with portions of any tumour develop new growths : some appear to be immune. Young mice are better subjects for inoculation than are older animals. Taking a series of susceptible mice, it is possible to continue the propagation of a tumour indefinitely, through any number of generations, the cells appearing to have no natural period of senescence or limitation of growth. But the vitality of the tumour-cells seems to ebb and flow somewhat, with alternating periods in which larger and smaller percentages respectively of the inoculated mice develop tumours. Heredity does not, so far as can be observed, influence the liability of the animals to spontaneous appearance of tumours, no larger proportion of mice so affected being found among the progeny of affected parents.

In a certain number of cases the inoculated cancerous material atrophies and disappears, and in such mice immunity to subsequent inoculation is induced. A similar immunity results from inoculating the animals with an emulsion of the cutaneous cells or with the blood of another mouse, or with cells derived from a mouse-fœtus ; but these procedures do not influence the growth of a tumour already established. It would seem that the immunity depends on a failure of the tissues of the inoculated mouse to form a new stroma and new bloodvessels for the nutrition of the foreign cells ; but the cause of this difference in reaction is quite obscure.

Wide divergencies are seen in the structure of the tumours formed in different mice by inoculation with pieces of the same original growth : one, for example, may exhibit a cystic adeno-carcinoma, another a spheroidal-celled cancer with solid cylinders of closely-packed cells. In some cases a development of sarcoma has occurred after inoculation with carcinomatous tissue, the connective tissue appearing to develop an increased power of growth. The cause of this curious development is quite unknown.

Such being the data supplied by actual observation and experiment, we have next to consider the various hypotheses which have been formulated to explain the formation of tumours.

1. **Theory of Embryonic Remains.**—Virchow discovered in the cancellous portions of some of the long bones small "islands" of unaltered cartilage-cells, which he suggested might form the starting-points of tumours. Cohnheim extended this suggestion and applied the principle to explain the origin of all kinds of new-growth. On his hypothesis, in certain instances, either more cells are formed than are necessary for the development of a part, or in the process of growth certain groups of cells are isolated and cut off from their fellows. These groups of superfluous cells may subsequently develop into tumours. The cells may either continue to develop in the ordinary way, so as to form mature tissue-cells of various kinds, or they may remain embryonic in character. In the former case, tumours of the benign variety will arise—resembling adult tissue and growing relatively slowly ; in the latter case malignant growths will occur. In favour of this theory the following facts may be adduced : (1) Dermoid cysts, which are practically innocent tumours, are almost certainly due to errors of development (p. 336), and congenital moles frequently serve as the starting-points of melanotic sarcomata in later life. (2) Tumours are very frequently found in the neighbourhood of points where the developmental process is complicated, and where, therefore, errors might naturally be expected to occur most frequently. Instances are seen in the common appearance of carcinoma in the rectum, where the junction takes place between the original hind-gut and the invaginated epiblast forming the proctodæum ; at the external os uteri, where Müller's ducts open into the uro-genital sinus ; and at points where different varieties of epithelium meet, as at the cardiac and pyloric orifices of the stomach. (3) In many cases there are formed in various

organs tumours consisting of cells differing entirely in character from those normally found in such positions, the presence of which can, however, be accounted for by supposing the inclusion of a portion of some neighbouring structure. Thus, for example, parotid tumours frequently contain cartilage, which may be derived from that forming the inferior maxilla (Meckel's cartilage); and renal growths may contain cells resembling those of the adjacent supra-renal body, or voluntary muscle-cells derived from the embryonic muscle-plates, which lie near the Wolffian body in the process of development.

On the other hand, several objections may be raised to Cohnheim's theory: (1) The "rests," or isolated cell-groups, upon which it is based, are not actually found with any frequency within the body. (2) Those which do occur, such as the cartilage-islands discovered by Virchow, and certain epithelial groups in the tonsils, do not show any actual tendency to develop into tumours—in other words, no transition-stages are found between these masses of cells and actual tumours. (3) Tumours do not occur *at* points of fusion between different embryonic structures, but rather *in the neighbourhood* of these points, which are in many cases specially liable, owing to their anatomical characters, to traumatism and mechanical irritation. (4) New growths may arise in scar-tissue, in which it is practically impossible to imagine the existence of primordial "rests." (5) Cohnheim himself admitted that certain instances of tumour-formation, in which chemical irritants were obviously the exciting causes, could not be explained on his theory.

The necessary conclusion appears to be that the theory of "embryonic remains," while indicating a method of causation which is possibly effective in the case of certain classes of tumours, is not adequate to embrace the whole of the group, and affords only an incomplete and partial explanation.

2. **The Parasitic Theory.**—The endeavour to find a parasitic organism as the cause of malignant growths has been the guiding principle in the greater part of recent research. When first *bacteria* were recognised as the cause of a number of diseases, several organisms were isolated, each of which was claimed by its discoverer as the cause of cancer. None of them, however, stood the test of further experience. Parasitic *protozoa* were next brought forward as the agents concerned. There is a disease of the rabbit due to an animal parasite (*Coccidium oviforme*), in which a proliferation of the lining epithelium of the bile-ducts occurs, resembling an adenoma in appearance. This was set up as the type of tumour-formation, and the so-called cancer-bodies (p. 323) were assigned to this class of animalcules. It is probable, however, that the growth in the bile-ducts of the rabbit is inflammatory in origin, and is analogous to certain papillomata of the bladder and larynx in man, which are produced by chronic irritation. The identification of cancer-bodies with protozoa is not now supported by many authorities, and champions of the parasitic theory are in favour of regarding these

peculiar bodies as parasitic yeasts (*blastomycetes*). Plimmer has cultivated from carcinomata a fungus which is capable, when injected into the peritoneal cavity of animals, of causing nodular proliferations of the endothelial cells of the serous membrane. Schueller and Schmidt also claim to have isolated and cultivated specific organisms from cancers ; but their researches need confirmation. Doyen has isolated a micrococcus which he calls *M. neoformans*, and believes to be the causal agent. Borrel suggests that the virus is ultra-microscopic, and believes that in some cases of epithelioma of the skin it may be conveyed by a minute acarus, *Demodex folliculorum*.

It may be pointed out in favour of the probability of a parasitic origin of malignant growths (1) that they tend to occur in old persons rather than in the young or adult, just as parasites attack weakly rather than strong individuals ; and (2) that the dissemination of malignant secondary growths, by bloodvessels and lymphatics, bears a considerable resemblance to the spread of a process such as tuberculosis. If it were satisfactorily proved that the peculiar cancer-bodies were in reality parasites, which occurred only in this disease, a fairly strong *prima-facie* case would exist for believing in this theory. This proof does not yet exist, most observers holding that these appearances are only masses of hyaline material, fragmented nuclei, leucocytes, vacuoles, or invaginated cells.

Against the theory, on general grounds, cogent arguments may be urged. (1) There is practically no evidence—either clinical or experimental—of infection taking place between different individuals ; nor does the disease appear in epidemic or endemic form. Instances of the occurrence of cancer in several successive inmates of certain houses (cancer-houses) are not proved to be more than coincidences. (2) The method of spread by secondary growths, when closely examined, is unlike that in any known infective disease. Thus, a parasite might set up irritation in the tissues with which it came into contact, and thereby cause proliferation of the cells affected. It might possess the power of stimulating either connective-tissue cells alone, as is the case with the bacteria causing inflammation ; or it might cause multiplication of the essential cells of organs attacked. As the parasite became distributed throughout the body, it would cause, in the former case, connective-tissue growths in various parts, or, in the latter, growths differing according to the organs invaded. In tumours, on the contrary, the secondary deposits exactly resemble the primary growth, whatever the parts may be in which they are situated. From this it almost certainly follows that they are due to embolism by fragments of the original growth. Such an occurrence is not known to take place in any recognised parasitic disease. (3) Finally, no observer has applied the parasitic theory to all tumours alike, nor has anyone succeeded in finding cancer-bodies in all specimens of cancer examined. The parasitic theory is not at the present time upheld by many pathologists, though certain recent observations by

Shattock and Dudgeon, Leyton and others have revived interest in this aspect of the question.

3. **Theory of Altered Tissue-Resistance.**—It has been suggested that tumours are due to an alteration in the mutual relations of tissues, from which it results that one kind of cell overcomes the resistance of neighbouring parts and grows more luxuriantly. Thus it is said that in old age the connective tissues suffer from depressed vitality, while epithelium is still vigorous: hence the appearance of carcinomata in advanced life. It is an obvious objection that sarcomata—connective-tissue tumours—may also occur in old age; and that senile atrophy of the more highly differentiated cells is generally accompanied by an increased growth of connective tissue. Ribbert has, on the other hand, suggested that carcinoma is due, not to overgrowth of epithelial cells, but to upward spread of connective-tissue masses, whereby clusters of epithelial cells are enclosed—the latter merely pursuing their natural process of development. The appearance of secondary deposits seems scarcely explicable on this hypothesis.

4. **Theory of Nervous Influence.**—It has been suggested that the nervous system has some connection with the origin of new growths. In favour of such connection may be adduced: (1) the supposed greater frequency of tumour-formation in man and the higher animals than in those lower in the scale—the development of tumours being thus *pari passu* with that of the nervous system; (2) the absence of nerves from tumours; (3) the facts that tumours have no function and that they grow independently of the other parts of the body, often flourishing luxuriantly while the rest of the organism is much emaciated—the latter peculiarity appearing to depend on some freedom from nervous control. (4) It may also be noted that the growth known as *molluscum fibrosum* appears to be definitely connected with nerve-distribution, and that alterations in neighbouring nerve-trunks have been found in certain cases of sarcoma (Campana). Cheatle has shown that in many instances rodent ulcer and cutaneous carcinoma tend to appear at Head's "maximum points" of nerve-distribution, and to limit their extension to areas supplied by particular nerves. So little is, however, known of the action of the nervous system on the tissues that this hypothesis is at present somewhat visionary.

5. **Biological Theories.**—Various theories have in recent years been propounded, based upon the peculiar facts observed in the case of the tumour known as syncytioma malignum and on the irregular forms of mitosis seen in the cells of malignant growths. Thus Beard has suggested that tumours have their origin in certain cells of the germinal epithelium, which go astray in the process of fœtal development and lie dormant in the tissues, subsequently exhibiting the power of continuous growth characteristic of germinal tissue. Farmer, Moore, and Walker also point to the analogy between tumours and germinal tissue afforded by the existence in

both alike of the so-called heterotype mitoses. They suggest that some unknown stimulus has caused the cells to revert to a primitive germinal type. In support of their view they point out that in cases of chronic inflammation, which is known to be a forerunner of cancer, irregular forms of mitosis are often found.

A curious feature connected with these irregular mitoses is their tendency to occur at certain stages in the growth of a tumour, alternating with periods in which normal mitotic figures prevail. Conjugation of the nuclei of the cells is said to occur during these phases of heterotype mitosis. If true, this phenomenon presents a curious parallel with the known development of protozoa, in which multiplication by simple fission takes place for a certain number of generations, until apparently the energy of the race becomes exhausted: then conjugation takes place between pairs of the organisms, by which their energy is renewed, and subsequently simple fission is resumed. It might seem, therefore, that the cells of malignant tumours have reverted to the primitive protozoan type, from which presumably all metazoa were gradually differentiated.

While these analogies are of great interest, it cannot be said that, thus far, they afford any assistance in explaining the origin of tumours.

Conclusions.—From the preceding considerations it seems legitimate to draw the following conclusions: (1) Tumours arise as local growths of cells, which have developed the power of indefinite multiplication. (2) In the case of syncytioma malignum the cells which form the tumour are derived from another individual—the fœtus—and experimentally tumours may be passed from mouse to mouse. *Tumours thus originate in cells or groups of cells which have become parasites*, instead of taking part in the work of the organism.

As to the cause of their irregular development, nothing certain is known. The most important factor clinically is chronic irritation. Now, it is well known that chronic irritation of tissues is accompanied by continual attempts at repair on the part of the tissues, which attempts are constantly interrupted by the irritant. In other words, there is irregular cell-multiplication. An example of this may be seen at the margin of a chronic ulcer. Here microscopical examination shows that there occur masses of epithelial cells imbedded among the granulation-tissue, and cut off from the surface epithelium in which they originate. It requires no great stretch of imagination to see in such isolated cells rudiments of potential tumours, analogous to the developmental "rests" which have been suggested as a source of new-growths. There are present in each instance *groups of cells which have become severed from their natural connections in the body*, whether this be the result of developmental errors or of acquired disease. What exactly is implied by "natural connections" requires further elucidation: it is possible that it is in this direction that we may look for the action, or failure of action, of the nervous system, as was suggested above.

In order that tumours may develop, a certain relation must exist between the vigour of the aberrant cells and that of the surrounding parts. It would seem that, if the free cells be vigorous and the tissues comparatively non-resistant, a rapidly-growing tumour results: this will infiltrate surrounding tissues, and portions will be easily carried away to form secondary deposits. If, on the other hand, the tissues are more resistant, the invading cells grow slowly and with difficulty, and there is time for a capsule of connective tissue to be formed around them: the tumour is then an innocent one, as in the case of an implantation-cyst. Should the resistance of the tissues be subsequently weakened, innocent growths may become malignant, as is occasionally seen to occur. Finally, if the resistance of the tissues is sufficient, any cells which are accidentally set free are absorbed and not permitted to establish a footing. This is presumably the case with the majority of mankind, who are exposed to the cause of tumour-formation equally with the minority who develop the disease: only those whose tissues are of feeble resisting-power against invading cells become the subjects of new-growths. Simple traumatism, such as blows, to which many patients attribute the origin of their trouble, may be the agency by which cells are torn from their connections and allowed to take on independent growth.

On the other hand, the observations made with regard to the immunity of certain mice to the cells of tumours which can establish themselves in other mice suggest that the development of the connective-tissue stroma and bloodvessels, which enables the injected cells to survive, is induced by some (chemiotactic ?) attraction existing between the epithelial cells and the tissues of the "host." The nature of this influence is quite obscure.

CLASSIFICATION.—In our present state of ignorance, no satisfactory classification of tumours is possible.* They naturally fall into two main groups: (1) those consisting of tissue resembling fully-differentiated cells ("*histioid*" tumours of Virchow); and

* It was formerly the custom to classify tumours according to the layers of the blastoderm from which they were supposed to arise: thus Groups I., II., III. (p. 288) were classed as mesoblastic growths, and Group IV. as epiblastic and hypoblastic. This classification separated certain forms of growth which histologically are very similar, and which cannot always be distinguished by the microscope—viz., the epitheliomata and the endotheliomata; while certain growths classed as carcinomata (*e.g.*, those of the kidney and suprarenal bodies) are probably derived from mesoblastic cells. Adami has suggested a division into (1) *lepidomata*—tumours derived from covering membranes (λεπίς, rind) and from the glands developed from the hypoblast, such as liver and pancreas—and *hylomata* (ὕλη, substance)—tumours derived from the supporting framework of organs. Each of these categories is subdivided into subordinate groups according to the origin of the tumours respectively, from epiblast, mesoblast, or hypoblast. Thus we get lepidomata divided into epi-, meso-, and hypo-lepidomata; and hylomata divided into epi-, meso-, and hypo-hylomata. These subtleties of classification cannot be discussed at length in an elementary textbook. Reference may be made to the article by Dr. F. W. Andrewes in Allbutt and Rolleston's "System of Medicine," vol. i., p. 593.

(2) those consisting of embryonic cells. (3) A third group is formed by the teratomata, which consist of more than one kind of tissue, and clearly represent portions of another individual. It is convenient to consider separately the epithelial tumours and those representing connective-tissue elements. The following arrangement results :

CLASSIFICATION OF TUMOURS.

I.—*Type of Higher Tissues.*

Growth of muscle	Myoma.
„ nerve	Neuroma.
„ bloodvessels	Angioma.
„ lymphatic vessels	Lymphangioma.

II.—*Type of Fully-Developed Connective Tissues.*

Growth of fibrous tissue	Fibroma.
„ mucous „	Myxoma.
„ adipose „	Lipoma.
„ cartilage	Chondroma.
„ bone	Osteoma.

III.—*Type of Embryonic Connective Tissues.*

The varieties of Sarcoma.

IV.—*Type of Epithelial Tissues.*

Growth of papillæ of skin or mucous membrane	Papilloma.
„ glands	Adenoma. Carcinoma.
„ fœtal membranes	Syncytioma.

V.—*Teratomata, or Congenital Mixed Tumours.*

For the sake of convenience, all cysts are grouped together at the end of the section dealing with tumours—though the great majority of cysts are not new-growths.

CHAPTER XIX

TUMOURS—*Continued*

MYOMA.

MYOMATA* are tumours consisting of muscular tissue. There are two varieties—*Rhabdomyoma* and *Leiomyoma*.

1. **Rhabdomyomata** consist of striated muscle combined with varied, but generally considerable, amounts of connective tissue. They are congenital and very rare. The kidney and testis are the commonest sites. The striated muscle-cells in congenital growths of these organs are probably due to the original inclusion, in the Wolffian body, of cells from the adjacent muscle-plates.

2. **Leiomyomata** consist of non-striated muscle-cells, more or less isolated or grouped into fasciculi of various sizes, with a varying quantity of connective tissue and bloodvessels (Fig. 111). The muscular elements either present an approximately regular arrangement, or pass in all directions through the tumour. The bloodvessels, which usually are not numerous, are distributed in the connective tissue.

Leiomyomata are most frequent in the uterus; they also occur in the prostate, the œsophagus, the stomach and the intestines. They frequently become pedunculated and form polypi. They are much commoner than the striated growths, and are probably strictly homologous. They may form distinctly circumscribed tumours surrounded by a fibrous capsule, or ill-defined irregular masses in the midst of the muscular tissue in which they grow.

The most frequent **secondary change** which myomata undergo is *calcification*. *Hæmorrhage, mucoid softening*, and the consequent formation of cysts, are occasionally met with; also *inflammation, ulceration* and *necrosis*.

Clinically, myomata are benign growths, but rare instances of malignant leiomyomata have been recorded.

Myoma of Uterus.—The uterus is by far the most frequent seat of myomata, and here they constitute the so-called "*uterine fibroids*." In most of these muscular tumours of the uterus there is a large proportion of connective tissue—hence the terms "fibroid" and "fibro-myoma." This is the case especially in older growths.

* Greek μῦs, a muscle; μάβδος, a rod; λεῖος, smooth.

Those newly developed, on the other hand, consist almost entirely of true muscular tissue. These tumours are often multiple. They either form firm hard masses imbedded in the uterine walls, or project into the uterine or abdominal cavities, thus forming the intra-mural, sub-peritoneal, and sub-mucous varieties. When projecting into the uterus they constitute a common form of *uterine polypus*. They do not form till after puberty, and are commonest in elderly sterile females. Their growth is usually slow. Pregnancy

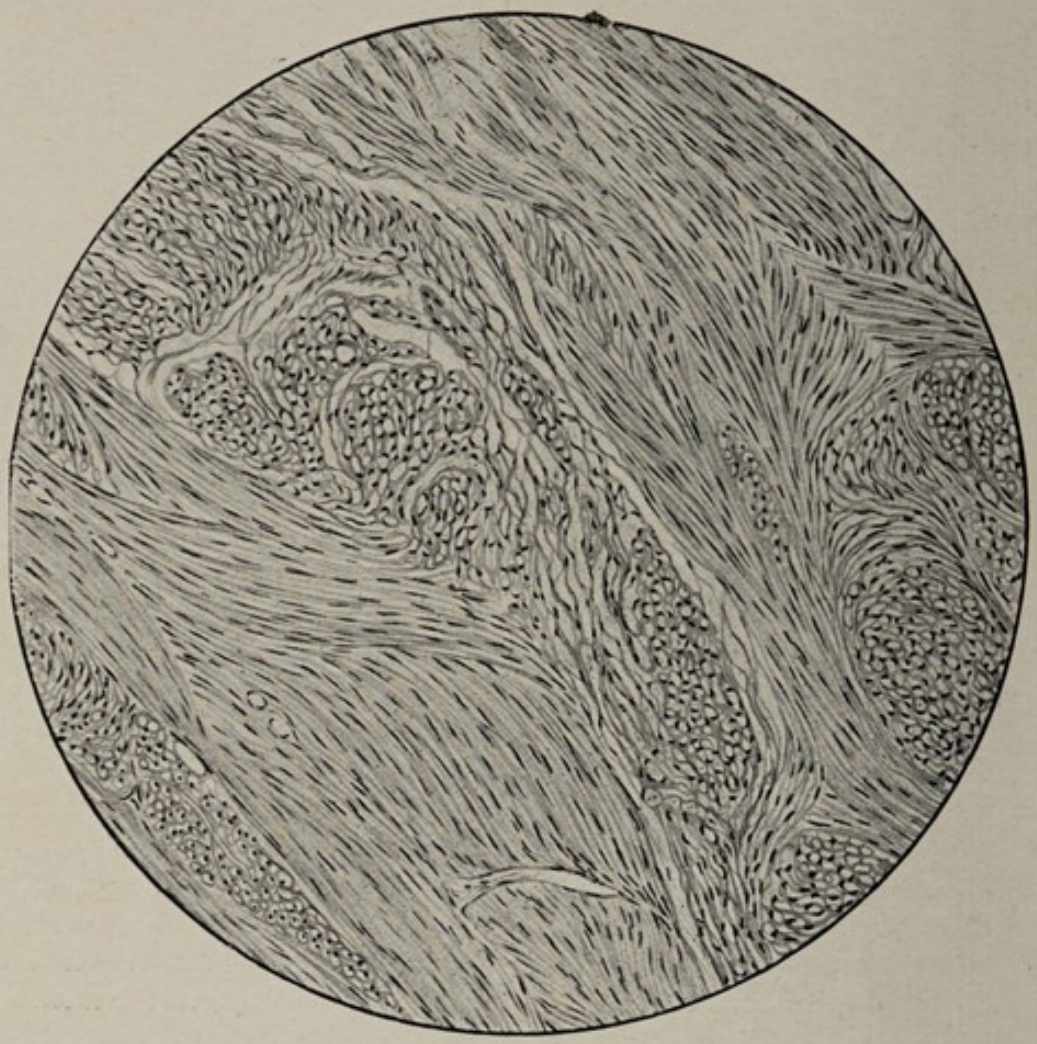


FIG. 111.—FIBROMYOMA OF UTERUS. (× 175.)

causes them to enlarge rapidly, and they undergo some involution after delivery. They generally atrophy at the menopause, the fibres undergoing fatty degeneration. The older ones are liable to become calcified. They also sometimes undergo mucoid softening, which gives rise to the formation of cysts in their interior; or they may be the seats of necrosis and suppuration. A peculiar form of degeneration in which the dying tissue is deeply stained with hæmoglobin or its derivatives is known as "red necrosis." Its nature is unknown.

NEUROMA.

Neuromata are tumours consisting of nerve-tissue, and are among the rarest of new growths.

They are usually made up of a mass of ordinary medullated nerve-fibres; they therefore resemble the cerebro-spinal nerves in structure. Virchow has also described, as exceedingly rare formations, tumours composed of non-medullated fibres and of ganglionic nerve-tissue. Neuromata are generally small, hard, and single tumours. They always originate from pre-existing nerve-tissue, which fact determines their site. Clinically, they are described as innocent, painful, and of slow growth.

Recent investigations have shown that most tumours formerly described as neuromata are really fibrous, fatty, or myxomatous growths occurring in connection with nerves, and so distributed among the nerve-fibres that it is difficult to ascertain whether any new growth of nerve-tissue has occurred other than elongation of the pre-existing nerve-elements. Most of the small, hard, painful tumours occurring in connection with nerves are probably fibromata. Of similar nature are the plexiform masses found in the skin and subcutaneous tissue, and known to be hereditary.

The term *amputation-neuroma* is applied to the bulbous ends of nerves sometimes found in stumps. They consist of fibrous tissue containing masses of rolled-up nerve fibres—attempts at repair rather than tumours. They are usually connected with the cicatricial tissue of the stump.

GLIOMA.

Gliomata* are tumours composed of neuroglia-tissue. The cells are similar to the stellate or spider-shaped cells with large nuclei, which normally form this tissue, but they may be so packed that their processes are hidden: the microscopic appearances of the tumour are, therefore, not unlike those of a round-celled sarcoma. In other cases the cells are comparatively few and their processes distinct, so that the structure resembles that of a myxoma. The vessels vary in number and size, and are frequently supported in fibrous septa derived from the pia mater. The adventitia of the vessels is generally thickened, and often undergoes hyaline change.

To the *naked eye*, these tumours are of almost the same consistency as the brain-substance, but generally of a greyer colour. As in other tumours, the larger the proportion of cells, the softer is the tumour. Although gliomata grow slowly, they are not encapsuled; and although they progressively infiltrate the tissues, they do not give rise to secondary growths unless they take on distinctly sarcomatous characters.

Among the **secondary changes** that may be found in these growths

* Greek γλία, glue.

are small *hæmorrhages* into their substance; they may also undergo *fatty degeneration* or *cystic* changes.

Gliomata **originate** in those parts which are outgrowths of embryonic cerebral vesicles—*i.e.*, brain, spinal cord, optic nerves, retina, and olfactory lobes. In the spinal cord the tumour grows along the peri-ependymal tissue around the central canal, giving rise, as its cells soften and break down, to the condition known as "*syringo-myelia.*"

Clinically, these growths are innocent, though they may occasionally become sarcomatous.

ANGIOMA.

Angiomata*—called also "hæmangiomata," to distinguish them from lymphangiomata—consist of bloodvessels held together by a small amount of connective tissue.

They may be divided into two **varieties,** (1) *simple* or *capillary* angiomata, made up of new vessels roughly resembling ordinary bloodvessels; and (2) *cavernous* angiomata, consisting of a cavernous structure similar to that of the corpus cavernosum of the penis.

1. **Capillary Angiomata.**—These tumours consist of a mass of bloodvessels, including arteries, veins, and capillaries in various proportions, bound together by a small quantity of connective tissue and fat. The lumen of the vessels may be cylindrical, sacculated, or fusiform. The thickness of the walls varies, those of the capillaries being often much thicker than is usual in normal vessels.

These growths occur principally in the skin and subcutaneous tissue; in the former, they give rise to the common *cutaneous nævi*, and the so-called *port-wine stains* or *mother's marks;* in the latter, they form soft, spongy tumours, imparting a bluish colour to the overlying skin. They are probably always congenital, though they may not be noticed for a few weeks after birth.

Capillary angiomata are often combined with other growths, such as lipoma, glioma, or sarcoma. Sometimes cysts containing altered blood form in them: these are probably due to hæmorrhage.

2. **Cavernous Angiomata** are made up of irregular fibrous alveoli, which communicate freely with one another, and are lined with an endothelium similar to that of the veins (Fig. 112). These spaces are distended with blood, which is supplied to them by numerous tortuous vessels, and circulates with varying degrees of rapidity. The arteries open directly into the spaces. These growths are commonly of a bluish colour, and may be diffuse, or form distinctly circumscribed tumours, sometimes exhibiting distinct pulsation. Their favourite seat is the skin and subcutaneous tissue, but they may also occur in the orbit, muscles, liver, spleen, and kidneys. They may develop by dilatation of the vessels of a simple angioma

* Greek ἄγγειον, a vessel.

They may be congenital ; but in the liver Ziegler thinks they develop after middle age, when the cells begin to atrophy.

Cirsoid Aneurysm.—This term is applied to a change in the arteries of an area, especially on the head, by which they become dilated, greatly elongated, and tortuous : it is doubtful whether new vessels are formed. Some cirsoid aneurysms are congenital ; others follow injuries.

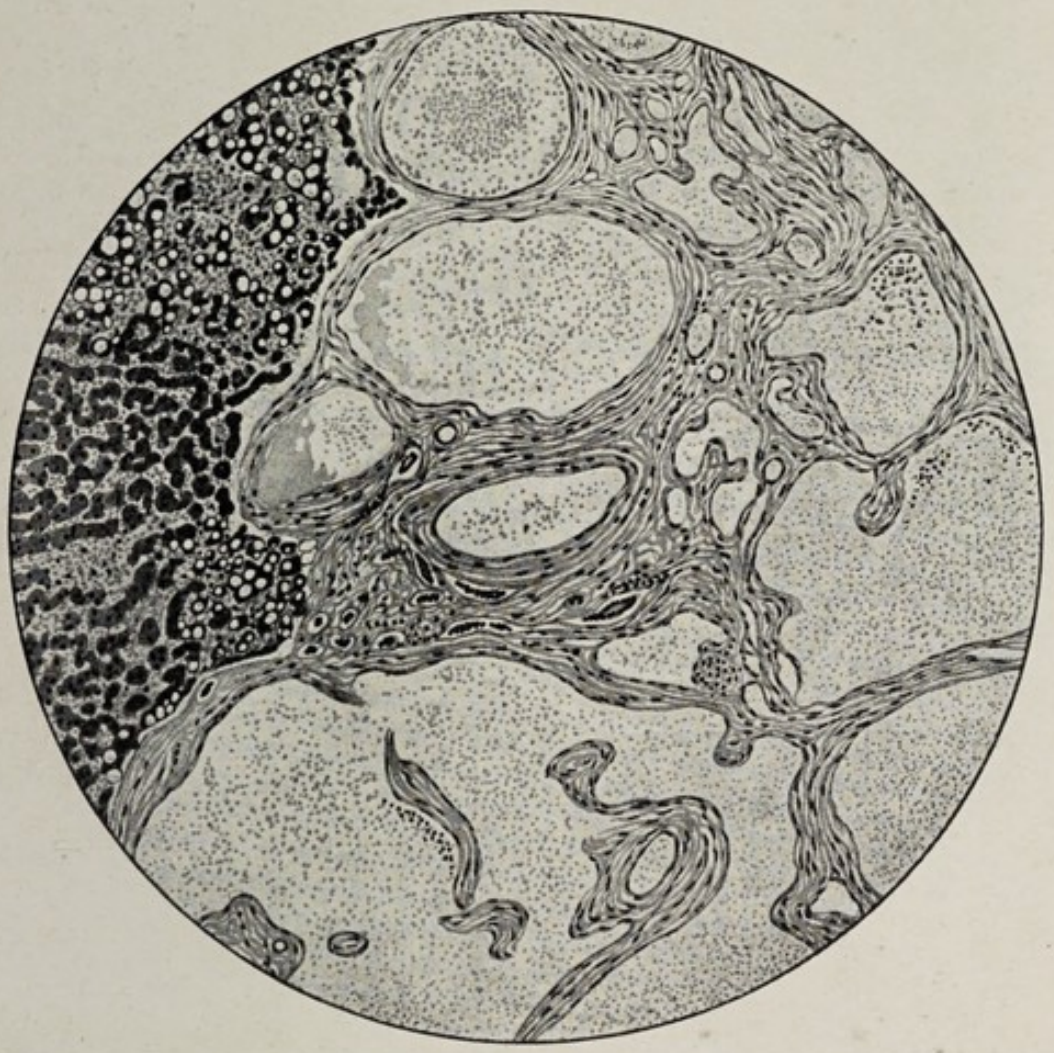


FIG. 112.—CAVERNOUS ANGIOMA OF LIVER.

Section from edge of tumour, showing liver tissue with areas of fatty degeneration on the left, and the large blood-spaces of the new growth. (× 79.)

Angiomata—both capillary and cavernous—are frequently found in the neighbourhood of embryonic clefts—either facial or branchial —as well as at the orifice of the urethra (*urethral caruncle*). In other cases, their position seems to correspond with nerve-distribution : thus, cutaneous angiomata (*nævi*) may be found limited to the area of distribution of one branch of the fifth nerve. In a large number of cases, however, the position of angiomata does not conform to either of these rules.

According to Thoma, the formation of the new vessels is dependent upon variations in the relationship which the intravascular pressure

bears to the normal pressure exerted on the vessels by the tissue concerned. He further points out that, when the different orifices of the body are being formed, various internal parts become external, and *vice versa*. In this way the relative pressure in different parts is liable to considerable alteration, and local growths of new vessels may, according to Thoma's hypothesis, easily occur. The same observer has shown that in fœtal life the growth of the section of a vessel is proportionate to the rate of flow through it, and that the lumen of the new vessels will be large or small accordingly.

Lymphangioma.

Lymphangiomata are tumours consisting of abnormally large lymphatic vessels. It is doubtful how much of the growth is due to simple dilatation and how much to new formation of lymphatic vessels. Strictly speaking, very few lymphangiomata are "tumours." The divisions are the same as those of angioma—**capillary** and **cavernous.** A section of the latter would scarcely be distinguishable from one of cavernous nævus, except by the contents of the spaces. There is generally fat in the stroma.

Each kind may be congenital or acquired. *Congenital* dilatations are found in the tongue (*macroglossia*), lip (*macrocheilia*), and labium, causing hypertrophy of the parts. They are also found in other parts of the skin.

Acquired dilatation of lymphatics is found in the skin and subcutaneous tissue, especially of the thigh and thorax. In this way tumours as large as an orange may be formed in the subcutaneous tissue. Dangerous loss of lymph may occur from rupture of one of the vessels. Fibroid thickening may take place in the parts from which the lymphatics pass to the tumour, which in the skin may assume the appearance of a wart.

FIBROMA.

Fibromata are tumours consisting of fibrous tissue.

The **fibres,** which constitute the chief part of the growth, are either loosely or densely packed, and are arranged in intersecting bundles of various sizes or in whorls around the bloodvessels (Fig. 113); in many cases no definite arrangement is recognisable. Yellow elastic fibres are very rarely met with.

Fibromata usually contain but few bloodvessels. In the softer growths, however, these are often more numerous, and may form an important constituent of the tumour (*fibroma telangiectaticum, angio-fibroma*). Dilated veins sometimes form a cavernous network, the walls of which are firmly united to the tissue of the tumour, so that, if divided or ruptured, they are unable to retract or collapse, and profuse hæmorrhage may ensue (*fibroma cavernosum*).

Partial *mucoid softening* and *calcification* are the most common **secondary changes;** *ossification* takes place in fibromata springing

from bone. *Ulceration* also sometimes occurs in those growths which are situated in the skin and submucous tissues.

Fibromata **originate** from *connective tissue*, from the cutis or subcutaneous tissue, from submucous or subserous tissue, from fascia, from periosteum, from neurilemma, or from the connective tissue of organs.

Clinically, fibromata are perfectly innocent; they grow slowly, and do not recur after removal.

Fibromata are generally divided into **two varieties,** *soft* and *hard*, corresponding with, and usually originating from, the loose and dense varieties of ordinary connective tissue respectively.

1. **Soft Fibromata.**—These consist of the looser and less dense form of fibrous tissue. They are met with as diffuse growths in the

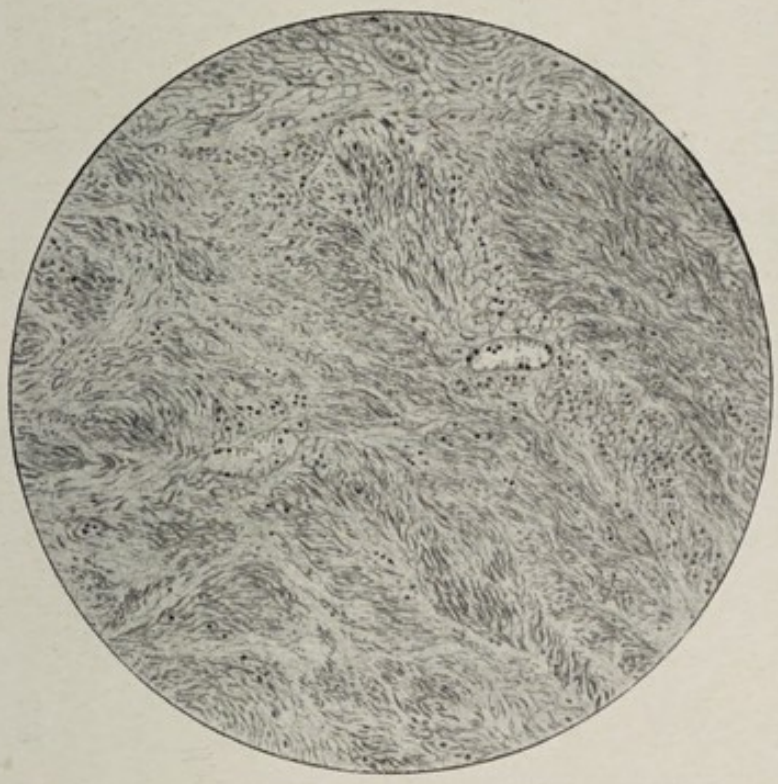


FIG. 113.—FIBROMA. (× 79.)

subcutaneous and submucous tissues. In the former situation they often form large pedunculated and non-encapsuled tumours, which are commonly known as *wens*. These are sometimes multiple. An extensive thickening of the skin and subcutaneous tissue over one or more limbs sometimes occurs, producing large masses which hang down from the thighs, buttocks, and other parts (*elephantoid fibroma*).

In addition to these diffuse growths, more circumscribed and encapsuled fibrous tumours of the soft variety are occasionally met with, growing from the scalp, scrotum, labium, intermuscular septa, or other situations.

2. **Hard Fibromata.**—These are composed of dense fibrous tissue like that in tendons. They are firm, hard, encapsuled tumours-presenting, on section, a greyish-white, glistening, fibrous appear,

ance. These tumours often occur in connection with bone—especially the upper and lower jaws—originating either in the centre of the bone or in the periosteum. Growing from the periosteum of the alveolus they constitute simple *fibrous epulis*. They are also met with in the naso-pharynx, springing from the front of the spine, or from the base of the skull. In these firm fibrous growths the veins may form cavernous spaces.

Some old tumours of the uterus are almost pure fibromata; but the so-called uterine "fibroids" are in most cases local overgrowths of the involuntary muscular tissue of the organ.

Tumours consisting mainly of hard or soft fibrous tissue are frequently met with in the breast; but in this situation they always contain at least a few foci of proliferated gland-tissue, and are generally described as *adeno-fibromata*.

Neuro-fibromata (*false neuromata*).—These hard fibrous tumours most frequently occur in connection with the superficial nerves. They grow from the perineurium and endoneurium, and as they increase in size the nerve-fibres become expanded over or buried in them. They are very firm, rounded tumours, and are frequently multiple and hereditary. The function of the nerves is not necessarily affected.

Small wart-like projections from the skin, consisting of soft fibrous tissue, grow in connection with the sheaths of cutaneous nerves (von Recklinghausen), and are known as *molluscum fibrosum*. They are probably, therefore, neuro-fibromata.

Fibro-psammomata.*—These are soft fibrous growths containing large numbers of concentrically laminated calcareous masses. They give rise to the so-called "brain-sand"—hence the name of the growth.

Psammomata grow from the pineal gland, the membranes of the brain, or the choroid plexus. In the last-named structure a psammoma often contains numerous cysts. Such growths are of no pathological importance except when of sufficiently large size to produce symptoms by pressure.

Cheloid.†—The peculiar formation known as Cheloid bears some resemblance to a tumour. It is, however, more probably the result of a chronic inflammatory process. The growths occur as hypertrophic masses of scar-tissue, starting from natural scars left after wounds, especially when the incision does not correspond with the natural "lines of cleavage" of the skin. They may attain considerable size and give rise to much disfigurement. So-called "spontaneous cheloids" probably originate in slight injuries which are overlooked.

MYXOMA.

Myxomata‡ consist of mucous tissue—*i.e.*, a fragile connective tissue of which the intercellular substance is translucent, homogeneous, and jelly-like, containing much fluid, and yielding mucin.

* Greek ψάμμος, sand. † Greek χήλη, a claw. ‡ Greek μίξα,, slime.

Physiologically, this tissue is met with in the *vitreous body* of the eye, in which the cells are rounded and isolated ; and in the *umbilical cord*, in which the cells are fusiform or stellate, and give off fine anastomosing prolongations. All embryonic connective tissue, especially that which subsequently becomes adipose, possesses an intercellular substance containing much mucin. Other tumours may undergo mucoid degeneration, and thus closely resemble myxomata in their physical and chemical characters ; but a myxoma consists of mucous tissue from the first. Myxomata are thus very closely allied to sarcomata, and by many are included in the same class of new formations. An œdematous fibroma or lipoma closely resembles a myxoma or myxo-lipoma.

Structure.—The majority of the cells are angular and stellate, with long anastomosing prolongations ; others are isolated, and fusiform, oval, or spherical in shape (Fig. 114). Their contour is very indistinct, owing to the refractive nature of the intercellular substance. The latter is very abundant, perfectly homogeneous, soft, gelatinous, and viscid, and yields large quantities of mucin : in it are a varying number of amœboid cells. Bloodvessels are not numerous, and are readily visible and easily isolated. A few elastic fibres are sometimes seen between the cells.

FIG. 114.—MYXOMA FROM THE ARM, SHOWING THE CHARACTERISTIC BRANCHED ANASTOMOSING CELLS. (× 200.)

To the *naked eye*, myxomata are of a peculiar soft gelatinous consistence, and of a pale greyish or reddish-white colour. Their cut surface yields a tenacious mucilaginous liquid, in which may be seen the cellular elements of the growth. They are usually separated from the surrounding structures by a very thin fibrous capsule. Fine prolongations extend from this into the growth, dividing it into lobules of various sizes. In exceptional cases a myxoma may increase by the continuous invasion of the surrounding tissues.

Among the **secondary changes** the most common is rupture of the capillaries, leading to *hæmorrhage*, and the formation of *blood-cysts ;* this, however, is less frequent than in sarcomata. The cells themselves may undergo *mucoid* or *fatty degeneration*, and thus be destroyed : this is usually accompanied by liquefaction of the intercellular substance.

The **varieties** of myxoma depend principally upon its combination with other growths ; a pure myxoma is very unusual. The most common combination is a myxo-lipoma. Combinations with sarcoma, fibroma, chondroma, and adenoma are also met with.

Myxomata **originate** from *connective tissue*, and are most common

in subcutaneous and subserous fat, and in submucous and intermuscular tissue. They also grow from the periosteum and medulla of bone, from the connective tissue of organs (especially the breast), and from the perineurium of nerves, forming one variety of *false neuromata*.

When situated in superficial parts they may become pedunculated. They are usually said to constitute one form of *nasal polypus*; these growths, however, most frequently result from chronic catarrh, and are inflammatory overgrowths rather than true tumours. In the skin myxomata are often papillary.

Clinically, myxomata occur chiefly after middle life, and are, for the most part, benign. Their growth is usually slow, but they may attain an enormous size. If completely removed, they rarely recur. Sometimes, however, they recur locally after removal, but they probably never reproduce themselves in internal organs. In speaking of their malignancy, their occasional association with sarcoma must be borne in mind.

LIPOMA.

A lipoma,* or fatty tumour, is a localised and circumscribed formation of fat.

Lipomata resemble in their **structure** adipose tissue. They consist of cells containing fat, and a variable quantity of common connective tissue. The cells are like those of adipose tissue, though usually somewhat larger. The nucleus and protoplasm are so compressed against the cell-wall by the fluid contents, that they are readily visible only when the cell is atrophied and contains less fat. More or less connective tissue unites the cells into masses or lobules which are larger than in normal adipose tissue, and forms in most cases around the tumour a thin capsule more firmly adherent to surrounding parts than to the tumour, so that the latter shells out easily. Bloodvessels are distributed in the fibrous septa. Mucous tissue is often associated with the fatty (*myxo-lipoma*).

To the *naked eye*, lipomata are more or less lobulated, and may be surrounded by a fibrous capsule. When subcutaneous they move freely over the deep fascia; but often the attempt to raise the skin from them causes it to dimple, showing that they are adherent to it. On section, they present the ordinary appearance of adipose tissue, with more or less dense fibrous septa between the lobules. In their growth they occasionally become pedunculated.

Secondary changes in lipomata are not common; their fibrous septa may, however, become *calcified*, or even *ossified*. Softening may occur occasionally from *mucoid* change.

The chief **varieties** are *fibro-lipomata*, in which the fibrous tissue is excessive; *myxo-lipomata*, or combination of mucous with fatty tissue; and *nævo-lipomata*, in which an angiomatous development of vessels is seen.

* Greek λίπος, fat.

Lipomata **originate** from *connective tissue,* and their possible distribution is almost coextensive with that of adipose and connective tissue. They occur most frequently in the subcutaneous tissue of the trunk, especially of the back and abdominal wall; sometimes in intermuscular septa, subsynovial and subserous tissues; and occasionally also in the submucous tissue of the stomach and intestines, and even in internal organs where there is normally no fat.

Clinically, lipomata are quite innocent; they grow slowly, but may attain a huge size; they are usually single, but are not infrequently multiple and hereditary. Sometimes they change their position considerably, presumably from the influence of gravity. However emaciated the individual may become, the fat of a lipoma only slightly diminishes, and never, under any circumstances, disappears.

CHONDROMA.

A chondroma* is a tumour composed of cartilage.

In minute **structure** these tumours consist of cells and of intercellular substance, both of which present all the variations observed in normal cartilage. The *intercellular substance* may be hyaline, fibrous, or mucoid. When fibrous, the fibres may be arranged like those of fibro-cartilage, or more or less concentrically around the cells, as in the reticular cartilages of the ear and larynx. The fibres may be distinct or hardly perceptible. When hyaline or mucoid, the intercellular substance is sometimes quite soft in consistence. The cells may be round, fusiform, or stellate, and either numerous or few in proportion to the matrix. In the fibrous form they are often small, and somewhat like those of connective tissue; in the hyaline forms they are usually large, and either round or oval; and in the rarer mucoid forms they are more commonly stellate and branched, like the transitional cells at the edge of articular cartilages where the synovial membrane ends. The cells occur singly or are arranged in groups, and are usually surrounded by a capsule, as in normal cartilage, although this is often very indistinct. A cell possesses one or more nuclei surrounded by granular protoplasm; sometimes a cell-wall cannot be distinguished.

To the *naked eye,* the *more slowly growing* chondromata are hard or slightly elastic tumours, smooth or lobulated, and seldom exceeding the size of an orange. They are encapsuled, and consist either of a single tumour or of several smaller masses held together by fibrous tissue in which the few bloodvessels run. On section, they present the appearance and consistency of cartilage, frequently modified by one or other of the secondary changes above mentioned. The appearances may be those of a fibroma, the cartilage-cells being unrecognisable without the aid of the microscope.

The *more rapidly growing* forms, such as often start from the

* Greek χόνδρος, cartilage.

pelvic bones or ribs—myxo-chondromata, osteo-chondromata, and chondro-sarcomata—are much larger, softer, and more vascular, and never present the appearance of pure cartilage; only a few islets at most will be distinct in the soft greyish tissue, which is not separated by any capsule from the adjacent tissues.

Calcification is the most common **secondary change.** It affects with peculiar frequency the largest group of chondromata—those of the phalanges and metacarpal bones of the hands. It spreads from many centres, commencing in the capsules, and then involving the intercellular substance. *Ossification* is especially frequent in chondromata which grow near the junction of the epiphyses and shafts of long bones. These ossify as they grow and form pedunculated exostoses. The common subungual exostosis of the great toe is generally an ossifying fibroma, chondroma, or fibro-chondroma. Fatty degeneration and mucoid softening are common changes, and may lead to the formation of large softened masses which present the appearance of cysts. In rare cases the skin covering the tumour ulcerates, and a fungating mass protrudes.

The **varieties** of chondroma depend upon the nature of the intercellular substance, and are, therefore, fibrous, hyaline, and mucoid: these are often combined in the same tumour. As a rule, those originating from the medulla of bone are of the hyaline and mucoid class, whilst those originating from connective tissue in other situations are more frequently fibrous. The rapidly-growing fibrous forms approach very closely to, and merge with, the sarcomata (*chondro-sarcoma*), while the mucoid forms resemble the myxomata (*myxo-chondroma*); and these two kinds of growth are often associated in the same tumour. Chondromata are rarely homologous in the strict sense.

A variety of chondroma has been described under the name of *osteo-chondroma*, which in structure more closely resembles bone than cartilage. It consists of a tissue similar to that met with between the periosteum and bone in rickets, which, from its resemblance to osseous, has been called *osteoid* tissue. This only requires calcifying to become true bone. Like bone, it is made up of trabeculæ and medullary spaces; but the trabeculæ, instead of being formed of bone-corpuscles and lamellæ, consist of small angular cells without a capsule, situated in an obscurely fibrillated matrix, which is in part calcified. The medullary spaces contain a fibrous stroma and many bloodvessels. Osteo-chondromata, although consisting mainly of this osteoid tissue, contain also a small proportion of cartilage. They originate beneath the periosteum, their common seat being the ends of the long bones. Their growth is very rapid, and they often attain an enormous size. They are much more freely supplied with bloodvessels than the ordinary chondromata, and hence they are much less frequently the seats of retrogressive changes. They are especially prone to become ossified, and to be thus converted into true bone.

Chondromata most frequently **originate** *from common connective*

tissue and bone (*enchondromata*). About *three-fourths* of them start in connection with bones, growing either *centrally* or *subperiosteally*. Their favourite seats are the bones of the fingers (Fig. 115) and toes, the lower end of the femur, and the upper ends of the humerus and tibia. Much less often, the ribs and the hip-bone are attacked.

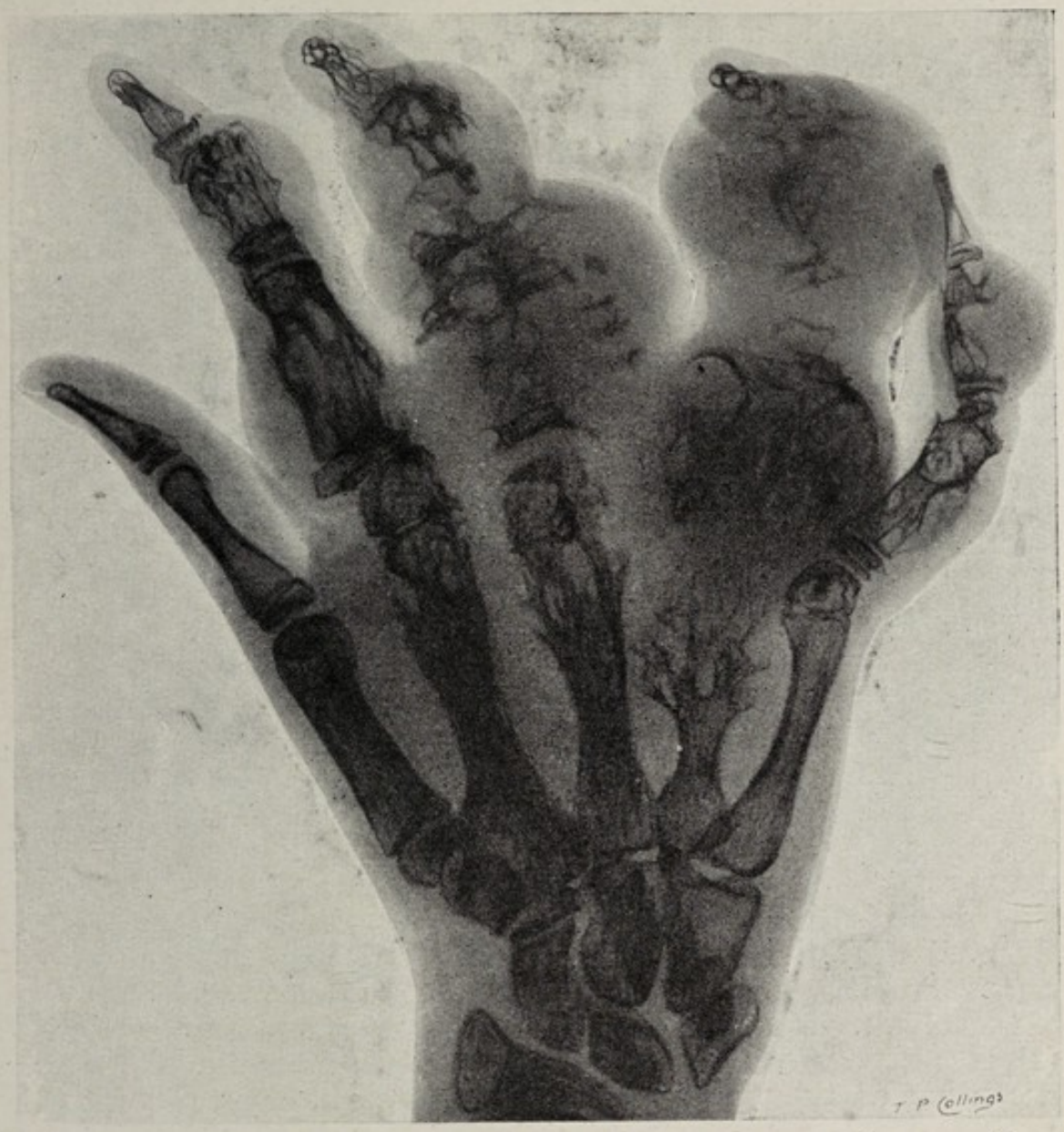


FIG. 115.—MULTIPLE CHONDROMATA OF HAND FROM A CHILD. (TWO-THIRDS NATURAL SIZE.) (FROM A PATIENT OF MR. CLINTON DENT'S. SKIAGRAM BY MR. SWINTON.)

The replacement of considerable portions of the phalanges and metacarpal bones by a mass of mingled bony and cartilaginous tissue is well shown.

Virchow has shown that islands of cartilage not uncommonly remain in the shafts of bones; and it is probable that many chondromata spring from such islands. The tumours generally begin before the ossification of the epiphyses, whilst the bone is actively growing and vascular. *Most of the remaining fourth* occur, in combination with other tissue-elements, as "mixed tumours" in the *parotid* and

testicle. Cohnheim suggests, as the source of cartilage in the parotid, an aberrant bit of the rudiment of the jaw; Virchow, a piece of the pinna. In the testis a portion of the rudiment of a vertebra may have been included. The intermuscular septa, the subcutaneous tissue of the breast, and the lungs are occasional seats.

Chondromata are sometimes seen on the surface of the articular cartilages, in the larynx and trachea, and on the costal and intervertebral cartilages. These are simply local overgrowths of hyaline cartilage.

Clinically, chondromata are for the most part innocent growths. They are usually single, except when occurring on the fingers and toes, in which situation they are more frequently multiple. The *central* growths of the phalanges and metacarpal bones occur in children, or before ossification is complete: the graver, *subperiosteal,* forms are commoner later on. Chondromata tend to stop growing about the time of puberty—probably when the epiphyses themselves cease to grow.

OSTEOMA.

Osteomata* are tumours consisting of bone, either compact or cancellous.

Osteomata are the result of the ossification of *newly formed connective tissue,* other than of inflammatory origin. They must be clearly distinguished (1) from the simple *ossification of normally existing tissues—e.g.,* costal, laryngeal, or bronchial cartilages, whole muscles (*myositis ossificans*), insertions of muscles (*rider's bone* in the adductor longus tendon), and membranes of the brain; and (2) from similar *ossification of inflammatory tissue*—such as nodes or general thickenings of bones, the sharp stalactitic processes which may grow round an inflamed joint or on the surface of bone, and the smooth round prominences which almost encircle a joint in rheumatoid arthritis. They must be distinguished also from *calcareous deposits,* in which there is no bone formed.

Osteomata are generally divided into two main **varieties:** (1) *Homologous osteomata,* subdivided into *exostoses* and *enostoses,* according as they project (i.) from the surface, or (ii.) into the medullary canal of a bone. (2) *Heterologous osteomata.*

1. **Homologous Osteomata.**—(1) *Exostoses* are again subdivided, according to the density of the bone of which they consist, into two kinds—(α) the *compact, ivory,* or *eburnated;* (β) the *cancellous* or *spongy.*

(α) The **compact** or **ivory exostosis** grows from periosteum. It occurs most frequently on the external and internal surfaces of the skull; the orbit is an especially favourite seat. It is also met with on the scapula, pelvis, and on the upper and lower jaws. In the last-named situation it may grow from the dental periosteum. An osteoma growing from the root of a tooth is known as a *dental*

* Greek ὀστεον, a bone.

osteoma. An *odontoma* is a tumour composed of dentine, or of some other constituent of a tooth or tooth-sac: it may grow from the root, neck, or crown of a tooth.

Such growths are smooth, low, rounded, wide-based, covered by the periosteum, and continuous with the old bone, from which they grow. On section, they are throughout of ivory-like density, and they are usually well defined from the adjacent tissue. Microscopically, the lamellæ are arranged concentrically and are parallel to the surface of the tumour; cancellous tissue is absent, and Haversian canals are few and narrow. Some specimens are less dense, the Haversian canals being as numerous as in ordinary compact bone, but less regularly arranged.

(β) The **spongy** or **cauliflower exostosis** is really an ossifying chondroma. It grows from cartilage, usually near the junction of an epiphysis of a long bone with the shaft. It is especially common at the lower end of the femur, and at the upper ends of the tibia and humerus. Its outline is less regular than that of the ivory growths; but it is prominent, more or less pedunculated, and, so long as it is growing, covered by a cap of cartilage. When this cap (*osteophyte*) ossifies, growth ceases. A section shows that the mass consists of spongy bone, directly continuous with the cancellous tissue of the bone whence it springs, and surrounded by a thin layer of compact bony tissue. The medullary spaces may contain embryonic, fibrous, or fatty tissue.

(2) The **enostosis** is a dense bony growth projecting into the medulla, and is very rare. Osteomata sometimes remain imbedded in the cancellous tissue, and are then termed *central osteomata*.

2. **Heterologous osteomata** are very rare as primary growths. They have been described as occurring in the subcutaneous tissue; but Malherbe has shown reason for believing that such growths are really sebaceous adenomata with ossified stroma. Bony tumours have very rarely been found in the brain and cerebellum. Parts of fibromata, lipomata, and chondromata may ossify. The secondary growths of ossifying sarcomata connected with bone often ossify.

The commonest **secondary change** is *inflammation*. Osteomata may also become *carious* or *necrose*. The last change is most likely to occur in ivory exostoses, effecting their separation and cure.

Osteomata generally **originate** from *bone* (*homologous*), commencing in the periosteum, medulla, or persistent islands of cartilage; but *connective-tissue tumours*, apart from bone (*heterologous*), may ossify.

Clinically, osteomata are perfectly innocent tumours. Their growth is very slow. They rarely attain a large size. They are often hereditary and multiple, in which case they usually occur in early life. Osseous growths which exhibit malignant characters are either sarcomata or chondro-sarcomata, which have undergone partial ossification. From these, true osteomata must be carefully distinguished.

SARCOMA.

Sarcomata* are tumours consisting of tissue resembling some stage in the development of any of the connective tissues.

The **cells,** which usually constitute almost the whole of the growth, are of three principal varieties of cell—*round, spindle-shaped,* and *myeloid.*† The round and spindle-shaped cells may be either *small* or *large.* The myeloid cells are much larger than the others. They are irregular and multinucleated, varying both in size and in the number and size of the contained nuclei. One cell may have as many as thirty nuclei. Though in any given tumour one form of cell usually predominates, two or more varieties may frequently be associated.

The **intercellular substance** or **stroma** usually exists in but small quantity. *It intervenes between all cells, and is as closely connected with them as in ordinary connective tissue.* These points are often relied upon to distinguish certain sarcomata from carcinomata, but they do not always hold good.

The stroma may be fluid and homogeneous, or more or less fibrous, or even chondrified and ossified. On its amount and nature the consistence of the growth depends.

The **bloodvessels** are usually very numerous. The larger lie in the stroma which supports them; the smaller are usually in direct contact with the cells. Their distribution is very irregular, and their walls are often formed by nothing but the cells of the tumour, though a single layer of endothelial cells may separate the blood from the cells. Hence, on the one hand, the ease with which portions of the tumour are carried away in the blood-stream and the tumour thus generalised; and, on the other, the frequency with which the vessels rupture and permit extravasation of blood into the substance of the growth. Lymphatics are unknown.

Physical Characters.—Portions of sarcomata which have undergone no secondary changes are soft, semi-translucent, and grey or pinkish-grey. These appearances are best seen near the circumference of the growth, where the zone of actively-growing cells may be narrow. The diagnosis—even with the microscope—between a sarcoma, especially a fibro-sarcoma, and the different forms of simple connective-tissue tumours may be exceedingly difficult. Degenerative processes, such as fatty degeneration, and especially hæmorrhage, may greatly interfere with the usual appearances: the occurrence of hæmorrhage may convert a solid tumour into a blood-cyst with a scarcely recognisable wall.

As a rule, the growing edge is ill-defined, there being no sharp line of demarcation between the tumour and the adjacent parts; but sometimes a slowly-growing sarcoma may acquire a capsule by stretching around itself the connective tissue of the organ in which it originates.

* Greek σάρξ, flesh or muscle.

† Greek μίελος, marrow.

Secondary Changes.—The most important of these is *fatty degeneration.* This always occurs to a greater or less extent in the older portions of the growth, causing either softening or the production of cyst-like cavities. It is frequently associated with rupture of the bloodvessels and *hæmorrhage;* the latter may give rise to the formation of blood-cysts. *Calcification, ossification,* and *mucoid degeneration* are less common. The occurrence of calcification, ossification, and pigmentation is influenced by the predisposition of the matrix from which the growth is produced—thus, calcification and ossification are more prone to occur in tumours originating in connection with bone, pigmentation in those originating from the cutis or eyeball.

Varieties.—Though all sarcomata possess the same general characters, they present histological and clinical differences which serve as bases for their classification.

The principal features which are thus utilised are (1) the predominant form of cell; (2) the nature of the intercellular substance; and (3) other characteristics, such as the presence of pigment.

(1) The predominant form of *cell* enables us to distinguish four groups: the *round-celled,* the *spindle-celled,* the *mixed-celled,* in which no one form predominates, and the *myeloid-celled.* Strictly speaking, this last group is one of mixed-celled sarcomata, but though the myeloid cells can never be said to predominate, they are frequently so numerous as to be the most striking objects in the field, when the growth is examined microscopically.

(2) The *stroma* may be mucous, fibrous, cartilaginous, or bony; hence we may have *myxo-sarcoma, fibro-sarcoma, chondro-sarcoma,* and *osteo-sarcoma.*

(3) There are other characteristics which serve to distinguish differing forms, inasmuch as the peculiarities are reproduced in the secondary growths. The chief of these are: *melanosarcoma,* characterised by the development of black pigment, and *chloroma,* a very rare form, with green pigment; and *calcifying sarcoma,* in which calcareous infiltration is marked.

Mode of Growth and Seats.—Sarcomata always spring from connective tissue, and may occur wherever connective tissue is present. It is doubtful whether they start from adult tissue or from some embryonic remnant. Congenital warts and pigment-spots often serve in later life as their starting-points. The skin and subcutaneous tissue, fasciæ, periosteum, medulla of bone, and lymphatic glands are the commonest seats of sarcomata.

Clinical Characters.—Sarcomata occur most frequently in early and middle life, and are among the most malignant of new formations. They are especially characterised by their great tendency to extend locally and to infiltrate the surrounding structures, so that they are exceedingly prone to recur *in loco* after removal. Like carcinomata, they are very liable to become generalised. The secondary growths occur most frequently in the lungs. *The dissemination is effected by means of the blood-stream,* and is a natural

result of the thinness of the vessel-walls. The dissemination of sarcomata is, on this account, sometimes more rapid than that of carcinomata, in which extension in the early stage takes place by the lymphatics, and dissemination by the blood occurs late in the disease. *Secondary* sarcomata usually resemble the *primary* growth, but in exceptional cases the several varieties may replace one another.

It has already been pointed out that the different varieties of sarcoma possess very different degrees of malignancy. As a rule, the softer and more vascular the tumour, and the less its tendency to form fully-developed connective tissue, the greater is its malignancy. The soft round-celled and large spindle-celled varieties are thus usually much more malignant than the firmer, small spindle-celled growths. Many small spindle-celled tumours, after removal, never recur; whilst others recur locally several times, and only ultimately reproduce themselves in distant parts. As a rule, largeness of the spindle-cells, and the existence in many of them of more than one nucleus, are together evidence of special malignancy. Central sarcomata of bone are much less malignant than the subperiosteal varieties; the latter, with sarcomata of the tonsil and testis, and melanotic sarcoma of the skin, being amongst the most malignant of tumours. The presence of a capsule limiting the growth must also be taken into account in judging of the degree of its malignancy. It must, however, be borne in mind that encapsuled sarcomata may invade the surrounding structures, giving rise to adjacent, but discontinuous, nodules. The myeloid growths are the least malignant; they do not give rise to secondary growths in internal organs, and "complete" removal gives a very good chance of non-recurrence. This result sometimes occurs with growths having every appearance of malignancy.

Round-Celled Sarcomata.

These are of softer consistence than the spindle-celled growths, and from their frequent resemblance in physical characters to encephaloid* carcinoma are sometimes known as "medullary," "encephaloid," or "soft" sarcomata. Histologically, they consist mainly of round cells imbedded in a scanty and usually soft, homogeneous, or finely granular intercellular substance (Fig. 116). The cells usually resemble those met with in the most elementary embryonic tissue; less frequently they are bigger, and contain large round or oval nuclei, with bright nucleoli. There is an almost complete absence of fusiform cells, and of the partial fibrillation which is so frequent in the more highly-developed spindle-celled variety.

Round-celled sarcomata are of a uniformly soft, brain-like consistence, somewhat translucent or opaque, and of a greyish or reddish-white colour. On scraping the cut surface, they yield a

* Greek ἐγκέφαλον brain.

juice which is rich in cells. They are exceedingly vascular: the vessels are often dilated and varicose, and, from their liability to rupture, frequently give rise to ecchymoses and to the formation of blood-cysts. The tumours grow from the cutis, the subcutaneous cellular tissue, the periosteum, the fasciæ, and the connective tissue of organs. They extend rapidly by peripheral growth, infiltrate the surrounding structures, reproduce themselves in internal organs, and often involve the lymphatic glands. From their clinical and physical characters these tumours are very liable to be confounded with encephaloid cancer: they are distinguished to some extent by the characters of their cells, but principally by the absence of

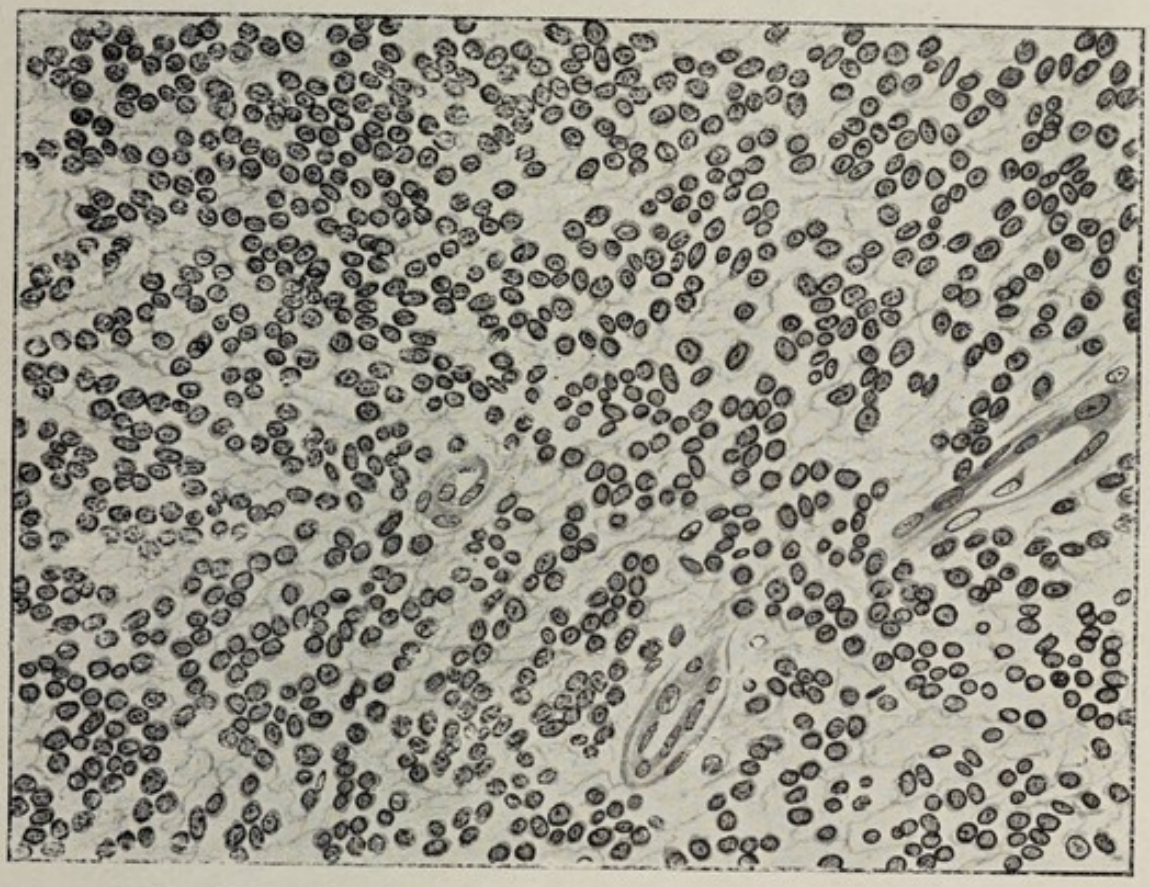


FIG. 116.—ROUND-CELLED SARCOMA. (× 325.)

an alveolar stroma, and by the penetration of the intercellular substance between the individual cells.

Lympho-Sarcoma.—This is a round-celled sarcoma, in which the matrix has developed into a more or less perfect reticulum, like that of lymphoid tissue. It may begin in lymphatic glands, or in connective tissue anywhere, and is a common form or mediastinal growth.

Alveolar Sarcoma.—This is a somewhat rare form of round-celled sarcoma which was first described by Billroth. The cells, which are large, sharply defined, and round or oval in shape, contain round prominent nuclei, and are separated from each other by a more or less marked fibrous stroma. In some parts this stroma forms small

alveoli within which the cells are grouped, but careful examination will always show that in most parts of the section the stroma really penetrates between the individual cells. This last-named character, together with the nature of the tissue from which they arise, serves to distinguish these tumours from the carcinomata, with which, in many cases, they may easily be confounded. The cells are generally in close connection with the stroma, though vessels never pass in among them. In this latter respect they resemble epithelial growths.

Alveolar sarcomata are met with principally in the skin, bones, and muscles. In the skin, where they are often multiple, they lead to ulceration. They tend to recur locally, and also to reproduce themselves in internal organs. Many alveolar sarcomata would now be placed under the heading "endotheliomata," as they appear to arise from endothelial cells. A certain proportion of melanotic sarcomata are of the alveolar type.

Spindle-Celled Sarcomata.

These are the most common of all sarcomata. They consist of cells, mainly spindle-shaped and fusiform, separated by only a little homogeneous or slightly fibrillated intercellular substance (Fig. 117). The cells contain well-marked oval nuclei, with one or more nucleoli. They are arranged in bundles which pass in all directions through the growth, and often give it the appearance of a fibroma or myoma. In those portions of the section in which the bundles of spindle-elements have been cut transversely or obliquely, they present the appearance of round or oval cells. The cells vary considerably in size in different tumours; hence the division into **small** and **large** spindle-celled growths.

Small Spindle-Celled Sarcoma.—In this the cells are small, often not more than $\frac{1}{1500}$ inch in length, and the intercellular substance is occasionally imperfectly fibrillated. These growths are therefore somewhat similar to fibromata, and histologically they must be regarded as occupying an intermediate place between embryonic and fully-developed connective tissue. They grow from periosteum, fasciæ, and connective tissue in other parts. They are usually firm, and whitish or pinkish-white, and present on section a translucent somewhat fibrillated appearance. They are much more frequently encapsuled than any other variety of sarcoma, but they are very liable to infiltrate the surrounding structures, and to recur locally after removal.

Large Spindle-Celled Sarcoma.—The cells in these tumours are not only larger than in the preceding, they are also plumper, and the nuclei are especially prominent and frequently multiple (Fig. 117). The intercellular substance is more scanty, and there is a complete absence of any fibrillation. These growths are much softer in consistence than the small-celled variety. They are of a pinkish-white colour, and are often stained by extravasations of

blood, and in parts are sometimes almost diffluent from extensive fatty degeneration. They grow rapidly, and are usually exceedingly malignant. They occasionally give rise to blood-cysts.

Melanotic Sarcoma.—This is a variety of sarcoma in which many of the cells contain granules of melanin,* quite distinct from the pigment of extravasated blood.

Melanotic sarcomata originate principally in two situations—in the pigmented tissues of the eye and in the superficial integuments.

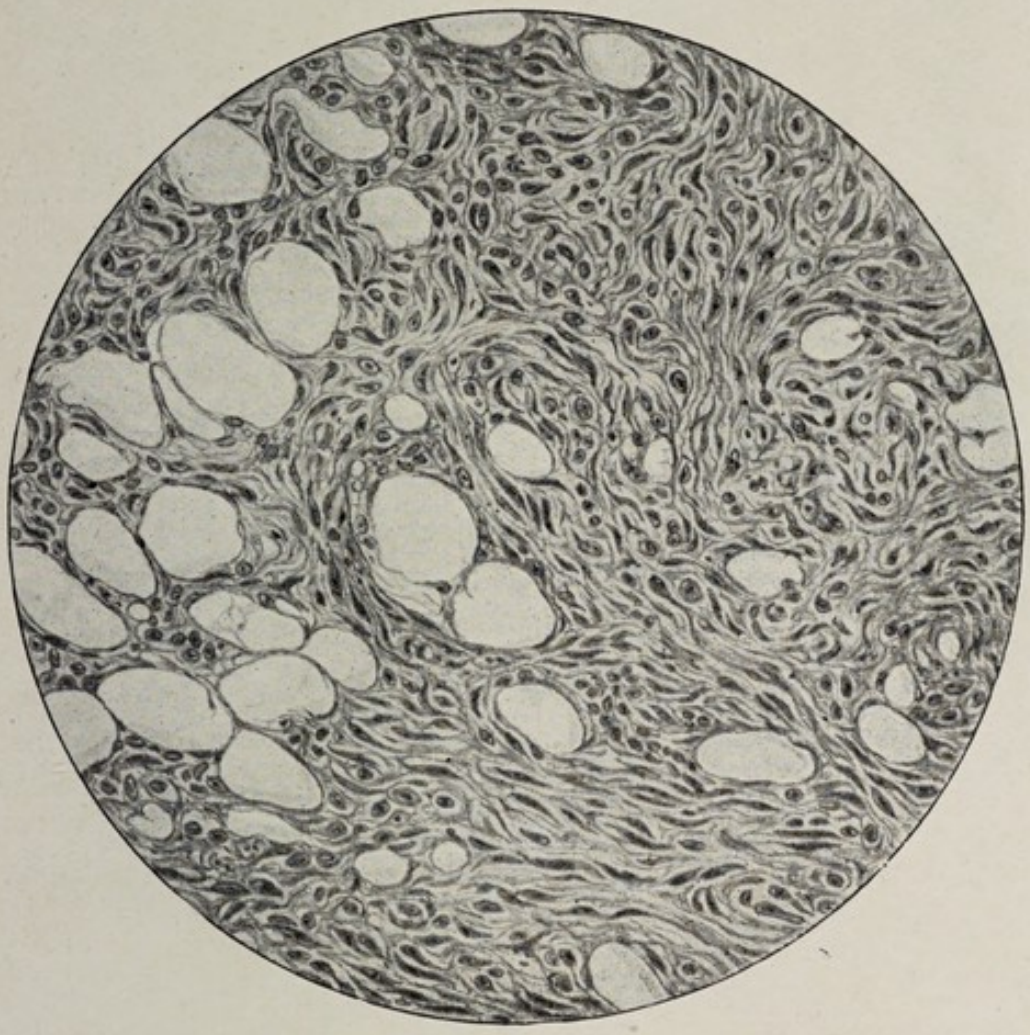


FIG. 117.—EDGE OF SPINDLE-CELLED SARCOMA.
The growth is invading the adjacent fat-tissue. (× 325.)

In both these situations pigment is a normal constituent of the tissues, and this tendency of pigmented structures to give origin to melanotic growths is exceedingly characteristic. These tumours often consist of spindle-shaped cells, and hence they are described in the present section ; but in some cases the prevailing type of cell is round or oval, and, as mentioned above, an alveolar arrangement may occur. The pigment, which gives to them their distinctive character, consists of granules of a brownish or dark sepia colour :

* Greek *μέλας*, black.

these are mainly distributed within the cells (Fig. 118), but are also found in the intercellular substance: in the latter position the pigment is not improbably derived from broken-down cells of the tumour. Frequently, only a very small proportion of the cells are pigmented, whilst in other instances the pigmentation is much more universal. In all cases, a large number of the elements will be found to be quite free from pigment.

These melanotic tumours are amongst the most malignant of the sarcomatous growths. Although they show comparatively little

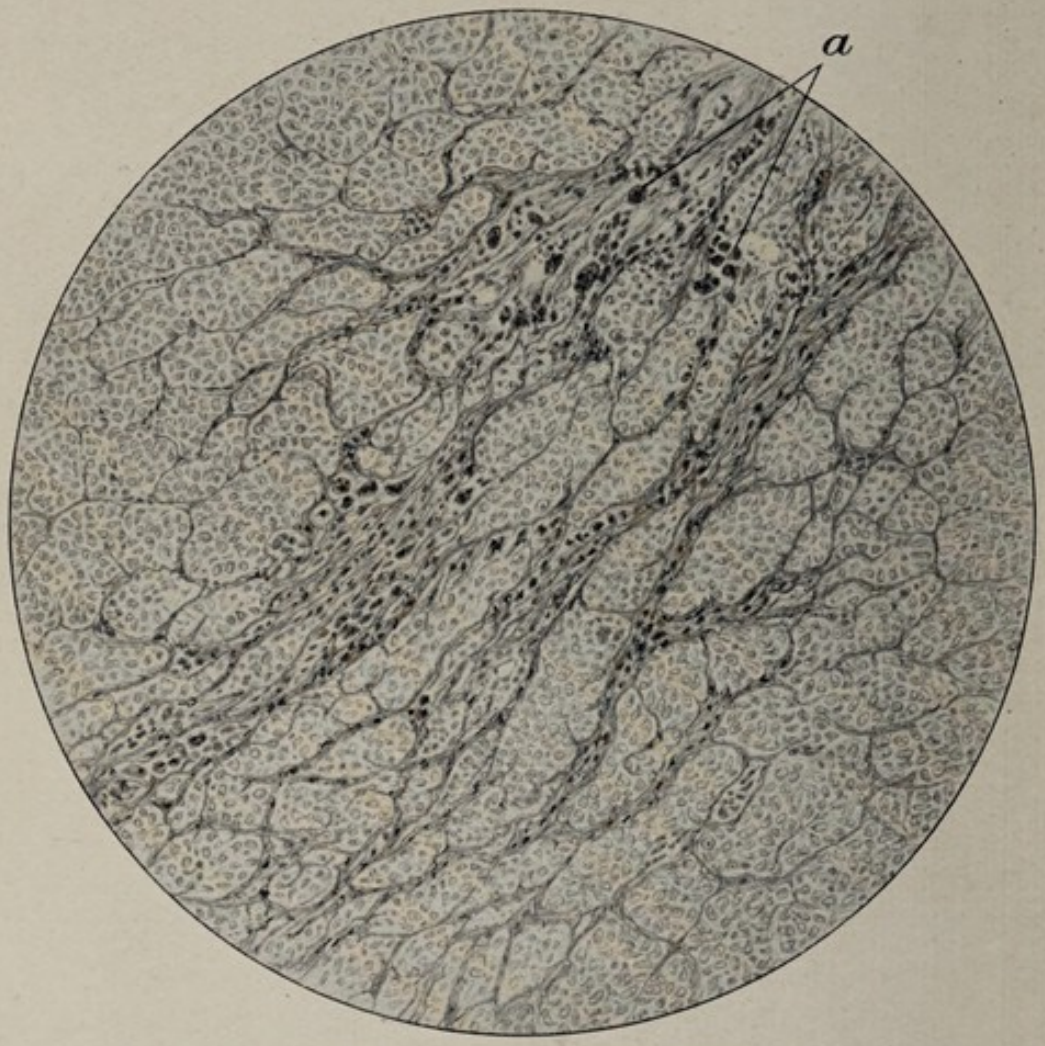


FIG. 118.—MELANOTIC SARCOMA.
a, Granules of melanin. (× 225.)

tendency to extend locally, they are rapidly disseminated by means of the bloodvessels, and occasionally also by the lymphatics: they thus reproduce themselves, often very rapidly, in distant tissues. Although the secondary growths almost invariably maintain their melanotic character, the degree of their pigmentation varies considerably. Whilst many of them may be perfectly black in colour, others may be much paler—perhaps only streaked with pigment. The secondary growths are soft, usually distinctly circumscribed, and often encapsuled. They may occur in almost every organ of

the body—the liver, the spleen, the kidneys, the lungs, the heart, the brain and spinal cord, the lymphatic glands, and the subcutaneous tissue, may all be simultaneously involved.

Chloroma.—The name chloroma* has been applied to a very rare form of tumour, closely resembling lympho-sarcoma histologically, but distinguished by its peculiar green colour. The nature of the pigment is unknown: it rapidly fades on exposure to air. The growths originate in connection with bone, especially with the bones of the face. The disease has some apparent relation to leucocythæmia, the blood presenting marked lymphocytosis. (See Leucocythæmia.)

Osteo-Sarcoma.—This is a variety of sarcoma in which the growth (usually spindle-celled) is either more or less calcified, or partially converted into true bone. As a primary growth it is met with almost exclusively in connection with bone, growing either from the periosteum or from the medulla; but the osteoid characters are usually reproduced in secondary tumours occurring in the lungs and other parts.

Calcification is much more common than true *ossification*. Each of these processes may occur separately, but they are often combined. Bands and patches of granular appearance, in which the outlines of cells may still be visible, or in which all structure has disappeared, and which stain but slightly, show where calcification has occurred. In other parts, especially near the bone, spicules having the structure of more or less perfect bone—Haversian canals, lacunæ, and imperfect canaliculi—will be seen penetrating the growth. The spicules are generally vertical to the surface of the bone. In some cases a skeleton of bony spines radiates from the bone through the growth.

Both calcification and ossification may be very complete, but *a thin margin of sarcoma-tissue is always present*. This distinguishes the growth from a simple osteoma, which has cartilage or periosteum on its surface, and is of much slower growth.

Myeloid Sarcoma.

These sarcomata, also known as *myeloid tumours* or *myelomata*, are allied to the spindle-celled sarcomata. They possess, however, certain histological peculiarities which probably depend upon the characters of the tissue from which they grow. They contain many of the large multinucleated cells, known as "myeloid cells"—which resemble the cells of the medulla of bone in a state of excessive nutritive activity—together with numerous fusiform cells like those met within the spindle-celled varieties (Fig. 119). There are also some smaller round and oval elements. The large myeloid cells, which give to these tumours their distinctive characters, are usually much more numerous in those growths which originate in the medullary cavity than in those which spring from the periosteum.

* Greek χλωρός, green.

The growths are sometimes so vascular as to give rise to distinct pulsation. They often contain cysts.

Myeloid tumours almost always grow in connection with bone, the ends of the long bones being their favourite seat: they most frequently originate in the medullary cavity of the long bones. They are also frequently met with springing from the periosteum of the upper and lower alveolar processes, where they constitute one form of *epulis*.* When originating within the medullary cavity, the compact tissue of the bone becomes "expanded" over them, and

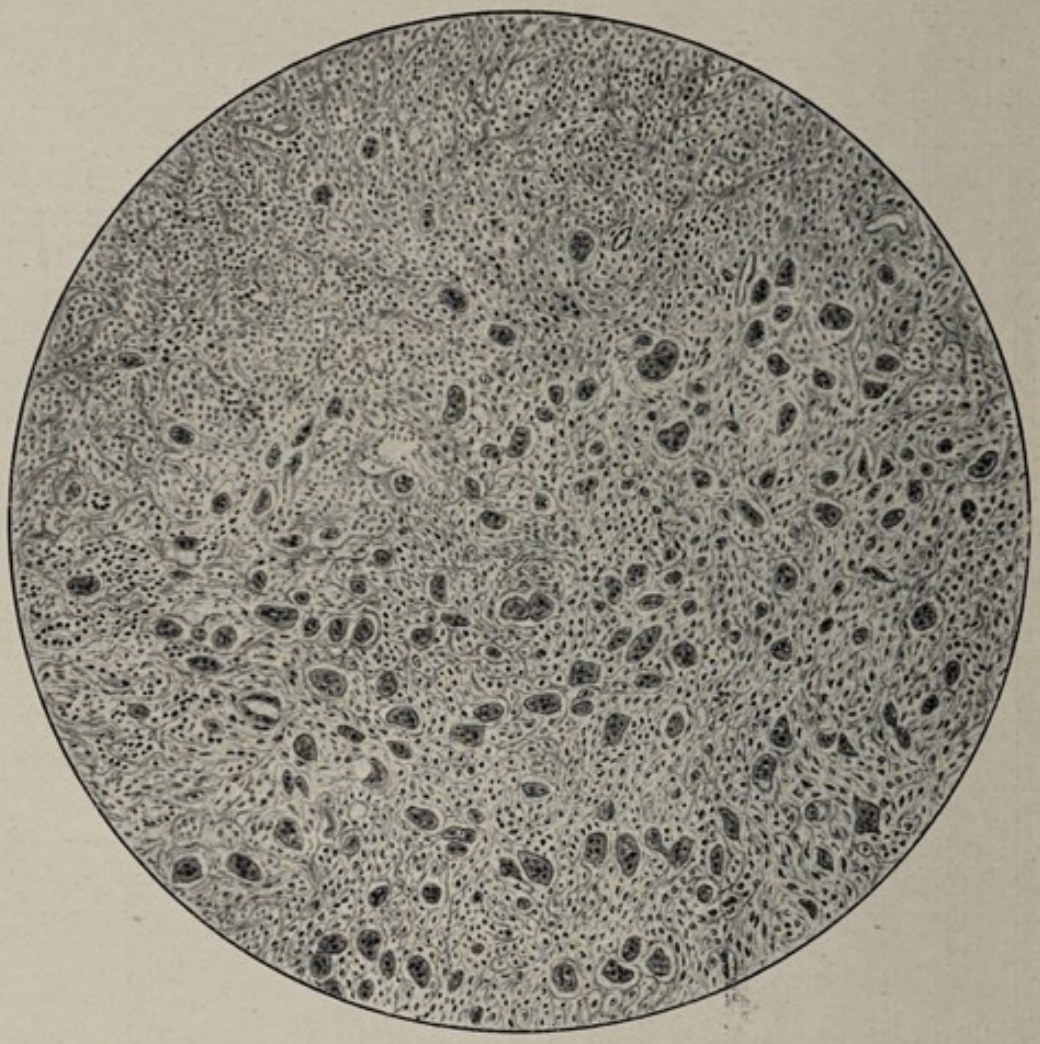


FIG. 119.—MYELOID SARCOMA, SHOWING MULTINUCLEATED CELLS. (× 79.)

they thus often communicate to the fingers, during examination, the peculiar sensation known to surgeons as "eggshell crackling." True expansion of bone is, of course, impossible; really, the old bone is absorbed from within by the tumour, and the periosteum lays down new bone on the surface; absorption is more rapid than new formation, and the thin surface-layer of bone yields and crackles under pressure, or is actually wanting at spots where pulsation is marked. Myeloid tumours may also originate in tendon-sheaths and synovial membranes.

* Greek ἐπί, upon; οὖλον, the gum.

These tumours are for the most part of firmer consistence than the other varieties of sarcoma. Many of them are firm and fleshy; others are softer. They are not pulpy and grumous like the soft sarcomata, nor do they present the fasciculated appearance of the spindle-celled varieties. Their cut surface has a uniform succulent appearance, often mottled with patches of red. This red-brown or maroon colour varies with the number of giant-cells present, and is very characteristic. The tumours are often encapsuled by the periosteal covering of the bone from which they grow. They are rare after middle life, and very rarely give rise to secondary growths. They are the least malignant of all sarcomata, and by some authorities are classed among the innocent growths as tumours of the medulla of bone or *myelomata*.

When occurring in other connective tissues, these sarcomata are generally found where congenital defects are common; and the myeloid cells and even cartilage (Waring), which they may then contain, are, therefore, probably due to the inclusion of some misplaced rudiment.

Small **multiple myeloid sarcomata** are occasionally found as primary tumours in bone and other connective tissues. In bone, the tumours grow from the medulla, invade the bony tissue, and expand the periosteum. The affected bones soften, and in their subsequent change simulate the condition met with in osteo-malacia. In these cases albumose is often present in the urine. These tumours are more malignant than the single myeloid sarcomata previously described.

Angio-Sarcoma.

Angio-sarcomata are round-celled, or less commonly spindle-celled, growths in which the vessels are so numerous and so large that in many cases the tumour appears to be made up of islets of sarcoma-cells, surrounded by a single layer of flattened spindle-cells, and separated from one another by larger or smaller spaces containing blood.

Perithelial Sarcoma.

Perithelial sarcomata are growths consisting of parallel columns or of globes (*cylindroma*), each of which is composed of a large central capillary vessel and three or four concentric layers of cells, probably derived from the adventitia of the central vessel. The cells forming the columns often undergo mucoid changes. Ziegler, to emphasise the large size and number of the vessels and the general character of the tissue around them, has suggested the name *Angio-sarcoma myxomatodes*.

Endothelioma.

Endotheliomata are growths sometimes found arising from the endothelial lining of serous membranes, and consisting of large, oval, or angular cells contained in well-defined alveoli. These tumours

are very similar in structure to carcinomata ; but parts of the growth may show multiplication of pre-existing endothelial cells, and other parts may consist of spindle-cells and transitional forms. Growths of a similar type occur with some frequency in the parotid glands,

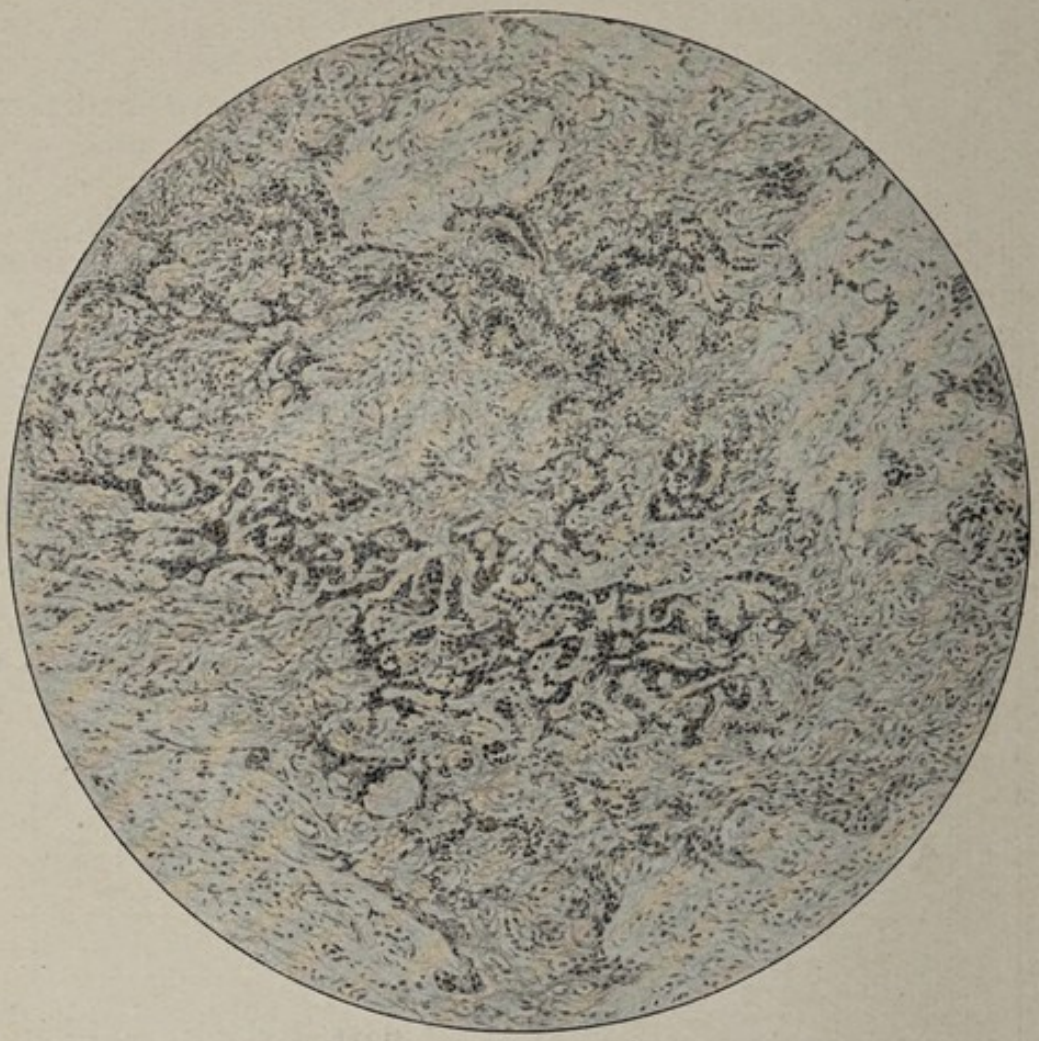


FIG. 120.—ENDOTHELIOMA OF PAROTID. (× 79.)

and less often in the other salivary glands (Fig. 120). In the case of the parotid growths, the tumour is often of a mixed type, containing, in many cases, islets of cartilage. The endotheliomata seldom produce glandular metastases, and are malignant only through direct extension, thus resembling the myeloid sarcoma.

CHAPTER XX

TUMOURS—*Continued*

PAPILLOMA.

PAPILLOMATA are new formations resembling in **structure** enlarged papillæ.

They consist of a basis of connective tissue which sends towards the surface numerous papillary processes, each supporting blood-

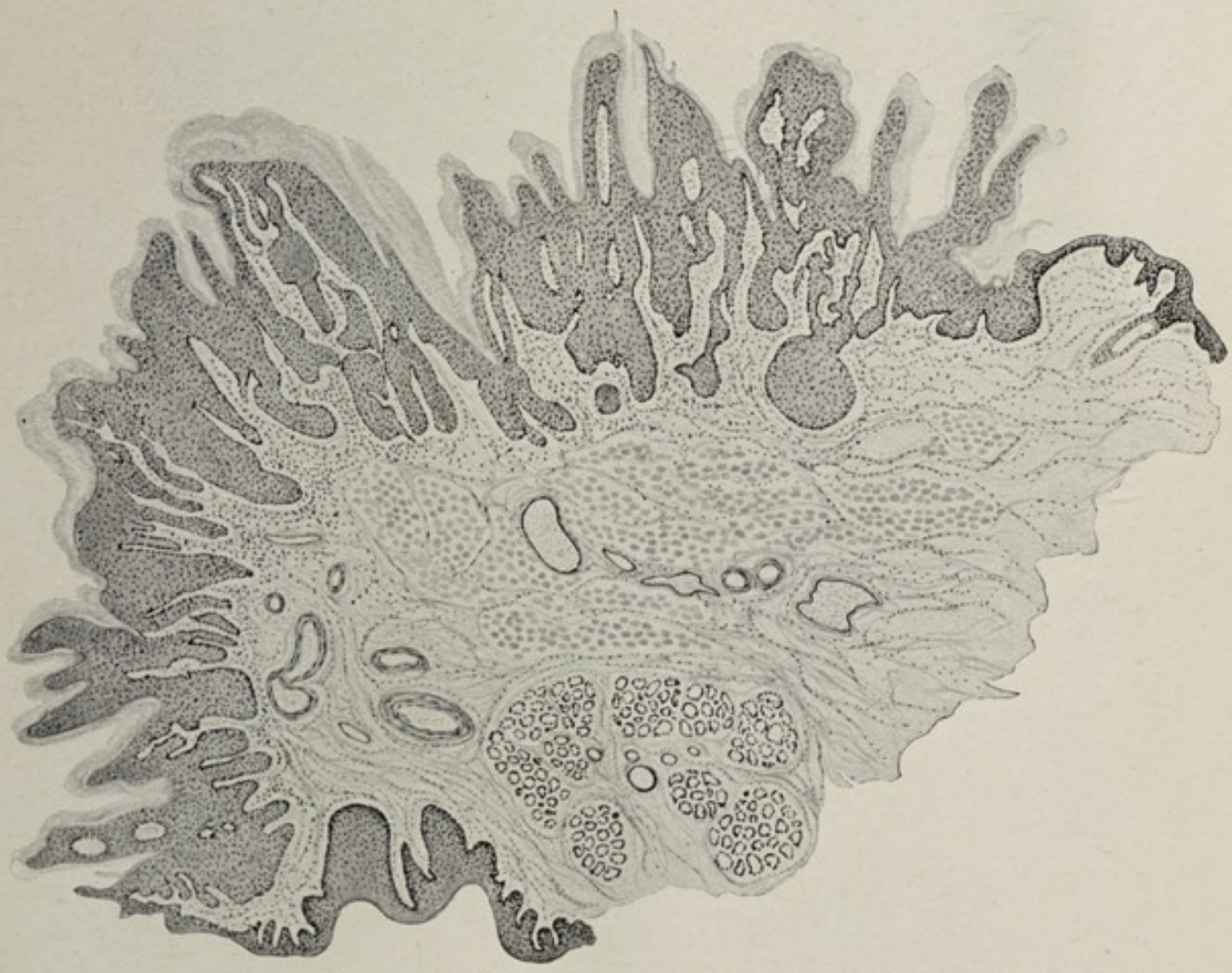


FIG. 121.—PAPILLOMA OF LIP. (× 24.)

vessels which end in a capillary network or single loop, the whole being enveloped in a covering of epithelium. The papillæ may be short and simple, as in most cutaneous papillomata ; or they may be

long, delicate, branching—giving off secondary and tertiary offsets —and very numerous, as in *villous tumours*. The covering epithelium in cutaneous growths is thick, hard, and stratified, and may actually bind the papillæ into a solid mass (Fig. 121) ; but on mucous membranes the slender vascular processes are covered by a small

FIG. 122.—A SINGLE SMALL PAPILLA, FROM THE VILLOUS PAPILLOMA OF BLADDER SHOWN IN FIG. 123. (× 150.)

The epithelial covering has been accidentally separated in three places from the central structure.

amount of delicate epithelium, and in consequence they are easily lacerable (Fig. 122). Papillomata on serous membranes may be covered by a single layer of endothelial cells.

Hæmorrhage and *ulceration* resulting from injury can hardly be classed as **secondary changes.** The only important change is the

possible *conversion of a papilloma into an epithelioma.* In a wart all the epithelium is *on the surface,* no matter how irregular that surface may be. As soon as the epithelium begins to *invade the tissues beneath it,* the wart has become a carcinoma. Pigmented warts not uncommonly form on the face in old age, and, especially if frequently irritated, may become epitheliomatous.

Four **varieties** can be readily distinguished:

1. The **ordinary cutaneous wart or papilloma,** with its covering of hard squamous epidermis. Condylomata and venereal warts, due to the irritation of the secretions of soft sores or gonorrhœa, deserve

FIG. 123.—VILLOUS TUMOUR OF BLADDER. (REDUCED ONE-THIRD.) (C. C. H. MUSEUM.)

a, a^1, a^2, papillæ; *b*, normal mucous membrane.

special mention. These, though covered by squamous epithelium, are much softer, more vascular, and more luxuriant in growth than the ordinary wart, and are granulomata rather than new growths.

2. The **villous papillomata** of all mucous surfaces. These are usually characterised by long, delicate, compound papillæ. The tongue, cheek, larynx, and bladder are the parts most often affected. The papillary enlargements of the synovial villi, which are common in chronic arthritis, may be included in this group.

3. **Corns.**—These *commence* as papillomata; but, as the epidermis thickens and is pressed by the boot into the soft parts, the papillæ ultimately atrophy.

4. **Horns** some inches long occasionally spring from the skin. These consist of epithelium and sebaceous secretion, and originate from sebaceous follicles or from a sebaceous cyst. It is said that long papillæ project into their bases, so that they seem to be allied to warts. The base must be removed with the horn, or the latter will recur.

To the **naked eye,** the ordinary wart is a hard, abruptly elevated little mass, apparently formed of epithelium. It presents an irregular ("warty") surface, often divided by deep fissures. If the investing epithelium be abundant, or the papillæ be very short, a rounded mass, having a merely furrowed surface, results; but as the papillæ lengthen and the epithelium thins, the growth presents first a "cauliflower," then a branched, and finally a villous appearance. This last appearance is best seen on placing a "villous tumour" of the bladder in water, when the long delicate papillæ float up (Fig. 123). They are exceedingly vascular. If a section of a papilloma be made, the relation between stroma and epithelium, above described, can be seen, even with the naked eye (Fig. 122).

Papillomata **originate** from *skin*, from *mucous*, *serous*, and *synovial membranes*, and from the *ducts of glands*. They most frequently grow from pre-existing papillæ; sometimes, however, they occur where no papillæ exist, springing directly from the subepithelial connective tissue: this is the case in the stomach and larynx. As all new growths on free surfaces tend to become "papillary," this form of tumour is probably the result of physical conditions.

Clinically, warts, so long as they remain warts, are quite innocent. They are common in childhood and early adult age, especially upon the hands and face. They may be single, but upon the hands they are commonly multiple. When not congenital, they generally disappear after a time, though they may persist for years. Papillomata on mucous surfaces give trouble, and may cause death by bleeding: in the bladder, difficulty may arise from obstruction to the inflow or outflow of urine, the entrance of the ureter being a favourite seat. Lastly, the tendency of warts and warty surfaces (*e.g.*, *ichthyosis linguæ*) to become epitheliomatous in advanced life must be remembered.

ADENOMA.

Adenomata*—or, as they are sometimes called, **glandular tumours**—are new formations of epithelial gland-tissue, more or less resembling, but distinct from, the glandular tissue of the organs in which the tumours arise. The new growths are incapable of performing the function of the tissue which they imitate, and their ducts do not enter those of the gland.

In **structure** adenomata consist of numerous tubules or acini, according to the gland in which the growth arises. These tubules or acini are generally lined with a single layer of epithelial cells,

* Greek ἀδήν, a gland.

though there may be two or three layers. A section cut very obliquely through the wall of one of these acini will, by cutting across adjacent cells at different levels, give the appearance of several superimposed layers. The connective tissue varies in amount; when it is much in excess of the normal, the growth is called an *adeno-fibroma* (Fig. 124).

Adenomata almost always **originate** from *pre-existing glands*. They generally grow slowly, and possibly, in many cases, from some hitherto quiescent, congenitally misplaced, rudiment; otherwise it

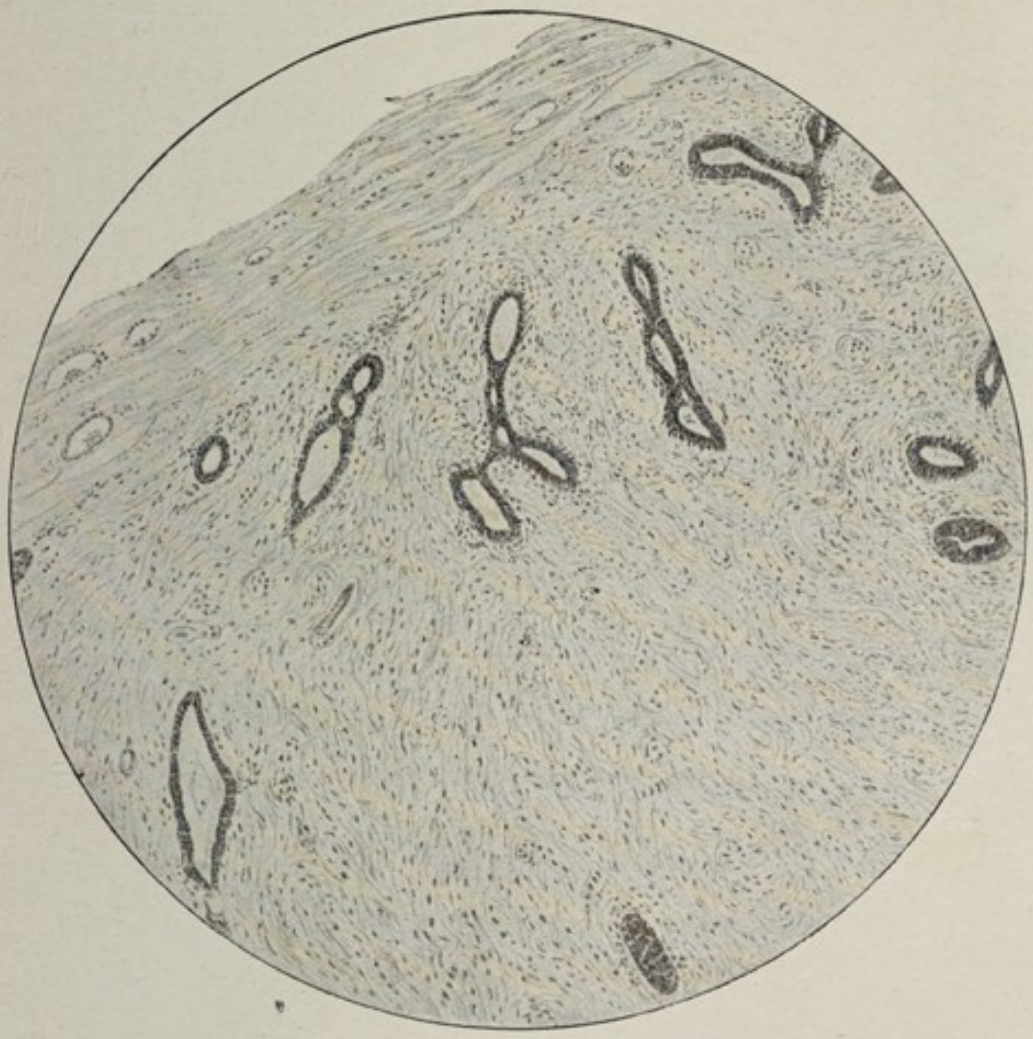


FIG. 124.—ADENO-FIBROMA OF BREAST. (× 79.

is difficult to explain the complete encapsulation and separation from the normal gland which distinguishes an adenoma from a localised enlargement. The latter swelling remains in intimate relation with the gland, and is probably often of inflammatory origin.

Adenomata are commonly met with in the following organs:

Mamma.—This is much the most common seat of adenoma, or rather of adeno-fibroma, for a glandular tumour which is structurally indistinguishable from normal breast-tissue is very rare. The arrangement of the epithelium, the number and size of the spaces, the proportion of stroma, and the number of cells it contains, are more or less abnormal (Fig. 124); hence the name "adeno-fibroma"

is generally most applicable. These tumours are encapsuled, and are round, oval, or lobulated lying in or on the breast. They are of hard elastic consistence. The surface on section is slightly convex, and not cupped as in chronic cancer (*scirrhus*). It is either lobulated and fibrous-looking, or shows distinct slits and a racemose structure even to the naked eye. These tumours are most common in early life. They may be multiple. Many adeno-fibromata contain cysts, which may be very numerous, and vary in size from slight dilatations of ducts and acini to cavities containing some ounces of yellow mucoid fluid, which may be reddish or brownish from extravasated blood. Many of these cysts are lined with cylindrical epithelium like that of the gland-spaces, but others appear to be formed by localised softenings of the stroma. At first they appear on section as irregular and branched fissures, then as spaces full of fluid; in other cases they are almost completely filled by papillary growths projecting inwards from the wall and covered with cubical epithelium. These cystic growths are called *cystic adenomata*. Papillary growths having an adenomatous structure may occur in the mammary ducts. The non-cystic growths must be distinguished from local and general hypertrophies of the gland, and from chronic mastitis, in which the fibrous tissue is less localised, and generally includes fat and atrophied acini.

Ovary.—Adenomata frequently arise in the ovaries. The acini of the growth are derived from ingrowths of the germinal epithelium of the surface of the ovary, while the fibrous or myxomatous septa take their origin from the stroma. Of the original acini the largest number remain little more than microscopic in size; some, however, enlarge considerably, and into the cavities of many of these compound papillary ingrowths occur (Fig. 125), consisting of a framework of stroma and a covering of columnar cells; while a still smaller number of acini enlarge enormously, and together form the well-known large compound multilocular cysts of the ovary. The contents are clear or turbid, mucoid or gelatinous. The tumours are as a rule innocent, but if carcinomatous or sarcomatous developments occur in their interior, they rapidly assume malignant characters.

Kidney.—The kidneys are the occasional seats of growths somewhat resembling those of the ovary, and tumours apparently derived from misplaced cells of the suprarenal body (*hypernephromata*) also occur in these organs. Many of these growths are really teratomata, and tend to be highly malignant.

Prostate.—Adenomata of the prostate consist of a varying amount of glandular tissue, and an abundant stroma containing both fibrous and myomatous elements. The "corpora amylaceæ," which are a feature of the normal gland, may usually be found in the acini of the growth (Fig. 126).

Thyroid.—Apart from the hypertrophy of this gland occurring in endemic goitre and in Graves's disease, distinct encapsuled tumours having the structure of the normal thyroid may rarely be found.

Liver.—Small encapsuled tumours having the structure of the liver have been described. The so-called "multiple adenomata" of the liver, associated with cirrhosis, appear to be simply masses of hepatic cells cut off by septa of newly-formed fibrous tissue.

Uterus.—The adeno-myomata occurring in the uterus contain true glandular tissue. They are not common.

FIG. 125.—SECTION OF WALL OF PAPILLIFEROUS OVARIAN CYST. (× 79.)

Glands of Mucous Membranes.—Gland-tissue enters largely into the structure of some of the "mucous polypi," which may spring from any mucous membrane. Polypi of the nose, stomach, intestines, rectum, and uterus are examples. The connective tissue is soft and œdematous; the surface is covered by the epithelium of the part.

Sebaceous and Sweat Glands.—So-called adenomata of these glands are uniform enlargements rather than tumours, though some degree of proliferation is always present.

Among **secondary changes** are *calcification*, which may affect the epithelial masses, and *ossification*, which may take place in the fibrous stroma. Tumours undergoing the latter change are rare, and have been called "osteomata of the skin."

Clinically, adenomata and adeno-fibromata are almost invariably innocent. They may, however, occasionally become malignant. A few cases occur which clinically and microscopically appear to be

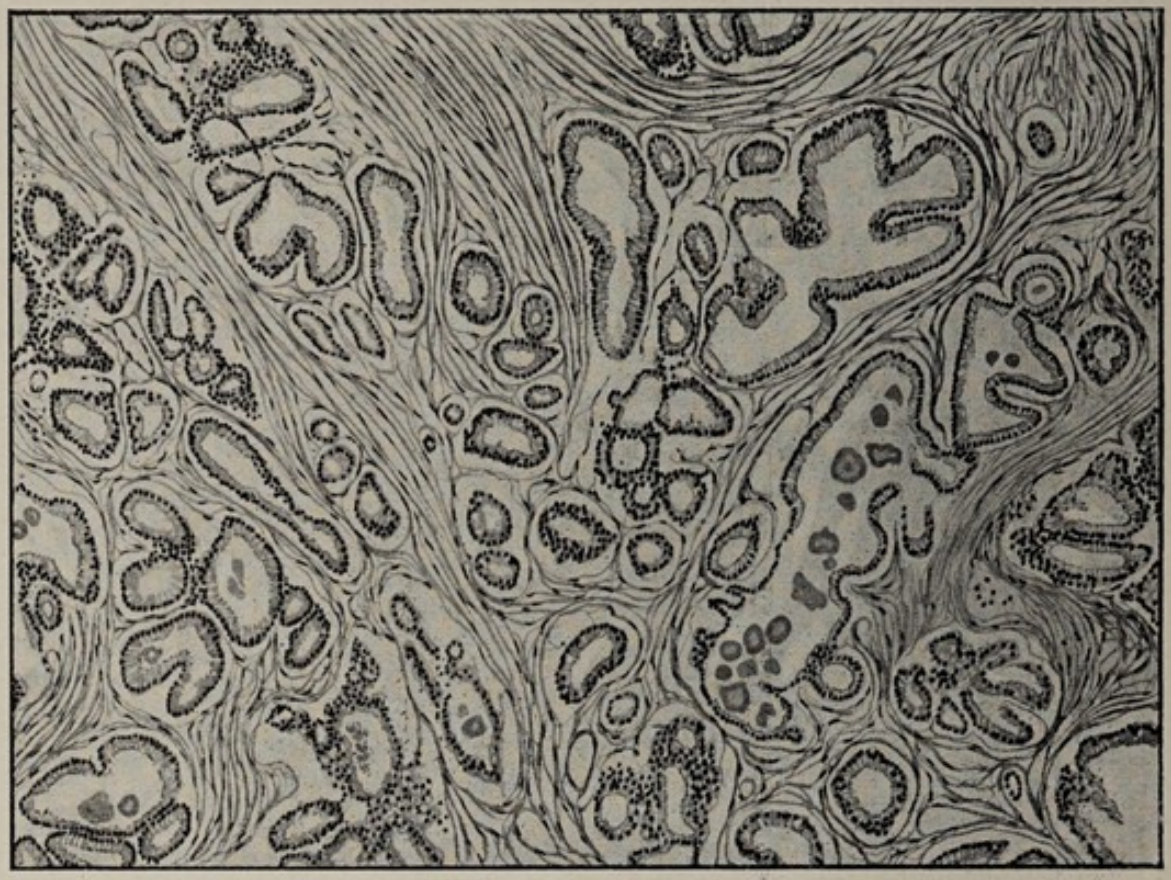


FIG. 126.—ADENOMA OF PROSTATE.

Note the presence of corpora amylaceæ in many of the acini. (× 79.)

ordinary adenomata, but which *recur locally* after removal. There are also cases on record of the *generalisation* of ovarian adenomata as well as of tumours having the structure of the normal thyroid gland.

CARCINOMA.

Carcinomata* or cancers are tumours consisting of epithelial cells lying in a network of connective tissue (*stroma*).

Origin.—It is now generally believed that epithelial cells can originate only in cells of the same type; it is, therefore, only from such cells that carcinomata can spring.

The stroma of the growth is, at first, formed by the normal connective-tissue bundles of the part; but, as the tumour enlarges,

* Greek *κάρκινος*; Latin *cancer*, a crab.

irritation of the surrounding parts is set up, round-celled infiltration occurs at the advancing edge of the growth, and fresh fibrous tissue is formed by multiplication of the connective-tissue cells. At first, other elements of the part may persist in the stroma (*e.g.*, fat-cells in the breast and muscle-fibres in the prostate), but such enclosed cells rapidly disappear as the tumour advances.

Growing in this way, carcinomata are scarcely ever encapsuled. In almost all cases they rapidly infiltrate surrounding structures. In many cases, a zone of small-celled infiltration may be seen for some distance beyond the borders of the tumour, so that there is no line of demarcation between it and normal tissues.

Structure.—It has already been stated that carcinomata consist of epithelial cells and connective-tissue stroma. The **cells** are characterised by their large size, by the variety of their forms, and by the magnitude and prominence of their nuclei and nucleoli. They are round, oval, fusiform, caudate or polygonal—exhibiting, in short, every diversity of outline. These variations in form are principally owing to the mutual pressure to which the cells are subjected in their growth. The nuclei are large and prominent, round or oval in shape, and contain one or more bright nucleoli. The nuclei are most frequently single, but two are often met with, and in the softer and more rapidly growing cancers there may be more. The cells lie in the alveoli in more or less close contact one with another: *no stroma passes between them.* Cells exactly similar to cancer-cells are met with in other morbid growths and in the normal epithelia: there is thus no distinguishing characteristic of cancer-cells.

In recent years the minute structure of carcinomata has been subjected to a very rigid examination in search of any parasite that may be present. It is generally admitted that, when suitable portions of cancerous tissues are hardened and stained by special methods, peculiar appearances are to be seen, the exact significance of which is still in dispute. These are known as *cancer-bodies* or cell-enclosures. They vary greatly in size, being on an average somewhat smaller than red corpuscles. They are for the most part spheroidal in form, and have a sharply-defined outline. They possess staining-affinities somewhat different from those of the ordinary cells of the growth. Their substance is usually homogeneous, but occasionally mottled or granular. At or near to the centre is a small deeply stained part which has been supposed to represent the nucleus or nucleolus. It is usually single, round or oval in shape, and there may be a faint radial striation visible between it and the periphery (Fig. 127). The number of cancer-bodies, or fragments of such, occurring in cells is said to be generally even, and this has been interpreted as being the result of a process of multiplication by binary division. Spore-formation has been said to occur by some observers, but is not generally admitted. Cancer-bodies are usually found enclosed within the cells of the growth, but they have also been described lying in the alveolar

spaces outside the cells and even in the lymphatics of the alveolar walls. Their position has no ascertainable influence on their general characters. The cancer-body may occupy only an insignificant part of the cell, or may fill nearly the whole of it and displace the nucleus to the periphery. Still more rarely these bodies may be found, singly or in numbers, within the nucleus itself; in this case they are generally smaller than when found elsewhere.

The cancer-bodies are most common in the growing edges of tumours and in secondary deposits, and are rarely, if ever, found in degenerated parts. On the other hand, there is no evidence that they excite any unusual activity of growth in the cells containing

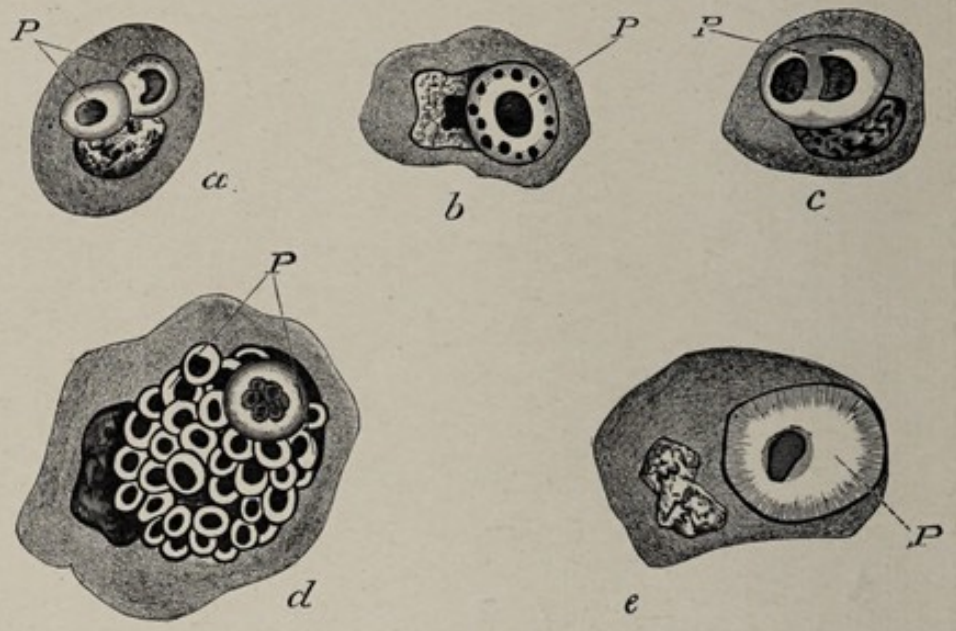


FIG. 127.

a, Two complete cancer-bodies in a single cell. (× 600.)
b, Cancer-body showing granules at its periphery. (× 600.)
c, Cancer-body with a dividing nucleus (?); the connecting threads are shown. (× 600.)
d, Cell containing a cluster of small cancer-bodies. (× 1,000.)
e, Cancer-cell from scirrhus of breast. Faint rays are seen at the periphery of the parasite (?). (× 1,200.) *P*, Cancer-body or supposed parasite.

(Specimens and drawings by Ruffer.)

them; indeed, it appears somewhat rare to find signs of nuclear division in such cells. As degeneration occurs, the bodies lose their sharp contour; and Ruffer has drawn attention to the fact that this not infrequently happens when a leucocyte invades a cell already occupied by a cancer-body.

The nature of these bodies is not as yet definitely ascertained. Soon after attention was first directed to them it was suggested that they were parasitic *protozoa*. Ruffer pointed out a resemblance to the protozoa of malaria, in which the "rosette-stage" is similar to an appearance which he met with in cancer-bodies. The occurrence in rabbits of a disease of which the morbid anatomy is some-

what analogous to tumour-formation, and which has been proved to be due to a minute organism of the class *Sporozoa*, lent additional weight to this view. Schaudinn, however, examined many specimens of cancer containing these bodies, and was unable to find any which he could regard as protozoa. Other observers (Roncali, Plimmer) have identified the cancer-bodies with parasitic *fungi*. Plimmer, indeed, succeeded in isolating and cultivating (anaërobically) certain fungi from cancers, which he considers may possibly be found to belong to the saccharomycetes. He finds that, when certain animals are inoculated intraperitoneally with the cultures, death results, with the production of endothelial tumours; and that cultures from these growths will, under similar conditions, produce similar results. Sanfelice also maintains that blastomycetes are responsible for the origin of cancer.

It is not yet satisfactorily proved, however, that parasites of any kind are constantly present. Many bodies which have been looked upon as parasitic in cancers undoubtedly admit of simpler explanation. Thus it is maintained that many of these so-called parasites are nothing more than the appearance produced by the invagination of a part of one cell into the substance of another, the section being made through both cells parallel to and just below the surface through which the imbedded cell enters. Other cancer-bodies may be merely leucocytes enclosed within the cells of the growth. Another suggestion is that these bodies are due to endogenous formation of new cells from those of the original growth. This may either occur from an arrest of the process of direct division (*amitotic*) or from some irregularity in that of direct division (*mitotic, karyokinetic*). Instances of such irregular karyokinesis may be seen at times in cancer-cells, there being a tripolar or quadripolar arrangement of chromosomes instead of the usual bipolar figure. It is possible that round a detached portion of chromatin a cell may form and grow rapidly, but may yet remain a daughter-cell within the substance of its parent. If, however, this be the case, it is difficult to see why the daughter and parent cells should present any marked differences from one another in their staining reactions. The most probable explanation of many of the unusual appearances seen in cancer-cells is that they are due to different forms of degeneration of the cell-protoplasm. Epithelial cells are liable to changes whereby various substances are formed in them (keratin, hyaline, colloid), and all new growths are specially subject to retrogressive changes in their constituent cells. The special forms of nuclear division which are found in cancer have been alluded to previously.

The **stroma** present in carcinomata varies considerably in amount, being much more abundant in some specimens than in others. There is a general tendency for the more rapidly growing tumours to contain relatively little stroma. It consists of a more or less distinctly fibrillated tissue, arranged so as to form alveoli of varying size and shape, within which the cells are grouped. It is not closely connected with the cells, and does not penetrate between them.

In the stroma are the **bloodvessels.** These are often very numerous, and form a close network round the alveoli. They are limited to the stroma, and never pass into the epithelial masses. This distribution of the bloodvessels is important, as it serves to distinguish carcinomata from sarcomata. Alveolar sarcomata and endotheliomata, however, resemble carcinomata in this respect. The bloodvessels leading to a carcinoma, as to other tumours, are often greatly enlarged. The cause of this enlargement, and the mechanism by which it is brought about, are not well understood. **Lymphatic** channels communicate freely with the alveoli. This explains the great tendency of cancer to infect lymphatic glands. In fact, the alveoli of the growth may be regarded as dilated lymphatic spaces, along which the epithelial columns grow, following the lines of least resistance.

The **physical characters** of carcinomata are so diverse that they will be separately referred to when the different varieties are under consideration.

Varieties.—Just as normal epithelium presents several varieties, squamous, columnar, and cubical, so the tumours which spring from different epithelia are of different anatomical structure, inheriting, to a greater or less extent, the form and tendencies of the variety of epithelium from which they originate. Thus, carcinoma cells springing from stratified epithelium tend also to undergo the same evolution, ending in cornification; and in many cases they show prickle-cells. Columnar epithelium often retains its typical arrangement, and continues to surround open spaces; in other cases the cells may multiply so as to fill these spaces, the outermost layer of cells generally, however, retaining a cylindrical shape. Cells of acinous glands undergo no evolution (*e.g.*, horny change); by multiplication they produce cells of their own kind, which may be much altered in shape by mutual pressure. Upon this retention by the cells of ancestral anatomical characters is based the classification of carcinomata into *Squamous, Columnar,* and *Spheroidal-celled* varieties. The squamous and columnar forms are often known as *epitheliomata,* owing to their resemblance to the structure of normal covering epithelium; but the cells of glands are equally epithelial in character, and no real distinction exists between glandular carcinoma and epithelioma. Indeed, ancestral peculiarities are not always retained. Thus, certain carcinomata springing from stratified epithelium—perhaps from the small glands in relation with it—undergo no horny change and are indistinguishable from spheroidal-celled cancer; and tumours springing from columnar epithelium may in many parts present an exactly similar appearance, or may even in some cases (uterus; bile-duct) resemble squamous epithelioma, exhibiting formation like the cell-nests characteristic of the latter variety of tumours (Fig. 128).

In all varieties of carcinoma the secondary growths tend to repeat the peculiarities of the primary tumour. The rate of growth and consequent proportion of stroma present may, however, vary;

secondary growths in internal organs often developing with great rapidity, and being softer and more vascular.

Secondary Changes.—The most important is *fatty degeneration*. This occurs in all the varieties of carcinoma. The more rapid the growth, the earlier does this retrogressive change take place. It produces softening of the growth, which may be reduced to a pulpy cream-like consistency. *Hæmorrhage, pigmentation, mucoid* and *colloid degeneration* may also occur, leading to *cyst-formation*. Cysts may also be due to blocking of ducts, as, for example, in the mamma. *Calcification* and true *ossification* are very rarely met with.

Clinical Characters.—Carcinomata occur with increasing frequency after the age of thirty-five: below that of thirty they are rare tumours. They occur in certain organs at an earlier period of life

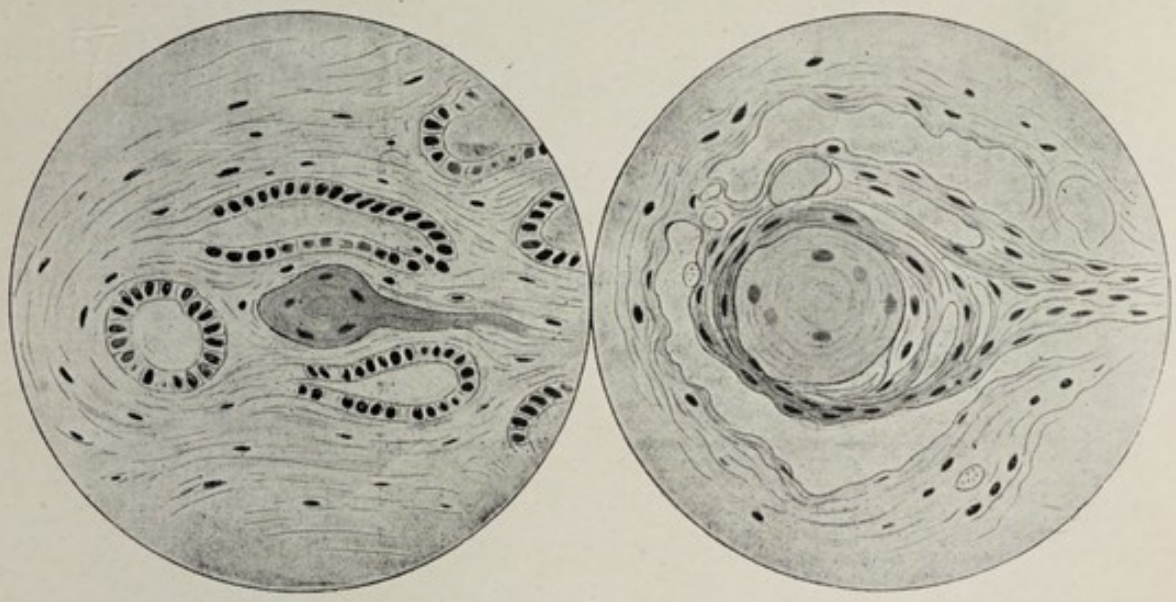


FIG. 128.—METAPLASIA OF EPITHELIUM, FROM A CARCINOMA OF THE BILE-DUCT.

The figure on the left shows the original columnar-celled growth; that on the right shows a cell-nest, typical of squamous epithelioma, into which the growth became in places transformed.

than in others, carcinoma of the mamma and cervix uteri being met with not infrequently in comparatively young subjects, while that of the lip or œsophagus generally arises in elderly persons. The uterus and mamma are the seat of carcinoma more frequently than any other organ, thus causing the female sex to present a slightly greater ratio of deaths from this disease than the male; but, apart from these organs, the incidence of the disease upon the two sexes is practically equal.

Primary carcinomata are almost always single. As a group they are among the most malignant tumours. They grow rapidly, widely infiltrate surrounding parts, largely infect lymphatic glands, and ultimately become generally disseminated throughout the system. Unless excised very early and very freely, they recur *in loco*. They frequently break down and give rise to very offensive ulcers, which

bleed readily. The different types of carcinoma vary considerably in malignancy. As a rule, those forms of acinous growth which exhibit a small relative amount of stroma and a richness in epithelial elements are the most speedily fatal. Occasionally an encapsuled tumour is met with, especially in the soft palate, showing no sign of malignancy, yet having the structure of acinous cancer. In the variety known as "atrophic scirrhus" the duration of the disease is not uncommonly from ten to twenty years, and extension is only local and glandular.

Squamous epithelioma is clinically much the least malignant variety. It extends locally, breaks down early, and often infects the neighbouring lymphatic glands, but it comparatively rarely reproduces itself in internal organs. This is probably owing to the size and character of its epithelial elements, which render them much less liable to transmission by the blood and lymph than the cells of the other varieties of cancer. Its malignancy varies curiously with its seat: thus, on the skin of the face, epithelioma has generally a very chronic course, and rarely affects the glands; on the lip, early excision gives a fair chance of cure; on the tongue, its course is often so rapid, infection of the glands so early, and cachexia and death so speedy, that it must be ranked as one of the most malignant tumours.

I.—Spheroidal-Celled or Acinous Carcinoma.

This is often divided into two separate varieties, according to the relative amount of stroma and cells, the harder growths, with much fibrous tissue and scanty epithelial cells, being known as *scirrhus*,* the softer kind, rich in cellular elements, being called *encephaloid* or medullary carcinoma. Encephaloid and scirrhus cannot, however, be regarded as in any way constituting distinct varieties of carcinoma. There are many intermediate stages between them, and it may happen that the same tumour presents in one part the characters of scirrhus and in another or in secondary growths that of encephaloid of cancer.

1. **Scirrhus Carcinoma** is characterised by the amount and density of its stroma, and by the comparative slowness of its growth. The latter point probably accounts in great measure for the peculiarities of its structure (Fig. 129).

The *physical characters* of scirrhus are due to the abundance of its stroma. The growth is firm and hard, and is usually depressed in the centre, owing to contraction of the fibrous tissue and atrophy of the cells. This contraction is very characteristic of scirrhus of the breast, where it causes retraction of the nipple and puckering of the skin. The tumour is very hard. The surface of the section is generally "cupped," and of greyish-white, semi-translucent appearance, like that of an unripe pear. It is more or less mottled with dots and streaks of opaque yellow, due to fatty epithelium in

* Greek σκιῤῥός, hard.

alveoli or milk-ducts. The latter may be cystic. The central parts are pale and fibrous, the more external are pinker—because contraction has not obliterated the vessels—and less firm than the central portions of the growth. They yield, on scraping, a juice which is rich in nucleated cells, free nuclei, and granules.

By far the commonest seat of scirrhus is the female breast. It is also found in the male breast, the stomach, the liver, the pancreas, the prostate, the skin, and the mucous membranes, where it starts from racemous mucous glands. The secondary growths to which it gives rise are often encephaloid.

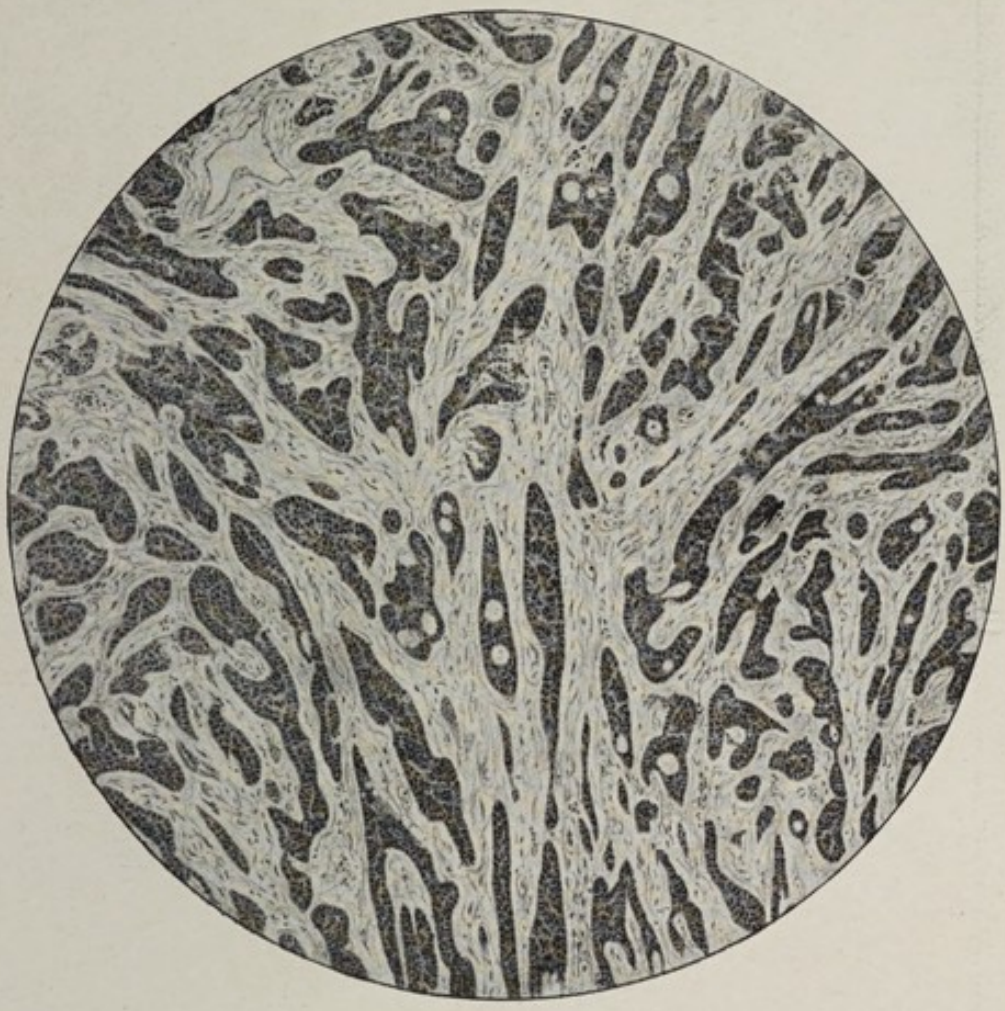


FIG. 129.—SCIRRHUS CARCINOMA OF BREAST. (× 79.)

2. **Encephaloid** or **Acute Cancer** differs from the preceding in the greater rapidity of its growth, and in the smaller amount of its stroma and the greater softness of its consistency (Fig. 130).

The epithelial growth is rapid and abundant.

The proportion of stroma is very small, and, owing to the rapidity of its growth, is much less fibrous than that of scirrhus, and does not undergo a similar cicatricial contraction. The bloodvessels are often very abundant, and the tissue supporting them is soft and non-resistant. Hæmorrhage into these growths is, therefore, frequent, and degeneration is common.

Encephaloid cancer is of a soft brain-like consistency and appearance (from which its name is derived), the central portions, where degeneration is most advanced, may be completely diffluent. The tumour is sometimes more or less lobulated. On section, the undegenerated parts are pinkish-grey, soft, and translucent, whilst the degenerated form a white pulpy mass, which is often irregularly stained with extravasated blood.

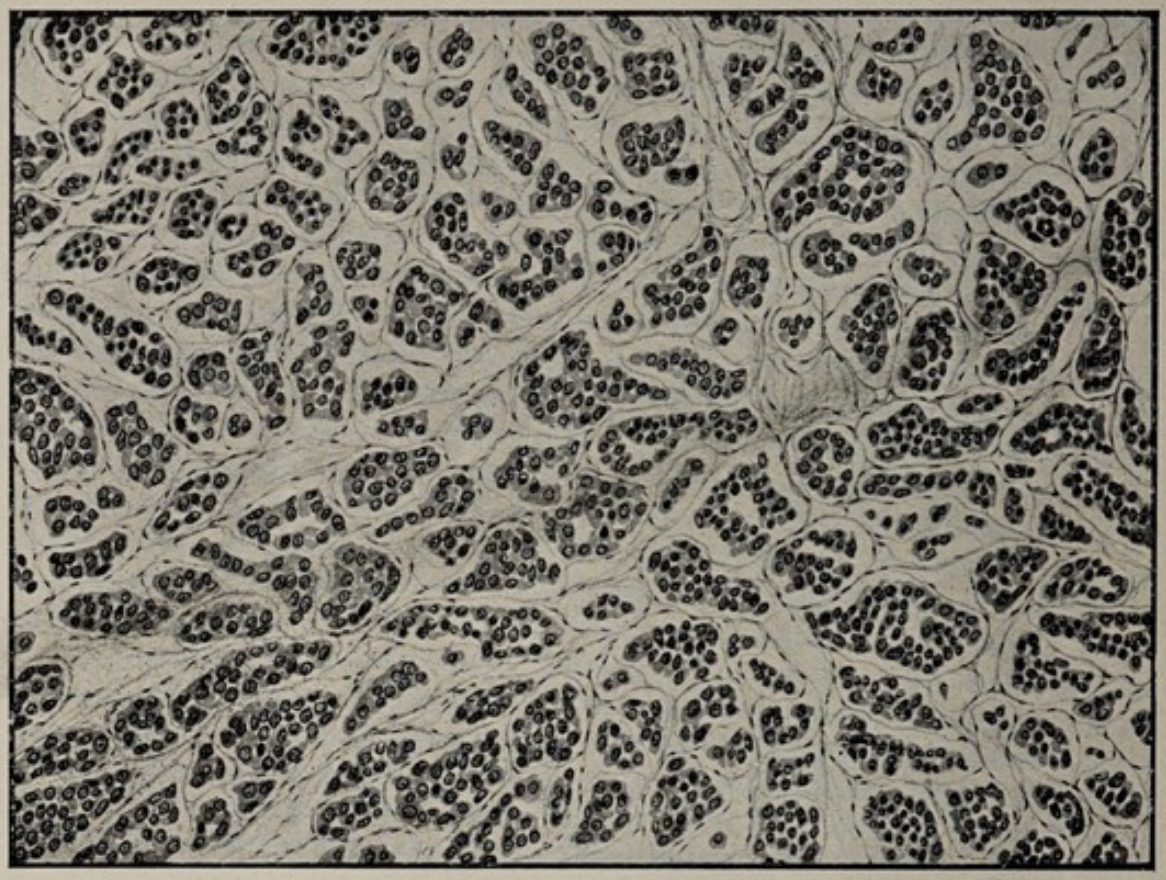


FIG. 130.—ENCEPHALOID CARCINOMA OF BREAST. (× 79.)

Encephaloid is much less common than scirrhus. It is most frequently met with in internal organs as a *secondary* growth. It is sometimes *primary* in the testis and mamma. It may fungate and bleed (*fungus hæmatodes*). Many growths formerly described as encephaloid cancers were really soft sarcomata.

II.—Squamous Epithelioma.

This constitutes a distinct variety of carcinoma. It always grows from a surface covered by squamous epithelium, either cutaneous or mucous (the junction of the two being a common seat). Its epithelial elements closely resemble those of squamous epithelium.

Many of the **cells** are considerably flattened and distorted in shape, resembling those of the superficial layers of the epidermis; others

are like those of the Malpighian layer. They grow down from the surface-epithelium into the lymph spaces of the connective tissue, and, pushing their way along these, form solid cylinders, which twist about, branch, and intercommunicate, swelling out at some points and becoming constricted or even interrupted at others (Fig. 131). The columns cut across appear as round or oval masses of cells, of which the outermost are usually large, whilst the central are more or less squamous and form a yellowish onion-like mass. Sometimes the central cells appear large and vesicular, whilst the

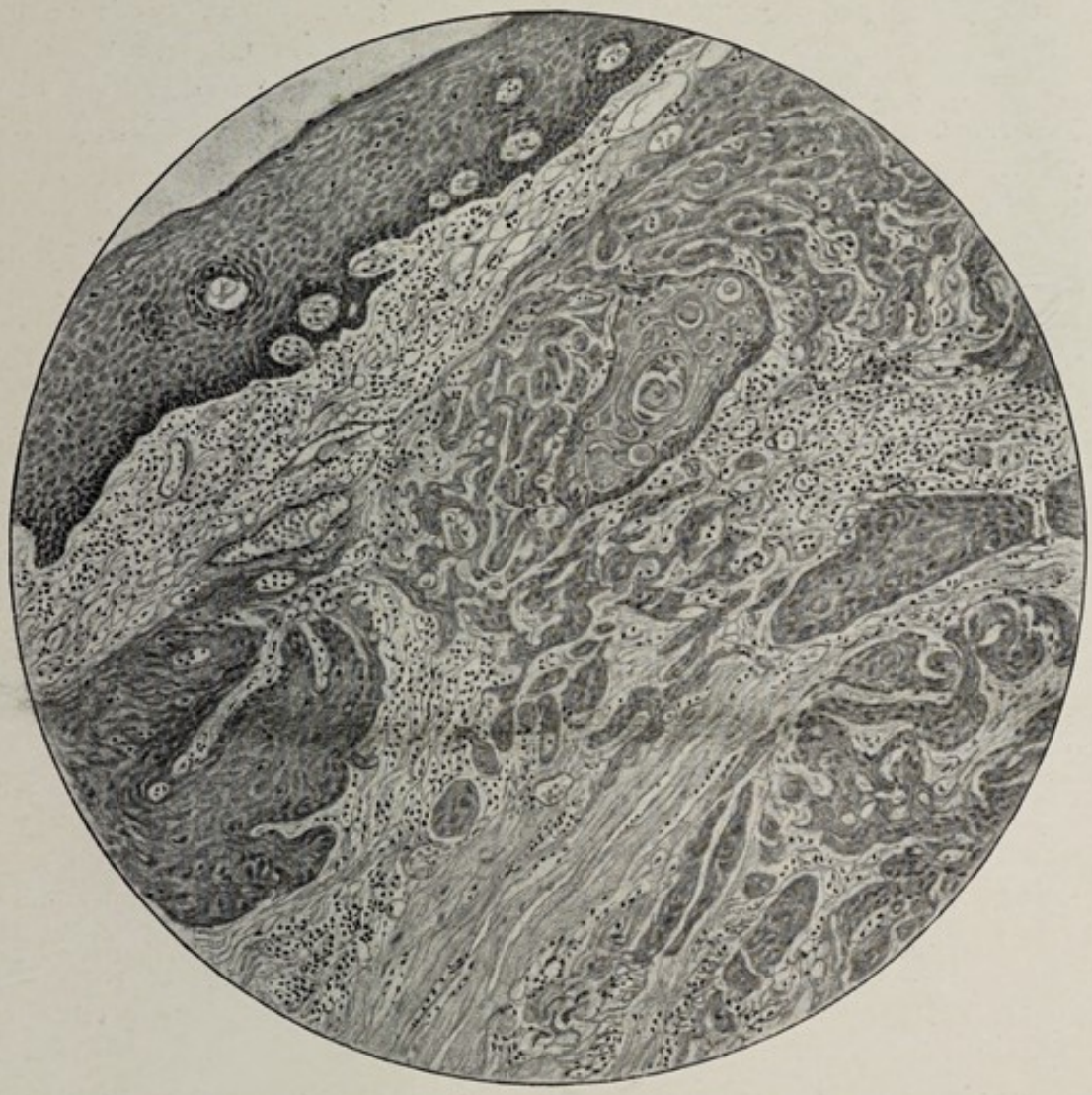


FIG. 131.—SQUAMOUS-CELLED CARCINOMA OF TONGUE. (× 79.)

outermost are scaly and flattened. These concentric masses of cells are called *concentric globes* or *epithelial nests*, and, though not distinctive or essential, they are exceedingly characteristic of epithelioma (Fig. 131). The cells forming them may be so closely packed as ultimately to become hard and dry like those of the nails and hair; the globes are then of a brownish-yellow colour and of a firm consistence.

The **stroma** presents every variation between rapidly-growing embryonic and incompletely fibrillated tissue. It may be fairly abundant or almost entirely wanting. It rarely forms such a marked alveolar structure as that which characterises the other varieties of carcinoma, and consists simply of the fibrous tissue of the part more or less infiltrated with small round cells.

The tendency of epithelioma is to break down and ulcerate at an early stage : the breaking down is due to degeneration of the cells, and not to inflammation.

To the **naked eye** epithelioma usually presents itself as a small hard ulcer ; as an indurated fissure ; or as a subcutaneous nodule, which subsequently breaks down. The surface of the ulcer is irregular, and may be sloughy. It is often clean, and covered with large, firm, bluish-red granulations, consisting largely of epithelium ; more rarely the surface is markedly warty. The tumour itself is firm in consistence, often more or less friable, and, on section, presents a greyish-white granular surface, sometimes intersected with lines of fibrous tissue.

Irritation is believed to have more to do with the causation of squamous epithelioma than of other kinds of carcinoma. Some, such as the epithelioma of the scrotum from soot, and epithelioma of the arm in workers with tar or paraffin, appear to be due simply to irritation in people the physiological resistance of whose connective tissue is diminished until invasion by epithelium is rendered easy. Other epitheliomata occur at points where, the process of development being complicated, errors are likely to have occurred. These places have been already enumerated ; many of these are points exposed to irritation. Squamous epithelioma usually infects the neighbouring lymphatic glands, but rarely forms metastatic growths in internal organs.

Rodent Ulcer.

Rodent Ulcer is a form of squamous epithelioma. It begins as a pimple upon the nose or cheek, and is liable to frequent irritation from rubbing or picking. After a time it breaks down, and the ulcer thus formed slowly spreads, destroying everything that it meets, including bones, and producing the most hideous deformity. This may go on for many years, the health remaining good and no gland being affected. Rodent ulcer is the least malignant form of carcinoma.

It occasionally shows a tendency to cicatrise, and at places may even become covered with normal epithelium. If differs from ordinary squamous epithelioma chiefly in the small size of the cells, in the absence of prickle-cells, and in the slight tendency shown by the cells to become scaly and to form nests (Fig. 132). Some authorities believe that rodent ulcer begins in the root-sheaths of the hairs or in the gland-epithelium of the skin. In some cases having the characteristic history of rodent ulcer, the structure is that

of an endothelioma. In rare cases a growth of this type may prove on microscopical examination to be an ordinary squamous carcinoma.

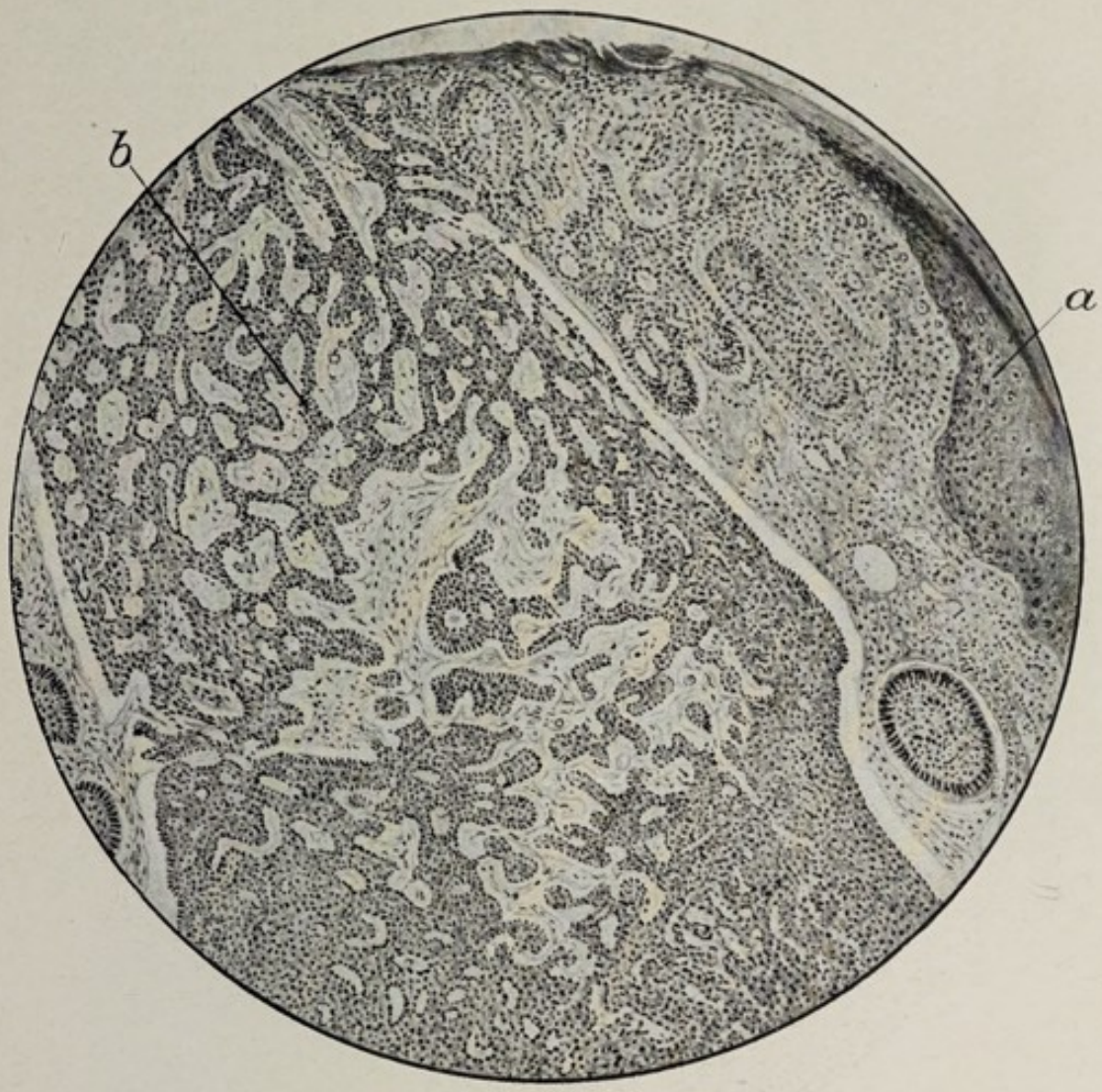


FIG. 132.—RODENT ULCER.

a, epithelium of epidermis; *b*, cells of neoplasm. (× 79.)

III.—Columnar Epithelioma.

The term *columnar epithelioma* is applied to those forms of epithelial cancer which grow from mucous membranes with columnar (cylindrical) epithelium—*e.g.*, the intestines, especially the rectum, and the uterus. In these tumours the epithelial elements are similar to those of the mucous membrane from which they grow. They are cylindrical in shape, and are arranged perpendicularly to the walls of the alveoli in a manner precisely analogous to that of the columnar epithelium on the mucous surface (Fig. 133). The slower the growth, the more typical the gland formation. In rapid growths, and in recurrences, the cells are small and the lumina imperfect. The latter may be filled up, and the growth be indistinguishable from acinous

cancer, except by its edge, where a low columnar or cubical form usually persists; but this too may be lost. The growths are of a soft and often gelatinous consistence; they show a marked tendency to undergo "colloid" degeneration (see p. 49). These tumours cause secondary growths in the lymphatic glands, liver, lungs, and bones: the secondary tumours possess the same characters as the primary cancers.

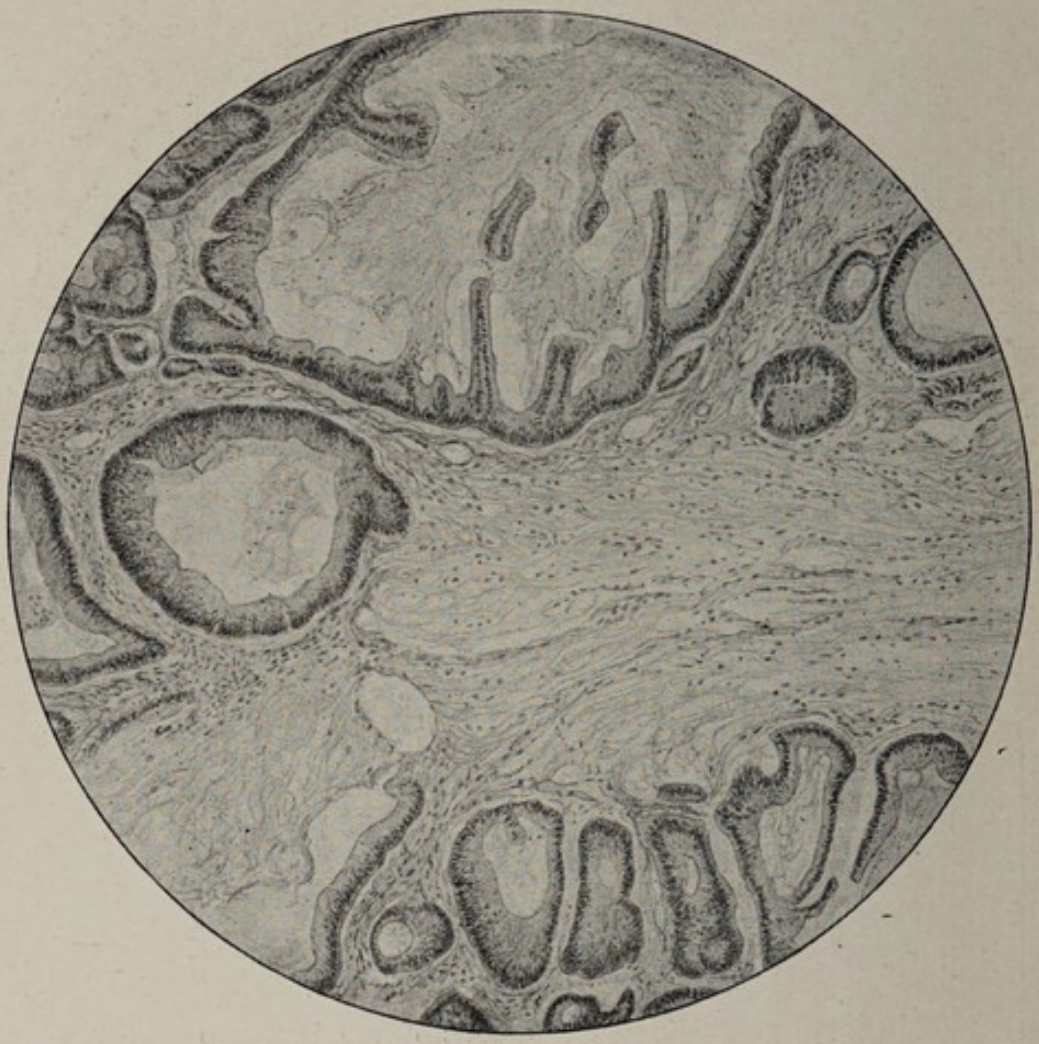


FIG. 133.—COLUMNAR-CELLED CARCINOMA OF RECTUM. (× 79.)

At an early stage the growth penetrates the muscularis mucosæ and invades the deeper structures, thus differing from an adenoma. It ulcerates with extreme readiness.

Colloid Cancer.

Colloid cancer is simply one of the preceding forms which has undergone mucoid or colloid degeneration. Sarcomatous and other non-cancerous growths may undergo the same change.

The alveolar structure in colloid cancers is very marked. The alveoli have very thin walls; they are large, distinct, and more or less spherical in shape. The large size and distinctness of the alveoli is owing to their distension by products of degeneration.

These products form a gelatinous colloid material, which is glistening, translucent, colourless, or yellowish, and of the consistence of thin mucilage or size. In the main it is perfectly structureless; within the masses of colloid material, however, are imbedded varied numbers of epithelial cells. Apparently the colloid change commences in the cells, which are gradually destroyed in the process.

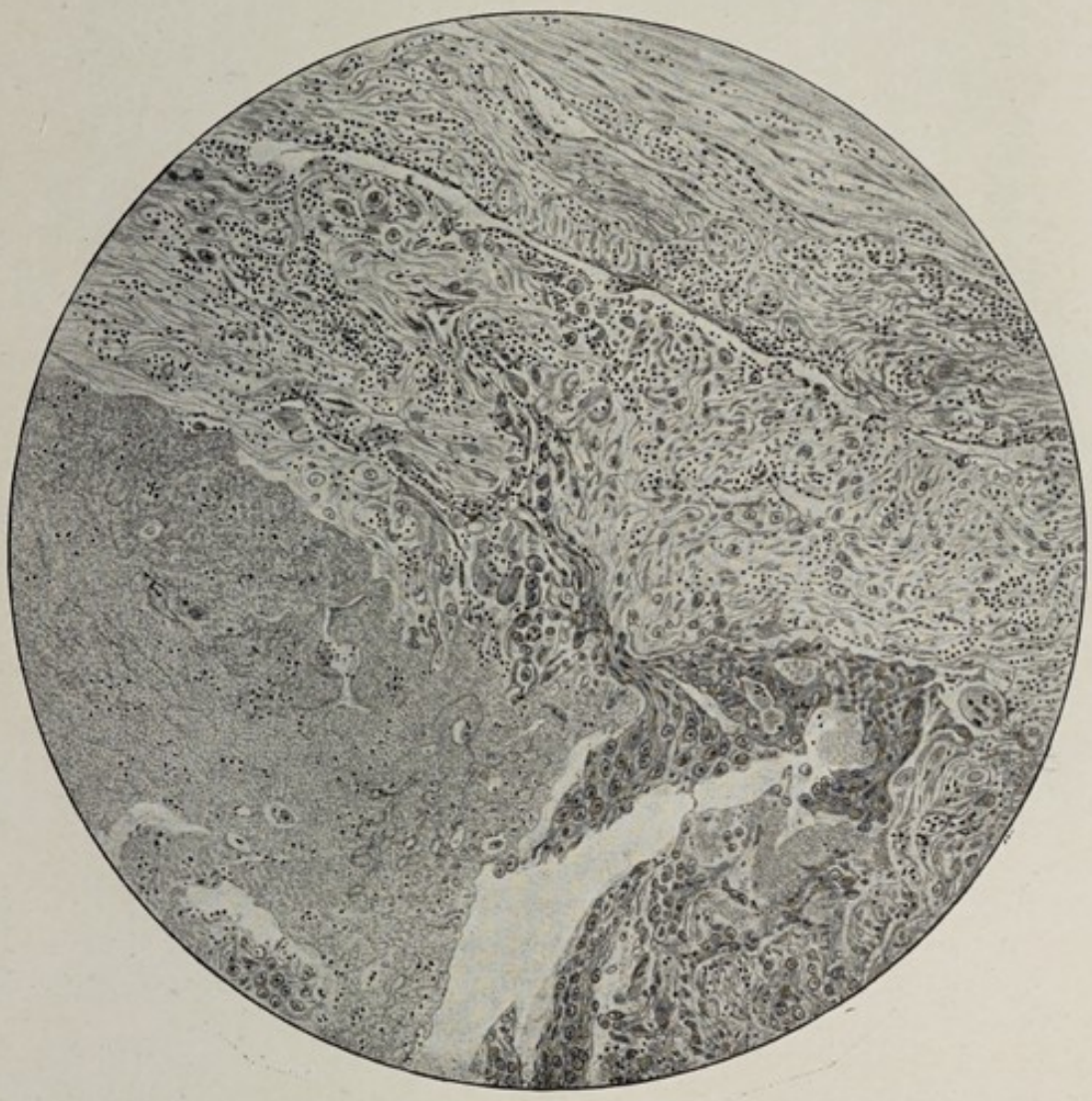


FIG. 134.—CHORION EPITHELIOMA OF UTERUS, SHOWING MASSES OF SYNCITIUM LINING THE CLEFT IN THE RIGHT-HAND LOWER PART OF SECTION. (× 79.)

In other cases, indistinguishable by the naked eye, the cells, with the exception of slight *fatty degeneration*, are but little affected, and the substance distending the alveoli is more viscid and mucoid in character. This is due to a *mucoid degeneration* (p. 48) of the intercellular substance, rather than to a colloid change commencing in the cells. The great majority of so-called colloid carcinomata are in reality of the mucoid variety.

This form of degeneration is most frequently met with in cancers of the abdomen, especially those of the intestine, ovary, and peritoneum.

SYNCYTIOMA.

The name syncytioma, chorio-epithelioma, or deciduoma malignum, has been applied to a peculiar form of growth occurring in the uterus after pregnancy, and associated with hydatidiform degeneration of the placenta. Histologically these tumours consist of cells resembling those forming the coverings of the chorionic villi (Langhans' layer), but grouped in columns, several cells thick, instead of in a single layer; along with these are found masses of protoplasm containing many nuclei, but not differentiated into cells (*syncytium*) (Fig. 134). The whole structure thus closely resembles that of the chorionic villi, from which the growth is supposed to arise. The great pathological interest of this form of tumour is due to the apparent possibility of one individual (the mother) being "infected" with cells from another individual (the fœtus), these cells then proceeding to form a malignant tumour. Metastatic growths occur in the lungs and other parts. Hæmorrhage often takes place into these tumours, so that their structure is obscured.

TERATOMATA.

These are congenital tumours occurring chiefly as projections from the sacral region (*coccygeal tumours*), or from the head or neck —points at which double monsters are often united. Sometimes teratomata* are found within the abdomen or other part of the body. Some of them are due to the inclusion and imperfect development of one embryo within another; others to the excessive and disorderly development of a portion of the tissues of a single fœtus. Teratomata are most complex, and may contain all the tissues of the body up to ganglion-cells, more or less confusedly mixed (Fig. 135). They may be very large at birth, or may not attract notice till later.

Dermoid Cysts† belong to the same group. Their walls (Fig. 136) are composed of skin and of any of the structures ordinarily arising from skin. All varieties of connective tissue may also be found in the walls. The cysts contain epithelial products, coils of long hair, teeth, and even bones. In many cases these accessory structures are absent, but a true dermoid cyst is lined with actual skin, showing a stratum granulosum, and not merely with squamous epithelium. They may occur anywhere, but are commonest in the ovaries, testicles, and subcutaneous connective tissue. In many cases they seem to be due to the inclusion of a piece of epiblast, and are analogous to the implantation-cysts which are occasionally produced by the inclusion or "healing in" of a piece of skin during life (Fig. 137).

* Greek *τέρας*, a marvel.

† Greek *δέρμα*, skin.

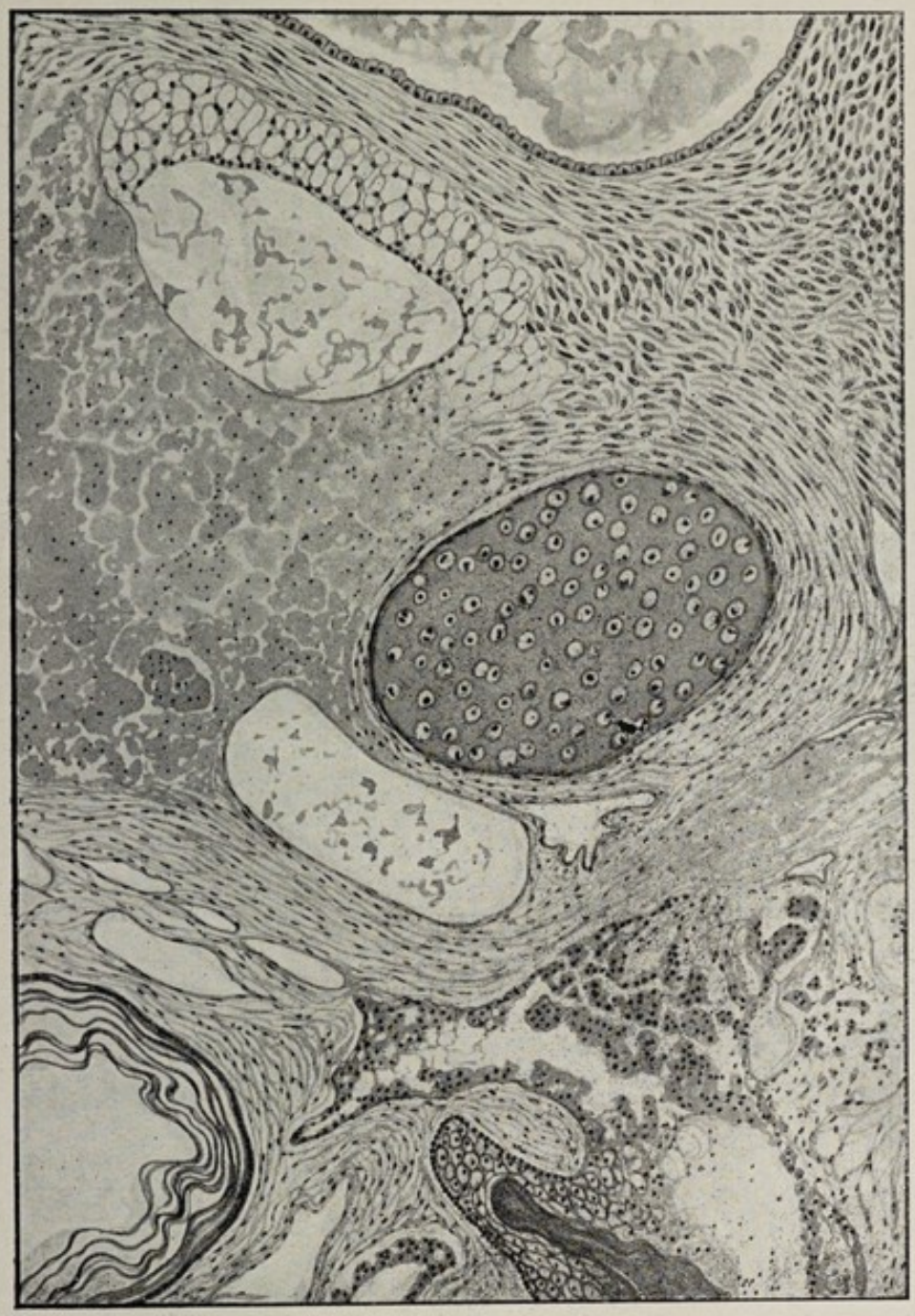


FIG. 135.—TERATOMA OF TESTICLE, SHOWING PRESENCE OF CARTILAGE, CUBOIDAL EPITHELIUM, SQUAMOUS EPITHELIUM, AND CONNECTIVE-TISSUE ELEMENTS. (× 175.)

CYSTS.

In addition to the new growths already described, there is a large class of formations, many of which cannot be regarded as "tumours," in the strict application of this term. These are the *cysts* or *cystic tumours*.

A **cyst** is a cavity containing liquid, gelatinous, or pultaceous material, which is separated from the surrounding structures by a

more or less distinct capsule. It may be (1) part of a new-growth; or (2) a pre-existing structure which has become distended by its own secretion, by a growth from its lining wall, by the extravasation of blood or other fluid into it, or by some more complex process. Only a minority of these come within the category of new-growths; but, for the sake of convenience, they will all be considered together.

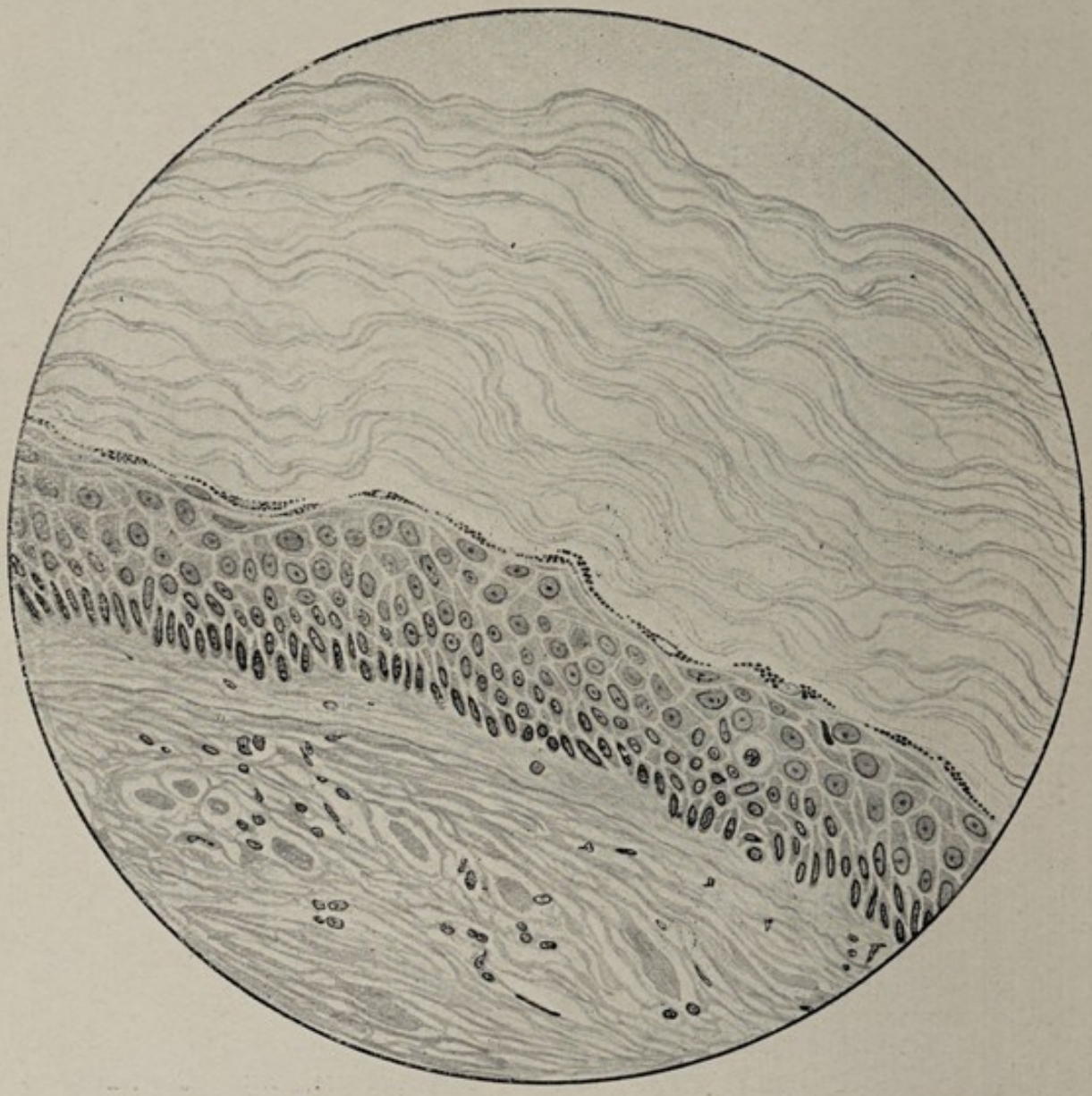


FIG. 136.—WALL OF DERMOID CYST, SHOWING THE PRESENCE OF THE STRATUM GRANULOSUM. (× 505.)

The accumulation of secretions and of other products within pre-existing cavities may be effected in the three following ways:

(1) By the retention of the normal secretion owing to the closure of the excretory ducts, as so often occurs in sebaceous glands (*retention-cyst*).

(2) By excessive secretion, the cavity being unprovided with an excretory duct, as in the distension of bursæ.

(3) By the extravasation of blood into the cavity, as into the sac of the tunica vaginalis (*hæmatocele*)* or into a bursa.

The independent formation of a cyst may take place—

(1) By the softening and liquefaction of the tissues in some particular part, owing to mucoid or fatty changes, or to colliquative necrosis. The tissues around the softened matters become condensed, and ultimately form a kind of cyst-wall, as in the small subchondral cavities sometimes seen in rheumatoid arthritis.

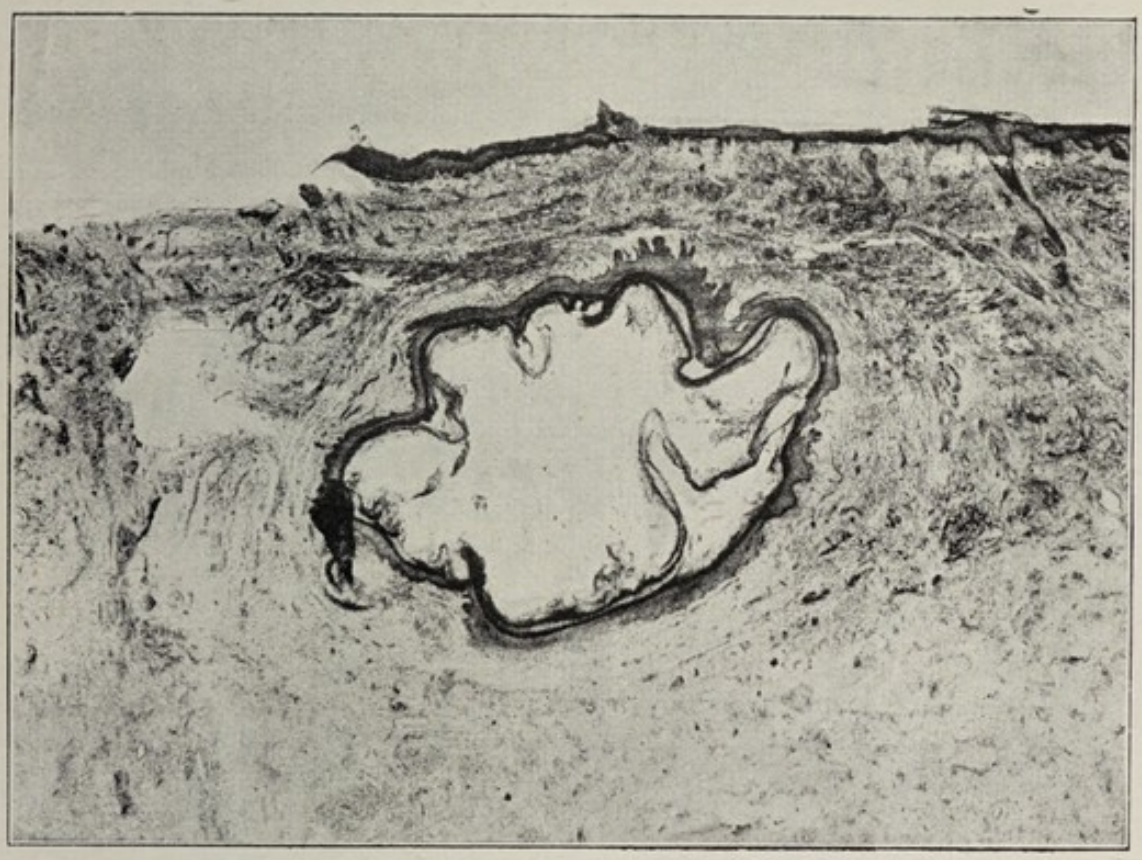


FIG. 137.—IMPLANTATION-CYST IN ABDOMINAL WALL, EXCISED ON THE SUPPOSITION THAT IT WAS A RECURRENT NODULE OF A GROWTH REMOVED BY LAPAROTOMY ABOUT A YEAR BEFORE. (× 9.) (FROM A SPECIMEN BY DR. H. D. ROLLESTON.)

It was probably due to the growth of a fragment of skin which had been inverted at the time of the operation and severed from its original connections.

(2) By the collection of fluid in certain connective-tissue spaces, and the subsequent enlargement and fusion of these spaces. The surrounding tissue becomes condensed, and forms a cyst-wall; and this may in some cases become lined with flattened connective-tissue cells (endothelium). In this way a *false bursa* is formed.

(3) By the formation of a cyst-wall round foreign bodies, parasites, or extravasated blood; the wall consists of fibrous tissue, and is the result of the reaction of the surrounding tissues to the irritation produced by the foreign substance. Smooth, heavy, sharp-edged foreign bodies are particularly liable, during the process of

* Greek αἷμα, blood; κήλη, a swelling.

"healing in," to produce cysts of this character, especially when the parts are not kept at rest.

STRUCTURE.—The **wall** of the cyst will vary in its nature according as it is that of a pre-existing or a newly-formed cavity. In the former case, it will possess a lining which will present the same characters as that of the gland, serous membrane, or other structure from which the cyst originated. If the cyst is of independent formation, there is at first no endothelial lining to the fibrous capsule, but one may develop later, as in false bursæ. The cyst-wall is sometimes firmly connected with the adjacent parts, so that it can only with difficulty be separated; in other cases the union is much less intimate. Instead of being a distinct structure, it may simply consist of the surrounding tissue which has become dense and fibrous in character.

The **contents** of cysts are very varied, and may serve as a basis for their classification. In the retention-cysts, they will vary with the nature of the normal secretion. Serum, sebaceous matter, saliva, milk, seminal fluid, and other substances are found in these cysts: they are more or less altered in character from having been retained in a closed cavity. In the exudation-cysts, serum is the most frequent constituent; and in extravasation-cysts, blood. In those cysts which originate from the softening and breaking down of tissue, the contents are formed of the products of degeneration, such as mucin, fatty matters, and serum.

Cysts may be **simple** or **compound.** A simple cyst consists of a single cavity (*loculus*). A compound or multilocular cyst is one consisting of numerous loculi, which either communicate with one another or remain isolated. Another variety of compound cyst is one with endogenous growths, or, in other words, a large cyst with others growing in its walls. A compound cyst may become a simple one by destruction of the walls separating individual loculi.

Cysts are frequently associated with other growths; hence the terms, "cystic sarcoma," "cystic cancer," etc. It is especially in those growths which originate in glandular structures, as in the mamma, testicle, and ovary, that this combination is met with. The cystic development may almost entirely obliterate the structure of the tumour in which it takes place, so that ultimately the latter may become converted into a mere congeries of cysts, as in *compound ovarian cysts* and *cystic kidneys.* In other cases large papillary masses of the tumour grow into the cystic cavities (*compound proliferous cysts*). Considerable difficulty in determining the nature of the original growth is thus not infrequently experienced.

SECONDARY CHANGES.—These may take place in the wall of the cyst or in its contents. The *cyst-wall* itself may become the seat of new-growths, and produce secondary cysts, or villous, glandular, and other structures: this process occurs in many compound ovarian cysts (p. 321). It may also be the seat of an inflammatory process, which terminates in suppuration and granulation; by this means the cyst frequently becomes obliterated, its contents being either

absorbed or discharged externally, and the cavity closing by granulation. Calcification and ossification of the wall may also occur. The *contents* may become altered in character, thickened, and viscid. Epithelial elements undergo fatty changes, and so give rise to cholesterin-crystals. Calcification of the contents is also common.

VARIETIES.—Cysts may be most conveniently classified according to their mode of origin, thus :

I. *Cysts formed by the accumulation of substances within the cavities of pre-existing structures.*

(1) **Retention Cysts.**—Cysts resulting from the retention of normal secretions. These include :

(*a*) *Sebaceous Cysts.*—These are formed by the retention of sebum in the sebaceous glands, or in the glands of the hair-follicles. The cysts possess a very thin connective-tissue wall lined by stratified epithelium. They contain a mass of fatty epithelium and its products, cholesterin, and amorphous débris. Many sebaceous cysts are really neoplasms, and should be classed as *cystic adenomata.*

(*b*) *Mucous Cysts.*—These are formed by the retention of secretions in the glands of mucous membranes.

(*c*) *Cysts from the retention of secretions in other parts,* including *ranula,* from occlusion of the salivary ducts ; *encysted hydrocele,* from occlusion of the tubuli testis ; *mammary cysts,* from obstruction of the lacteal ducts ; *simple and some compound cysts of the ovary,* from dilatation of the Graafian follicles ; and simple *cysts of the kidneys,* from local obstruction.

(2) **Exudation-Cysts.**—Cysts resulting from excessive secretion in cavities unprovided with an excretory duct. These include *bursæ, ganglia, hydroceles, meningoceles, cystic bronchoceles,* and many *cysts in the broad ligament.*

(3) **Extravasation-Cysts.**—Cysts resulting from extravasation into closed cavities. These include *hæmatocele,* and some other forms of sanguineous cysts.

II. *Cysts of independent origin.*

(1) **Cysts from Softening of Tissues.**—These are especially common in new formations, as in chondroma, lipoma, sarcoma, etc.

(2) **Cysts from Extravasation into Solid Tissues**—*e.g.*, into the brain, or into soft new-growths.

(3) **Cysts from Expansion and Fusion of Spaces in Connective Tissue**—*e.g., false bursæ,* originating from irritation and exudation into the tissues.

(4) **Cysts formed around Foreign Bodies, Extravasated Blood, and Parasites.**

(5) **Congenital Cysts.**—Many persistent fœtal structures. *Dermoid cysts.*

(6) **Cysts forming Part of the Growth of Parasites**—" cystic stage " —(*Cysticercus cellulosæ Hydatids*). (See p. 87.)

CHAPTER XXI

LOCAL DISTURBANCES OF CIRCULATION

THE efficiency of the circulation depends on the maintenance of a correct relationship between the action of the heart, the size and elasticity of the bloodvessels, and the quantity and composition of the blood, as well as on the preservation of a healthy lining-membrane throughout the whole of the vascular tract. It is altogether out of the scope of this work to deal fully with the many ways in which these various factors may deviate from the standard of health. Practically, in disease, such lesions are nearly always combined. Structural defects of the heart, arteries, and veins, together with their results on the general circulation, will be dealt with subsequently. It is here only necessary to give a brief review of the causes and effects of *diminution* and of *increase* in the blood-supply of a part, and then to deal at greater length with the phenomena of *passive congestion, dropsy, thrombosis,* and *embolism.*

LOCAL ANÆMIA.

By *local anæmia* is meant diminution in the amount of the blood in a part owing to deficiency of the supply. It may be partial or complete.

CAUSES.—The causes of diminished arterial supply comprise all those *conditions which either narrow or completely close the lumen of the supplying artery.* The lumen of an artery may be diminished by disease of its walls—atheroma, calcification, or syphilitic thickening—or by pressure exercised upon it from without, by new growths, constricting scars, inflammatory exudations, and mechanical effusions, especially when it is surrounded by unyielding tissues, such as bones or tendon-sheaths. Complete closure of the vessel may result from some of the foregoing conditions, or, more commonly, from thrombosis, embolism, or ligature. In some cases the supply of blood is diminished by an increase in the natural resistance, due to irritation of the vaso-motor nerves, and resulting spasm of the arteries. This occurs in some neuralgic and other nervous affections (Raynaud's disease); or from the action of certain poisons, such as ergot of rye; or, again, merely as the result of a low temperature.

It is sometimes attributed to the presence in the blood of products of metabolism, either in excessive amount or of abnormal character. Anæmia of one part may be secondary to hyperæmia of other parts, as, for instance, anæmia of the brain and skin in congestion of the abdominal viscera; or it may be due to a general diminution in the total quantity of blood, as after hæmorrhage, in which case the parts most distant from the heart suffer most.

RESULTS.—A part with a diminished arterial supply is usually paler, less tense, and of a lower temperature than natural. Its nutrition is defective; its functions are impaired; and it is liable to fatty degeneration, atrophy, or death. These results have been exemplified in the chapters on Fatty Degeneration, Atrophy, and Necrosis.

Obstruction of a large artery causes rise of pressure (transient under healthy conditions) everywhere except in its own area, and this increased pressure endangers the safety of delicate or diseased vessels, until the extra blood thrown into the suddenly curtailed vascular system is accommodated in some way. The raised vascular tension affects the vaso-motor centre, and dilatation of vessels sufficient to restore the normal pressure is soon brought about by reflex nervous action. But the vessels which dilate most markedly and persistently are those going to the anæmic part and anastomosing with branches from the trunk beyond the obstruction (p. 367). These "collateral" vessels become larger, longer (tortuous), and thicker, until the circulation in the part has again become normal —*i.e., collateral circulation* is established. At first, all vessels having anastomoses with the obstructed one probably dilate; but those which enlarge permanently are almost invariably branches on the same side of the body as the obstruction—*e.g.*, the *right* inferior thyroid and vertebral arteries dilate after ligature of the *right* carotid. The primary anæmia, the blush and heightened temperature of vascular dilatation, and the final return to the normal, can be seen in limbs after ligature of their main vessels.

HYPERÆMIA.

Hyperæmia, or *congestion*, is excess of blood in the more or less dilated vessels of a part. It may be (1) **active** (*arterial*), or (2) **passive** (*venous*). These two varieties must be considered separately.

Active or Arterial Hyperæmia.

Active hyperæmia means excess of arterial blood in a part, with in most cases, acceleration of flow.

CAUSES.—The immediate cause of active hyperæmia is in all cases *diminished arterial resistance.*

Diminished arterial resistance may be produced pathologically—

1. *By certain agencies which have a weakening or paralysing effect upon the Involuntary Muscle of Vessel-Walls.* *Fatigue* from previous

prolonged contraction has this effect, as seen in the hyperæmia of the hands which follows snowballing. *Warmth*, too, is generally placed under this heading. *Injuries* of all kinds, apart from the reflex hyperæmia due to their effect on sensory nerves, cause dilatation by direct damage to the vessel-wall; and, so long as it is more than sufficient to counterbalance the increased resistance which always accompanies it, the quantity of blood passing through the part is greater than the normal—*i.e.*, the part is hyperæmic.

2. *By the removal, either directly or reflexly—i.e., by inhibition—of the Vaso-tonic Action of the Sympathetic.* Thus, active congestion follows pressure by an aneurysm upon the sympathetic in the neck. Certain drugs, taken internally, are believed to paralyse the vaso-tonic nerves—*e.g.*, nitrite of amyl, alcohol, tobacco.

The *reflex* process is generally due to stimulation of sensory nerves, the diminution in tonus thus produced being more or less accurately confined to the region supplied by the nerve. Friction and slight irritants in the early stages of their action produce hyperæmia in this way. It seems probable that vascular dilatation in deep organs may be produced reflexly by stupes and other applications to the skin over them, or, more accurately, to those portions of the skin in connection with the same spinal segments. Conversely, visceral disturbances may possibly give rise to vaso-motor changes in the corresponding cutaneous areas, or, indeed, in areas less limited than these; for Head has shown that in anæmia and other diseases the effects of such disturbances are less definitely localised.

Anæmia of any large part—as of a limb, compressed by Esmarch's bandage, or of the skin from cold—necessarily causes *hyperæmia* of other parts—*compensatory hyperæmia*. But all parts do not suffer equally, as they would do were the hyperæmia the result simply of increased arterial pressure. Certain vessels, as the great abdominal veins, dilate, showing that the vaso-motor system arranges for the accommodation of the surplus blood by producing local diminution of vascular resistance. After extirpation of one kidney, its share of blood passes mainly to the other.

3. *By excitation of vaso-dilatator nerves*, such as the chorda tympani. Nothing is certainly known of this as a cause of hyperæmia; but the hyperæmia associated with facial neuralgia, and that of the thyroid gland in exophthalmic goitre, have been referred to vaso-dilatator neuroses, and also to inhibition of vaso-tonic nerves.

Results.—The results of active hyperæmia are principally such as might be expected from increase, in any particular organ or tissue, in the amount of arterial blood and in the rapidity of its flow. The symptoms in a superficial part are—increased redness and pulsation, a subjective sensation of throbbing; some increase in bulk, and marked elevation of surface-temperature, until this approaches that of internal organs. If the hyperæmia be of long duration, or frequently repeated, the small arteries remain permanently enlarged, their walls gradually thicken, and the epithelium and connective tissues of the part increase. This may be seen in

the growth of hair and epidermic thickening round a callous ulcer of the leg, and the occasional spread of ossification from the tibia into the granulation-tissue, though *irritation* may possibly be an additional factor. The capacity for work is increased, and hypertrophy will follow if the increased work is maintained. Hyperæmia of the nervous centres causes great excitability, paræsthesia of sight and hearing, and even convulsions. In some glands, hyperæmia produced experimentally is followed by increased secretion, as in damage to the renal plexus, which is followed by the increased secretion of watery and even albuminous urine.

Passive or Venous Hyperæmia.

In passive or venous hyperæmia, the excess of blood is in the veins and capillaries, and the flow, instead of being accelerated, is retarded. This is so frequently produced by some obvious mechanical obstacle to the return of blood through the veins that it is often called *mechanical* hyperæmia. The congestion of a finger, produced by a moderately tight band tied round it, may be taken as the type of passive hyperæmia.

Causes.—Anything which weakens the forces carrying on the venous circulation, or which opposes unusual resistance to this circulation, must tend to produce venous hyperæmia. Such causes may exist in any part of the vascular system—heart, arteries, capillaries, or veins—some having a local, others a general effect. They may be arranged under two headings—(1) those which diminish the propelling force; and (2) those which introduce a source of resistance by causing some impediment to the return of blood by the veins.

1. The important factor in the first group is **diminished cardiac power.** The heart may act so feebly or be so damaged structurally (see Endocarditis) that too little blood enters the arteries at each stroke, and this generally at a pressure less than normal. As a result, the arterial supply of all parts is diminished, blood lags in the veins, and a smaller quantity than normal returns to the heart during each diastole. This is very evident in prolonged febrile diseases, such as typhoid, and in those degenerative conditions of the walls of the heart which lead to dilatation of its cavities. In whichever of these ways the propelling force is impaired, the diminished fulness of the arteries and overfulness of the veins, so familiar clinically as the result of *cardiac failure,* will be produced. If this condition be of long duration, there is necessarily so much interference with the oxygenation of the blood, with the functions of the blood-forming organs, and with the processes of digestion and assimilation, that the blood itself becomes altered in composition, and thus the nutrition of all the tissues suffers.

When, by various combinations of the above conditions, the circulation is much retarded, **hypostatic congestion** occurs. The commonest seats of this are the posterior edges and bases of the lungs, the skin over the sacrum, and any parts kept constantly dependent.

Slowing of the circulation causes distension of the veins and increase of the intravenous pressure. In any such part which is also dependent, the intravenous and capillary pressure is further increased by *gravity*. The force of gravity is in proportion to the vertical distance between the highest point of the body for the time being and the part in question. If the patient is so weak as to be unable to change his position, this pressure constantly acts upon the same veins and capillaries, dilating them, and greatly increasing the tendency to leakage through their badly nourished walls. Thus, the part is redder and softer than normal, and is œdematous. In bedridden patients breathing is often very shallow, and the effect of expiration in driving blood on to the left auricle is therefore diminished. (See Hypostatic Pneumonia.) In people who are walking about, dropsy from heart-disease generally begins in the legs. This is due largely to the action of gravity.

2. The return of blood through the veins may be interfered with in many ways. Thus, congestion of the stomach, intestines, pancreas, and spleen, from compression of the portal capillaries, occurs in cirrhosis of the liver; congestion of the lung follows mitral constriction or regurgitation; congestion of the systemic circulation results from insufficiency of the tricuspid valve; and in the lower extremities the same result may be due to pressure of the gravid uterus on the iliac veins.

The circulation will also be slowed by: (1) absence or diminution of contractions on the part of the skeletal muscles, especially in the lower extremity; (2) such dilatation as produces incompetence of valves, thus rendering muscular action useless as an aid to circulation; and (3) by anything which lessens the suction-action exerted upon the great veins by the respiratory movements of the thorax. Forcible expiration will replace the normal *minus*-pressure within the thorax by a *plus*-pressure. Thus, playing wind-instruments impedes the entry of blood from the veins into the heart. Emphysema, effusion of air or fluid into the pleural cavities, and large new growths of the lung act similarly.

In addition to the above causes the *sudden removal of pressure* may produce hyperæmia. Thus, congestion of the abdominal vessels follows the removal of much ascitic fluid, or of a large ovarian tumour; bleeding from the pleura occurs when the cavity is rapidly emptied by aspiration or strong syphon-action; bleeding may also follow the complete emptying of a chronically distended bladder. In organs subject to extrinsic pressure the walls of the vessels, being thus provided with external support, gradually lose their power; if, then, the support is suddenly removed, the vessels dilate fully, and small ones may even rupture.

Results.—Whether there be a direct impediment to the return of blood by the veins, or a failure in the forces of circulation, the veins and capillaries dilate, and the blood, moving with diminished velocity, accumulates in them. The subsequent changes will depend upon the degree of obstruction to the venous return, and upon the

arterial pressure; in other words, upon the injury sustained by the vessel-walls from impaired nutrition, and upon the increase of pressure in the veins and capillaries. In addition to the immediate effects, such as the diminished secretion of urine, the more gradually induced changes are the exudation of serum, the escape of red blood-corpuscles, hæmorrhage, fibroid induration, atrophy, thrombosis, and necrosis.

1. **Exudation of Serum** is one of the most important results of passive hyperæmia. It is discussed on p. 353.

2. **Escape of Red Blood-Corpuscles** occurs when obstruction to the venous return is very great; they transude with the fluid from the veins and capillaries. Observation of a tissue thus affected (*e.g.*, by a ligature) shows that the blood-stream in these vessels stagnates, and the red corpuscles become packed into a coherent mass which oscillates to and fro with the arterial pulsation. Then, suddenly, some of the red corpuscles penetrate the walls of the capillaries and smallest veins, and escape into the surrounding tissues. This seems to occur without rupture of the vessel, for if the ligature be removed the blood again circulates in a perfectly normal manner. The corpuscles rarely escape in great numbers. It has been suggested that they pass between the endothelial cells.

3. **Hæmorrhage** is another result of passive hyperæmia, and usually occurs only when the obstruction to the venous current is very great, and when the nutrition of vessels and tissues has suffered from long congestion. Healthy vessels can bear very heavy strains without giving way. Those vessels which are the least supported are the first to give way. Hæmorrhage into the stomach in cirrhosis of the liver, and into the lung in mitral stenosis, are familiar examples of this result.

4. **Fibroid Induration** is due to a gradual increase in the connective tissue round the bloodvessels, and is one of the most important results of long-continued passive hyperæmia. This interstitial growth was formerly supposed to lead to atrophy of the higher structures, and thus to impairment of the functions of the organ. In the stomach, it was said to produce atrophy of the glandular structures; in the kidney, compression of the tubules; and in the heart, diminution in motor power. It is probable, however, that the **atrophy** in these cases is primary, following the deficient supply of arterial blood, and that the increase in the stroma is due to the fact that the latter is the only tissue present that can thrive in the existing conditions. We must also take into consideration the possible stimulating effects of irritant products arising from dead cells on the growth of the fibrous tissue; but the importance of this factor is difficult to estimate. The alterations which this change produces in the physical characters of the organs—viz., induration associated with abnormal redness, due to the excess of blood or to pigmentation from hæmatoidin—are exceedingly characteristic.

5. **Thrombosis** (see p. 355).

6. **Necrosis** occurs from passive hyperæmia only when the obstruction is very general and complete.

To sum up, long-continued passive hyperæmia leads to impairment of vitality and function. The tissues gradually undergo retrogressive changes and atrophy, although from the amount of exudation and blood which they contain their size and absolute weight may be increased. This form of hyperæmia has no tendency to cause multiplication of tissue other than the *connective*, and, in the case of skin and mucous membranes, the *epithelial*. In the latter instance the proliferation is associated with catarrhal inflammation to which the congestion predisposes.

Post-Mortem Appearances.—Parts which were actively hyperæmic during life frequently show no signs of this condition after death; for if coagulation does not occur immediately, contraction of the arteries or of the elastic capsules of organs forces the blood on into the veins, thus rendering the recognition of arterial or capillary hyperæmia impossible. Further, under the influence of gravity alone, fluid blood will tend to run to the more dependent parts, and thus a hyperæmic organ—whether actively or passively congested—may be emptied of blood, and may thus appear pale.

On the other hand, dependent parts—the posterior portions of the lungs, the lowest coils of the intestines, the skin on the posterior surface in dorsal decubitus—which may have been healthy during life, now become full of dark blood. It is often difficult to say how much of the congestion of the base of a lung is ante-mortem and how much post-mortem.

When large veins are distended with blood, the injection is said to be "ramiform," from their branching form and dark blue colour. In the intestine, skin, and kidney, hyperæmia may appear punctiform from the arrangement of the vessels in villi, papillæ, or Malpighian corpuscles, as the case may be. Minute punctiform hæmorrhages must not be mistaken for such congestion.

Pigmentation (slate-grey, black or brown) from the altered hæmoglobin of disintegrated corpuscles generally remains after chronic hyperæmia, as is often seen in the stomach and intestines after portal congestion, and in the bladder and the lungs after chronic catarrh.

Passive Hyperæmia of the Liver.

Passive hyperæmia of the liver is the result of some obstruction to the blood-stream in its course from the hepatic veins until it reaches the aorta. It may thus be due to the pressure of scar-tissue or exudation upon the inferior vena cava; to fibrosis or emphysema of the lung; and especially to disease of the mitral or the tricuspid orifice associated with failing compensation on the part of the walls of the heart. Long-continued passive hyperæmia of the liver gives rise to the condition known as *Nutmeg Liver* (Fig. 138). The change is characterised by a large accumulation of blood in the sublobular and intralobular veins, which dilate and thicken; by

distension of the supplying capillaries and venules; by atrophy of the hepatic cells in the central portions of the lobules (*cyanotic atrophy*); and rarely by increase of the interlobular connective tissue. The impediment to the return of blood by the hepatic veins leads to atrophy of the cells in the central portions of the acini and to the deposit of pigment, so that, when examined microscopically these portions of the acini are seen to consist of masses of broken-down cells and granules of pigment, separated from one another by the distended vessels (Fig. 139). The intralobular veins and their radicles are much dilated, and filled with red blood-corpuscles. Their walls are thickened, and there often appears to be some thickening of the intercellular network which immediately surrounds the central vein. Owing to this thickening of the central vein and of the adjacent intercellular network, and to the destruc-

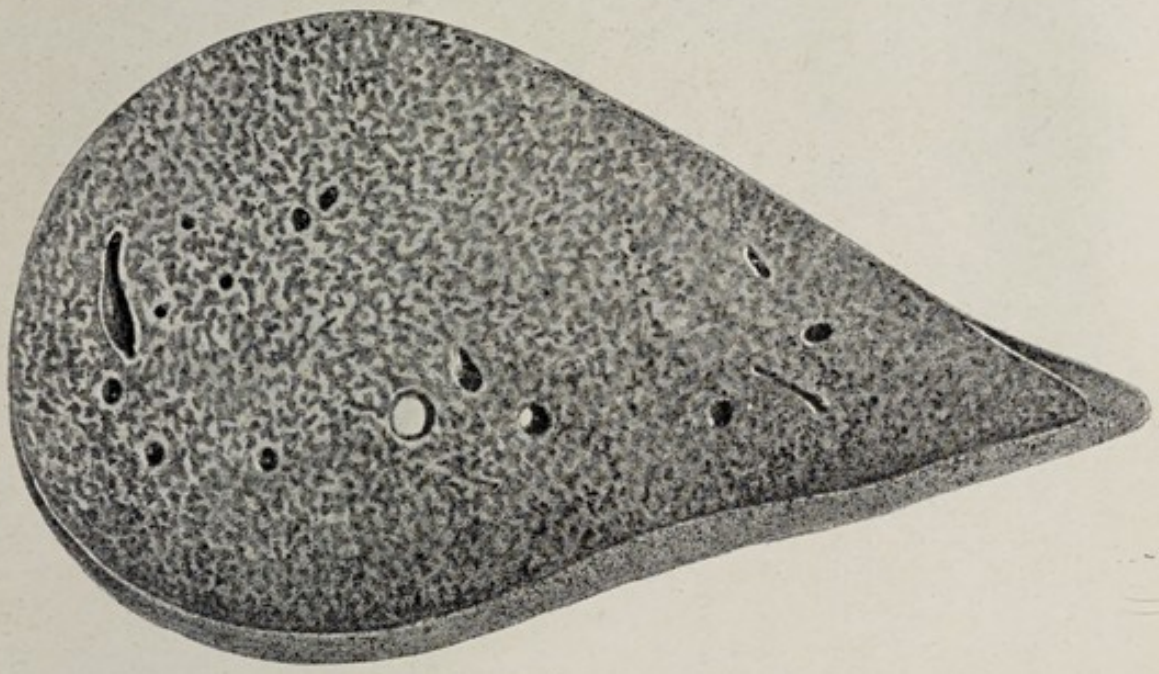


FIG. 138.—PASSIVE CONGESTION OF LIVER (NUTMEG LIVER), SHOWING ALTERNATING LIGHT AND DARK AREAS. (× ½.)

tion of the liver-cells, the most central portions of the acini, in advanced stages of the disease, may appear to show a greater increase of fibrous tissue than has actually occurred. At the peripheral parts of the acini new fibrous tissue is occasionally seen between the almost unaltered liver-cells. In a few instances this may be a prominent feature.

In the earlier stages of this affection the liver is smooth and often considerably increased in size from the large amount of blood which it contains. On section it presents a peculiar mottled appearance, the centre of the lobules being of a dark red colour, whilst the peripheral portions are of a yellowish-white. This latter appearance is occasionally increased by fatty accumulation in the peripheral liver-cells. The appearance of such a section is not unlike that of a nutmeg (Fig. 138). Ultimately the organ may undergo a gradual

diminution in size, becoming more or less irregular on the surface This is due to atrophy of the central cells of the lobules, mainly

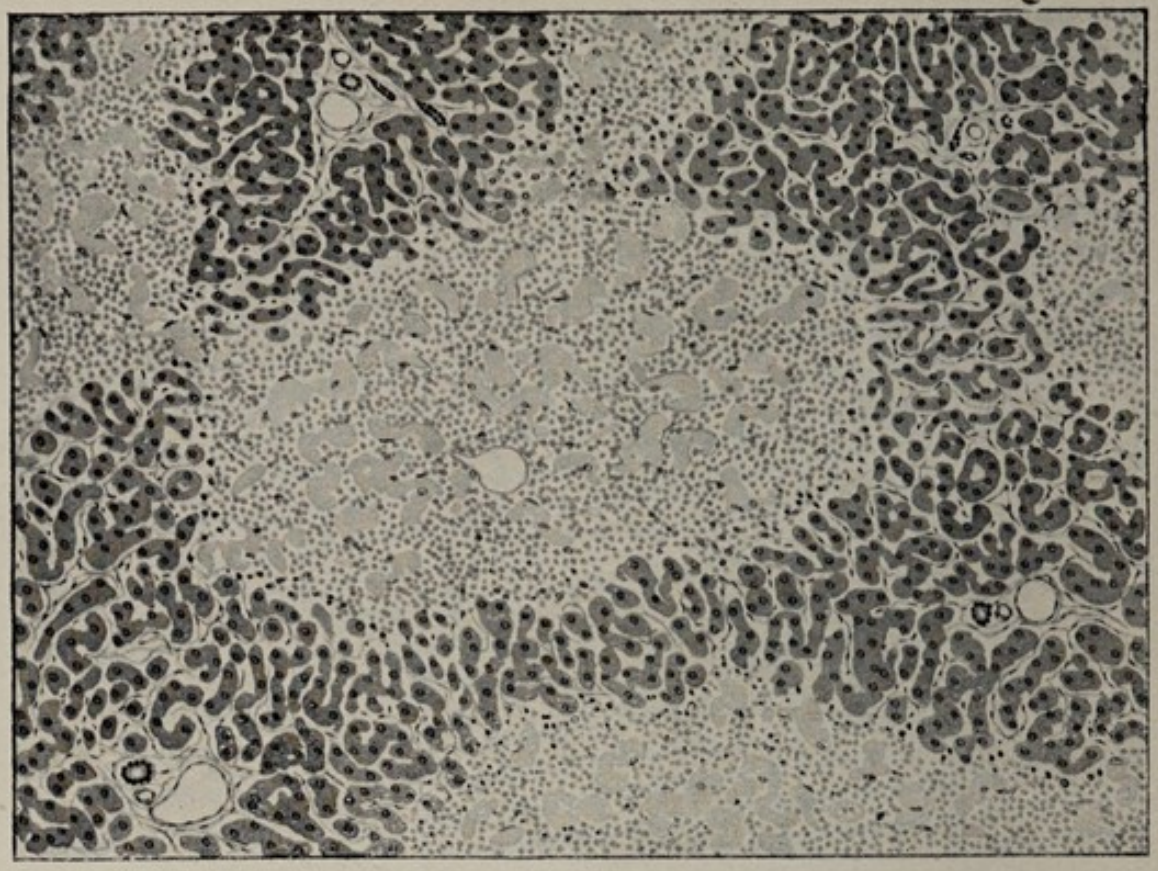


FIG. 139.—PASSIVE CONGESTION OF LIVER. (× 54.)

from malnutrition, but partly from pressure of the dilated central veins and the contracting interlobular growth.

Passive Hyperæmia of the Lungs.

In the lungs, long-continued passive hyperæmia produces that peculiar induration and pigmentation which is known as **Brown Induration.** This most frequently results from stenosis of the mitral orifice or from insufficiency of its valves. The consequent changes consist, in the first place, of elongation and dilatation of the pulmonary capillaries, so that even in uninjected preparations the alveolar walls appear abnormally tortuous. The epithelial cells lining the alveoli become swollen, probably multiply, and are seen in large numbers, filled with dark brown pigment, covering the alveolar walls, and frequently lying free within the alveolar cavities (Fig. 140). These changes are followed by an increase in the interlobular connective tissue, by the formation of large quantities of brownish-black pigment, and often by a thickening of the alveolar walls. The bronchial mucous membrane is dark, and the small peribronchial vessels are dilated. Sometimes these vessels rupture,

and blood is extravasated into the tissue of the lung. Not infrequently these changes occur with and after infarction (p. 367).

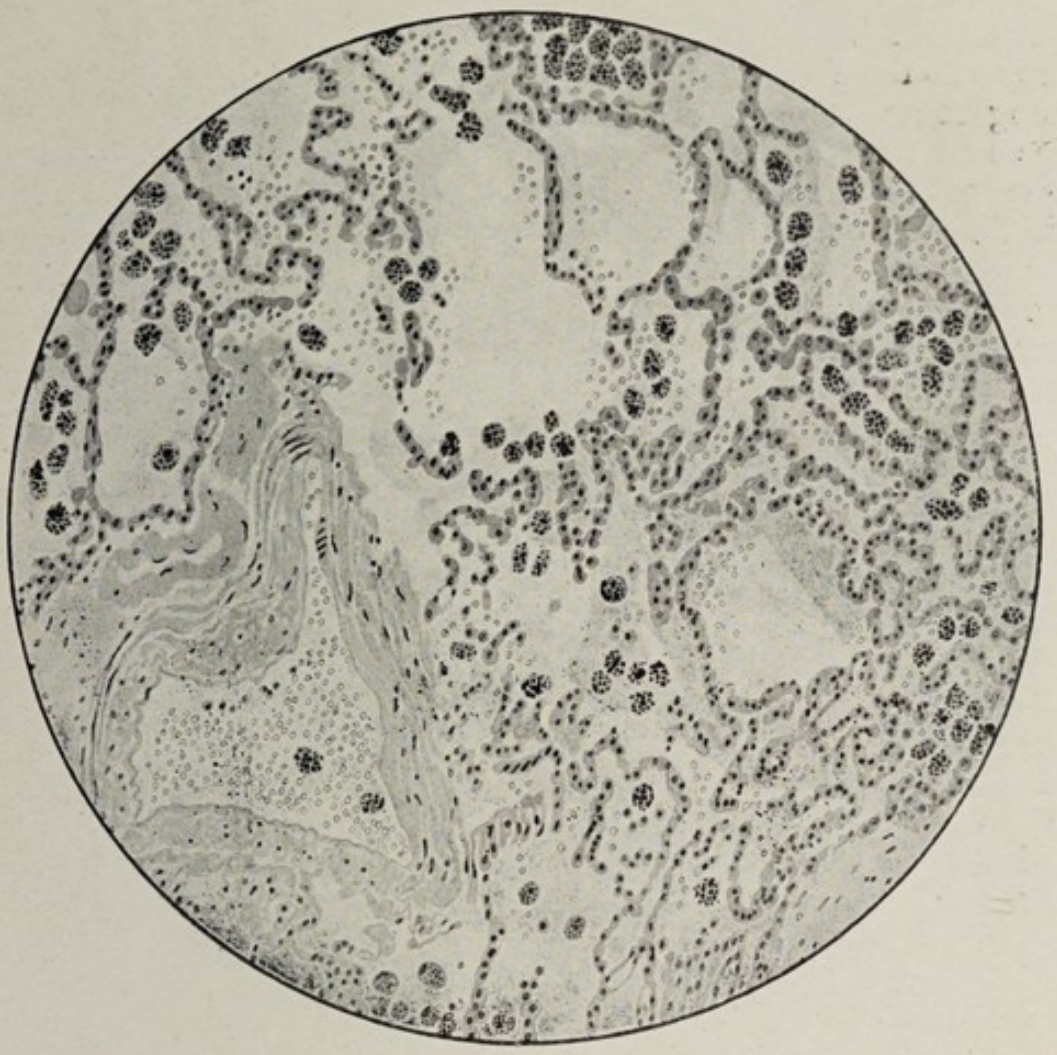


FIG. 140.—CHRONIC PASSIVE CONGESTION OF LUNG. (× 79.)

Lungs in which these changes are at all advanced present a more or less uniform brownish-red tint, mottled with brown or blackish-coloured specks and streaks. They are heavier, tougher, and denser, as well as less crepitant than normal.

ŒDEMA.

The normal tissues are continuously bathed in, and nourished by, the lymph, which derives its nutritive material from the blood, and passes on into that fluid the products it receives in exchange from the tissues. These products find their way, either by the veins or by the lymphatics, back to the heart, and thence to the lungs, skin, and kidneys. In all probability the veins are quite as much the soil-pipes of the tissues as the lymphatics. To state that there is, in all parts of the body, a constant circulation of lymph, transuding from the capillaries and returning by the lymphatics, is more than is justified by our present knowledge. In the dog, at any rate, we

know that during rest there is no flow at all from the lymphatics of the limbs. The lymphatics seem to perform most of their work during active exercise, or in any local emergency.

Formation of Lymph.—Lymph varies both in amount and in composition. The two factors which are mainly operative in determining these are—(1) the excess of the pressure within the capillaries over that in the tissues immediately around them; and (2) the special properties of the cells of the capillary walls.

1. The **capillary pressure** is, in general terms, a sort of resultant between the arterial and the venous pressure. It usually follows most closely that in the veins. If either the arterial or the venous pressure rise or fall, while the corresponding venous or arterial pressure remains *constant*, the capillary pressure will rise or fall too, as the case may be. If, however, one of them, either the arterial or the venous pressure, rise or fall while the other moves in a *contrary* direction, the resulting capillary pressure may rise, remain constant, or fall. Under such circumstances the capillary pressure is difficult to estimate. Most often, as has been said, it follows that in the veins. A statement regarding the arterial pressure alone is rarely a safe guide to the capillary pressure, partly for the reason just given, and partly because the arterioles may interpose an additional indeterminate factor.

2. The influence exercised by the **capillary walls** upon the production of lymph has been supposed by Heidenhain and others to be of the nature of an active secretory process, but by many it is still regarded as a passive factor, the efficacy of which depends only on the efficient nutrition of the vessel-walls. According to this second view, a vessel-wall is said to be more or less "permeable" in proportion to (1) the readiness with which it allows fluid to transude (sensitiveness to pressure); and (2) the resemblance which the transuded fluid bears to the plasma of the blood. Thus, so long as the pressure remains constant, the *permeability of the capillaries* determines both the amount and the composition of the lymph. For example, the capillaries of the liver are said to be more permeable than those of the intestine, and those of the intestine than those of the limbs. By this is meant that the same increase of pressure induced in each case will not be followed by identical results, but that there will be a marked increase of the lymph-flow from the liver, a less increase from the intestines, and the smallest increase of all from the limbs; and that in any case the lymph from the liver will contain more proteid matter than that from the intestines, and that from the intestines more than that from the limbs. The saline constituents are the same in all cases, and correspond in amount with that found in the blood-plasma. It is well known that ascitic fluid contains more albumen than œdematous fluid from the legs, and that this is so under all conditions, and does not depend on the disease producing the dropsy. *Damage*—such as dipping a limb into very hot water—increases the permeability of the capillaries, and, therefore, both the amount of fluid transuded and the resem-

blance which it bears to blood-plasma. It is probable that a somewhat similar, but less pronounced, change may be caused by gradual alterations in nutrition, due to the circulation of defective or vitiated blood, and that increased friction and greater permeability may result.

Heidenhain found that by introducing certain substances into the blood he could produce an increase in the flow of lymph. These substances he called "lymphagogues," believing that they in some way stimulated the supposed secretory power of the capillary walls. Starling has, however, shown that, in the case of dextrose, the first effect of its introduction is to cause a reabsorption of fluid into the bloodvessels, and a consequent increase in the total quantity of fluid they contain. This in its turn produces a rise in the venous, and therefore in the capillary, pressure; and to this increased pressure, rather than to any special secretory process, he attributes the additional lymph-flow. Starling further showed that if an amount of blood equal to the expected absorption—caused by the introduction of the dextrose—be previously withdrawn, no increase in the total amount of blood, no rise of the venous pressure, and no addition to the ordinary lymph-flow, will occur. It seems, therefore, that *permeability* should still be regarded as depending on a diminished power of retention rather than as an active secretory process.

In opposition to Starling's view it has been pointed out that increased flow of lymph may continue even after the pressure has fallen—in some instances even after death of the animal—so that the pressure alone cannot account for this flow. Asher believes that flow of lymph is influenced solely by the activity of the tissues, and that the capillary walls are always passive. This view does not help in explaining pathological œdema.

Nature of Œdema.—In popular language the term *dropsy* is applied to the retention of lymph, either in connective-tissue spaces or in serous cavities. The term *œdema* is clinically employed to denote accumulation of fluid in the connective-tissue spaces, while *anasarca* means œdema of the subcutaneous tissue. Thus we may speak of "general dropsy," "œdema of the lungs," "anasarca of the legs." Pathologically the term "œdema" is used for all these conditions.

It is practically certain that the causes of increased lymph-flow are also the causes of œdema. It is quite certain that the most marked examples of this condition are, in practice, associated with **marked increase in venous pressure** acting over a long period. Among these, *local obstruction* to the return of venous blood plays the chief part. This may be caused by the pressure of cicatricial tissue, or of a tumour, or by thrombosis. *Inefficient action of the heart*, such as that occurring in late stages of valvular disease, causes a fall in arterial, but a rise in venous, pressure, with a consequent slowing of the circulation. As the veins become distended, their valves become incompetent, and the action of gravity on the enlarged blood-column adds greatly to the pressure in the capil-

laries of the legs, and thus produces anasarca. A slighter form of œdema of the legs, in women whose occupation involves much standing, is due to the combined influence of constipation, garters, and gravity. In all these cases the passive congestion probably increases the *permeability* of the capillary walls. The certainty that the increased venous pressure is the cause of the œdema rests mainly on the constancy with which the dropsy disappears when the increase in pressure is removed.

Increased arterial pressure is sometimes credited with the production of œdema, but it is uncertain whether, in the absence of increased venous pressure, it is a sufficient cause. No convincing proofs of such a mode of causation have been given.

An experiment of Heidenhain's shows how fallacious it is to trust to arterial pressure as a guide to capillary pressure. By obstructing the thoracic aorta this observer enormously reduced the arterial pressure. Notwithstanding this reduction, he found that the combined lymph-flow from the intestines and liver together showed no proportional fall, though the lymph obtained included an appreciably larger amount of proteins. Heidenhain's inference was that no process of mere tissue-filtration could possibly explain the result. Starling repeated this experiment, but took the precaution of measuring the pressures in the portal vein and in the inferior vena cava, as well as in the femoral artery. He found that the enormous fall in the arterial pressure was accompanied by a considerable drop in that in the portal vein, but by a distinct rise in that in the inferior vena cava; so that, though the pressure in the intestinal capillaries was almost nil, the pressure in those of the liver was probably increased. He further showed that the flow of lymph from the intestines ceased, while that from the liver (normally the more concentrated) continued, as might have been inferred from the pressure-conditions. In this way the changes in capillary pressure were found to explain the alterations in both the quantity and character of the lymph.

The second great cause of œdema is at work in cases associated with the various forms of nephritis and deficient urinary secretion. In renal dropsy the exuded fluid contains a smaller percentage of proteins and a larger percentage of extractives than in that due to increased venous pressure, although the same proportionate difference between the composition of the ascitic and subcutaneous fluid obtains. Probably the dropsy is due to the action of some toxic substances upon the capillary-walls, whereby their permeability is increased. There is, however, no constant relationship between dropsy and uræmia, which is also believed to depend on a similar cause. It has been suggested that in these cases there are substances circulating in the blood which act like the experimentally-injected dextrose, and that these substances produce a condition of *plethoric hydræmia—i.e.*, an increase in the total volume of the blood owing to increase in the fluid plasma—with a consequent general rise of blood-pressure, followed by œdema. Recent experi-

ments tend to show that in chronic renal disease there is deficient excretion of sodium chloride, which consequently tends to accumulate in the tissues. The œdema of Bright's disease may be consequent upon this accumulation, which may cause withdrawal of fluid from the blood into the spaces of the connective tissue in order to reduce the concentration of the saline fluid here present.

In cardiac failure there must be some hindrance to the exit of lymph from the thoracic duct, and this may be an adjunct in dropsy due to cardiac causes. Local pressure on the lymphatics does not usually produce œdema, though the occasional presence of chyle in the urine, or in the pleural or peritoneal cavities, is generally attributed to blocking of the respective lymphatics by growths or parasites, or to rupture of the thoracic duct or receptaculum chyli.

In anæmia, neuralgia, exophthalmic goitre, tumours of the spinal cord, and other diseases, slight degrees of œdema are occasionally met with. Section of the spinal cord produces vaso-constrictor paralysis, and tumours probably act in a similar manner. In the other conditions mentioned vaso-motor derangements are common, and though their cause is less definitely ascertained, paralysis of vaso-constrictor, or direct action of vaso-dilatator nerves is probable, and would furnish a sufficient cause. Experimental anæmia gives rise to no increased lymph-flow, but it does not follow that defective blood acting over a long period might not increase the permeability of the capillaries. Experiments on the spinal cord, and on the splanchnic and vagus nerves, have hitherto failed to afford satisfactory evidence of the existence of any nervous cause of œdema apart from vaso-motor changes.

Localised areas of œdema of the skin are met with in the condition known as *urticaria*. This disease is often associated with the presence of toxic matter in the blood, derived as a rule from the alimentary canal. In some instances a similar condition is apparently produced by the action of the nervous system, slight stimulation of the skin (pressure) being followed by the appearance of urticarial weals (*urticaria factitia*).

THROMBOSIS.

Thrombosis is the *coagulation* of the blood within the vessels during life. The product is called a **thrombus,** in opposition to a *coagulum* or *clot,* the result of post-mortem coagulation. Thrombosis may occur in the heart, arteries, capillaries, and *especially in the veins.* It is by no means certain that the process of coagulation is the same in all cases.

CAUSATION.—Thrombosis is generally said to be due to one or more of *three causes* : damage or absence of the lining cells of the vessel-walls; retardation of the blood-stream; and changes in the blood itself, increasing its coagulability.

I. Damage or Absence of the Lining of the Vessel-Wall.—When coagulation of circulating blood occurs, it is usually upon some

obviously diseased surface. In contact with the smooth lining endothelium of the healthy vessel-wall the blood has no tendency to coagulate, just as it may be kept fluid for long periods in contact with such substances as vaseline, paraffin, and castor oil. When, however, it touches rough solid matter to which the corpuscles can adhere, coagulation occurs, and the same effect is produced by roughening of the vascular endothelium in disease, but here ferments may also be at work, derived from damaged cells.

Fatty and calcareous changes of the deeper structures of the vessel-wall do not cause thrombosis so long as the endothelium is intact; but atheromatous ulcers, foreign bodies, and nodules of new growths—all uncovered by endothelium—may do so; moreover, severe injury of capillaries, which possess only endothelium, causes thrombosis in them. Thus, *damage or absence of the endothelium* of the bloodvessels is the most important condition in the production of thrombosis. This damage or absence, as already stated, may be due to many causes.

1. *Injuries may destroy or injure the endothelium.* Among the most important of these are section, rupture, ligature, and torsion of vessels. In section and rupture, thrombosis starts from the damaged intima, and constitutes part of the process by which hæmorrhage is naturally and temporarily arrested. Cauteries and caustics furnish other examples of the effect of injury in producing thrombosis.

2. *Diseases of the vessel-walls may affect the endothelium.* Thus, thrombosis may occur on atheromatous ulcers, on bare calcareous plates, or on an intima damaged by syphilitic inflammation, or by the extension of spreading inflammations from other parts.

Venous thrombosis is a frequent complication in many chronic wasting diseases, specific fevers, and other disorders, and in many of these cases it is difficult to be certain of the causes at work. Pyogenic or other micro-organisms are present in most of the thrombi occurring in these cases, and in some of the instances there is but little doubt that an infective phlebitis has preceded the thrombosis (Welch). The organisms may be derived from the blood circulating in the affected veins, and may first cause necrosis of the endothelium, thus giving rise to fibrin-ferment, while, later on, they lead to inflammatory changes in the vessel-wall. It is possible that in other cases the organisms may reach the vessels by way of the vasa vasorum or lymphatics.

3. *The presence of foreign bodies in the vascular system.* These comprise such things as needles, horsehair, or wire introduced into the sac of an aneurysm; pre-existing clots (thrombi or emboli); parasites, such as Distomata, which have penetrated the vessels; and new growths which project into the interior of veins. In all these instances the thrombus forms first upon the foreign substance itself. The roughness of the surface of the foreign body seems to be a factor of some importance. Zahn introduced small glass balls without producing any thrombosis.

II. Retardation of the Blood-Stream.—Sometimes the causes just considered (abnormality of surface) are insufficient to cause extensive clotting, until retardation of the blood-stream is added. For example, in the *aorta* we sometimes find calcareous plates uncovered by endothelium, but with little or no adherent fibrin. In *aneurysms*, too, the wall is always abnormal and the circulation somewhat retarded; but sufficient clotting to effect a cure may not occur until, by treatment, we still further reduce the current, and thus prolong the contact of the blood with the abnormal surface. In *veins*, however, where the blood-current is slow, slight lesions in the walls are rapidly followed by thrombosis.

On the other hand, retardation, or even arrest, seems unable by itself to produce thrombosis. So long as the endothelium is kept fairly nourished, and the blood is of normal quality and free from micro-organisms, the stagnant blood does not coagulate.

A tendency to stagnation of blood may be due to many causes, of which the most important are cardiac weakness, general diminution of vascular tonus, and dilatation (*varix*) of veins. All these are often present in a single case, and, combined with the action of micro-organisms, are the principal factors in the causation of the "marasmic clots" of Virchow. These form *in the most dependent veins*—*e.g.*, those of the lower limb, pelvis, or back; *in the cerebral veins and sinuses* where the venous circulation is ordinarily very slow and difficult; and *in those parts of the heart* in which blood tends to remain when the organ first fails to contract efficiently—*e.g.*, the auricular appendices, the apices of the ventricles, and the spaces between the trabeculæ. In veins these clots begin just behind the flaps of valves (Fig. 141). The force of the venous current is so slight, or the resistance to it so great, that it no longer opens the valves completely; the blood consequently stagnates, and, after a time, coagulates behind the cusps. Such clots occur in the course of many exhausting diseases—as phthisis and cancer—in which thrombosis is materially facilitated by the quiescent state of the patient.

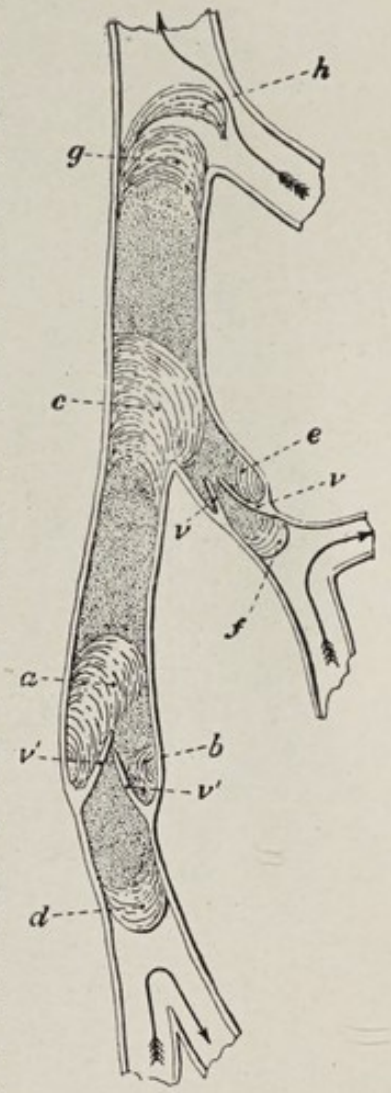


FIG. 141.—DIAGRAM TO SHOW PHENOMENA OF VENOUS THROMBOSIS. (MODIFIED FROM THOMA.)

v v', valves of veins; *a*, *b*, primary thrombus (white); *c*, *d*, *e*, *f*, *g*, secondary white thrombi connected with primary white thrombus by various red thrombi; *h*, piece of white thrombus becoming detached by blood-current.

In varicose veins, which are frequently the seats of thrombosis, the circulation is extremely slow, and the endothelium, owing to imperfect nutrition, can scarcely ever be healthy, though it is not always so damaged as to excite coagulation.

III. Certain Conditions of the Blood seem to favour coagulation and to promote the occurrence of thrombosis. It is said that the tendency to coagulation is increased during the later months of pregnancy, after profuse hæmorrhage, and in certain acute inflammatory diseases, such as acute rheumatism, erysipelas, pneumonia, and pleurisy. The only two ascertained changes in the blood, likely to lead to thrombosis, are (1) the presence of micro-organisms, and their products, and (2) an increase in the platelets. The *platelets* may be found in large numbers at the end of many of the acute fevers, constituting a "platelet-crisis" (Hayem), while a moderate increase has been often observed in anæmia, splenomedullary leucocythæmia, and other diseases. To whatever cause it may be due, an increased tendency of the blood to coagulate is probably never more than a predisposing cause of thrombosis.

It is well known that the presence of calcium salts is essential to the coagulation of the blood; while the addition of oxalates will neutralise the effect of their presence and prevent coagulation. So also, among the products of cell-action, substances allied to nuclein aid coagulation, while albumoses hinder it. The bearing of these facts upon the phenomena of thrombosis is at present unknown.

Characters of Clots and Thrombi.—Post-mortem coagula in the *heart* are generally *buffy*. The thickness and firmness of the pale layer generally varies with the time which elapses before the changes in the heart-substance allow coagulation to begin, but is to some extent dependent on the tendency of the red corpuscles in certain diseases—*e.g.*, pneumonia—to form dense clumps instead of more open meshes or rouleaux: its position indicates the part that was uppermost after death. Though not adherent, the clots are often so much entangled among the chordæ and trabeculæ, that they cannot readily be removed. Post-mortem clots in the *vessels* are *red*, *soft*, and never adherent. They do not *fill* the vessels, and can be easily drawn out of them as long strings.

Thrombi, or **ante-mortem clots,** are of two kinds—**red** and **white,** according as they originate from *stagnant* or from *circulating* blood.

In the former case, as seen in an artery or vein after ligature, more or less of the stagnant blood on either side of the knot coagulates into an ordinary **red** clot—soft, uniform on section, and adherent to the vessel-wall where this is injured. The thrombus, still adhering to the wall, then contracts, becomes drier and less elastic, but still remains red. This is the state in which a red thrombus is generally found. If the surface of a *red* thrombus be exposed to circulating blood, a layer of *white* thrombus may be deposited on it (Fig. 141).

When coagulation occurs in blood *which is still circulating*, as in the sac of an aneurysm or on a cardiac vegetation, a **white** or **mixed** thrombus results.

This is made up of a mass of blood-platelets, fibrin and leucocytes. According to Welch, the first deposit in a white thrombus consists of platelets in the form of pale roundish bodies, in size averaging a quarter of that of a red corpuscle. In a short time, between and at the edges of the masses of platelets, a deposit of uninjured multinucleated leucocytes begins, and shortly afterwards fibrin appears at the same places. Ordinary *white thrombi* are greyish-white or reddish in colour, firmly adherent to the vessel-wall, and usually stratified. Examined microscopically, they are found to consist of granular masses made up of altered platelets, and separated from one another by fibrin, leucocytes, and a larger or smaller number of red corpuscles.

A thrombus may be either *parietal* (forming one or more laminæ attached to the vessel-wall) or *obstructive* (completely filling up the lumen), thus causing either partial or complete occlusion of the vessel. A *parietal* thrombus is always of the white variety, while an *obstructive* thrombus may be either *red* or *white*. Once formed, both varieties extend in the same way, by the formation of a red thrombus where the blood is stagnant, and by the deposition of platelets, fibrin and leucocytes where it is circulating. A parietal may be thus converted into an obstructive thrombus. The extension of the latter is generally checked by the rapidity of the blood-current at the junction of the first large collateral branch in each direction (Fig. 141); but sometimes, especially in veins, the thrombosis continues, and a clot may extend from the veins of the foot to the vena cava. Both in arteries and veins, extension is most likely to take place in the direction of the circulation, though it may occur in an opposite direction. Obstructive thrombi generally adhere to the wall throughout their whole length, but sometimes they do so only at their points of origin.

A few rare forms of thrombus are occasionally met with: (1) *Hyaline thrombi.* In the smallest vessels, and especially in the capillaries, there are sometimes found refractive homogeneous translucent plugs, readily coloured dark blue with Weigert's fibrin-stain. These are probably derived either from platelets or directly from red corpuscles. (2) *Fibrinous thrombi.* Masses of fibrin are occasionally found blocking the smaller vessels, especially in the consolidated portions of the lung in acute pneumonia. (3) *Leucocytic thrombi.* Vessels are sometimes found filled with leucocytes, but it is doubtful if these should be regarded as true thrombi.

Final Changes in Thrombi.—Thrombi may remain with but little change beyond *decolorisation*, or they may undergo *softening* or become *organised*.

Decolorisation.—The first change in a red thrombus is a breaking-down of the red corpuscles. Their stromata become unrecognisable, and the hæmoglobin is set free and in great part absorbed,

though some may remain as granular hæmatoidin. As a result, the thrombus loses its deep red colour, and acquires a finely mottled reddish-grey tint. The process begins in the centre, and takes weeks or months before it is completed.

Long thrombi, such as occur after ligature of the lower part of the carotid, as well as large laminated thrombi, like those in aneurysms, may remain for long periods as more or less granular masses of fibrin, without any sign of organisation or of softening.

Calcification may occur in these thrombi as a late change, and thus give rise to *phleboliths*. These are especially common in the prostatic plexus.

Softening.—That thrombi can disappear and leave the lumen of the vessel pervious is certain; for when it was the custom for venesection to be performed at regular intervals, the repeated bleedings were frequently effected from the same vein. In modern times also, re-establishment of the circulation is known to have occurred through the spermatic veins and through the superficial veins in the leg, in cases where thrombosis had undoubtedly taken place.

The process by which this occurs is not known, but in a large number of cases it is probably the result of some form of softening process. Softening may be *simple* or *infective*. Infective softening is invariably due to pyogenic or putrefactive organisms.

1. *Simple Softening*.—The changes commence by the disintegration of the centre of the thrombus and by the formation of a more or less fluid, pappy substance, which has a reddish-grey colour, varying with that of the thrombus which is undergoing the change. To the naked eye the fluid often looks like pus, and the process is still sometimes spoken of as the "puriform" softening of a clot. But Virchow long ago pointed out that the fluid consisted of the débris of corpuscles and fibrin—albuminous, fatty, and pigmentary granules. There may be a few recognisable white corpuscles in it, which have probably migrated from without. In cases of constriction of the mitral orifice of the heart, with consequent dilatation of the left auricle and slowing of the circulation, large clots undergoing this change may be found in the auricles. They consist of little more than bags of thick, grumous fluid. The outer laminæ generally form a firm case for the softened central part, and if the softening approach the surface, this case is often thickened at that point by the formation of fresh protective clot. Not infrequently, however, the encasing clot may be perforated and the contents discharged into the circulation. The larger particles may form emboli, probably too minute to cause symptoms. When the contents of an obstructive thrombus occurring in an artery or vein are thus discharged, the circulation in the vessel may be re-established through the centre of the thrombus. This process constitutes one form of *canalisation* of a thrombus.

2. *Infective Softening*.—Certain cases of *puriform* softening, similar, so far as the naked eye can detect, to the above, are accom-

panied by all the symptoms of septic poisoning. The wall of the affected vein is found acutely inflamed, and often converted into granulation-tissue, from which pus may be formed; while any portions of the clot which enter the circulation are so charged with organisms that suppuration ensues wherever they are lodged. (See p. 229). In many cases, however, no direct infection can be traced.

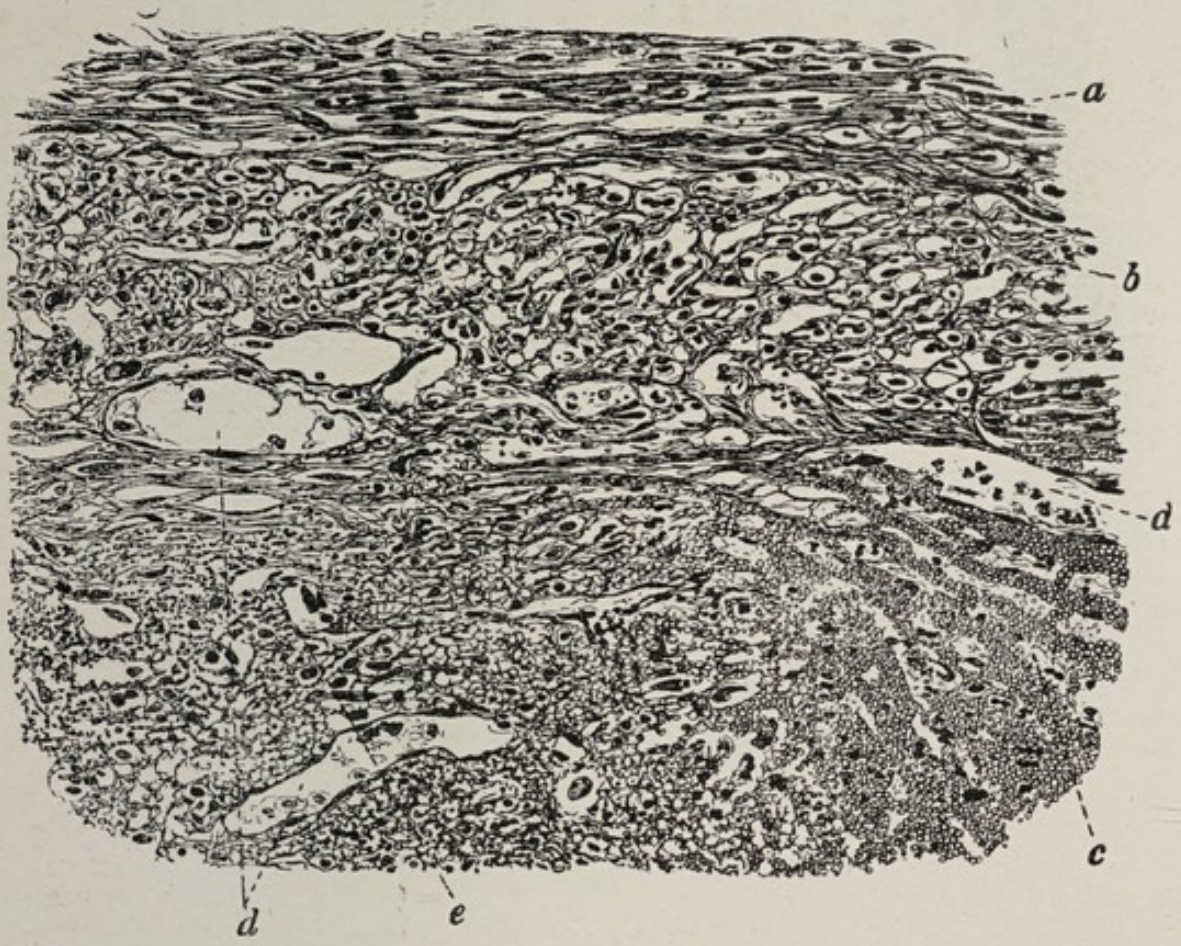


FIG. 142.—ORGANISATION OF A THROMBUS. (× 200.) (FROM A SPECIMEN BY DR. J. D. ROLLESTON.)

a, middle coat of vein; *b*, proliferation of cells of internal coat; *c*, portion of unaltered thrombus infiltrated with leucocytes; *d*, spaces lined by endothelial cells forming the new vessels in the organised thrombus; *e*, site of old thrombus now occupied by spindle-cells and fibrillated tissue.

Organisation.—Organisation of thrombi is most frequently observed in arteries which have been ligatured. By this procedure the middle and internal coats are divided; the cut ends of these at once retract and become inverted, while a red thrombus forms on each side of the ligature, extending from the divided ends until it almost for quite reaches the first collateral branch. The thrombus thus ormed undergoes the changes describe d under decolorisation, and gradually disintegrates, playing a purely passive part in the subsequent process. The cut ends of the vessels undergo proliferative

inflammatory changes. The intima becomes thickened, and the internal elastic lamina obscured and in places broken up. The clot becomes gradually invaded and replaced by new cells derived from the endothelium and fixed connective-tissue cells of the vessel (Fig. 142) by what is apparently a proliferative inflammation. Channels lined with these cells traverse the clot, and here and there separate it from the vessel-wall (Fig. 143). These ultimately form blood-

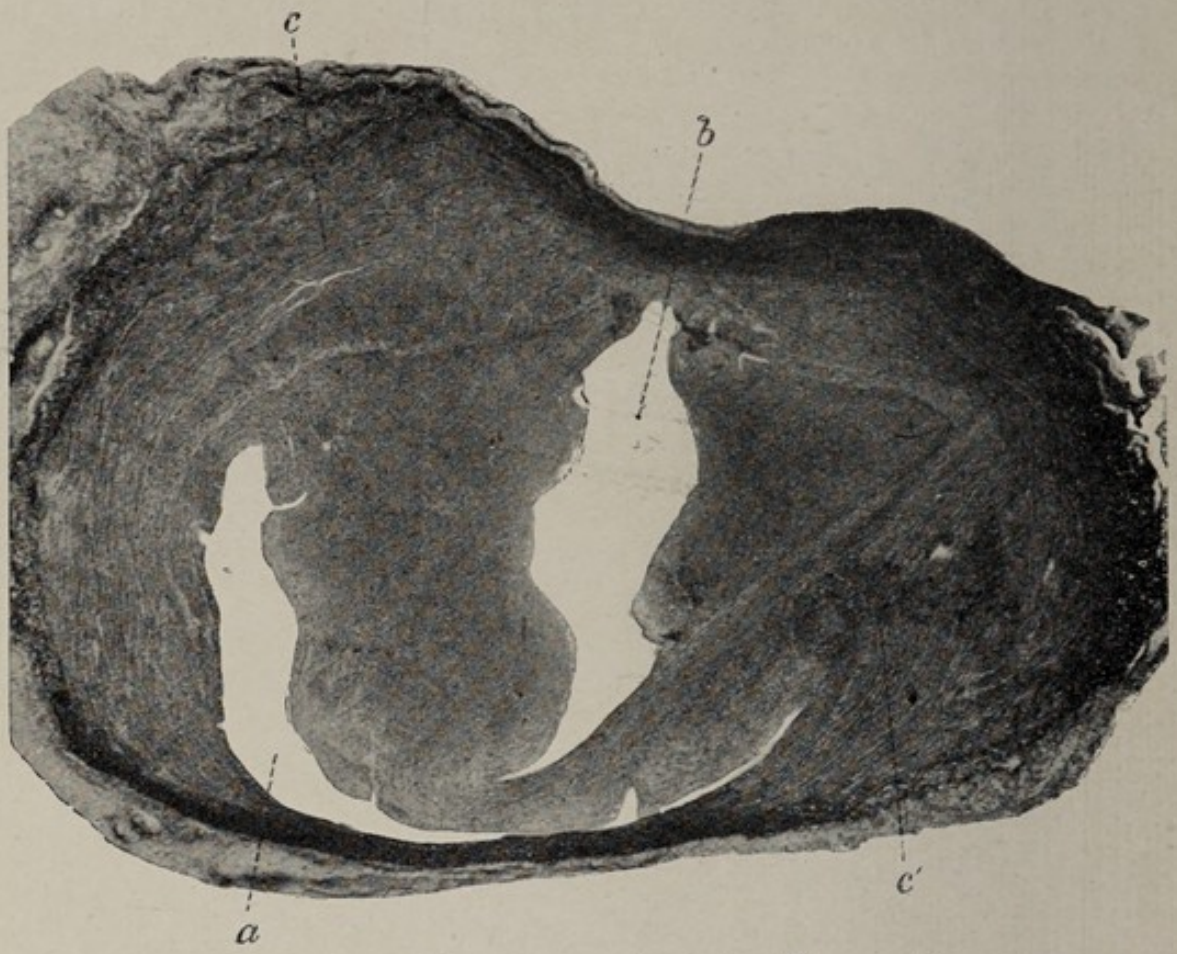


FIG. 143.—ORGANISED THROMBUS. (× 15.) (FROM A SPECIMEN BY DR. H. D. ROLLESTON.)

The thrombus is replaced by a mass of fibrous tissue lined with endothelium. Two large channels have been formed, one (*a*) between the wall of the vein and the thrombus; the other (*b*) through the thrombus (canalisation). Where the organisation is most complete (*c*, *c'*) the wall of the vein is thickest.

vessels connected with the now enlarged vasa vasorum, by means of vessels entering by the cut end or by the spaces where the internal elastic lamina has disappeared. The vessels and channels in the clot occasionally communicate with the blood in the ligatured vessel; eventually the clot becomes entirely replaced by fibrous tissue, reducing the affected portion of the vessel to a mere cord. In venous thrombosis the vessels and channels in the thrombus may communicate with the lumen of the vessel on both sides. In this way, by another form of *canalisation*, the circulation may become more or less completely re-established. This is especially

frequent at the junction of the common iliac veins in cases of *white leg* (*phlegmasia dolens*). It is rare in arteries. Complete organisation depends to a large extent upon the nutrition of the affected vessels, the maintenance of asepsis, and the general health of the patient.

RESULTS.—The results of thrombosis comprise certain changes in the walls of the vessels, more or less obstruction to the circulation, and embolism. These must be considered separately.

1. **Changes in the Vessels.**—Changes in the wall of the vessel are an invariable consequence of the formation of a thrombus. The changes which occur in the *organisation of a thrombus* are really changes in the vessel-wall; and when the thrombus undergoes a process of *infective softening*, acute inflammation takes place in the vessel-wall. In many cases, however, the inflammation precedes as well as follows the thrombosis, and must be regarded as its immediate cause.

2. **Obstruction to the Circulation.**—The consequences of the obstruction to the circulation, resulting from the formation of a thrombus, will depend upon the rapidity and manner of its formation, the nature and size of the vessel obstructed, the situation and number of the collateral branches, and the force of the circulating current. The rapidity with which the obstruction is affected is of considerable importance, inasmuch as the more gradual the process the longer is the time allowed for the establishment of a collateral circulation. For this reason the interference with the circulation caused by thrombosis is, for the most part, less marked than that which results from the more sudden obstruction caused by embolism.

The obstruction to the circulation may lead, in the case of an artery, to (1) *necrosis* of the tissues supplied by it (Chapter II.), with or without *infarction* (p. 367), and, in the case of a vein, to (2) *œdema*. Necrosis is especially likely to result from obstruction in the *cerebral vessels*, as the nutrition of highly specialised tissues, like the brain, suffers directly their blood-supply is interfered with. Infarction is a more frequent sequel of embolism than of thrombosis, and will be considered in the next section.

In the *veins*, when thrombosis occurs in a vessel of small size and when collateral branches are numerous, as in the prostatic or uterine plexuses, the circulation is but little interfered with, and no symptoms of obstruction result. If, however, the main trunk of a large vein, as the ilio-femoral, becomes obliterated, the obstruction is followed by passive hyperæmia and œdema, the extent and duration of which will depend upon the facility with which the circulation can be restored by the collateral vessels. It must be remembered, however, that the valves in veins (when they exist) may, by preventing back-flow, offer a great impediment to collateral circulation. Thrombosis in the ilio-femoral vein frequently occurs, as already stated, in the later stages of many chronic debilitating diseases, especially in phthisis and in enteric fever; also in the puerperal state, where it is frequently found in

phlegmasia dolens. The extent of the *thrombus*, the number of collateral branches which it blocks, and the strength of the circulation, will do much to account for the amount of œdema. The results of obstruction in arteries are considered elsewhere (p. 367).

3. **Embolism.**—Portions of the thrombus may be carried away by the circulation, thus constituting embolism. This, which is the most important result of thrombosis, will be considered in the following section.

EMBOLISM.

Embolism is the impaction of solid substances, circulating in the blood, in vessels which are too small to allow them to pass. A mass thus arrested is termed an *embolus*.*

The most frequent sources of emboli are (1) *venous thrombi*, portions of which are carried by the blood-stream from the seat of their formation. The other sources are: (2) fragments, especially of thrombi, detached from the walls or inflamed valves of the heart (see Endocarditis), or less frequently from the inner surface of arteries; (3) portions of new growths—as sarcomata—which, having perforated the vessels, have been carried away by the current; and very rarely (4) parasites which have made their way into the interior of vessels. (5) Fluid fat which has escaped from the fat-cells and entered open lymphatics—an occasional occurrence in fractures and contusions—may perhaps produce embolism, but the possibility of this occurrence is doubtful.

A **thrombus** may produce emboli in various ways. (1) It may soften and break down, and its fragments be distributed by the blood-current. (2) Portions of a parietal thrombus, not filling the vessel, may be detached by the passing stream. (3) *The most frequent way* is that illustrated by the accompanying diagram. A thrombus usually ceases at the junction of the vessel containing it with the first large collateral branch. The end of the thrombus—in arteries as well as in veins—nearest to the heart often extends as a firm conical projection into the lumen of this collateral branch (Fig. 144); and the strength of the blood-current, which is the chief factor in preventing the further extension of the clot towards the heart, may break off this projecting end and sweep it into the general circulation. Some sudden movement or exertion often determines, in these cases, the separation of the fragment which is to form the embolus. Thrombi in the veins of the lower extremities, in the uterine veins, and in the jugular veins are the most frequent sources of this accident.

Emboli become arrested in the first vessels which are too small to allow them to pass. Usually, therefore, the seat of impaction will be at the bifurcation of a vessel, or at some point where, from the giving off of large branches, the calibre diminishes suddenly (Fig. 145). The particles may be so small as to pass through even

* ἔμβολος, a plug.

the finest capillaries, and not give rise to any symptoms; or they may pass through large capillaries, like the pulmonary, to be arrested in a finer set beyond; but, as a rule, they are impacted either in the first set of capillaries to which they come, or in some larger vessel between these and their seat of origin. Thus emboli originating in the systemic veins, in the right cardiac cavities, or in the pulmonary artery, will most commonly become arrested in the vessels of the lungs. Emboli originating in the pulmonary veins, in the left cardiac cavities, or in the arteries, will be similarly impacted in the systemic arteries and capillaries, especially in those of the spleen, where the circulation is slow; and of the brain and kidney where the capillaries are very small. Finally, emboli originating in any of the organs supplying the portal venous system will block branches of the portal vein in the liver. With the exception, therefore, of emboli originating in the portal system, the seat of arrest is usually the arteries or capillaries.

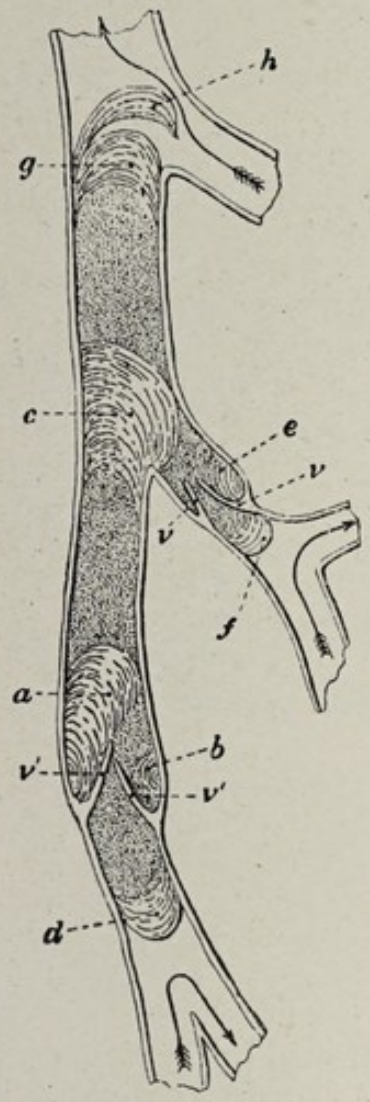


FIG. 144.—DIAGRAM TO SHOW PHENOMENA OF VENOUS THROMBOSIS. (MODIFIED FROM THOMA.)

v, *v'*, valves of veins; *a*, *b*, primary thrombus (white); *c*, *d*, *e*, *f*, *g*, secondary white thrombi connected with primary white thrombus by various red thrombi; *h*, piece of white thrombus becoming detached by blood-current.

FIG. 145.—EMBOLUS IMPACTED AT THE BIFURCATION OF A BRANCH OF THE PULMONARY ARTERY, SHOWING THE FORMATION OF THROMBI BEHIND AND IN FRONT OF IT, AND THE EXTENSION OF THESE AS FAR AS THE ENTRANCE OF THE NEXT COLLATERAL VESSELS. (VIRCHOW.)

E, embolus; *t*, *t'*, secondary thrombi.

Emboli are usually carried in the direction of the main current; hence those carried by the aortic stream pass into the thoracic aorta more commonly than into the carotid or subclavian vessels, and into the left carotid or left renal artery more often than into the corresponding artery of the opposite side. Gravitation also influences the direction in which they are carried, especially those of large size, which move somewhat more slowly than the blood-stream; hence, they are more common in the lower lobes and posterior parts of the lungs than in the superior and anterior portions of these organs (p. 373). It is found experimentally that small bodies injected at intervals into the jugular vein are often swept into the same division of the pulmonary artery.

It is not uncommon to find that the small vessels of an area, of which the supplying artery is plugged, also contain emboli. This may be accounted for in *two* ways. *First*, if, as is frequently the case, the arrest takes place at a point of bifurcation, the embolus may not be large enough to block either branch, but may allow a small stream of blood to pass into each vessel; this may break off portions of the original embolus, and so produce secondary emboli, which become impacted in the smaller divisions of the same main trunks. The *second* mode is by the detachment of several small fragments from some distant source, which subsequently yields a mass large enough to block the main trunk.

The amount of obstruction which immediately follows the arrest will depend upon the *nature* of the embolus as well as upon its size and shape. If the embolus be from a soft, recently-formed thrombus it will be at once moulded to the cavity of the vessel, which will thus be immediately and completely plugged. If, on the other hand, it is irregular in shape and firm in consistence, as when derived from a calcified cardiac vegetation, it may not completely fill the vessel, but may allow a slender stream of blood to pass.

The arrest of the embolus, and the consequent obstruction to the circulation, is followed by the formation of *thrombi* (secondary) behind and in front of it, which extend as far as the junction of the first large collateral vessels (Fig. 144). If the embolus does not completely fill the vessel, successive layers of thrombus are deposited upon its surface until the occlusion of the vessel is complete, and then the secondary thrombus extends, as in the former case, until it meets with a current of blood strong enough to arrest its progress. If the embolus be a portion of a red thrombus, it will in most cases be impossible to distinguish it from the secondary thrombus which surrounds it. If, however, it is a calcareous mass, or a portion of a white thrombus, it may usually be distinguished from the more recent secondary coagulum.

Fragments of a damaged liver have, in rare cases, been carried from the right auricle through a patent foramen ovale, and thus lodged in the kidney or the brain without passing through the lungs. To this phenomenon the name of *paradoxical* or *crossed embolism* has been applied. In other equally rare instances,

portions of venous thrombi or of new growths projecting into the interior of the veins seem to have made their way upstream towards the capillaries. This procedure is possibly due to some intermittent and local reflux of blood. The condition is known as *retrograde embolism.*

Emboli, derived from thrombi, may undergo the same secondary changes as the latter (p. 359).

EFFECTS.—The results of embolism may be divided into (1) those depending upon obstruction to the circulation, and (2) those due to the composition of the emboli.

I. Effects due to Obstruction to the Circulation.—Sudden and complete arterial obstruction may produce (1) no noticeable effects beyond certain changes in the vessels, such as are necessary for the restoration of the circulation under the altered conditions; (2) slight damage to the tissue-elements, in some cases only noticeable from the consequent functional defects; or (3) necrosis of the whole area supplied by the obstructed vessel. These effects again depend upon (1) the extent of the arterial anastomoses, (2) the readiness with which these can be utilised, and (3) the dependence of the affected part on its blood-supply.

1. *Extent of Arterial Anastomoses.*—When the arterial anastomoses are free and the vessels concerned are healthy, the sudden and complete obstruction of an artery, such as the radial, is followed by contraction of the central end of the obstructed artery—from the site of the block to the nearest collateral branch—and by dilatation of the arteries in the area supplied by the blocked vessel, as well as of those through which blood can be conveyed to them. The dilatation of the latter vessel follows, and possibly depends upon, increased velocity of the blood-stream (Thoma); and both changes are probably due to the lowered resistance in the anastomosing vessels, and not to increased pressure from behind, as is shown by the contraction of the upper part of the obstructed vessel already alluded to, and by the limitation of the increased blood-flow to those arteries which actually supply the anastomosing vessels.

Infarction.—In some organs, such as the spleen and kidney, the arteries have capillary, but no arterial, anastomoses with the neighbouring vessels. Such arteries are called *end* or *terminal* arteries. Each of these arteries supplies a conical compartment of the organ in question. The base of the cone is on the surface of the organ, while its apex points towards the centre, and corresponds with the point at which the artery enters and the vein emerges. The possible means of access which the blood has to such a portion of tissue are: the main artery and vein just mentioned, the small vessels passing from the capsule into the cortical part of the organ, and the capillary anastomoses with the neighbouring vessels on each side.

If the main artery supplying one of these conical segments of tissue becomes blocked, necrosis and degenerative changes will occur in it; for the capsular vessels and the lateral anastomoses together are unable to maintain the nutrition of the part. If the

tissue thus deprived of blood be freely supplied with coagulable lymph, it will undergo coagulation-necrosis, and form a pale, solid, clearly-defined cone, known as a **white infarct** (Fig. 146). In some organs and under some circumstances the necrosed area will gradually become infiltrated with red corpuscles, and a blackish-red cone with a slightly raised base will be formed. This is known as a **red infarct** (Fig. 149). Recent infarcts of both kinds are surrounded by a hyperæmic zone (Fig. 146). *Red infarcts* are common in the lungs and intestine, and *white infarcts* in the kidney and retina. Infarcts in the spleen and in the muscular walls of the heart may be white or red. When no coagulable lymph is present, as in the brain, necrosis occurs without infarction.

Later Changes in Infarction.—In the case of a small red infarct, *if the embolus is free from virulent organisms*, the coagulated blood gradually loses colour, becoming brown or yellow, and absorption proceeds slowly. In the case of a similar small white infarct, the

FIG. 146.—WHITE INFARCT OF THE KIDNEY.

The whole of the pale area is necrosed, and the darker central part is undergoing secondary changes. The dark area outside is due to hyperæmia.

tissue-changes are more clearly seen than in the red infarct, where they are obscured by the extravasated blood. In the white infarct, lymph reaches the part by transudation from parts around; the cells swell, lose their nuclei, and blend—in fact, undergo coagulation-necrosis and autolysis (p. 22): thus the well-known white wedges are formed. The more external portions of this mass of coagulated blood and necrosed tissue become infiltrated with multinulceated and mononuclear leucocytes, and external to this is an area of hyperæmia (Fig. 147). The necrosed cells are gradually disintegrated and absorbed. The peripheral zone of leucocytic infiltration is subsequently replaced by fibroblasts and later by fibrous tissue; this contracts, and ultimately a depressed scar may be all that remains to indicate the change. The central parts of a large infarct may liquefy and form a cavity, but the general changes and ultimate results are the same.

If pyogenic cocci are present, suppuration will follow, and the infarct becomes converted into an abscess.

2. *The effects of arterial obstruction will also depend upon the readiness with which the existing anastomoses can be utilised.* Bier

maintains that there is a marked physiological difference between the limbs and the viscera in this respect—the existing anastomoses being readily available in the limbs, but not in the viscera. In some instances, however, the inefficiency of existing anastomoses is capable of a mechanical explanation. Spasm of the intestine interferes with the circulation in its walls (Mall), and spasm of the intestine is one of the earliest results of embolism of the superior mesenteric artery. The spasm is, therefore, a sufficient reason for the failure of the anastomoses to preserve the nutrition of the

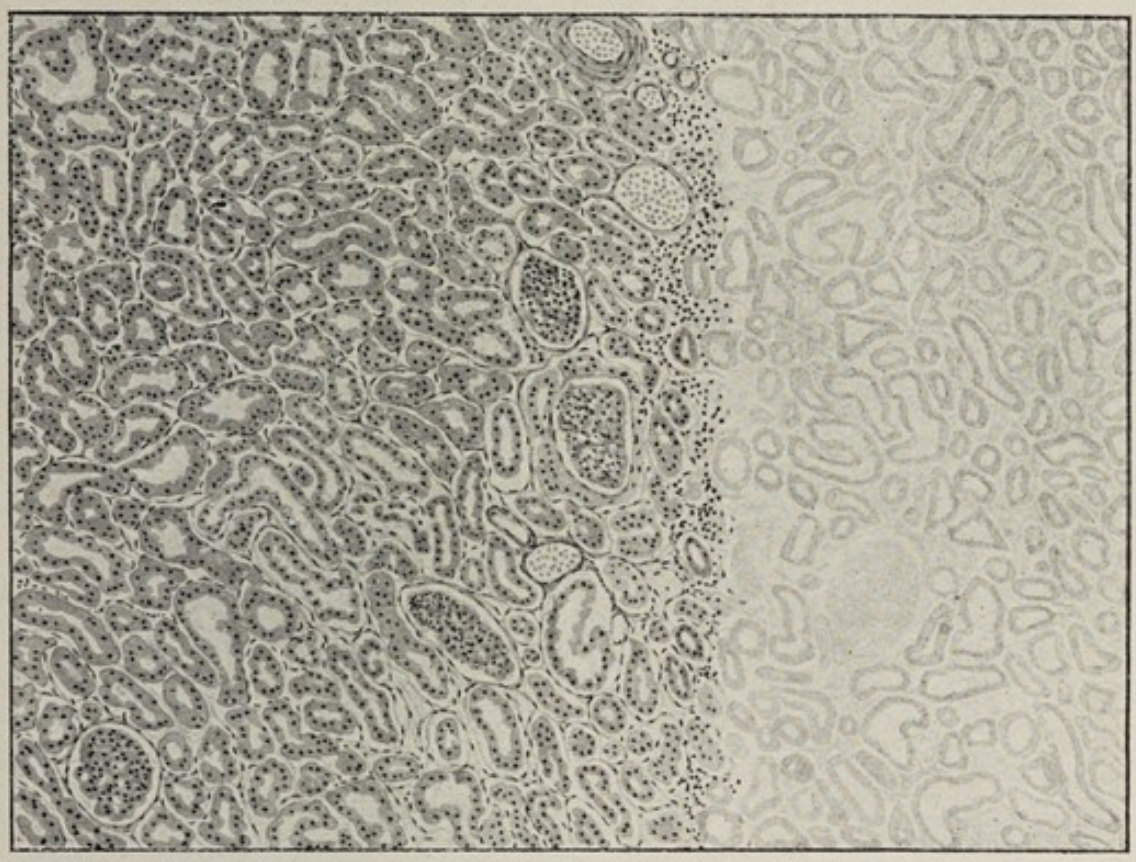


FIG. 147.—INFARCT OF KIDNEY. (× 79.)

Section through marginal zone. To the right is the necrosed tissue, adjacent to this the zones of infiltration and hyperæmia.

intestine, which generally undergoes gangrene when a branch supplying more than two inches of its length is blocked.

Calcification or other disease of the anastomosing vessels, or of the arteries supplying them, by preventing dilatation may interfere with the restoration of the circulation in the affected part, and thus lead to gangrene.

¶3. *The organs in the body vary much in the extent to which they depend upon the regularity of their blood-supply.* Among those which are most susceptible to defects in the circulation are the cells of the central nervous system, intestine, and kidney. Obstruction of one common carotid artery may be followed by partial hemiplegia, and, if it be maintained, by cerebral necrosis, although no other

artery supplying the circle of Willis is blocked. The ganglion-cells of both brain and spinal cord die if deprived for half an hour of their blood-supply. Temporary blocking of the renal artery in a rabbit for two hours is followed by necrosis of many of the epithelial cells (Litten). The tissues of the skin and periosteum are probably the least susceptible of all.

Cessation of function soon follows cessation of nutrition. The effects of this may be extremely serious; thus, plugging of one of the larger cerebral arteries is generally followed by sudden loss of consciousness and paralysis; plugging of the pulmonary artery, by sudden asphyxia; and plugging of one of the coronary arteries, by immediate cessation of the heart's action.

Pathology of Red Infarction.—Very different explanations have been offered of the exact source of the blood in a red infarct.

Cohnheim thought that when emboli blocked terminal arteries, hæmorrhagic infarction was the almost invariable result. In his opinion, and according to his results, blocking of the artery was at once followed by regurgitation of blood from the principal veins into the capillaries, which thus became engorged. Red corpuscles then made their way through the capillary walls into the surrounding tissues, the permeability of the capillaries having been increased by deprivation of arterial blood. This view at the present time finds but few supporters. Other observers, repeating Cohnheim's experiments, failed to see the regurgitation which he described; while it has been conclusively shown (1) that, if both artery and vein are simultaneously blocked, the subsequent hæmorrhage will be still more marked; and (2) that if, in addition to the main artery, every other source of blood-supply except that through the principal vein be closed, necrosis without any hæmorrhage will result; or, in other words, that red infarction will not occur. Nor does increase in the permeability of the vessel-walls appear to be an important factor; for though, as Cohnheim pointed out, deprivation of the blood-supply for many hours will cause increased permeability of the capillary walls, yet hæmorrhagic infarction can take place long before any such change in the vessel-wall has been produced.

In all probability the diapedesis of the red corpuscles depends on marked slowing of the arterial current, by which all distinction between the axial and peri-axial streams is lost, combined with marked increase in the capillary and venous pressure. The red corpuscles are thus brought into contact with the capillary walls, and possibly pass, along with the lymph, between the endothelial cells (Welch). The natural permeability of the capillaries, which is known to be different in different parts of the body, may not improbably be a factor in the process.

Litten showed that red infarction of the kidney usually depends on the integrity of the capsular arteries, and that it does not occur if these are separated from the kidney before the main artery is blocked. The results of Mall and Welch, however, furnish the most convincing proofs. These observers ligatured all the vascular com-

munications of the intestine, with the exception of the main artery and vein, and then tied the bowel above and below so that the included portion was supplied by the main artery, and the blood returned by the main vein. Under these circumstances no infarction resulted. They then gradually constricted the main artery, and found that when it was sufficiently compressed to stop the lateral pulsations in its branches, or, in other words, to reduce the pressure in them to about one-fifth of the normal, hæmorrhagic infarction appeared. The same observers in other experiments found that the same reduction of arterial pressure generally occurred when infarction was in progress. Why some infarctions are red, and others white, seems therefore to depend, as has been suggested, on local differences in the blood-pressure. If the arterial pressure does not fall more than 75 per cent., no infarction occurs; if it falls between 75 and 80 per cent., red infarction results; and if it falls to zero, white infarction follows. Daniel finds that red infarcts are usually associated with infective embolism, white infarcts with impaction of aseptic material.

These observations will also explain why, in the large majority of cases, hæmorrhagic infarction does not occur when a truly terminal artery is blocked; and why an infarct in the spleen may follow thrombosis in the splenic veins without any obstruction in the artery.

II. Effects due to Composition of the Embolus.—A *simple embolus*, such as a piece of non-infective fibrin or a fragment of a calcareous plate, with its secondary thrombi, will usually be absorbed or lead to proliferative arteritis and organisation. An *infective embolus*—that is, one containing micro-organisms and derived from an infective source—may in some instances only produce results similar to those caused by a non-infective embolus. Infective emboli of somewhat greater virulence may lead to a more acute form of arteritis in which the intima and internal elastic lamina are destroyed and the media weakened—an aneurysm not infrequently resulting. This is, indeed, now held to be the pathology of most aneurysms occurring in persons too young to be suffering from atheroma or acquired syphilis; and, as the emboli are usually small or of moderate size, aneurysms from embolism affect especially the cerebral arteries and the smaller arteries of the limbs, from the size of the brachial downwards.

Emboli containing virulent infective organisms give rise in most cases to suppuration in addition to the other results already described. (See Pyæmia.)

Capillary Emboli.

It has been stated that fat, masses of organism, clumps of white blood-corpuscles, pigment-granules, and bubbles of air, may all give rise to embolism of capillary vessels.

Fat-Embolism.—In fractures, contusions of subcutaneous tissue, ruptures of fatty liver, acute osteo-myelitis, and other morbid con-

ditions in which fat-cells are broken up and the fat set free, the droplets are absorbed by the lymphatics and veins, especially when pressure in the part is increased by inflammatory effusion or hæmorrhage. On reaching the right side of the heart they are carried into the pulmonary arterioles and capillaries, where their presence may easily be demonstrated by staining with osmic acid (Fig. 148). One by one these soft and easily moulded plugs are swept on to the left side of the heart, and distributed by the systemic circulation to other organs, in which also they may be very numerous. For a time fresh globules are constantly reaching the lungs, but when this ceases the fat-masses are passed on to other organs and eliminated, in part at least, through the kidneys. Fat-embolism is believed by some to be the cause of death after simple fractures—a very rare event. But as large quantities of fat may be introduced into the vessels of the lungs of animals without causing any symptoms whatever, some scepticism is justifiable. If a sufficiently large number of the capillaries of the lungs, or any other organ, be blocked by fat, its function will, of course, be interfered with; and in the case of some organs this would mean speedy death. It is probable that the lungs always contain, proportionately, many more emboli than any organ supplied by the systemic circulation. It has been ascertained that half the pulmonary blood-path may be obstructed without the general circulation being thereby disturbed (Cohnheim). It is therefore supposed that, as a rule, the onward passage of fat into the systemic circulation keeps the number of plugged capillaries below the point of danger. It must be borne in mind that fat is practically fluid at the temperature of the body, so that it is doubtful whether embolism can result except from displacement of whole groups of fat-cells. In acute osteo-myelitis it is possible that the fat-drops may serve as carriers of pyogenic cocci from the seat of inflammation, and cause the impaction of these organisms in vessels through which they would otherwise pass freely.

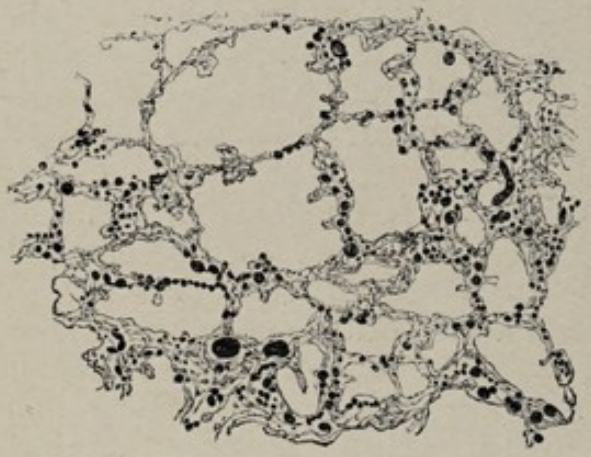


FIG. 148.—FAT-EMBOLISM OF LUNG. (× 40.) (BOYD.)

From bad compound fracture of leg and severe subcutaneous laceration. The black masses are drops of fat, stained with osmic acid, lying in capillaries and arterioles of alveolar walls.

Air entering the veins has been stated to give rise to embolism; but as air is not a solid substance, but is capable of passing through the vessels, it is doubtful whether such an occurrence is possible. The most probable explanation of death after the entrance of air into veins is that the right ventricle becomes filled with a mixture

of air and blood, which is churned into a foam; this the heart is unable to force through the pulmonary vessels. Death is due to failure of the right side of the heart.

Clumps of leucocytes, and possibly of bacteria, may form emboli, giving rise to petechiæ, in septic fevers. *Pigment-granules,* probably parasitic in origin, may cause capillary embolism in malaria.

Infarction of the Lung.

The so-called infarcts of the lung are most commonly met with in cases of mitral stenosis, and to a less extent in those of mitral regurgitation. They are found in the lower lobes and in the lower

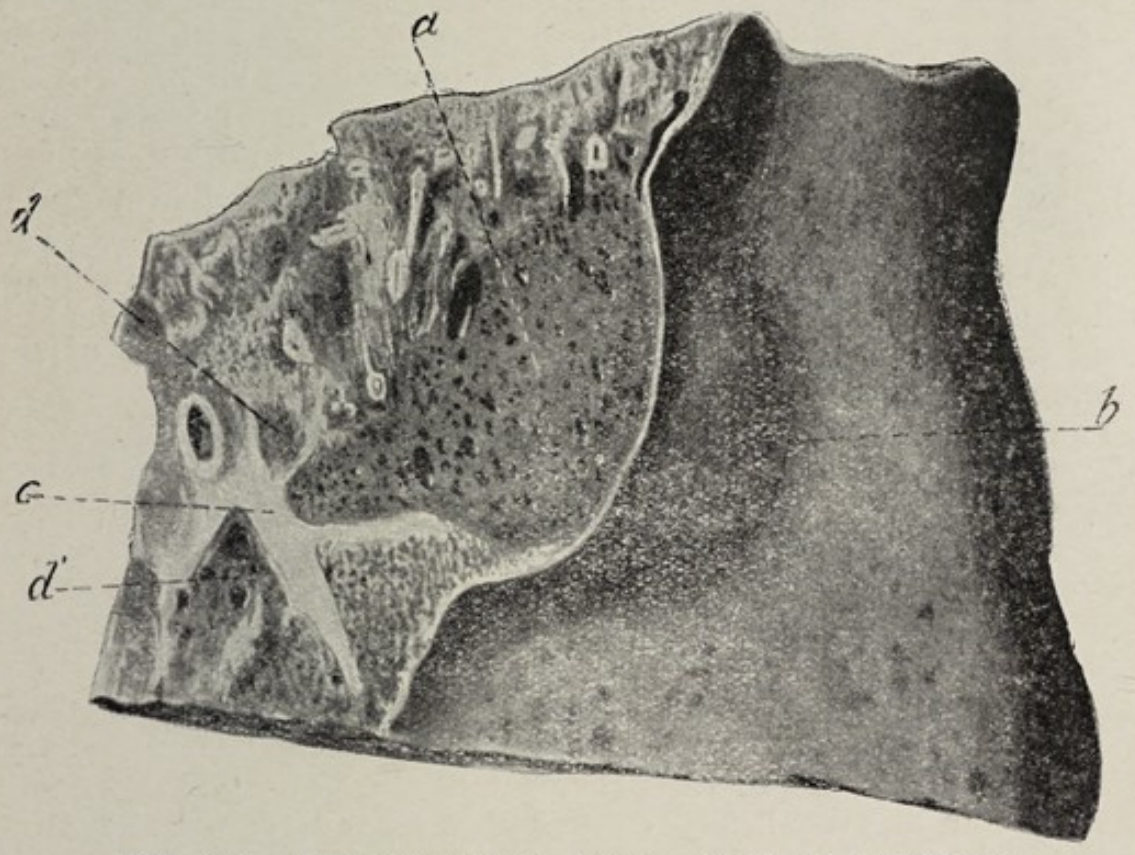


FIG. 149.—INFARCT OF THE LUNG. (C. C. H. MUSEUM.)

a, centre of infarct; *b*, base of infarct causing projection on surface; *c*, section through artery, a branch of which supplies infarcted area; *d*, *d'*, hyperæmic lung-tissue.

and outer parts of the upper lobes. In most cases they are irregularly conical (Fig. 149), but occasionally nearly globular. In diameter they vary from that of an entire lobe to a fraction of an inch. Blackish-red, firm, dry, with well-defined margin, often multiple, and occasionally confluent, they present superficial resemblances to tumours on the one hand, and to lobar pneumonia on the other. From the former they are distinguished by their colour, shape, position, and the conditions under which they occur; from the latter, by their number, shape, darker colour, and more sharply-defined limits. They are not infrequently the starting-point of a hypo-

static pneumonia, and are then less easily recognised. In such cases the adjacent portion of the visceral pleura is roughened by the inflammatory exudation on its surface, while in the substance of the organ the masses are welded together, their colour mottled, and their edges obscured.

Mode of Formation.—There can be no doubt but that these masses consist of extravasated blood and of tissue which has undergone coagulation-necrosis; or, in other words, they are red infarcts; but there is considerable difference of opinion concerning the reason of their appearance in the tissues. They are variously regarded as the products of **embolism, thrombosis,** or **rupture** of the pulmonary vessels.

In favour of **embolism** of one or more branches of the pulmonary artery may be urged (1) the frequent existence of a thrombus in the right auricle; (2) the occasional discovery of an embolus in the largest artery entering the infarct; (3) the general resemblance which these masses bear to infarcts of the spleen and kidney; and (4) the possibility of producing them experimentally. *Against* **embolism** as the sole cause are (1) the not infrequent absence in these cases of thrombosis and of all other known causes of embolism either in the systemic veins or in the right auricle; and (2) the still more frequent failure to find an embolus in any branch of the pulmonary artery itself.

That **thrombosis** is at least an occasional cause of pulmonary infarction is inferred from (1) the existence, in a few of the cases, of atheroma in the pulmonary artery; (2) the presence of a thrombus (without any sign of embolism) in the main artery supplying the infarct; and (3) the extreme retardation of the blood-current at the time the infarct is formed. On the other hand, all these phenomena may exist without any infarction.

Unquestionably the most constant condition present in these cases is a marked diminution in the velocity of the circulation and a long-continued and marked increase in the pressure in the pulmonary vein and capillaries, combined in most cases with blocking of the main artery supplying the infarct.

It will be readily understood from what has already been remarked that these conditions are exactly those likely to produce infarction; it is therefore reasonable to suppose that both embolism and thrombosis may be factors in its causation, and that it may in some cases occur without the presence of either of these conditions.

Embolism of a large branch of the pulmonary artery causes rapid death from heart-failure and asphyxia ("pulmonary apoplexy"): experimental embolism of a medium-sized or small branch generally produces no marked change, as the anastomoses are free and usually sufficient. In disease, however, the lungs have in most cases undergone the changes described under Passive Congestion, and the heart's action is generally feeble. It is therefore natural to find that in disease, more often than in experiments, embolism and thrombosis give rise to infarction.

Infarction can be produced in the lung experimentally by many different procedures. Simple plugging of a small branch of the pulmonary artery is never a sufficient cause; but Fujiami found that infarction occurred if a main artery was simultaneously blocked.

Cone-shaped hæmorrhages into the lung-tissue very closely resembling infarcts may be due to the *rupture* of overdistended vessels. Obstruction of a small bronchial tube occurs, and leads to collapse of the corresponding part of the lung. The external pressure on the walls of the vessels in the collapsed area is consequently diminished, and this condition leads to the overdistension of the vessels, and occasionally to their rupture.

CHAPTER XXII

INTOXICATIONS, AUTO-INTOXICATIONS, AND NUTRITIONAL DISEASES

Poisons are generally divided into groups according to their most striking effects upon the body. Thus the *corrosive poisons*, including the strong mineral acid and alkalies, act principally on the cells with which they come into immediate contact, and cause death mainly by the local lesions produced, and by the pain and shock that ensue. Mineral acids, if given in smaller doses, tend to reduce the alkalinity of the blood, and abstract from the system an increased amount of alkali to neutralise them. Intense fatty accumulation in the liver may be met with in some instances.

Irritant poisons are closely related to the corrosive poisons, but act rather less destructively upon the tissues with which they come into contact, setting up a local inflammation of varying degrees of severity, and subsequently producing chemical effects upon the whole body or upon particular parts of it. As instances of such substances may be mentioned arsenic, which induces intense gastritis and enteritis by its local action, with remoter effects seen in neuritis, conjunctivitis, and affections of the skin; and cantharides, which act locally as a vesicant, remotely as a cause of nephritis.

Another large group of poisons (*neurotic*) acts principally upon the central nervous system, producing on the one hand drowsiness and coma (alcohol, morphine, etc.), or on the other hand convulsions (strychnine) by increasing the reflex activity of the spinal cord.

No sharp line can be drawn between the different groups. Thus alcohol, a narcotic poison, is capable of producing inflammation of the stomach, intestines, and peripheral nerves, in the same way as does arsenic, an irritant poison. Phosphorus, which is a local irritant, induces fatty degeneration of the liver as a remote chemical effect. As a general rule, concentrated poisons act locally, while diluted poisons are absorbed into the circulation and act upon distant parts. Different poisons select different tissues for which they have special affinity; thus phosphorus affects principally the liver, cantharides the kidneys, lead or alcohol the nerves, curare the nerve-terminals in the muscles, strychnine the spinal cord, and morphine the brain.

Chemically, poisons may be classified into: (1) **Inorganic poisons,** including *non-metallic* bodies, such as phosphorus, and *metallic* salts, notably those of arsenic, lead, and mercury; (2) **organic poisons,** derived chiefly from the vegetable kingdom, but including also such chemical substances as chloroform and hydrocyanic acid; and (3) **toxines,** formed by bacteria, and by some animals and plants.

Snake-Poison.—The poisons contained in snake-venom are not yet identified, but their action resembles that of bacterial poisons. Thus, it is said that venom contains a copula capable of activating a complement already present in the body. In some instances lecithin appears to be the complement at work, and compounds of this substance with the copula present in snake-venom have been isolated by Kyes (*cobra-lecithides*). An antitoxic serum can be prepared as an antidote to venom, but it seems that the poisons of different snakes differ in their constituents, so that the antitoxine prepared against one variety of snake is ineffectual against the bite of another. Besides a neurotoxine which acts on the nervous system, snake-venom contains substances which affect the coagulability of the blood, and break up the corpuscles; and some kinds of venom contain bodies which have the power of dissolving the cells forming the lining of the small bloodvessels, so that petechial hæmorrhages are produced (*hæmorrhagins*).

Some other animals, such as *scorpions, spiders,* and *centipedes,* also possess the power of secreting poisons, useful in attack or defence.

Vegetable Poisons.—Apart from the toxines mentioned above, vegetable poisons fall chiefly into two main groups—(1) the *alkaloids,* and (2) the *glucosides.* **Alkaloids** are typically carbonic-acid esters, containing nitrogen; they are derivatives of such bodies as pyridine, pyrrolidin, and chinolin. The most important of them are morphine and its congeners, codeine, narcotine, etc., from the poppy; strychnine, from *Nux vomica;* aconitine, from monkshood; hyoscine, or scopolamine, from hellebore; veratrine, from *Veratrum viride;* and cocaine, from *Erythroxylon coca.* With them may be classed certain alkaloids of animal origin—choline, neurine, and muscarine.

The **glucosides** are bodies which, on hydrolysis, give rise to a molecule of sugar—the sugar varying with the particular glucoside. They fall into three main groups: (1) The glucosides which act on the heart, including digitalin and strophanthin; (2) those which act upon the red blood-corpuscles, of which saponin is the type; and (3) the nitril-glucosides, which give rise to hydrocyanic acid, such as amygdalin and laurocerasin.

Tolerance of Poisons.—When poisons have been taken in small doses over long periods of time, the cells of the body become accustomed to make use of a lymph containing small quantities of the poison, and adapt their chemical processes to this new environment (*drug-habits*). If now the poison be discontinued, the cells cannot immediately become accustomed to do without it, and great physical

discomfort, and even death, may ensue if the withdrawal of the poison is sudden (morphine, arsenic).

In the case of dogs habituated experimentally to increasing doses of arsenic it has been shown that the tolerance gained is only operative towards doses of the poison given by the mouth, the animals being as susceptible as others to hypodermic administration of the drug.

Experiments made by Ehrlich with regard to the resistance acquired by certain races of trypanosomes to poisons, such as arsenic and antimony, have led him to suggest that these substances act upon cells through their receptors, and that death of a cell (protozoon) occurs when all its receptors are occupied by molecules of poison, so that nutrition can no longer be effected. He holds that the increased resistance manifested by the surviving organisms in the cases which he investigated was due to the fact that only those individuals survived which had no receptors capable of anchoring the particular poison, all susceptible forms having been killed.

Excretion of Poisons.—Poisons are eliminated by various different channels—by the urine, by the intestine with the fæces, by the bile, by the sweat, by the saliva, by the gastric glands, and by the lungs. In the process of excretion poisons may cause irritation of the organs by which they are thrown off. Thus, turpentine may cause inflammation of the kidneys as it passes out by the urine; and toluylenediamine is said to be eliminated in the bile, and to cause catarrhal inflammation of the small bile-ducts, with resulting jaundice. Iodide of potassium is excreted to some extent in the sweat, and gives rise to papular inflammation of the skin by irritation of the sweat-glands. It would seem that the liver plays an important part in neutralising bacterial toxines which are absorbed from the alimentary canal.

AUTO-INTOXICATIONS.

The term "auto-intoxication" should properly be applied only to poisoning by toxic substances formed in the course of the metabolism of the tissues themselves. It is, however, often used for conditions of poisoning brought about by the *products of bacterial action taking place in the intestine:* this is obviously no more an auto-intoxication than any other form of sapræmia.

Little is definitely known of the toxines produced in the bowel. In cases of intestinal obstruction the breath may be offensive, and the urine may contain excess of indican formed from indol-compounds absorbed from the gut.

The condition is termed *indicanuria,* the substance actually appearing in the urine being potassium-indoxyl sulphate ($C_8H_6N.K.SO_4$). The exact degree of toxicity possessed by indol is not well established; but Herter holds, as the result of experiments on himself, that small doses may produce frontal headache, irritability, and restlessness, larger amounts giving rise to insomnia and mental confusion. He thinks that chronic poisoning with this

substance may cause neurasthenia. The cells of the liver possess the power of protecting the body against the action of indol, which is by them broken up into innocuous bodies.

The rise of temperature sometimes associated with constipation in children and in convalescent patients may be due to some poison absorbed from the intestine. Mental depression is sometimes relieved by attention to the bowels; and it has been suggested that some forms of serious mental disease (*melancholia, epilepsy*) may be of autotoxic origin. (See Chapter XXXIII.) A similar causation has been suggested for some cases of anæmia.

Besides indol, other metabolic products have been asserted to cause auto-intoxication. Among these are the so-called leucomaines, such as putrescin, cadaverin, and sepsin, but their toxicity seems to be very slight. Choline is said to be formed in destructive affections of the nervous system, but its action as a poison is problematical.

Absorption of hydrogen sulphide from the bowel has in rare instances caused the appearance in the blood of sulphæmoglobin, giving rise to a dusky colour of the patient's skin (*sulphæmoglobinæmia*).

Auto-intoxication properly so-called may arise from (1) retention of secretory materials which should be passed out from the body; (2) from elaboration of some toxic body by perversion of the normal process of metabolism; or (3) by production of excess of some normal product. We may include under this heading for convenience of arrangement (4) failure of some organ to produce a substance necessary for the welfare of the organism.

1. **Retention of Secretory Materials.**—The kidneys being the most important secretory organs, we naturally look for examples of this form of auto-intoxication to cases of renal disease. Two main conditions at once suggest themselves as instances in which the urinary secretion is abolished: (*a*) Obstruction of the ducts of the kidneys (ureters), and (*b*) extensive disease of the kidneys themselves, in both of which conditions anuria, or suppression of urine, may occur. The phenomena in the two cases are strikingly different. In the former case (*obstructive anuria*) the patient may live for two weeks or more, exhibiting no symptoms beyond increasing weakness and drowsiness, and may at last die suddenly. In the latter case (*non-obstructive anuria*) convulsions rapidly occur, and the patient dies comatose within a few days (*uræmia*). The cause of the difference between the two conditions is not clear: we may suppose that the former state represents the effects of mere retention of waste products which should be excreted in the urine, whereas in the latter the whole of the functions of the kidney are in abeyance, and, perhaps, that some "internal secretion" necessary for life is no longer manufactured. (See below.)

As to the exact retention-product to which uræmic poisoning is due, nothing certain is known. Urea itself is not toxic, merely acting as a diuretic. It is therefore generally held that some inter-

mediate product of proteid metabolism, which is normally converted into urea and thus secreted, is the toxic agent, and attempts have been made to identify this substance as ammonium carbamate. Besides excess of urea and of this salt, observers have found in uræmic blood increased quantities of lactic acid, of glycocoll, and of sodium chloride. Œdema of the brain and meninges is usually found after death, and this condition may be responsible for some of the nervous symptoms. Chromatolysis is well marked in the cerebral cells.

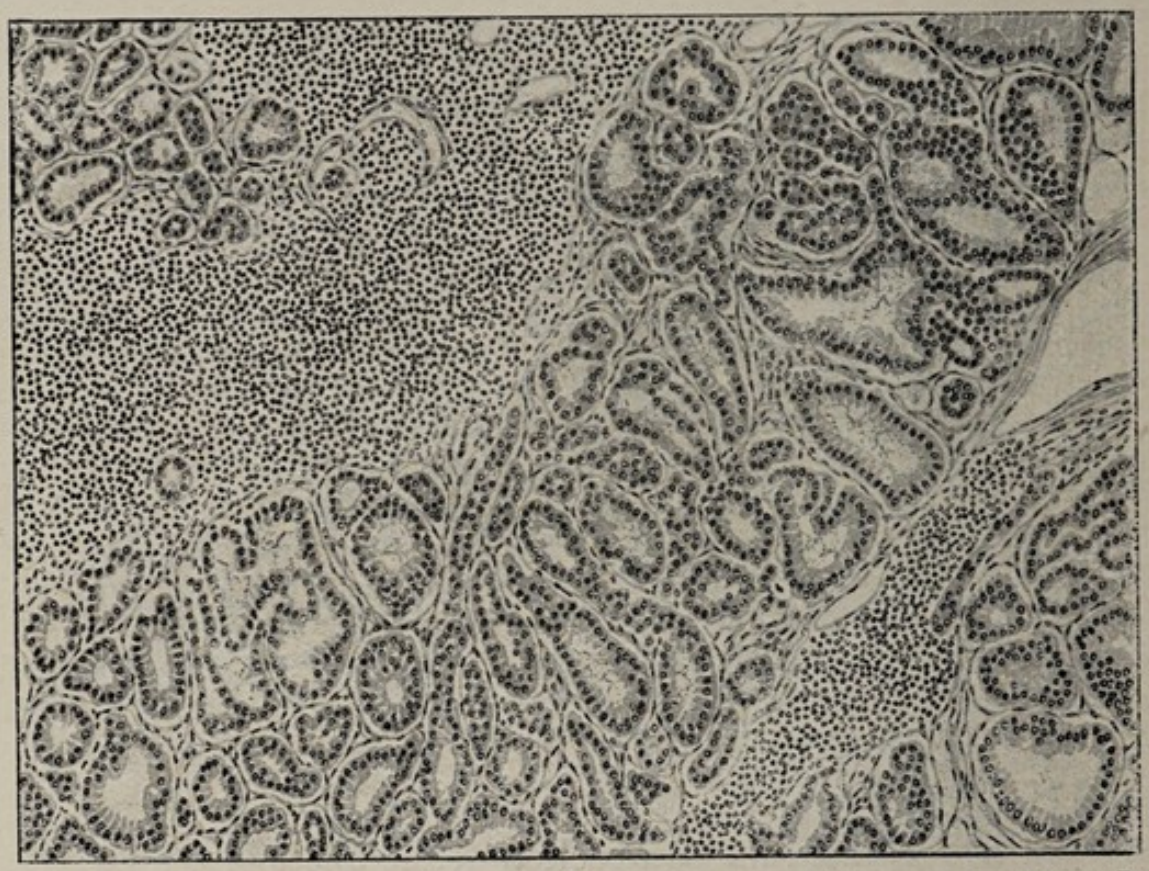


FIG. 150.—THYROID FROM CASE OF EXOPHTHALMIC GOITRE, SHOWING INFOLDING OF VESICLES, COLUMNAR EPITHELIUM, DIMINUTION OF AMOUNT OF COLLOID AND COLLECTIONS OF LYMPHOCYTES. (× 79.)

Direct absorption of *bile* into the circulation, as in the many varieties of jaundice, is associated with certain toxic symptoms (*cholæmia*), of which the most noteworthy are itching of the skin and slowing of the heart-beat.

2. Of **perversion of secretions** owing to disease in the organs which form them we know nothing as a cause of intoxication: the condition is purely hypothetical.

The poison at work in *puerperal eclampsia* may perhaps be provisionally placed under this heading, as it seems to be some abnormal substance formed in the course of pregnancy. The phenomena of the disease closely resemble those of uræmia (albuminuria, coma, and convulsions), but changes are found in the organs—notably necrosis of the cells of the liver—suggesting that some poison is at

work which gives rise both to this lesion and to the renal affection (toxic nephritis), which is therefore secondary. The poison seems to be formed in the placenta, as eclampsia may occur after parturition, and is usually much improved by removal of the placenta. On the other hand, some authors have traced a connection between eclampsia and defective action of the thyroid gland, while others, again, believe the condition to be a form of anaphylaxis associated with absorption of foreign protein from the chorionic villi.

3. **Excess of a secretion normally formed in the body** is probably responsible for the disease known as exophthalmic goitre or Graves' disease. In this condition there occurs great enlargement of the thyroid gland, along with palpitation and rapid action of the heart, prominence of the eyes, sweating, pigmentation of the skin, tremor of the hands, and great nervous excitability. The patients are generally women. The cause of the onset of the condition is not known. The arguments in favour of its being due to an excess of thyroid secretion are, first, the almost exact contrast which Graves' disease presents to the malady known as myxœdema, described below, which is proved to be due to defective action of this gland; and, secondly, the fact that somewhat similar symptoms may be produced by administration of large doses of thyroid extract. It must be noted, however, that the thymus, as well as the thyroid, is usually enlarged.

Histologically the thyroid shows distinctive changes (Fig. 150). The vesicles are irregular in outline and their walls show numerous infoldings. The epithelium is columnar, instead of being of the normal low cuboidal type. The colloid is diminished in amount and no longer fills the vesicles, while in many areas it is almost entirely absent. Scattered throughout the gland are small areas of massive infiltration with small mononuclear cells.

4. **Diminution or Absence of a Normal Secretion.**—Internal secretions—that is, say, substances useful to the organism, poured directly into the blood without the mechanism of a recognisable duct—are supposed to be formed by several organs. The existence of such a function in the case of the thyroid gland is absolutely proved, and in the case of the suprarenal bodies it is fairly well established. The formation of internal secretions by the ovaries, testes, kidneys, and pancreas is exceedingly probable, while in the case of the pituitary body and the thymus gland the evidence is less convincing.

Defective **thyroid** secretion is the cause of *myxœdema*. The condition is the same whether the gland be removed by operation or rendered functionless by some inflammatory or degenerative process. In children who are the subjects of congenital defect of the gland (*cretinism*) the symptoms are mental dulness, stunted growth, broad clumsy hands, coarse features, expressionless face, prominent abdomen, and a tendency to umbilical hernia. In the adult, in whom the disease arises from unknown causes, the face is also expressionless, and has been compared to a mask; the hands are broad and spade-like; the skin is dry, and the hair coarse and

scanty; the mind is dull, and thought and speech are slow and hesitating. The pulse is slow, the urinary secretion small, and the bowels constipated. A curious flush is often seen on the malar eminences, while the rest of the face is pale or earthy. These patients are very sensitive to cold. If thyroid secretion be supplied, either by feeding with dried gland-substance, or by injection of an extract of the gland hypodermically, the symptoms of the disease rapidly disappear. The children become bright and intelligent, and growth is resumed; the adults regain their former health and mental capacity.

It is evident that the thyroid gland secretes a substance which is necessary for the nutrition of the cells of other tissues, notably of the nervous system. What this substance is, is not known, beyond the fact that it contains iodine (thyro-iodin). It is scarcely imaginable that more than a very small quantity of it can be daily absorbed, so that it is difficult to suppose that it acts as a direct food-material.

Defective secretion on the part of the **suprarenal bodies** is supposed to be the cause of the condition known as *Addison's disease.* The symptoms of the malady are great weakness; feebleness of the pulse, with very low blood-pressure; pigmentation of the skin and mucous membranes; and sometimes vomiting, diarrhœa, and attacks of syncope. After death the suprarenal bodies are found, in a proportion of cases, to be the seats of caseous degeneration due to tuberculosis. These glands normally contain a substance which produces powerful constriction of the bloodvessels; it is natural to attribute the circulatory disturbance met with in Addison's disease to lack of this material. Feeding patients with extract of the glands has not, however, appeared to produce any such beneficial effect as is the case with thyroid feeding in myxœdema; as to the effect of subcutaneous injection of such an extract, the evidence is contradictory. It has been supposed that these glands normally aid in the excretion of pigment derived from breaking-down of blood-corpuscles, and that the pigmentation of the skin is due to accumulation of such products.

In the case of the **ovaries,** it is found that removal of these organs induces atrophy of the uterus and an artificial menopause. If they be removed in a pregnant animal, abortion occurs, suggesting that the ovarian secretion is necessary for the nutrition of the fœtus. It has been stated that in cases of carcinoma of the breast, removal of the ovaries is followed by involution of the growth, but this result is not constant. Cases of chorio-epithelioma of the uterus have been found by Lockyer to be often associated with cystic degeneration of the luteïn-tissue of the ovaries; and Fraenkel believes that the cells of the corpus luteum are the source of an internal secretion necessary for the life of the fœtus. Removal of corpora lutea causes abortion, but this does not occur if a corpus luteum be grafted in some other part of the body.

The existence of an internal secretion from the **testes** is supported by the effects of removal of these organs in young animals. The special characteristics of the male sex fail to appear. In eunuchs

the voice remains shrill, as in women; the beard may not appear, and the general anatomical form of the body approximates to the female type.

Removal of the **pancreas** in animals is followed by a condition identical with the *diabetes mellitus* of human beings. The urine is increased in quantity, and contains much sugar; there are great thirst and voracious appetite, with rapid wasting of the body; acetone and diacetic acid appear in the urine; and death may be preceded by a comatose condition. In persons who have died of diabetes there is often found atrophy of the pancreas, extensive fibrosis of the organ, or fatty degeneration; hæmorrhage into the pancreas may be associated with diabetes. Opie has found in some cases a hyaline degeneration limited to the special groups of cells called Islands of Langerhans, and other writers also have found these structures diseased. The suggestion has been made that these cells are the source of the internal secretion of the pancreas. This cannot as yet be regarded as proved; in many cases of diabetes no visible affection of these islands, or, indeed, of the pancreas at all, is present. It is supposed by some that the internal secretion of the pancreas is necessary for the assimilation of sugar by the cells of the body, especially the muscles; by others that it neutralises a poison, formed elsewhere, which is capable of interfering with this process.

Disease of the **pituitary body** has been found associated with the peculiar condition known as *acromegaly*, in which there is great enlargement of the extremities and of some of the cranial bones. The nature of the relation between such lesions of the pituitary body and the disease is not established. It is certain that extensive affections of this body (cancer, gumma) may exist without acromegaly. Certain cases of giant-growth are associated with disease of this body, and some forms of defective development (*infantilism*) seen to be due to lack of its internal secretion. A chemical substance, commercially named *pituitrin*, has recently been obtained from this gland, which possesses properties closely resembling those of adrenalin.

The assumption of the formation of an internal secretion by the **kidneys** has been already alluded to as an explanation of the phenomena of uræmia. Certain experiments made by Bradford, in which removal of one kidney along with the greater part of the other kidney was followed by increased excretion both of water and of urea, may point in the same direction, but subsequent repetition of the experiments appears not to have entirely confirmed his observations.

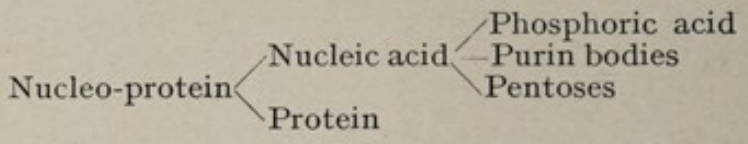
The phenomena which result from the removal of some of the above-mentioned organs (pancreas, kidney) may be equally well explained upon the supposition that in health it is the function of these glands to neutralise poisons which otherwise accumulate in the system and cause injurious effects. Possibly such poisonous substances are utilised by the respective glands for their own nutrition; or the latter may form antitoxic materials.

NUTRITIONAL DISEASES.

Under this heading two important, but exceedingly obscure, diseases must be alluded to—namely, gout and diabetes. Little is known of the true pathology of either of them.

Gout is a condition characterised by the presence of excess of urate of sodium in the blood; this salt is deposited in the cartilages of the joints, and also in bursæ and connective tissues, under certain conditions which are not fully understood, the precipitation in the joints being accompanied by attacks of severe pain and by symptoms of inflammation.

Uric acid, which is converted into sodium urate by the salts in the blood, is supposed to be formed in two ways: (1) By breaking-down of the nucleo-albumins of the tissues, and especially, perhaps, of those contained within the leucocytes; and (2) from similar substances contained in the food. Chemically, uric acid is one of a group of substances collectively known as "purin-bodies," the relations of which to each other and to nucleo-protein are shown below and in the accompanying graphic formulæ (Fig. 151):



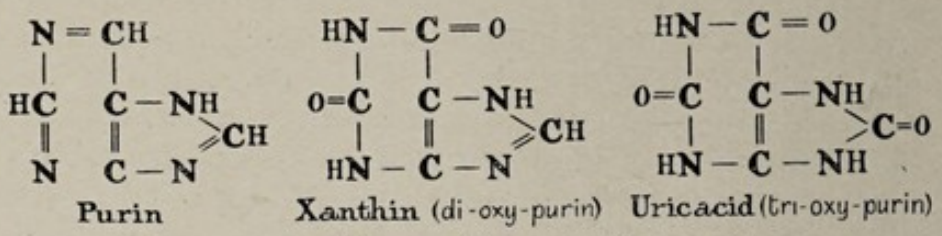


FIG. 151.—FORMULÆ OF THREE TYPICAL PURIN-BODIES, SHOWING RELATIONSHIP OF URIC ACID.

Excess of uric salts in the blood may be produced either by increased formation of these purin-bodies, or by diminished excretion of those normally produced, or by failure of the tissues to utilise or destroy them in their metabolism. Which process is at fault in gout is not known. The association of the disease with granular kidney might appear to point to defective excretion as the probable cause; but this association is not constant. Gouty attacks are often preceded by disturbances of digestion, and some authors have supposed that the disease is a toxæmia due to poisons formed in the alimentary tract. Indulgence in alcohol and in rich food is almost certainly a factor in many cases of gout. It is not impossible, on the other hand, that the disease is due to a defect of assimilation, dependent upon a perversion of the normal chemical action of the cells. It is asserted that the liver normally breaks up uric acid, with formation of urea, by means of a special ferment. This may be absent in gout. The most surely established fact in

the ætiology of the disease is its hereditary transmission. Males are more often affected than females—a peculiar feature of most hereditary maladies.

The presence of an excess of urates in the blood may be demonstrated by acidulating some of it in a watch-glass and placing a few threads in the fluid: crystals of uric acid will then be deposited on the threads in the course of a few hours. After death deposits of sodium urate are found in the cartilages of joints, in those of the ear, in bursæ, and in periarticular tissues (tophi). The relationship of the deposits to the gouty exacerbations is not well understood. The attacks of pain and inflammation may be due to irritation caused by the uratic deposit, or the deposit may take place at seats of inflammation. On the whole, the latter is the more probable, as almost exactly similar attacks may occur in the subjects of rheumatoid arthritis, without any excess of urates being present, while the bony changes are the same in both diseases, taking the form of rarefaction of the bone, readily visible in X-ray photographs. Hence it is not impossible that the articular changes in gouty subjects are really rheumatoid in nature, and the deposit of urates merely secondary and unimportant. On the other hand, the gouty state seems to be accompanied by changes in the direction of premature old age, and may be one of the causes leading to the rheumatoid changes in the joints. Other conditions associated with gout are—in addition to the granular disease of the kidney already mentioned—bronchitis, asthma, phlebitis, arteriosclerosis, and eczema.

Gout is especially common in those who work in lead, and an acute attack may be induced by administration of a dose of lead subacetate.

Diabetes is a disease characterised by the continued passage of large quantities of urine containing sugar (dextrose). Along with this there are wasting, increased appetite, and great thirst. The appearance of sugar in the urine is due to the presence of this substance in the blood in largely increased amount. As with the urates in gout, so with the sugar in diabetes, excess may be due either to increased production or to diminished excretion, or to defective utilisation of the substance in the chemical life of the cells. To decide definitely which of these causes is at work is not at present possible.

Claude Bernard, soon after his original discovery of the existence of glycogen in the liver, showed further that puncture of the floor of the fourth ventricle would produce glycosuria; this was apparently due to disturbance of the circulation in the liver, with resulting rapid conversion of glycogen into sugar and passage of the sugar into the blood. The *glycosuria* which accompanies some forms of cerebral injury and disease is almost certainly of this nature; it is more persistent than the transitory glycosuria of the "puncture" experiment merely because the cause persists. Such cases are perhaps hardly to be called diabetes. True diabetes may, however,

result from traumatism of various kinds, and in such instances some other factor seems to enter into the causation of the condition.

A condition almost exactly identical with diabetes mellitus is produced by poisoning with the glucoside phloridzin. Injection of suprarenal extract produces a very similar condition, apparently by a direct reducing action upon the pancreas. The effect of experimental removal of this organ has been already mentioned.

In true diabetes it has been suggested (1) that the liver is unable to retain the glycogen which is usually stored up in it, and which therefore passes rapidly into the blood (Claude Bernard); (2) that some ferment normally contained in the blood, by which sugar is destroyed, is absent in diabetes (Lépine); (3) that some toxine is formed which interferes in some way with the production or utilisation of sugar; (4) that carbohydrate food, which is usually absorbed from the intestine in the form of fat (or, according to a later suggestion, transported by the lymphocytes), is in diabetes absorbed as sugar, which passes into the blood-stream and acts as a poison (Pavy). There are not at present sufficient data available to settle which, if any, of these views represents the true nature of the disease.

In severe cases of diabetes sugar is undoubtedly formed by breaking-down of the tissues of the body; and in the very similar condition produced by poisoning with phloridzin the sugar which appears in the urine is admittedly derived from some compound in which it is united with protein. It is not improbable that this process is active throughout the affection. If this be so, the appearance of sugar in the blood may, like that of uric acid, be attributed to two sources—endogenous and exogenous—part being absorbed from the food, and part derived from internal tissue-change. Alimentary glycosuria may then depend mainly on the former factor, true diabetes on the latter.

In diabetes it is found that the alkalinity of the blood is diminished, owing to the formation in the system of organic acids (aceto-acetic, β-oxybutyric, sarcolactic, etc.). This **acid-intoxication** is very characteristic of diabetes, in which it occurs with the greatest intensity; it is found, however, in other conditions, such as infantile enteritis and starvation; also in so-called "delayed" chloroform-poisoning, in cyclical vomiting of children, and occasionally in pregnancy. The source of the acids formed is not certainly known, but there is reason to believe that they arise by the breaking-down of fat, to which oxybutyric acid is closely related. Under normal circumstances oxybutyric acid is excreted as acetone, the substance which gives the sweet smell to the breath of diabetic patients; but in diabetes this acid and aceto-acetic acid may appear in the urine along with the acetone, which is present in very large amount. Probably as much acetone may be eliminated from the body by the breath as in the urine. The organic acids enter into combination with ammonia derived from the proteins of the body, and are

excreted as ammonium-salts in the urine. The effect produced is stated to be equivalent to poisoning by a mineral acid; indeed, Bunge held that the acid substance which actually accumulates in the body in acid intoxication is sulphuric acid.

Acid intoxication has been ascribed to defective action of the liver, which normally breaks up the acids at work. The direct dependence of the increased quantity of ammonia secreted in the urine upon the acidosis is not quite certain, as the excess of ammonia may be due also to defective hepatic action—the liver usually changing this substance into urea.

It is now generally held that the *coma* in which patients suffering from diabetes often die is due to the acid-poisoning. Attempts have been made to identify the toxic agent with one or other of the substances formed—acetone, β-oxybutyric acid, β-amido-butyric acid—but so far without success. It is not impossible, however, that a definite toxic agent may ultimately be identified.

The nature of **Obesity,** which appears also to constitute a "nutritional disease" in many instances, has already been discussed (pp. 36–38); and **Rickets** is dealt with along with diseases of the bones.

The following anomalies of metabolism, characterised by the appearance of abnormal substances in the urine, must be briefly mentioned:

Pentosuria.—Pentose found in the animal system may have either an exogenous or an endogenous origin, as pentoses (sugars containing five carbon elements, as contrasted with the six present in the ordinary forms or hexoses) are, on the one hand, contained in fruits and vegetables, and, on the other, are among the products of cleavage of nucleo-proteins. In some individuals the occurrence of pentose in the urine may be noted throughout life, without the co-existence of any symptoms of disease, such individuals apparently having no power of breaking up these bodies and utilising them in their metabolism.

Cystinuria.—Cystin, an amino-acid containing sulphur, may sometimes be found in the urine, and may give rise to calculi owing to its insolubility. The condition of cystinuria may be hereditary; it is not usually associated with signs of ill-health. The source of the cystin is uncertain, but it is generally supposed to be derived from the cells of the body, representing the sulphur-constituent of protein, and to be independent of the food taken.

Alkaptonuria.—This condition also depends on some abnormality of proteid metabolism, and may constitute an hereditary peculiarity not amounting to disease. Attention may be drawn to the presence of some abnormal substance in the urine by the tendency of this fluid to darken when exposed to the air, and by its power of reducing Fehling's solution. The abnormal bodies present belong to the aromatic series, and are known as *uroleucic* and *homogentisic* acids; they are derived from tyrosin and phenyl-alanin—products of cleavage of protein. Normally these acids are destroyed in the

body, the benzene-ring being broken up. Alkaptonuric persons fail to accomplish this process, and the acids accordingly appear in the urine unchanged. It is possible that some part of the supply of uroleucic and homogentisic acid may come from the food taken. In some instances alkaptonuria has been associated with the peculiar pigmentation of cartilage called *ochronosis*.

PART II

DISEASES OF SPECIAL TISSUES AND ORGANS

CHAPTER XXIII

AFFECTIONS OF CONNECTIVE TISSUE, OF JOINTS, AND OF BONE

AFFECTIONS OF THE CORNEA.

SENFTLEBEN'S experiments have shown that injury of the cornea produces none of the vascular signs of inflammation unless the marginal vessels are affected, or unless leucocytes are admitted from the conjunctival sac. Anteriorly and posteriorly the cornea is limited by membranes sufficiently stout to resist the passage of leucocytes; but in severe lesions, leucocytes and fluid exudation from the vessels enter freely from the margin, passing along the lymph-channels in which the cells and nerves lie. The leucocytes thus accumulate in clusters around the corneal cells. Such exudation is accompanied by softening and opacity of the corneal structure, and may lead to alteration in its curvature. This happens in *vascular keratitis* and in the *interstitial keratitis* of congenital syphilis.

When a slight proliferative inflammation occurs beneath the roughened epithelium as a consequence of the irritation of granular lids, the condition is known as *pannus*. Pus, forming between the layers of the cornea, constitutes *onyx ;* and *ulcers* of the cornea are common. Healing in all such cases is by scar-tissue, and some opacity and a more or less altered corneal curve (*anterior staphyloma*) are thereby produced. In the most intense forms of purulent conjunctivitis the injury to the cornea may be so great that it undergoes extensive *necrosis*.

AFFECTIONS OF CARTILAGE.

Mucoid degeneration is met with in cartilage, especially in the intervertebral discs of old persons. **Calcification** of cartilage, notably in those of the ribs, is another form of senile change.

A peculiar pigmentation of all the cartilages of the body is met with in the condition called **ochronosis.** The pigment is allied to melanin, and is supposed to be formed from the proteins of the body, the intermediate stages being tyrosin and phenyl-alanin. In some instances absorption of phenol from surgical dressings is stated to have been responsible for this deposition of pigment, which may therefore perhaps sometimes be exogenous in origin. The cartilage may be almost black, and the kidneys and the organs may also contain pigment.

Cartilage being non-vascular, **inflammation** here resembles that seen in the cornea. In the most acute inflammations of joints the cartilage may slough from injury and lack of nourishment. It then either peels off in flakes, or softens and wears away at points of pressure. In less acute cases it may be invaded by leucocytes from the joint-cavity or from the bone. Enlargement and multiplication of cartilage-cells may often be seen, as well as the accumulation of leucocytes within the capsules.

AFFECTIONS OF SYNOVIAL MEMBRANES AND JOINTS.

Mechanical violence may produce dislocations of the bones forming a joint or displacement of articular cartilages. Fractures of bones may also extend into the joint-cavities. In certain disorders, such as hæmophilia and scurvy, blood may escape into the joint-cavity (*hæmarthrosis*).

A mild form of inflammation affecting the synovial membrane alone is known as simple *synovitis*. It may result from sprains or blows, or from infection by organisms of low virulence (rheumatism, some cases of gonorrhœal and syphilitic disease). The synovial membrane is hyperæmic and œdematous; the fluid in the joint-cavity is increased, and may be turbid from the presence of flakes of fibrin and desquamated endothelial cells. The other structures in and around the joint are not visibly affected.

More severe forms of inflammation, in which cartilages, ligaments, and even the tissues outside the joint may be involved, constitute acute (infective) *arthritis*. This may arise from penetrating wounds, by which virulent organisms are carried into the joint; by extension of infection from neighbouring parts (osteo-myelitis, abscess of bone); or by deposition of organisms from the blood, as in str ptococcic, pneumococcic, and other infections. Here, in addition to the changes mentioned above, the ligaments are œdematous and infiltrated with round cells, the surfaces of the cartilages are destroyed, and the whole cavity of the joint becomes lined with a layer of granulation-tissue. The fluid in the joint is turbid with leucocytes, and may be almost pure pus, sometimes stained with blood. The cartilages may be destroyed by ulceration, or may slough in large flakes, leaving the bone exposed; and the process may extend into the tissue around the joint, with formation of abscesses or fistulæ.

Healing takes place by the formation of scar-tissue from the new cells. Short, extremely strong and wide adhesions often bind the surfaces together, producing *fibrous ankylosis;* some of these bands may calcify. If the bone is laid bare, some or all of the adhesions will ossify—true *bony ankylosis*.

The most typical form of chronic arthritis is that due to tuberculosis. The process may start either in the synovial membrane or in the adjacent end of a bone. A section through the thickened synovial membrane in such a case may show the following appearances: externally, we find ordinary granulation-tissue, with some developing scar-tissue; passing towards the joint-cavity, we next find a layer of young connective-tissue cells in which *giant-cells* become increasingly numerous, and even typical *giant-cell systems* may occur; nearer the joint, yellow spots and patches of fatty degeneration become frequent; and the surface may be composed of granular débris in which cell-forms are no longer distinguishable. A thin puriform fluid may occupy the cavity; it contains, however, very few pus-cells, but consists mainly of fatty granules—formed by degeneration of the superficial cells—suspended in an albuminous fluid.

Rheumatoid Arthritis (*Arthritis Deformans; Osteo-Arthritis*).—It is probable that more than one condition is included under the term "rheumatoid arthritis." One form which occurs in young persons and rapidly involves many joints, is not improbably an infective disease, due to some micro-organism; while the more common chronic form, whether one joint or many suffer, seems to be a degenerative or perhaps a "trophic" condition. The resemblance between the changes seen in osteo-arthritis and those of "Charcot's joints" in tabes dorsalis is very close. Some authorities maintain that these chronic cases are due to the action of micro-organisms of feeble virulence, or to toxines derived from local foci of infection—*e.g.*, septic conditions of the mouth; while recently French writers have attributed the malady to tuberculosis, the joints being either directly invaded by the bacilli or injured by toxines absorbed from foci at a distance, but the evidence adduced is unsatisfactory.

The chronic form of the disease is characterised by degeneration and atrophy of certain of the articular cartilages as well as by overgrowths from the margins of these cartilages and from the synovial membrane.

The first change observed in the cartilage is fibrillation of the matrix, followed by softening and erosion. The centre of the cartilage may be quite worn away, and the bone beneath hardened and highly polished (*eburnation*). The outgrowths from the margins of the articular cartilages are subject to considerable variation in size. Sometimes they ossify and cause distinct limitation of the movements of the joint; sometimes they are so slight that no obvious deformity occurs. From the synovial membrane a large number of small fibrous nodules develop; some of them become calcified and present a rough worm-eaten appearance, and nearly all of them

contain a small central cavity. The bands connecting these nodules to the membrane may occasionally become obliterated, and the small fibrous masses persist as loose bodies in the joint. These outgrowths are probably due to a *proliferative inflammation* of the normally existing villi of the synovial membrane.

The chronic changes which occur in joints, as the result of continued rheumatism, differ from the foregoing in so far as the cartilages become fibrous and not eroded, while no outgrowths occur from their margins, and but little from the synovial fringes.

Gouty Arthritis has been referred to above.

AFFECTIONS OF PERIOSTEUM AND BONE.

Inflammation of bone always originates in its vascular structures —the periosteum and medulla. Although the term *periostitis* only implies that the *periosteum* is inflamed, the adjacent layers of the *bone* are always involved. When the inflammation chiefly affects the medulla and other soft parts lying in the Haversian canals or cancellous spaces, the condition is called *osteitis*; but when the medulla in the canal of a long bone is most markedly involved, the term *myelitis* has been applied. Inflammation is never strictly limited to either of these parts; hence the term *osteomyelitis* is usually adopted.

Periostitis may be conveniently divided into three varieties—serous, proliferative, and suppurative.

(*a*) *Serous periostitis* is rare, and is the mildest form of infective inflammation of the part. The membrane is infiltrated with inflammatory exudation and leucocytes, and the fluid may accumulate here and there, and separate the periosteum from the bone.

(*b*) *Proliferative periostitis* is common as a result of injury and of syphilis. A projecting node is formed by proliferated cells from the deeper layer of the periosteum, as well as of emigrated leucocytes. These cells may disappear, or may, as in other cases, be succeeded by fibrous tissue. This may ossify; it very rarely breaks down. Ossification begins in that part of the new tissue which is in contact with the surface of the bone. The vessels entering the Haversian canals in the latter are, on account of the elevation of the periosteum, more or less vertical to the surface; hence the new Haversian canals have the same direction. These new canals are at first well defined and easily separable from the old, but both ultimately become blended. The periosteum of bones lying just beneath the skin is especially liable to proliferative inflammatory changes. Inflammatory enlargement of a bone is always due to periostitis.

(*c*) *Suppurative periostitis* is generally a part of the infective disease known as *acute necrosis* or *osteomyelitis*. It affects growing bones, and rarely, if ever, occurs after union of the epiphyses. This disease is often associated with obvious injury: in other cases it is not improbably preceded by some minute lesion, such as a capillary

hæmorrhage or partial separation of an epiphysis. Pyogenic organisms are thus enabled to lodge in the wide capillaries of the shaft, close to the epiphysial disc, and excite suppuration. This spreads outwards along the disc, and then beneath the periosteum. Sometimes the organisms may affect the periosteum primarily. In both cases pus, forming beneath the periosteum, rapidly separates it from the bone. The vessels passing inwards from the periosteum are thus greatly stretched, and this, together with the primary damage to the vessels, induces thrombosis in many of them. Hence *superficial* necrosis is the usual result; but if the medulla also has suppurated, the necrosis will be *total—i.e.*, will involve the whole thickness of the shaft. Pyæmia may occur if the abscess is left unopened; and this is the condition in which infective fat-embolism is most likely to occur. In **suppurative osteomyelitis,** a diffuse suppurative inflammation attacks the medulla, and, to a less extent, the periosteum, causes total necrosis of large portions of bone, and very frequently produces a fatal result from pyæmia.

Inflammation of Bone, or *Osteitis,* is generally divided into two principal varieties: (1) rarefying osteitis, or caries; and (2) condensing osteitis, or sclerosis.

1. *Rarefying Osteitis* (*Caries*).—In the mildest form, which occurs much oftener in cancellous (vertebræ, tarsus, carpus, epiphyses of long bones) than in compact bone, a round-celled infiltration takes place in the medulla, and presses into the Haversian canals; the fat-cells and the hard substance of the bone disappear before it—cancellous trabeculæ are eaten through, and Haversian canals widened. A section shows spaces crowded with cells, often developing here and there into fibrous tissue. On the surface of the bone, bordering these spaces, are seen semilunar erosions, as if small bites had been taken out of it. These are called "Howship's lacunæ." Each contains leucocytes and epithelioid cells (osteoblasts), and often a giant-cell (osteoclast). The giant-cells erode the bone. The normal bone-corpuscles remain unchanged so long as they are distinguishable. This process may be described as an ulceration or *caries* of bone without formation of pus (*caries sicca*). Bones thus weakened readily yield to pressure; thus the affected bodies of vertebræ may almost disappear, those above and below becoming approximated (*Pott's disease*); while the shafts of long bones bend, as is seen in *osteitis deformans* and other diffuse inflammations.

In a very early case absorption of the inflammatory exudation may occur, and regeneration make good any loss of bony tissue which has taken place; but when marked destruction of bone has occurred, healing can only be effected by the formation and ossification of scar-tissue. This occurs in cases of healed spinal curvature without abscess. Often, however, the cells degenerate, and a *cold abscess* results. When this is opened, the ulcerating, *carious* surface of bone is exposed. If healing occur, it is by the process just described. Caries resulting in *cold abscess* is generally a manifestation of tuberculosis.

2. *Condensing Osteitis* (*Sclerosis*).—In the most chronic forms of osteitis no rarefaction of bone occurs; the new growth slowly ossifies and the Haversian canals and cancellous spaces diminish. The bone consequently becomes extremely heavy and ivory-like; it is generally thickened irregularly from coincident periostitis. Syphilis is the commonest cause of this change, especially in the long bones and in the bones of the skull. It is said that simple closure of a large number of Haversian canals may lead to death of the affected bone. In syphilitic necrosis of the skull the sequestrum is often very dense; it has probably been killed by degeneration and death of the inflammatory products in the bone around the sclerosed patch, with consequent destruction of the few vessels which entered it.

It is common to find rarefying and condensing osteitis combined. Osteoplastic periostitis and condensing osteitis frequently exist around carious patches: the surrounding bone is thus rendered thicker and denser. It may be that this less acute inflammatory process is coupled with true hyperplasia of the bony tissue.

Necrosis of Bone.—It has already been shown that death of bone may follow, in several ways, different forms of inflammation, each leading, however, to obliteration of vessels and arrest of nutrition.

This result may be brought about by any *injury* which strips off the periosteum and breaks up the medulla; but the extreme rarity of necrosis, even in the most serious simple fracture, shows that injury alone, with such inflammation as it excites, is scarcely to be regarded as a sufficient cause. It may, however, act indirectly by preparing a nidus for pyogenic and other infective organisms, as in compound fractures. Such intense irritants so diminish the vitality that more or less extensive thrombosis of the vessels ensues, with death of the parts which they supply.

Suppuration, beneath the periosteum and in the medulla, is the commonest cause of necrosis. This result is more often produced in compact than in cancellous tissue, owing to the greater ease with which the exudation can compress the vessels in the smaller and less numerous channels of the harder tissue.

The piece of dead bone is called a *sequestrum*; it is cast off by a process of caries which destroys the attachments of the sequestrum to the living bone beyond. It may be *total*—involving the whole thickness of the bone—*superficial*, or *central*, the last being much the rarest.

Considerable difficulty is often experienced in the removal of the sequestrum, especially if it be deeply seated. This difficulty is occasionally (*in central necrosis*) due to the persistence of a layer of the old bone enclosing the necrosed portion. Much more frequently, however, it is owing to the participation of the periosteum in the inflammatory process. The inflamed periosteum produces new bone, and the bony capsule (*involucrum*) thus formed encloses the sequestrum. Openings (*cloacæ*) exist in this capsule leading to the dead bone, and through these openings the inflammatory

products are discharged. When the sequestrum is quite superficial its removal is, of course, more readily effected.

Mollities Ossium.

Mollities Ossium, or *Osteomalacia,* is a rare disease, occurring only in adults, and especially in pregnant women who have borne many children. It is characterised by progressive decalcification of the bones, whilst the marrow increases steadily and becomes converted into a vascular round-celled structure. All bone is gradually absorbed, except a thin layer beneath the periosteum; so that in extreme cases the bones become mere shells. They are very light, easily cut with a knife, and bend or break readily. Early in the disease fractures may still unite. On section, in early stages, the cancellous spaces and Haversian canals are enlarged and full of a reddish, gelatinous substance, which at a later period may become yellow and fatty.

The nature of the disease is obscure. Lactic acid has been found in the bone—the reaction of which is said to be acid—and in the urine. The latter usually contains excess of calcium salts which have been removed from the bone and excreted.

The pelvic deformity resulting from the disease is clinically the feature of chief importance: the sacrum is pushed downwards by the weight of the body, and the acetabula upwards and inwards by the resistance of the femora, thus greatly shortening the two oblique diameters (*cf.* p. 397).

Rickets.

This disease of children may conveniently be considered here, as the most characteristic changes are found in the bones. It is so frequent in the large towns of England that it has acquired on the Continent the name of the "English disease." It appears to be caused by defective hygienic conditions, especially by bad air and improper feeding. It is particularly common in children brought up by hand, especially in infants which receive starchy food at an age when they cannot properly digest it. It may probably be said that all conditions which materially interfere with the nutrition of a child aid in the causation of rickets; among these, the absence of *fresh* food ranks high. Diets deficient in fats or in carbohydrates seem sometimes to be sufficient causes.

The disease is mainly characterised by changes affecting the growing parts of bones, and is therefore most marked where growth is most active—viz., at the epiphyses and under the periosteum of long bones, and at the margins of flat bones. These changes produce undue thickness and softness, which, in their turn, lead to projections and curves, according to the direction and degree of pressure on the softened bones. The bone-lesions are accompanied by symptoms of general ill-health, and often by enlargement of the liver and spleen, and, less often, of the kidneys and lymphatic glands, due chiefly to increase of their interstitial connective tissue.

The essential changes in the bones are (1) an excessive absorption of pre-existing bony tissue, and (2) an extensive formation of osteoid tissue, which very gradually and very imperfectly undergoes calcification. It will be remembered that if a section of the end of a *healthy* growing long bone be examined, a straight line is seen where the white epiphysial cartilage is adherent to the shaft (Fig. 152, B), which here consists of loose cancellous tissue, with spaces filled with red marrow. Between the bone and the epiphysis is a blue, semi-translucent band about one millimetre broad, with practically straight margins. Microscopically, the blue line is found to consist of the one or two layers of cartilage-cells which normally multiply and enlarge, forming the well-known oval groups among which

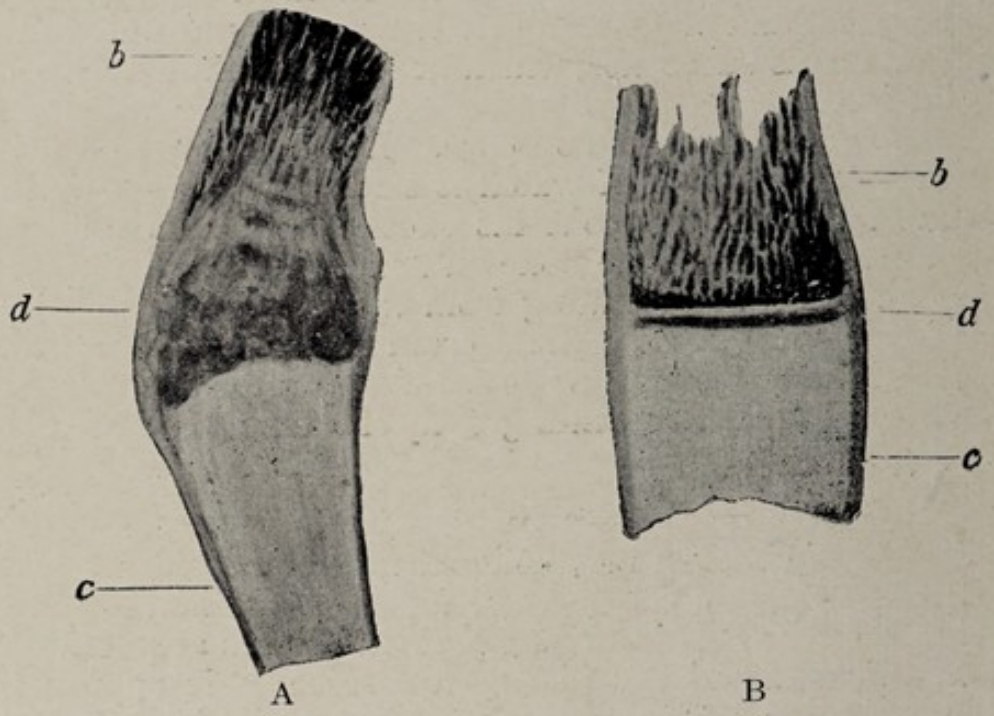


FIG. 152.—GROWING ENDS OF (A) RICKETY AND (B) NORMAL RIBS. (× 3.)
B is taken from an older child, and is therefore larger. (See text.)
b, rib; *c*, costal cartilage; *d*, transition zone.

ossification proceeds. The septa between these groups become very thin, and, in the immediate neighbourhood of the shaft, undergo calcification. A sudden transition from the cartilage-cells to those of the vascular red marrow is seen in these spaces. As soon as these spaces (*primary areolæ*) with calcified walls become occupied by the round-celled marrow, absorption begins, and adjacent spaces open into each other and form the larger *secondary areolæ*. On the walls of these, laminæ of bone are deposited, including osteoblasts in the lacunæ between them; and thus Haversian systems are gradually developed. The calcified cartilage-matrix is darker and more granular than the bone laid down by the medulla which gradually replaces it.

In a rickety bone the blue transition-zone is at least ten times

wider than normal, affecting many rows of cartilage-cells; while its outlines, both towards the bone and towards the cartilage, are very irregular (Fig. 152, A). The calcification of the matrix occurs without any regularity. In the cartilage, among the long rows of proliferated cells, will be found spaces which arise as outgrowths from the medulla, and contain vessels and medullary tissue. Just reaching and partly surrounding these are thick, irregular trabeculæ of osteoid tissue, which enclose masses of cartilage, here and there calcified, and of medulla. The trabeculæ are thickest and most extensive on the medullary side of the proliferating cartilage-cells. In the central parts of some of the thickest trabeculæ small patches of true bone may be seen. A few of the cartilage-cells may become converted into marrow-cells, as in normal ossification; but a large number are converted directly, without any rupture of their capsules, into the cells of the osteoid tissue (Fig. 153).

In flat bones the process begins by a very marked absorption of the bony trabeculæ already formed. Upon the remnants of the old bone, as well as in the spaces between them, osteoid tissue is deposited so as to form new trabeculæ in the marrow. The formation of the osteoid tissue is preceded by a spindle-celled embryonic tissue. Beneath the periosteum osteoblasts form and osteogenic fibres appear. From these, osteoid tissue is formed. In general terms, the growth of osteoid tissue in the medulla may be said to resemble the formation of internal callus, while that deposited from the periosteum similarly resembles external callus (Ziegler).

Bones consisting of soft rickety structure yield more or less readily under pressure, or break under slight violence. The fracture, however, is generally incomplete. As bending occurs, a buttress of bone is deposited along the concave side of the curve. This is often seen in the femur and tibia, giving the bones a flat, somewhat razor-like appearance. The position and extent of the curving will depend to some extent upon the relative proportion which the changes at the epiphyses bear to those beneath the periosteum.

These changes afford a ready explanation of (1) the thickening of epiphyses; (2) the displacements which occur about the junction of shafts with epiphyses; (3) the thickenings of the edges, and the irregularities on the surface, of cranial bones; and (4) the abnormal curvature of bones under pressure—all of which are common phenomena in rickets.

The process just described seems to be injurious to the subsequent growth of the epiphyses. They often join the shafts prematurely, and thus cause permanent shortening of the bones.

Among the most important of the deformities resulting from this disease is the **rickety pelvis.** There are two forms. The first shows *shortening of the antero-posterior diameter* only, and occurs in cases in which the child, being unable to walk, is kept lying down. The second resembles the *osteomalacic pelvis,* both in its shape and in the mechanism of its production, for it occurs in children who are able to walk about (p. 395). In a **rickety thorax,** the growing

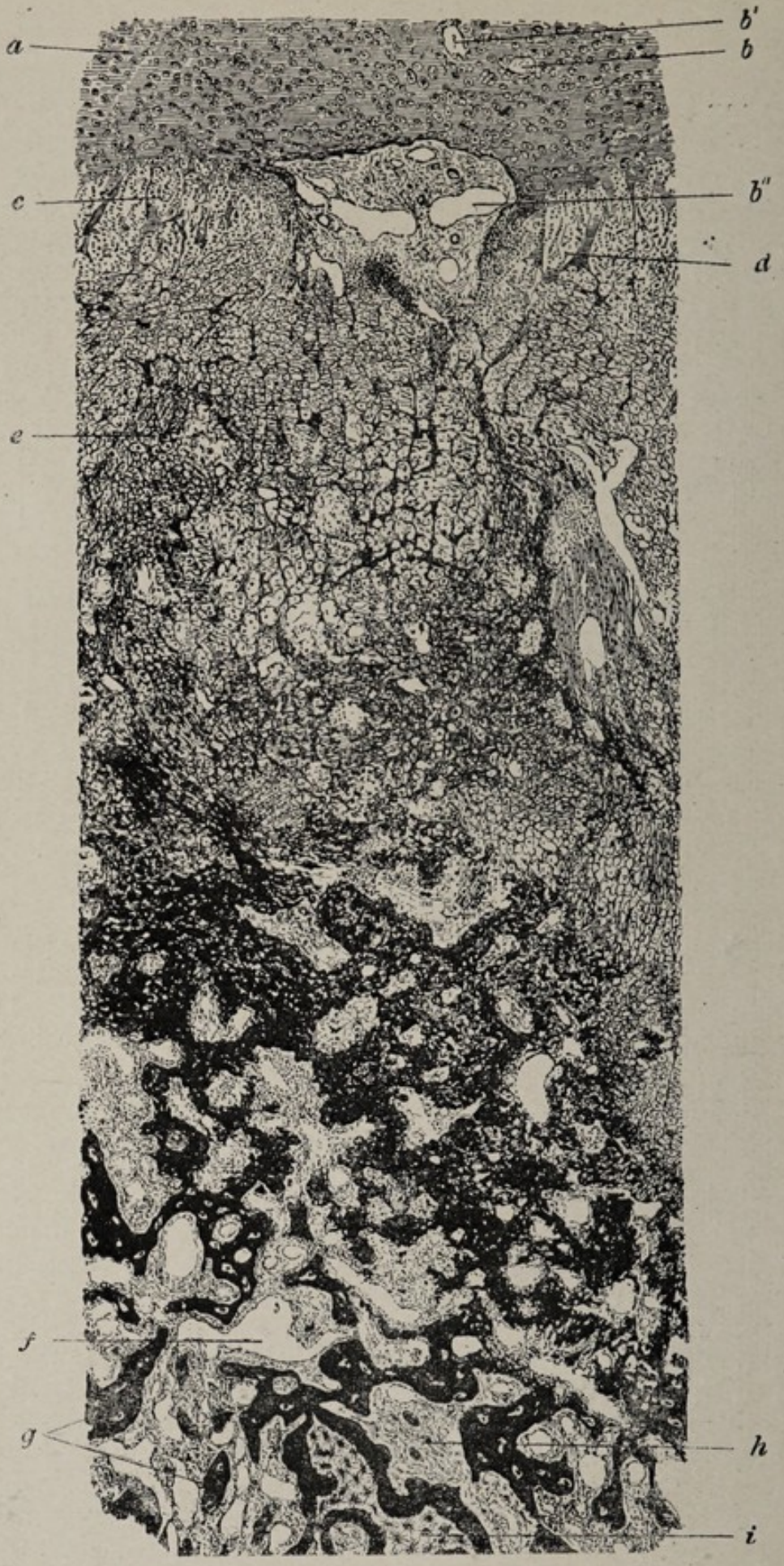


FIG. 153.—GROWING END OF RICKETY RIB.

a, cartilage; *b*, *b'*, *b''*, vascular medullary spaces within cartilage; *c*, *d*, proliferating cartilage-cells; *e*, calcified cartilage; *f*, vascular channels; *g*, trabeculæ of osteoid tissue; *h*, vascular medulla; *i*, true ossification occurring in osteoid trabeculæ.

anterior ends of the ribs are softened and much enlarged, especially on the visceral side. *The softening* leads to a sinking in of the softened parts and to a corresponding pushing forward of the sternum; while *the enlargements* produce a row of nodules on each side of the thorax, diverging from above downwards (*rickety rosary*).

Along with the changes in the bones just described the principal features of rickets are: delayed dentition, early decay of the milk-teeth, late closure of the fontanelle, laxity of the ligaments surrounding the joints, a tendency to catarrh of mucous membranes, and an undue irritability of the nervous system; to this last condition are due the convulsions which occur in rickety children on slight provocation, and the special forms of spasm known as tetany and laryngismus stridulus.

Achondroplasia.

Achondroplasia* (chondro-dystrophia *fœtalis*) was formerly known as "fœtal rickets," but is due to a pathological process entirely different from that just described. It consists in a failure of development in those parts of the bony skeleton which are formed from cartilage—especially in the long bones of the limbs and the bones forming the base of the skull. In the long bones the ends of the diaphyses are markedly expanded and overlap the epiphyses. In consequence of this failure, the limbs are short and stunted, the fingers scarcely reaching below the iliac crests, and the legs being so short that the affected person is a dwarf in stature, although the trunk may be of nearly normal proportions. The cranial bones, being formed from membrane, develop normally, and the upper part of the head is thus out of proportion to the base of the skull. The intelligence is unaffected—a point of distinction from cretinism, with which the disease has sometimes been confused.

Osteogenesis Imperfecta.

Somewhat resembling the above, and of equally obscure origin, is the condition known as osteogenesis inperfecta. It occurs in young children, and consists in abnormal weakness and fragility of the bones, so that spontaneous fractures occur on the slightest pressure. The bones of the skull are defective, and the head looks unduly large, with peculiar bulging in the temporal regions. The eyeballs may be depressed, and the condition mistaken for slight hydrocephalus.

Leontiasis Ossea.

In this disease there is irregular enlargement of the bones of the face. The condition starts in the superior maxilla, and irregular masses of bone are formed and protrude externally and into the antra of Highmore and nose. The frontal eminences and other bones of the cranium and face may be affected, giving a lion-like appearance. The causation of the disease is unknown.

* Greek ἀ, not; χόνδρος, cartilage; πλάσσω, I form.

CHAPTER XXIV

AFFECTIONS OF THE LYMPHATIC SYSTEM AND OF THE SKIN

LYMPHATIC GLANDS.

EXAMPLES of **acute inflammation** of lymphatic glands (*acute lymphadenitis*) are furnished by the inflammation of the axillary glands which may follow a wound on the hand; of the inguinal glands, in a case of soft chancre; and of the lymphoid follicles of the intestine in inflammation of the intestinal mucous membrane.

In acute inflammation of lymphatic glands the bacteria which produce the inflammatory reaction are generally conveyed from a primary focus of inflammation (diphtheritic, erysipelatous, scarlatinal, chancrous, etc.), existing in the area of skin or other tissue drained by the lymphatics leading to the gland: occasionally no seat of infection is apparent, and the bacteria seem to have been conveyed directly to the gland without causing any lesion elsewhere. A gland affected by acute inflammation becomes intensely vascular, and the seat of free exudation. The escaping leucocytes accumulate in its tissues and sinuses, until all distinction between medulla and cortex has disappeared, while the gland is swollen and its substance is soft, pulpy, and often dotted with hæmorrhages. Leucocytes in the lymph coming from the primary focus are also detained in the gland.

Upon the removal of the injurious influence, the process may gradually subside, and the new elements undergo disintegration and absorption, the gland gradually returning to its normal condition (*resolution*).

In other cases the process may be more intense and go on to *suppuration*. Scattered areas may necrose, trabeculæ be destroyed, many of the cells become disintegrated, and the loculi of the gland become filled with pus. This is usually associated with inflammation and suppuration of the surrounding connective tissue. In the glands of a mucous membrane the process gives rise to what is known as *follicular abscess*. In still more acute cases the exudation may be largely hæmorrhagic,

Chronic inflammation of lymphatic glands results from the presence of irritants which, while less intense, are more prolonged in their action than those which give rise to the acute form. The commonest infective causes are tuberculosis and syphilis, and the commonest non-infective cause is the presence of dust, and especially particles of carbon. The gland may be enlarged to many times its natural size. In some cases the reticulated network becomes thicker and more fibrous, its meshes becoming smaller and smaller ; the lymph-cells diminish in number ; and the gland becomes hard and fibrous. Probably in these chronic cases the cells of the gland-substance and the flat connective-tissue cells covering the trabeculæ multiply, and assist in forming the new cells. In lymphadenitis due to the presence of dust the thickening of the reticular network is the principal change. This may also form the final stage of *acute* lymphadenitis.

"Post-nasal" Adenoids.

Masses of adenoid growth not infrequently develop from the roof and posterior surface of the naso-pharynx in weakly children. These masses consist of ordinary soft lymphoid tissue with the cells here and there more closely aggregated into follicles. The growths are covered by ciliated epithelium, but this is often destroyed by the catarrhal processes to which they are liable. They interfere with the passage of air through the nose, and often block the orifices of the Eustachian tubes. In a few instances they show tubercular changes.

Hodgkin's Disease (Lymphadenoma).

This disease is characterised by the enlargement of the lymphatic glands and lymphoid tissue in various parts of the body, together with the development of lymphatic growths in internal organs, especially in the spleen, and by a progressive anæmia of the secondary type (Chapter XXVII.).

The larger lymphatic glands are usually the earliest seats of the growth. At first only a single group of glands may be enlarged; subsequently, however, the process becomes more general, and the glands throughout the whole body may be more or less involved. The groups of glands most often affected are, in the order of frequency, the cervical, the axillary, the inguinal, the retro-peritoneal, the bronchial, the mediastinal, and the mesenteric. The growth, which in the earlier stages is limited to the glands, gradually breaks through the capsules, so that the enlarged glands ultimately become confluent, and form large lobulated masses, but the agglomeration of glands in Hodgkin's disease is generally a later and less prominent feature than in tuberculosis of lymphatic glands. The growth may also extend still farther beyond the confines of the gland, and invade and infiltrate the adjacent structures.

This new growth of lymphatic tissue, which commences in and often extends beyond the confines of the lymphatic glands, is ultimately followed by the formation of lymphoid growths in various internal organs wherever lymphoid tissue exists, but more especially in the spleen, which is affected in a large proportion of cases. Here the new growth originates in the Malpighian bodies, and so gives rise to disseminated nodules. These vary in size from minute points to masses as large as a hazel-nut or walnut. They are usually

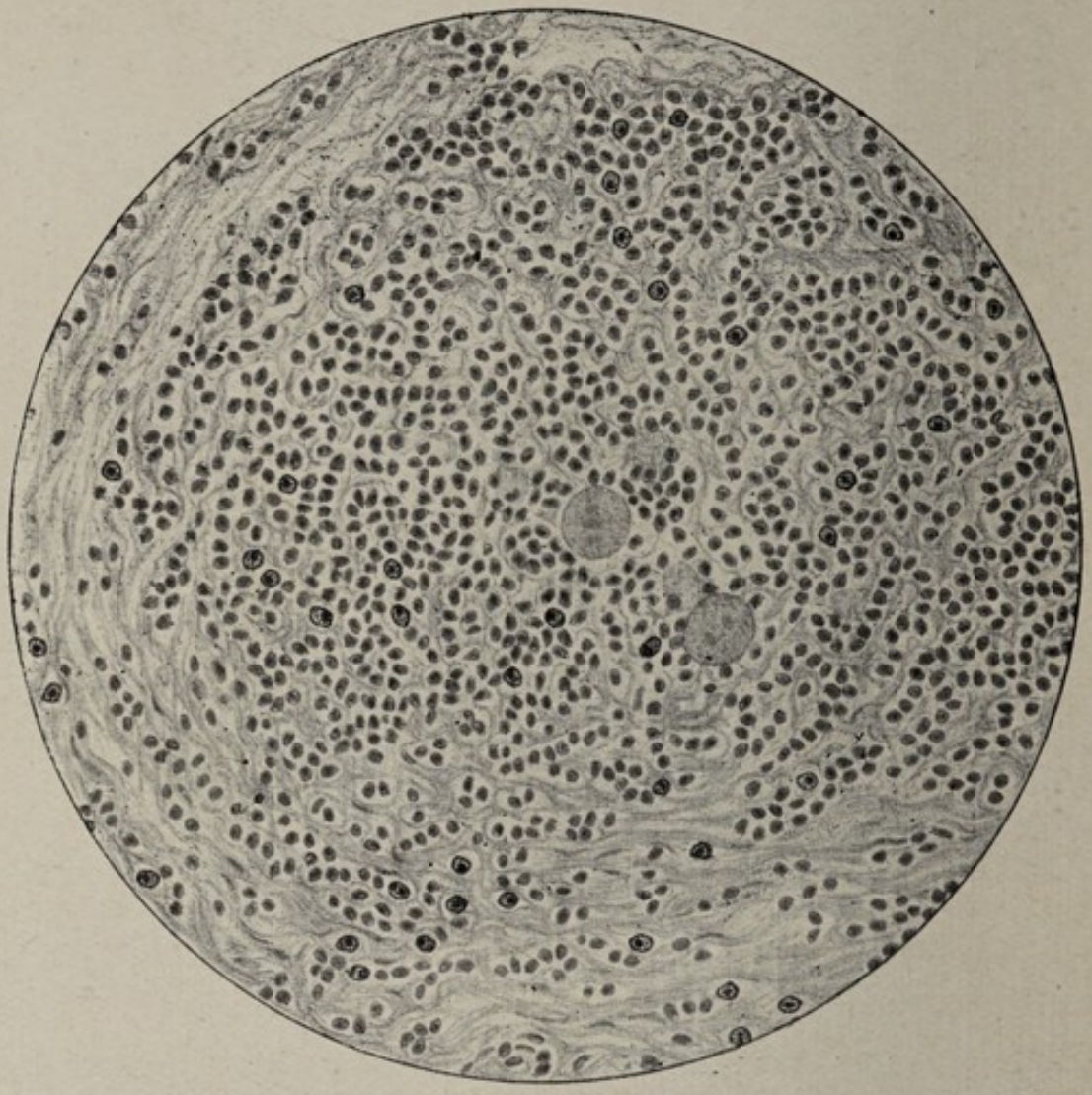


FIG. 154.—LYMPHADENOMA (LYMPHATIC GLAND). (× 325.)

more or less irregular in shape, of a greyish or yellowish-white colour, firmer in consistence than the splenic tissu , and not encapsuled. In addition to these, wedge-shaped infarctions surrounded by a zone of hyperæmia are sometimes met with, similar to those which are often seen in leucocythæmia. The spleen itself is generally markedly increased in size, and its capsule is usually thickened, and often adherent to adjacent organs. In quite exceptional cases the spleen is not the seat of these disseminated growths, but is simply enlarged, like the leucocythæmic spleen.

The liver, kidneys, alimentary canal, medulla of bone, lungs, and subcutaneous tissue may all become involved, the new growths occurring either as nodules of various sizes scattered through the organs, or in a more infiltrating form, like many of those met with in leucocythæmia.

The affected glands usually present typical histological changes (Fig. 154). The distinction between cortex and medulla largely disappears. The lymphocytes are greatly diminished in number, while the endothelial cells and the connective-tissue elements are markedly increased, and this may ultimately lead to a definite fibrosis. A varying number of giant-cells are usually present. These have no resemblance to the giant-cells of tuberculosis. They are large cells of the endothelial type, having two or more nuclei, situated centrally, and sometimes showing mitotic figures. They are known as Virchow's cells, since they were first described by him as characteristic of the disease. There is usually, also, a definite increase in the number of eosinophile cells present in the glandular tissue, and this increase often forms a most striking feature. The secondary deposits of lymphadenoid tissue throughout the body have a similar structure.

The pathology of the disease is undoubtedly obscure. The development of the new growths cannot in most cases be regarded as the result of infection, though one instance is recorded in which an assistant, shortly after being concerned in the clinical investigation of a case, developed the disease in a very acute form. The disease occurs in many of the lower animals.

Of the causation of lymphadenoma nothing certain is known. It resembles, on the one hand, an infective condition such as tuberculosis; on the other hand it has affinities with the tumours. The infective origin seems the more probable. A bacillus has been credited with the production of the disease, but further evidence is necessary before this theory of causation can be accepted. Much found acid-fast granules in these cases which he believed to be a stage in the life-history of the tubercle bacillus. Pröscher and White found a spirochæte present in a case of this affection, but in other instances these organisms have been sought in vain.

A special form of tumour, **lymphosarcoma,** originates in lymphatic glands, especially in those of the mediastinum (p. 307).

AFFECTIONS OF THE SPLEEN.

Atrophy of the spleen may occur in old age and in wasting diseases, the capsule becoming wrinkled and the organ tough in consistency. **Amyloid degeneration** has already been described (p. 51).

Enlargement of the spleen owing to **passive hyperæmia** is found in cases of heart-failure and of cirrhosis of the liver, and as a result of thrombosis of the splenic vein. The spleen is also a favourite seat of **infarction** in cardiac disease. An **active hyperæmia** occurs in many infective diseases, notably in typhoid fever and relapsing fever, in

both of which the causal organisms may be found in the spleen; areas of necrosis produced by the toxines of the bacilli may be met with in the former disease.

Acute inflammation and **abscess-formation** are not common affections, but may occur in septicæmic conditions, or by extension from neighbouring viscera. **Chronic inflammation** may be due to syphilis or to malaria ("*ague-cake*"). **Pigmentation** with altered hæmoglobin occurs in the latter disease.

Great **enlargement** of the spleen occurs in leucocythæmia (p. 445) and in lymphadenoma (p. 401), while less degrees of enlargement are seen in splenic anæmia (p. 441), in congenital syphilis, in malaria, and in rickets.

In generalised **acute tuberculosis** the spleen is usually studded with grey or yellow granulations or with conglomerate tubercles. It is, however, rarely the seat of **malignant tumours,** and when it suffers it is more often involved by direct extension from some focus in the surrounding parts than by embolic infection with secondary (metastatic) growths.

Thickening of the capsule of the spleen (*perisplenitis*) is very commonly found after death, often in the form of localised dense patches of almost cartilaginous hardness; the cause of the condition is often obscure.

AFFECTIONS OF THE SKIN.

Congenital Defects.—The most notable congenital defect in the skin is the condition known as *Ichthyosis*. In the worst cases the fœtus is born dead, and appears as if encased in a suit of armour, formed of hypertrophied horny epidermis (*harlequin fœtus*). Milder degrees (*ichthyosis, xerodermia*) appear later in life, and take the form of roughness and dryness of the skin, rendering it liable to crack and to develop secondary dermatitis. It has been attributed to persistence of a special fœtal layer, the epitrichium.

Atrophy affects all the layers of the skin, but especially the rete Malphigii. It may result from pressure or from traction (*striæ atrophicæ, lineæ albicantes*), as in the skin of the abdomen after pregnancy or ascites. Occasionally similar lines appear after an infective disease—*e.g.*, enteric fever—and are due to the resulting malnutrition. Atrophy of the skin is also a senile change, and may accompany lesions of the nervous system.

Hypertrophy, or overgrowth of the horny layer (*hyperkeratosis*) occurs as a result of venous congestion, or of the action of a poison, such as arsenic, or of the inoculation of micrococci of low virulence. It accompanies overaction of the sweat-glands (*hyperidrosis*) of the palms and soles, and may result from local irritation by such substances as tar and soot; in these last instances, and in arsenical conditions, it may be followed by the development of epithelioma. *Corns* and callosities are instances of hypertrophy of the horny layer due to local irritation by pressure or friction. Cutaneous *horns*, in

which the overgrowth involves only a few papillæ and attains an extraordinary bulk, may also be seats of epitheliomatous change. In the condition known as *pityriasis rubra pilaris* hyperkeratosis affects the mouths of the hair-follicles, and may extend over almost the whole body. The term " porokeratosis " has been applied to a similar change at the orifices of the sweat-ducts. In the common affection known as *comedo*, the underlying condition in acne, the mouth of a follicle becomes blocked by a mass of overgrown horny cells, and the secretion of the sebaceous gland accumulates behind the obstruction. Staphylococci grow in the retained material, and set up inflammation in the walls of the follicle, thus causing small boils and pustules (*acne*).

Hypertrophy of the rete Malpighii is known as *acanthosis*, and occurs in warts and condylomata, and in the infective granulomata (*e.g., lupus verrucosus*). It is also seen in the rare affection *acanthosis nigricans*, accompanied by hyperkeratosis and increased deposit of pigment.

Pigmentation of the skin may be due to deposit of hæmatoidin, as after bruises and other effusions of blood; to increase of melanin, as after exposure to strong sunlight (freckles, ephelis) or heat; or to the action of poisons (arsenic, syphilis); and is seen in Addison's disease and in pregnancy. In the curious disease *leucodermia*, or *melanodermia*, the pigment is apparently extracted from certain areas of skin which become white, and deposited in others which are unduly pigmented.

Tumours of the skin need not be separately considered (see Chapter XX.), and **tuberculosis** of the skin is dealt with on p. 261.

The vascular phenomena which follow on irritation by poisons or infective agents, and to which the name of **inflammation** is applied, were largely studied by early observers in the skin, and the description of the process already given applies especially to this tissue. The earliest stage is seen in simple hyperæmia (*erythema*), which may be followed by exudation (*weals, vibices*, local *œdema*). If the exudation accumulate beneath the horny layer, and raises it up, a *vesicle* is formed; and if the contents of this be largely formed of leucocytes, it is called a *pustule*. If these contents dry up, a *crust* results. Hæmorrhage beneath the epidermis or among the cells of the rete gives rise to *petechiæ*. In the condition called *purpura* numerous small petechiæ are scattered over the skin, owing to the action of bacterial or other poisons on the walls of the capillary bloodvessels.

Certain common diseases may be considered in greater detail.

Eczema.—The name " eczema " is applied to certain forms of dermatitis not very clearly defined. They may arise from external irritation or from internal toxæmia. The skin is first hyperæmic; then exudation occurs between the prickle-cells, and may cause separation of the horny layer, which is rubbed off by the patient's efforts to allay the irritation. A raw surface is then left, from which plasma exudes. Leucocytes escape from the dilated bloodvessels

in the corium, and infiltrate the surrounding tissue; and if the process becomes chronic, some hypertrophy of the horny layer and of the rete may take place (Fig. 155).

A form of dry, scaly dermatitis accompanies overaction of the sebaceous glands (*seborrhoic eczema*, or *dermatitis*), and seems to be due to some infective agent, probably a feebly virulent staphylococcus.

Psoriasis.—In this affection discrete rounded patches of scaly hyperæmic skin appear, scattered over the body, especially on the

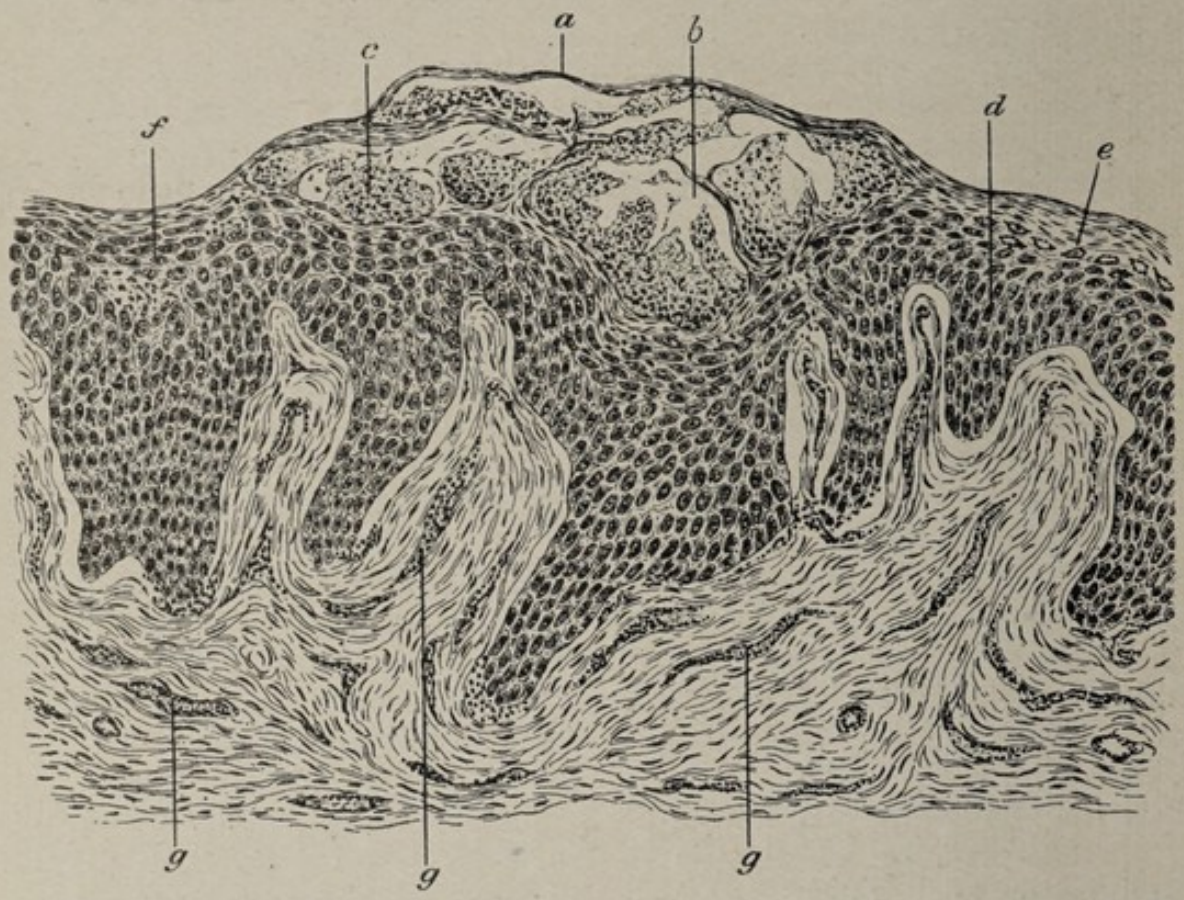


FIG. 155.—SECTION OF SKIN, THE SEAT OF ECZEMA. (AFTER MACLEOD.)

a, horny layer forming roof of vesicle (*b*); *c*, débris of cells in vesicle; *e*, stratum granulosum; *f*, flattened cells forming base of vesicle; *g*, dilated blood-vessels and round cells in corium.

extensor surfaces of the limbs. Histologically, there is elongation of the papillæ, increase in the rete Malpighii, and hyperkeratosis, with some exudation into the lymphatic spaces and accumulation of round cells along the vessels. There are also collections of similar cells between the layers of the epidermis, and the cells of this structure show defective keratinisation, becoming closely adherent one to another, and thus forming scales, which owe their silvery whiteness to infiltration with air (Fig. 156). The cause of the disease is unknown: the peripheral extension of the lesions, with central healing, suggests a parasitic origin; but the symmetrical distribu-

tion of the malady agrees rather with a toxic or trophoneurotic cause. A special organism, the micrococcus of Unna, may occur

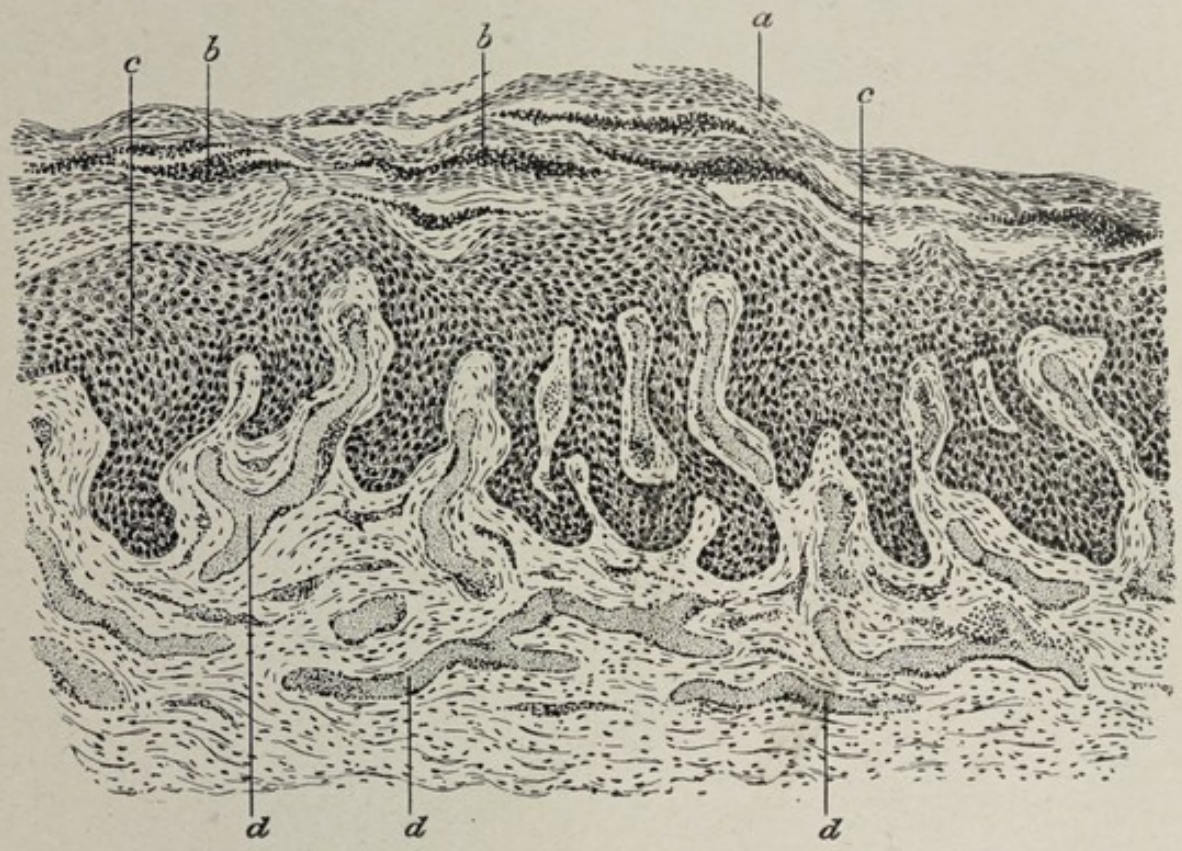


FIG. 156.—SECTION OF SKIN, SHOWING LESIONS OF PSORIASIS. (AFTER MACLEOD.)

a, horny layer, imperfectly cornified, forming scale; *b*, collections of round cells in epidermis; *c*, enlarged interpapillary processes; *d*, dilated blood-vessels surrounded by some round cells.

in the lesions both of eczema and of psoriasis. It appears to be closely allied to the *Staphylococcus albus*, and may be identical with it. Its causal relationship to these diseases is not established.

CHAPTER XXV

AFFECTIONS OF MUCOUS MEMBRANES, AND OF THE STOMACH AND INTESTINES

THERE is sufficient similarity between the diseases of the various mucous membranes to justify a general consideration of their characters.

INFLAMMATION OF MUCOUS MEMBRANES.

It is convenient to distinguish certain varieties of inflammation of mucous membranes according to the degree of damage to the tissues, the depth to which it extends, and the general character of the exudation. In each of these varieties the usual changes in the blood-stream and vessel-walls occur, leucocytes and fluid escaping into the tissues and on to the surface of the membrane. The two main varieties into which inflammation of mucous membranes may thus be divided are (1) *catarrhal*, in which the exudation remains fluid; and (2) *fibrinous*, in which it coagulates, forming the so-called *false membrane* on the surface.

Catarrhal Inflammation.—In this form the exudation may be serous, mucous, muco-purulent, or purulent, according to the nature and intensity of the irritant.

Serous Catarrh.—In acute cases the earliest signs of simple inflammation (p. 191) are rapidly followed by a copious watery exudation from the surface, and the tenderness and pain are soon relieved. When the onset is less acute the early changes are less marked, the exudation being usually the first thing noted. These changes are frequently met with in ordinary nasal catarrh.

Mucous Catarrh is characterised by increased production of mucus derived from the surface-epithelium or secreted by the mucous glands (Fig. 157). The mucus escapes with the serous exudation, or remains more or less adherent to the surface, as is often seen in chronic pharyngitis. Sometimes the sero-mucous discharge is practically clear; at others, it is more or less opaque: in the former case, it contains only a few cells; in the latter, a large number. The cells are either escaped leucocytes or desquamated epithelial elements, detached, for the most part, singly.

Purulent Catarrh.—If the irritation be more intense, the number of leucocytes escaping will be still greater, and the secretion will be purulent or muco-purulent. In such cases the epithelium is often detached in considerable masses, and the underlying tissue markedly infiltrated with leucocytes. The basement-membrane is œdematous and the whole mucosa swollen. All *lymphoid struc-*

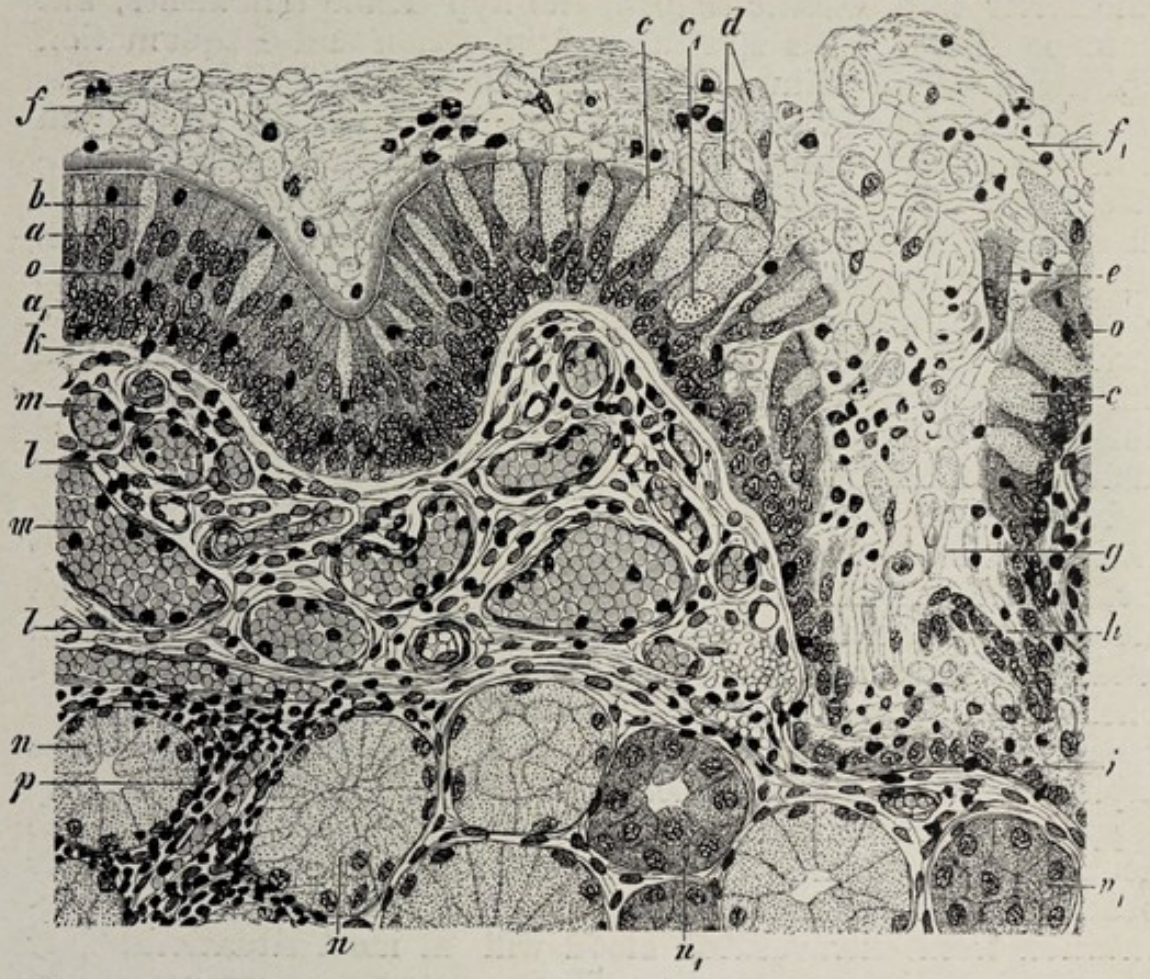


FIG. 157.—RECENT CATARRHAL BRONCHITIS. (× 120.) (ZIEGLER.)

a, ciliated cells; a_1, deep layers of cells; *b*, goblet-cells; *c*, cells that have undergone extreme mucoid change; c_1, mucoid cells whose nuclei have undergone a similar change; *d*, desquamated mucoid cells; *e*, desquamated ciliated cells; *f*, deposit consisting of mucus-droplets, and f_1, of mucus-filaments and pus-corpuscles; *g*, excretory duct of a mucous gland filled with mucus and cells; *h*, desquamated epithelium of the excretory duct; *i*, persistent epithelium of the duct; *k*, swollen hyaline basement-membrane; *l*, connective tissue of the mucosa somewhat infiltrated with cells; *m*, *m*, distended bloodvessels; *n*, mucous glands filled with mucus; n_1, acini of mucous gland without mucus; *o*, migratory cells in the epithelium; *p*, cellular infiltration of the connective tissue of the mucous glands.

tures in the mucous membrane are generally affected. The lymph-follicles swell, their contents soften, and minute abscesses are formed: the latter burst and leave the small ulcers (*follicular ulcers*) so often seen in severe catarrh of the intestines, appendix vermiformis, and pharynx. The ulceration in some cases extends beyond the confines of the follicle. Not infrequently the proper *glandular*

structures also become involved, and their ducts may become choked with the products of their altered secretion.

The acute process may quickly subside, or it may become chronic. In the former case the damaged epithelium is soon replaced, the repair often beginning before the vascular changes have disappeared. In the latter case (*chronic catarrh*) the hyperæmia diminishes, but the escape of leucocytes and the multiplication and desquamation of epithelial cells continue, while the sub-epithelial tissue remains extensively infiltrated with leucocytes. Later on, the epithelium and the glands may undergo atrophy, while the sub-epithelial connective tissue may become more and more extensively infiltrated with small cells due to multiplication of connective-tissue cells, leading ultimately to marked fibrosis. When stretching of the mucous membrane accompanies atrophy of the glands, as in chronic catarrh and dilatation of the stomach, the membrane is often much thinner than normal. The changes in the sub-epithelial connective tissue are usually accompanied by enlargement of the lymphoid structures—an enlargement which sometimes gives to the membrane a nodular or granular appearance. This is well seen in the pharynx (*follicular pharyngitis*). The enlarged lymphoid structures may ulcerate, and the muscular and elastic tissues, although they lie some distance from the surface, may be so far weakened that when considerable pressure is put upon them—as by the cough of chronic bronchitis—they may give way, and permit dilatation of the tubes they surround. The muscularis mucosæ, when damaged, is never completely repaired. After death any hyperæmia present rapidly disappears, and is seldom recognisable even in severe cases: the mucous membrane may even look paler than natural; but after repeated inflammation of any intensity more or less dark grey pigmentation from extravasated blood will, in most situations, bear evidence of the former attacks. These appearances can readily be seen in a chronically inflamed bladder, such as is associated with stricture of the urethra or enlarged prostate.

ÆTIOLOGY.—The causes of catarrhal inflammation are (1) the entrance of mechanical or chemical irritants into the cavities or tubes lined by mucous membranes; and (2) the presence and growth of bacteria and other parasites.

As examples of the first of these causes may be quoted the production (1) of bronchitis by metallic particles or irritating vapours in the respired air; (2) of gastric catarrh by the action of alcohol; and (3) of intestinal catarrh by the passage of irritating ingesta. As examples of the second group may be quoted the catarrh of the large intestine due to the presence of thread-worms, and the urethral catarrh caused by the introduction and growth of gonococci.

The two causes above mentioned may frequently be combined. They are probably assisted to some extent by exposure to cold, as in intestinal catarrh, and by certain abnormalities in the circulatory blood, such as are believed to exist in gout.

Fibrinous Inflammation.—This term is applied to those inflam-

mations of mucous membranes and open wounds which are characterised by the production of a fibrinous layer or so-called *false membrane*—such as is seen in diphtheria. On mucous surfaces the exudation may exist in little patches or may cover a large area.

It is usually of a yellowish or greyish-white colour, and its consistency varies from a firm and tough membrane to a soft, pultaceous material; it may be deeply blood-stained. It is more or less easily separable from the subjacent tissue, and when removed carries at least the surface-epithelium with it. In thickness it may vary considerably in different parts. The words *croupous* and *diphtheritic* are often applied to conditions of fibrinous inflammation, and are sometimes used to distinguish different degrees of the process. Thus, some authorities call an inflammation *croupous* when the membrane involves no more than the *epithelium* of a mucous membrane, and *diphtheritic* when it involves the whole *mucosa*. This difference in the depth of the tissues involved is probably due to variation in the intensity of the irritant, the extent of the *false membrane* in diphtheritic inflammation being due to the coagulation-necrosis (p. 22) of the involved mucous membrane. The use of the term diphtheritic in this connection is unfortunate, as it does not imply any necessary connection with *diphtheria*, although this disease undoubtedly furnishes the best examples of diphtheritic inflammation. It is better therefore to discard these unnecessary terms, and to speak of fibrinous inflammation, recognising that this may vary in intensity, and consequently in the degree of destruction of tissue that it induces. According to Cohnheim, the process is more likely to be superficial in those situations where a distinct basement-membrane exists—as in the pharynx and respiratory tract—than in those where this is not the case—as in the intestines and conjunctiva.

False membranes differ in character according to the depth of tissue involved. If only the epithelium be destroyed, the membrane is thin and easily stripped off. It consists of several layers of fibrin containing in their meshes leucocytes, desquamated epithelial cells and débris; and lies on the surface of the hyperæmic mucous membrane, which is denuded of its epithelium, and infiltrated with leucocytes. If the whole mucosa be involved, as in diphtheria, the false membrane is separated with difficulty, and its deeper parts are found to contain necrosed tissue. In such cases a bleeding surface is left when the membrane is removed. In advancing cases there is no sharp line between the coagulated and the living tissue-elements.

ÆTIOLOGY.—The apparent causes are very varied. False membranes are found (1) on the tonsils, larynx, and other parts in affections due to the *B. diphtheriæ* and to other organisms (streptococci, pneumo-bacilli), or as a result of scalds or the application of caustic chemicals; (2) in the bladder after parturition (when a complete cast may be expelled), and in the most acute cystitis; (3) in the vermiform appendix, sometimes from the irritation of a concretion; (4) in

the lower part of the large intestine in dysentery; and (5) as a chronic change in the air-tubes in plastic bronchitis. It may be noted here that false membranes sometimes form upon granulating wounds, and it is held by some that there is no real distinction between such cases and those of true diphtheria of wounds and of hospital gangrene. It seems most probable, however, that there is an ætiological difference, for false membrane on granulations may be induced by merely blistering the surface.

Although the above facts show that false membranes may result from the action of simple irritants, the great majority met with in man are due to the action of pathogenic organisms, for most of them are contagious, and organisms are found in almost all cases.

Effects.—The effects of inflammation of mucous membranes, whether catarrhal or fibrinous, depend very largely upon the size and function of the tubes or cavities involved. Acute catarrh generally gives rise to pain and to spasm of the involuntary muscular tissue, as is seen in the intestinal catarrh of children. When the tubes affected are small, obstruction to the passage of the secretions which they convey may lead to serious results. Thus catarrh of the small bronchial tubes, or diphtheritic inflammation in the larynx and trachea, may so obstruct the entrance of air that the oxygenation of the blood is gravely interfered with; while catarrh of the bile-ducts may similarly prevent the bile reaching the intestine and lead to jaundice. When much inflammatory fibrosis has occurred, marked irregularity or narrowing (*stricture*) of the lumen of the affected tube may result. The best illustration of this termination is seen in the result of repeated attacks of gonorrhœa. In this disease the purulent catarrh of the urethra is often followed by so much proliferative inflammation of the submucous tissue that the lumen of the tube is almost occluded. In structures of less importance, if the occlusion be complete, retention-cysts may be formed by distension behind the stricture (p. 340). When the obstruction is permanent, but not entire, hypertrophy of the muscular walls above the stricture is usually found (p. 73).

AFFECTIONS OF THE STOMACH AND INTESTINES.

Gastritis.

Acute gastritis may occur from ingestion of irritant substances (arsenic, decomposing food), the mucous membrane alone being affected. Rarely an acute inflammation of the whole wall of the stomach may occur, due to infective organisms, usually streptococci (*acute phlegmonous gastritis*).

A chronic catarrhal inflammation (*chronic gastritis*) may be due to continued alcoholic excess. It may result in atrophy of the mucous membrane and of the digestive glands in it, with consequent failure in the secretion of gastric juice (*achylia gastrica*).

Gastric Ulcer.

It occasionally happens that the nutrition of some small area of the wall of the stomach is interfered with, either by some local disturbance in its blood-supply or by some injury to its mucous surface. When this occurs the gastric juice, especially if its acidity be increased, acts upon the damaged or necrosed area and rapidly produces an ulcer. Such lesions may be found both in the *stomach* and in the upper part of the *duodenum*, but are commonest near the pyloric end of the lesser curvature of the former organ.

When seen in their most acute stage these ulcers are generally less than an inch in diameter. The inflammatory changes in the walls of the ulcer are so slight that the latter are not appreciably thickened. The ulcer varies in depth; in some cases it only reaches the submucous tissue; in others it may penetrate the muscular and even the peritoneal coat as well. In the latter case the aperture in each coat is smaller than that in the coat immediately above it, so that the hole or ulcer has a funnel-shaped or shelved appearance when seen from the interior of the organ (Fig. 158). When the process of formation is more gradual, this shelved appearance is lost, and some slight thickening of the walls is visible. Any organ adjacent to the ulcerated part of the stomach—*e.g.*, pancreas or liver—may become adherent, and the ulceration may extend into its substance, so that it may form the floor of the ulcer. The longer the ulcer has existed, the less typical are its appearances; when some weeks or months have elapsed, its outline becomes irregular, its walls thickened, its floor roughened, and its extent often considerably increased.

Healing may occur by regenerative proliferation of the adjacent undamaged tissues. In this process even the glands may to some extent be reproduced; but some puckering always remains as a result of the inflammatory repair, and the muscular layers are rarely, if ever, regenerated. In the course of such an ulcer, especially of the acute variety, two accidents are very liable to occur. The first of these is severe *hæmorrhage*. When it is remembered that the principal vessels supplying the walls of the stomach lie in the submucous tissue, it is easy to understand how readily one of these main trunks may be laid open by the necrotic process just described. The second accident is *perforation* of the wall of the stomach. In the case of deep and acute ulceration the peritoneal coat is not infrequently perforated before the wall of the stomach has become firmly adherent to any other organ. Copious or repeated hæmorrhage may give rise to fatal anæmia and syncope; perforation is almost invariably followed by acute suppurative peritonitis. Cicatrisation of a chronic ulcer may be accompanied by so great a contraction of the resulting scar that either obstruction of the pylorus may occur, if the ulcer be situated near to this opening, or the stomach may be much deformed (hour-glass contraction) if the scar be situated towards the central part of its wall.

The mode of *causation* of gastric ulcers has been much debated. It has been suggested that embolism or thrombosis of a small artery may occur, and that death of a portion of the mucous membrane may result; but of this occurrence there is no sufficient

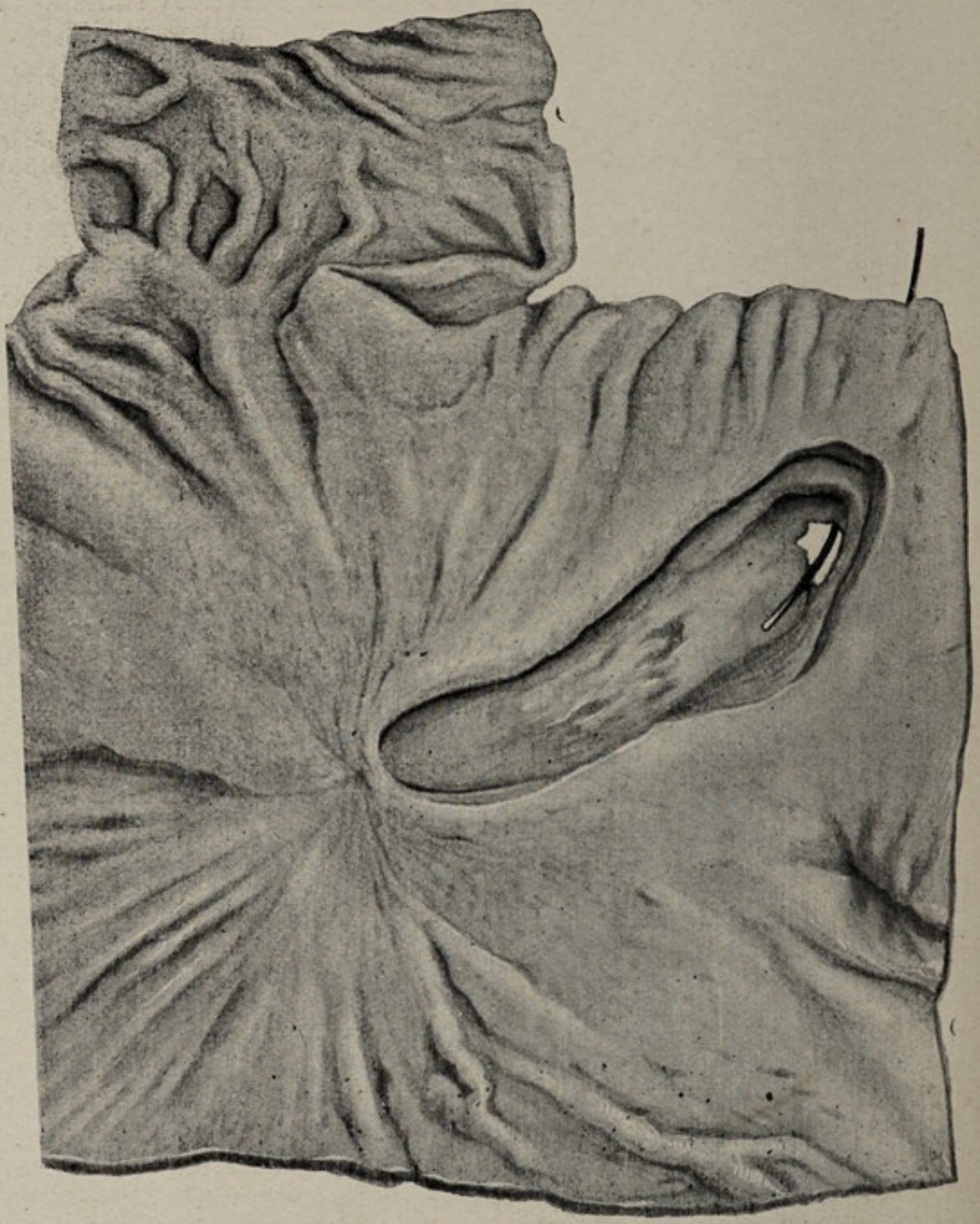


FIG. 158.—SUBACUTE GASTRIC ULCER, SHOWING PERFORATION. (FROM A SPECIMEN IN C. C. H. MUSEUM.)

evidence. Ulcers have been produced experimentally in dogs by feeding them with very hot food, but this mode of causation is unlikely to occur in mankind. Bolton produced ulcers in guinea-pigs by injecting them with a cytolytic serum produced by injecting

rabbits with macerated gastric mucous membrane derived from other guinea-pigs, and showed that their occurrence was intimately associated with the degree of acidity of the gastric juice. The association of gastric ulcers with chlorosis and with hyperacidity of the gastric juice seems well established. Micro-organisms have been found in the tissues round the ulcers, especially streptococci, but it is difficult to be certain how far their presence is the result of secondary infection after the lesion has occurred.

In the **duodenum** ulcers may be met with after severe burns of the skin: they then appear to be due to necrosis of the glands of Brunner. More often they are in all respects similar to gastric ulcers, and are doubtless due to the same cause. They occur in the first part of the duodenum or in the second part above the point of entrance of the bile and pancreatic juice. Similar ulcers may occur in the jejunum after gastro-jejunostomy.

Ulceration of the Small Intestine.

In the small intestine the forms of inflammation which require special consideration are principally those in which the lymphoid tissue is mainly involved. Some inflammatory swelling of Peyer's patches and of the solitary glands occurs in *diphtheria* and in *scarlet fever*, but in neither of these diseases does the lymphoid tissue often undergo necrosis, and only rarely, therefore, does ulceration occur. On the other hand, in *tubercular* infection of the intestine, ulceration is usual; and in *typhoid fever*, almost invariable. Tubercular infection has already been considered (p. 255): the lesions occurring in typhoid fever will now be described.

Typhoid fever is an acute infective disease, due to the action of the *Bacillus typhosus* (p. 127).

The ordinary duration of the fever is three or four weeks, and the temperature as a rule both rises and falls gradually. The most characteristic lesions are found in the solitary and agminated follicles of the intestine, in the corresponding lymphatic glands, in the spleen, and sometimes in the red marrow. The *intestinal* lesions are the most constant, and their various stages correspond so closely with definite clinical conditions, that we can usually judge of the state of the intestine from the symptoms and the day of the disease. It is generally believed that infection occurs from the intestine, and that the intestinal lesions are points of inoculation. Thence the organisms gain entrance into the blood-stream, and may be found in the mesenteric glands, spleen, liver, and kidneys. The disease is thus a general infection (septicæmia), the bacilli especially affecting the lymphoid tissue. The bacilli escape from the body in the fæces and in the urine, by both of which infection may be conveyed to other persons.

The pathology and morbid anatomy of typhoid fever include other conditions due (1) to the direct action of the bacterial toxines, and (2) to the depressing effects exerted by them upon the vitality

of the tissues generally, which are therefore more than usually liable to invasion by other bacteria, such as pyogenic cocci and pneumococci. Thus, evidence of general toxæmia is seen in the continued fever. Cloudy swelling is found in many organs (p. 32), and the muscles are also especially liable to undergo the changes known as Zenker's degeneration (p. 51). Endocarditis is rare. Ulceration of the larynx, especially about the epiglottis, is occasionally present, and may lead to œdema of the glottis or to necrosis of the cartilages. Bronchitis is usual, and broncho-pneumonia may supervene; œdema of the lungs is common in fatal cases; and lobar pneumonia is a rather frequent complication in some epidemics.

The Intestine.—The most characteristic changes in typhoid fever take place in the solitary glands and Peyer's patches. In most cases the process is limited to those in the ileum and cæcum; and those glands are always most affected which are situated nearest to the ileo-cæcal valve. The cæcum is involved in one-third of the cases; ulcers may be present even in the rectum, but in the great majority of cases they are not found *below* the ascending colon. It is, moreover, unusual to find ulcers higher than nine feet *above* the valve. The appendix vermiformis may also be affected.

The first change observed is a hyperæmia and **cell-infiltration** of the glands. Both Peyer's patches and the solitary glands thus become considerably enlarged and prominent, and stand up, as sharply circumscribed, evenly raised areas, above the surface of the intestine. Sometimes they slightly overlap the adjoining mucous membrane, and are surrounded by a hyperæmic zone. They are of a greyish-white or pale red colour, and of a soft brain-like consistence—the larger the size, the paler the colour. The surrounding mucous membrane is also hyperæmic, and is the seat of an acute general catarrh, which is most pronounced before the glands swell. The cellular infiltration, in many parts, rapidly extends beyond the confines of the glands into the immediately surrounding and subjacent tissues, and in some cases even into the muscular and serous coats. Bacilli can be readily found during this stage, which ends in the first half of the second week of the disease.

The process now passes into the second stage—that of the death and disintegration of the newly formed tissue. Many of the enlarged glands subside, the new elements are absorbed, and the inflammation thus undergoes a gradual process of **resolution.** But in other glands the intensity of the bacterial poison causes death of the inflamed lymphoid tissue. The necrosed tissues then separate. If a few scattered follicles in each patch have alone been destroyed, only small sloughs will be formed; and after the separation of these, the Peyer's patches thus affected will assume a peculiar reticulated appearance. If, on the other hand, as is most usual, the entire lymphoid mass be killed, this will separate as one or more large sloughs (Fig. 159), and the typical **ulceration** will be produced.

Resolution or necrosis *begins* during the latter half of the second week. In the case of necrosis, the sloughs *separate* towards the end of the third, or during the beginning of the fourth week. This is the period of danger, in which either severe hæmorrhage or perforation into the peritoneal cavity may take place.

Although, as already stated, the cell-infiltration may extend beyond the confines of the glands, this is rarely the case with the ulceration. The peripheral infiltration undergoes resolution, and hence the ulcers have the same configuration as the original glands —those originating from the patches being oval, with their long diameters in the direction of the gut; and those originating in the solitary glands being circular in shape, like those arising from

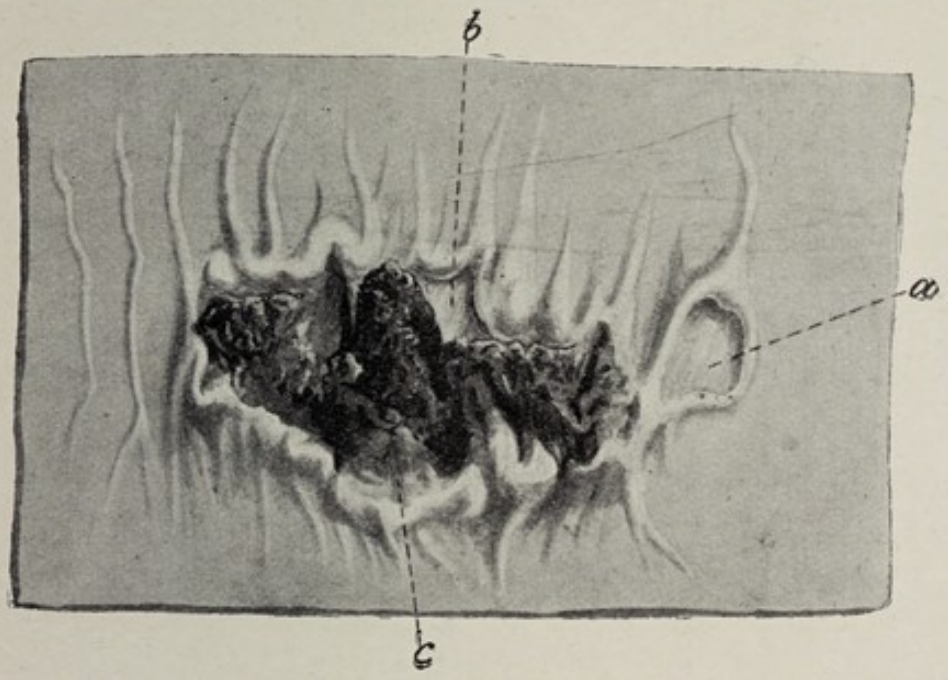


FIG. 159.—A PEYER'S PATCH FROM A CASE OF TYPHOID FEVER, IN WHICH DEATH OCCURRED AT THE BEGINNING OF THE FOURTH WEEK. (C. C. H. MUSEUM.)

a, a small ulcer from which the slough has separated, leaving a clean floor (muscular layer) and undermined edges; *b*, centre of Peyer's patch, from which the slough is in process of separation as a single mass, being only adherent at *c*.

partial sloughing of a patch. In rare cases, when there is much infiltration of the surrounding mucous membrane, the ulceration may extend slightly beyond the confines of the glands. An ulcer from a single Peyer's patch may be five inches long, and the blending of ulcerated patches and follicles in the neighbourhood of the ileo-cæcal valve may affect so large an area that this part of the intestine may seem to have lost almost all its mucous membrane.

With the sloughing and disintegration of the new tissue the process of infiltration ceases, and hence there is no induration or thickening of the base or edges of the ulcer. The base is smooth, and is usually formed of the submucous or muscular coat of the intestine. In other cases the sloughing is deeper, and extends

through the muscular layer to the peritoneum. The edges are usually thin and undermined, and consist of a well-defined fringe of congested mucous membrane (Fig. 160). This is best seen when the gut is floated in water. On histological examination of the base of a typical ulcer, the submucosa is found to be infiltrated with mononuclear cells, including a varying proportion of plasma cells, and numerous large cells of the endothelial type (Fig. 161). The bloodvessels are dilated, and may show thrombosis. After separation of the slough the exposed surface of the submucosa often shows a narrow zone of infiltration with polymorphonuclear

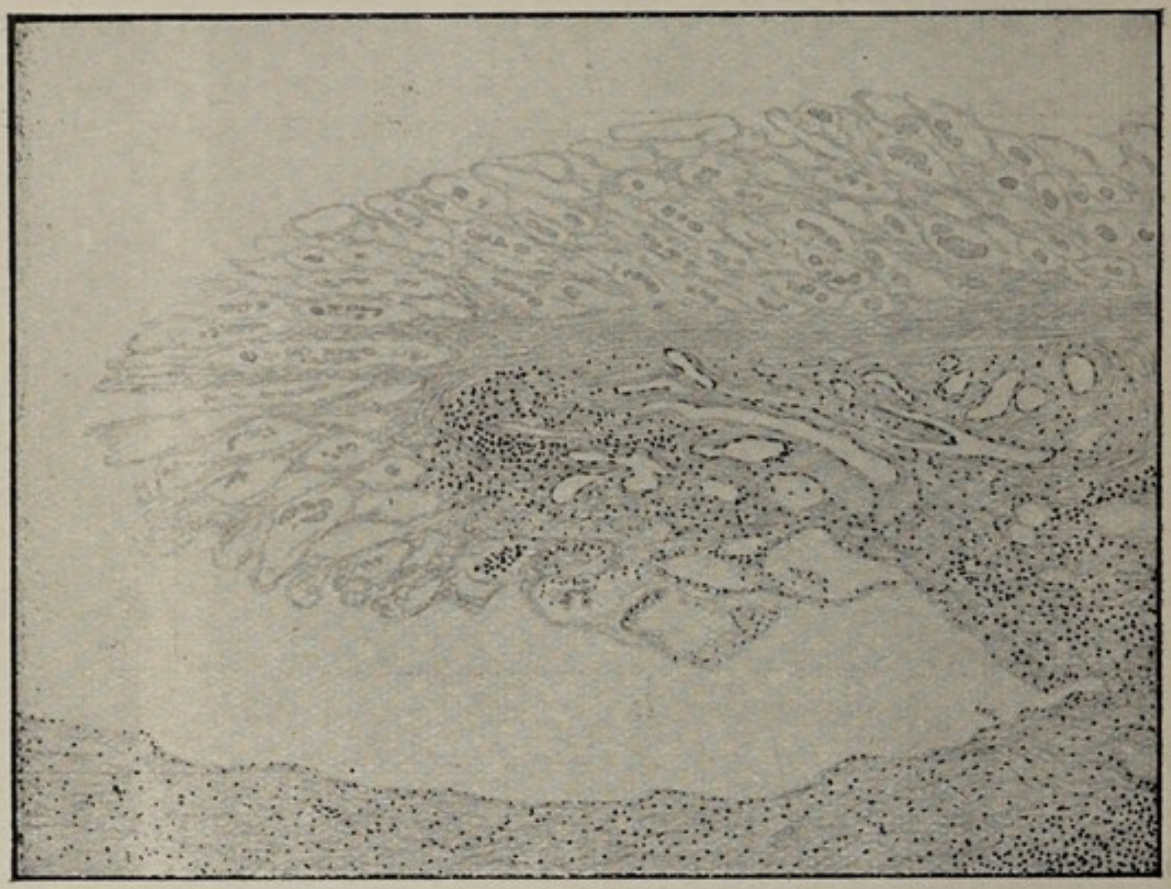


FIG. 160.—EDGE OF TYPHOID ULCER OF ILEUM. (× 79.)

cells, limited to that portion which immediately adjoins the lumen of the intestine.

Perforation of a typhoid ulcer is not uncommon. The perforation is generally small. As a rule, *diffuse peritonitis* (purulent) results: rarely, adhesions form and localise the inflammation. Peritonitis may also occur by simple extension from the gut, from an inflamed gland, or from a splenic abscess. *Hæmorrhage* may occur from any vessel opened up during the separation of the slough. It is due either to insufficient plugging by thrombosis or to mechanical displacement of the thrombus after it is formed.

The third stage of the process is that of **cicatrisation,** which usually begins in the fourth week. This takes place by the resolution of the peripheral infiltration, the approximation of the

undermined edges and their union with the floor of the ulcer, and the gradual formation of an epithelial covering by growth from the margin. There is no puckering or diminution in the calibre of the gut. In some cases, however, cicatrisation does not take place so readily, and the floor of the ulcer becomes the seat of a *secondary* and more extensive ulceration. This may take place after the general disease has run its course, or during a relapse. Profuse hæmorrhage and perforation are common results of secondary ulceration. Only one ulcer may be affected by this secondary process, the rest having either healed or being in a fair way to become so.

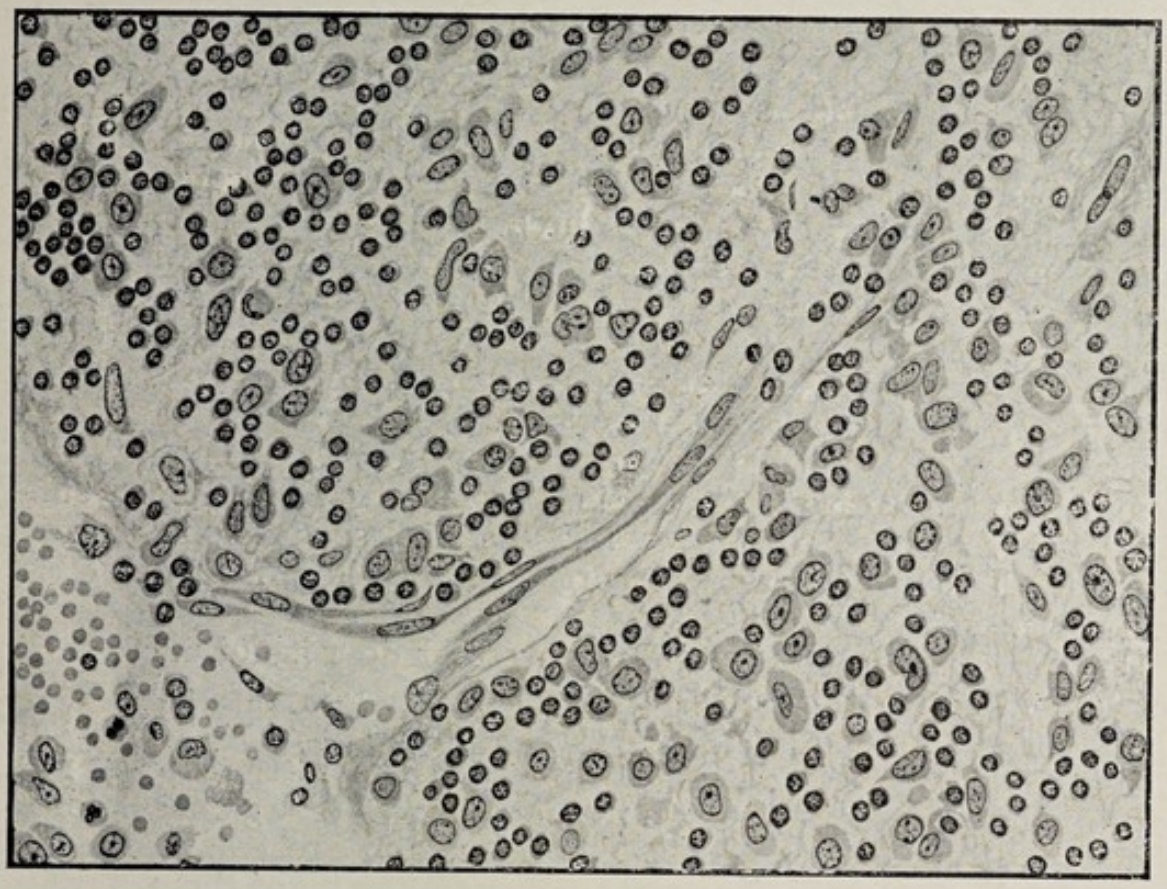


FIG. 161.—PORTION OF SUBMUCOSA FORMING THE BASE OF A TYPHOID ULCER. (× 325.)

Comparison between Typhoid and Tubercular Ulceration.—From the foregoing descriptions of typhoid and tubercular (p. 255) ulceration of the intestine, it will be noted that these two conditions have one important character in common—viz., the uniformity with which *both arise in the lymphoid tissue.* Hence in both cases the ulcers are most marked in the ileum opposite the mesenteric attachment, and may be limited to the Peyer's patches and the solitary glands. There are, however, two characters possessed by tubercular ulcers which generally suffice to distinguish them from typhoid ulcers. The first is the much greater tendency of tuberculosis to spread by means of the lymphatics, and the

second is the presence of outlying tubercles which invariably precede the advance of the ulceration. Thus, the typhoid ulcer, remaining limited to a Peyer's patch, usually has its long axis *parallel* to that of the intestine. On the other hand, the tubercular ulcer, often spreading transversely along the lymphatics before it has involved more than half the patch, often has its long axis *at right angles* to that of the intestine, round which it may form a band. Again, as the slough separates, the floor of the typhoid ulcer tends to become cleaner and smoother, and its edges thinner and more undermined. On the other hand, the floor, base, edges, and adjacent peritoneum are, in the case of the tubercular ulcer, always thick and irregular from the presence of developing and degenerating tubercles.

The Spleen.—In the spleen, the change resembles that which ordinarily occurs in acute febrile diseases, although it reaches its maximum in typhoid fever; but it may be absent, especially in older patients. The splenic vessels are greatly distended and the pulp is crowded with corpuscles. The spleen is consequently enlarged, often attaining two or three times its natural size. Its consistence is fairly firm during the first week, but softer in the second and third. On section, the organ is at first dark red and opaque-looking; a week later the Malpighian bodies are often prominent and enlarged. Clumps of typhoid bacilli are found in the spleen, but no local tissue-reaction is discoverable around them. Necrotic areas somewhat resembling anæmic infarcts, but not confined to the cortex, are occasionally found. As the fever subsides (fourth week), the hyperæmia diminishes, and some fibrous overgrowth occurs; otherwise the organ regains its normal characters and dimensions.

The Gall-Bladder.—Infection of the gall-bladder is not uncommon in typhoid and paratyphoid infections. This probably occurs via the blood-stream and liver, the bacilli being secreted with the bile.

The Mesenteric Glands.—The change in the mesenteric glands is probably secondary to that in the intestine. These glands become the seat of an acute cellular infiltration, and are enlarged, soft, and vascular. Usually, as in the spleen and many of the glands in the intestine, the inflammation gradually subsides.

The Marrow.—Ponfick has shown that in typhoid fever the marrow of bones, like the *splenic pulp*, may contain large cells, in which may be as many as twenty-five red corpuscles: these break down, and in the convalescent stage the large cells only contain pigment.

The condition of the **blood** in typhoid fever differs from that in most other infective diseases in that there is a diminution in the number of leucocytes (*leucopenia*) instead of a leucocytosis.

Inflammation of the Appendix Vermiformis.

The vermiform appendage is subject to the same morbid conditions as the rest of the intestines. **Catarrhal inflammation** of the mucous membrane is a common affection: if mild, it may give rise to no serious trouble; if acute, it may spread to the muscular and serous coats of the organ (*appendicitis*), and thus give rise to local or general peritonitis. Other results of catarrh are blocking of the orifice of the appendix communicating with the cæcum, and the formation of concretions within its cavity. (1) When the orifice of the appendix is blocked, owing to the swelling of the mucous membrane or to actual stricture due to cicatrisation of an ulcer, mucous secretion accumulates behind the obstruction and *distension* of the organ results. Under these circumstances, as in cases of strangulation of a portion of intestine, the *Bacillus coli communis*, normally present, may develop increased virulence, and may pass through the wall of the distended appendix, reaching the serous surface and setting up peritonitis in the neighbourhood (*perityphlitis*). (2) **Concretions** may form within the lumen of the appendix by deposit of earthy salts around a nucleus of desquamated epithelium or inspissated mucus. These concretions may closely resemble foreign bodies, such as grape- or date-stones. In very rare instances actual *foreign bodies* (pins, bristles) may lodge in the appendix; *fæcal material* may also accumulate there and be moulded to the shape of the cavity. As a result of catarrh or of irritation by concretions, **ulcers** may form in the walls of the appendix and perforation may occur. Typhoid fever, tuberculosis, and, in rare instances, actinomycosis may also cause ulceration of this organ.

Gangrene of the appendix may be brought about by very intense inflammation, or by cutting off the blood-supply, owing to torsion of the organ upon its long axis or to acute kinking produced by contraction of its mesentery.

Inflammation of the peritoneum in the neighbourhood of the appendix may lead to *adhesion* between neighbouring parts, or may result in the formation of an **abscess,** the walls of which are formed by adjacent coils of intestine and the abdominal parietes. If the pus contained in such an abscess be not evacuated, it may burst into the cæcum or any other neighbouring hollow organ, into the general peritoneal cavity, or through the anterior abdominal wall. In other cases the abscess may burrow behind the ascending colon and reach the under, or even the upper, surface of the liver. In cases of rapid perforation or gangrene of the appendix, *general purulent peritonitis* may result, sufficient time not being allowed for the formation of adhesions.

Dysentery.

Dysentery is a disease mainly characterised by ulceration and sloughing of large areas of the mucous membrane of the intestine (Fig. 162). The changes are practically limited to the large intestine.

The initial lesion occurs in the submucosa. This becomes enormously thickened (Fig. 163), partly as the result of infiltration with various cells, but much more from proliferation of the fixed connective-tissue elements. The cells present consist of large and small mononuclear cells, plasma cells, fibroblasts, and occasional polymorphonuclear cells (Fig. 164). The necrosis and eventual sloughing of the mucous membrane appears to be secondary to

FIG. 162.—PORTION OF LARGE INTESTINE, SHOWING DYSENTERIC ULCERATION. (FROM A SPECIMEN IN C. C. H. MUSEUM.)

the changes in the submucosa, and these changes can always be made out, extending beneath the apparently healthy mucous membrane adjoining an area of ulceration.

In the most severe forms of this disease the necrosis is very extensive. Large portions of the mucous membrane are converted into sloughs, and the submucous tissue is infiltrated with hæmorrhagic exudation; this is generally followed by suppura-

tion, by means of which the necrosed portions of tissue are removed.

If the inflammatory process subsides before death occurs, the ulcers may gradually heal. When the loss of substance has not been considerable, the edges of the ulcers may, by the contraction of the submucous tissue, become completely approximated. More commonly, however, the loss of substance is so great that large

FIG. 163.—SECTION OF THE WALL OF THE LARGE INTESTINE FROM A CASE OF DYSENTERY, SHOWING THE GREAT THICKENING OF THE SUBMUCOSA. (× 39.)

portions of the interior of the intestine are left uncovered, save by fibrous tissue and islets of mucous membrane.

When the inflammatory process becomes chronic, the changes in the submucous connective tissue become more marked, and the new fibroid growth gives rise to considerable thickening and induration of the intestinal wall, and to contraction and narrowing of the lumen. Sometimes fibrous bands are formed, projecting into the gut. Abscesses and fistulous passages not infrequently occur in the thickened intestinal wall.

The name "dysentery" is applied to affections caused by more than one infective agent. *Tropical* or *amœbic dysentery* appears to be due to the action of the *Entamœba histolytica* (p. 144), but in temperate climates and also not infrequently in the tropics an almost exactly similar clinical and pathological condition may be brought about by bacteria (*B. dysenteriæ*), belonging, apparently, to several closely allied strains. It seems possible that the para-

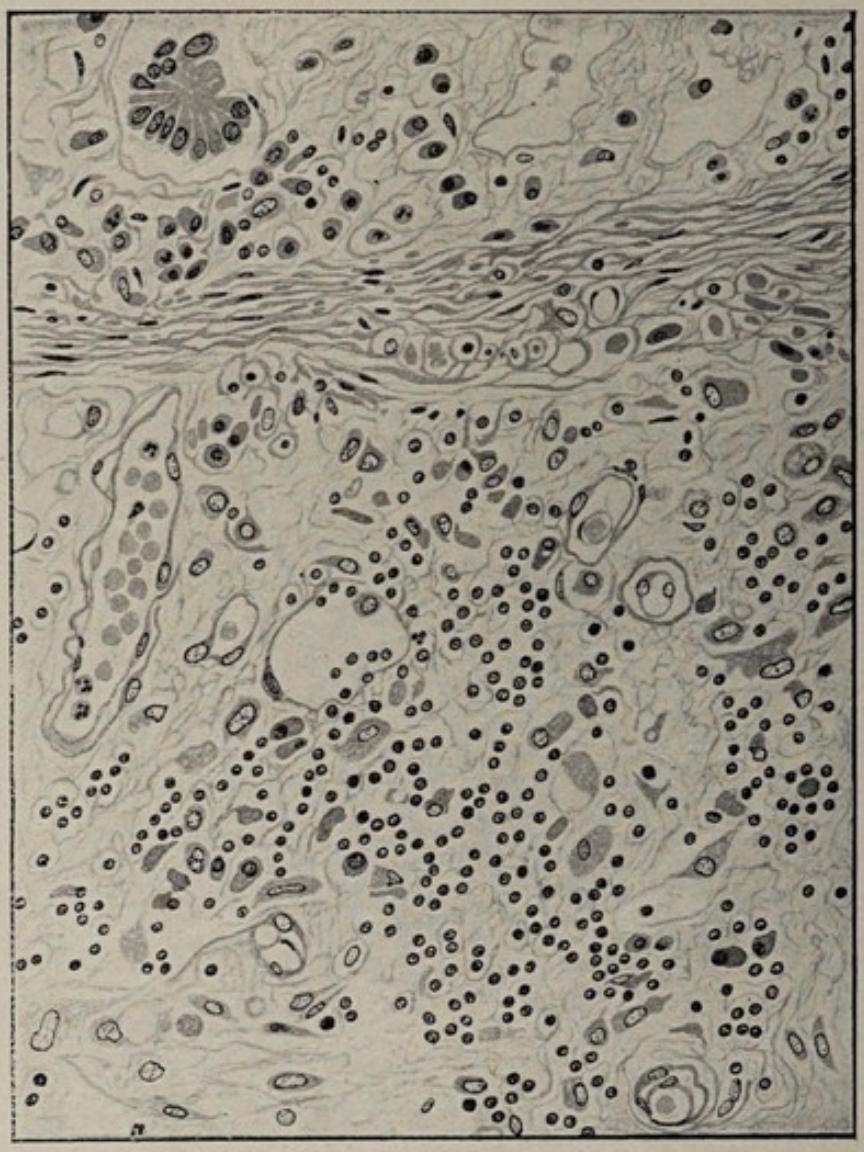


FIG. 164.—SHOWING THE INFILTRATION OF THE SUBMUCOSA IN A CASE OF DYSENTERY. (× 325.)

typhoid bacilli may occasionally give rise to this condition. *Ulcerative colitis*, which occurs in England sporadically and also in epidemic form in lunatic asylums, appears to be a form of bacillary dysentery.

Tumours of the Stomach and Intestines.

Stomach.—Primary carcinoma is the only new growth frequently found in the stomach. In the male the stomach is the commonest seat of primary cancer, but in the female both breast and uterus

are more frequently affected. The form of cancer found varies, to some extent, with its position. At the pylorus, which is affected

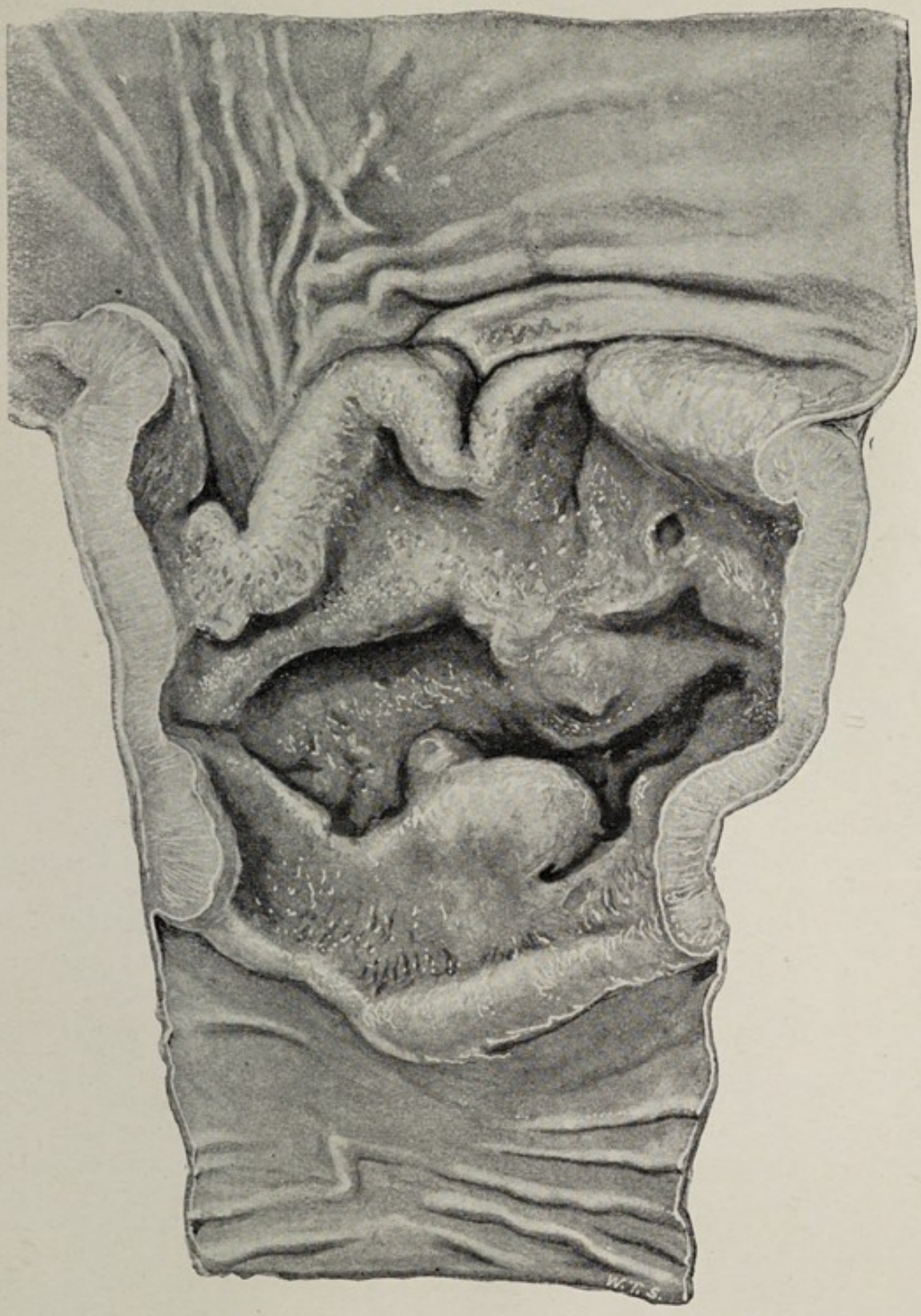


FIG. 165.—CARCINOMA OF PYLORUS. (FROM A SPECIMEN IN C. C. H. MUSEUM.)

in two-thirds of the cases, scirrhus, encephaloid, or even columnar epithelioma may be found. At the cardiac end, squamous epithe-

lioma is not infrequent, while all forms are liable to undergo colloid degeneration. In whatever part of the organ the cancer arises, it spreads most rapidly in the submucous layer, but always involves, to some extent, the muscular coats. As it extends, it gives rise, in the interior of the organ, to fungating masses or to ulcers with hard edges and rough floors (Fig. 165); and on the exterior, to adhesions to neighbouring organs, due to the direct spread of the growth. Secondary growths in the glands and liver are exceedingly frequent. When situated at the pylorus, the growth causes thickening and eversion of the valve into the duodenum, and narrowing of the orifice, leading to marked dilatation of the stomach at a comparatively early stage of the disease. The secretion of hydrochloric acid by the gastric glands is usually diminished or arrested in cases of cancer; but this functional defect is found also in other morbid conditions of the stomach.

Intestine.—Two varieties of new growth are commonly found in the intestine—*adenoma* and *carcinoma*.

Intestinal adenomata are generally polypoid in form. The glandular elements in the mucous membrane covering them are often so little increased that some of the tumours may with equal correctness be classified as *papillomata* or *fibromata*. They are found in both small and large intestine.

Almost every form of carcinoma may occur primarily in the intestine, but *columnar epithelioma* is certainly the commonest. The growth invades the submucous and muscular walls, but mainly projects into the interior, rapidly encircling, and seriously narrowing, the lumen of the intestine. Carcinoma of the intestine is a common cause of chronic intestinal obstruction in old people. The rectum, the flexures of the colon, and the cæcum are the commonest parts involved. Secondary growths occur in the mesenteric glands and in the liver, sometimes before any symptoms have been produced by the intestinal growth.

The peritoneum may be involved by direct extension or by metastasis.

CHAPTER XXVI

AFFECTIONS OF SEROUS MEMBRANES

The phenomena of inflammation affecting serous membranes vary with the nature and intensity of the irritant to which the condition is due. It is convenient to distinguish three varieties of cases: (1) the so-called "dry" cases, in which little exudation occurs; (2) those accompanied by free escape of serous or sero-fibrinous effusion; and (3) those in which the fluid is purulent.

(1) **"Dry" or Plastic Inflammation.**—The sequence of events constituting inflammation is the same in serous membranes as in other vascular parts, comprising dilatation of bloodvessels, alteration in the characters of the blood-stream, exudation of fluid, and escape of leucocytes and occasionally of red corpuscles. The earliest visible sign of inflammation is hyperæmia, shortly followed by a loss of the natural polish of the endothelial surface. The cells of the endothelium become swollen and granular; they multiply rapidly, and many cells, injured by the irritant, are cast off from the surface (*desquamation*) (Fig. 166). At the same time leucocytes escape from the vessels and infiltrate the subendothelial tissue, some escaping on to the actual surface, accompanied by a slight exudation of fibrinous lymph, which forms a white or yellowish-white layer, more or less closely adherent to the damaged endothelium. This deposit of fibrin tends to accumulate at points where pressure is least, as in the angles between adjacent coils of intestine. Microscopically, the exudation is seen to consist of a network of coagulated fibrin containing within its meshes numbers of emigrated leucocytes.

Fig. 166.—Inflamed Omentum of a Rabbit, showing Changes in the Endothelium. (× 250.) (Cornil and Ranvier.)

As the inflammation subsides, the hyperæmia diminishes, and more or less adhesion takes place between the roughened surfaces of the serous membrane where they are in contact. The connective-

tissue cells multiply and shoot processes into the layer of fibrin, which is gradually absorbed; new vessels are formed in this connecting mass, and complete union by fibrous tissue thus takes place. Owing to the movements of the opposing surfaces one upon another it often happens that the newly formed fibrous connections are pulled out into threads or bands of varying thickness. In this way are formed the peritoneal bands, which are important as a possible cause of subsequent intestinal obstruction, and the curious shaggy condition of the pericardium occasionally resulting from inflammation (*cor hirsutum*).

(2) **Serous Inflammation.**—The hyperæmia and roughening of the serous surface take place in this as in the previous case, but the effusion of fluid from the vessels is much greater, and widely separates the usually contiguous surfaces, forming a large cavity bounded by the serous membrane. In many cases scarcely any lymph coagulates on the endothelium, and the effusion remains fluid and almost clear. In other instances a layer of lymph is deposited on the walls of the cavity, and the fluid itself contains flakes of coagulated fibrin (*sero-fibrinous effusion*). In the latter cases the fluid may coagulate to a jelly-like substances when withdrawn from the body. Occasionally the escape of red blood-corpuscles is so free that the fluid is more or less deeply blood-stained (*hæmorrhagic effusion*). Subsidence of the inflammation is followed by absorption of the effused serum through the veins and lymphatics. In cases in which the effusion is very large, and the pressure produced upon the walls of the cavity correspondingly great, such absorption is hindered by the resulting compression of these vessels, and it may be necessary to withdraw artificially some of the fluid, so as to diminish the tension and allow natural absorption to occur. When the fluid has disappeared, union of the opposed surfaces of the serous membrane will take place, as in the previous instance, wherever the endothelium is sufficiently damaged.

(3) **Purulent Inflammation.**—In certain cases the nature of the irritant is such that it causes a very free exudation of polymorphonuclear cells into the serous cavity. The effusion will then be purulent or sero-purulent, according to the proportion of leucocytes and fluid which escape. Such purulent effusions do not tend to undergo spontaneous absorption, and must be artificially evacuated. If the pus remains in the serous cavity for any length of time, great thickening of the serous membrane occurs, as a result of the chronic inflammation existing in the subendothelial tissue; the endothelial cells, to a great extent, disappear, and the cavity is lined with granulation-tissue throughout. Obliteration of the cavity takes place, as above, when the walls are allowed to come into contact.

Ætiology.—Inflammation of a serous membrane is generally the result of the presence of pathogenic organisms, which may be admitted either (1) by direct traumatism (penetrating wounds, rupture of viscera) or (2) by means of the blood-stream or lymphatics.

Exposure to cold was formerly considered to be an exciting cause, and the possibility of such an occurrence is not absolutely disproved. It may undoubtedly act as a predisposing condition, rendering the tissues unable to resist bacteria accidentally present. The frequent occurrence of inflammation of serous membranes in diseases of the kidney shows that either the toxic substances circulating in the blood in such conditions act as exciting causes of this form of inflammation or that resistance to bacterial infection is diminished. Serous membranes may be involved secondarily by extension of inflammation from the viscera which they invest, as happens to the pleura in cases of pneumonia, or to the peritoneum over a gumma in the liver or over an ulcer of the intestine.

The same irritant cause is capable, under different conditions, of producing all the varieties of inflammation here distinguished. An example may be seen in the inflammation of the peritoneum due to the *Bacillus tuberculosis* (*tubercular peritonitis*). The simplest form consists in the deposit of a number of miliary tubercles in the subperitoneal tissue, as may frequently be seen over a tubercular ulcer. These tubercles may be scattered throughout the whole of the peritoneum. As the process advances, a dry fibrinous exudation may become the most prominent feature, and the coils of intestine be subsequently matted together by fibrous tissue. In other instances a large serous effusion takes place into the peritoneal cavity (*ascites*); and, very rarely, a true suppurative peritonitis may be produced. It is certain, however, that in these last cases other organisms must aid the *Bacillus tuberculosis* in producing the suppuration.

Effects.—Simple dry inflammation of serous membranes is accompanied by considerable pain, owing to the friction between the inflamed surfaces. Large serous effusions embarrass the action of the neighbouring viscera, as of the heart in pericardial effusion, or of the lung in pleurisy: in the latter case collapse of the lung may take place owing to the pressure of the fluid. In very chronic conditions, as in purulent pleurisy (*empyema*), the fibrous tissue, formed by the union of the opposing surfaces, may subsequently, by its contraction, cause some local falling-in of the chest-wall and consequent deformity. The inflammatory process may extend from the serous membrane into the substance of the underlying organs, as is seen in the myocarditis which results from pericardial inflammation, and in the interstitial pneumonia which follows chronic pleurisy; this fibrosis of the lung takes part in producing the retraction of the chest just alluded to. (See Bronchiectasis.) In peritonitis the extension of the inflammation into the muscular coat of the gut leads to paralysis of the muscle and consequent distension of the intestines (*tympanites*).

In the case of the pericardium, the obliteration of the cavity by adhesions (*adherent pericardium*) results in throwing additional work on the heart, the contraction of which is impeded. Great hypertrophy of the heart may be produced to compensate for this

impediment. In a few cases the tightness of the coat of fibrous tissue formed around the organ is such that no enlargement can occur, and cardiac failure is an early and necessary result.

The fibrous material produced in tubercular peritonitis may be unevenly distributed, giving rise to irregular masses of matted intestine or omentum. Caseation occurs in the new tissue, resulting in the formation of collections of puriform material. These "cold abscesses" may burst either into the intestine or through the abdominal parietes; if perforation occurs in both directions, a *fæcal fistula* will result. Movement of the intestines is prevented by the fibrous adhesions between the coils, and obstruction of the lumen of the gut may occur as the result of kinking produced by contracting adhesions.

It is worthy of note that the adhesion of the two surfaces of a serous membrane resulting from inflammation is, in many cases, a *protective condition*. Thus fusion of the pleural surfaces over a tubercular vomica prevents the possibility of the ulcerative process extending into the pleural cavity with consequent pneumothorax; while adhesions around a gastric or intestinal ulcer are protective against perforation and resulting general peritonitis.

CHAPTER XXVII

DISEASES AFFECTING THE COMPOSITION OF THE BLOOD

THE composition of the blood as it is obtained from the peripheral vessels is susceptible of fairly exact analysis, so far, at least, as concerns its cellular content and many of its chemical and biological characteristics. We have thus come to possess a considerable mass of knowledge as regards its normal constitution and the various alterations which may occur in health and disease. Further, as the result of the work of Haldane and Lorrain Smith, we have at our disposal a method for determining the total volume of blood in a given subject; so that we are able to differentiate a case in which the concentration of a given constituent is less than normal, while the total quanttiy in the whole volume of blood remains constant, from a case in which there is an actual total deficiency of this same constituent.

The composition of the blood is subject to variation during certain physiological processes and as the result of pathological conditions affecting various parts of the body. In cases where the lesions are not primarily related to the blood-forming or blood-destroying organs, the abnormal blood-condition must clearly be regarded as a secondary manifestation; but there is a group of diseases in which the blood-changes form the most striking feature in the clinical picture displayed, and in which distinctive morbid anatomical changes are found in those organs, which are credited with the principal share in the processes of formation and destruction of the formed elements of the blood. These disorders are often spoken of as **primary** diseases of the blood. Since, however, the ætiology of these conditions is still obscure, and since it is certain that in almost every case it is the blood-forming or blood-destroying organs which are at fault rather than the blood itself, it must be remembered that the term is one of convenience only, unless we include in the term "blood," as well as the fluid and its contents, all those organs which, under normal or abnormal conditions, are concerned with its production and the maintenance of its correct volume and constitution.

A normal human being possesses about 500 c.c. of blood per kilogramme of body-weight. This consists of a fluid medium,

the plasma, in which are contained a variety of cellular elements.

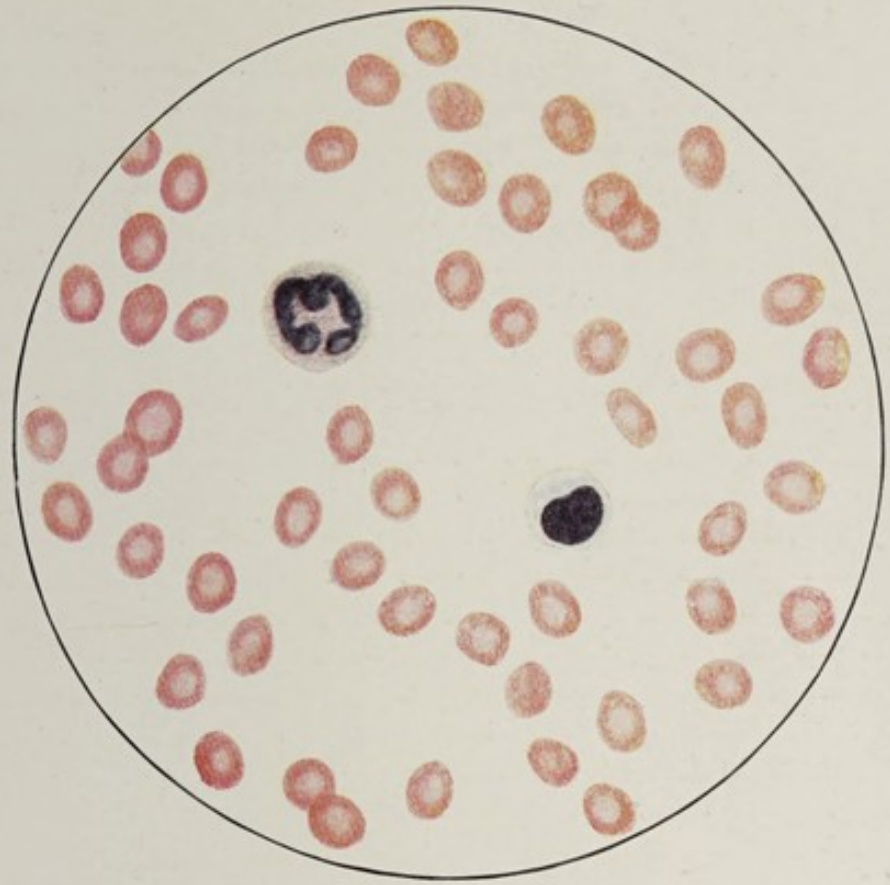
The blood possesses the property of **clotting** within a certain definite time after its withdrawal from the body, unless it is collected with certain very definite precautions, and this "coagulation time" is subject to marked variations under certain conditions, such as hæmophilia. Further, if the blood be collected as a thin film and prevented from drying too rapidly, it is found that the red cells tend to run together into rouleaux, while a fine meshwork of fibrin gradually makes its appearance. This rouleaux-formation and fibrin-formation also show definite departures from the normal in certain diseases.

The whole blood—that is, plasma plus cells—possesses a definite specific gravity approximating to 1059. It is slightly alkaline to litmus, and the degree of this reaction is subject to considerable variations in the course of various diseases, notably in scurvy, in which it is much diminished. The complexity of the blood, regarded as a chemical substance, makes the exact degree of alkalinity difficult to determine, and in practice it is found that different methods give rather different results; but these results retain their comparative value when one method is employed throughout.

The cellular elements of the blood fall into two main groups: the red cells and the leucocytes. In addition to these, the blood contains a varying number of small ovoid elements of definite structure known as "blood-platelets." The origin and function of these bodies are still the subject of much discussion, and we have as yet no exact knowledge of the alterations which they may undergo in disease. Evidence has, however, been accumulating, which points to these bodies playing an important part in maintaining the normal coagulability of the blood, and a marked deficiency in the platelets has been found in cases of such diseases as purpura, which are associated with the occurrence of multiple hæmorrhages. Ledingham has recently shown that the injection of an "anti-platelet" serum into guinea-pigs produces a condition closely resembling purpura.

The red cells number about 5,000,000 per c.mm. of peripheral blood in the case of a healthy adult male, slightly less in the female. They are biconcave discs, of an average diameter of 7·5 μ, and stain a reddish-pink colour with the Romanowski stains, such as those of Leishman, Jenner, or Wright. They possess no nuclei (Plate I.). The amount of **hæmoglobin** in a unit volume of blood is also approximately constant in health, and the concentration of this substance present in any given case is expressed as a percentage of this normal average, the comparison being carried out by some type of colorimetric method. Variations in the concentration of hæmoglobin and the number of red cells per c.mm. of blood do not necessarily run parallel to one another, and thus the relation between the two quantities becomes of importance, and often possesses the highest diagnostic significance. This ratio is known as the "colour

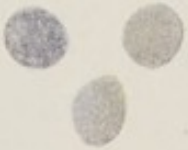
Film of Normal Blood



Abnormal forms of Red Blood Corpuscles

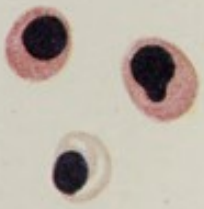
Poikilocytosis

Punctate Basophilia

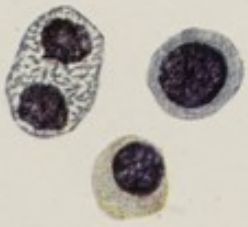


Polychromatophilia

Nucleated Red Corpuscles



Normoblasts



Megaloblasts.

To face page 432.

index," and is really an expression of the average amount of hæmoglobin in each corpuscle. It is obtained by dividing the percentage of hæmoglobin by the percentage of red cells, taking the normal as the standard in each case. In the normal subject the colour index will obviously approximate to unity.

The red cells have also a certain very definite **fragility** when exposed to the action of hypotonic solutions of salt. Thus, while a solution containing 0·85 per cent. of sodium chloride is approximately isotonic with the blood-plasma, it is only when the salt-concentration is reduced to 0·4 to 0·375 per cent. that lysis of the red cells commences. This normal fragility is subject to marked variations in certain diseases. Thus, it is increased in family cholæmia and decreased in jaundice.

The **leucocytes** in normal blood number from 4,000 to 10,000 per c.mm., and are of five different varieties.

The *polymorphonuclear neutrophile cell* (Plate II.) is rather larger than the red cell, having an average diameter of 9 to 12 μ. It possesses a deeply staining nucleus which shows varying degrees of lobulation in individual cells, there being some evidence that the lobulation increases with the age of the cell. The protoplasm is finely granular, the granules taking on a neutrophile or faintly acidophile stain. These cells are amœboid and actively phagocytic, and play an active part in acute inflammation.

The *lymphocytes* (Plate II.) are mononuclear cells possessing a single nucleus which is circular in outline or only very slightly indented. The protoplasm is clear, often showing the presence of a few isolated granules which take on a bright blue stain with the Romanowski dyes. The lymphocytes may be divided into two subvarieties according to their size. The small variety is about 6 to 9 μ in diameter, and the nucleus takes up the greater part of the cell. The large type has a diameter of from 10 to 15 μ, and there is a large amount of protoplasm as compared with the nucleus. The small variety is by far the more numerous in normal blood.

The *large hyaline cell* (Plate II.) is a large leucocyte, having a diameter of 10 to 15 μ. It has a single nucleus, which shows marked indentations, and is often of a horseshoe shape. The protoplasm is sometimes almost completely hyaline in type, but usually shows more or less granularity. This cell is amœboid and actively phagocytic. It seems to be concerned with the phagocytosis of cells rather than of micro-organisms, the latter being dealt with mainly by the polymorphonuclear leucocytes. It is closely related to, and may be derived from, the endothelial cells.

The *eosinophile cell* (Plate II.) has a diameter of 10 to 12 μ. It possesses a slightly lobulated nucleus, and the protoplasm contains numerous granules which are of large size and stain intensely with acid dyes. It is apparently phagocytic, but its rôle, from this point of view, seems to be an unimportant one.

The coarsely granular *basophile cell*, or mast cell (Plate II.), is of approximately the same size as the eosinophile, though large forms

may occur. The nucleus, which is slightly lobulated, stains faintly. The protoplasm contains a variable number of large granules which stain deeply with basic dyes. This cell is so scanty in normal blood, and so frequently absent altogether, that it is hardly to be looked upon as a normal blood-cell.

The relative percentages of the various types of leucocytes in normal blood are approximately as follows:

	Per Cent.
Polymorphonuclears	60–70
Lymphocytes	20–35
Large hyalines	2–5
Eosinophiles	0·5–2
Basophiles	0·5 or less.

The normal constitution of the blood, as briefly described above, is subject to modifications in many directions. Thus, the **number** of **red cells** in a unit volume of blood may be diminished (*oligocythæmia*) or increased (*polycythæmia*); while, as stated above, the **hæmoglobin** concentration in the red cells also undergoes variation. In addition to the numerical decrease of these cells, the individual corpuscles may show signs of abnormality. The changes observed include—

1. **Changes in Shape.**—The normal circular disc may give place to many abnormal forms, the most characteristic change consisting in the presence of elongated pear-shaped cells, often showing a stalk-like process. These abnormal forms are known as *poikilocytes* (Plate I.).

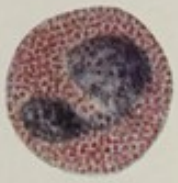
2. **Changes in Size.**—Cells markedly larger or smaller than the normal may occur, and are known as "macrocytes" and "microcytes" respectively.

3. **Changes in Staining Reaction.**—As noted above, the normal red cell stains a uniform reddish-pink colour. In many abnormal blood-conditions corpuscles are found which depart from this normal condition either by showing the presence of minute blue dots scattered throughout the protoplasm, or by taking on a uniform purple stain. The former condition is known as *punctate basophilia* (Plate I.), the latter as *polychromatophilia* (Plate I.). Both types of cell are normally present in the bone-marrow, and are simply immature red cells.

4. **The presence of nucleated red cells.** These cells may be of two distinct kinds. The *normoblast* (Plate I.) is a cell of approximately the same size as the normal red cell, and contains a nucleus, usually single, but sometimes double, which stains deeply and uniformly. The protoplasm takes on the normal red tint. The *megaloblast* (Plate I.) is usually larger than the normoblast, often considerably so, but it differs in kind as well as in size, and in this its real difference lies. The nucleus stains unevenly and often shows a distinct chromatin network. The protoplasm almost always shows more or less polychromatophilia, and it often needs some experience to recognise the cell as a red blood-corpuscle.

Normal Leucocytes

Polymorphonuclear Neutrophile



Coarsely granular Eosinophile

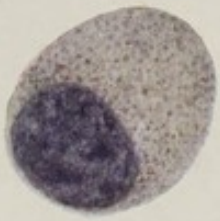
Basophile (or Mast cell)

Large Hyaline

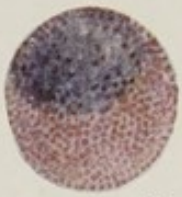
Small Lymphocyte

Large Lymphocyte

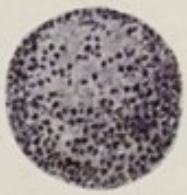
Abnormal Leucocytes



Neutrophile Myelocyte



Eosinophile Myelocyte



Basophile Myelocyte

Amphophile Myelocyte

Myeloblast

Transitional Leucocyte

To face page 434.

The **leucocytes** also undergo numerical changes in the direction of excess (leucocytosis or leucocythæmia), or of deficiency (leucopenia). The relative proportion of the various types of cell is subject to considerable variation, and cells which are normally absent from the peripheral blood may make their appearance. These changes will be considered in detail when dealing with the conditions in which they occur.

Anæmia.—This term, though well recognised clinically, has no definite scientific meaning. It is used to describe conditions associated with more or less pallor, in which an examination of the blood shows a diminished concentration of red cells or hæmoglobin. It does not involve a deficiency in the total volume of blood, nor of necessity any diminution in the total amount of hæmoglobin or red cells, since in certain anæmic conditions the total bulk of blood is so increased as to more than compensate for the diminished concentration of these constituents.

Anæmias have been divided into *primary* and *secondary* types, these terms being used in the limited sense discussed above.

PRIMARY ANÆMIAS.—The two conditions which are commonly classed as primary anæmias are chlorosis and pernicious anæmia.

Chlorosis.—The disease known as "chlorosis" is classed as an anæmia because with the clinical sign of extreme pallor there is associated a diminished concentration of hæmoglobin and of red cells in the blood. The red cells per c.mm. of blood are decreased, usually only to a slight or moderate degree (3,000,000 to 4,000,000 per c.mm.), occasionally to a more marked extent (2,000,000 to 3,000,000 per c.mm.), but never to the extreme degree seen in pernicious anæmia. The hæmoglobin percentage shows, however, a great decrease, so that the colour index falls below the normal, the actual figure obtained usually falling between 0·3 and 0·6.

Quantitative estimations of the blood in chlorotic patients have shown that the total volume is greatly increased (Lorrain Smith). It follows that the total amount of hæmoglobin, and hence the total oxygen-carrying power of the blood, may, and often does, remain practically unaltered, or may even be increased; but the circulation will have to deal with a greatly increased bulk of fluid, and even then cannot eliminate the disadvantage to the tissue of the decreased hæmoglobin concentration. The disease is, thus, not due to excessive destruction of red cells, nor is there any evidence of defective formation of these cells. The fault would appear to lie in the excessive formation of plasma, and the disease should be regarded as an anæmic plethora.

The red cells when examined in stained preparations show changes which support this view. Variations in size are common, the usual abnormality consisting in the presence of numerous undersized cells or microcytes. A slight degree of poikilocytosis is common, but an extreme degree of this condition is very rare. Polychromatophilia and punctate basophilia are hardly ever found, except in the severest cases. Nucleated red cells are rare, and when present

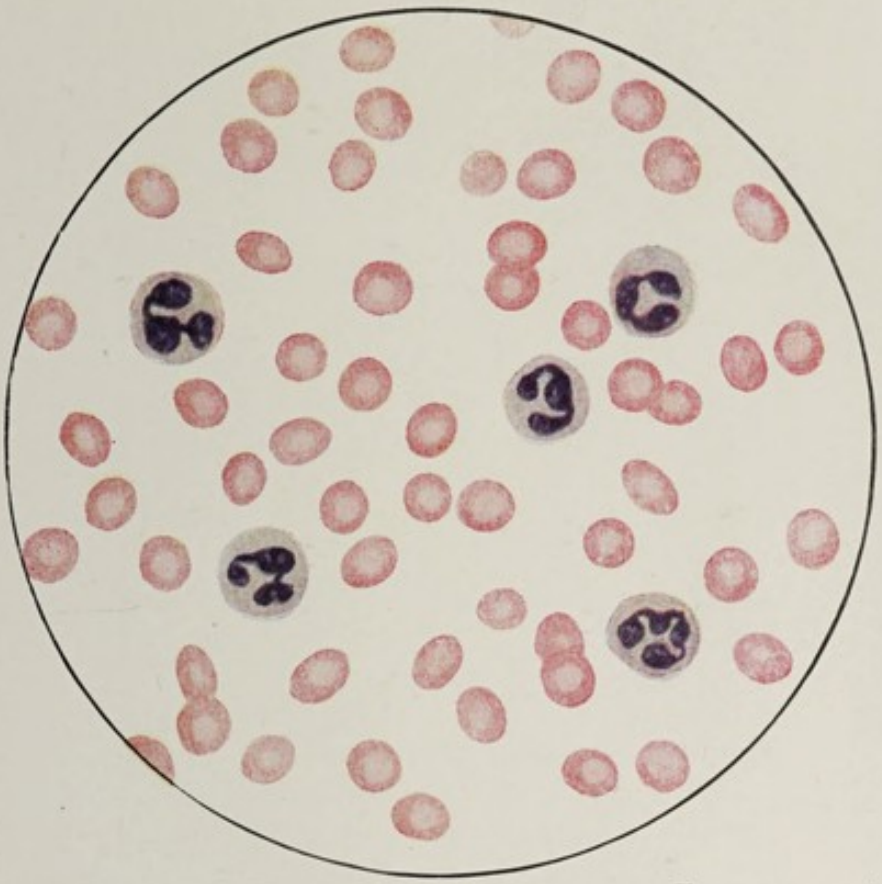
consist entirely of normoblasts. The whole picture suggests an excessive red-cell formation of normal type, induced by the necessity for maintaining a minimum concentration of hæmoglobin, and leading to the output of slightly immature cells. The number of leucocytes per c.mm. of blood is diminished, and associated with this leucopenia there is a decrease of the polymorphonuclear cells, and a corresponding increase in the percentage of lymphocytes. The eosinophile cells may be slightly increased in number. The blood-platelets may also be increased in number, and fibrin formation is usually excessive.

Of the morbid anatomy of chlorosis we are almost entirely ignorant, since death never occurs in uncomplicated cases; and hence we do not know what changes, if any, occur in the bone-marrow and the other hæmopoietic organs.

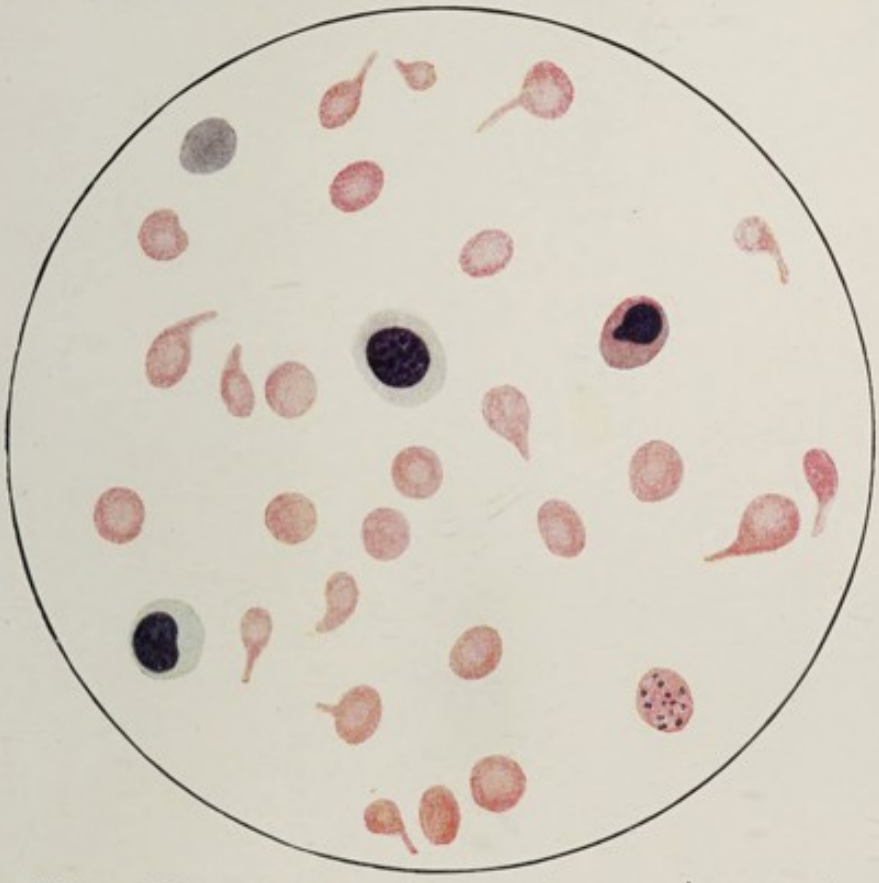
Of the cause of this disease we are equally ignorant. The condition occurs mainly in young females, and when the diminished concentration of hæmoglobin was regarded as the most striking feature, defective red-cell formation, depending in its turn on a deficiency of iron, was offered as an explanation of the facts observed. This view, which was never supported by any very definite facts, became untenable when the increase in the total volume of blood was demonstrated, and was shown to account for the great majority of the clinical phenomena present in the disease. It seems most probable that the plethora is the primary and essential change, though we are no nearer understanding by what means this plethora is itself brought about.

Pernicious Anæmia.—This type of primary anæmia differs completely from that described above. It affects males rather than females, and is more common after the age of forty than before it. Moreover, it is almost uniformly fatal, though it is subject to long remissions, and the fatal termination may be delayed for ten years, or even longer. The majority of cases, however, reach a fatal issue within five years after first coming under observation.

The blood-picture presented is striking and definite, and is not, so far as is known, found in its entirety in any other condition. The *total bulk* of blood may be normal or increased up to twice the normal amount, but this increase is never relatively so great as the *decrease in hæmoglobin concentration*, so that the total amount of this substance present in the body is always less than normal. The number of red cells per c.mm. of peripheral blood is strikingly diminished (1,000,000 to 2,000,000 or even less). The hæmoglobin percentage is also diminished, but usually not to so great an extent as the red cells, so that the colour index tends to be above normal. It varies between 0·9 and 1·6. Rouleaux formation is poor or absent. The examination of stained films shows far wider departure from the normal on the part of the red cells than is the case in chlorosis. Megalocytes are constantly present, and usually numerous; indeed, the cells are almost uniformly larger than normal. Poikilocytosis is well marked. Polychromatophilia and



Blood showing Polymorphonuclear Leucocytosis



The Blood in Pernicious Anæmia

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punctate basophilia are present in most cases, though in a very varying degree. Nucleated red cells are often numerous, and consist largely of megaloblasts (Plates III.-I.). These changes are found in a patient actually suffering from an attack of the disease; but, as mentioned above, definite and frequent remissions occur, and during these periods the blood-picture may return practically to normal. The colour index, however, usually remains high throughout, thus forming a point of great diagnostic importance.

The fatality of pernicious anæmia has resulted in extensive investigation of the morbid anatomy of the disease, and the changes present have been found to be well marked and characteristic. The *superficial fat* has often a characteristic bright yellow colour. The long bones and the ribs contain a marked excess of *red marrow*, which may completely fill the cavity of the bone. On section, the marrow shows evidence of marked activity of an abnormal kind, the abnormality consisting mainly in the great preponderance of megaloblasts. Histological examination of the liver shows marked fatty degeneration in most cases, and appropriate staining, either of macroscopic or microscopic specimens, shows the presence of free iron, situated mainly towards the periphery of the lobules (Fig. 167). Similarly, free iron may be demonstrated in the kidneys. Chemical analysis has shown that the liver in these cases contains an excess of total iron, amounting in some cases to four times the normal, and up to fifty times the normal in the case of the kidneys. The iron is also present in an abnormal form.

Small hæmorrhages into the skin or under serous or mucous membranes are fairly common, while the retina may show the presence of flame-shaped hæmorrhages scattered round the disc. The heart muscle and the diaphragm, in addition to the liver and kidneys, show fatty degeneration, and degenerative changes may be present in the posterior and lateral columns of the spinal cord. The tongue shows, in the great majority of cases, naked-eye and microscopical evidence of chronic glossitis, and the mucous membrane throughout the alimentary tract shows areas of acute or subacute inflammatory change. The skin of a patient suffering from pernicious anæmia often acquires a distinctive yellow tinge, and the blood-serum is tinged a bright straw colour. The urine usually contains excess of urobilin.

Considering the data at our disposal, it becomes evident that there are two abnormalities to be accounted for. (1) There is excessive red-cell destruction, as evidenced by the enormous increase in iron-content of the liver and kidneys (and to a less extent of the spleen), and by the urobilinuria, which shows a definite tendency to run parallel to the rate of blood-destruction as estimated by counting the cells in the peripheral blood. (2) The second abnormality consists in the fact that the regeneration of red cells is of an abnormal type. Marked activity of the red marrow would be a natural sequence of the great loss in red cells which obviously occurs, but the activity in this case is quite different to that which

takes place, for instance, as the result of a severe hæmorrhage, and the difference consists in the great preponderance of megaloblasts in the marrow and their appearance in the peripheral blood-stream.

The obvious question which presents itself is that of priority. Are the red cells destroyed because they are of an abnormal type, or is the abnormal type of regeneration the result of a special stimulus produced by an unusual kind of red-cell destruction? On this question authorities have divided themselves into two main

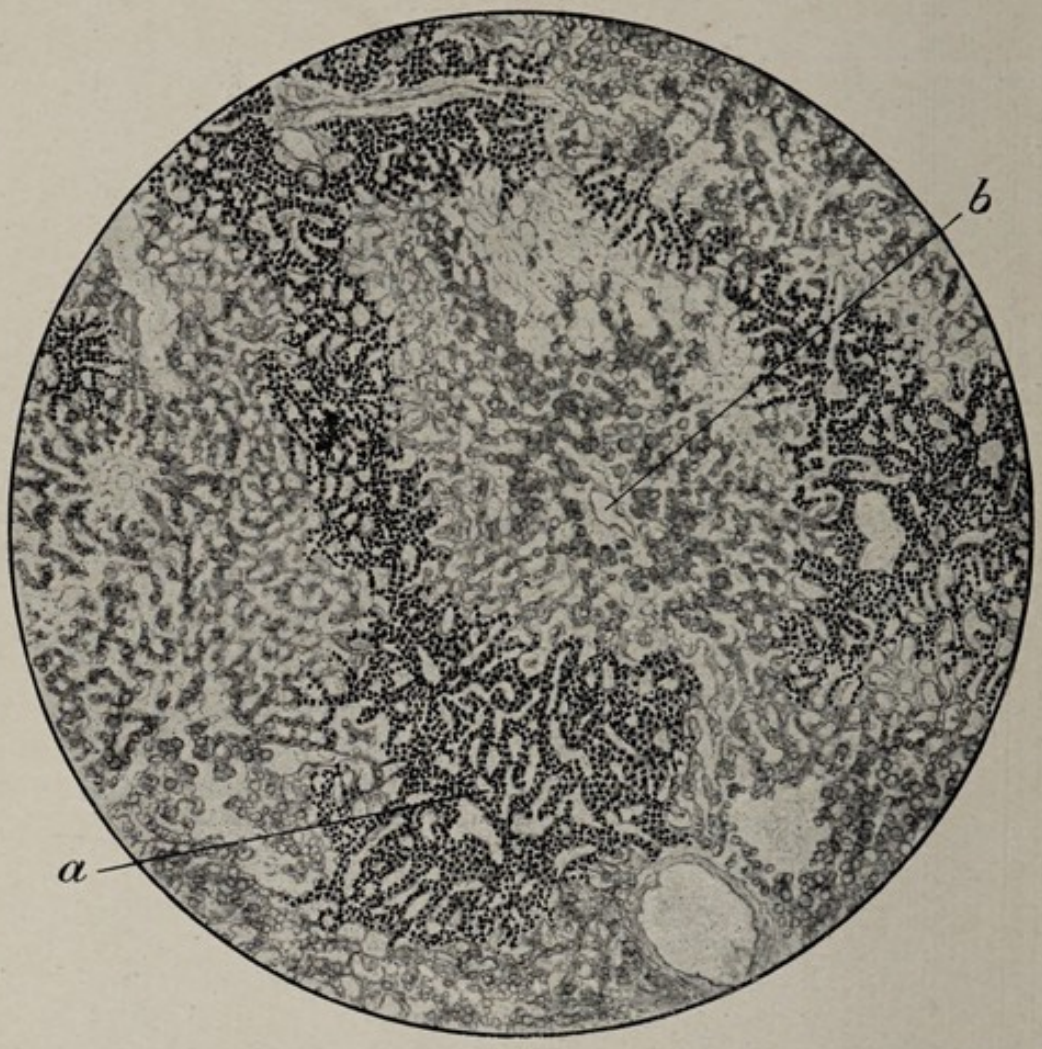


FIG. 167.—SECTION OF LIVER FROM A CASE OF PERNICIOUS ANÆMIA. (×79.)
a, deposit of iron at periphery of lobules; *b*, intralobular vein.

groups. The one sees the primary fault in the bone-marrow, which, through some misplaced activity, produces red cells of so abnormal a type that those organs, which are normally employed in the destruction of senescent red cells, rapidly remove them from the circulation. The other believes that excessive destruction is the primary factor, but there is little agreement as to the destructive agent.

All the evidence so far adduced is against the occurrence of anything in the nature of massive intravascular hæmolysis, since

hæmoglobinæmia and hæmoglobinuria have never been demonstrated; but this affords no argument against some hæmolytic agent being the ultimate cause, since it has been shown that, in animals, red cells may be largely destroyed as the result of injecting a specific hæmolytic serum, without the occurrence of either of these phenomena.

It is natural to suspect the presence of some infective agent, and the febrile periods which occur, the remissions and exacerbations, and the seasonal incidence which has been demonstrated by Hunter certainly lend support to such a view. On the other hand, we must be careful not to lay too much stress on the fact that certain micro-organisms, such as many streptococci, are known to produce a hæmolysin, for all attempts to demonstrate the causal relationship of any organism to this disease have hitherto failed.

Conditions closely resembling pernicious anæmia have been produced in animals by the inoculation of various hæmolytic agents, but the interpretation of the results obtained is complicated by the fact that blood-regeneration in the animals employed seems to differ in important points from the same process in man, and these differences are just those which would tend to produce a blood-picture simulating pernicious anæmia.

The abnormal type of marrow activity cannot be justly urged against the theory of excessive destruction, since it is quite possible that the stimulus resulting from excessive destruction of red cells within the body would be quite different from that produced by the loss of large quantities of the whole blood as the result of hæmorrhage. In the present state of our knowledge the issue must remain undecided.

The table (p. 440) indicates the main changes found in the blood in chlorosis and in pernicious anæmia.

SECONDARY ANÆMIAS.—The constitution of the blood undergoes well-marked alterations in the course of a large number of diseases, as the result of injuries involving loss of blood and during certain physiological processes. In many cases one of these changes consists in a diminution of the concentration of hæmoglobin, and hence anæmia is produced. It is impossible to discuss at all fully the various types of secondary anæmia which occur in different conditions, but it may be stated that this phenomenon supervenes in many acute infections, such as acute rheumatism, severe streptococcal infections, etc., as the result of infection with certain parasitic worms, during many chronic diseases associated with marked cachexia, as the result of certain poisons (such as lead), in the course of other blood-diseases (such as the various types of leukæmia), and in all cases of severe or repeated hæmorrhage.

The type of anæmia varies widely. Thus, in the case of the anæmia associated with ankylostomiasis the condition is one of anæmic plethora giving the same blood-picture as chlorosis, while in other cases pernicious anæmia may be closely simulated.

Of the secondary anæmias in general, it may be said that the red

cells may show any degree of reduction, usually slight or moderate, but sometimes of the most marked type. Poikilocytosis is common, polychromatophilia and punctate basophilia rare, except after severe hæmorrhage or in myelæmia.

TABLE SHOWING THE CONDITION OF THE BLOOD IN CHLOROSIS AND IN PERNICIOUS ANÆMIA.

	Normal Blood.	*Chlorosis.*	*Pernicious Anæmia.*
Rouleaux formation	Normal	Slightly decreased	Poor or absent
Fibrin formation	Normal	Increased	Decreased
Red cells per c.mm.	5,000,000	2,500,000–4,000,000	1,000,000–2,000,000
Colour index	1	0·3–0·5	0·9–1·6
Leucocytes per c.mm.	4,000–10,000	2,000–5,000	1,000–4,000
Differential count of leucocytes	Polymorphonuclears (60%–70%) Lymphocytes (20%–35%) Large hyalines (2%–5%) Eosinophiles (0·5–2%) Basophiles (0·5% or less)	Polymorphonuclears relatively decreased, and lymphocytes correspondingly increased; eosinophiles may be slightly increased	Polymorphonuclears relatively decreased, and lymphocytes correspondingly increased; a few myelocytes may be present
Changes in red cells	Nil	Slight poikilocytosis; numerous microcytes; nucleated red cells scanty, and all normoblasts	Well-marked poikilocytosis; numerous macrocytes; polychromatophilia; punctate basophilia; nucleated red cells more numerous; megaloblasts and normoblasts

Nucleated red cells are usually scanty, and consist almost entirely of normoblasts, the blood in myelæmia again forming an exception. The leucocytes vary according to the primary condition. Thus, in many acute infections, in many cases of malignant disease, and after severe hæmorrhage, there is a more or less marked polymorphonuclear leucocytosis. On the other hand, in certain acute

infections and in many other conditions associated with anæmia, there is a leucopenia, while in scurvy and some other diseases there may be a well-marked lymphocytosis.

Certain conditions which may be classed as secondary anæmias, because some other feature is more striking from the clinical point of view, deserve a little further mention, since it is in the blood and blood-forming organs that the main morbid changes are found.

Splenic Anæmia is a slowly progressive anæmia associated with marked and often enormous enlargement of the spleen. Sometimes the liver is also enlarged and shows cirrhotic changes, and the condition is then known as "Banti's disease." The anæmia itself shows definite remissions and exacerbations. The blood-picture conforms to the secondary type in that the colour index varies between 0·5 and 0·7. The reduction in red cells, at first slight, may become extreme just before the fatal issue, or after any one of the severe hæmorrhages, usually gastric or intestinal in origin, which form so frequent a feature of the disease. Nucleated red cells are very scanty, and almost always of the normoblast type. A well-marked leucopenia is a constant feature of the disease.

Purpura.—This term is used to denote a variety of conditions associated with hæmorrhages into the skin and beneath serous and mucous membranes. It really describes one phenomenon which occurs in a variety of diseases. In some cases the primary condition is known, as in the purpura occurring in certain acute infections or after the administration of certain drugs. In the majority of cases, however, the pathology is altogether obscure, and the term is employed to describe several more or less well-defined conditions, of which the purpura itself forms a part. Thus, in purpura rheumatica, or Schönlein's disease, there is an associated multiple arthritis; in Henoch's purpura there are visceral hæmorrhages, especially into the wall of the intestine; in Wehrlhoff's purpura, or purpura hæmorrhagica, there are repeated and severe hæmorrhages from mucous surfaces, especially from the gums, and a varying degree of fever; moreover, in this form a fatal issue is frequent, and may be extremely rapid. As stated above, nothing definite is known of the ætiology of most of these conditions, but, as has been mentioned already, Ledingham has recently succeeded in producing a condition simulating severe purpura by the inoculation of antiplatelet serum into guinea-pigs.

Paroxsymal Hæmoglobinuria and Blackwater Fever.—These two conditions are the only instances of the undoubted occurrence of extensive intravascular hæmolysis.

Blackwater Fever occurs during the course of a very small proportion of cases of malarial infection, and is characterised by well-marked hæmoglobinuria. Its pathology is still undetermined. It is variously attributed to the action of the malarial parasites and to the action of quinine, especially of certain of its salts. The latter hypothesis has never been satisfactorily established, and

clinical evidence points to the irregular use of quinine, rather than the actual administration of the drug, as a predisposing cause.

Paroxsymal Hæmoglobinuria, which may be associated with Raynaud's disease, is a condition in which sudden severe attacks of hæmoglobinuria occur, and are almost always brought on by exposure to cold. In this condition the red cells themselves are normal, but there seems to be some hæmolytic immune body present in the plasma which will combine with the red cells only in the cold, and which then so sensitises them that, upon subsequent warming, the complement of the plasma can produce hæmolysis.

Family Cholæmia (*Acholuric Jaundice*) is a curious condition which almost always affects several members of one family. Persistent slight jaundice is associated with a varying degree of splenic enlargement and with some degree of secondary anæmia. There are several facts which point unmistakably to a definite abnormality of the red cells. Forms showing changes in size and in staining reaction are present in stained films, and the fragility of the red cells is so increased that hæmolysis commences in a concentration of 0·55 to 0·65 per cent. of sodium chloride, instead of with the normal 0·4 per cent.

Anæmia Infantum Pseudoleukæmica (*Von Jaksch's Anæmia*).—This term has been applied to a group of cases occurring exclusively in young children, in which a severe anæmia is associated with a marked leucocytosis (up to 50,000 or more). The leucocytes vary greatly in kind, and many abnormal forms occur which cannot be accurately classified. It is usual to find a certain percentage of myelocytes, but in some cases the most striking feature is the marked lymphocytosis. Nucleated red cells, including megaloblasts, are common. Similar cases have been reported by many observers, and a critical survey of the whole series leaves no doubt that the group is an absolutely heterogeneous one, and that the condition cannot be regarded as a uniform specific disease. The truth is that the blood in young children differs in important respects from the blood in adults, and changes which may be held to have a certain definite significance in the latter cannot be credited with a similar meaning in the former. The descriptions given above, of the blood-picture in various conditions, apply exclusively to adults or to adolescents, and not to children in the early part of the first decade of life.

Polycythæmia.—This term is used to denote an increased concentration of red cells, and hence of hæmoglobin in the blood. The total volume of blood may be less than normal or it may be increased; in the latter case the condition is one of polycythæmic plethora. Like anæmia, polycythæmia is divided into primary and secondary varieties.

Primary Polycythæmia (Splenomegalic Polycythæmia) is an extremely rare disease associated with an increase in the number of red cells per c.mm. of peripheral blood up to double the normal. There is a relatively less marked increase in the concentration of hæmoglobin, so that the colour index falls slightly. A moderate

leucocytosis is usually present. A striking feature of the disease is the enormous secondary enlargement of the spleen.

There is evidence of increased marrow activity on post-mortem examination, and slightly immature cells may make their appearance in the general circulation. The condition seems to be one of purposeless over-production of red cells, showing obvious similarity to the over-production of tissue cells in the various forms of malignant disease. The total blood-volume is always increased, and hence the actual excess of red cells is even greater than is indicated by an examination of the peripheral blood. The great splenic enlargement is almost certainly a secondary phenomenon, and indicates an attempt on the part of this organ to deal with the enormous excess of red cells in the circulation.

Secondary Polycythæmia is caused by loss of plasma without corresponding loss of red cells, as in severe cases of cholera, etc. There is abundant evidence to show that the tissues actively resent any diminution in the total blood-volume, and hence it is only in very rapid and extensive loss of the body fluids that this form of polycythæmia occurs.

A *Compensatory Polycythæmia* occurs when for any reason the oxygenation of the blood falls below the normal limits. Thus, when a person moves from a low-lying district to considerably higher altitudes—such, for instance, as the higher Alps—the decrease in the partial pressure of oxygen leads to a compensatory polycythæmia, which gradually disappears on returning to lower levels. Again, patients suffering from certain types of heart disease, especially congenital pulmonary stenosis, acquire a compensatory polycythæmia of a more or less marked degree.

Conditions associated with Changes in the Leucocytes.

The total number of leucocytes per c.mm. of blood, and the relative proportion of the different leucocytes present, are subject to variation in health and disease. In certain conditions, both physiological and pathological, an increase in one particular type of leucocyte is brought about by certain definite stimuli; the increase in these cases is known as a "leucocytosis," and should be qualified by the name of the cell specially affected. In other cases, as in the various types of leuchæmia, the increase in leucocytes is the most striking feature of the condition, and possesses abnormal features which clearly differentiate it from the leucocytic response to the stimuli which produce the various types of leucocytosis.

Polymorphonuclear Leucocytosis (Plate III.), often spoken of simply as "leucocytosis," is a condition in which the total number of leucocytes per c.mm. of blood is considerably increased (12,000 to 40,000), with a corresponding increase in the relative proportion of polymorphonuclear cells (75 to 95 per cent.). There are various physiological conditions which are associated with a leucocytic reaction of this particular type. Thus, a polymorphonuclear

leucocytosis occurs after the midday meal, and is generally spoken of as "post-prandial leucocytosis"; but further investigations have shown that this leucocytosis is usually absent or very slight after the morning and evening meals, and it would seem that this increase is as much a diurnal variation as the result of digestion. The new-born show a leucocytosis; so also do moribund patients in a large proportion of cases. Cold baths and active exercise produce the same result. It was long believed that a leucocytosis accompanied pregnancy, but more extended observations have thrown grave doubts on this, and the most recent observers state that it is only with the actual onset of labour that a leucocytosis occurs. This lasts beyond delivery into the first few days of the puerperium, though, according to some, a temporary fall occurs immediately after the completion of labour.

The pathological conditions associated with a polymorphonuclear leucocytosis include the following: (*a*) *Suppuration:* This condition in almost all cases results in a leucocytic reaction of this type. If the lesion be very slight, no increase in leucocytes may be noticed; if the infection be very severe, as, for instance, in a case of acute streptococcal peritonitis leading to a rapidly fatal issue, there may be an actual leucopenia. The most marked degree of leucocytosis is found with moderately extensive and extending suppuration accompanied by a high degree of resistance on the part of the patient. Repeated leucocyte counts yield especially valuable information in cases where suppuration is suspected, since an increasing leucocytosis is the rule with a recent and extending suppurative focus. (*b*) Most of the *acute specific fevers* are accompanied by this type of leucocytic reaction. Exceptions are typhoid and paratyphoid infections, influenza, tuberculosis, Malta fever, whooping-cough, mumps, and some others. (*c*) *Malignant Disease* is often associated with a polymorphonuclear leucocytosis, which, if present, does not usually undergo any marked alteration over a short period of time. (*d*) A *severe hæmorrhage* is followed by a secondary polymorphonuclear leucocytosis which persists for some weeks, but gradually declines to normal limits. (*e*) Following *severe operations*, especially those involving laparotomy, there is a definite leucocytosis lasting from two to five days.

The polymorphonuclear leucocytes in this condition show certain changes, in addition to the numerical increase, which point to an abnormal activity and rate of regeneration. If stained with a solution of iodine in potassium iodide, they show the presence of numerous granules of glycogen. Abnormal types, known as "stimulation forms," are often present, and the proportion of cells with slight or moderate lobulation of the nucleus is increased.

Lymphocytic Leucocytosis (*Lymphocytosis*).—This condition is much less common than the polymorphonuclear variety, and occurs mainly in children. It is perhaps most marked in whooping-cough, but may occur in cases of congenital syphilis, in rickets, and in some cases of scurvy.

Eosinophile Leucocytosis (*Eosinophilia*).—Any case in which the eosinophile cells number more than 5 per cent. of the total leucocytes may be considered to show eosinophilia, though the percentage is often much higher, and may reach or exceed 50 per cent. Eosinophilia occurs in infection with the various parasitic worms, in certain skin diseases, such as dermatitis herpetiformis, urticaria, and pemphigus, and in some cases of asthma. Other pathological conditions have been reported to show an increase in the eosinophile count, but this seems to be inconstant and usually slight in degree.

Large Hyaline Leucocytosis.—An increase in the large hyaline percentage occurs in infection with protozoal organisms, such as malaria, syphilis, and trypanosomiasis.

Leuchæmia.—This term signifies a condition in which the leucocytes of the blood are enormously increased. There are two main varieties of this disease. In one, **myelæmia,** all leucocytes of the granular type are enormously increased, and in addition a differential count shows a considerable percentage of myelocytes, cells which are normally absent from the general circulation. In the other type, **lymphæmia,** the cell which predominates is the lymphocyte; but the enormous increase observed (up to 400,000 or more per c.mm., with 95 per cent. or more of lymphocytes) differentiates this condition sharply from a lymphocytosis. Moreover, each of these types presents a definite clinical picture, proceeds eventually to a fatal termination, and shows constant post-mortem changes, so that each may justly be regarded as a definite clinical entity and as constituting a true disease, and not merely a sign or symptom. These two main types may be further subdivided into acute and chronic forms. In the case of myelæmia this division must still be regarded as uncertain, since it is possible that the acute cases which have been hitherto observed really constitute the terminal phase of the ordinary chronic form. In the case of lymphæmia the two forms would appear to be absolutely distinct.

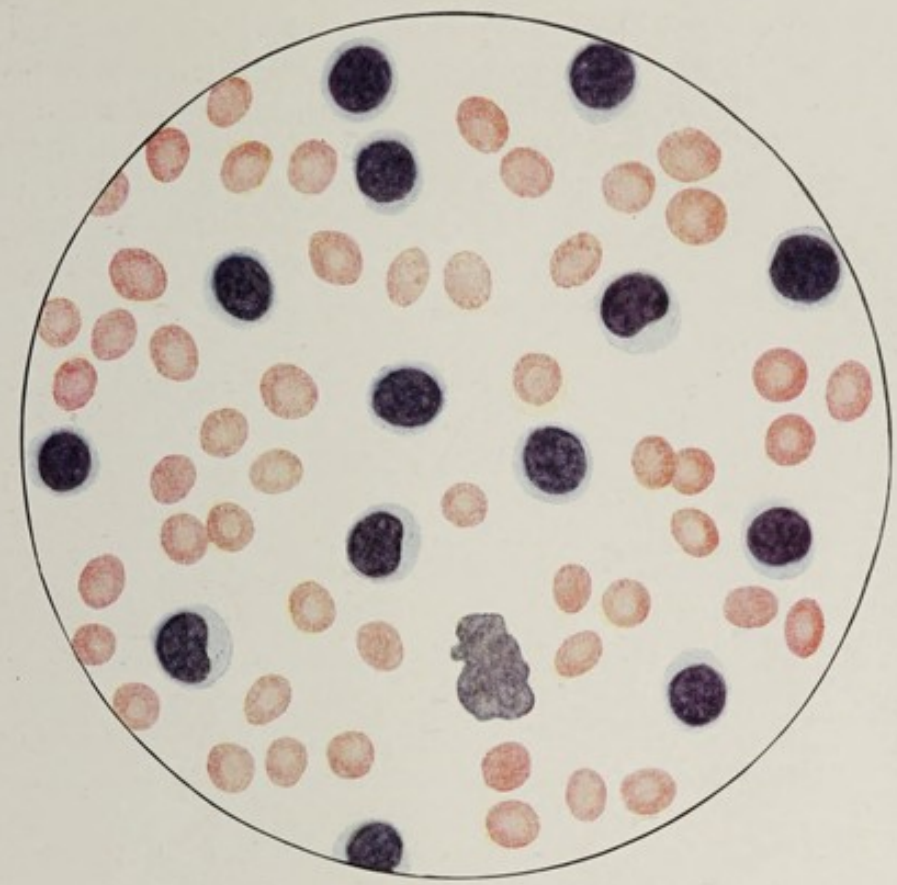
Myelæmia (Plate IV.).—This is a condition in which an enormous increase in the number of leucocytes per c.mm. of peripheral blood is associated with great enlargement of the spleen, and in many cases of the liver. Glandular enlargement is usually slight or absent. There is a varying degree of anæmia. The disease is uniformly fatal, and death occurs, in the great majority of cases, within two years of the patient first coming under observation. The condition is subject to remissions and exacerbations, and during its course there are irregular febrile attacks.

The blood-picture is distinctive. In a well-marked case the leucocytes number from 50,000 to 500,000 per c.mm., but it is often possible to diagnose the disease with certainty from examination of stained films when the leucocytes are only slightly in excess of normal. All types of leucocyte are represented, but the most striking feature is the presence of a large percentage of myelocytes, cells usually confined to the bone-marrow, and which are regarded

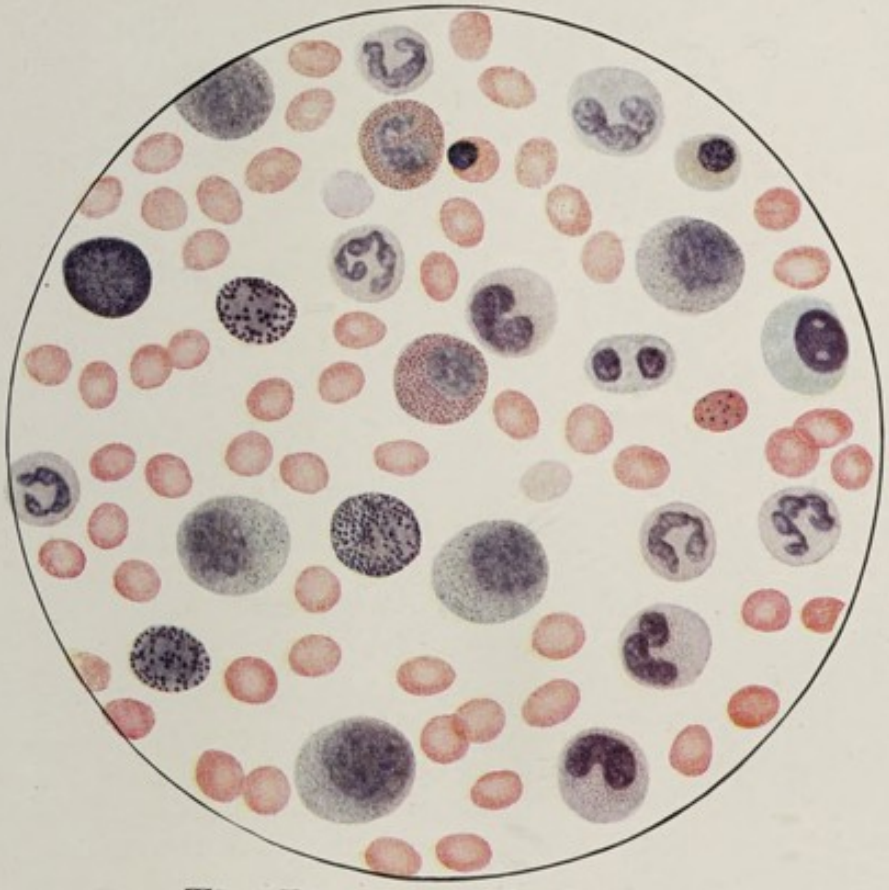
as the precursors of the granular cells of the blood. These cells are usually of large size, 10 to 20 μ in diameter, though smaller forms may occur. The nucleus is usually excentric, and does not stain deeply. The cytoplasm of the cell shows a very varying degree of granularity, and the granules may be neutrophile (neutrophilic myelocytes), eosinophile (eosinophilic myelocytes), basophile (basophilic myelocytes), or the latter varieties may coexist in the same cell (amphophilic myelocytes) (Plates II. and IV.). These cells are regarded respectively as the precursors of the polymorphonuclear neutrophile, the eosinophile, and the basophile, or mast-cell. In addition to these forms, there are usually present a certain number of cells which resemble a myelocyte, save for the fact that the cytoplasm is non-granular and stains a distinctive "pigeon's egg" blue colour with Leishman's stain. These cells are named "myeloblasts," and are regarded as precursors of the myelocytes (Plates II. and IV.). The myelocytes usually number 20 to 60 per cent. of the total leucocytes, and in consequence most other varieties of cell are relatively diminished, though, with the possible exception of the lymphocytes, they are absolutely increased. The coarsely granular basophile leucocyte, or mast-cell, is an important exception. It is usually absent from normal blood, or, if present, forms only 0·5 per cent. or less of the total leucocytes; but in myelæmia it usually constitutes 5 to 20 per cent. In most cases a considerable proportion of cells are found which appear to be intermediate between the myelocyte and the polymorphonuclear cells, and these are classed together as transitional forms. The large hyaline cells may also be relatively as well as absolutely increased in numbers, and in some rare cases they are so numerous that the condition might justly be regarded as a hyalæmia. The red cells are always slightly diminished (2,500,000 to 4,000,000 per c.mm.), and the hæmoglobin is disproportionately decreased, so that the colour index falls (0·5 to 0·7). Nucleated red cells are present in numbers altogether out of proportion to the degree of anæmia present, and of these megaloblasts form a considerable percentage. Polychromatophilia and punctate basophilia are usually well marked. Towards the end of a typical case of myelæmia the red cells are still further diminished in number and a severe anæmia occurs. The same phenomenon may take place during the exacerbations which occur in the course of the disease. In conjunction with this, there is often a marked increase in the percentage of myeloblasts, and such an increase is always of ill omen.

As mentioned above, an acute type of the disease seems to occur, which may lead to a fatal termination within a few weeks or months. In this variety the anæmia is usually marked from the first, and the myeloblasts form the preponderating type of leucocyte. Hæmorrhages are relatively common in this form of the disease, and splenic enlargement is often slight or absent.

Morbid Anatomy.—Post mortem the marrow, as one would expect, shows definite hyperplasia, with the presence of a large



The Blood in Lymphæmia



The Blood in Myelæmia

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excess of myelocytes. The bloodvessels throughout the body, when examined in sections, show the enormous increase in leucocytes; and in many situations, such as the liver, kidney, lungs, brain, etc., there are found, surrounding the capillaries, areas of infiltration with myelocytes. The spleen shows fibrosis, and the Malpighian corpuscles are usually obscured, while large numbers of myelocytes are present throughout its substances. The heart, liver, and kidneys, show fatty degeneration.

The ætiology of the condition is still entirely obscure. It is difficult to imagine any infecting organism which would provide a stimulus resulting in such a general proliferation of the marrow cells, since we know how specific is the stimulus usually supplied in such cases. The condition seems most to resemble a malignant growth, in the purposeless proliferation of the leucoblastic tissue, but we have not at present sufficient data on which to come to any definite conclusion.

Lymphæmia (Plate IV.).—As stated above, there would seem to be two distinct varieties of this disease. By far the commoner of the two is the acute form. This usually attacks young adults. It is a rapidly fatal disease, death always occurring within a few weeks or months. There is an enormous increase in the leucocytes (100,000 to 500,000 per c.mm.), of which 80 to 99 per cent. are usually lymphocytes. The small or large type of lymphocyte may predominate, and it is fairly common to find a high proportion of cells so malformed and degenerate that an accurate classification is impossible. Associated with this great increase in leucocytes there is a profound anæmia, the red cells often numbering 1,000,000 or less per c.mm. The hæmoglobin is disproportionately diminished, as in myelæmia, and the colour index usually falls between 0·5 and 0·7. Stained films, in marked contrast to myelæmia, show only slight abnormalities in the red cells. Nucleated red cells are very rarely present, and polychromatophilia and punctate basophilia are seldom found. There is general glandular enlargement throughout the body, but it is rare to find splenic enlargement in any degree approaching that found in myelæmia. A varying degree of pyrexia is the rule, and the temperature may reach a high level. Hæmorrhages, especially from the gums and mucous surfaces, are common.

Morbid Anatomy.—Post mortem the bone-marrow shows the presence of an enormous excess of lymphocytes, and histological examination of the tissues shows areas of infiltration with these cells similar to those found in myelæmia, but often attaining a larger size.

Chronic Lymphæmia is a very rare disease. The leucocytes show the same changes as in the acute form, but the red cells are very little affected—at all events in the early stages. They usually vary between 3,000,000 and 4,000,000 per c.mm., while the hæmoglobin, as in the other forms of leuchæmia, is disproportionately decreased. Stained films show no abnormalities in the red cells. There is usually marked general glandular enlargement, and the

spleen may attain an enormous size. So few cases of this type have been recorded that the clinical course of the disease is still not accurately known, but it is certain that cases may continue for years with but slight deterioration in health. Late in the disease a more marked anæmia occurs, and may lead to a fatal issue. The rarity of the disease also accounts for our ignorance of its morbid anatomy.

Much discussion has taken place in regard to the relation between the myelæmic and lymphatic types of leuchæmia. Some authorities regard them as variations of one and the same condition, and believe that in many cases the mononuclear cells present in so-called "lymphæmia" are in reality non-granular myelocytes. It is certain that the cells present in most cases of lymphæmia are not myeloblasts, but it is impossible to assert that they may not be some earlier form. However, in the present state of our knowledge we have no sufficient data on which to found a theory of the essential unity of leuchæmia, and the various types show such well-marked differences that it is wiser to regard them as distinct diseases.

The following table shows the main changes found in the blood in the various types of leuchæmia.

TABLE SHOWING THE CONDITION OF THE BLOOD IN THE VARIOUS TYPES OF LEUCHÆMIA.

	Myelæmia.	*Acute Lymphæmia.*	*ChronicLymphæmia.*
Rouleaux formation	Unaltered	Poor or absent	Unaltered
Fibrin formation	Unaltered	Poor	Unaltered
Red cells per c.mm.	2,500,000–4,000,000	1,000,000–2,500,000	3,000,000–,4000,000
Colour index	0·5–0·7	0·5–0·7	0·5–0·7
Leucocytes per c.mm.	50,000–500,000	100,000–500,000	100,000–500,000
Differential count of leucocytes	Myelocytic cells (20%–60%) Basophile cells (5%–20%) Transitional cells (5%–20%) Large hyalines (5%–20%) Other types relatively decreased	Lymphocytes (80%–99%)	Lymphocytes (80%–99%)
Changes in red cells	Polychromatophilia; punctate basophilia; nucleated red cells numerous, both megaloblasts and normoblasts	Slight	Slight or absent

Chloroma.—This is a condition, usually occurring in young children, which is distinguished by the presence of greenish-coloured tumours situated particularly in the orbits and over the bones forming the cranial vault. These tumours have the histological structure of lymphosarcomata. The blood gives the typical picture of acute lymphæmia, though here, again, some authorities would regard the cells as non-granular myelocytes. The condition would seem to lie midway between lymphosarcoma and lymphæmia, or rather, perhaps, to be a combination of these two conditions.

CHAPTER XXVIII

AFFECTIONS OF THE HEART

Malformations of the Heart.

In general terms, malformation of the heart comprises the following principal defects—singly or in combination: (1) deficiencies in the septa; (2) dilatation or narrowing of the pulmonary and aortic orifices; (3) redundances or deficiencies in the valves; (4) persistence of fœtal channels; and (5) transposition of the arterial trunks and other parts.

The *septa* may altogether fail to appear, or their formation may be arrested at any stage of their development. The *entire absence* of any one of these septa produces the earliest forms of malformation. In this way there may be produced a heart with a single auricle, a single ventricle, and a single arterial channel, supplying both systemic and pulmonary circulations, as in fish. If the defect is less extensive, a heart with two auricles, but with a single ventricle and a single artery, may result, as in the frog. These and other corresponding varieties are rare. In all of them extra-uterine life is only possible for a few days. *Incomplete formation* of septa is, however, a more frequent malformation. In this way many forms of persistent channels, connecting the two sides of the heart, may result.

In one of the commonest varieties of malformed heart the *orifice of the pulmonary artery is much narrowed* and that of the aorta correspondingly enlarged, while the upper part of the interventricular septum (the last part to be developed) is absent. The aorta may subtend both ventricles, and the wall of the right ventricle will then attain the same thickness as that of the left. In these cases the uctus arteriosus is generally patent, and so, not infrequently, is the foramen ovale. In most instances, the narrowing of the pulmonary artery seems to be the primary defect, the rest naturally following from the interference with the normal course of the fœtal circulation; for the blood from the right ventricle, being unable to pass through the pulmonary orifice and ductus arteriosus into the systemic circulation, is driven over the upper edge of the incomplete septum and there meets that coming from the left ventricle, passing upwards

with it into the aorta. After birth the aorta supplies the pulmonary artery by way of the ductus arteriosus.

Stenosis or absence of the aortic orifice is less common. When either of these occurs, both foramen ovale and ductus arteriosus are usually patent, while the left ventricle atrophies.

The *valves* may be excessive or defective in number and in size, but these changes need not seriously interfere with the action of the heart.

Persistence of the foramen ovale and of the ductus arteriosus, although generally associated with the defects before mentioned, may occur alone, without leading to any further pathological change.

In the majority of cases the arrest of the normal development of the heart seems to depend primarily upon some inherent embryonic defect, and only in exceptional cases upon fœtal endocarditis or other intercurrent disease.

Results.—Malformations of the heart do not necessarily give rise to secondary changes, especially if limited to some slight defect, such as a patent foramen ovale or persistent ductus arteriosus, or some abnormality in the number of segments in a valve—none of which need cause any appreciable impairment of the circulation. If, however, the malformation be sufficiently severe to affect the normal order of the circulation without rendering life impossible, two phenomena generally occur: (1) *cyanosis,* constant or intermittent; and (2) a *high specific gravity of the blood,* due to an increased proportion of its red corpuscles.

(1) The *cyanosis* has been attributed to the admixture of arterial and venous blood; but this explanation appears inadequate. Admixture, as in the case of a single ventricle, may exist without cyanosis; and, conversely, cyanosis without admixture. Moreover, it is in those cases in which the right ventricle is most hypertrophied that the cyanosis is most marked. With more reason, therefore, its presence is attributed to defective aeration of the blood and to passive (venous) congestion. The defect of aeration may depend on structural alterations (stenosis of pulmonary artery with incomplete interventricular septum) whereby the amount of blood passing through the lungs varies. The aeration may be sufficient to meet the ordinary requirements, but insufficient to meet any slightly increased demands. In the same way the venous congestion is mainly due to the partial exhaustion of the normal reserve power of the heart, this having been already largely used up in compensating for the structural defects, and to the consequent inability of that organ to meet any further demand. Blueness of the skin and mucous membranes, and clubbing of the fingers, are the chief results of the venous congestion.

(2) The *concentration of the blood,* as shown in the large amount of red corpuscles and increased percentage of hæmoglobin, has been attributed to the persistence of a condition obtaining in late fœtal life, when the specific gravity of the blood is also abnormally high.

Gibson suggests that the corpuscular excess is due to the diminished wear and tear, and the consequently longer life, of the individual corpuscles; but this view has not yet met with general acceptance.

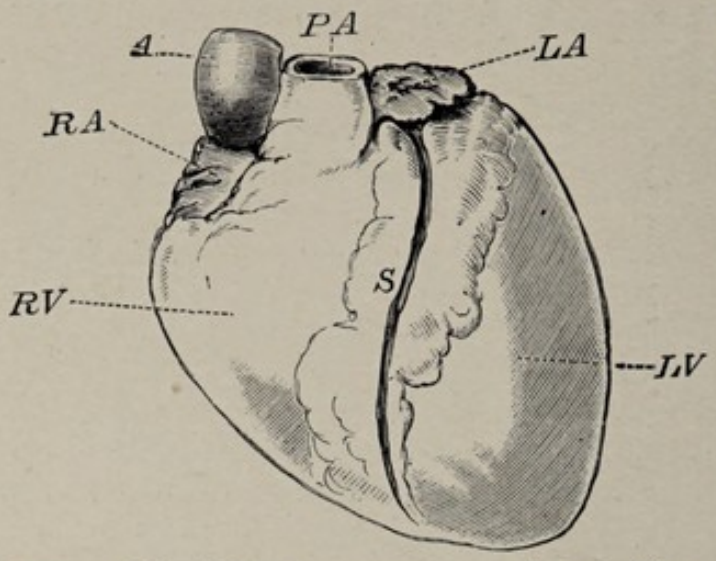


FIG. 168.—HYPERTROPHY OF LEFT VENTRICLE (FRONT VIEW).

The heart is elongated. The septum occupies the middle of the anterior surface. From a case of granular kidney. *A*, aorta; *PA*, pulmonary artery; *RA*, *LA*, right and left auricles; *RV*, *LV*, right and left ventricles; *S*, septum.

Hypertrophy of the Heart.

Hypertrophy of the heart has been already referred to, but its varieties are of sufficient importance to merit a more detailed account. It must be recognised that hypertrophy of the heart is not in itself a disease, but that it takes place in response to altered conditions in the circulation, which the heart can only overcome by increased vigour of contraction. It is therefore of the nature of an attempt to remedy a defect elsewhere, and is beneficial, not the reverse. It is only pathological as being a departure from the normal condition.

The whole heart may be uniformly affected or the enlargement may be mainly confined to one of the two ventricles.

1. **Uniform hypertrophy** of the whole organ is a common result of adherent pericardium. By this change the sliding action of the heart is interfered with, and the work thrown upon its muscular walls proportionately increased. A heart thus enlarged may weigh from twelve to thirty ounces—even after the parietal layer of the pericardium has been dissected off. The normal shape of the heart is preserved, but its general dimensions—both external and internal—and the thickness of its walls are alike increased.

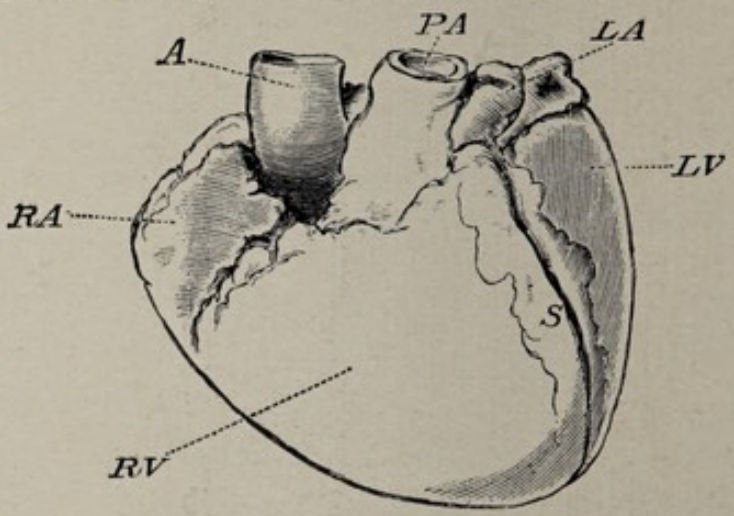


FIG. 169.—HYPERTROPHY OF RIGHT VENTRICLE (FRONT VIEW).

The heart is as broad as it is long, and the septum is displaced to the left. Right auricle is dilated. From a case of chronic bronchitis and emphysema. *A*, aorta; *PA*, pulmonary artery; *RA*, *LA*, right and left auricles; *RV*, *LV*, right and left ventricles; *S*, septum.

2. **Hypertrophy of the left ventricle** follows any changes that give rise to obstruction at the aortic orifice, or permit regurgitation from the aorta. It also follows obstruction in the arterioles such as occurs in arterio-capillary fibrosis (granular contracted kidney). The weight of the organ frequently exceeds twenty ounces. In shape it is elongated; the septum, and therefore the left coronary artery, is displaced to the right of its usual position on the anterior surface (Fig. 168). On examining a vertical section the apex is seen to be formed entirely by the wall of the left ventricle, and the walls of this cavity are themselves thickened (Fig. 170).

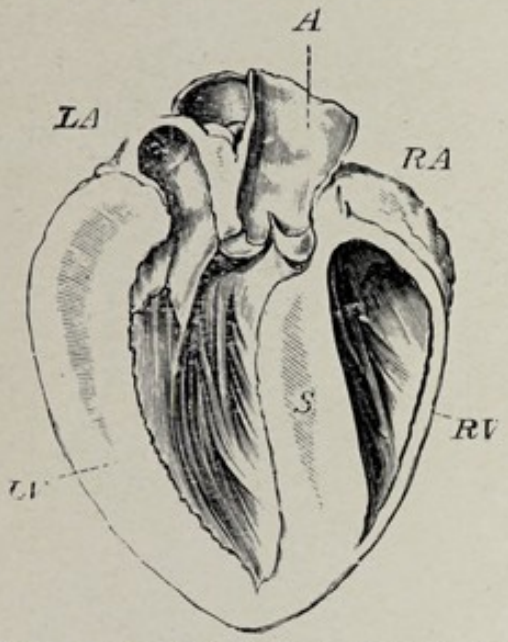


FIG. 170.—ANTERIOR HALF OF HEART (FIG. 168) SEEN FROM BEHIND.

Left ventricle forms the whole of apex. Wall of left ventricle: wall of right ventricle: : 10: 2 (normal proportion 5: 2).

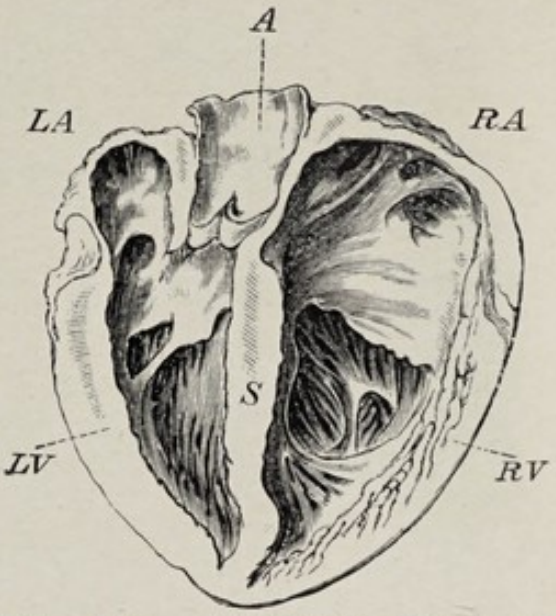


FIG. 171.—ANTERIOR HALF OF HEART (FIG. 169) SEEN FROM BEHIND.

Right ventricle is seen to take greater share in formation of apex than left ventricle does. Wall of right ventricle is much thickened, but not so thick as that of left. Tricuspid orifice and right auricle are dilated.

3. **Hypertrophy of the right ventricle** follows any changes in the mitral orifice, or in the lungs, which hinder the passage of the blood from the right ventricle to the systemic circulation, and thus impose additional work on the right side of the heart. Emphysema of the lungs and incompetence of the mitral valves are its principal causes. The heart is somewhat square in shape, and its anterior surface consists, almost entirely, of the wall of the right ventricle (Fig. 169). On section, both ventricles are found to take about an equal share in the formation of the apex of the organ, while the usual difference between the thickness of the walls is much diminished (Fig. 171). Except in cases of congenital disease, the thickness of the right ventricle never reaches that of the left. These distinctions are well shown in the accompanying illustrations.

Pericarditis.

Pericarditis may be apparently primary or may follow infection elsewhere. It is most commonly met with in rheumatic fever, but may complicate any acute infective disease (septicæmia, enteric fever, scarlatina, etc.). In acute pneumonia it appears to occur by direct spread of infection from the pleura. Pericarditis occurs in two forms: the simple and the suppurative.

Simple Pericarditis. — The exudation is accompanied by an extensive destruction of the endothelium, and, in the vast majority

FIG. 172.—FIBRINOUS PERICARDITIS OF TWO WEEKS' DURATION. (× 6.)

a, parietal pericardium with artery and vein; *b*, organising layer of fibrin, with engorged vessels appearing as dark points on its visceral edge (*b'*); *c*, fibrinous meshwork; *d*, organising layer of fibrin adjoining visceral pericardium (*e*); *f*, muscular wall of heart with subpericardial fat and vessels; *g*, line of union of the two inflamed surfaces, showing that by far the larger amount of fibrinous exudation is on the visceral side.

of cases, is of a sero-fibrinous character. A fibrinous layer covers both visceral and parietal pericardium, and a few ounces of flaky albuminous fluid fill the intervening cavity. The fibrinous layer varies from a fine deposit, just concealing the natural gloss of the surface, to a layer $\frac{1}{4}$ inch thick, or a rough shaggy coat (*cor villosum*). The fluid effusion may in some cases reach a large amount, and considerably distend the pericardial sac.

The subsidence of the inflammation is followed by absorption of the fluid, and by organisation of some, or all, of the fibrinous layers

(Fig. 172). This results in obliteration of a proportionate amount of the pericardial cavity, or in the formation of fibrous bands passing across it.

During the acute stage the heart's action is slightly hampered (1) by the friction between the roughened surfaces, especially of the auricles and right ventricle, and (2) by the pressure of any marked effusion of fluid. There is also usually some extension of the inflammation to the outer layers of the myocardium. In later stages the action is also impaired by (1) the presence and contraction of such adhesions as have not been torn asunder, during the earlier stages of their development, by the movements of the muscular walls of the heart; and (2) by the contraction of the inflammatory fibrous tissue in the visceral pericardium and in the outer layers of the myocardium itself. The impairment is often sufficient to cause uniform hypertrophy of the heart.

On the surface of the pericardium smooth, white, "*milk patches*" are not infrequently observed. In a few cases these represent the most favourable termination of an old acute pericarditis; but the great majority are probably due to some source of pressure outside the pericardium, leading to considerable local friction between the visceral and parietal surfaces. At such places the pericardium becomes thickened and, therefore, whiter and more opaque.

Suppurative Pericarditis.—This occurs especially as a complication of acute pneumonia, and in cases of pyæmia. The changes are identical with those which take place in suppuration in any serous cavity.

Endocarditis.

Inflammation of the Endocardium, or *endocarditis*, is, for the most part, limited to the *valves* of the heart, although it occasionally involves the adjacent parts. When the disease occurs *after birth* it is almost exclusively confined to the *left* side of the heart, and thus, in the great majority of cases, commences in, and seldom extends beyond, the confines of the mitral and of the aortic valves and the corresponding orifices; but when it arises during *fœtal life* endocarditis is usually found on the *right* side and, by the production of lesions which interfere with the normal development of the heart, becomes one of the causes of congenital malformation of that organ.

Those portions of the valves which normally come into contact, and are thus most exposed to friction, are those in which the morbid changes commence. In the *mitral valve*—the most commonly affected of all—the auricular surface of the segments, at a little distance from the attachment of the chordæ tendineæ, is first involved (Fig. 173). In the *aortic* valves it is the convex or ventricular surface of the segments which is affected. The change does not commence at the free edge of the segment, but along the little band

of tissue which passes from the attached border to the corpus Arantii in the centre (Fig. 174).

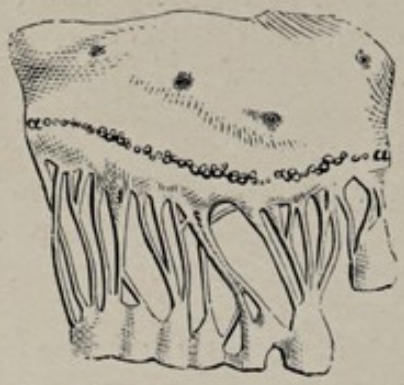


FIG. 173.—INFLAMMATION OF MITRAL VALVE.

The earlier stage of the process. Valve seen from the auricular surface, showing the situation of the inflammatory granulations.

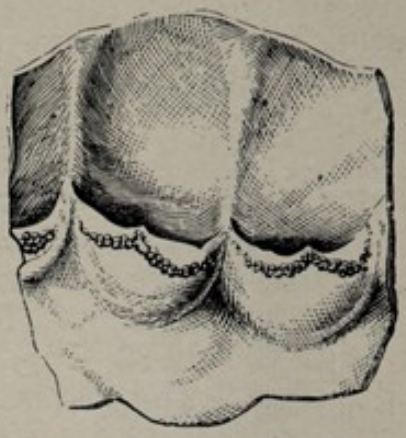


FIG. 174.—INFLAMMATION OF AORTIC VALVES.

The earlier stage of the process, showing the situation of the inflammatory granulations.

The changes themselves may, for the purposes of description, be arranged in three groups, although they frequently occur together.

(1) Upon the surface of the parts already indicated are found a number of pale, closely aggregated projections, varying from a band of mere specks or beads, which cannot exert any appreciable mechanical effect on the

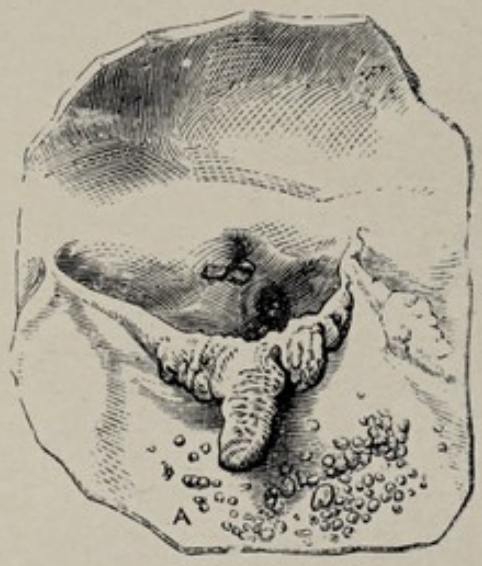


FIG. 175.—ENDOCARDITIS DUE TO FRICTION.

The drawing represents a long vegetation on one of the segments of the aortic valve, which by contact with the endocardium below has produced numerous inflammatory granulations (A).

FIG. 176.—ACUTE ENDOCARDITIS. (× 10.) (RINDFLEISCH.)

A granulation from the mitral valve, showing a fibrinous coagulum upon the surface of the granulation (*d*).

heart's action (Fig. 173) to large cauliflower-like masses almost completely obstructing the affected orifice (Fig. 175). These projections, in the large majority of cases, consist of thickened endocardium and adherent, and often organised, blood-clots (Fig. 176).

(2) The affected valves and their attachments may be much thickened throughout, and, at places, coherent and even calcified. In this way the mitral orifice may be reduced to a rigid funnel or a button-hole slit (Fig. 177), and the aortic valves may so lose their elasticity that they stand out into the lumen of the aorta, neither falling back during systole nor completely closing the orifice during diastole (Fig. 178). Thus the passage of blood through the orifices may be seriously interfered with (*stenosis*) and its regurgitation permitted (*incompetence*).

(3) Less frequently, and combined with the other changes, ulcers and minute abscesses may be found penetrating into the deeper

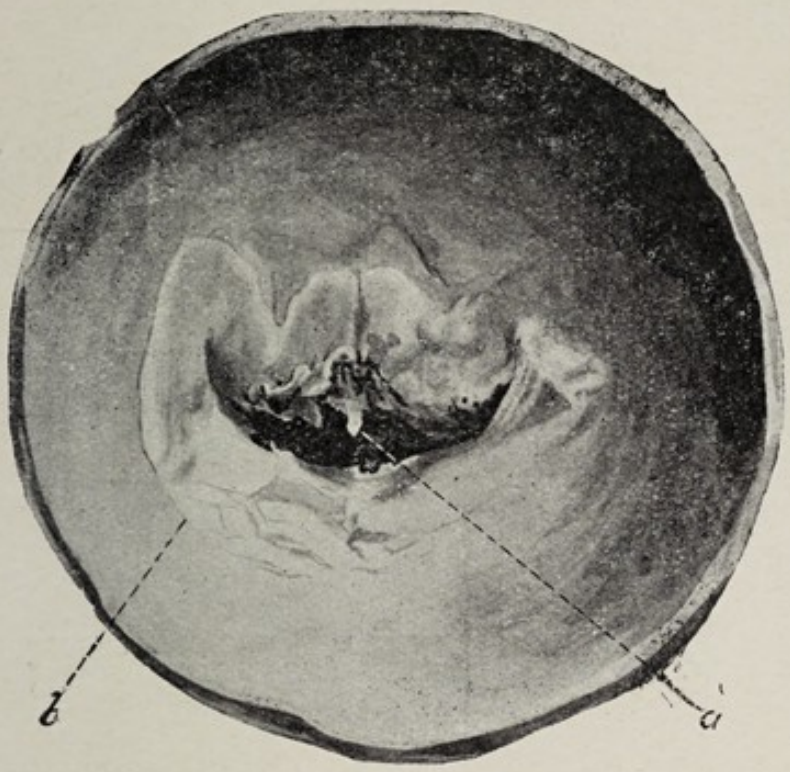


FIG. 177.—MITRAL STENOSIS. (NATURAL SIZE.) (C. C. H. MUSEUM.)
Mitral orifice seen from the left auricle in a case of old inflammation of the mitral valves. The orifice is in the centre of a calcified mass, the outer edge of which can be seen at (*b*). A calcareous spicule projects into the orifice (*a*).

layers of the endocardium and even involving the myocardium beneath. Portions of the valves may be wholly destroyed and disappear, while the superjacent and loosely adherent thrombi, being easily detached, broken up, and carried on by the circulating blood, may give rise to multiple embolism of the brain, spleen, kidney, skin, and other parts (Fig. 179).

PATHOLOGY.—Endocarditis is an infective disease. Organisms have not only been found and cultivated from the lesions, but it has also been shown experimentally that various organisms, and especially certain types of streptococci, are capable, when injected into the circulation, of producing endocarditis. This probability is greatly increased when small solid particles are simultaneously

introduced, or when the valves are in any way previously damaged. The disease frequently arises in the early stages of acute rheumatism and of chorea. It is an occasional complication of pyæmia, puerperal fever, gonorrhœal arthritis, scarlatina, typhoid fever, and chronic Bright's disease. The limitation of the disease, after birth, to the left side of the heart seems to be mainly due to the higher blood-pressure and greater friction. In fœtal life, on the other hand, the right side is more subject to strain than the left, and it is also more readily infected from the placenta.

The initial lesion consists in a localised infiltration of the sub-endothelial tissue with mononuclear cells, and proliferation, and

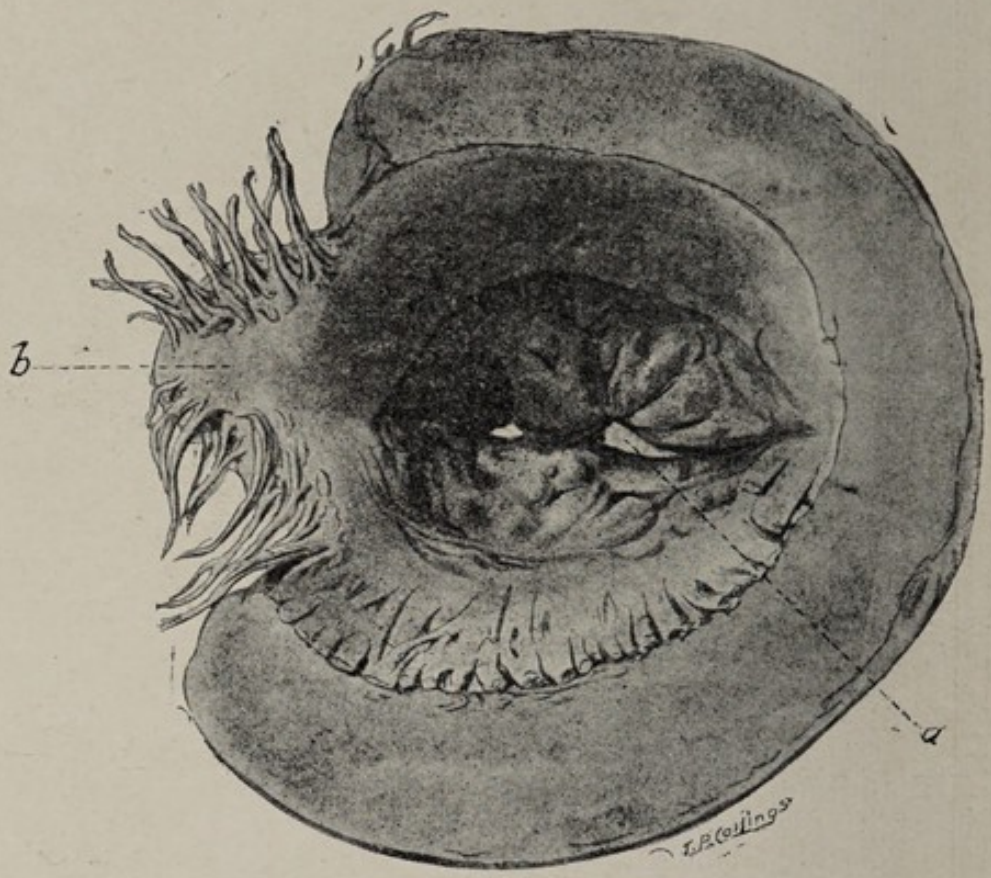


FIG. 178.—AORTIC STENOSIS. (NATURAL SIZE.) (C. C. H. MUSEUM.)

a, aortic orifice seen from below in a case of old inflammation of the aortic valves. The valves are calcified, and meet in the centre and at the sides. *b*, mitral valve (foreshortened).

later necrosis, of the endothelium itself. Upon these necrotic patches the passing blood coagulates in laminated thrombi. In many of the milder cases, no further change occurs until reparative processes begin.

The next stage varies according to the extent of the lesion. (1) When the original invasion is slight and the necrosis superficial, the proliferation of tissue-cells, characteristic of repair, quickly follows. The superficial parts of the firm and minute thrombi disappear, and the remainder becomes organised. The final result is a

slight, permanent thickening of the affected parts with very slight narrowing or distortion of the orifice and its valves. (2) When the lesion is more severe, the necrosed patches are bigger and more numerous, while the adherent thrombi are proportionately larger. The term "warty" endocarditis is often applied to this form (*endocarditis verrucosa*) (Fig. 175). Distinct and considerable swelling of the endocardium follows, and the orifices may be partly blocked, and the valves rendered, to some extent, incompetent. Fragments of sufficient size to cause embolism may be detached from the thrombi, while pressure of the blood—*e.g.*, on the aortic valves during diastole—may produce a local bulging (*aneurysm of valve*), or even a rent in that part of the valve where the necrosis of the endocardium

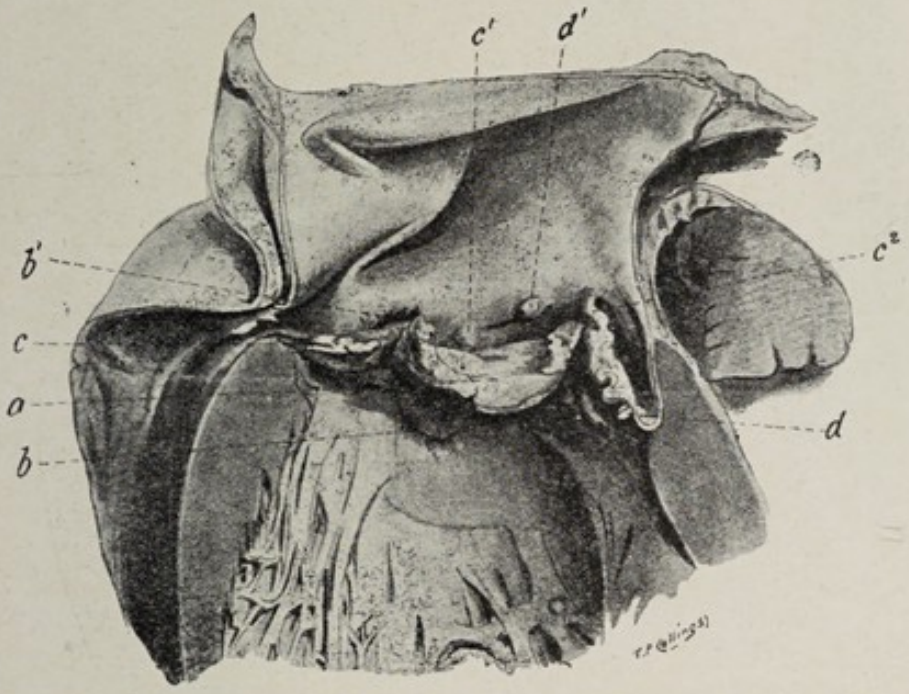


FIG. 179.—ULCERATIVE ENDOCARDITIS. (REDUCED ONE-THIRD.)

a, adherent fibrinous masses concealing the attachments of the valves (*c*, c^1, c^2); *b*, *b'*, ulcers on endocardium and aorta; *d*, *d'*, inflammatory foci with adherent thrombi.

on the opposite side has seriously weakened its resisting power. In these cases the reparative process is delayed; but when it does occur, it is attended by much organisation and later on, in some cases, by calcification of the adherent thrombi and by the formation of much new cicatricial tissue in the valves and their attachments. In this way the extremest forms of distortion and rigidity, already alluded to, are produced. Sometimes there is but little evidence, either clinical or post mortem, of any preceding acute disease. The changes are limited to thickening and rigidity of the orifices and their valves (Fig. 180). It is possible that prolonged mechanical strain without any acute endocarditis may give rise to these changes, especially as œdema of the chordæ tendineæ has been observed, experimentally, to follow strain, and as the condition is often

associated with chronic endarteritis, a disease also largely attributable to the same cause.

(3) When the disease is due to an invasion by virulent bacteria, and especially when it affects a valve already injured by a previous attack, the wall of the heart becomes the seat of ulcers and miliary abscesses, and the *ulcerative, malignant,* or *infective* type of the disease occurs (Fig. 179). The lesions in these cases are often not confined to the valves, but readily spread to all parts which come into contact with them. Rupture of an aortic valve and aneurysm of the heart, though never common accidents, occur

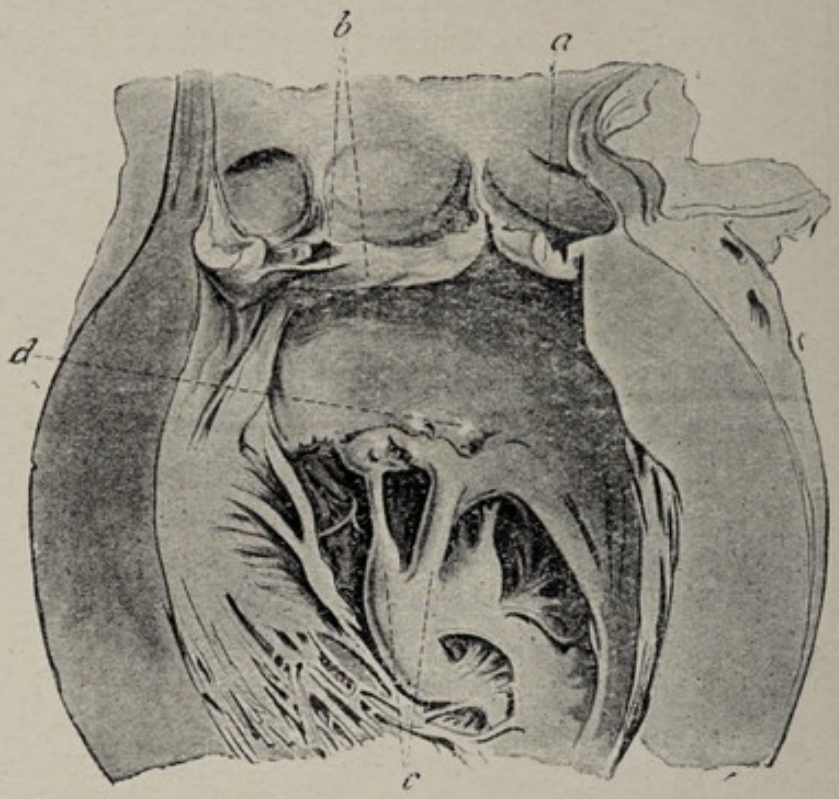


FIG. 180.—OLD ENDOCARDITIS, TWENTY YEARS AFTER ACUTE ATTACK. (REDUCED ONE-THIRD.)

Aortic valves generally thickened (*a*), adherent (*b*), and somewhat rigid. Mitral valves thickened, adherent, and calcified; *c*, chordæ tendineæ thickened and shortened; *d*, calcified masses projecting through to the ventricular side of the valve. Orifice behind valve is reduced to a rigid button-hole slit.

more often in this than in other forms. Owing to diffusion of the infective agents by the blood-stream septic infarcts and miliary abscesses may occur in distant parts, and the condition is accompanied by high fever and often by a series of shivering fits (*rigors*).

Myocarditis.

Myocarditis, or inflammation of the heart-muscle itself, may be either acute or chronic, and the acute type may be suppurative or non-suppurative.

Acute Suppurative Myocarditis may occur as part of a general pyæmic infection, in which case the cardiac muscle will be found to

be studded with minute abscesses, or it may arise from direct extension from a suppurative pericarditis, in which case the acute inflammatory changes will be more generalised and most marked in the neighbourhood of the inflamed pericardium. In either case the areas of acute inflammation are marked by dilatation of blood-vessels, infiltration with polymorphonuclear leucocytes, degeneration and eventual necrosis of the muscle fibres, and all the changes which characterise acute suppurative inflammation wherever it occurs.

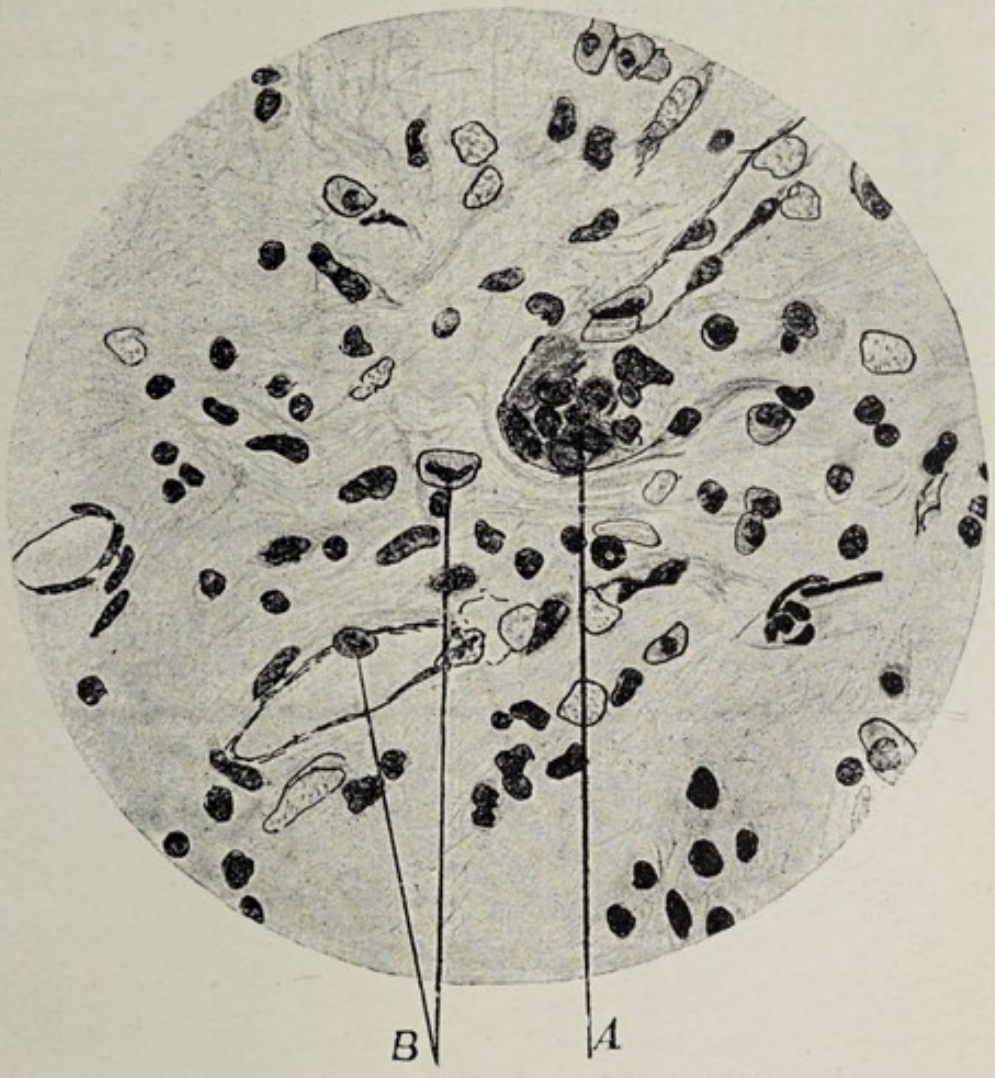


FIG. 181.*—SECTION OF A SUBMILIARY NODULE.
A, giant cell; *B*, mononuclear cells.

Acute Simple Myocarditis is a condition which is frequently associated with endocarditis and pericarditis. Like the former, it may occur in connection with many of the acute fevers, but here, also, it is in cases of acute rheumatism that the condition is most often met with. The changes present consist mainly in a slight degree of dilatation of the vessels, the presence of scattered areas of infiltration with small mononuclear cells, plasma cells, and occasional spindle cells, and a varying degree of degeneration of the muscle

* Fig. 181 is reproduced with permission of the authors from Poynton and Paine's "Researches on Rheumatism." (Churchill.)

fibres. In some cases a few large, multinucleated giant cells are found in such an area of cell-infiltration, which usually occurs in the immediate neighbourhood of a small arteriole (Fig. 181). Such a collection of cells has been called a *submiliary nodule*, and is believed by many authorities to be distinctive of acute rheumatic infection.

Chronic (Fibroid) Myocarditis.—In this condition there is a progressive increase in the connective tissue of the muscular wall. Eventually, this leads to a marked fibrosis, the muscle fibres being largely replaced by fibrous tissue (Fig. 182). The remaining

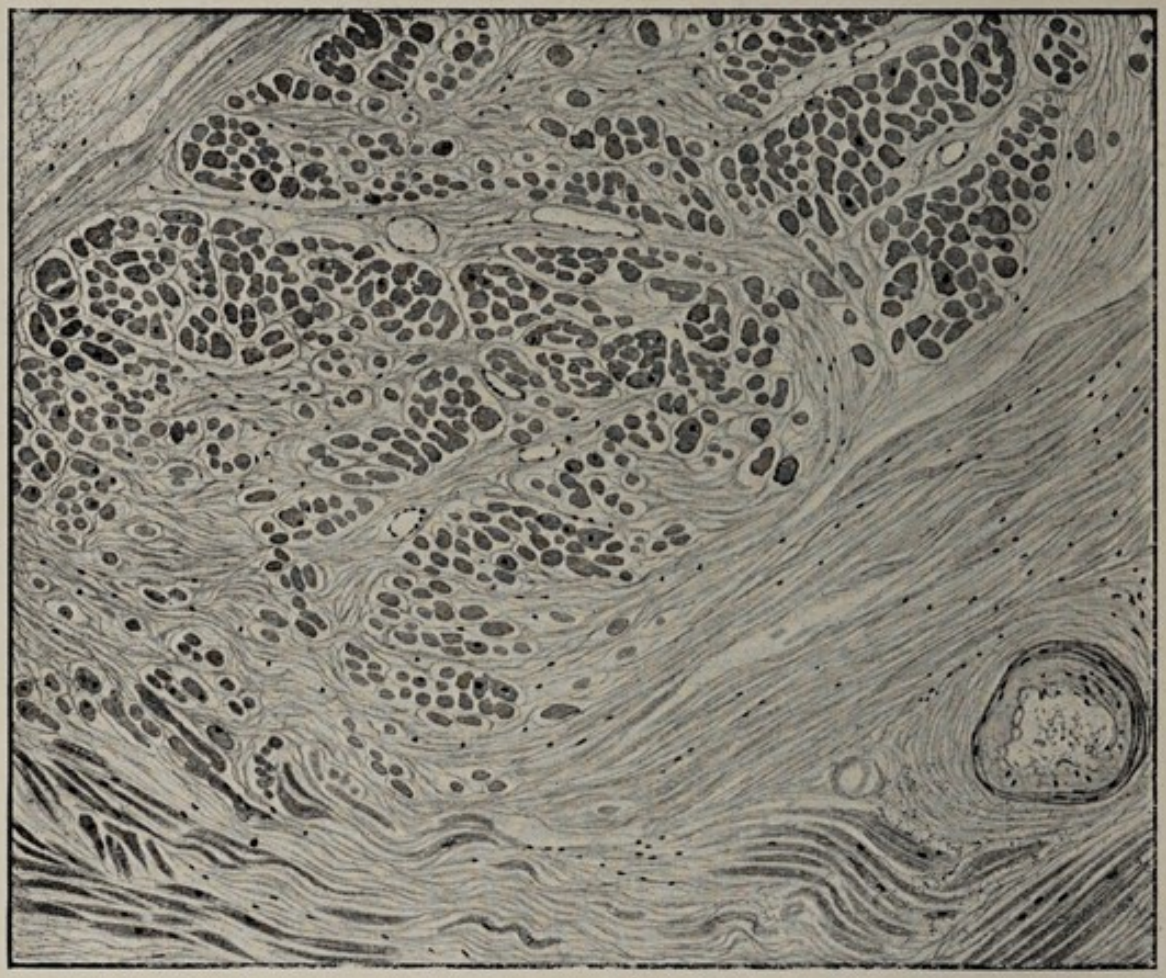


FIG. 182.—FIBROID MYOCARDITIS. (× 79).

muscle fibres usually show a varying degree of degeneration. Together with the fibrosis, there is, in most cases, a more or less marked infiltration of the tissues affected with mononuclear leucocytes. In many cases, this condition is associated with definite gummata of the heart-wall. Endarteritis of the branches of the coronary artery is commonly present, and there is little doubt that a very large proportion of such cases are syphilitic in origin. In other instances definite fibrosis of the myocardium may be found in patients who have succumbed to cardiac failure following a simple endocarditis or myocarditis. In many of such cases it seems probable that the increase in fibrous tissue is secondary to the degeneration of the muscle fibres.

Myomalacia Cordis.

Myomalacia cordis is the term applied by Ziegler to the occurrence of necrosed areas in the myocardium as a result of the local deprivation of arterial blood. Usually this is due to thrombosis in some branch, large or small, of an atheromatous or otherwise

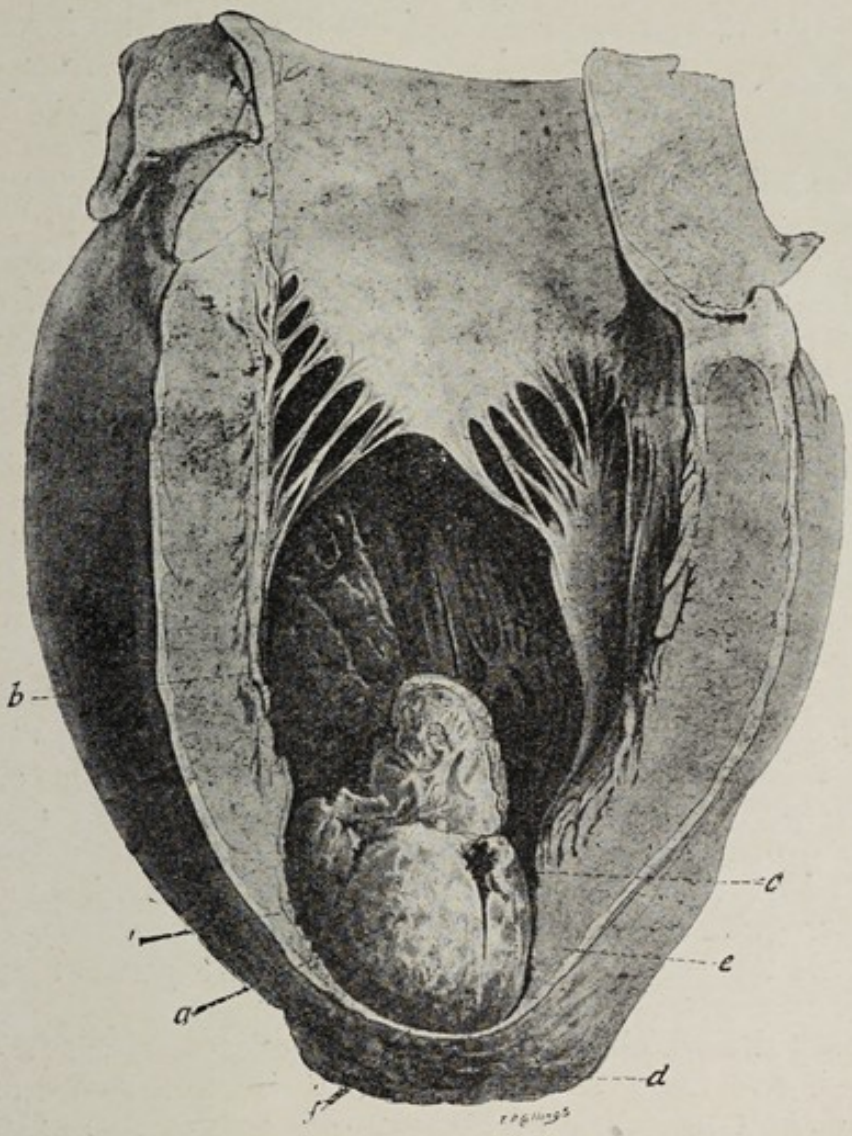


FIG. 183.—ANEURYSM OF THE HEART, WITH THROMBOSIS IN THE CAVITY OF THE LEFT VENTRICLE, AND COMMENCING PERICARDITIS, FROM A CASE OF MYOMALACIA CORDIS. (REDUCED ONE-THIRD.) (C. C. H. MUSEUM.)

a, laminated thrombus with softened centre occupying the aneurysmal pouch in the ventricular walls; *b*, extension of laminated thrombus adherent to the septum in the direction of the aorta; *c*, incision to show nature of thrombus; *d*, fibrinous exudation on inflamed pericardium; *e*, *e'*, wall of aneurysm formed by myocardium; *f*, wall of aneurysm formed by pericardium.

diseased coronary artery. Occasionally it may be due to embolism. The left ventricle is more commonly affected than the right, and the apex more often than any other part. If the necrosed areas be large or numerous, and extend to the endocardium, aneurysm of the heart and thrombosis in the cavity of the left ventricle (apex) may follow (Fig. 183).

Effects of Cardiac Disease.—The effect of almost every lesion of the heart, whether of the myocardium or of the valves, is to diminish the driving-power of the organ, and thus to impair the circulation of the blood. The general result is to render the patient short of breath on exertion, owing to lack of reserve power. If the valves be diseased, compensation may at first be effected by hypertrophy and increased work of the heart; and no further symptoms may be apparent. If compensation fail, either owing to myocardial disease, or to some obstruction to the flow of blood, or to increased exertion, disorder of the circulation ensues. If the *mitral valve* be affected, the blood tends to collect in the pulmonary veins; the pressure in the bloodvessels within the lungs is raised; and more work is thrown upon the right ventricle, which has to contract more vigorously to overcome the pressure in front of it. If it in turn fail, engorgement of the systemic veins ensues, with resulting cyanosis and œdema. The results of venous engorgement upon the various organs of the body are described elsewhere (pp. 345), and the causation of cardiac dropsy is also considered in Chapter XXI. If the *aortic valves* be the seat of disease, and failure of compensation occur, the arteries are insufficiently filled with blood and the nutrition of the body suffers. Cerebral anæmia may result in attacks of syncope. The dilatation of the left ventricle which occurs in aortic disease may finally be so great as to cause relative incompetence of the mitral valves through stretching of this orifice, and symptoms of mitral failure will be superadded to the aortic. Severe cardiac pain (*angina pectoris*) often accompanies aortic disease, and is called out by any sudden rise of blood-pressure in the arterial system.

Failure of the heart is generally accompanied by frequency, and often by irregularity, of its action; but in some cases, especially in myocardial disease, an unduly infrequent pulse may be encountered.

As the impulse which starts the cardiac systole arises in the great veins, passing to the auricles and then to the ventricles, any interruption in the continuity of the muscular tract forming its path will result in disturbance of the cardiac rhythm. Such interruption is liable to take place in the small tract of fibres (bundle of His) connecting the auricles with the ventricles, these fibres being at times destroyed or injured by vascular defects. In such instances the beat of the ventricles may be rendered infrequent (20 to 40 per minute), while that of the auricles may be less affected, so-called extra-systoles of the latter being then recognisable. This condition is often accompanied by attacks of syncope (*Stokes-Adams disease*).

A peculiar condition (fibrillation) in which the muscular elements of the auricles contract irregularly is sometimes observed.

Disturbance of the heart's action may occur without actual disease of the organ itself. Such affections are often spoken of as "functional." Instances are seen in the increased frequency

of action (tachycardia) encountered in Graves' disease and in neurasthenic conditions, and in the irregularity met with as a result of flatulent distension of the stomach or intestines. In all anæmic conditions the action of the heart tends to be frequent and feeble. The rate of its beat is also affected by many poisons, being increased, for example, by alcohol and belladonna, diminished by digitalis, rendered irregular by tobacco.

CHAPTER XXIX

AFFECTIONS OF BLOODVESSELS

It was formerly held that the middle and inner coats of arteries are non-vascular, the *vasa vasorum* not penetrating beyond the external coat; and that the intima is nourished by the blood in the lumen of the vessel. But Mott has shown that the vasa vasorum enter the media, even in normal arteries, and has suggested that the apertures in the membrana fenestrata may allow fluids to pass from the vasa vasorum into the intima. In support of the view that the intima is not nourished solely by the blood within the lumen of the vessel, Mott has shown that it may persist round thrombi, which must have cut off that source of supply. Moreover, the proliferative arteritis, which occurs in the organisation of thrombi, affords additional support to this conclusion. It is quite certain that, in chronic inflammation of the arteries, vasa vasorum frequently penetrate into the middle, and even the inner, coat (Fig. 184).

Degenerative Changes in Arteries.

The walls of arteries are liable to various forms of degeneration. *Fatty degeneration* may affect the intima or the media; *hyaline degeneration* is generally limited to the intima; while *amyloid disease*, though commencing in the intima, frequently involves all three coats. *Calcification* is generally secondary to sclerotic changes.

Inflammation of Arteries.

(1) *Infective Arteritis.*—In this disease, pyogenic cocci are conveyed to the wall of an artery, either by its vasa vasorum or by the blood within its lumen, and there give rise to an *abscess*. In most cases this is found in the media, or between the media and the adventitia. The wall is softened and infiltrated with leucocytes, and, in places, all trace of its original structure may be lost. Thrombosis, dilatation of the lumen (*aneurysm*), and rupture of the vessel are common results of this condition.

An acute form of arteritis, known as *periarteritis nodosa*, is described. It may affect all arteries except the pulmonary, and

is characterised by the presence of nodules on the outside of the vessels, representing inflammatory foci and involving the adventitia and media. Such cases are probably of infective origin; many are attributable to syphilis, a similar condition being found in gummata.

(2) *Proliferative Arteritis.*—Thickening of the intima and media, by proliferation of their component cells, is sometimes met with. It is accompanied by diminution of the lumen of the vessel, and occasionally by complete obliteration. This condition frequently follows torsion, ligature and other injuries, embolism, and throm-

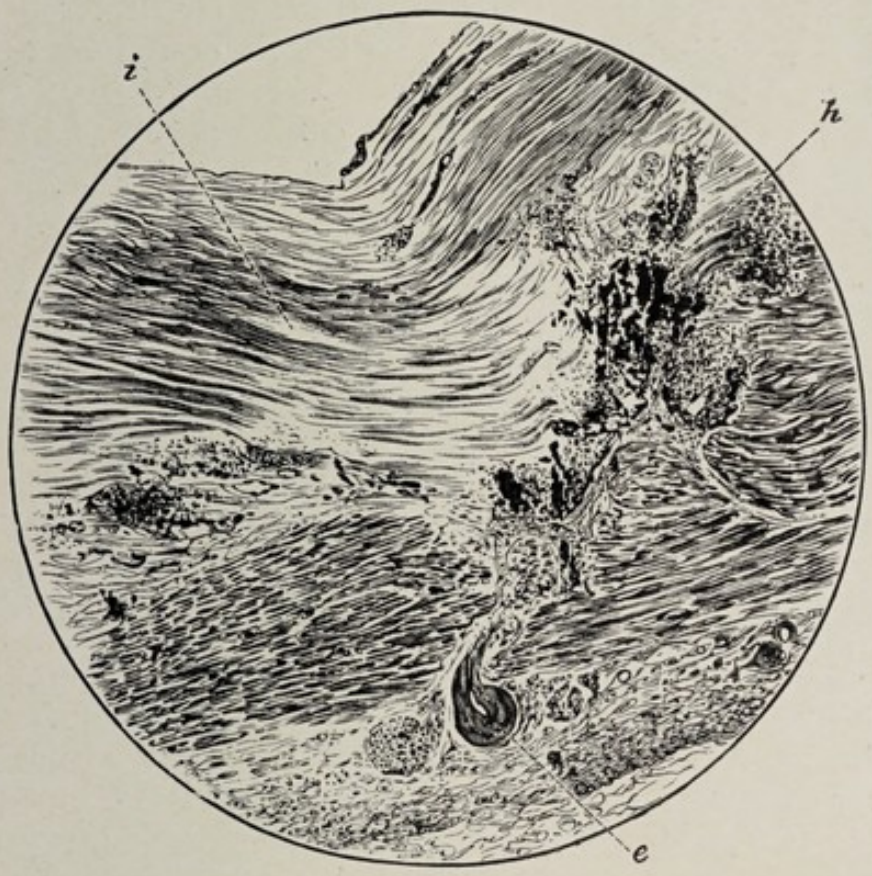


FIG. 184.—SECTION OF AN ATHEROMATOUS AORTA. (MOTT.)

The intima is much thickened (*i*); passing in from the externa through the media are vessels, about which hæmorrhage (*h*) has occurred; the lumina of the main trunks of these (*e*) in the external are almost obliterated by endarteritis.

bosis. The cause, whether it be some irritant conveyed by the vasa vasorum, or some kind of mechanical damage, is, in most cases, non-infective, but micro-organisms are occasionally met with, presumably of a low degree of virulence.

(3) *Aortitis.*—A special form of arteritis is described in connection with the aorta. It leads to the formation of small, pearly, pinkish patches slightly raised above the surface of the intima. These are mainly due to a proliferation of the cells of the part: parietal thrombi may be deposited on their surface. In many cases the condition appears to be due to syphilis.

Arterio-Sclerosis.

This term includes all chronic degenerative changes peculiar to arteries, other than those immediately due to syphilis.

Two forms are generally described, the *nodular* and the *diffuse*.

(1) The **nodular** form, often known as *atheroma*, affects chiefly the larger vessels and those at the base of the brain. In its early stages it takes the form of gelatinous, slightly raised, yellowish patches, covered by endothelium. In cases of long standing, firm, fibrous, or calcified plates, covered with endothelium or exposed to the blood-stream, may be present. The circumference of the lumen is not uniformly affected, although complete rings may be found round the mouths of branches where they leave the main trunk. The arch of the aorta, a common seat of the change, is often so studded with small, thickly set, raised plaques, that it resembles crocodile-skin. Sometimes the patches of new tissue may undergo fatty degeneration, and subsequently softening. In the latter case, soft, yellowish, pultaceous material, consisting of fatty débris and cholesterin-crystals, is found in the deeper layers of the intima. This has been termed an *atheromatous abscess*. If the superficial layers of the intima degenerate or are torn, the degenerated products may be discharged into the blood-stream and an *atheromatous ulcer* be left.

The orifices and branches of the coronary arteries are particularly liable to atheromatous changes, and are often much narrowed. The blood-supply of the heart is, in these cases, proportionately lessened, and the tendency to fatty degeneration of its muscular walls increased. It is by no means certain that the patches which project into the lumen after death (Fig. 185) do so during life; for Thoma found that if atheromatous arteries were injected with melted paraffin, at a pressure equal to that of the blood-stream, the solid casts obtained were cylindrical and showed no corresponding depressions.

Under the microscope, in the earliest stages of the process, the deeper layers of the intima are found to be much thickened. The thickening is due to a proliferation of the component cells, together with a varying, though usually slight, degree of infiltration with mononuclear cells. Many of the new cells may develop into fibrous tissue, resulting in a dense fibroid plaque or in a more diffuse thickening. Areas of fatty degeneration are generally found in the central and deepest parts of these patches of fibrous tissue. The muscle-fibres of the middle coat become swollen and undergo hyaline degeneration, while the elastic tissue atrophies, its fibres being sometimes ruptured.

(2) The **diffuse** form affects smaller arteries and causes great thickening of their walls, with a marked, if not proportionate, diminution of their lumina. The changes are more uniformly distributed than in the nodular form of the disease. Both the intima and media undergo hyaline degeneration, and the internal

elastic lamina in many places disappears. This condition corresponds with the *arterio-capillary fibrosis* of Gull and Sutton, and is found associated with hypertrophy and fibrosis of the heart and atrophy of the kidneys (*granular contracted kidney*)—the commonest form of chronic Bright's disease.

RESULTS. — It is obvious that the changes which have been described will gradually impair the strength and elasticity of the vessel-walls, and thus affect the circulation in the parts beyond. Moreover, the diminution of the lumen, and the change in the lining membrane of the vessel, will predispose to thrombosis and occa-

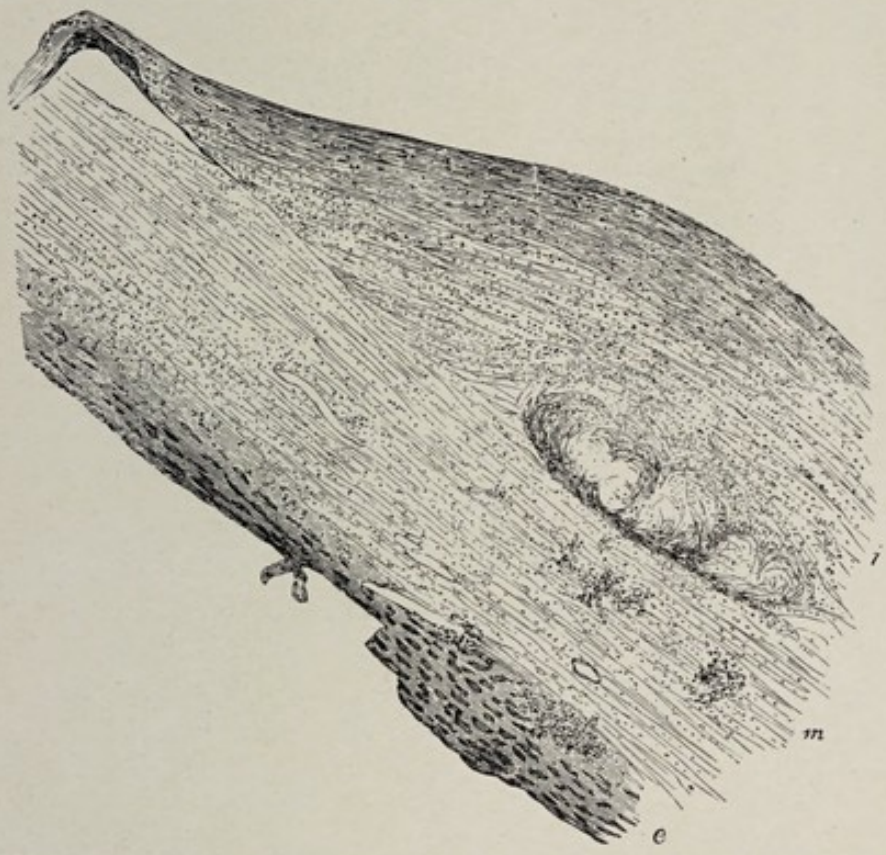


FIG. 185.—ARTERIO-SCLEROSIS (ATHEROMA) OF THE AORTA. (× 25.)
Showing the localised thickening of the inner coat, and the apparent bulging inwards of the vessel. Some of the new tissue has undergone fatty degeneration. There is also some thickening of the middle coat. *i*, internal; *m*, middle; *e*, external coat of vessel.

sionally give rise to embolism. On rare occasions the narrowing of the vessel may be so great as practically to obliterate the lumen and to produce gangrene of the parts supplied. This condition is often spoken of as *obliterative arteritis*, and is by some regarded as a distinct disease. The loss of strength in the vessel-wall will cause it to give way under the constant pressure—**aneurysm.** General dilatation of the vessel may result: when this is extreme, it is known as a *fusiform* aneurysm. When the vessel is especially weakened at one spot—for instance, by the formation of an atheromatous ulcer, or by the rupture of its middle coat—a local dilatation or *sacculated* aneurysm may occur. When this has reached

a certain size, its walls may rupture, and fatal hæmorrhage result. If the external coats have been uniformly strengthened by the formation of chronic inflammatory tissue in them, this result will be proportionately delayed. If an atheromatous abscess bursts before the tissues round its margin have been matted together by fibroid growth, the blood may find its way into the substance of the *media*, and, making for itself a cavity between the coats of the vessel, form a *dissecting* aneurysm. This occurs only in the aorta and its largest branches. Ultimately the blood may burst either through the *externa* into the surrounding tissues, or through the *intima* into the lumen of the vessel.

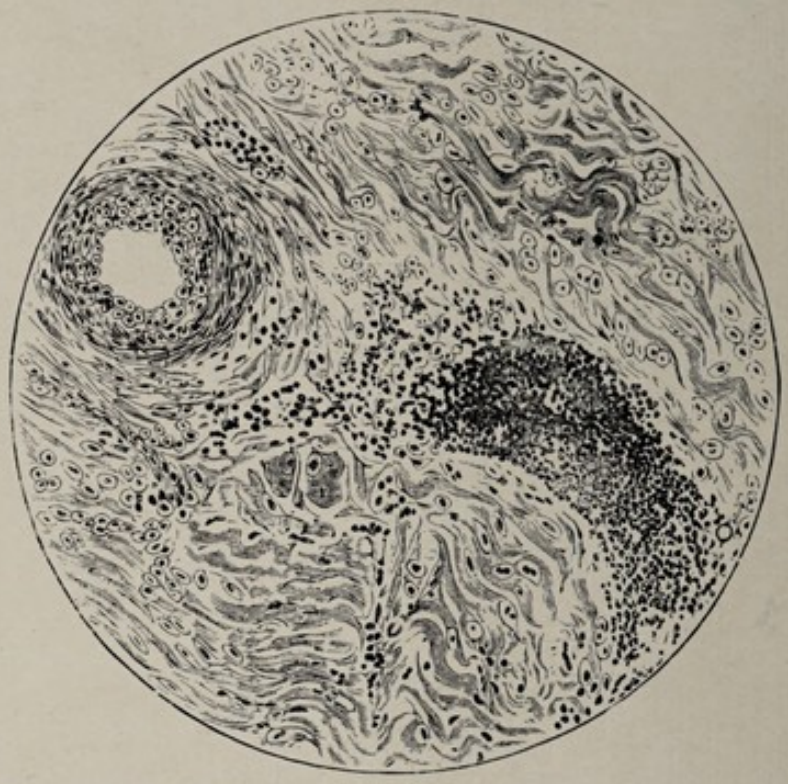


FIG. 186.—EXTERNAL COAT OF AORTA AFFECTED WITH SYPHILITIC PERI-ARTERITIS, SHOWING CELL-INFILTRATION FROM THE VASA VASORUM. (× 110.) (MOTT.)

The walls of the latter seen in section are much thickened.

ÆTIOLOGY.—Arterio-sclerosis must unquestionably be classed amongst *senile* changes. Like other senile manifestations, it occurs much earlier in some persons than in others. It is highly probable that it is also *hereditary*, a belief mainly based upon the early occurrence of arterial degeneration in those whose ancestors have succumbed to apoplexy. Its advent is also accelerated by the presence of gout, alcoholism, plumbism, syphilis, mechanical strain, and any cause which increases the blood-pressure. *Gout* is associated with the presence of toxic bodies, while alcohol and lead probably exert a direct poisonous action upon the vessels. *Syphilis* not only causes similar injury to the vessel-wall, but leads to endarteritis of the vasa vasorum (Fig. 186). There is little doubt that this

infection plays a far greater part than has been realised in the past in the causation of many forms of arterial disease. The results obtained by the Wassermann reaction in very large numbers of cases have demonstrated that syphilitic infection is present in a high proportion of patients who are found to be suffering from arterial disease in early adult life, and in practically every case of aneurysm. The proofs that *mechanical strain* has a special influence in the production of arterio-sclerosis are: (1) the much greater frequency of the affection in the aortic than in the pulmonary system; (2) its occurrence in the latter when its blood-pressure is raised, as in mitral obstruction; (3) its relative frequency in those systemic arteries which are most exposed to strain, especially the arch of the aorta; and (4) its presence in conditions accompanied by rise of blood-pressure. Athletes, and those engaged in laborious occupations, are specially liable to the disease.

PATHOLOGY.—There is no generally accepted explanation of the processes which culminate in advanced arterio-sclerosis. Thoma, whose work on this subject is very exhaustive, believes that loss of elasticity in the arterial walls is the primary change. This is followed by distension of the affected vessel and slowing of the blood-stream. Compensatory thickening of the intima follows, tending to reduce the calibre of the dilated vessels to its original size, and so to maintain the normal rate of blood-stream. Unfortunately the nutrition of the new tissue cannot, in most cases, be maintained—hence degeneration of the thickened intima follows. Thoma found that the local patches of thickened intima exactly corresponded with the places where the media was giving way, and obtained additional evidence in favour of his view by the injection of the bloodvessels already referred to. In Thoma's opinion, the thickening of the intima is a conservative process. By these changes the vessel is converted into a more or less rigid tube, and the circulation is proportionately impaired. This difficulty is overcome by the increased action and hypertrophy of the left ventricle of the heart. But this hypothesis does not explain why primary weakening occurs. Mott's view, that this is due to an endarteritis of the vasa vasorum, which is frequently present, is in many cases highly probable (Fig. 184), especially in the localised nodular form of the affection (atheroma).

A condition closely resembling atheroma may be induced in the bloodvessels of animals by injections of suprarenal extract, which causes a great rise of blood-pressure.

Inflammation of Veins.

Inflammation of veins (*phlebitis*) is very analogous to inflammation of arteries. *Acute infective phlebitis* is decidedly more frequent than acute infective arteritis. In most cases it is due to the presence and growth of organisms (*acute suppurative phlebitis*). The wall of the vein becomes swollen and densely infiltrated with multi-

nucleated leucocytes. All appearance of normal structure is lost; the cells nearest the lumen die and are cast off, as in the wall of an abscess, into which the wall of the vein has been practically converted. Septic thrombosis follows and, in many cases, pyæmia.

Non-infective and *proliferative phlebitis* are due to the same causes, and present the same appearances, as the similar affections of arteries. A recurrent phlebitis, especially common in the internal saphenous vein, is frequently met with in gout, and a condition of endophlebitis is found in syphilitic gummata, and closely resembles the corresponding arterial disease.

A *phlebo-sclerosis*, somewhat similar to arterio-sclerosis, may be found in the pulmonary veins in cases of mitral stenosis, and in the portal veins in cirrhosis of the liver, as well as combined with arterio-sclerosis, and due to the same causes.

Varicose Veins.

In some persons especially predisposed, constant but comparatively slight increase of the pressure in the veins of the legs, spermatic cord, or rectum will produce an irregular but very marked dilatation, lengthening, and tortuosity of the vessels in question. Portal obstruction will produce the same results in the veins of the hæmorrhoidal plexus apparently *without* any predisposition. Other veins are similarly, but less frequently, affected. The dilatation and other changes are accompanied by thickening of the walls, due to the formation of fibrous tissue.

When the dilatation is mainly saccular in form, the walls may be exceedingly thin and easily rupture; this is frequently the case when the rectal veins are involved (*hæmorrhoids*). The skin over and in the neighbourhood of varicose veins is ill-nourished owing to stagnation of blood, and is often the seat of dermatitis, which may be followed by ulceration (*varicose ulcer* of the leg); this only heals when the increased venous pressure is removed. Thrombi and phleboliths may be found within the dilated veins.

In some instances varicose veins may perhaps be angiomatous in nature.

CHAPTER XXX

AFFECTIONS OF THE RESPIRATORY ORGANS

In the lungs, inflammatory processes may, for convenience of description, be divided into three varieties: (1) *Croupous*, lobar, or acute pneumonia; (2) *catarrhal*, lobular, or broncho-pneumonia; and (3) *interstitial*, or chronic pneumonia.

1. Acute, Croupous, or Lobar Pneumonia.

Acute pneumonia is an infective disease characterised by inflammation of the lung, leading to the solidification of a considerable area of the organ. It is usually limited to one lung, and the right is more frequently affected. The inflammation starts in the substance of the lung, from a focus which, in the majority of cases, is in the lower part of the lower lobe. The disease extends by continuity of tissue from this primary focus. The consolidated portion may exactly correspond with a single lobe, though quite as often it is less or more than this. In some cases, however, the disease may affect scattered areas in both lungs, being "lobular" instead of "lobar" in distribution. This form is frequently seen in children, and has been confused with catarrhal pneumonia (broncho-pneumonia): hence it has been asserted incorrectly that acute pneumonia is uncommon in children.

The inflammation of the lung is always accompanied by inflammation of the pleura over the inflamed area, and sometimes, owing to the spread of the infection, by suppurative pericarditis. The bronchial glands are inflamed and swollen, and the mediastinal connective tissue is frequently œdematous. A more or less intense bacteriæmia always occurs, and secondary infection of the peritoneum, meninges, or other serous membranes may occur. The disease is accompanied by a high temperature, beginning with a sudden rise and ending by crisis: cloudy swelling of organs results. Death, when it occurs, seems to be due to cardiac failure, induced by general toxæmia.

Acute pneumonia is a general infective disease in which the inflammation of the lung is the characteristic local lesion. This is shown by the typical course of the fever, ending usually in a crisis between the fifth and eighth days, and by the absence of any constant relationship between the extent of the local inflammation and the

intensity of the fever. The gravity of the disease is proportional to the intensity of the toxines at work, the actual interference with the respiratory function being only of secondary importance. Death occurs by cardiac failure resulting from the toxæmia, not by deficient aeration of the blood.

PATHOLOGY.—This disease was formerly attributed to a chill; and, in certain cases, its connection with exposure to cold and damp is very striking. Exposure is, however, only a *predisposing cause*, for it occurs in but a small minority of the cases. Moreover, although the disease is most prevalent in the early spring, it does not especially affect those who are most exposed to the vicissitudes of the weather, nor does its prevalence rise and fall with that of bronchitis.

Any condition of depressed health may act as a predisposing cause. Typically healthy people are indeed not infrequently affected, but the disease is especially liable to occur as a complication in cases of chronic alcoholism, erysipelas, typhoid fever, influenza, and certain other conditions. Pneumonia is prone to recur in a person who has once suffered from it.

The disease is occasionally so prevalent as to be practically epidemic. Small outbreaks occasionally occur in wards, prisons, and similar places; and the disease is sometimes endemic in a house, from time to time attacking different people in it; but there is in most cases no evidence of contagion.

In the large majority of cases the infective agent at work is the *Diplococcus pneumoniæ* (p. 116). Less commonly Friedländer's bacillus, streptococci, or the bacilli of tuberculosis, typhoid fever, or diphtheria, have been found, especially in pneumonia occurring in the course of other diseases. But even in these secondary pneumonias the *Diplococcus pneumoniæ* (pneumococcus) is the organism most frequently met with.

The precise method of infection is unknown. The pneumococcus exists normally in the mouth, and can generally be found on the surface of the tonsils. Indeed, all the organisms just mentioned may be met with in the air-passages of persons free from pneumonia. Experimentally, any of these organisms may be blown into the trachea of animals without causing this disease; but pneumonia follows (1) if dust be simultaneously injected; or (2) if the animals, after being kept warm, are suddenly immersed in a cold bath at the time of the injection.

MORBID ANATOMY.—The local process is characterised by intense inflammatory hyperæmia of the lung, and by the exudation of a large amount of coagulable material into the pulmonary tissue. It is termed "croupous" from the fibrinous * character of the exuda-

* The word "croup" originally denoted a disease of children characterised by a hoarse cry; it was therefore applied to diphtheria particularly. As diphtheria is distinguished by its dense fibrinous exudate (false membrane), the name "croupous" came to be applied to inflammations accompanied by formation of fibrin.

tion. The term "lobar" is applied to it because it usually affects a continuous portion of the lung. The process is commonly described as consisting of three stages—(1) that of *engorgement;* (2) that of *red hepatisation;* and (3) that of *grey hepatisation.*

In the *first* stage, that of **engorgement,** small patches of lung-tissue become intensely hyperæmic, and rapidly run together to form a large uniformly engorged dark-red area. The weight of this congested portion of the lung is increased, its elasticity is diminished, its substance is less crepitant and more friable than natural, and its surface pits upon pressure. On section, it yields a reddish, frothy, tenacious liquid.

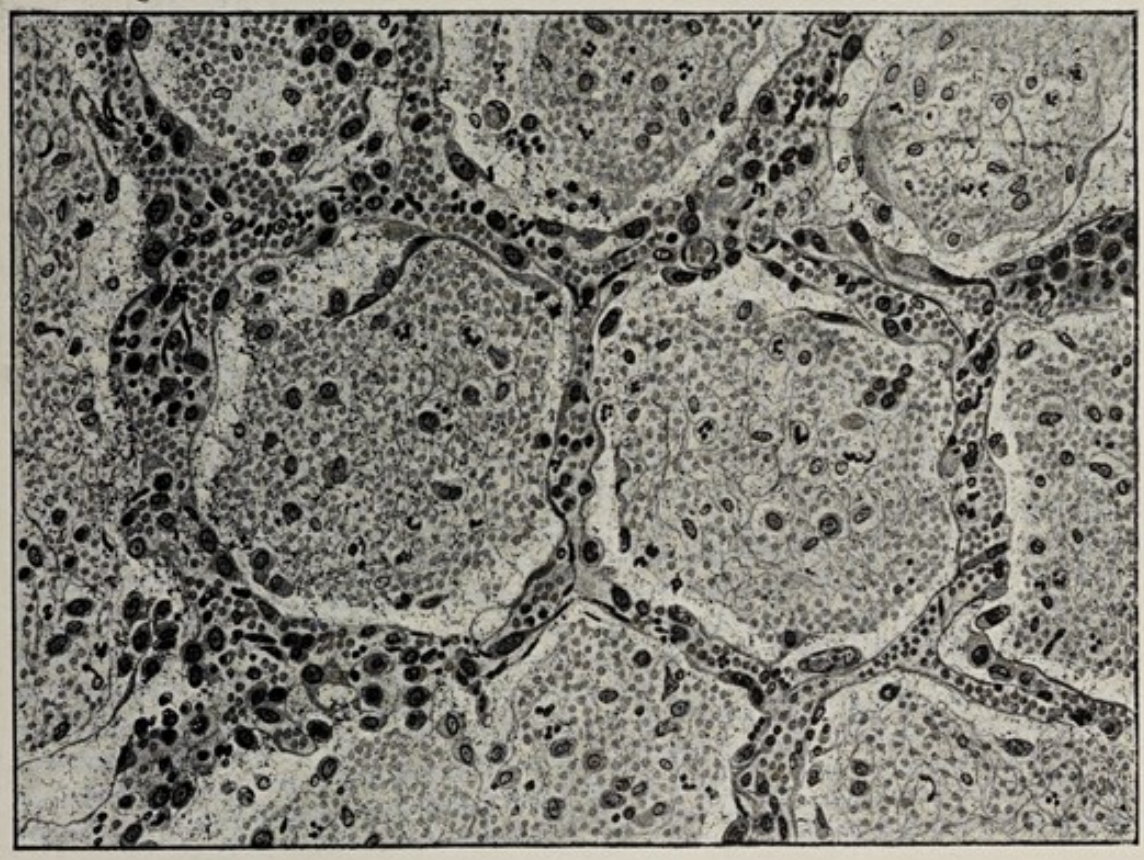


FIG. 187.—ACUTE LOBAR PNEUMONIA, STAGE OF RED HEPATISATION. (× 325.)

In the *second* stage, that of **red hepatisation,** there is an exudation of fluid and blood-corpuscles into the pulmonary tissue. Some of the vessels may also rupture and small extravasations occur. The exuded liquids coagulate within the air-vesicles and terminal bronchioles, and form a semi-transparent coagulum enclosing red corpuscles and leucocytes in its meshes (Fig. 187). The lung is now much heavier than in the preceding stage, and is increased in size, so as to be often marked by the ribs. The affected portion can be recognised before a section is made, for the pleura over it is hyperæmic, opaque, and covered with fibrinous exudation, while the distension, firmness, and dark-purple colour of the lung beneath cannot escape notice. It is quite solid, sinks in water, and cannot be artificially

inflated. It does not crepitate under the fingers, and is remarkably friable, breaking down readily under pressure. The cut surface has a granular appearance, which is seen still better when the tissue is torn. This is owing to the small masses of coagulated exudation, which project from the alveoli they fill. There is no lobulation of the margin of the inflamed area, and no outlying racemose nodules or other indication of infection spreading by the bronchi. The colour is of a dark reddish-brown, here and there passing into grey. This admixture with grey sometimes gives a marbled appearance. The red colour is due chiefly to vascular engorgement, but partly to extravasated red corpuscles. Throughout this stage the vessels in

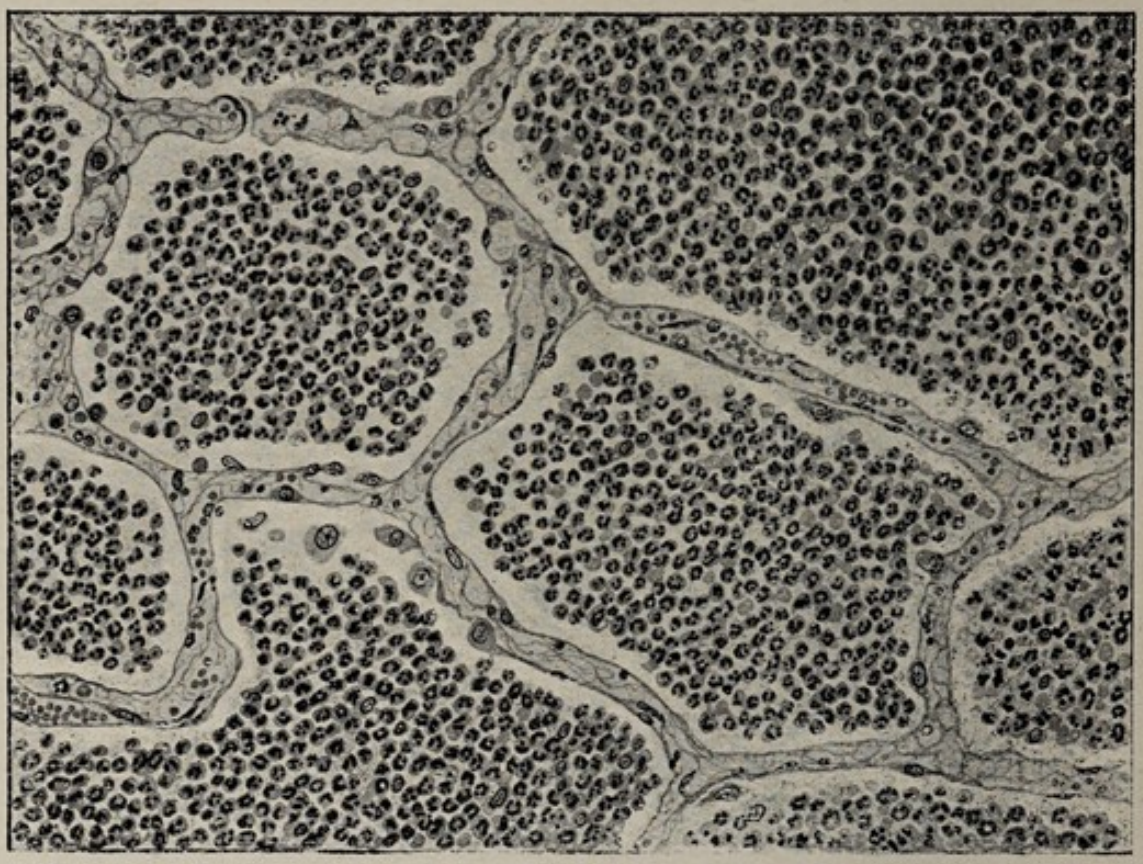


FIG. 188.—ACUTE LOBAR PNEUMONIA, STAGE OF GREY HEPATISATION. (× 325.)

the alveolar walls are engorged, while the alveolar epithelium is usually swollen and granular. If a section of the spreading edge be examined at this stage, it will be found intensely hyperæmic. The hyperæmia extends irregularly into the adjacent tissue.

The *third* stage, that of **grey hepatisation,** is characterised by a marked emigration of leucocytes, and by more extensive degenerative changes in the alveolar epithelium. The walls of the alveoli are infiltrated and their cavities distended with the emigrated leucocytes. The walls and the contents of the alveoli now assume a uniform appearance, and the granular appearance of the red stage is lost (Fig. 188). The fibrinous material next disintegrates, and the leucocytes rapidly undergo fatty changes, whilst the red

cells are decolorised, so that the alveoli are seen to be full of granular elements, which in many parts have lost their distinctive outlines. Occasionally, when this stage is unusually advanced, the alveolar walls may be found, here and there, partially destroyed. The weight, density, and friability of the lung are now even greater than in the stage of red hepatisation. The tissue is soft and pulpy, and a puriform liquid exudes from its cut surface. The most prominent feature, however, is the difference in the colour of the organ. Instead of a dark reddish-brown colour, the section now appears a grey or yellowish-white, marbled by the tracts of pigment-bearing connective tissue. The pallor is owing partly to the fatty degeneration which the cells have undergone, and partly to the pressure exercised upon the bloodvessels by the exuded substances and newly formed cells; but since Rindfleisch has shown that it is always easy to inject the vessels, it would seem likely that a good deal of the pallor is due to the fall in blood-pressure after death. The stage of grey hepatisation, when far advanced, has been termed "suppuration, or purulent infiltration, of the lung." Some authorities believe that this only occurs in fatal cases.

Although these three stages of the pneumonic process have been described as succeeding one another in orderly succession, it must be remembered not only that each stage does not occur simultaneously throughout the whole of the affected area of the lung, but that in some cases it is more accurate to speak of only two stages—*engorgement* and *hepatisation*. Patches of grey hepatisation may be found in recently invaded parts of the lung, and patches of red hepatisation in those portions which were earliest affected. The exact characters of these changes not improbably depend on the presence of centres of infection, on the nature and virulence of the organisms present, and on the local conditions influencing their growth. According to this explanation, the exudation first filling the alveoli remains unaltered until degeneration and disintegration set in. The bronchi in the affected area are always inflamed, and usually contain a viscid, blood-stained, rust-coloured mucus, which forms the characteristic expectoration. Sometimes the sputum is dark and watery, like prune-juice. This is probably owing to the addition of serous exudation from neighbouring parts of the lung.

TERMINATIONS.—If the patient survive the stages of the disease already described, the pneumonic process will end in one of four ways.

1. **Resolution.**—The gradual return of the lung to its normal condition is the most frequent termination of croupous pneumonia. This is effected by the fatty degeneration and liquefaction of the inflammatory products which have accumulated within the alveoli. Thus altered, they are removed principally by absorption and, to a less extent, by expectoration. This process is assisted by the return of the bloodvessels to a normal condition and the re-establishment of the circulation.

2. **Gangrene.**—This result is rare, and is chiefly found in drunkards

and in persons of debilitated constitution. Two conditions appear to be principally concerned in bringing about this result: (1) interference with the supply of blood, caused by the formation of coagula in the pulmonary and bronchial vessels, together with considerable hæmorrhage into the pulmonary tissue; and (2) the local toxic influence of some special form of septic infection. The gangrene is usually limited to a small area of the pneumonic lung, and is either *diffuse* or *circumscribed*. In the former, the exudation and lung-tissue in the gangrenous area form an ill-defined, semi-diffluent dirty grey, fœtid substance; in the latter, an abscess-cavity containing a pulpy slough of similar colour and odour.

3. **Abscess.**—The formation of an abscess is also a rare result of pneumonia. It occurs under conditions similar to those which predispose to gangrene, which indeed it not infrequently follows. Abscess is commoner in the upper than in the lower lobes. It may follow circumscribed gangrene, or it may arise, as in other places, from the growth of pyogenic cocci without any necrosis visible to the naked eye. When gangrene precedes, the necrosed tissue may be expelled through the bronchi, and the resulting cavity heal by granulation and cicatrisation. Abscesses formed in these ways are usually single, and thus differ from those due to pyæmia. It is often difficult to distinguish clinically between an abscess which has formed in the substance of the lung and an empyema which has burrowed inwardly and excavated the pulmonary tissue. Interlobular empyemas are especially liable to simulate abscesses.

4. **Chronic Pneumonia.**—If the inflammatory process does not subside, and the exudation is not absorbed, the alveolar walls gradually become thickened by the growth of fibrous tissue. In rare cases the intra-alveolar exudation becomes organised. These changes lead to a general induration of the affected part of the lung. This termination of croupous pneumonia is comparatively rare.

2. Broncho-Pneumonia.

Broncho-pneumonia (*Lobular* or *Catarrhal Pneumonia*) is an inflammation of the lung, due to an irritant entering by the bronchi. This irritant gives rise to an inflammation of the smaller bronchi, spreading to the bronchioles and alveoli. As soon as the alveoli are involved, the term " broncho-pneumonia " is applicable.

Pathology.—Broncho-pneumonia is especially frequent in young children and in aged persons, and often, in such cases, ends fatally. This result is due to the interference with the entrance of air through the inflamed bronchioles, to the limitation of the oxygenating area, and, mainly, to the absorption of toxines.

There are many irritants which, gaining access to the air-passages, can excite inflammation of the bronchioles and subsequently of the alveoli. Among these may be mentioned (1) irritant gases; (2) dust of various kinds, such as particles of carbon (p. 491), steel, iron, or stone, which differ in their irritant qualities, and, therefore, in

the acuteness of the inflammation to which they give rise; and (3) micro-organisms, the pneumococcus and various types of streptococci being the organisms most commonly found in acute cases. It must also be remembered that broncho-pneumonia is the principal lesion in pulmonary tuberculosis (*phthisis*). Various pyogenic organisms, conveyed with portions of food or of saliva, may enter the air-passages, especially when the glottis is insensitive or paralysed. Blood and discharges may be sucked into the bronchi during operations on the mouth or nose, or when they occur in wounds or diseases of these parts. Among other organisms which may enter the lungs by aspiration are the actinomyces and the bacilli of diphtheria and of glanders. (4) Bronchitis, whether simple or occurring in specific diseases such as measles, whooping-cough, and variola, is a common antecedent of broncho-pneumonia.

All conditions depressing the general health and strength predispose to broncho-pneumonia. Collapse of scattered lobules often seems to precede the inflammation, and, by interfering with the circulation in the affected alveoli, may weaken the resistance of the tissues. But, whenever bronchitis has reached the smallest tubes, extension of the inflammation to the alveoli may occur without collapse.

Broncho-pneumonia has been produced *experimentally*. Thus animals have been made to inhale irritant gases or suspended particles of various kinds; or, by division of the vagus, saliva and food have been permitted to enter the air-passages. The resulting changes vary (1) with the *size* of the inhaled particles, and (2) with the *intensity of the irritation* which they are capable of exciting. Thus, very fine particles cause inflammation of widely separated lobules; larger ones block some of the smaller bronchi, and cause collapse and secondary inflammation of lobules—results which have led to the name of "lobular pneumonia." The aspiration of a quantity of septic discharge or other fluid into a bronchus may affect many lobules or even a whole lobe. According to the intensity of the inhaled irritant, the result may vary from slight inflammatory œdema in a collapsed patch, through all stages of inflammation up to gangrene.

Morbid Anatomy.—The *bronchi* and *bronchioles* are always more or less inflamed and contain thick muco-pus. The lung-tissue contains a varying number of solid patches, due either to (1) *collapse* or to (2) *inflammatory consolidation*. Emphysema, with more or less congestion and œdema, is commonly found in their neighbourhood (Fig. 189).

Collapsed patches are particularly common in the lower lobe, especially along its thin borders. Sometimes a large portion of a lobe is thus involved; at other times only a few small, isolated patches. The surface of the collapsed part is depressed below the general surface of the lung. It has a dark-bluish colour, and is easily inflated from the bronchi. On section, it is dark red, smooth, and shiny. It is tough and non-crepitant, and portions of it sink

in water. On closer inspection the patches are seen to be more or less conical, with their bases towards the surface of the lung and their apices towards the bronchi with which they are in connection. The pleura over a patch of collapsed lung is normal.

Pneumonic patches are of conical form, and are airless, like the collapsed parts; moreover, they are similarly distributed. But the base of a pneumonic patch is raised above, never depressed below, the surface, while the patch forms a less pliable and more nodular

FIG. 189.—EARLY BRONCHO-PNEUMONIA. (× 18.)

mass. Occasionally, when it is of considerable size, its pleural covering may be opaque with inflammatory exudation. On section, pneumonic patches may be clearly defined, but their outlines are generally less distinct than those of collapsed patches; they usually range in size from that of a pea to a hazel-nut. The surface of the section tends to rise slightly above the surrounding tissue: the substance is soft, friable, opaque-looking, smooth or faintly granular, at first dark red in colour, then passing through greyish-red to greyish-yellow—the lighter colour being central. A turbid red or

greyish juice can be pressed from it. Neighbouring lobular patches often blend; and as the diffuse consolidation thus formed becomes paler, firmer, and drier, it may occasionally resemble in appearance ordinary grey hepatisation. Sometimes the pneumonic process is found involving patches of collapsed lung: these consequently become swollen, opaque, and œdematous.

When broncho-pneumonia is so extensive that the consolidation is practically "lobar," it is difficult to distinguish it from acute

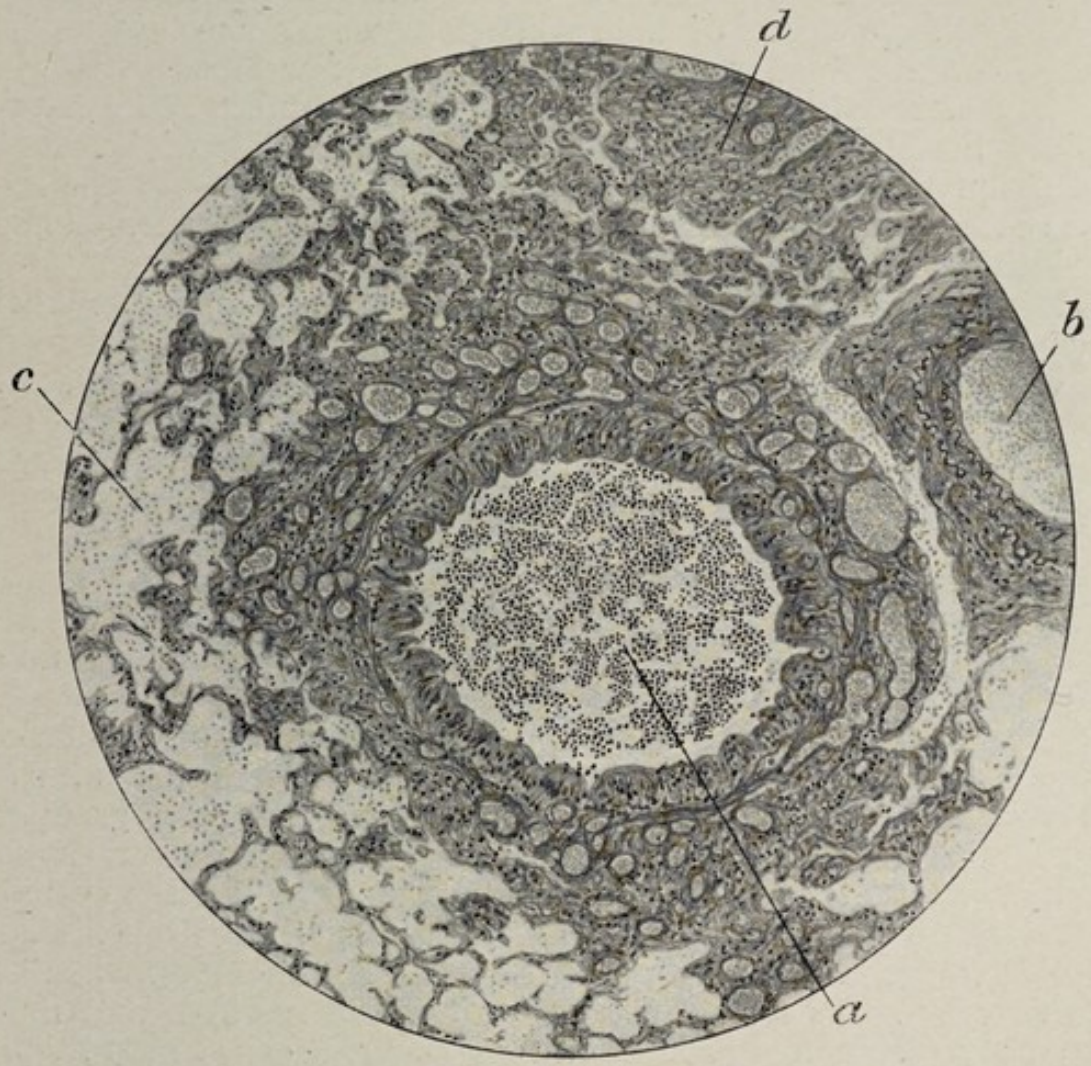


FIG. 190.—ACUTE BRONCHO-PNEUMONIA. (× 79.)
a, bronchiole; *b*, bloodvessel; *c*, commencing exudation into an alveolus; *d*, area of solidification.

pneumonia. Evidence of the blending of lobular masses, and especially the presence of outlying patches in the neighbourhood of the main mass, are the most important points to observe macroscopically. The microscope will reveal the changes typical of catarrhal inflammation. The *absence* of adherent inflammatory exudation from the pleural surface is evidence against acute pneumonia; but it must be remembered that, as such exudation may form over a broncho-pneumonic area, its *presence* is of little pathognomonic importance.

In *septic* broncho-pneumonia—the commonest cause of death after operations on the jaws, mouth, and pharynx—abscess-formation may occur. The *abscesses* thus formed are sometimes fœtid and contain sloughs of lung-tissue: such sloughs are surrounded by more or less extensive consolidation; and inflammatory hyperæmia and œdema of the lung are marked.

Microscopically (Fig. 190) the smaller bronchi and bronchioles show congestion, swelling, and ultimately desquamation of their lining membrane, and contain within them a purulent exudate showing the presence of numerous polynuclear leucocytes. The alveoli contain fluid, red corpuscles, and a few leucocytes, while the alveolar epithelium is swollen and granular. The alveoli rapidly become filled with a cell-mass, consisting of leucocytes and desquamated epithelium in varying proportions. In the most acute cases, either suppuration and sloughing occur, or hæmorrhagic exudation with subsequent gangrene.

Contrast with Lobar Pneumonia.—In broncho-pneumonia the onset is less acute and the termination by lysis, as opposed to the sudden onset and critical defervescence of lobar pneumonia: the temperature is of the remittent or intermittent type, instead of a continued pyrexia: the consolidation is lobular, instead of lobar in distribution: the alveoli are filled chiefly with desquamated endothelial cells, leucocytes, and mucoid exudation, as contrasted with the contents of the air-cells in acute pneumonia, which are first blood-corpuscles and fibrin, and, later on, leucocytes: the walls of the alveoli are considerably thickened in broncho-pneumonia, much less affected in lobar pneumonia.

TERMINATIONS.—**Resolution** is the most common termination. The contents of the alveoli undergo fatty degeneration, and are removed by expectoration and absorption, the lung gradually regaining its normal character. This process, however, is less rapidly effected than in croupous pneumonia, and it often occupies such a lengthened period that some thickening of the bronchial and alveolar walls, with dilatation of the smaller bronchi, remains. In chronic cases, this **fibroid thickening** is more marked, and much irregularly distributed induration may occur, accompanied by pigmentation and bronchial dilatation (p. 483).

Hypostatic Pneumonia.—Allusion must be made to a form of consolidation which is often described as pneumonia, but which, for the most part, is not inflammatory in its nature. This is the so-called "hypostatic pneumonia." This condition is met with at the bases and most dependent portions of the lungs in the course of both chronic and acute diseases, and also in aged and debilitated persons. It consists in the main of collapse, passive hyperæmia, and œdema of the lung-tissue, resulting from weak inspiratory power, feeble circulation, and gravitation. The consolidation thus mechanically induced is increased by exudation of fluid and blood-corpuscles into the alveoli. This exudation is due to the damage of the walls of the capillaries, caused by the imperfect circulation.

The passive hyperæmia of the alveolar walls is accompanied by some desquamation of the endothelial cells; and in chronic cases breaking-up of exuded blood-corpuscles results in some pigmentation of the lung-tissue, while the fibrous tissue is increased in amount (*brown induration*).

3. Interstitial or Chronic Pneumonia.

Interstitial or chronic pneumonia is characterised by a gradual increase in the connective tissue of the lung, which leads to thickening of the pulmonary texture and to progressive obliteration of the alveolar cavities. It is commonly associated with catarrh and dilatation of the bronchi, and often with ulceration of the bronchial walls and excavation of the indurated lung (p. 488).

ÆTIOLOGY.—In the large majority of cases interstitial pneumonia is secondary to some inflammation of bronchi, alveoli, or pleura; it results also from persistent atelectasis or collapse. It may be stated generally that all inflammatory processes in the lungs, when they become chronic, lead to an increase of the connective tissue and consequently to fibroid induration of the organs.

Congenital Syphilis gives rise to a gummatous inflammation, and also to a diffuse interstitial pneumonia (*white pneumonia*). The latter is characterised by fibrosis with proliferation and desquamation of the alveolar epithelium. In adults, syphilitic changes in the lung are probably rare; but it is impossible to be certain of the nature of some localised fibroid changes.

The chief causes of interstitial pneumonia are—

1. **Croupous Pneumonia.**—The consolidation of acute croupous pneumonia usually undergoes complete and rapid resolution; but occasionally this is more protracted. Then the hepatised lung tends to become slightly indurated, mainly owing to thickening of the walls of the alveoli, and sometimes to organisation of their contents. This indurated hepatisation differs but little in its physical characters from ordinary red and grey hepatisation; the lung is, however, firmer, more resistant, and less granular.

2. **Broncho-Pneumonia.**—Broncho-pneumonia is a more frequent cause than the preceding. The greater liability of this form of pneumonia to lead to pulmonary induration is to be accounted for partly by its longer duration and greater tendency to become chronic, and partly by the existence of bronchial dilatation, with which it is so frequently associated (p. 482). The existence of this dilatation favours the persistence of the catarrhal and pneumonic process. The removal of secretion is rendered difficult; and the retained secretion tends to keep up and increase the irritative process both in the dilated bronchi and the alveoli, and this persistence of the bronchial and pulmonary inflammation leads to fibroid thickening of the bronchial and alveolar walls. In this way areas of fibroid induration are produced, which, as the process extends, may ultimately involve large portions of the lung. The

progressive tendency of the process is, probably, partly to be explained by the fact that pulmonary fibrosis is itself a cause of bronchial dilatation. When, therefore, fibrosis is once established, the new tissue in contracting induces further dilatation of the bronchi; and this again, as before explained, favours the still further extension of the bronchial and pulmonary induration.

Under this head may also be included those cases of induration and ulceration of the lung which result from *obstruction of a main bronchus*—such as is produced by the pressure of an aneurysm. Here the retained bronchial secretion sets up inflammatory changes in the bronchial and alveolar walls, which gradually lead to induration and ulceration of the lung.

3. **The Inhalation of Solid Irritating Particles.**—This is the commonest cause of interstitial pneumonia, leading to the fibrosis of the lung so common amongst miners, potters, stonemasons, grinders, and others. The continuous irritation of the inhaled particles induces a bronchial and alveolar inflammation, and ultimately a progressive fibrosis, with dilatation and ulceration of the bronchi (p. 490). Such cases often become tuberculous.

4. **Pleurisy.**—This, in exceptional cases, leads to the development of an interstitial pneumonia. Such a result is most likely to occur in those cases of pleurisy which are more or less chronic, and in which the effusion remains long unabsorbed. The induration thus induced is often partial, consisting merely in an increase of the interlobular connective tissue, originating and extending inwards as dense bands from the thickened visceral pleura. In other cases, pleurisy gives rise to a much more general fibrosis.

5. **Atelectasis,** or failure of part of the lung to expand after birth, and **persistent collapse** lead to marked fibrosis of the affected area. Later on, bronchiectasis and obliteration of most of the alveoli occur. The original positions of the latter may be merely indicated by a few epithelial cells.

Morbid Anatomy.—The appearances presented by the lung, when the fibrosis is general and well advanced, are very characteristic. The organ is diminished in size; the tissue is smooth, dense, firm—in parts, almost cartilaginous in consistence—and is irregularly mottled with black pigment. The alveolar structure of the lung is in most parts completely destroyed, and on section the dilated bronchi are seen as numerous large openings scattered over its surface. These dilated bronchi frequently become the seats of secondary inflammatory processes, which may lead to ulceration and ultimately to extensive excavation of the indurated tissue; but there is a complete absence of any of those caseous changes which are so characteristic of pulmonary tuberculosis. This secondary inflammation of the dilated bronchi is induced by the irritating and often putrid secretion which they contain, and which is, as a rule, incompletely removed by expectoration. The pleura is considerably thickened and generally adherent.

Microscopically, fibrous tissue is found in the interalveolar, peri-

bronchial, and interlobular connective tissue. This new tissue, as it increases and contracts, gradually replaces and obliterates the alveolar structure. The character of these changes, however, varies somewhat according to the nature of the cause. When it is the result of a *croupous pneumonia*, the primary change takes place in the walls of the alveoli, although ultimately the interlobular tissue is involved. The alveolar walls become thickened by the growth of fibrous tissue. The new tissue, in its earlier stages, contains new bloodvessels, but, later on, contraction occurs, and many of these are destroyed. The alveolar cavities which are not obliterated are either empty or contain exudation-products or a few epithelial cells. Cases occur in which, in addition to the growth in the alveolar walls, the intra-alveolar exudation becomes organised. There is nothing peculiar in the macroscopic characters of the lungs, and many of the alveoli are filled with leucocytes and a fibrinous meshwork, similar to that met with in red hepatisation. The contents of some of the alveoli differ, however, in this respect—that many of the cells are long and spindle-shaped, and bloodvessels are distributed amongst them, communicating with those in the alveolar walls. These changes are often confined to the parts adjacent to the pleura. The affected areas are ill-defined, as they pass gradually into the normal lung-tissue.

When the fibrosis is secondary to an ordinary *broncho-pneumonia* or to that induced by the *inhalation of irritating solid particles*, the alveolar walls are also involved, though the peribronchial and interlobular connective tissue plays a more prominent part in the process.

The *pleurogenic* form results chiefly from empyemata. In these cases the new fibrous tissue extends inwards in bands along the interlobular lymphatic vessels which communicate freely with those of the thickened pleura; thence it spreads to the peribronchial tissue. The lung is thus surrounded by a dense capsule, and a meshwork of anastomosing fibrous bands permeates its substance, obliterating many of the alveoli and leading to bronchiectasis. More or less bronchitis is usually present.

Atelectasis and *collapse* are said to lead first to slight hæmorrhages. The subsequent changes in the hæmoglobin lead to the formation of some of the black pigment usually found in fibroid areas due to this cause. The alveolar walls become fibrous, the epithelium is more or less shed, and the surfaces of the walls ultimately cohere.

Vesicular Emphysema.

Vesicular emphysema consists essentially in a *permanent* overdistension of the infundibula and air-cells, due to atrophy of the intervening septa and to general diminution in the elasticity of the lungs. It should be distinguished from the acute overdistension often seen, especially in children, after death from bronchitis or whooping-cough. The condition of the lungs met with in these diseases is sometimes called "acute emphysema."

VARIETIES.—Two varieties are described: (1) Hypertrophic or "large-lunged" emphysema—by far the most important, and always indicated when the term "emphysema" alone is used; (2) atrophic, small-lunged, or senile emphysema.

1. In **Hypertrophic Emphysema** the lungs are enlarged, sometimes so much that they actually cross in the mid-line in front, obliterate the superficial cardiac dulness, project into the neck, and push down the diaphragm. Owing to the loss of their elasticity the lungs collapse but slightly when the chest is opened, and their usually sharp edges (in front and round the base) are pale, thick, round, and more or less irregular from the protrusion of soft, pale, round swellings. Similar swellings frequently project towards the diaphragm; the tongue-like piece of the left lung below the notch is often extremely swollen, and the lungs may bear distinct grooves corresponding with the ribs. Everywhere, in advanced cases, the air-cells are seen through the visceral pleura with abnormal distinctness; but the apices and sharp edges are first and chiefly affected, and spaces of considerable size are here met with. Abnormal pigmentation is usual. The lungs feel much like a down-pillow; they "pit" easily, and crepitate but little. On section, the emphysematous parts are pale, dry, and bloodless; and when large spaces are present in the part cut, the collapse of the affected areas is very marked.

Microscopic investigation shows: that the dilatation commences in the infundibula, and extends thence into the alveoli opening into it; that the interalveolar septa atrophy and ultimately become perforated, their elastic fibres yielding and then disappearing; that the stretched capillaries become thrombosed, and then likewise vanish. The apertures in the interalveolar septa enlarge; and others form later between the infundibula: thus are developed irregular cavities (Fig. 191), which are sometimes as large as a filbert. The largest are situated in the pale, rounded, bleb-like swellings. Fatty degeneration of the alveolar epithelium is commonly present, and is probably secondary to vascular disturbance.

The obliteration of capillaries in the stretched or destroyed alveolar walls necessarily causes some obstruction to the pulmonary circulation. This is followed by hypertrophy of the right ventricle of the heart. By this means the increased resistance in the pulmonary circulation is overcome. The communications between the pulmonary and bronchial vessels become dilated. The connective tissue round the smaller bronchi may be increased as the result of bronchitis.

Results.—The atrophy of the elastic tissue of the lung, by diminishing the expiratory movements of the chest, lessens the normal interchange of gases. As a result, the blood, which is thus inefficiently aerated, stimulates the respiratory centre to an unusual degree, and thus gives rise to deeper inspirations, which, in the absence of the normal elasticity of the lungs, lead to a permanent enlargement of the thorax—the so-called "barrel-shaped chest."

2. **Atrophic Emphysema** occurs usually in thin old people who seem to be undergoing general atrophy. The lungs during life may leave the heart unduly exposed; when the thorax is opened they collapse excessively, falling together "like an inflated bag of wet paper" (Jenner). They are excessively pigmented, and their apices and borders, even after collapse has occurred, usually show appearances resembling those in the large-lunged variety, and due to similar naked-eye and microscopic changes. In this form, apparently, the elastic tissue is not so generally affected as in the hypertrophic variety.

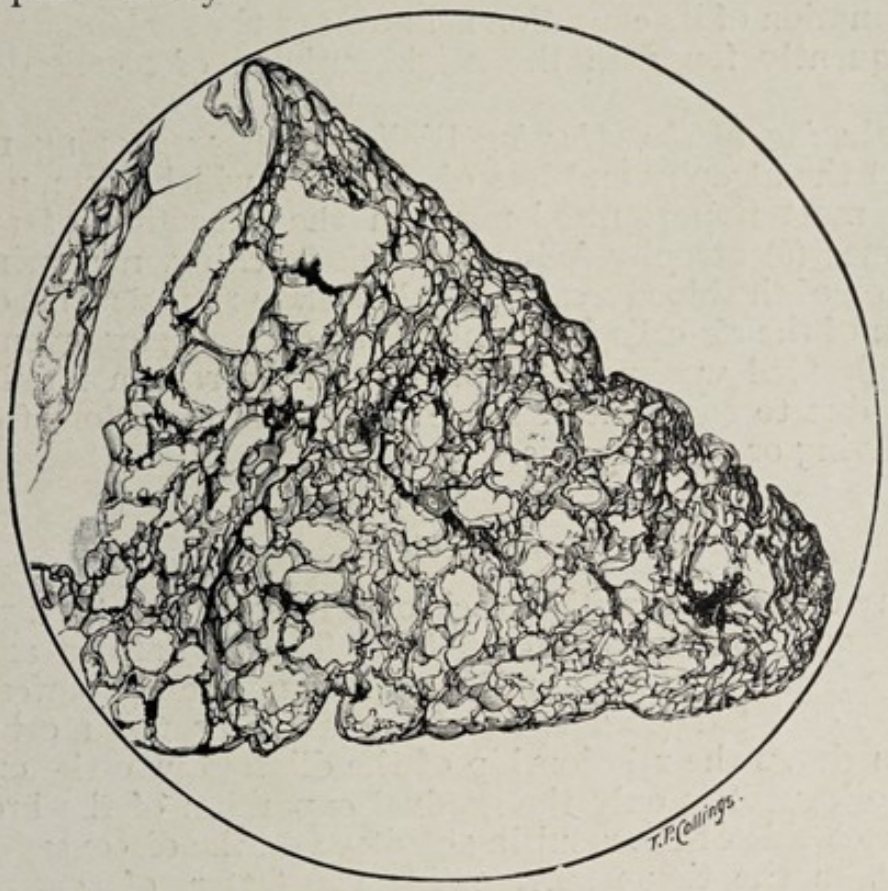


FIG. 191.—EMPHYSEMA OF THE LUNG. (× 8.)

From a case of chronic bronchitis. A portion of the rounded anterior edge of the lung. The varied size of the cavities formed by distension of the alveoli and atrophy of the partitions is well shown.

PATHOLOGY.—All conditions which (1) increase the pressure on the inside of the air-vesicles, (2) which withdraw the support normally furnished by the surrounding parts, or (3) which weaken the alveolar walls, may act as causes of emphysema.

1. *Increase of Intra-Alveolar Pressure.*—Increased pressure in the air-cells may be due to violent expiratory efforts with closed glottis, as in coughing; to violent muscular efforts in which the glottis is closed and the thorax distended; and to the blowing of wind-instruments. Those parts of the lungs which are least supported—the apices and edges—will be most distended. This is the *expiratory theory* of Jenner. Emphysema due to these causes may be *primary*, but more often is associated with chronic bronchitis.

2. *Withdrawal of External Support from Alveoli.*—By reason of collapse, compression, or consolidation, the entrance of air into any part of a lung may be interfered with and its expansion consequently diminished. Such portions will, during inspiration, afford less support to the air-cells in their immediate neighbourhood, and these air-cells will therefore tend to become more distended than those in other parts. Similarly, when from the same cause a whole lung fails to expand, its fellow stretches over towards it, and even the mediastinal contents may be displaced in the same direction. This form of emphysema is termed *vicarious, compensatory,* or *secondary,* and this explanation of its causation is known as the *inspiratory* theory. It is frequently found in the neighbourhood of localised fibroid changes.

3. *Weakening of the Alveolar Walls.*—This weakening may be due to (*a*) the atrophy and loss of elasticity which accompany old age—the most important element in the causation of atrophic emphysema; (*b*) atrophy following the stretching, narrowing, and obliteration of the bloodvessels, which in its turn is a result of overdistension of the air-cells from any of the causes before mentioned; and (*c*) inherited weakness (emphysema may run in families), or weakness due to some interference with their nutrition, from the mode of living or other causes.

Bronchiectasis.

In many different varieties of chronic lung-disease the bronchial tubes are occasionally found dilated. The dilatations are most frequently found in the lower lobes, and may be cylindrical, fusiform, or sacculated (Fig. 192). In some cases the most casual inspection shows the relationship of the dilatation to the ordinary tube; in others, it is only the gradual expansion of the bronchial tube on each side of the resulting cavity, and the discovery, microscopically, in the tissue surrounding the latter, of some of the rudiments of the original bronchial wall, that elucidate the nature of the lesion. This is especially the case in some instances of the sacculated form, in which the cavities are large and irregular, and their walls composed principally of fibrous tissue.

The causation of bronchiectasis is, in great measure, analogous to that of emphysema. The principal forces concerned are three: (1) increased pressure within the lumen of the tube, tending to dilate it at its weakest points—such pressure occurring during either inspiration or expiration; (2) weakening of the wall of the tube through atrophy, inflammation, or ulceration; and (3) traction upon the walls of the tubes exerted by bands of cicatricial tissue in the lungs. These forces usually act in combination: it will therefore be necessary to consider them together.

The only good examples of bronchiectatic cavities due solely to changes in pressure occur in those stages of congenital atelectasis in which the alveoli, in the whole or part of a lung, are unable to

expand. The act of inspiration, by causing a flow of air into all those parts in direct communication with the trachea, not only

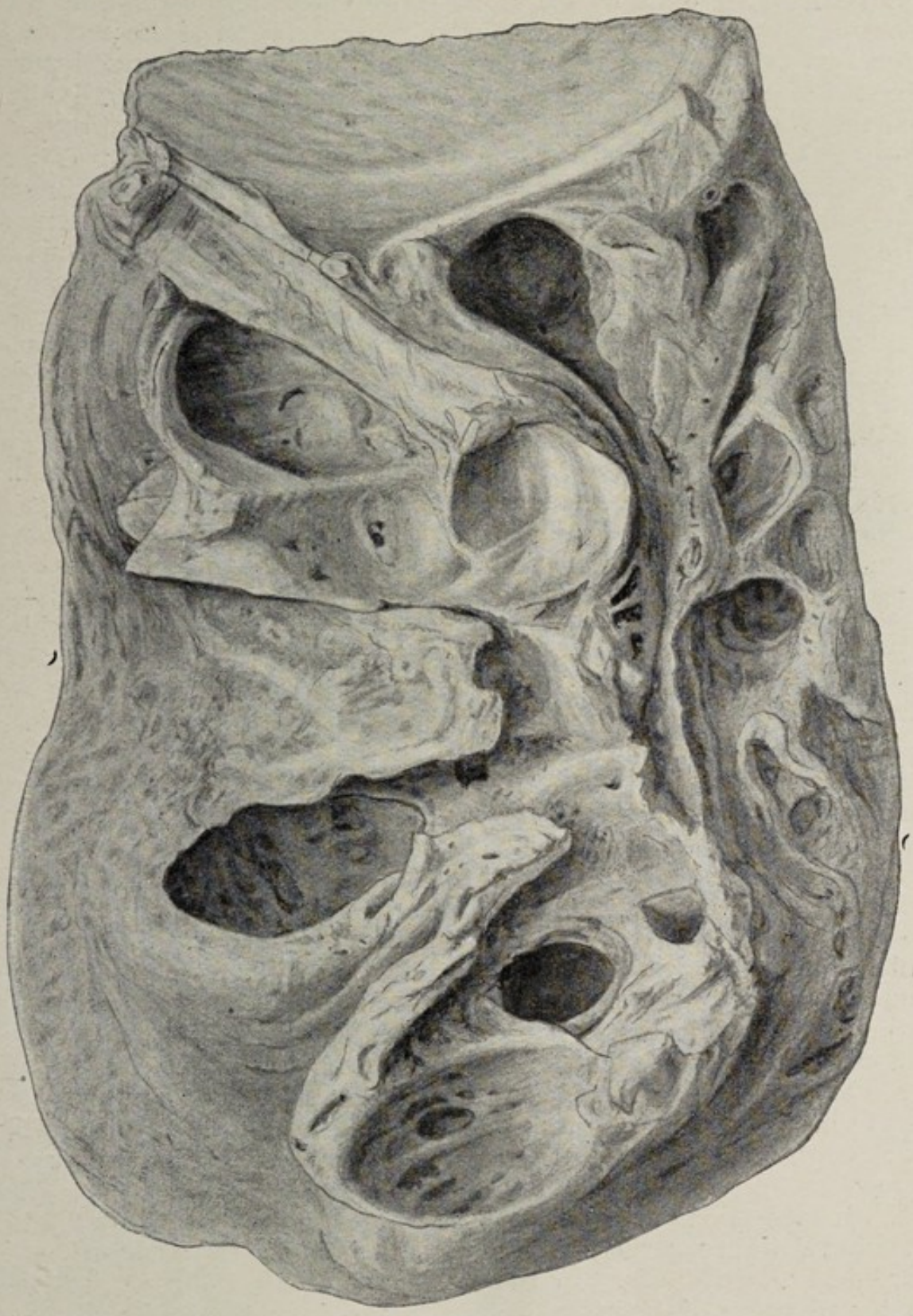


FIG. 192.—LUNG, SHOWING THE PRESENCE OF BRONCHIECTATIC CAVITIES. (FROM A SPECIMEN IN C. C. H. MUSEUM.)

distends each normal alveolus, but also thereby affords support to those in its immediate neighbourhood. Those alveoli immediately

in contact with the imperfectly developed portion of the lung will undergo emphysematous changes. The resistance, however, which the young elastic tissue offers to this overdistension will in the same way, by lessening the support, cause dilatation of the pervious bronchial tubes imbedded in the interior of the unexpanded portions. These bronchial tubes will accordingly become gradually distended, and may frequently develop club-shaped terminations.

Acute or chronic inflammation of the bronchial tubes, especially in children, is often accompanied by a slight amount of dilatation of the cylindrical or fusiform type, combined with slight emphysema. This depends partly on the inflammatory weakening of the muscular and elastic tissues in the walls of the bronchial tubes, and partly upon the increased expiratory pressure in coughing, combined with the traction exerted, especially during inspiration, by the ordinary elastic tissue of the lung. Should, however, pyogenic organisms lodge in a tube so dilated, and, by setting up a slow suppurative inflammation, still further weaken a portion of its wall, the forces just mentioned will lead to the formation of an extensive cavity, with ragged, irregular walls. As a rule, however, inflammatory changes in the bronchial tubes do not lead to much dilatation, unless there is, in addition, some obstruction to the entry of air into the alveoli. The combination is well illustrated in the local bronchiectasis—not uncommon in children—which occurs as a result of bronchopneumonia or persistent collapse of the lung. In such cases, the air, being unable to enter the alveoli, tends during inspiration to dilate the tubes, the walls of which are weakened by the bronchitis and unsupported by properly filled surrounding alveoli. The accompanying cough will act still more effectively in the same way; for during expiration the air, which would by this means ordinarily be driven into and overdistend the alveoli, will under these conditions tend instead to dilate the weakened tubes. As a result, the affected portion of lung presents, on section, a large number of small holes about one-eighth of an inch or more in diameter. Should the inflammation become chronic, this dilatation will become more pronounced; partly because chronic inflammation, when it affects the bronchial tubes, leads, as it does elsewhere, to replacement of the muscular and elastic elements by a connective tissue, which is easily stretched in its early stages; and partly because there is an increase in the interstitial fibrous tissue of the lung which, later on, tends, as it contracts, to pull upon the walls of the tubes, as explained below.

The contraction of chronic inflammatory fibrous tissue throughout the lung is often regarded as an important factor in the production of chronic bronchiectasis. In the repair-stage of all chronic inflammatory diseases of the lungs, fibrous tissue of this type is found. In the large majority of these diseases the pleural surfaces are adherent, so that the fibrous tissue is firmly attached on each side. In these cases the contraction of the new tissue should, theoretically, lead to a rise in the level of the diaphragm; to sinking-in of the wall of the

chest; to dilatation of the bronchial tubes; and, if the disease be unilateral, to displacement of the mediastinum. In some cases all these changes actually occur, sometimes one, and sometimes another being the most prominent. This contracting fibrous tissue will act at greatest advantage during inspiration, when the movements of the chest and diaphragm tend to enlarge all the diameters of the lung.

The contents of bronchiectatic cavities are chiefly mucus, putrefactive organisms, and tissue-débris. Stagnation of the secretion in the dilated tubes is favoured by the destruction of nerve-terminals in their walls, brought about by chronic inflammation. The accumulating secretion thus sets up no irritation until it reaches a sound portion of the bronchus: cough is then excited and the irritant expelled. The stagnating secretion undergoes putrefaction, and consequently has, as a rule, an extremely offensive odour.

Pneumokoniosis.

Ordinary atmospheric air always contains dust. When the amount of dust inhaled is comparatively small, it gives rise to pigmentation of the lungs without apparently producing any injurious effects. This pigmentation, absent at birth, gradually increases with advancing age, especially in the case of those who dwell in towns.

Pigmentation of the lungs is principally due to the presence of particles of carbon and other substances inhaled with the inspired air. These may be arrested in the smaller bronchial tubes or, when the fullest inspiration follows the most extreme expiration, be drawn into the alveoli. In both of these places they may be taken up by leucocytes. Many of these are expelled in the greyish-black sputum frequently expectorated in the early morning, but a large number penetrate into the alveolar walls and into the interlobular tissue. Most of the pigment is found contained within the connective-tissue cells or free among the fibres.

The means by which the particles of carbon make their way into the interalveolar tissue is explained in different ways. (1) The branched connective-tissue cells of the alveolar walls send processes, consisting of a greater or less portion of their bodies, between the epithelial cells of the alveolus into the alveolar cavity. As these connective-tissue cells lie in the serous canals which constitute the commencement of the perivasal lymphatics, and are themselves phagocytic, it is easy to understand how readily they may serve as the principal carriers by which the particles are withdrawn from the alveoli and conveyed to neighbouring parts of the lung. When once the carbon has made its way into the interlobular tissue, some of it is taken up by the fixed cells in this situation, whilst the remainder passes on to the lymphatics, and is deposited in the bronchial lymphatic glands, in which black particles are also found. (2) Wandering phagocytic leucocytes are found in the small bronchi

and alveoli. They probably convey particles into the tissue and lymphatics of the lungs.

In many occupations the respired air contains an altogether abnormal proportion of dust, often consisting of some special material, such as coal, stone, iron, or other substances. The first result of breathing air overcharged with such particles is the production of chronic bronchial catarrh from the mechanical irritation of the mucous membrane of the bronchi. This leads to frequent coughing, followed by deep inspirations, and, therefore, to the

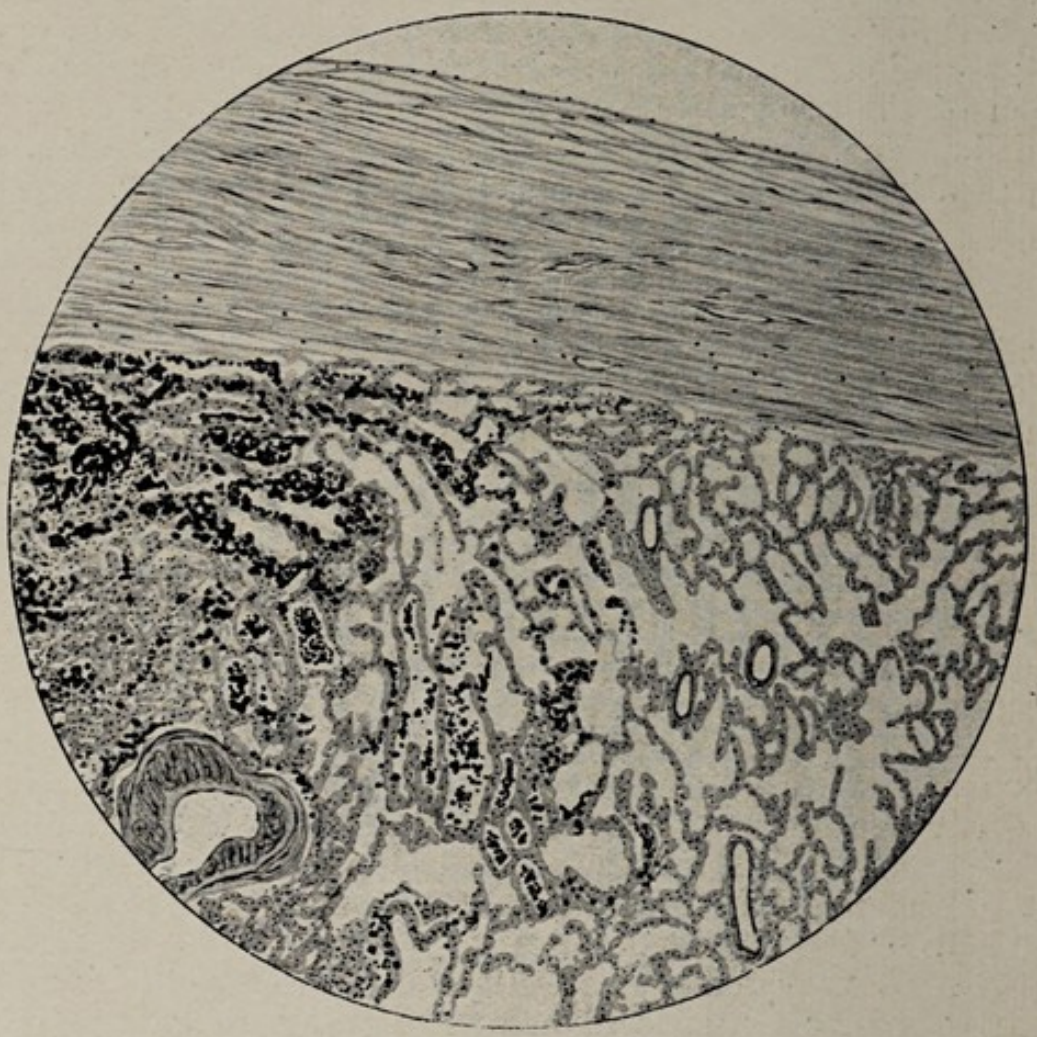


FIG. 193.—PNEUMOKONIOSIS. (COAL-MINERS' LUNG, OR ANTHRACOSIS.) (× 79.)

aspiration of similar particles into the alveoli. Inflammatory changes in the alveoli follow; leucocytes escape; the cells of the epithelial lining proliferate, and many are thrown off. Cells charged with the inhaled particles are found free in the alveoli. Some of these cells may be expectorated, but most are absorbed as just described. In the tissues further changes may gradually take place, according to the nature and number of particles deposited. These changes comprise chronic inflammatory thickening of the alveolar walls, patches of broncho-pneumonia, and general increase of the fibrous tissue throughout the organ (Fig. 193). Furthermore, these

changes render the affected parts especially liable to invasion by tubercle bacilli and other parasites.

In the case of miners the particles of coal enter the lungs in such large quantities as to give to them an almost uniform black colour (*anthracosis**). The black colour of the lungs in these cases is not entirely due to the presence of the inhaled substances, but partly to that of altered blood-pigment. The inflammatory changes in the bronchi and pulmonary tissue, already referred to, cause marked consolidation of the lungs, which thus become tough and fibrous. In the most severe forms, ulceration, starting from the bronchi, produces cavities (*colliers'* and *knife-grinders' phthisis*). Owing to these structural changes there is a considerable escape of red corpuscles from rupture of capillaries or inflammatory exudation, and hence a large formation of pigment, to which much of the dark colour of these lungs must undoubtedly be ascribed. The lungs of stonemasons (*silicosis*†) and grinders (*siderosis*‡) are, like those of miners, deeply pigmented, though to a less degree; but the black colour in the former cases cannot be accounted for on the supposition that it is due to the presence of inhaled particles, for the particles are pale or rust-coloured, as the case may be. Carbon-particles are black, angular, and very variable in size and shape. They are unaffected by strong acids and alkalies. Pigment derived from the blood is generally brownish and granular; it is rarely met with in a crystalline form.

Pigmentation of the lungs from the presence of hæmatoidin occurs as the result of many other morbid conditions, many diseases of these organs being attended by the formation of pigment. In *chronic phthisis*, pigmentation occurs, partly as the result of the inflammatory process, and partly from the obstruction of the vessels caused by the new tissue: lines of pigment are constantly seen surrounding the nodules of consolidation. In *acute croupous pneumonia*, the blood which is extravasated into the air-vesicles, and which in the early stages gives to the expectoration a rusty or prune-juice colour, subsequently gives rise to pigment, and the sputum consequently becomes greyish-black, the pigment-granules being visible in the desquamated cells. The cells met with in the sputum of *bronchitis* also contain granules of pigment; and pigmentation plays an important part in the condition of the lungs known as *brown induration* (p. 350). In all cases in which hæmatogenous pigment is found in any quantity in the lung, it is also found in the bronchial glands. It is taken up by the lymphatics, and, like the inhaled carbon, becomes arrested in its passage through these glands, where it remains permanently.

* Greek ἄνθραξ, cinder. † Lat. *silex*, flint. ‡ Greek σίδηρος, iron.

CHAPTER XXXI

AFFECTIONS OF THE LIVER AND OF THE PANCREAS

Perihepatitis.

INFLAMMATION of the capsule of the liver, leading to more or less thickening, and often to adhesions with adjacent parts, is met with under various circumstances. Its most common causes are—the chronic peritonitis of Bright's disease, chronic alcoholism, and syphilis. Localised patches may be produced by pressure from without, as by tight-lacing. The changes are usually slight and of little pathological importance.

In some cases, however, especially in cases of chronic peritonitis, the process is more extensive, and leads to marked interference with the circulation in the liver and with the functions of the organ. The whole capsule becomes considerably thickened and gradually contracts, thus causing compression of the organ, which assumes a globular form. The portal circulation is often interfered with by the squeezing process, and ascites, with other symptoms of portal obstruction, may result. The liver itself may show no changes with the exception of some atrophy and fatty degeneration of its cells; but sometimes it is irregularly intersected, and even divided into lobe-like masses, by bands of fibrous tissue passing inwards from the capsule (*centripetal cirrhosis* of Adami).

These conditions have been variously attributed to syphilis, tuberculosis, and alcoholism.

Abscess of the Liver.

1. **Multiple.**—Small multiple abscesses are most frequently due to some inflammatory lesion in connection with the portal system—such as dysentery, appendicitis, ulcerative colitis, typhoid fever, or some other form of ulceration of the gastro-intestinal tract. In these cases the abscesses are due to infective embolism of branches of the portal vein (*suppurative pyle-phlebitis*). Small abscesses also occur as a manifestation of generalised pyæmia, and are then due to infective embolism of the small branches of the hepatic artery. Suppuration within the bile-ducts (*suppurative cholangitis*) may also give rise to abscesses.

2. **Single.**—Single abscesses may follow injury, either external or internal—in the latter case being due to some foreign body which has perforated the walls of the stomach or duodenum. They may also result from the presence of gall-stones or parasites. In all these cases the abscess is really due to the additional presence of pyogenic organisms. Breaking-down gummata may give rise to extensive abscess-cavities.

The *tropical abscess* is, in three-fourths of the cases, single; and is generally believed to depend upon infection through the portal vein. In a large proportion of the cases it is associated with amœbic dysentery. It is commonest in countries near the Equator, and generally selects the white races. It is due to infection with the *Entamœba histolytica*, and this parasite can usually be found in scrapings from a section of the abscess wall, though examination of the pus often yields negative results (p. 145).

Cirrhosis of the Liver.

Cirrhosis* is the term applied to all diseases of the liver mainly characterised by an increase in the connective tissue of the organ.

Although the changes which occur in the diseases included in this definition vary within wide limits, three types may, for convenience of description, be distinguished—(1) *Portal*, (2) *Biliary*, and (3) *Pericellular*.

1. **Portal Cirrhosis.**—In this form the increase in the connective tissue occurs around the branches of the portal vein, and is, therefore, interlobular in its arrangement. Between many of the lobules, however, no new tissue appears, so that the distribution is exceedingly irregular, and the lobules become grouped into masses of varied size (*multilobular cirrhosis*) (Fig. 194); while the component cells tend to lose their radiating arrangement, and, at the periphery, to undergo fatty degeneration, atrophy, and pigmentation with bile (Fig. 195). The new connective tissue is plentifully supplied with bloodvessels from the hepatic artery. Later on it contracts, and forms hard cicatricial tissue, obstructing the portal circulation, and thus giving rise to ascites, and to hæmorrhage from any part of the gastro-intestinal tract, as well as pressing on the cells of the liver. Short columns of cubical cells, which are usually found in biliary cirrhosis (*vide infra*), are occasionally met with among the new tissue.

Naked-Eye Changes.—In the earlier stages the liver is uniformly enlarged, and the edge is rounded and thickened. This increase in size occasionally persists, without any contraction, until the disease ends fatally; but in the large majority of cases the atrophy of the liver-cells and the contraction of the new tissue are followed by some diminution in size. In some cases this may be so extreme—especially in the left lobe—that the liver is less than half its normal weight (*atrophic cirrhosis*); but in at least half the cases the organ

* Greek κιῤῥός, yellow.

at the time of death is larger and heavier than normal. The capsule is thickened and the surface is uneven (Fig. 196). When the unevenness is extreme, the liver is termed *hobnailed*—the extent of this depending upon the distribution and contraction of the new tissue and upon the atrophy of the cells. As a rule, the more fatty the liver, the less the contraction. The consistence of the organ is also proportionately increased, and may approximate to

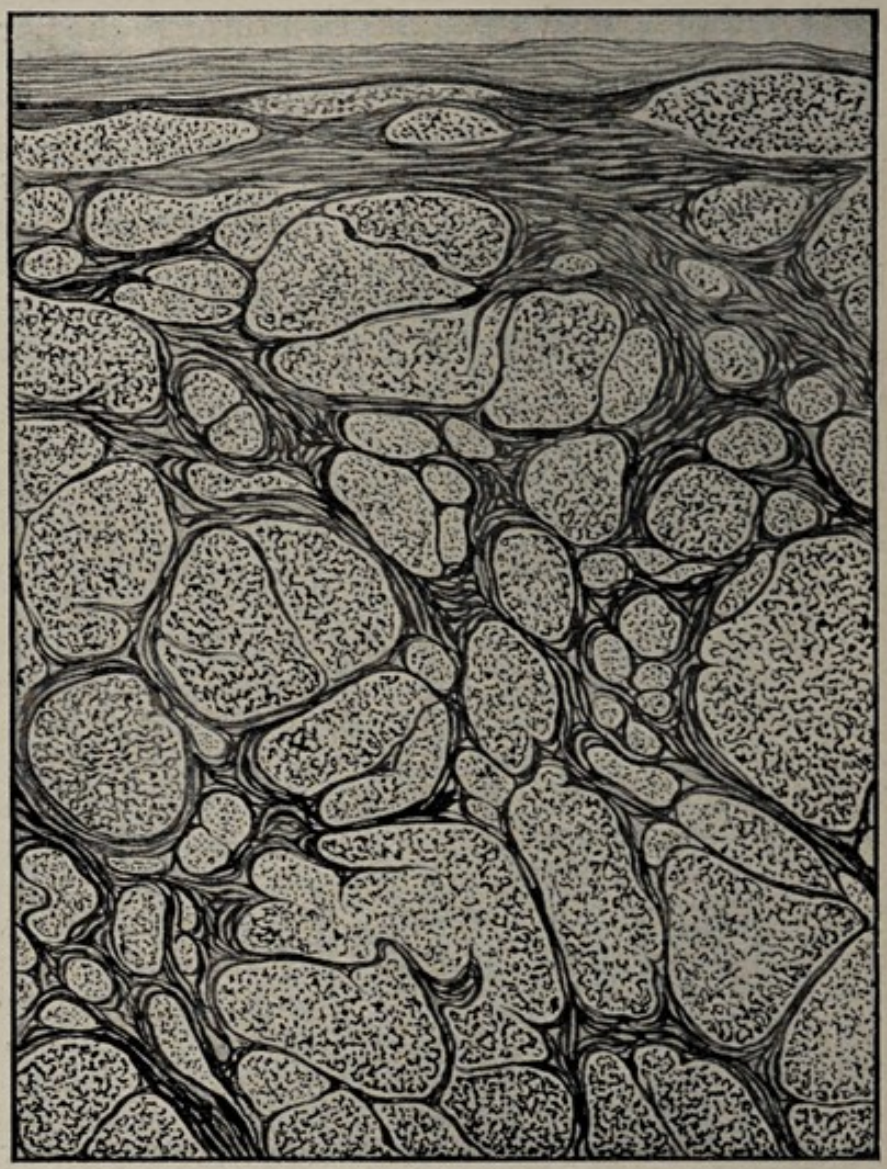


FIG. 194.—MULTILOBULAR CIRRHOSIS OF LIVER, SHOWING IRREGULAR ARRANGEMENT OF FIBROUS TISSUE. (× 14.)

that of hard fibrous tissue. Both the irregularity of the surface and the induration are most marked along the anterior edge, especially of the left lobe. On section, the new tissue surrounding the lobes, and in many parts completely replacing them, is visible to the naked eye. This gives to the cut surface a mottled granular appearance, the lobules contrasting with the new interlobular tissue, and often appearing as yellow or orange foci in a pink,

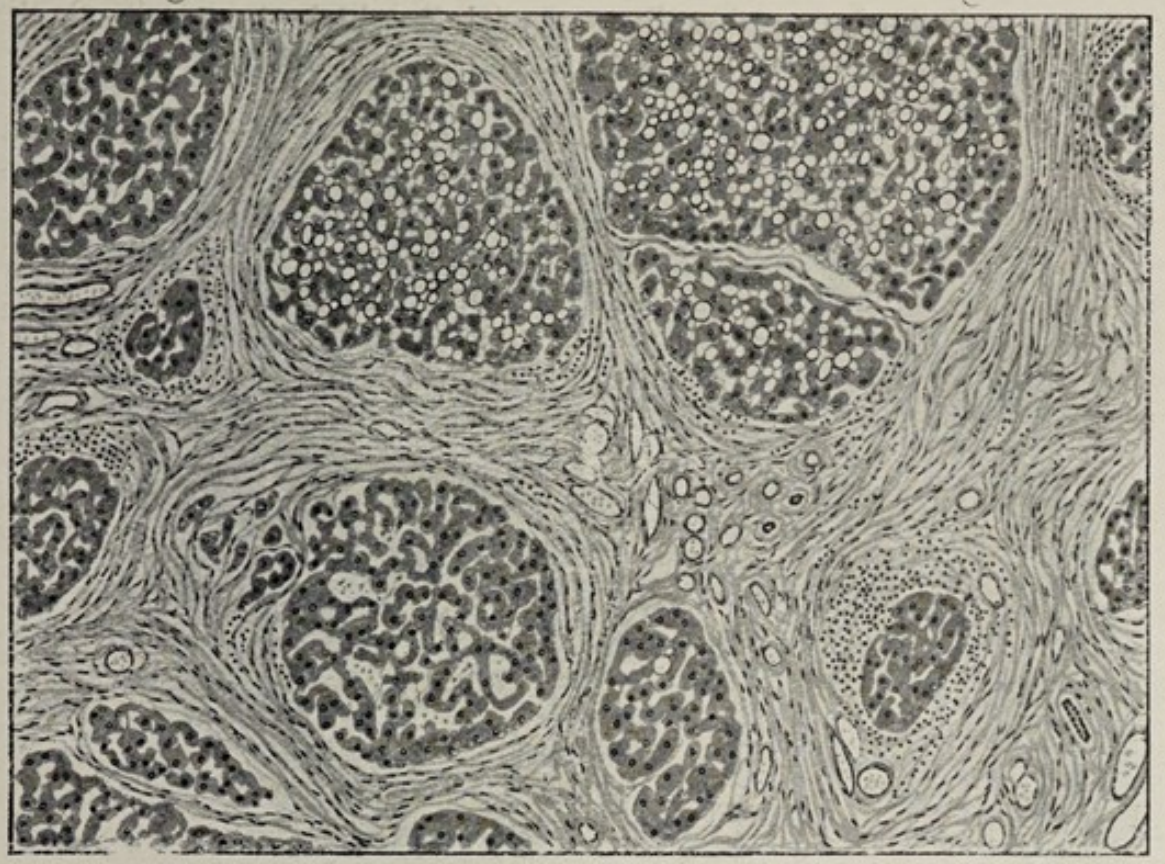


FIG. 195.—MULTILOBULAR CIRRHOSIS OF LIVER. (×79)

FIG. 196.—MULTILOBULAR CIRRHOSIS OF LIVER. (FROM A SPECIMEN IN C. C. H. MUSEUM.)

glistening network. In advanced cases the fibrous tissue is dense and white. In the large majority of cases the spleen is much enlarged, being often double its normal size.

An acute form is occasionally met with in which the new tissue is abundantly infiltrated with leucocytes (*red atrophic liver*), the disease ending fatally in a few months.

2. **Obstructive Biliary Cirrhosis.**—In the typical instances of this comparatively rare form of cirrhosis the new fibrous tissue is evenly distributed between all the lobules (*unilobular cirrhosis*), and may even invade the intercellular network (Fig. 197). The bile-ducts outside the lobules are large and tortuous, and their external coat is thickened, while the bile capillaries themselves are distended with bile (Fig. 198). Scattered through the new tissue—in the majority of cases—are short columns of cubical cells, often arranged

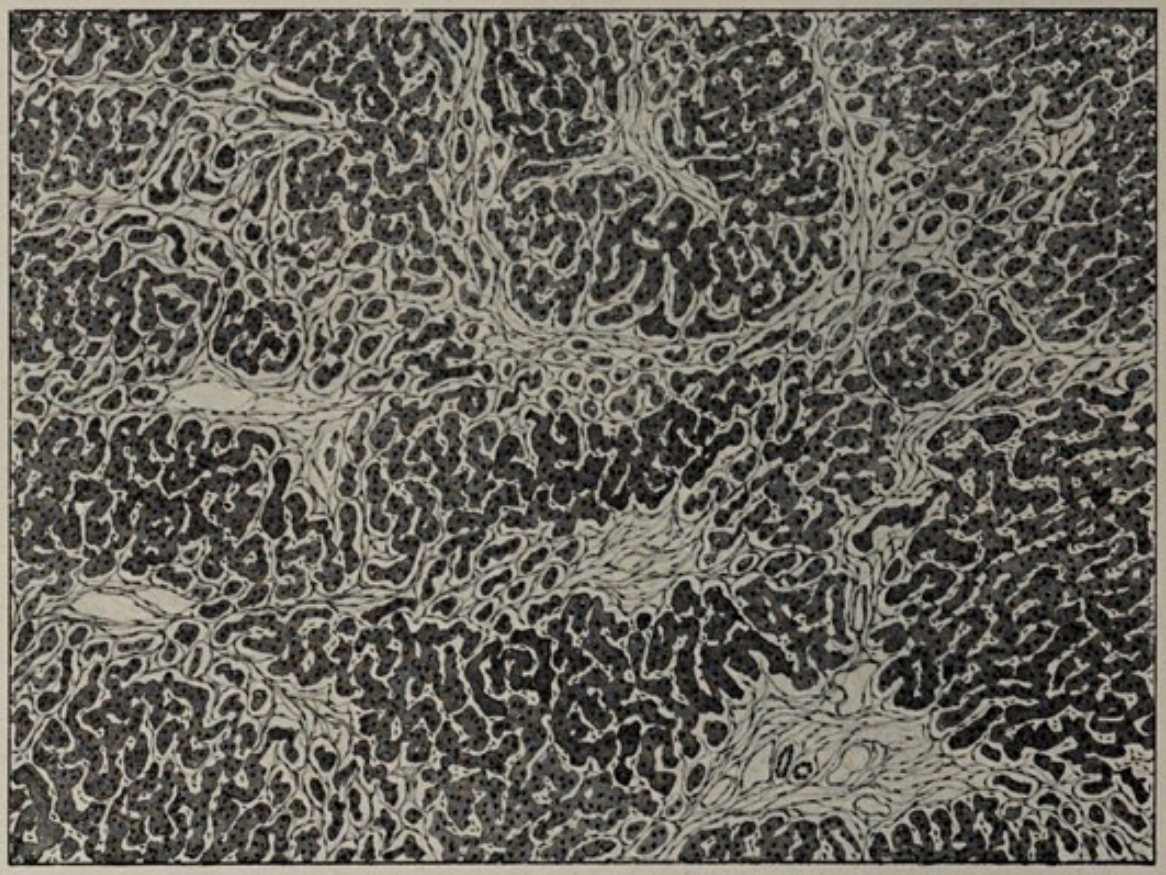


FIG. 197.—BILIARY (UNILOBULAR) CIRRHOSIS OF LIVER. (× 79.)

in double rows. By some, these are regarded as attempts at regeneration on the part of the liver-cells or bile-ducts; by others, as degenerated liver-cells or as the surviving remnants of bile-ducts. Adami considers the condition is due to a partial reversion to the original hepatic follicles found in the earliest stages of the development of the liver, and suggests the name "reversionary degeneration."

To the naked eye, the liver is uniformly, and often enormously, enlarged. Its surface is smooth, its consistence firm, and its colour yellow or olive. On section, the new, evenly distributed tissue can be readily made out. No marked contraction occurs.

3. **Hanot's Hypertrophic Cirrhosis.**—In this form of cirrhosis, which resembles in many respects the obstructive biliary type, the liver is greatly enlarged, is firm in consistence, and has a smooth surface. It is usually olive-green in colour, but sometimes of a dark red tint.

Microscopically, the cirrhosis is found to be unilobular in distribution. There is evidence of bile-stasis, and the proliferated bile-capillaries are very numerous.

Clinically, there is usually marked jaundice, associated with irregular fever. Ascites is extremely rare, and the spleen is usually found to be considerably enlarged.

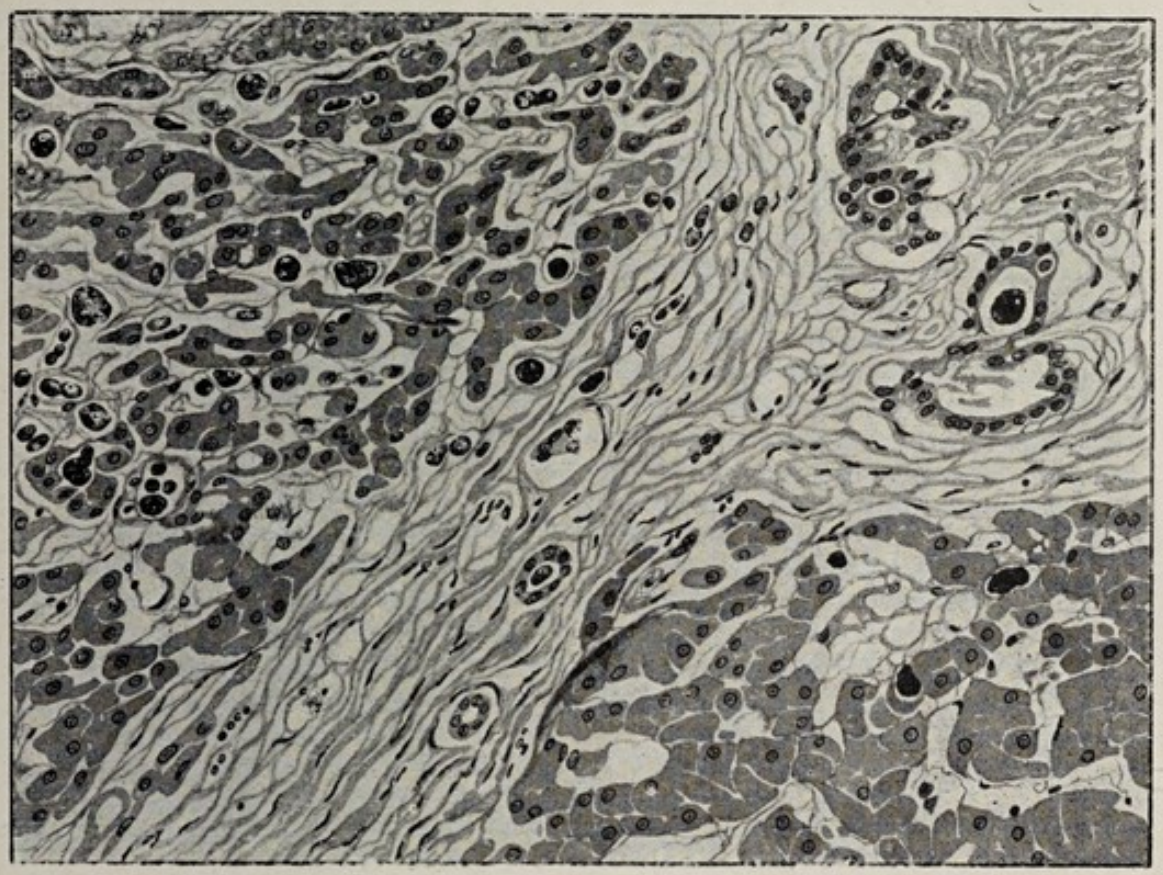


FIG. 198.—BILIARY (UNILOBULAR) CIRRHOSIS OF LIVER, A PORTION OF THE SAME SECTION MORE HIGHLY MAGNIFIED. (× 325.)

4. **Pericellular Cirrhosis.**—In adults, on rare occasions, and frequently in infants dead from congenital syphilis, new connective tissue is found uniformly infiltrating the whole organ, and penetrating everywhere between the degenerating liver-cells. Scattered groups of small round cells suggest the commencement of gummata. The liver is large, and, in most cases, pale in colour.

Other rare forms of cirrhosis are occasionally met with. (1) Arterio-sclerosis may, in the liver, as in other organs, lead to slight fibroid changes. (2) Long-continued passive congestion may also produce a development of fibrous tissue around the intralobular veins (p. 349). (3) Cirrhosis may occur with perihepatitis (p. 494), and (4) in a localised form with syphilis (p. 272).

Irregular Forms.—A large number of cases also occur in which the characters of the three types described are so intermingled that many writers deny the utility of the classification adopted, which, indeed, can only be regarded as representing a provisional arrangement of the facts known.

Boix, under the name of "dyspeptic cirrhosis," describes a uniformly enlarged liver in which the infiltration is interlobular and intralobular, but which does not affect the nutrition of the cells. The disease may disappear under treatment, or, after about ten years, pass into the atrophic form. The spleen is not enlarged, and there is neither jaundice nor ascites. Lancereaux and many other authorities recognise a definite variety of cirrhosis, due to *malaria*. In this form an irregular intralobular fibrosis precedes a similar intercellular change. A form also occurs in which a large amount of iron-containing pigment is deposited in the liver-cells and in the capillary walls (hæmochromatosis), and a few instances in which adenomatous and even carcinomatous growths may be intermingled with the fibrous tissue. In *splenic anæmia* (p. 441) there is usually some degree of cirrhosis of the liver as well as enlargement of the spleen, and the condition is known as *Banti's disease*.

The term *hypertrophic cirrhosis* is not infrequently used as a synonym of biliary cirrhosis; it is also employed to designate the enlarged stage of portal cirrhosis; and again to denote a form of portal cirrhosis, not unlike that which Boix describes, supposed to remain stationary without any contraction throughout its course.

PATHOLOGY.—The site and gradual development of *portal cirrhosis* establishes a probability that the disease is due to some slowly-acting irritant conveyed by the tributaries to the portal vein, and, therefore, derived either (1) from the gastro-intestinal tract, or (2) from the spleen.

1. In the great majority of instances the irritant seems to be absorbed from the stomach or intestine. In most cases there is a clear history of chronic alcoholism. The form in which the alcohol is taken does not seem to be of much importance. In one country it is beer; in another, wine; in a third, spirits. But how the alcohol acts, and to what causes are due those cases in which no such antecedents have occurred, are vexed questions. According to the old view, the alcohol itself was the irritant; according to later authorities, the products of fermentation to which the ingestion of alcohol would contribute, and in which acetic acid takes the most prominent part, are believed to be the chief toxic agents; and, according to a third theory, the actual causes of the disease are the toxines of organisms which are enabled to thrive among the tenacious mucus which lines the alimentary tract in those suffering from chronic alcoholic catarrh, or which actually find their way to the portal zone of the lobules of the liver (Adami). Most of the later views are based principally upon experimental evidence—viz., the impossibility of producing cirrhosis of the liver in animals by

administration of alcohol. This evidence is not conclusive, for the periods over which the poisons were administered to animals were much shorter than those usually required to develop chronic cirrhosis in man. Clinically, however, cases occur from time to time in which cirrhosis of the liver is found in persons of eminently temperate habits.

2. Chauffard has suggested that substances derived from the spleen may act as causes of portal cirrhosis. He points out, in addition to various *a priori* considerations, that in several diseases, of which malaria and typhoid fever are typical examples, the spleen acts as a storehouse of infective parasites, and that, in these diseases, secondary phlebitis of the splenic vein and subsequently hepatitis have been found. According to Chauffard, the poison is probably derived from the spleen in those cases in which enlargement of this organ appears to precede the cirrhosis of the liver. There is more evidence in favour of a splenic origin of acute hepatitis and of malarial and biliary cirrhosis than of a similar causation of the ordinary atrophic form.

Biliary Cirrhosis is generally believed to be of infective origin, and is most likely due to inflammation of the bile-ducts produced by (1) the elimination of some poisons excreted in the bile—for certain poisons (toluylenediamine) have been shown capable of causing such an inflammation; or more rarely by (2) direct extension from the duodenum up the bile-passages.

From these hypotheses it will be seen that the occurrence of the mixed forms of cirrhosis can be readily explained on the supposition that the poisons capable of producing each form occur simultaneously in a single case.

Different views have been held as to how far the atrophy of the liver-cells in cirrhosis is due to the immediate effect of the poison and how far to the pressure exerted by the new tissue. Many facts seem to preclude an exclusive reply in either direction. On the one hand, atrophy does not always occur, and the new tissue is coarser than, and far in excess of, that required to compensate for the atrophy that has occurred, while the atrophy may commence before any apparent pressure is exerted; on the other hand, the existence of an injurious degree of pressure is shown by the puckered shape of the liver in some instances. There seems to be no good reason why the cause of the cirrhosis should not in many cases, if not in all, have a direct influence upon the nutrition of cells, and thus tend to cause their atrophy; and, further, when the new tissue has commenced to contract, it is highly probable that the nutrition of the cells upon which the pressure is exerted will be still further impaired.

Effects.—The pathological effects which can be directly traced to cirrhosis of the liver are principally disturbances in the portal circulation produced by contraction of the fibrous tissue. The blood thus prevented from traversing the liver, and dammed back in the portal system, causes increase of pressure in this vascular area,

which can only be relieved by means of anastomosing channels. The principal anastomoses between the portal and the general venous system are (1) round the anus, by means of the junction between the inferior and upper hæmorrhoidal veins; (2) round the umbilicus, by the anastomosis of branches of the veins in the abdominal wall with those of the vein of Sappey in the round ligament of the liver; (3) connections between the mesenteric and retroperitoneal veins; and (4) the anastomoses of the coronary veins of the stomach with the lower œsophageal veins. The enlargement of the anastomosing branches causes (1) hæmorrhoids; (2) the *caput Medusæ*, or circle of enlarged vessels visible round the umbilicus; (3) great enlargement of veins beneath the peritoneum throughout the abdominal cavity; and (4) dilatation of the veins at the lower end of the œsophagus. If rupture of these last vessels occur, as not infrequently happens, severe hæmorrhage may ensue, the blood passing into the stomach and being subsequently vomited. In other cases the blood vomited is derived from the stomach, in which eroded vessels may be found after death. Bleeding may also occur from the hæmorrhoids.

The increase of pressure on the branches of the portal vein is followed by exudation of serous fluid, giving rise within the intestines to a watery condition of their contents and resulting watery motions, and within the peritoneal cavity to ascites. This last is probably aided by—and in many cases principally due to—accompanying chronic peritonitis.

Symptoms arising from interference with the functions of the liver are difficult to recognise in these cases. In some forms of intense cirrhosis, however, there occur fever, jaundice, a hæmorrhagic tendency, delirium, and coma—the whole constituting a picture closely resembling that seen in acute yellow atrophy of the liver.

Acute Yellow Atrophy.

This rare disease of the liver is characterised by a rapid diminution in the size of the organ, accompanied by the degeneration and subsequent destruction of the hepatic cells. Hæmorrhages from any part, jaundice, and delirium are among the principal manifestations of the disease. The malady is commonest in women, and is, in this sex, generally associated with pregnancy. The liver may, in the course of a few days, be reduced to less than half its normal bulk, being especially diminished in thickness. It is soft and flabby in consistence, bloodless, and of a mottled yellowish-red colour. A section through the organ shows numerous intermingled patches, dark red and bright orange in colour; in the lighter parts the lobules are generally indistinguishable. When examined *microscopically*, it is found that the protoplasm of the liver-cells is completely replaced by granular débris, fat-granules, and pigment, and that many of the cells have absolutely disappeared. In the earlier stages, the small bile-ducts are filled with débris. Tyrosin and

leucin have been found in the disintegrated liver-tissue and in the hepatic veins; and the appearance of these substances in the urine is characteristic of the disease. Branched tube-like collections of cubical cells, suggestive of bile-ducts, are frequently seen among the surviving stroma. The kidney and spleen undergo very similar changes.

The *pathology* of this disease is exceedingly obscure. It is generally regarded as an acute degeneration, depending on some unknown toxic cause derived from intestine or spleen. The presence of fever suggests that it may be due to some infective organism, but none has so far been identified. The jaundice is probably due to the blocking of the smallest ducts with the products of degeneration. The existence of leucin and tyrosin in the urine may be due to abolition of the functions of the liver, one of which has been supposed to consist in converting into urea certain intermediary products of proteid metabolism; but it is equally probable that these bodies are merely formed by autolysis of the hepatic cells, and are then eliminated in the urine.

A somewhat similar condition occurs in acute phosphorus-poisoning; although in this case the liver is enlarged, and the patches of yellow and red are never so distinct.

For **syphilitic** disease of the liver, see p. 272

New Growths of the Liver.

The only benign tumours of the liver which are at all common are *angeiomata* (p. 292) and *adenomata* (p. 318). The latter tend

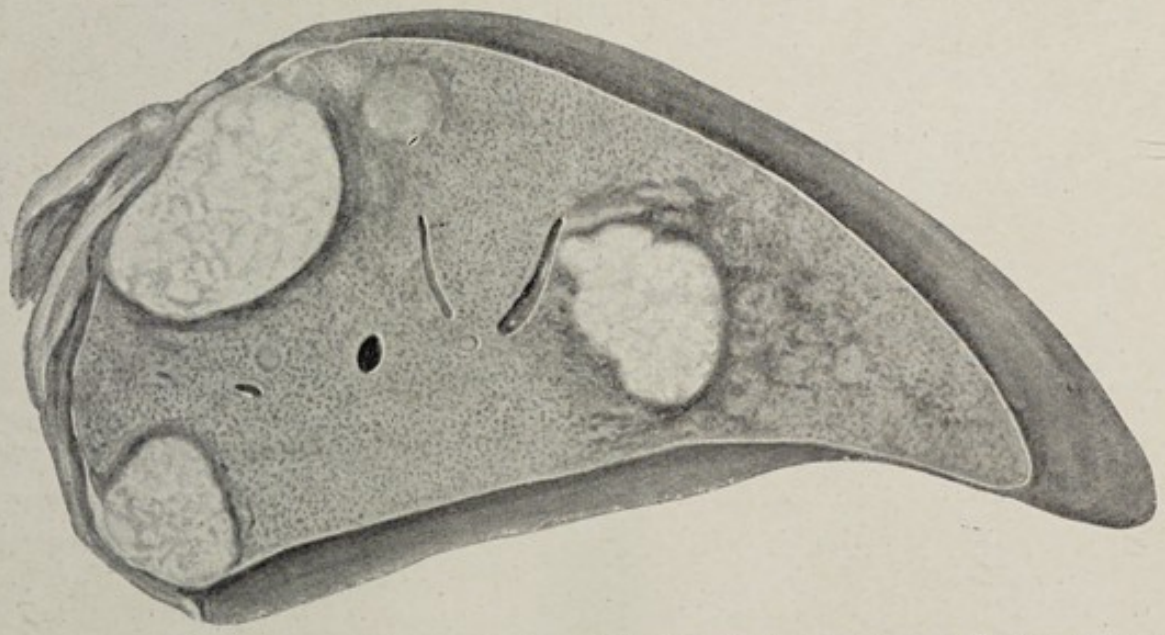


FIG. 199.—SECONDARY CARCINOMA OF THE LIVER. (FROM A SPECIMEN IN C. C. H. MUSEUM.)

to occur particularly in cirrhotic livers, but it is uncertain whether the structures described are really neoplasms.

Primary malignant tumours of the liver are extremely rare, but

secondary metastases are very common, especially in the case of carcinomata, and particularly when the primary growth is situated in some part of the gastro-intestinal canal. These secondary carcinomatous deposits are usually multiple, and are scattered throughout the organ. When situated near the surface they tend to project from it. Later, the centre of the nodule of growth frequently undergoes necrosis, softens, and becomes depressed or umbilicated (Fig. 199).

Cysts of the Liver.

The liver is one of the commonest situations for the occurrence of a hydatid cyst (Fig. 200). The structure and mode of formation of these cysts have already been described (p. 87).

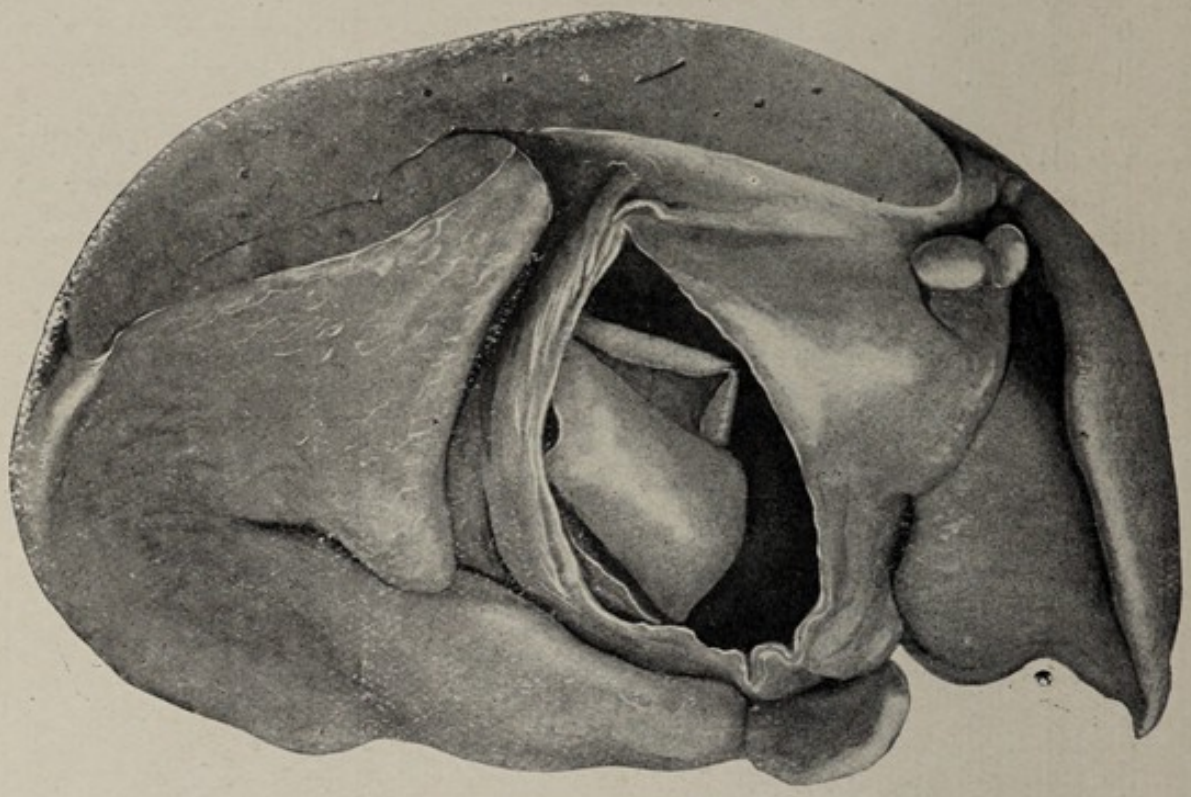


FIG. 200.—HYDATID CYST OF LIVER. (FROM A SPECIMEN IN C. C. H. MUSEUM.)

The thin layer of liver tissue covering the cyst and the cyst-wall itself have been partially excised, and a large endocyst is seen, partially collapsed, within the cavity.

Single "simple" cysts may be found, and occasionally multiple cysts of the liver are associated with congenital cystic disease of the kidneys.

Gall-Stones.

Gall-stones are concretions, generally formed during late adult life, either in the hepatic ducts or in the gall-bladder. In size they range from mere gritty particles to masses as large as pigeons' eggs.

The number found in a single gall-bladder varies from one stone to several thousands. In colour they vary from a pearly-white to a greenish-black. Occasionally, when distinctly crystalline to the naked eye, they may be pale yellowish-green and semi-transparent. As a rule, they can be easily crushed between the fingers, and are so light that when dried they float on water. They are generally quadrilateral or prismatic in shape, with some sides flattened, owing to mutual pressure while the stones are still soft. These flattened surfaces are termed *facets*. Single stones are never faceted; neither are very small ones, as they can roll easily on one another without exerting any marked pressure. Facets occur chiefly in calculi of

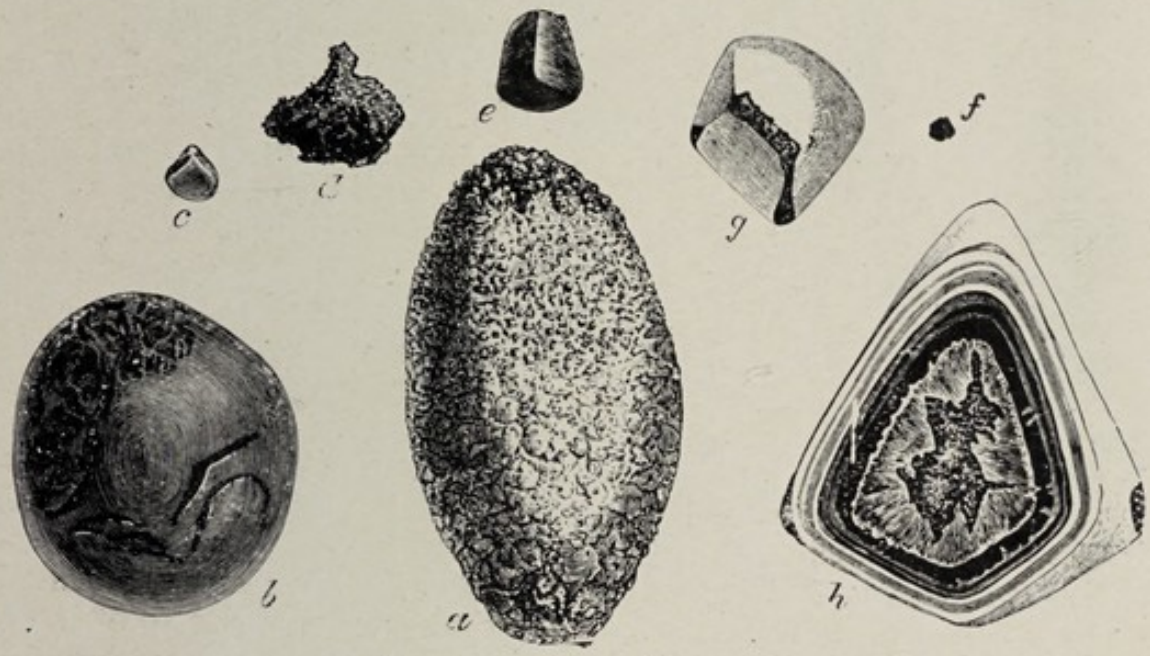


FIG. 201.—GALL-STONES.

a, *b* are gall-stones formed in each case singly; *a* is composed of almost pure cholesterin; *b* consists of bilirubin-calcium and cholesterin; *c*, *d*, *e*, *f* are examples of various forms occurring in different cases, and in each instance in large numbers; *g*, ten similar stones were removed from a gall-bladder; the white portions of the outer layer are composed of cholesterin, the dark edges of bilirubin-calcium; *h* is a magnified view of one of the other stones from the same case, showing the origin of the central cavity with its crystallised contents and the various added layers.

medium size, if more than two or three be present; they are not due to erosion after the stones are formed, as, on section, the same laminæ can be traced all round the stone (Fig. 201).

When carefully examined, a gall-stone is found to consist of a soft nucleus and a harder laminated crust. Within the nucleus there is often a cavity. Both nucleus and crust may be of the same composition. Cholesterin and bilirubin-calcium are the most important constituents. Crystalline stones consist mainly of the former, and the largest calculi are generally made up of pure cholesterin; but a stone consisting mostly of this substance is by no means always crystalline.

PATHOLOGY.—It was formerly supposed that foreign bodies acted as the nuclei of gall-stones, and that cholesterin and other biliary constituents were deposited from concentrated or otherwise altered bile. It has, however, been shown experimentally that the introduction of foreign bodies into the gall-bladders of dogs does not cause any such precipitation, and that if gall-stones themselves are introduced into a normal gall-bladder they dissolve and disappear. It has also been shown that an important source of cholesterin is an extensive destruction of the lining epithelium, and that the precipitation of bilirubin-calcium is induced by the presence of albumen in the bile. From these and other facts it is believed that a mildly-infective catarrh of the lining membrane of the ducts is the first stage in the production of calculi. Such catarrh can be produced experimentally by the introduction into the gall-bladder of attenuated cultures of the colon bacillus, of the typhoid bacillus, and of the ordinary pyogenic cocci. The catarrh is accompanied by the desquamation and disintegration of the epithelium, and by the exudation of albuminous fluid. Bilirubin-calcium next separates out, especially from stagnant bile, and, with the desquamated epithelium, forms a nucleus round which a shell of more bilirubin-calcium is deposited. As the epithelium disappears, a central cavity is left which, later on, is generally filled up with cholesterin derived from the disintegrated epithelium. Further layers are subsequently deposited, but always together with albuminous matter; for if the salts be dissolved out artificially, a complete organic framework remains.

EFFECTS.—A gall-stone may block the duct in which it is formed, or to which it may be carried, and in that way give rise to obstructive jaundice. By the irritation of its presence it may produce inflammation and ulceration of the wall of the duct or bladder, and, if pyogenic organisms be present, give rise to a suppurative cholecystitis. From the gall-bladder, or from the ducts, calculi may escape into the duodenum. In some instances, a stone in the gall-bladder, or in the common duct near its entrance into the intestine, may produce inflammatory adhesions of the neighbouring parts and subsequent ulceration. By this means a stone too large to pass through the orifice of the duct is enabled to make its way into the bowel, and lower down, where the lumen of the intestine is smallest, to give rise even to intestinal obstruction. Carcinoma may arise as the result of the irritation caused by gall-stones.

AFFECTIONS OF THE PANCREAS.

Disorders of the pancreas arise for the most part from the entrance of pathogenic organisms into its ducts. In cases of invasion by very virulent germs the whole organ, or large parts of it, may undergo **necrosis,** or an acute interstitial inflammation may ensue. Less virulent infection results in a process of chronic **fibrosis.** Two

varieties of this have been distinguished by Opie: (1) *Interlobular* fibrosis, in which the fibrous tissue is irregularly distributed between the lobules of the gland; and (2) an *Interacinar* form, in which it is uniformly distributed, passing between the individual acini (Fig. 202). The pancreas is generally shrunken, and its cells atrophied, in both these conditions; but occasionally fibrosis may be associated with great enlargement of the gland. The resemblance of these fibrotic

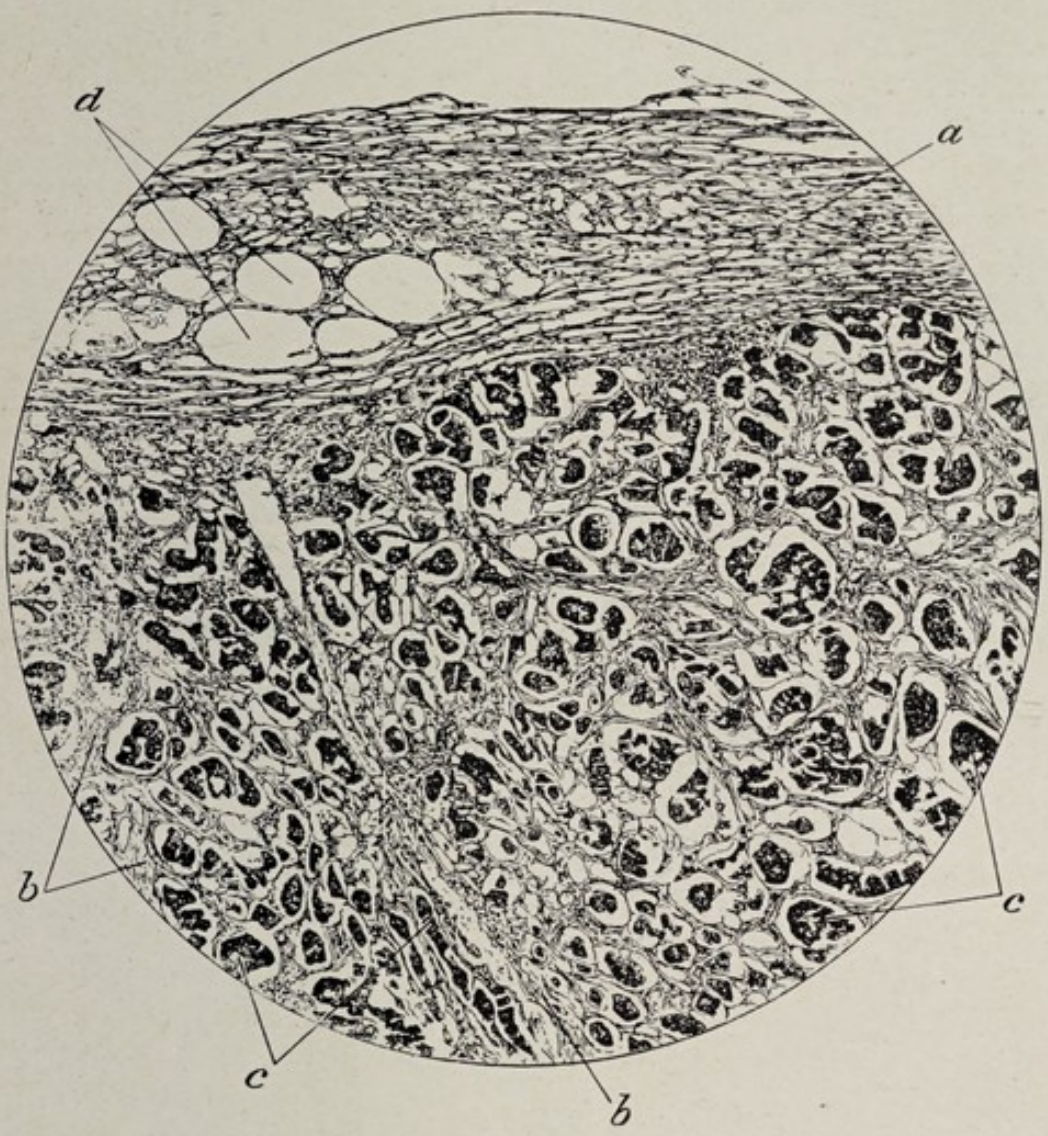


FIG. 202.—INTERACINAR FIBROSIS OF PANCREAS.

a, thickened capsule of gland; *b*, strands of fibrous tissue running between the groups of glandular cells (*c*); *d*, adipose tissue.

conditions to the different varieties of cirrhosis of the liver is very marked. Some writers attribute the causation of pancreatic fibrosis to the action of gall-stones. (See above.) Not improbably the same infective cause may be responsible for both the concretion and the changes in the gland.

The pancreas and the tissues round it are often the seats of **hæmorrhage,** due apparently to the destructive action of trypsin, which causes rupture of the vascular walls, as well as necrosis of the

glandular tissue. **Calculi** may also form in its ducts; and these, by blocking the ducts, or by obstructing the opening of the ampulla of Vater into the duodenum, and thus causing the regurgitation of bile into the pancreas, may give rise to fibrosis of the gland or to the formation of **cysts.** **Fatty degeneration** is liable to occur in this organ, and **atrophy** of the cells is also described. The latter is often accompanied by some secondary fibrosis. The vessels in it may be affected by **amyloid** change. **Carcinoma** as a primary disease is not very uncommon in the pancreas. The questions of the relation of the pancreas to fat-necrosis and to diabetes mellitus are discussed elsewhere. (See p. 23, and Chapter XXII.)

CHAPTER XXXII

AFFECTIONS OF THE KIDNEY

Suppurative Nephritis.

SUPPURATIVE nephritis results from the transmission to the kidneys of pyogenic bacteria from some primary focus. It may occur (1) as one of the lesions in pyæmia; or (2) may be associated with some pyogenic inflammation of the lower urinary passages. In pyæmia, the infective organisms are transmitted by the bloodvessels; in the other cases they may reach the kidney by direct infection from the lower urinary passages.

As, however, regurgitation of urine from the bladder into the ureter does not occur, bacteria often thrive in the former organ for considerable periods without infecting the ureter and kidney. When infection does take place, it is usually the result of the transmission of bacteria by the lymphatics of the ureters.

1. The abscesses met with in the kidney, as the result of pyæmia, are confined principally to the cortex, and resemble pyæmic abscesses in other organs. They are usually multiple, and are often surrounded by a narrow zone of red hyperæmic tissue. They usually originate around the glomeruli, in the capillary tufts of which the organisms have been arrested. Their size varies from a mere point to that of a filbert.

2. When the suppurative inflammation is due to infection from the lower urinary passages (*acute surgical kidney, acute consecutive nephritis*), the pelvis of the kidney is generally acutely inflamed, and many of the convoluted tubes are crammed with micrococci. These seem to ascend from the pelvis along the tubes, distending them, and giving rise, along their line of growth, to cloudy swelling, coagulation-necrosis, multiple small abscesses, and infiltration of the interstitial tissue with leucocytes (Fig. 203). The urine in such cases contains pus cells and pyogenic organisms, usually *B. coli*.

It is believed by some authorities that infection of the pelvis of the kidney may be the primary lesion in many cases of acute pyelonephritis.

The cortex of such a kidney is thickened, soft, and pale, as compared with the deep red pyramids; its consistence, however, will

vary with the presence or absence of chronic interstitial changes. The capsule strips easily, often tearing the substance a little, and exposing on the surface groups of yellow spots. These yellow dots are never larger than a split pea; each is surrounded by a red zone,

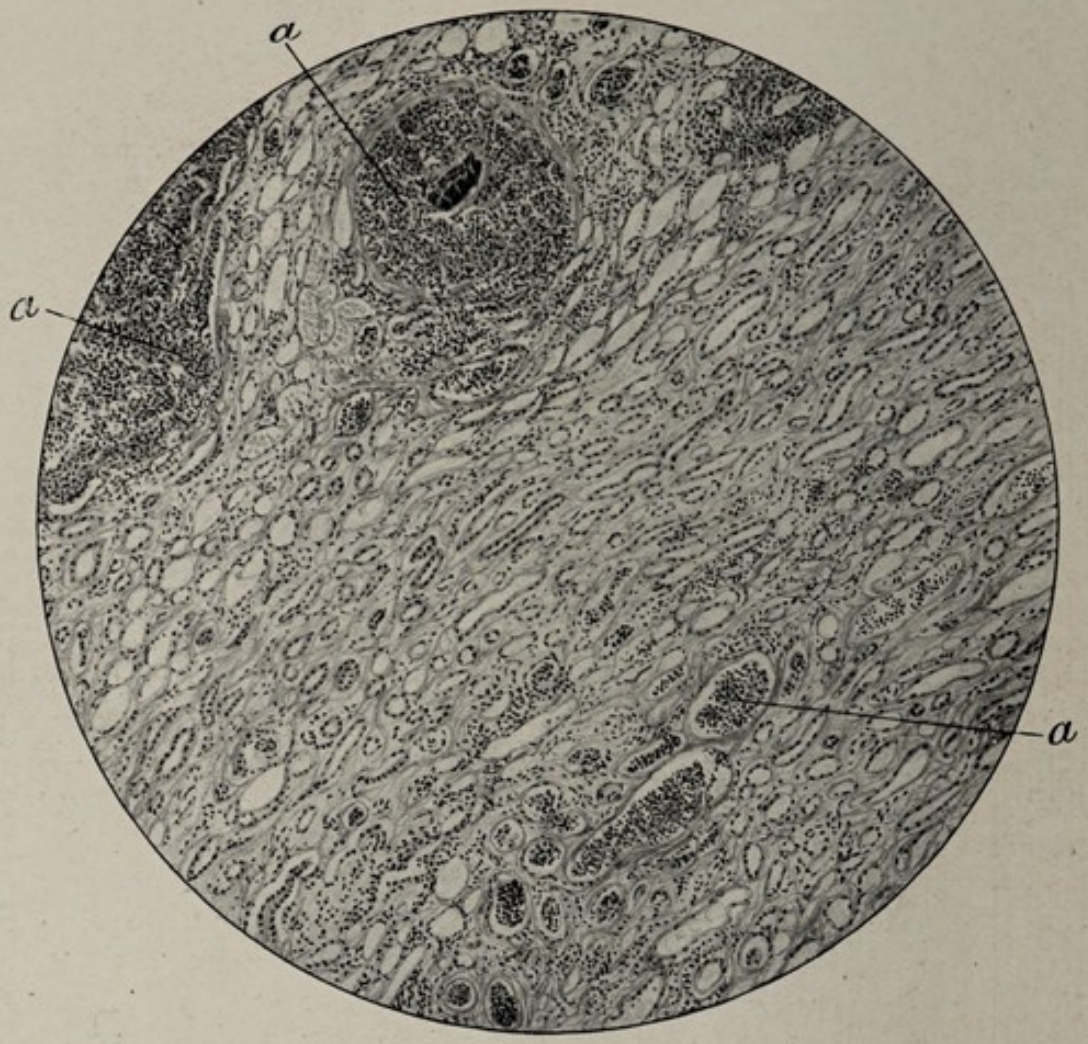


FIG. 203.—SURGICAL KIDNEY (SUPPURATIVE NEPHRITIS). (× 79.)
a, *a*, *a*, minute abscesses in the kidney-substance.

and many of them contain a drop of pus. On section, yellow streaks are often seen extending from the superficial lesions into the cortex: others exist in the pyramids.

Tuberculosis of the kidney has already been considered (p. 250).

Hydronephrosis.

Chronic changes in the kidney result from diseases causing obstruction in the lower urinary passages. They occur in association with renal and vesical calculi, obstructed ureter, urethral stricture, and enlargement of the prostate.

When the flow of urine from the ureter into the bladder is permanently impaired by any form of obstruction, the pressure of the

secretion gradually dilates the ureter, the pelvis, and the pyramids, and, finally, the tubules even to their closed ends (*hydronephrosis*), leading to atrophy of the tubular epithelium and increase and induration of the interstitial tissue. When the obstruction to the outflow is confined to *one* kidney, that organ is alone affected. It should be noted that for the production of hydronephrosis the obstruction must be incomplete or intermittent. Complete and permanent obstruction does not lead to this condition.

The overgrowth of the interstitial tissue is exceedingly irregular in distribution and amount. It occurs both in the pyramids and cortex (*chronic consecutive nephritis*). The tubules are in some parts found blocked with epithelium, whilst in others they are wasted or obliterated. Owing to these changes, the kidneys are somewhat enlarged, the capsule is slightly adherent, the cut surface is paler than natural, and the consistence of the organs is abnormally tough. The walls of the small arteries are not thickened. As the process advances, the pyramidal portions gradually become absorbed, the absorption commencing at the papillæ and extending, until ultimately not only the pyramids but also the thickened cortex may disappear, and the kidney be converted into a large cyst divided into sacculi by fibrous septa (*hydronephrosis*). If, on the other hand, the urinary obstruction be removed, the processes of inflammation and absorption may cease, and the indurated kidney will then become contracted.

Bradford has shown that if hydronephrosis be artificially induced, atrophy of the tubules and shrinking of the remaining epithelium occur even when the obstruction is removed and the kidney completely drained.

Pyonephrosis.

The same conditions which lead to hydronephrosis will, if infection with pyogenic organisms be superadded, lead to pyonephrosis. In this condition, the distended pelvis and calices contain pus, which is sometimes fluid and serous, but in long-standing cases is often converted into a semi-solid caseous material closely resembling that found in tuberculosis lesions.

Parenchymatous Nephritis.

Parenchymatous nephritis includes those forms of inflammation of the kidneys in which the secreting tissues are primarily affected. The damage is caused by substances reaching the kidneys by way of the blood-stream. While in ordinary metabolism the waste products escape by the glomeruli or are excreted by the tubular epithelium, without any injury to the structures concerned, the substances giving rise to parenchymatous nephritis cause damage to the tissues in the process of their excretion, and in this way lead to changes in the glomeruli or in the renal tubules, or in both of

these. These changes, supplemented by more or less inflammatory reaction, give rise to the morbid appearances characteristic of the disease.

The actual substances producing these results are, to a limited extent, known. Thus (1) cantharides, turpentine, oxalic acid, compounds of phosphorus, and salts of mercury and arsenic are recognised causes. (2) Bacterial toxines, and the products of the disordered metabolism occurring in diseases, the bacterial origin of which cannot yet be positively affirmed, form another important group, including, among others, diphtheria, scarlatina, typhoid fever, acute pneumonia, and septicæmia. In some of these the actual organisms reach the kidneys and produce local lesions there. (3) Other diseases, such as gout and diabetes, accompanied by grave disorders of metabolism, also act as causes of parenchymatous nephritis. (4) Many instances of the disease occur apart from the foregoing causes. Some cases occur in persons suffering from alcoholic excess, from prolonged exposure to cold and wet, from extreme exhaustion, or from any combination of these. To these cases no definite causation can be assigned, but in most of them the existence of disordered metabolism is highly probable.

The altered composition of the urine furnishes the first evidence of the damage to the kidneys. The injured glomeruli permit the escape of serum-albumen, serum-globulin, and, in severe cases, of blood. The necrosed or degenerating tubular epithelium becomes entangled in the blood or albuminous fluid thus secreted, and forms moulds of the renal tubules. These block the tubules and prevent the escape of urine, while portions of them appear in that secretion as cylindrical *casts*. The amount of urine and of urea secreted is diminished, and œdema of the loose connective tissue occurs. That these results are not due solely to the diminished amount of renal tissue available for secretion is probable from the experiments of Bradford, who has shown that the effect of excising large portions (two-thirds of the total amount) of kidney-substance is to increase the quantity of urine and of excreted urea, although at the same time the amount of urea produced in the body is so great that it accumulates in the blood. This result may be due, as Bradford hints, to the cessation of the action of an internal secretion normally supplied by the kidney.

Varieties.—Parenchymatous nephritis is generally divided into two varieties—*glomerular nephritis* and *tubular nephritis*. In the glomerular variety the glomeruli are the principal seats of the disease, and may be the only parts affected. In the tubular variety the tubules are affected equally with, and sometimes even more than, the glomeruli. Tubular nephritis is subdivided into acute and chronic varieties.

Morbid Anatomy.—In the **glomerular** form—of which the most typical instances occur in scarlatina—the *naked-eye appearances* may be absolutely normal, though occasionally the glomeruli stand out as sharply-defined grey points.

Microscopically, the changes are often confined to the Malpighian bodies. The intracapsular spaces are found to contain a number of desquamated cells. Some of these are derived from the cells which once covered the vascular tuft and lined the capsule, which may have thus lost all its epithelium. Mixed with these may be a few leucocytes and a varying number of red corpuscles. In addition to the cellular elements, there is usually an exudation of albuminous fluid, and this may be so great that the vascular tuft is compressed and the circulation through it thereby impeded. Some of the capillary loops are distended, and contain an unusually large proportion of leucocytes, which not infrequently show signs of degeneration, while the endothelial cells are much swollen and often proliferated. In some cases the intima of the minute arteries, especially of those supplying the glomeruli, undergoes hyaline degeneration, with consequent narrowing of the lumen of the affected vessels. The walls of the smaller arteries may also be thickened. Cloudy swelling of the epithelium in the convoluted tubes may be superadded.

In the most acute cases, a cellular infiltration of the intertubular connective tissue may occur, with marked degeneration of the epithelium and a crowding of the tubes with leucocytes. The cellular infiltration is especially prone to occur in the neighbourhood of the interlobular and stellate veins, but these cases closely approximate to the tubular variety.

In **tubular nephritis** the kidneys are always larger than normal, and may be increased to twice their natural size. The enlargement is due partly to hyperæmia, partly to distension of the tubules, and partly, in some cases, to œdema of the intertubular tissue. The capsule separates readily, exposing a smooth and often hyperæmic surface. The consistence is diminished, and the substance soft and friable. On making a longitudinal section, the increase in the size of the organ is seen to be mainly due to swelling of the cortical portion. This may be pale or dark, but is generally mottled—reddish patches being mingled with those of an opaque white or buff colour. The differences in colour depend upon the proportion which the hyperæmia and hæmorrhage, on the one hand, bear to the accumulation of degenerated tubular epithelium, on the other. In the earliest stages of the most acute forms of the disease the cortex is generally redder than natural, but it soon becomes pale and opaque. This is owing to the progressive necrosis, degeneration and accumulation of the tubular epithelium. When hæmorrhage has occurred into Bowman's capsules, the Malpighian bodies stand out as prominent red points. The pyramids in the medulla are of a deep red colour, contrasting strongly with the pale opaque cortex.

Microscopically, the glomeruli are found to have undergone much the same changes as in the previous variety. Tubular nephritis is, however, generally more intense; the hyperæmia is therefore more marked, and hæmorrhage into Bowman's capsule and into the

tubules is more frequent (Fig. 204). In the kidneys of persons dying in an early stage of the disease, large numbers of red corpuscles may accordingly be seen in the Malpighian bodies, pushing to one side the vascular tufts, as well as in the tubules, which may be distended.

The tubules show marked changes. These are generally most prominent in the convoluted tubes, although they may be almost as advanced in the straight tubes. In the most acute cases many of the epithelial cells are necrosed and their nuclei remain unstained (Fig. 204). More frequently, especially when the onset of the disease is less intense, the cells undergo cloudy swelling and fatty

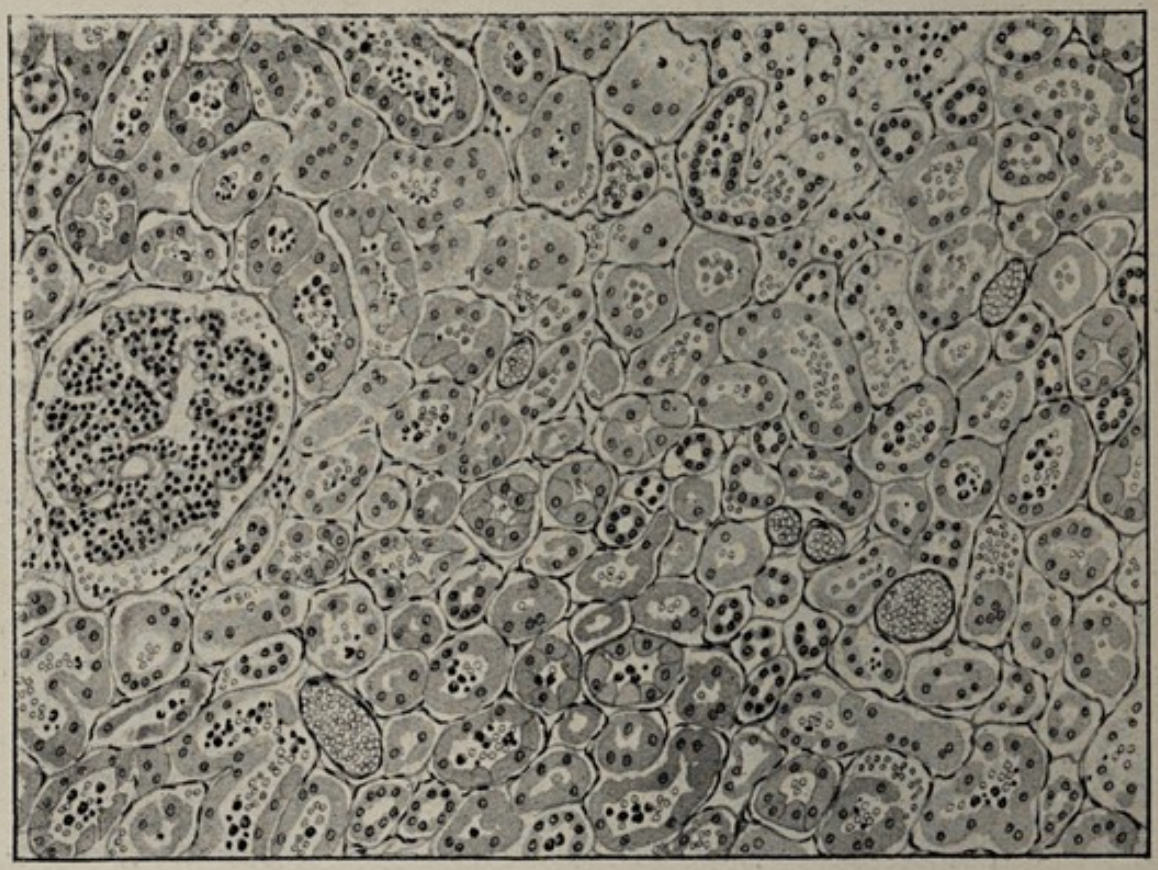


FIG. 204.—ACUTE TUBULAR NEPHRITIS. (× 79.)

degeneration. The dead and damaged epithelium becomes detached and collects in the tubules.

The coagulable exudation, which now enters the tubules from the Malpighian bodies, forms the basis of the numerous **casts** which block the tubules and give rise to a scanty deposit in the urine. The basis or matrix of these casts is transparent, and when no other material is imbedded in them they are known as *hyaline casts*. Casts containing blood, desquamated epithelium, leucocytes, granular débris, or fatty molecules, are named according to their respective contents.

Recovery.—At this stage the changes already described may subside, and with the exception of some desquamation of damaged

epithelium, no further degenerative changes take place in the kidneys. Many of the surviving epithelial cells proliferate, but in all probability the repair is never absolutely complete. Thus the organs return to about their normal condition, although, for some weeks longer, casts and albumen may be passed in the urine.

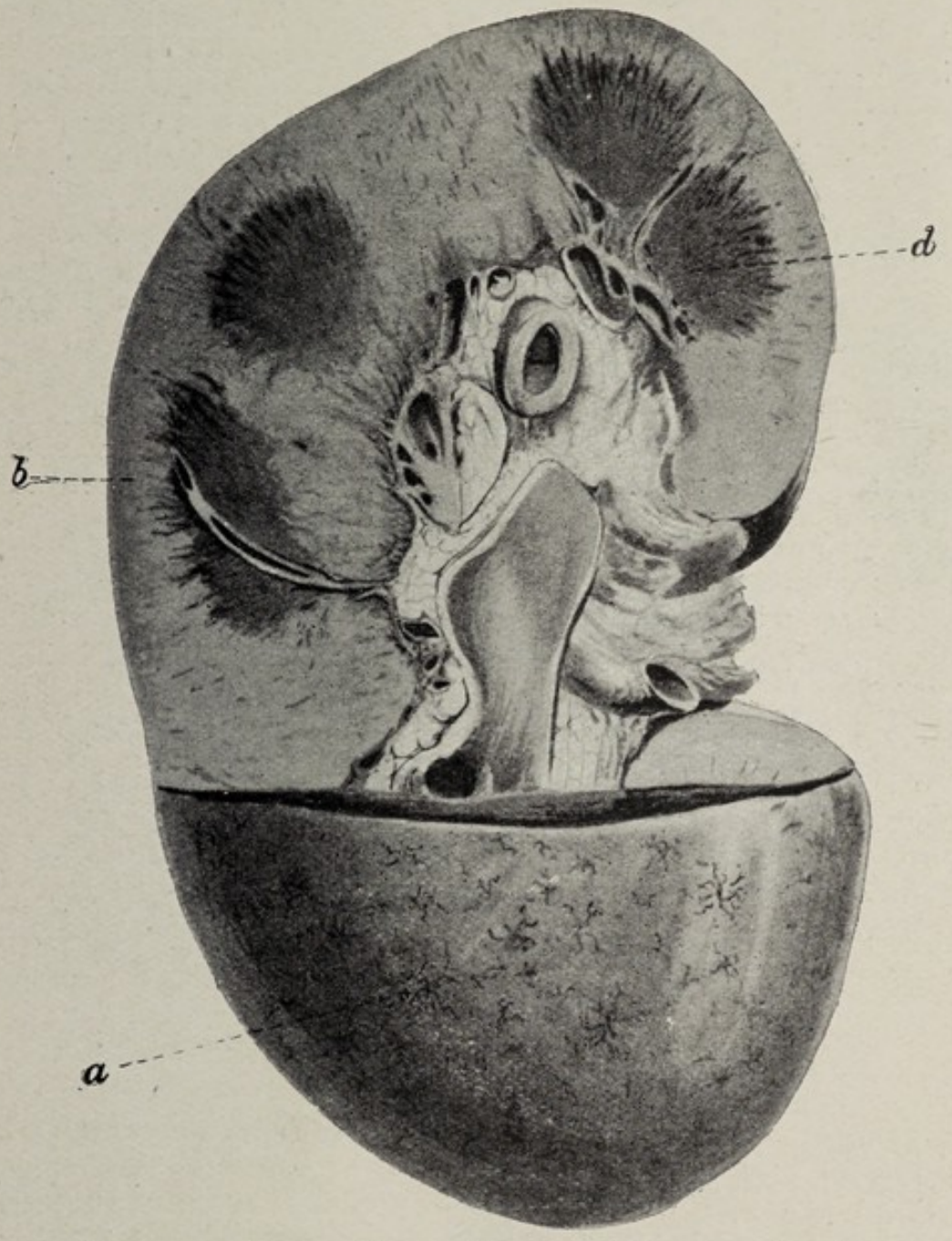


FIG. 205.—LARGE WHITE KIDNEY. (NATURAL SIZE.)
a, smooth surface with venules; *b*, pale and thickened cortex; *d*, dark pyramids.

Chronic Tubular Nephritis.—This condition may follow on an attack of acute nephritis, or may apparently arise independently. Its ætiology is uncertain, but, in cases which are not preceded by acute lesions, syphilis, alcoholism, and exposure seem to play an important rôle. The kidney is enlarged, and this enlargement is mainly

due to an increase in the thickness of the cortex. It is pale in colour (*large white kidney*) (Fig. 205), and often presents yellowish streaks. In general the surface is smooth and the capsule strips readily, but this is not always the case, though the surface is never so granular, nor the capsule so adherent as in the chronic interstitial form.

Microscopically, the main change is found in the epithelium of the convoluted tubules, which is swollen, frequently desquamating, and shows marked fatty degeneration. The changes in the interstitial tissue vary greatly in different specimens. In the most typical form the interstitial changes are slight, and consist of some degree of œdema and infiltration with mononuclear leucocytes.

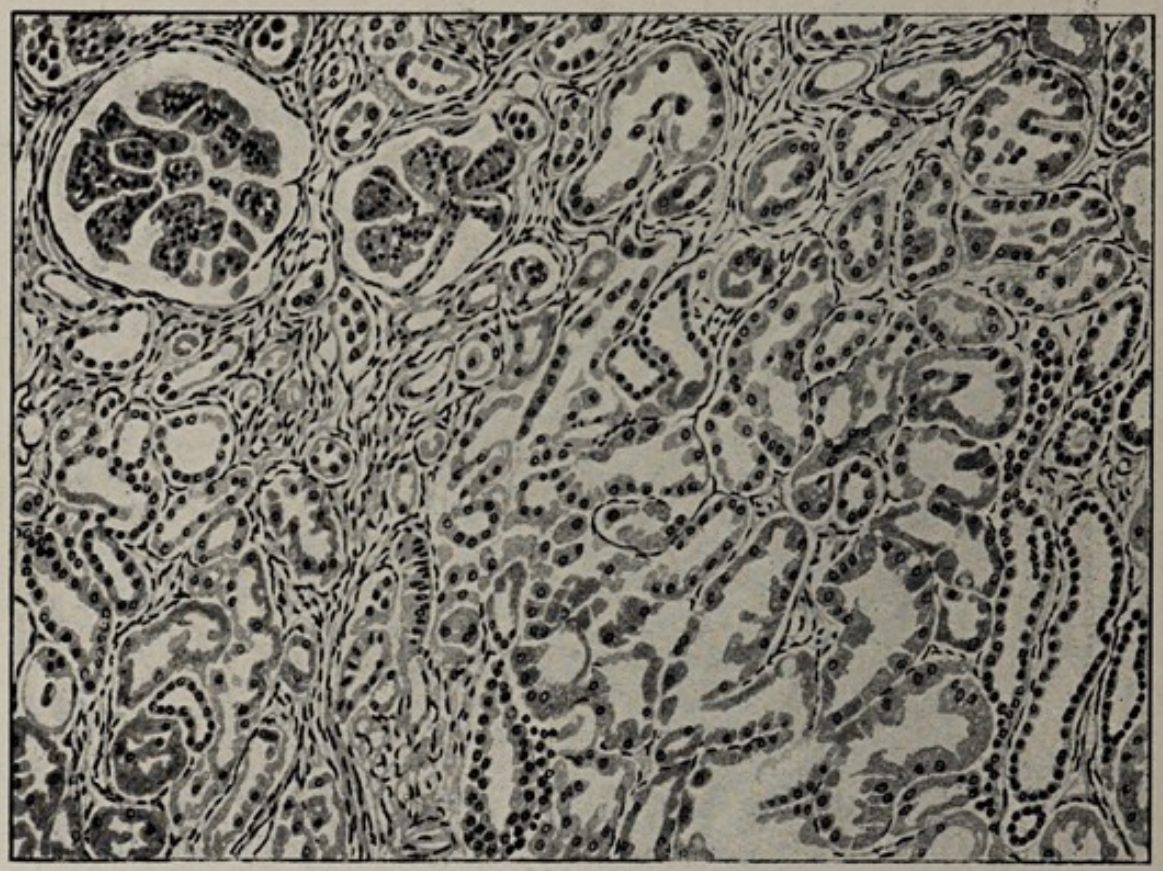


FIG. 206.—CHRONIC TUBULAR NEPHRITIS. (× 79.)

It is more usual, however, especially in long-standing cases, to find some degree of proliferation of the interstitial connective tissue (Fig. 206), and this may in some cases be considerable.

Combined with this there is often some degree of thickening of Bowman's capsule, though here again the changes are never so intense as in the interstitial form.

In cases which persist over very long periods, this increase in connective tissue may lead to true fibrosis with contraction, and the form of interstitial nephritis known as the *small white kidney* is then produced.

Chronic Interstitial Nephritis.

It has already been shown that an increase in the interstitial tissue of the kidney occurs in the more advanced stages of tubular

(p. 516) and of chronic consecutive nephritis (p. 511). But this change is especially prominent in that most chronic of all varieties of disease of the kidneys known as *contracted kidney, granular kidney, cirrhosis of the kidney, gouty kidney,* or *chronic interstitial nephritis.* In this disease, the development of fibrous tissue is associated with atrophy of the glomeruli and tubules, and changes in the walls of the arteries. Clinically, the disease is characterised by an insidious onset, increased arterial tension, polyuria, hyper-

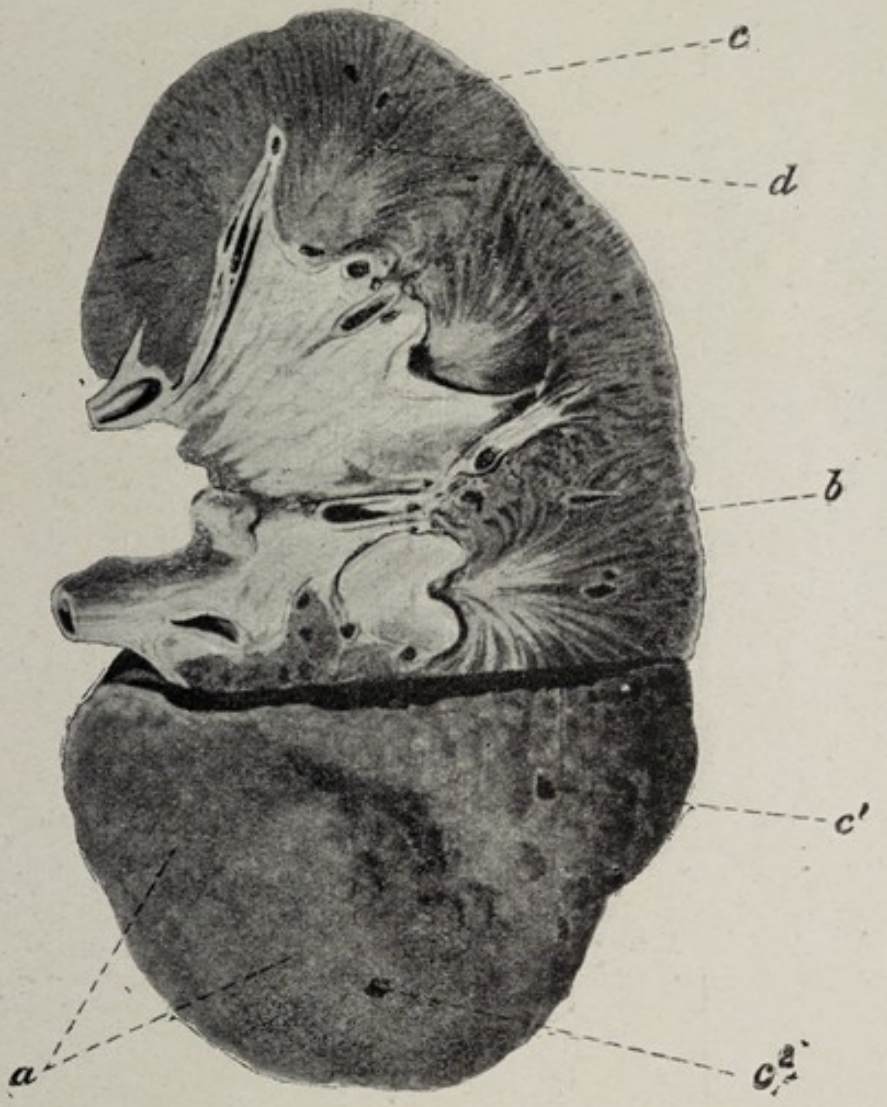


FIG. 207.—GRANULAR CONTRACTED KIDNEY. (NATURAL SIZE.)
a, rough, granular surface; *b*, dark narrow cortex; *c*, c^1, c^2, cysts; *d*, pyramids.

trophy of the left ventricle of the heart, and degenerative changes in other tissues. Albuminuria, if present, is slight, and dropsy is said to be absent, except as a result of cardiac failure. (See p. 353.) The disease is most frequent in the declining period of life. It is often associated with gout, chronic lead-poisoning, overindulgence in alcohol, and, perhaps more often than is generally believed, with syphilis.

MORBID ANATOMY.—In a well-marked case (Fig. 207), the kidney is much diminished in size. Its capsule is thick and very adherent

it cannot be removed without tearing the substance. The surface is coarsely granular and of a reddish-grey tint. On section, the colour of both pyramids and cortex is seen to resemble closely that of the surface, the distinction between cortex and pyramid being often by no means clear. The cortex is, however, more mottled, and small patches can sometimes be made out corresponding with the depressions between the minute nodules on the surface. Moreover, it is much narrower and tougher than normal; and small

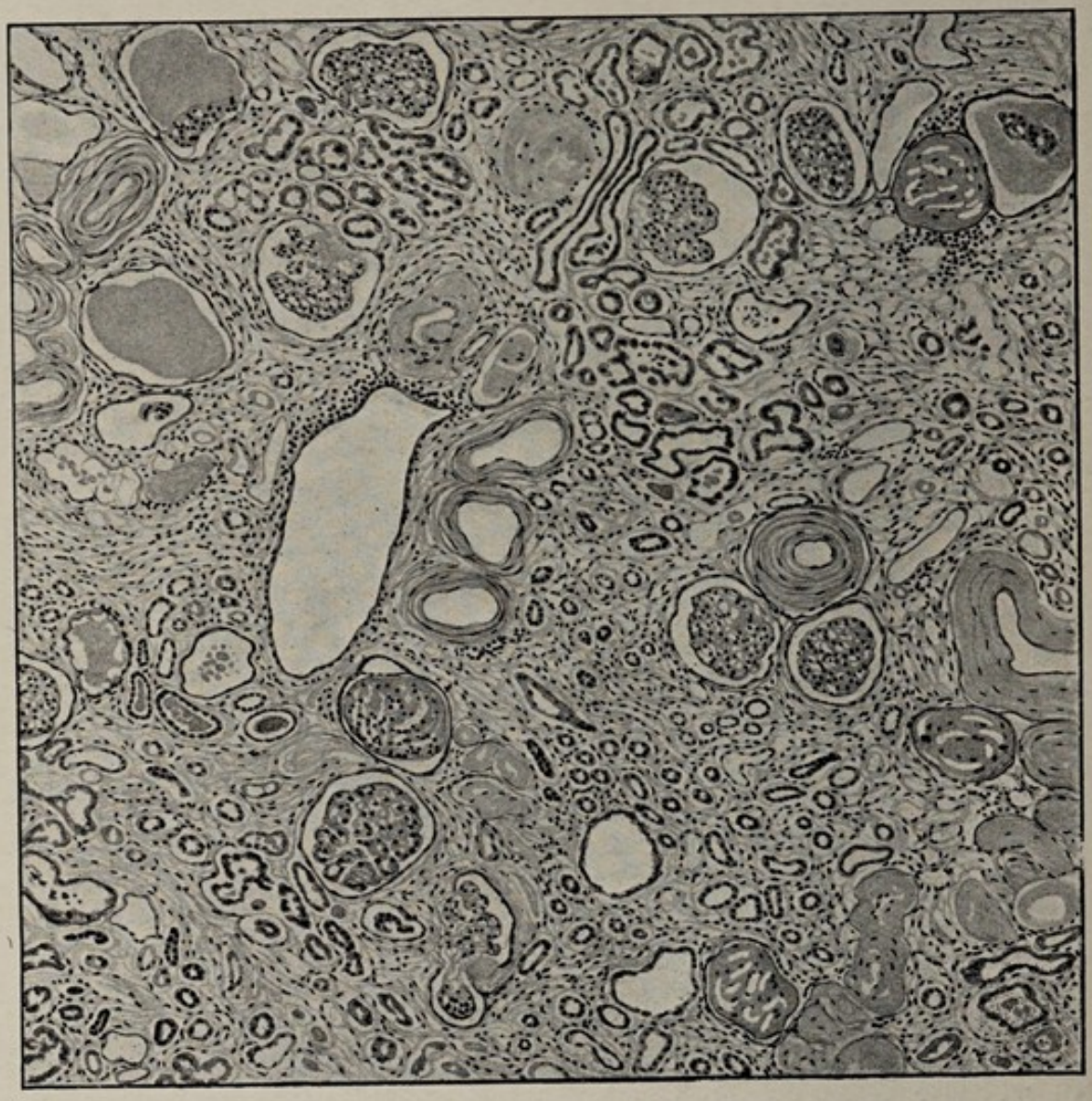


FIG. 208.—CHRONIC INTERSTITIAL NEPHRITIS. (× 79.)

cysts are often found, especially on its surface. Calcareous deposits may occasionally be seen as white streaks among the tubes of the pyramids. In the earlier stages of the disease all these changes will be much less marked.

Microscopically there is found to be great thickening of Bowman's capsule, and in many cases the glomerulus is completely obliterated (Fig. 208). There is a marked increase in the amount of interstitial tissue, but the changes are by no means uniformly distributed. In

many parts, the tubes are diminished in size or completely obliterated; in others, they are dilated and filled with degenerated epithelial products. Their walls are often thickened. The intertubular tissue is increased throughout, but by no means uniformly, so that not infrequently the cortex may be traversed by irregularly-disposed fibrous bands. The new tissue may be largely cellular or densely fibrous. The atrophy of the Malpighian bodies and adjoining tubes may be out of proportion to the amount of interstitial overgrowth.

The walls of the interlobular arteries and of the smaller cortical vessels are much thickened. Sometimes the external coat is principally involved, and appears to be continuous with the new intertubular tissue. Sometimes the middle coat is thickened. Johnson attributed this to hypertrophy of the circular muscular fibres. Recent observers emphasise the frequency with which the intima is involved; the endarteritis thus produced most closely resembles that form already described as syphilitic (p. 271). The changes in the arteries are by no means limited to those of the kidneys, but are found in the arteries of almost any part of the body.

In some cases there is marked thickening of the arterial walls and atrophy of the glomeruli and tubules, but no new fibrous tissue (*arterio-sclerotic kidney*, Ziegler).

PATHOLOGY.—The relationship which these changes bear to one another is but imperfectly known. It is by no means certain that the relationship is, in all cases, the same. Two explanations have been suggested. (1) According to the first and older view, the changes are due to the action of some unknown irritant, conveyed by the blood to the kidneys, which causes *proliferation of the connective tissue* in the immediate neighbourhood of the vessels. According to this explanation, a granular kidney is analogous to a cirrhotic liver. The thickening in the vessels and the increase in the intertubular tissue are the earliest, and practically simultaneous, changes; while the atrophy of the secreting tissue is due to the results of the contraction of the chronic inflammatory tissue.

(2) According to another view, this order of events is reversed, and *atrophy of the secreting cells* is the primary affection. This atrophy may be due to overwork, to the premature exhaustion of their inherited vital capacity, to some toxic disturbance, or to defective blood-supply arising from arterio-sclerosis or anæmia. The changes in the bloodvessels and the increase in the interstitial tissue are secondary. The latter is in many cases more apparent than real, being partly due to mere condensation of the previously existing, but more widely separated tissue. As was noted in regard to the cirrhotic liver (p. 501), so in the case of the granular kidney, it is possible that the same irritant may cause both degeneration of the secreting cells and also proliferation of the connective tissue.

The subsequent contraction of the new tissue necessarily constricts many tubules. The arrest of the flow of urine, in those supplied by glomeruli whose vessels are still permeable, will lead

to the formation of small *retention-cysts*, such as have been previously described.

Sometimes, as stated above, the arterial changes are more marked than the atrophy of the glomeruli and tubules. In these cases the endarteritis, by diminishing the lumen and hence the blood-supply, is possibly responsible for the production of the atrophy (*arterio-sclerotic kidney*). Cohnheim held that the supply of blood to the kidneys was regulated by some reflex mechanism according to the amount which it contained of those substances which the kidneys normally eliminate (*e.g.*, urea). Atrophy of part of the excretory apparatus, by throwing more work on the remainder, might not improbably lead to an increase in the percentage of these substances in the blood. Now, the only way in which the more free elimination of these by the kidneys can be brought about is by the increased action of the left ventricle and a simultaneous increase in the resistance in the arterioles of other parts. By this means a larger amount of blood may be supplied to the kidneys, and their excretory functions thereby assisted. It is possible, however, that toxic substances, which should be eliminated by the kidneys, cause spasm of the arterioles, and thus raise the pressure in the arteries. The heart has to work harder to overcome this, and hypertrophy of the left ventricle results. This increased cardiac action still further raises the tension in the vessels. Thickening of the vessels results from the continued action of the ætiological factors and from the increased strain produced by the hypertrophy of the heart.

The enlargement of the left ventricle is a true hypertrophy, though it is often combined with a small amount of chronic myocarditis.

Effects.—The phenomena of *uræmia*, resulting from defective action of the kidneys, have been discussed in Chapter XXII. (p. 379).

In some forms of renal disease excretion of salts is defective, and the characteristic *œdema* has been attributed to accumulation of sodium chloride in the tissues and its osmotic effect upon the blood in the capillaries. The excretion of water is, however, also defective in acute affections, and a condition of hydræmia may result, increasing the tendency to escape of fluid into the tissues. The appearance of albumen in the urine is due to damage to the renal epithelium which normally prevents the passage of this substance from the blood.

Urinary Calculi.

Any of the passages or cavities of the urinary tract lined with epithelium may be the seat of hard concretions of mineral matter, known as calculi. The two principal seats of these bodies are (1) *the pelvis and calices of the kidney*, and (2) *the urinary bladder*—positions in which stagnation of urine is most liable to occur.

In *size* calculi vary from mere particles of grit to masses more than an inch in diameter. When calculi are small, they are frequently multiple; when large, they are usually single. Small calculi are often irregular in *shape*, though they tend to assume gradually the

special forms obtaining among the larger varieties. The shape of a large calculus varies with the situation in which it is formed. Thus a large stone in the pelvis of the kidney generally possesses irregular projections, corresponding with the openings of the calices (*coral calculi*); while a calculus in the bladder is generally round or oval. On *section*, a calculus is seen to be made up of a central nucleus and a crust composed of a large number of thin concentric laminæ. The colour, hardness, surface, and sectional appearance of a calculus depends almost entirely upon its composition (Fig. 209).

The three most important groups of substances found in calculi are (1) uric acid and its salts, (2) calcic oxalate, and (3) calcic and ammonio-magnesic phosphates; although other substances, such as calcic carbonate and cystin, are occasionally met with.

(1) The uric-acid calculus is of a dirty fawn colour; its consistence is hard, and its surface smooth or slightly granular. (2) The calcic-oxalate calculus is dull greyish-brown, intensely hard, and coarsely granular. (3) A phosphatic calculus is white, friable, and smooth.

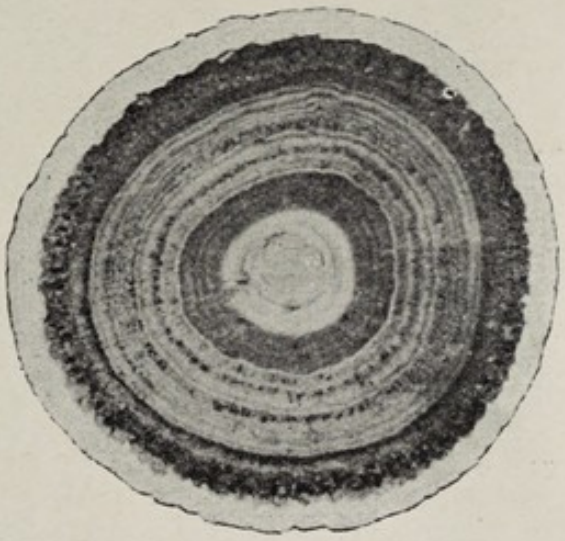


FIG. 209.—VESICAL CALCULUS. (NATURAL SIZE.)

The pale external zone consists of calcic phosphate. Immediately internal to this is an irregular layer of calcic oxalate. Within this are a number of thin layers of calcic oxalate and mixed phosphates. The innermost ring consists of calcic oxalate surrounding a nucleus of urate of ammonium,

The three types are not infrequently combined in the same calculus, giving rise to laminæ with corresponding differences in appearance and consistency. Thus, a calculus may contain uric acid in the centre and oxalate of lime in the crust, or may consist of a nucleus of oxalate of lime with laminæ of calcic phosphate and of ammonic urate around it.

In addition to the mineral constituents, a urinary calculus contains a complete organic framework infiltrating the whole calculus and supporting and cementing the mineral particles.

ÆTIOLOGY.—Although the conditions giving rise to the formation of calculi are but imperfectly understood, it may be stated that they depend partly upon general causes and partly upon local changes. Heredity, age, climate (cold), and diet (nitrogenous), have each a marked influence in the production of certain calculi; while such local changes as may lead to damage of the epithelial lining of the urinary passages, and to stagnation of the urine, are in all probability still more important causes. Calculi due to the former causes (uric acid, calcic oxalate) might be described as *primary*, those due to the latter (phosphates) as *secondary* (Daniel). But the conditions

are frequently combined. Tuffier showed that dogs fed on oxamide developed calculi, and that particles of oxamide could be traced in both the desquamated and the still-living epithelium at the sites of the calculi. It seems, therefore, probable that degenerated epithelium may have an influence in producing calculi, somewhat analogous to that possessed by the epithelium of the biliary passages in the production of gall-stones, and that the organic matter found in the calculi is derived from the destroyed epithelium. This is the more probable from the fact that while phosphatic concretions may form round foreign bodies introduced into the bladder, this does not happen until the irritation of the foreign body has produced a recognisable amount of inflammation. Vesical calculi are very common in sufferers from bilharziosis (p. 95), being formed, as the result of the cystitis present, around nuclei consisting of blood-clot or of the ova of the parasite.

Changes in the reaction of the urine may also aid in the precipitation of mineral matter. Thus uric acid and its salts tend to be precipitated when the acidity of the urine is abnormally increased, while calcic and ammonio-magnesic phosphates are deposited in precisely the opposite circumstances. When excess of carbonate of lime exists with oxalic acid in acid urine, oxalate of lime calculi are most likely to be formed. It is also probable, in view of Tuffier's results, that the general causes may lead to definite local changes in the renal tissue, dependent on the nature and concentration of the substances conveyed to the kidneys, and that the precise result may be modified by the antecedent and subsequent local changes. Thus, in one kidney was found a calculus with a uric acid nucleus and a crust of calcic phosphate, while in the opposite kidney was a stone with a similar nucleus, but with a calcic oxalate crust. In the condition known as cystinuria (p. 387) calculi of cystin may form, owing to the insolubility of this substance.

Some observers have attached considerable importance to the rôle of bacteria in producing calculi, but the action of these is certainly not essential. It is not improbably responsible for the deposit of phosphates which occurs secondarily.

Effects.—Urinary calculi give rise to irritation of the lining wall of the cavity in which they lie, and not infrequently obstruct the outflow of urine.

Renal calculi lead to atrophy of the glandular substance, hydronephrosis, and concomitant fibrosis of the kidney. Blood is frequently present in the urine, and desquamated epithelial cells may be found. If infection with pyogenic organisms occur, a purulent inflammation of the pelvis (*suppurative pyelitis*) may ensue, sometimes involving the kidney-substance (*pyelo-nephritis*) or producing a purulent hydronephrosis (*pyonephrosis*). Inflammation of the tissue around the kidney (*perinephritis*) is a less usual result. Calculi frequently occur in connection with malignant disease. The nature of the association is not understood, but it is not improbable that the irritation produced by the concretion gives rise to the new growth. (*Cf.* Gall-Stones, p. 506.)

Vesical calculi lead to changes in the bladder of a similar nature, as well as, in some cases, to hypertrophy of the muscular coat. They give rise to severe pain and to hæmaturia.

DISEASES OF THE OVARY.

The ovary is very commonly the seat of **inflammation** (*oöphoritis*). In some cases this may start as a local or general peritonitis (*peri-oöphoritis*), involving chiefly the surface-epithelium and cortex of the organ. The tendency of such a condition is, however, to spread inwards and produce a general oöphoritis. Inflammation of the ovary may end in resolution, or in fibrosis (*sclero-cystic disease*) and atrophy with loss of function; or it may result in suppuration or hæmatoma. The effused blood in the latter case may undergo calcification. The commonest causes of suppurative inflammation (*ovarian abscess*) are puerperal fever and gonorrhœa; a less frequent cause is tuberculosis.

Tubercular oöphoritis is nearly always a secondary infection, resulting from a tubercular peritonitis or from primary disease of the Fallopian tube. Primary tuberculosis of the ovary is very rare.

In chronic oöphoritis **blood-cysts** are not uncommon, and in rare instances they may undergo calcification. These cysts and the calcareous bodies so formed are almost invariably associated with imperfect development or retrogression of the corpus luteum.

Owing possibly to its special functions, the disposition of the ovary to the formation of tumours exceeds that of almost any other organ of the body. **New growths** arise both from the parenchyma and from the stroma of the ovary. The parenchyma consists principally of the epithelium lining the Graafian follicles, but also to some extent of germinal epithelium. Both these elements are confined to that part of the gland which is called the oöphoron, and which roughly corresponds with the peripheral zone; they are absent from the paroöphoron or hilum of the ovary. Of parenchymatous growths the most common is *cystic adenoma; carcinoma, dermoid cysts*, and *teratomata* also occur. The last two growths arise from the ovum, and are therefore termed "ovigenous." Of tumours which arise in the stroma there are four groups—*fibromata, sarcomata, endothelioma*, and *perithelioma*. These last arise from the endothelium or from the tunica adventitia of the bloodvessels and lymphatics.

The ovary is the seat of three types of **cysts**: (1) *distension-cysts*, including hydrops folliculorum and cysts of the corpus luteum; (2) *tubulo-cysts*, including the paroöphoritic or "hilum" cysts, which arise from the tubular relics of the Wolffian body, and the par-ovarian cysts, which arise from Wolffian tubules lying outside the ovary in the mesosalpinx; and (3) *degeneration-cysts*, embracing cystic adenoma, a multilocular growth which is by far the most common tumour of the ovary, and some lutein-cysts which arise from degeneration of lutein-cells.

The question of the internal secretion of the ovary is considered in Chapter XXII.

CHAPTER XXXIII

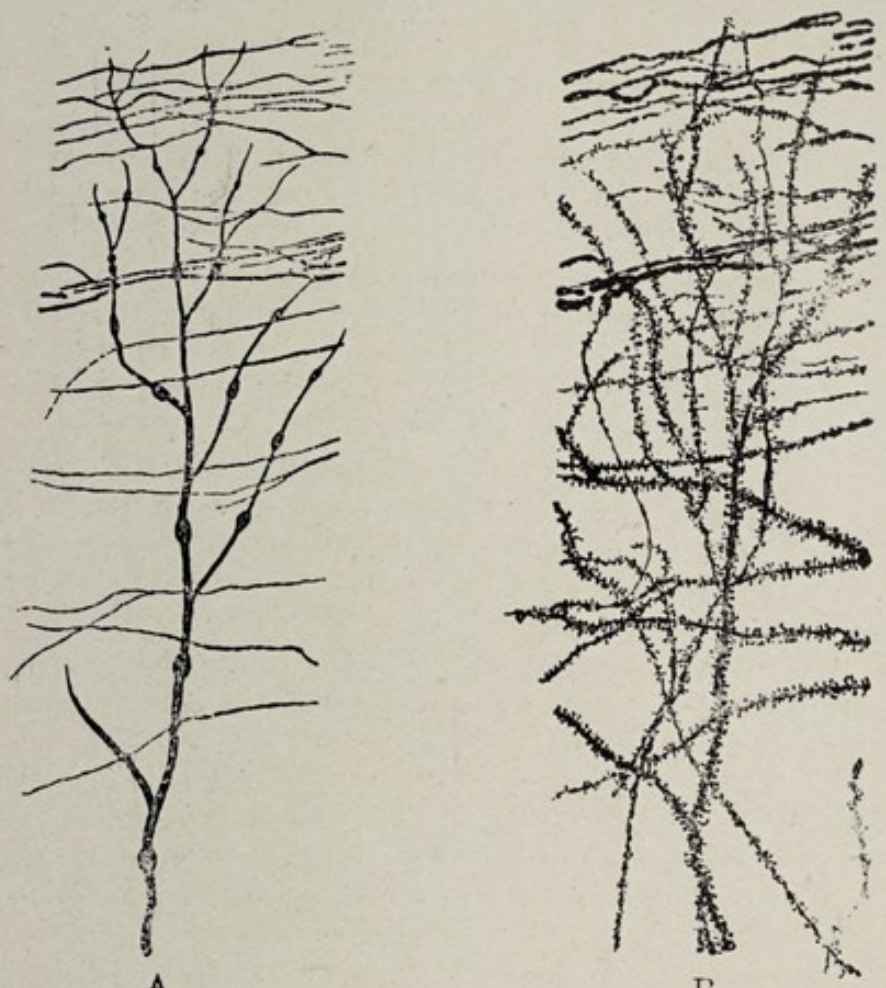
PATHOLOGY OF THE NERVOUS SYSTEM

THE morbid processes affecting the nervous system are usually divided into two groups: (1) *Organic disease*, (2) *Functional disturbance*. Such a classification depends upon whether or not symptoms observed during life can be associated with changes in the nervous system, gross or microscopical, recognisable after death. As was previously stated (p. 5), functional disorder necessarily involves the existence of structural change, although this may be so minute (molecular) as to escape notice. Many diseases of the nervous system which are classed as functional are probably due to the action of poisons: others depend upon inherited instability (tendency to chemical change) of the cell-substance. The paroxysmal neuroses and psychoses, *e.g.*, epilepsy, migraine, certain forms of mania and melancholia, are not improbably brought about by causes belonging to one or other of these last categories.

MORPHOLOGY.—The histological elements which make up the nervous system are derived from the outer and middle layers of the blastoderm. The epiblast furnishes the nerve-cells and their processes, the neuroglia, and the epithelium lining the ventricles and the central canal of the spinal cord. The mesoblast furnishes the bloodvessels, lymphatics, and membranes of the brain, and the neurilemma or nucleated sheath of Schwann. The origin of the myelin-sheath is not known. The study of the development of the nervous system, and observations made by the method of Golgi or by modifications of it, have demonstrated that in all vertebrates the true nervous elements consist of independent complex cells which are generally spoken of as "neurones." The morphological characters of all *neurones* at one period of development are fundamentally similar—viz., a cell consisting of spongioplasm and hyaloplasm, containing a nucleus and nucleolus. From this cell processes grow out, and these processes, which are probably made up of delicate fibrillæ, are continuous with, and of the same bio-chemical nature as, the framework of the cell-substance. One process of the cell gives off collaterals and becomes the *axon* of a nerve-fibre; the others, termed *dendrons*, branch many times like a tree, and terminate in an apparently inextricable network (Fig. 210).

The chrome-silver and mercury methods have shown that studded all over the branches of the dendrons (*dendrites*) are little buds or gemmules (Figs. 210 and 212) ; and that fine branches (*collaterals*) are given off from the axon. The nervous impulses or molecular vibrations are transmitted towards the nerve-cell by the dendrons and away from it by the axon.

Within the cell-body, lying in the spaces of the spongy network (*spongioplasm*), is the so-called *hyaloplasm*. The staining method of



A B

FIG. 210.—PROCESSES OF NERVE-CELLS. (MOTT.)

A. Diagrammatic representation of the dendron and dendrites of a cortical pyramidal cell, with the tangential fibres running at right angles.

B. Dendron and dendrites with tangential fibres, from a microphotograph of a section of the brain of a dog kept for four hours under chloroform. Stained by Cox's method. All the processes are seen studded with little buds or gemmules. Contrast this with A.

Nissl shows that the spongioplasm and hyaloplasm differ in chemical constitution, for the former is unstained by basic aniline dyes, and is therefore termed "achromatic," whereas the latter is "chromatic" and readily takes the stain. The blocks of colourable substance, seen in the large motor cells of the brain and spinal cord, are termed *Nissl-bodies* (Fig. 211). They consist of extremely fine particles suspended in a fluid, and are said to represent a store of energy or food. It will be observed that Nissl-bodies in the form of spindles

exist also on the dendrons ; in fact, the axon can always be recognised by the absence of these chromatic bodies. In all probability these Nissl-bodies do not exist in the living cell, but precipitation occurs on the death of the nerve-cell, as in the case of myosin from dead muscle-plasma, since Ehrlich's *intra-vitam* methylene-blue method does not exhibit Nissl-bodies. The value of the results obtained by Nissl's method is, however, undoubted. For the study of pathological alterations it matters little whether the Nissl-bodies are preformed bodies existing *intra vitam* or are the result of precipitation, as long as it is known that a healthy nerve-cell differs from a diseased nerve-cell in the appearances of the stained substance (*vide* Fig. 211).

Relations between Neurones.—The fundamental conception of the neurones as independent morphological units, in contact, but not in continuity one with another, yet withal possessing physiological association and mutual interdependence, is of the greatest importance in the study of nervous diseases, and especially as affording an explanation of those morbid conditions which are termed functional.

The cerebro-spinal neurones may be divided into *afferent, efferent,* and *association* systems ; but the last are by far the most numerous, and constitute the great bulk of the brain. All these systems are connected together, the dendrites of every neurone being in intimate physiological relation with the dendrites of the next in the series (*e.g.*, the motor efferent system, Fig. 233). In a system or series of nervous units with multitudinous points of contact, it is conceivable that physiological interneuronic relations may vary owing to retraction of the dendritic processes of one from contact with the terminal arborisations of the axons of another, so that the molecular vibrations may pass through systems, or communities, of neurones with a variable degree of intensity or rapidity.

Many apparently inexplicable problems relating to normal and pathological functional conditions of repose and activity could be

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FIG. 211.

1. Large Betts' cell, fairly normal, showing the Nissl-granules in the body of the cell and on the processes. 2. Degenerated cell from anterior horn in a case of general paralysis. 3. Ditto, more advanced degeneration, with vacuolation. 4. Posterior spinal ganglion-cell, showing the different distribution of the chromophile substance. 5. Degenerated cell from experimental cerebral softening. Compare this with 1 and 9. The cell is swollen, the Nissl-granules are absent and replaced by a fine dust of colourable substance staining the cell uniformly. 6. Posterior spinal ganglion-cell, showing pigmentation at one pole. 7. A pyramidal cell from the cortex in acute softening from ligature of cerebral arteries, showing phagocytes sticking to the dead cell and devouring it. 8. Large pyramidal cell of the cortex cerebri, showing absence of the Nissl-granules in the body and the processes, and uniform staining (from a case of hyperpyrexia). 9. Large pyramidal cell of the cortex cerebri, showing little, if any, change (from a case of septicæmia of considerable duration, but without high fever). All the figures are exact representations of microphotographs. The magnification of 1, 2, 5, 8, 9 is 700 diameters; of 3, 4, 7, 350 diameters ; of 6, 200 diameters.

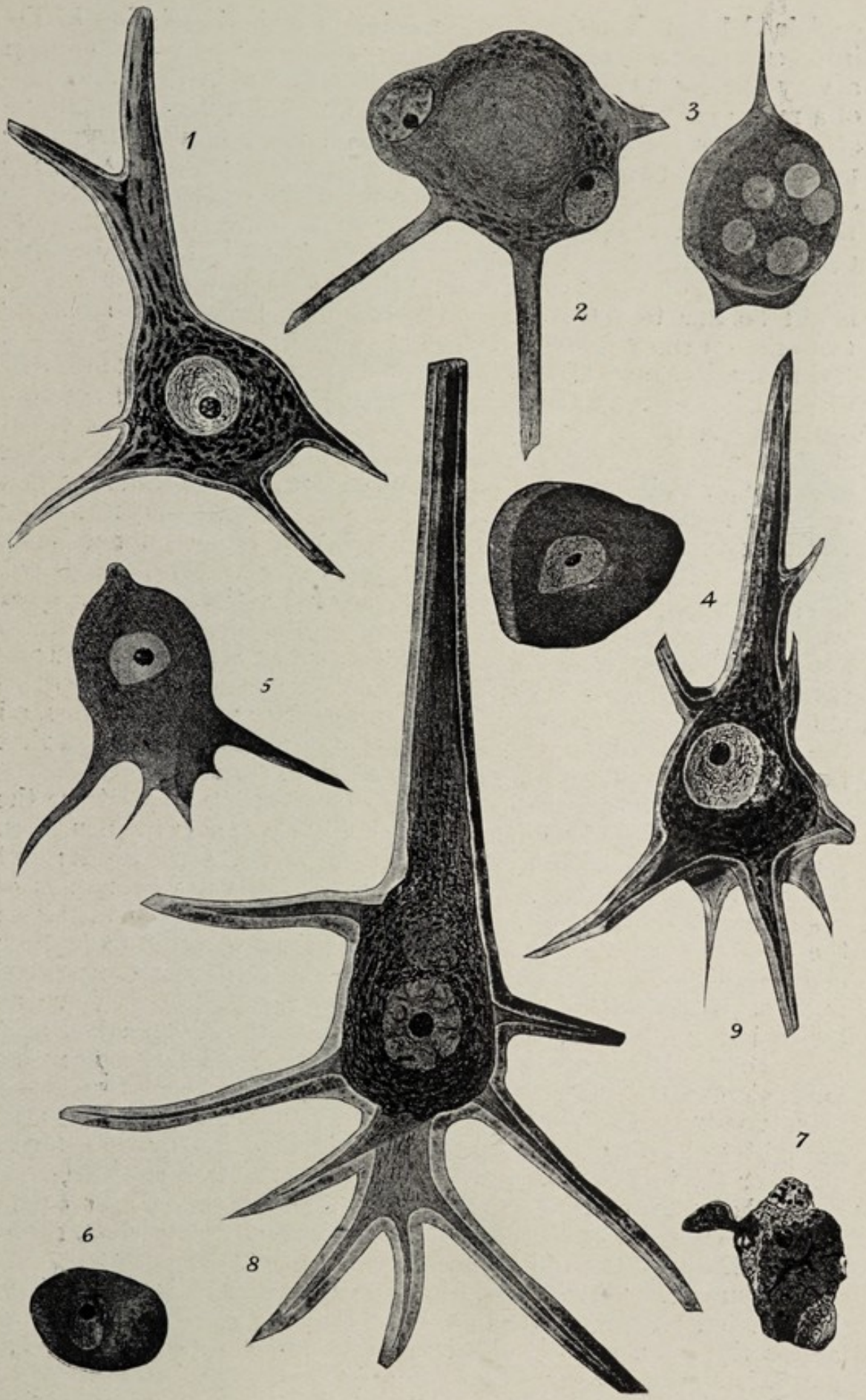

FIG. 211.—For description, see opposite page.

explained by such a theory of association and dissociation of the interneuronic connections. The theory, however, as yet rests upon a very slender foundation of facts. Movements in the nerve-cells of a minute aquatic animal having been observed under the microscope, it was conceived that the terminal twigs of the nerve-fibre processes might elongate and so come into better contact with the dendritic processes of the next neurone of the series. This led to the idea that sleep and unconsciousness from anæsthetics and narcotics, also trance and hypnotic state, hysterical paralyses and anæsthesia, and other conditions such as catatonia, catalepsy, etc., might be due to retraction of the terminal twigs of the sensory neurones on the surface of the brain, so that contact is broken and the transmission of nervous currents is thereby interrupted. The attempt has been made to find a basis for this theory of retraction of the terminal buds or points of contact of the branching processes of the dendrons by fixing in various fluids small pieces of the brain of animals which have been anæsthetised with chloroform, morphia, or other narcotics, and comparing the appearances presented by the dendrons with those seen in the brain of an animal killed suddenly. The results obtained have been divergent. *A priori*, it would seem more probable that cerebral activity is associated with a cutting-off of the great majority of interneuronic connections and a strengthening of the current traversing a few; that during repose or under narcotics there is a general expansion of the gemmules, due to exhaustion of their contractility; and that thus, all the neurones being in contact, nervous currents are so diffused that they are not of sufficient intensity to rise into consciousness.

The other histological elements derived from the epiblast are the neuroglia-cells and fibres. Their function is to support the neurones. According to Weigert the cells are independent of the fibres; but it is generally believed that the neuroglia-cells have numbers of branching processes (Fig. 212) which pass in all directions between the processes of the neurones, and various theories have been elaborated giving to the neuroglia-cells important functions apart from mere supporting properties. Some neuroglia-cells have an expansion on the minute bloodvessels, and the opinion has been expressed that they are capable of contracting, and thereby causing expansion of the vessel, thus determining more blood to nervous structures which are in functional activity. They have also been thought to have the function of contracting and thereby drawing together the terminal process of the neurones. It is possible, however, that variations may occur in the conducting power of the substance lying between the related terminals of the neurones rather than in the apposition of the terminals themselves.

The junctions between the neurones, whatever their nature, have been called *synapses*. It is probable that the passage of impulses across these junctions is affected by the action of certain poisons, and it has been supposed that a similar result may be produced by auto-intoxication (p. 378). Thus, it has been suggested that

neurasthenia may result from decrease of resistance at the synapses impulses thus radiating in all directions rather than following their normal courses ; and that the phenomena of *hysteria* may be due to diminished resistance in certain directions (spasm, hyperæsthesia), and increased resistance in others (paralysis, anæsthesia).

CAUSES OF NERVOUS DISEASE.—The causes of pathological processes occurring in the nervous system may be divided into *internal*,

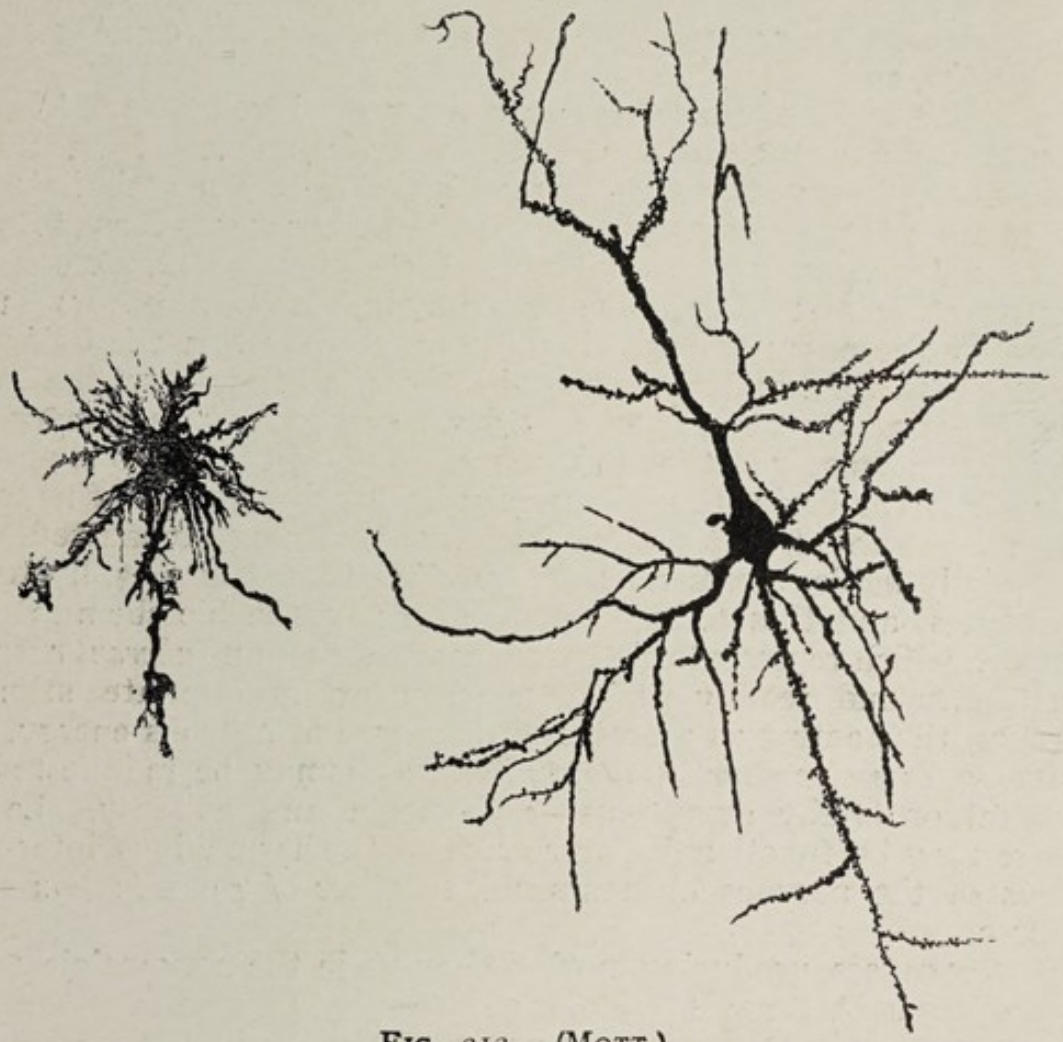

FIG. 212. (MOTT.)

A. Pyramidal cell of cortex, from a case of acute softening, due to experimental ligature of vessels. Stained by chrome-silver method. Shows practically normal appearances of the cell and its processes ; but by Nissl's method profound changes were evident. It is, therefore, probable that this method is not suitable for studying acute changes in the neurones.

B. Normal neuroglia cell. Stained by chrome-silver method.

or hereditary, and *external*, but in nearly all cases except those due to direct injury the two are more or less combined.

Of all the causes of nervous disease, **hereditary predisposition** stands pre-eminently first. It may come directly from one or both of the parents, or from more distant ancestors. Strictly speaking, it is the tendency to nervous disease and insanity rather than the disease itself that is inherited, and this is frequently spoken of as

"neuropathic tendency." There are, besides, a number of *inherited diseases* which affect members of a family; the disease frequently commencing in each individual at about the same age. These are termed "family diseases"—*e.g.*, *hereditary ataxia* (Friedreich's disease), *hereditary chorea*, and various forms of *idiopathic muscular atrophy*. Alcoholism and syphilis in the parents, especially if one or both came from a neuropathic stock, frequently engender, by the production of defects in the germinal plasm, arrest, imperfect development, or premature decay of the neurones, causing *idiocy*, *imbecility*, and *dementia*.

Like all cells, the neurone depends for its development, life, and functional activity, upon a suitable environment. It must also possess an inherent vital energy, by which it can assimilate and store up nutrient material, which may be regarded as *potential* energy, to be converted into nerve-force as required. A constant constructive and destructive bio-chemical process occurs in the nervous elements; and in a healthy nervous system the *balance of potential* is high, and the sense of fatigue is the natural indication for sleep and repose by which nervous energy may be recuperated. It may be conceived that in some portions of the nervous system, especially the brain, there may exist systems or groups of neurones with *inherited low potential*, rapidly becoming exhausted, and especially liable, therefore, to *depression of function*—*e.g.* hysterical paralyses, anæsthesiæ, and melancholia; or the bio-chemical substance, which represents potential, may possess an *inherent chemical instability* and readily fulminate when an appropriate stimulus occurs, thus acting as a centre of discharge of nervous energy, and causing *excessive functional activity*, which may be manifested by mental or bodily symptoms—*e.g.*, mania and epilepsy. Lastly, there may be functional disturbance of the harmonious inter-relations of the nervous elements, with *failure of co-ordination*—*e.g.*, chorea.

Other causes, producing morbid changes in the nervous elements, are dependent upon (*a*) abnormal conditions of the blood and lymph, by which the neurones are poisoned, and their metabolism affected; (*b*) excess or deficiency of normal excitation, or the existence of abnormal excitation.

A. **Abnormal Conditions of Blood and Lymph.**—A frequent cause of disease of the nervous system is a *failure of the blood-supply* to some portion of the brain. (See Embolism and Thrombosis, Chapter XXI.) *Insufficiency of oxygen*, due to anæmia, leads to functional depression, lassitude, and mental fatigue. Impoverishment of the blood in women, by frequent pregnancies and excessive lactation, causes neuralgia, nervous exhaustion, and, in neuropathic subjects, hysteria, neurasthenia, melancholia, and mania. Probably there is an alteration in the composition of the blood, in the nature of an auto-intoxication or a "sub-minimal" deficiency. The most striking examples we have, however, of the effect of absence or "sub-minimal" *deficiency of a normal constituent* of the blood, upon

the development and functions of the nervous system, are afforded by cretinous idiots, whose brains are arrested in development in consequence of the absence of the thyroid gland, and by the subjects of myxœdema (p. 381). The proof of this is shown by the disappearance of the nervous phenomena of myxœdema on making up the deficiency by administration of the gland by the mouth.

More important than defects of necessary materials are the **toxic** causes of disease of the nervous system. Thus *excess of normal constituents of the blood*, such as carbonic acid and nitrogenous waste-products, may give rise to symptoms of disease. Again, in Graves' disease, nervous phenomena in the form of exophthalmos, palpitation, fine tremors, and mental excitement may be ascribed to excess of thyroid secretion escaping into the blood.

More often *abnormal substances* are responsible, and these may be either (1) poisons produced within the body by perverted function of the organs or tissues (auto-intoxication), or by the action of micro-organisms upon the living tissues and fluids of the body; (2) poisons introduced into the body from without.

1. *Poisons produced within the Body.*—The best example of auto-intoxication (see Chapter XXII.) is afforded by *uræmia*, the nervous manifestations of which are headache, drowsiness or coma, and epileptiform convulsions; sometimes symptoms of polyneuritis. Excess of *uric acid* in the blood, which is associated with high arterial pressure, may induce headache and nervous irritability; and *diabetes* (a result of imperfect metabolism) may cause multiple neuritis and coma, the latter being often heralded by *acetonæmia*, which may be regarded as a form of auto-intoxication. *Cholæmia*, resulting from obstructive jaundice, may be attended by stupor and psychical depression. In *acute yellow atrophy of the liver*, the nervous phenomena of delirium, motor irritation, delusions, stupor, and coma, result from the profound alteration existing in the blood. In *pernicious anæmia*, and in other grave anæmias, degenerative changes in the spinal cord, of the nature of a combined sclerosis, are frequently found, and are probably not so much due to the deficiency of red corpuscles as to some toxic substance arising from imperfect metabolism. Choline, a product of the breaking-down of nervous tissue (p. 541), has been shown by Donath to be capable of producing convulsions.

In infective diseases due to micro-organisms, *delirium* is a frequent complication; it may be the result of the high fever, or of the poison, or of the fever and the poison combined. In severe cases, stupor and *coma* may occur, and it has been shown that in this extreme stage the nerve-cells of the cerebral cortex, and also of the spinal cord, undergo an acute morbid bio-chemical change (*vide* Fig. 211). These particular poisons have not a selective action upon any special part of the nervous system, but many cases of neurasthenia, insanity, neurosis, and neuritis date their onset from an acute specific fever.

In cerebro-spinal meningitis, posterior basic meningitis, tuber-

cular meningitis, acute delirious mania, and leprous neuritis the inflammation of the enclosing and supporting tissues is due to the growth therein of the specific organism, and syphilitic affections of the nervous system are due to the specific micro-organism (*Spirochæta pallida*) attacking its enclosing, supporting, and vascular tissues.

Some micro-organisms and their toxines have a selective influence upon some part of the nervous system. A striking instance of this selective action is shown in the fact that only in persons affected with acquired or inherited syphilis is the symptom known as the *Argyll-Robertson pupil* found (this is the absence of reflex contraction of the pupil to light, while that to accommodation persists). Again, syphilis when it attacks the supporting, enclosing, and nutrient vascular mesoblastic tissues shows a disposition to affect structures about the base of the brain; thus paralysis of the third nerve is almost pathognomonic of this disease. In *rabies*, although the whole nervous system is charged with the poison, the medulla oblongata (as shown by the symptoms) is especially affected. Again, in *tetanus* the bacilli elaborate a virulent poison which affects particular groups of neurones. The fact that "lock-jaw" nearly always occurs first shows that the poison selects the motor nucleus of the fifth nerve. Experiment has proved that the tetanus-toxine, if mixed with an emulsion of nervous matter before injection into an animal, loses its toxicity, thus showing its affinity for nervous matter. Another example is offered by *diphtheria;* a neurotoxine is produced by the local action of the bacilli, the effects of which are shown by paralysis of the soft palate, paralysis of the muscles of accommodation, weakness and inco-ordination of the limbs, which may amount to paralysis, absence of knee-jerks, and often cutaneous anæsthesia; and the disease occasionally terminates fatally from cardiac or respiratory paralysis.

2. *Poisons introduced from Without.*—The most widespread and potent cause of nervous and mental disease is excessive indulgence in *alcohol.* To people with unstable nervous systems a small quantity of alcohol acts as a poison. It may produce acute delirium with fine tremor, and generally visual hallucinations of a horrible nature, indicating acute toxic influence on the brain. This acute form of alcoholic poisoning is much commoner in men than in women, and it is remarkable how a severe illness, such as pneumonia, will bring out delirium tremens in a drunkard. Alcohol acts especially upon the higher centres of the brain, and a drunken man may exhibit "the abstract and brief chronicle of insanity, going through its successive phases in a short period of time" (Maudsley). The functions of the brain are stripped off successively in an inverse order to their development—viz., moral control and responsibility, judgment and deliberation, attention and concentration, memory and receptivity. The effect on the nervous system of chronic tippling is dementia, a very characteristic manifestation of the mental degradation being absence of knowledge of time and place,

personal illusions, and loss of memory of recent events, indicating a failure of receptivity and of the formation of memory-pictures in the higher centres. The improvement which generally occurs when total abstinence is enforced shows that the poison has damaged, but not destroyed, the nervous elements. Besides mental symptoms of alcohol-poisoning, there are frequently sensory disturbances and motor paralysis due to polyneuritis affecting especially the lower limbs, although the upper limbs and even the respiratory muscles may be affected in severe cases.

Lead is peculiar in selecting the nerve which supplies the extensor muscles of the wrist and fingers, so that " dropped wrist " is almost characteristic of this form of toxic neuritis. Lead also produces a chronic inflammation of the cerebral cortex (*encephalitis saturnina*), which gives rise to a complex of symptoms—viz., dementia, loss of memory, weakened intellect, paresis and epileptiform seizures, hallucinations of sight and hearing, and mental exaltation or depression. *Arsenic* has a special selective influence upon the peripheral nerves, causing polyneuritis. Generally all four limbs are affected. Sometimes psychical troubles and in rare cases epilepsy occur. Workmen at india-rubber factories, owing to the inhalation of the fumes of *bisulphide of carbon,* may suffer from severe mental disturbance and polyneuritis.

There are a certain number of poisons besides alcohol which act on the nervous system when continually entering the body as the result of a *habit*—viz., absinthe, ether, cocaine, opium, morphia, hashish, and tobacco. Not only does absinthe produce epileptic fits when taken for some time, but if intravenously injected into an animal it produces epilepsy.

B. **Deficiency or Excess of Normal Stimulation or Existence of Abnormal Stimulation.**—A structure which is not used will gradually lose its function, while its nutrition will also suffer, and in time atrophy may occur. Amputation of a limb in early life causes atrophy of the nervous structures which presided over the sensation and movement of the part. This is seen both in the grey and in the white matter of the spinal cord of the same side. A function not used will gradually disappear, and become more and more difficult to evoke. This fact is of importance in functional neuroses and psychoses—*e.g.*, hysterical paralysis and melancholia—because the longer a mental or bodily function is left in abeyance, the more likely is the defect to become permanent. The converse is also true—the longer a perverted function exists, the more unlikely is it to disappear. Thus, auditory hallucinations, a very important and frequent symptom in the insane, commence with indistinct noises; these are followed by *voices;* and eventually the voices are so distinct and real that the greater part of the patient's psychical existence is concentrated upon, and determined by, this abnormal stimulus from within. Thus is shown the progressive strengthening and *fixation of the perverted* functions of the mind, and progressive weakening and *dissolution of the normal functions.*

Abnormal Psychical Stimuli.—Mental pain in the form of grief, worry, anxiety, fright and shock, violent emotions (pleasurable or painful), disappointed love, sexual excesses or perversions, and excessive brain-work, frequently precede and determine, in persons with the insane or neuropathic taint, various forms (*a*) of psychoses—*e.g.*, mania, melancholia, delusional insanity; (*b*) of neuroses—*e.g.*, chorea, hysteria, epilepsy, hystero-epilepsy; (*c*) or organic brain-disease—*e.g.*, apoplexy, thrombosis, and general paralysis. The effect of stress in determining neuritis and degenerative processes in the central nervous system can often be observed in practice. The most striking examples of *psycho-motor functional paralyses* from stress are afforded by writer's, pianoforte-player's, violinist's, and typewriter's cramp, and hammerman's palsy, in all of which the nerve-paths most frequently employed in the patient's occupation are affected as the result of overwork.

Physical Stimuli.—Visceral reflex irritation may act as an exciting cause of neuroses and psychoses: thus, intestinal worms, teething, and indigestible food, severally or combined, often produce in infants and rickety children convulsions, spasm of the glottis, and tetany. Various functional and organic diseases of the female reproductive organs act as exciting causes in the production of hysteria, hystero-epilepsy, melancholia, and mania; moreover, paroxysmal attacks in these diseases are more liable to occur at the menstrual period or the menopause. The irritation of a carious tooth may produce trigeminal neuralgia. Wax in the ear may occasion vertigo and tinnitus aurium, and errors of refraction may be the cause of attacks of migraine, and even tend to excite epileptic fits in a person suffering from epilepsy. Numerous other examples of peripheral disturbance could be mentioned as exciting causes of nervous affections—*e.g.*, irritation of the terminals of the vagus in almost any part of its widespread visceral distribution may lead to reflex vomiting. The characteristic pain of angina pectoris, which radiates down the inner side of the left arm, is explained by the fact that the cardiac branches of the sympathetic arise from the same segments of the spinal cord as the sensory branches of the ulnar nerve; consequently the pain is referred to the corresponding skin-area supplied by this nerve. This is one example of a great number of *referred pains*.

DEGENERATION AND REGENERATION OF NERVES.

The changes which take place in nervous tissue as the result of injury are collectively termed "degeneration." If the lesion has not resulted in actual death of cells, but only in destruction of their processes, regeneration of these processes (*nerve-fibres*) may occur. Whereas, however, there is conclusive proof that regeneration of peripheral nerves takes place, there is no evidence to show that fibres in the central nervous system, when they are separated

from their trophic centres, undergo regeneration. Whatever return of function may occur is due to the fact that other associated neurones carry on the work. On the other hand, when a peripheral nerve is cut across, or even an inch or two is cut out, regeneration will in time take place. The process will be greatly hastened if the divided ends of the nerve are sutured; or if a piece has been excised, regeneration can be hastened by introducing a piece of nerve, or a piece of catgut or a decalcified chicken-bone, between the cut ends to conduct the outgrowing axons from the proximal portion of the nerve. The rapid return of sensibility which sometimes takes place after a nerve has been cut and sutured has led some authorities to believe in union by first intention. This, however, is not so. It is due to the overlapping of sensory nerves in the skin, and to the opening up of new and previously unused paths when the main road is blocked.

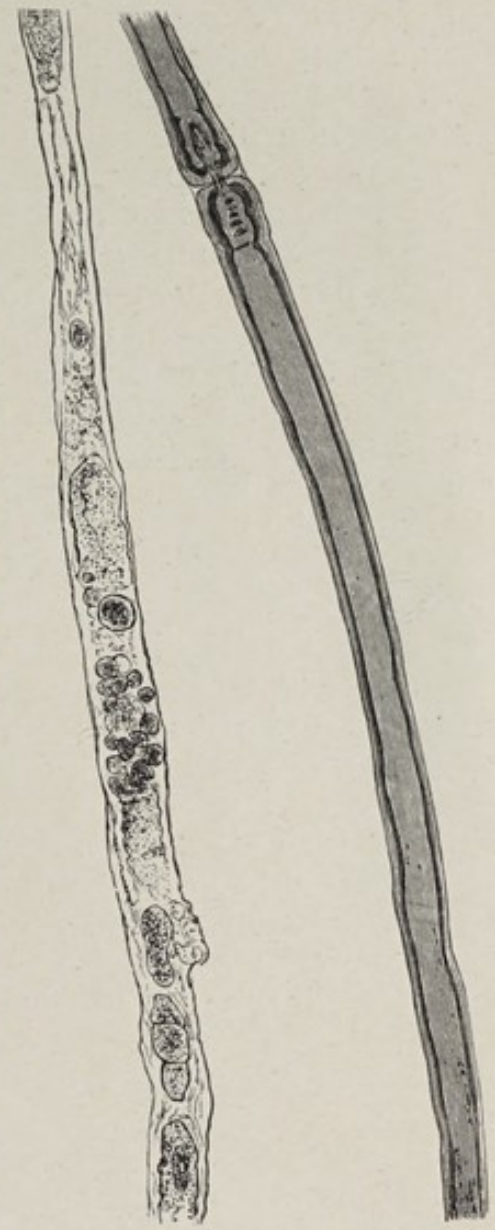

FIG. 213.—FIBRES FROM THE PERIPHERAL END OF A NERVE TEN DAYS AFTER SECTION. (× 200.) (MOTT.)

Stained with osmic acid. One fibre shows the masses of degenerated myelin, the other is healthy.

Histology of Degeneration.—Waller showed that when a nerve is cut off from its trophic and genetic centre (cell of origin), degeneration of the whole of the portion so separated takes place (*Wallerian degeneration*). This process of degeneration neither creeps up nor down, but the morphological changes are simultaneous throughout the whole peripheral portion of the cut nerve. It was previously taught that no changes occurred in the central portion of the neurone, but the researches of Nissl, Marinesco, and others prove that bio-chemical changes occur in the cells of origin. We have, therefore, to consider the changes in the peripheral portion of the cut nerve, the changes in the nerve-cell, and the process of regeneration.

After cutting a nerve the following changes can be observed in preparations of the peripheral portion stained with osmic acid. Within twenty-four hours the myelin commences to lose its straight regular outline and to exhibit an irregular appearance. The next day changes can be recognised in the axis-cylinder process; it is

swollen in some places, thin in others, while the myelin commences to break up, and a little later the axis-cylinder ruptures. On the third day the nuclei of the primitive sheath show signs of mitosis, the prelude to nuclear and cellular proliferation. On the fourth or fifth day there are evidences of proliferation of the nuclei and surrounding protoplasm, and these nuclei with surrounding protoplasm breaking through the sheath of Schwann cause a further fragmentation of the myelin, which continues until the tenth day (Fig. 213). The appearance of the degenerated fibres on the eighth to the tenth day is characterised by swellings alternating with constrictions. The swellings are due to accumulations in corresponding parts of the nerve-tubules of degenerated myelin-globules, proliferated nuclei, and protoplasm. On the fifteenth day the fibres in the greater part of their course consist merely of tubes containing protoplasm and proliferated nuclei, and little or no myelin; but here and there alternating with the constricted portions are fusiform swellings caused by distension of the sheath of Schwann with drops of liquefied myelin, nuclei, and often curled up portions of the axis-cylinder. The degenerated myelin is absorbed by leucocytes, and fatty granule-cells are thus formed. The nerve consists eventually of fibrous connective tissue and shrunken tubes containing proliferated nuclei and protoplasm. The latter becomes fibrillated, and thus prepares the way for the new axis-cylinder processes which will grow down from the central stump.

Regeneration of Nerves.—This process commences about the fourth or fifth week by a sprouting of the axis-cylinder process; this divides into several separate fibres, which insert themselves into and between the old primitive sheaths. Growth of the axis-cylinder always begins from a node next above or close to the section. The number of new axis-cylinder processes is in excess of the nerve-fibres destroyed; consequently it may be presumed that many atrophy and disappear (Fig. 214). At first the new fibres are non-medullated, but later they acquire a medullated sheath and nodes of Ranvier, which are at first placed at short intervals, as in young nerves. In the scar, primitive sheaths are at first wanting, but they ultimately form from the surrounding connective tissue. It may take months or a year or more before function is restored. The time varies with the length of nerve beyond the point of division, and with the distance between the cut ends. Sensation returns before movement. It is not generally admitted that regeneration can occur from the periphery, although there is some evidence forthcoming to that effect.

Changes in the Cells of Origin.—It has long been known that the myelin and axis-cylinder undergo degenerative changes in the central portion of the cut nerve, as far as the node of Ranvier above the point of section. It has now, however, further been shown, that if a nerve—*e.g.*, the hypoglossal—be cut on one side, and sections of the medulla be stained by Nissl's method, microscopical examination of the cells of origin forming the nucleus of that side

exhibits a marked contrast in shape and mode of staining as compared with the other, indicating a *reaction of injury* in the trophic and genetic centre. A short time after the section of the nerve the cell-bodies and nuclei of the group of neurones concerned appear somewhat swollen, and there are marked changes in the appearance of the protoplasm. The chromophilic elements are no longer

FIG. 214.—DIAGRAM MODIFIED FROM HOWELL AND HUBER, SHOWING STAGES IN REGENERATION OF A PERIPHERAL NERVE. (MOTT.)

1. Central end of nerve 21 days after section. 2. Peripheral end of nerve 21 days after section. 3. Central end of nerve 100 days after section, showing sprouting axis-cylinder with three branches. 4 and 5. Peripheral end of nerve 100 days after section. *a*, Axis-cylinder; *b*, myelin; *c*, nuclei.

distinct, but are replaced by a dust of fine coloured granules, and there is a diffuse staining of the achromatic substance. About the time when the axis-cylinder begins to grow out, the normal chromophilic character of the cell begins to return; and eventually, when function has been restored, the majority of the cells present a normal appearance.

Neuritis.

It is convenient here to consider the subject of neuritis; for it must be remembered that *parenchymatous neuritis* really is a degenerative change of spinal motor and sensory neurones, although the effects of the toxic agents in the blood are only visible in the remoter portions of the neurones forming the nerve-fibres. "Stocking anæsthesia" of the legs and "glove anæsthesia" of the arms, characteristic of polyneuritis, indicate that the sensory disturbance does not correspond with spinal segmentation, but is dependent upon distance from the trophic and genetic centres, and possibly, also, upon distance from the heart, and consequently impaired circulation. In four fatal cases of alcoholic polyneuritis examined by Mott, marked changes were present in the cells of the anterior horns and of the posterior spinal ganglia.

Parenchymatous neuritis is toxic in origin and usually symmetrical, and affects a number of nerves (*polyneuritis*); it may be associated with some interstitial change, but generally this is secondary to the degenerative process.

The changes in the nerves are those of primary Wallerian degeneration—viz., breaking-up of the myelin, proliferation of the nuclei of the sheath of Schwann, swelling of the axis-cylinder in some places, attenuation in others, and finally its rupture and destruction. The process commences at the periphery, and spreads centrewards. If the poison is eliminated before destructive changes have occurred in the cells of origin, it is possible for regeneration to occur; but often the paralysis is permanent. The difference in the microscopical appearances between parenchymatous neuritis and degeneration from section of a nerve is that in the former the fibres are much more unequally affected, some exhibiting comparatively little change, while others show advanced degeneration.

Interstitial neuritis is an inflammation affecting the vascular, interstitial, and supporting connective tissue, sometimes causing permanent, sometimes temporary, loss of function, according to whether the inflammation is productive of degenerative changes in the nerve-fibres or not. It may occur as a result of injury or cold, especially in a rheumatic or gouty subject, sciatica and Bell's paralysis affording examples of this affection. In anæsthetic leprosy and syphilis the interstitial vascular connective tissue is the seat of a specific inflammatory process; the former disease is known to be due to a specific bacillus, and the latter is caused by the *Sp. pallida*.

Degeneration of the Central Nervous System.

Methods of Staining.—The methods employed for studying Wallerian degeneration of the central nervous system—taking, for example, the spinal cord, where the afferent and efferent tracts are clearly defined—are as follows: If posterior spinal roots be cut, or

there be a transverse lesion of the spinal cord, it is possible, if the patient survive for ten days, to recognise naked-eye changes in definite tracts of the spinal cord, provided the cord be hardened in Müller's fluid for a month or so. The cord is then cut transversely, and the degenerated tracts are recognised by their *lighter yellow colour*, as compared with the healthy white matter, which is now stained a brownish-yellow. For microscopical examination of such an early degeneration, there is no method to compare with that of Marchi. It consists in placing thin transverse slices of the central nervous system thus hardened in a solution of *one* part of a 1 per cent. solution of osmic acid and *two* parts of Müller's fluid for one to three weeks, then washing for several days in running water, and cutting by the celloidin method. Sections should be

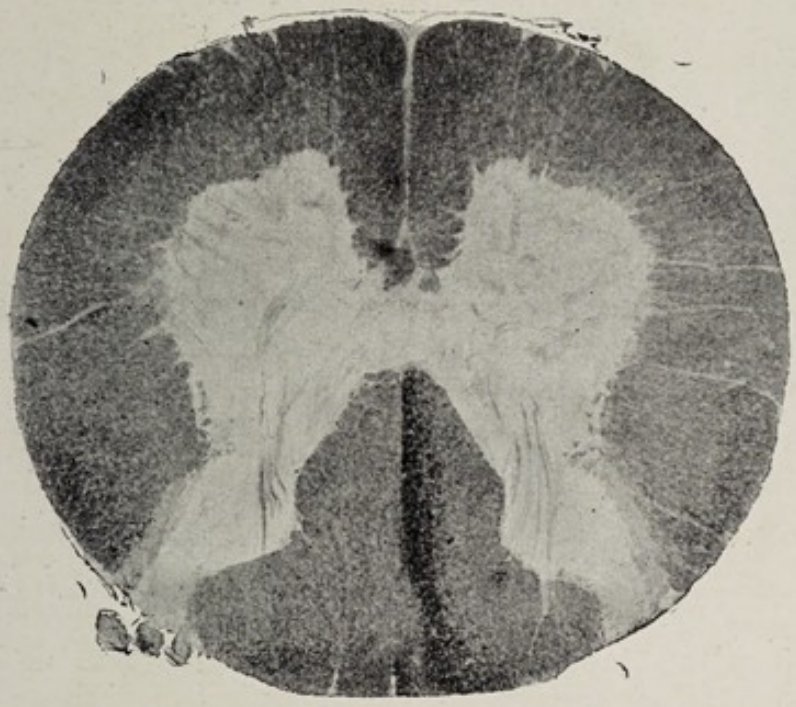

FIG. 215.—SECTION OF LUMBAR ENLARGEMENT OF SPINAL CORD OF MONKEY, SHOWING DEGENERATION IN THE POSTERIOR COLUMN ON ONE SIDE, THE RESULT OF SECTION OF THE FIRST SACRAL POSTERIOR ROOT. (MOTT.)

cut longitudinally and transversely. The early changes in the axis-cylinder and myelin sheath are beautifully shown, and even single degenerated fibres can be followed the whole length of the spinal cord. The healthy fibres are stained a light greenish-grey, but both the axis-cylinder process and the breaking-up myelin are stained *black*, owing to fatty degeneration (Fig. 215). This method is most suitable for *early* degenerations one week to one month after the lesion. For *later* degenerations, the Weigert and Weigert-Pal methods are most suitable. When sclerosis has taken place, it is better to adopt one of the latter methods; the healthy white matter is then stained blue, and the *sclerosed* tissue is yellow or unstained, according to the method adopted. Wallerian degeneration of the nerve-fibres of the central nervous system must occur in all organic

lesions, and its extent and distribution will depend entirely upon the ganglion-cells destroyed, or upon the fibres which have been interrupted in their continuity with the cells of which they are outgrowths.

Microscopical Changes.—The changes in the fibres, as a result of degeneration, are a breaking-up of the myelin-sheath (there is no neurilemma), an alteration in its chemical composition, and swelling of the axis-cylinder process owing to a fatty degeneration; the clear distinction between the central axis-cylinder and the surrounding myelin thus being lost. Later, as the altered myelin is carried away by phagocytes, spaces may be seen with the swollen axis-cylinder in the middle; or empty spaces in the neuroglia-tissue occur owing to rupture and absorption of the degenerated axis-cylinder processes. As the atrophy of the nervous structures proceeds, there is a hyperplasia of the neuroglia, and proliferation of the glia-cells. The process during the early stages has been one of softening; it is now a true *sclerosis* with shrinking, but there is no tendency (in uncomplicated primary or secondary systemic degeneration) for the sclerosis to extend its limits, and it may even be limited to a microscopic transverse area. Eventually a cicatricial tissue may be formed; and the presence of this impenetrable tissue may be the reason why in the higher animals there exists no definite proof that regeneration of nerve-fibres can take place in the central nervous system.

The Chemistry of Degeneration.—The nervous system is composed chemically of very complex bodies—*e.g.*, *proteins*, *nucleo-proteins*, *neurokeratin*, and *protagon* or *lecithin*, which forms the principal constituent of the myelin-sheath. This is a complex *phosphoretted fat* which stains black with osmic acid like all other forms of fat; but the myelin-sheath differs from tissues containing ordinary fat, such as olein, palmitin, stearin, by the fact that, when white nervous matter is placed for some time in Müller's fluid, the constituent myelin no longer stains black with osmic acid, but an ashy grey. This difference in chemical reaction is the basis of the Marchi method. It is probable that the chemical decomposition which occurs when myelin undergoes degeneration is a breaking-up of the complex molecule of protagon (lecithin) thus:

$$\underset{\text{(lecithin)}}{C_{44}H_{90}NPO_9} + 3\underset{\text{(water)}}{H_2O} = 2\underset{\text{(stearic acid)}}{C_{18}H_{36}O_2} + \underset{\text{(glycero-phosphoric acid)}}{C_3H_9PO_6} + \underset{\text{(choline)}}{C_5H_{15}NO_2}.$$

For if a spinal cord which shows well-marked degeneration on one side be divided longitudinally into two halves, and each half dried, weighed, and the fat of each separately extracted with ether, it will be found that while on the degenerated side there is an increase of ether-extract (fat) as compared with the healthy side, there is less phosphorus, the presumption being that the above decomposition has taken place. Examination of sections stained by the Marchi method shows that not only does the myelin-sheath

stain black, but the axis-cylinder process as well; the protoplasm has therefore undergone fatty degeneration. It has been shown (Halliburton and Mott) that *choline* exists in the cerebro-spinal fluid of patients suffering with extensive degeneration of the nervous system—*e.g.*, general paralysis—and that it does not exist in the normal fluid. The existence of choline in the cerebro-spinal fluid of general paralytics renders it probable that auto-intoxication may occur in extensive degenerative processes of the nervous system. The action of choline is to produce a fall in the blood-pressure, partly by its effect on the heart, but mainly by dilating the splanchnic arteries, owing to a toxic influence on the peripheral neuro-muscular mechanism. *Neurine*, a product of the decomposition of choline by micro-organisms, is a very powerful poison; it produces a preliminary fall, and then a rise, of blood-pressure with respiratory convulsions. These two bodies belong to the same group, chemically, as *muscarine*.

EFFECTS OF NERVE-LESIONS.

The effects arising from lesions of the nervous system may be seen in (1) *Disturbances of motion*—*e.g.*, paralysis or failure of voluntary movement, and paresis or weakness; (2) *Disturbances of sensation*—anæsthesia or absence of sensation, paræsthesia or perversion of sensation, hyperæsthesia or excessive sensibility, and spontaneous pain. Defects in the sensory apparatus are associated also with *inco-ordination* or lack of proper control of movements, and with *trophic* or nutritive disturbances; (3) *Reflex actions* may also be disturbed in the direction either of excess (exaggeration) or defect (absence, weakness), and the *electrical reactions* seen in connection with nerves are altered.

These various disturbances may be conveniently studied in association with diseases of the spinal cord.

Symptoms of Disease of the Spinal Cord.

The spinal cord has two sets of functions: (1) the direct reflex control of definite visceral and somatic regions of the body, by means of its thirty-one pairs of segmental nerves, and (2) the function of transmitting sensory impulses to the brain and motor impulses from the brain.

Hence the principal *symptoms of disease of the spinal cord* are: (1) paralysis, (2) changes in reflex activity, (3) alterations of gait and posture, (4) disturbance in the control of the sphincters of the bowel and bladder, (5) sensory defects, (6) sensory inco-ordination, "ataxy," and (7) trophic disturbances. The symptoms arising from disease of the medulla and pons are especially related to affection of the nuclei of the cranial nerves, combined with interruption of the motor and sensory tracts. Owing to the existence

of so many important structures close together, small vascular lesions or tumours in these regions produce serious and generally fatal consequences.

Paralysis.—There are two types of paralysis, according to whether a lesion affects the upper (cortico-spinal) motor neurone, or the lower (spino-muscular) neurone. *Paralysis of the cortico-spinal type* ("upper segment" lesion) is met with in brain-disease producing hemiplegia; it also occurs in both lower limbs after a transverse lesion of the cord, as in caries of the spine, tumours, focal myelitis; also in primary lateral sclerosis. If a transverse lesion exists in the cervical region, the arms are also affected. The characteristics of this form of paralysis are complete or partial loss of volitional power, with stiffness and rigidity of the limbs. The muscles are not wasted except from disuse; the deep reflexes are exaggerated; and there is no alteration in the electrical reaction of the muscles. *Paralysis of the spino-muscular type* ("lower segment" lesion) is due to a morbid process affecting the motor neurones in the anterior horn, or their homologues (the nuclei of the motor cranial nerves) in the medulla and pons, or the nerve-trunks containing the axons of these neurones. It occurs in infantile paralysis, acute and chronic poliomyelitis, myelitis, progressive muscular atrophy, bulbar paralysis, syringomyelia, tumours and hæmorrhages within the cord, medulla and pons, and softening of the cord from embolism and thrombosis. The characteristics of this form of paralysis are that the muscles affected are completely paralysed, and that if they recover, they do so imperfectly and slowly. Although all the muscles of a limb may be paralysed, as a rule certain groups suffer particularly. The limb is not rigid, the muscles being relaxed and flabby, and the articular surfaces of the joints no longer held in close approximation. The deep reflexes are lost completely. The muscles rapidly atrophy, and upon electrical examination there is an early appearance of the reaction of degeneration. Sensory disturbances do not necessarily accompany this form of paralysis. Vasomotor disturbances are manifested by coldness and blueness of the limb. Fibrillary twitchings are very characteristic of this neuro-muscular degenerative process.

Disturbance of Reflex Action.—The reflex acts are: (1) Tendon or deep reflexes; (2) cutaneous or superficial reflexes; (3) reflex functions of the bladder and rectum. Such reflexes may be increased, diminished, or lost.

The **knee-jerk** is the best example of a so-called deep reflex, but although it depends upon the integrity of the reflex arc of the third and fourth lumbar segments of the spinal cord, yet careful time-measurements have shown that it is not a true reflex, but is due to direct stimulation of the stretched muscle by the blow, which causes traction upon its tendon. Hence the presence of the reflex depends on the trophic integrity of the muscle, and this demands a healthy condition of both afferent and efferent nerves. Thus, destruction of the reflex arc of the third and fourth lumbar

segments in either its afferent or efferent portions will abolish the knee-jerk, because it will either paralyse the vastus crureus muscle or destroy its " myotatic " irritability.* The knee-jerk is produced by striking the quadriceps tendon *put on the stretch* by flexing the knee; the hamstring musclec are thus at the same time relaxed, so that the action exerted by them in antagonism to the quadriceps (Sherrington) is done away with. This is not, however, so much due to the fact that relaxation of the flexor muscles of the knee leaves that joint more free to move when the quadriceps extensor is excited to contraction by tapping its stretched tendon, as to the removal of an antagonistic tonic influence through afferent nerves (fifth and sixth lumbar roots), which the flexor group of muscles exert through the spinal reflex arc upon the correlated extensor group (Fig. 216).

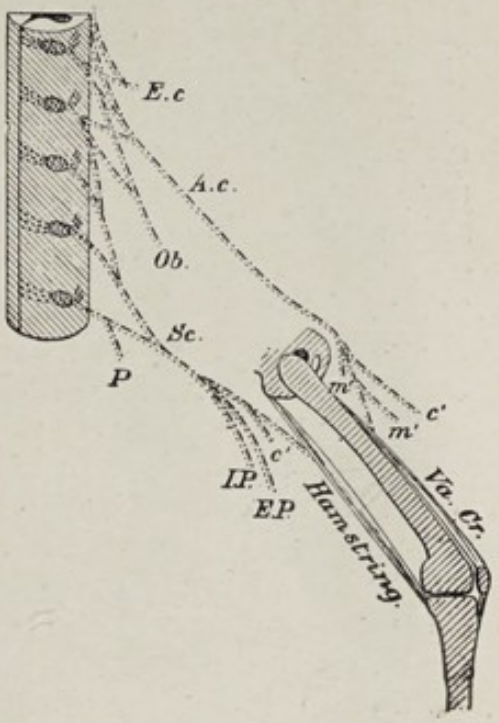

FIG. 216.—DIAGRAM TO EXPLAIN THE KNEE-JERK. (SHERRINGTON.)

E.c., external cutaneous nerve; *A.c.*, anterior crural nerve with (c^1) cutaneous and (m^1) muscular branches, coming from the third and fourth lumbar segments of the spinal cord; *Ob.*, obturator; *Sc.*, *sciatic nerve* with (*I.P.*) internal popliteal; *E.B.*, external popliteal branches; *Va.*, *Cr.*, the vasti and the crureus muscles, the internal portion being especially concerned in the knee-jerk.

Absence of the tendon-reflex without wasting and degeneration of muscle indicates degeneration of the posterior columns of the cord. Absence of the tendon-reflex with wasting of muscle and sensory disturbance indicates peripheral nerve-degeneration or destruction of the central grey matter of the anterior and posterior horns. Absence of the tendon-reflex with wasting and degeneration of muscles, but without sensory disturbance, indicates degeneration of the anterior-horn cells or primary progressive myopathy. By muscular degeneration is not meant disuse-atrophy, but a wasting accompained by changes in electrical excitability of the nerve and muscle.

Bastian has pointed out that complete destructive transverse lesions of the spinal cord high up in the dorsal or cervical regions (in which *presumably the reflex arc is intact*) are often followed by absence of the knee-jerk. Here the pyramidal tracts will be degenerated, and it is difficult therefore to understand why the

* *Myotatic irritability* is the term used by Gowers to embody his view that the knee-jerk and other deep reflexes depend on the increased irritability of a *stretched* muscle. This is increased when cerebral influence has been removed by pyramidal degeneration.

knee-jerks are lost. It has been thought by Bastian to be due to the removal of cerebellar influence. The knee-jerk is diminished in old age, during sleep, and in anæmia of the spinal cord.

In cases in which the restraining influence exercised by the higher centres in the cerebral cortex upon the lower (reflex) centres is cut off owing to degeneration of the pyramidal tracts, the knee-jerk is "exaggerated" (excessive in degree and elicited by slight stimuli). In such cases another phenomenon is often obtainable; if the calf-muscles which extend the ankle-joint are suddenly put on the stretch by pressing the hand against the sole of the foot, a quick contraction occurs, and by keeping up the pressure there is a recurrence of the contractions at a regular rate (about eight per second); the foot is thus thrown into a series of clonic spasmodic contractions termed the *foot-clonus* or *ankle-clonus*. Conditions which give rise to ankle-clonus are usually accompanied or followed by *contracture*, a state of permanently increased muscular tonus, both alike depending on removal of cerebral control.

The *superficial skin-reflexes* (epigastric, gluteal, cremasteric, plantar) may be lost in those diseases of the spinal cord in which the tendon-reflexes are exaggerated. They are frequently lost in organic brain-diseases, in which also the tendon-reflexes are exaggerated. In functional conditions, such as hysteria, in which the deep reflexes may be exaggerated, they are not lost. In diseases in which the lateral columns of the spinal cord undergo degeneration, a peculiar modification of the plantar reflex may occur, characterised by contraction of the extensor muscles of the toes (*extensor response, Babinski's sign*).

The importance of healthy reflex action exerted by the spinal cord (*reflex spinal tonus*) is shown by the effects of spinal disorders upon the sphincters of the bladder and rectum. The tonic contraction of these muscles is abolished by destruction of the lumbar enlargement of the spinal cord—hence the resulting incontinence of fæces and of urine. If, on the other hand, a transverse lesion of the spinal cord be present above the lumbar enlargement, no loss of these reflexes will occur; but in the absence of volitional impulses from the brain, the sphincter of the bladder may remain contracted, impeding the outflow of urine, and dilatation of the bladder will ensue as the urine accumulates; this dilatation may produce a secondary incontinence as the sphincter finally undergoes stretching.

Disturbance of Sensation.—*Irritation* of the sensory areas of the cord may cause *hyperæsthesia*—an excessive sensibility of the skin to ordinary stimulation; or *paræsthesia*—viz., burning, tingling, creeping, and numbness—*referred* to particular parts of the skin and limbs which correspond with the segments of the cord irritated. Pressure on nerve-roots also gives rise to very severe localised pain; and at the level of a focal lesion of the cord, as in transverse myelitis, there is a feeling as if a cord were tied round the waist (*girdle-sensation*).

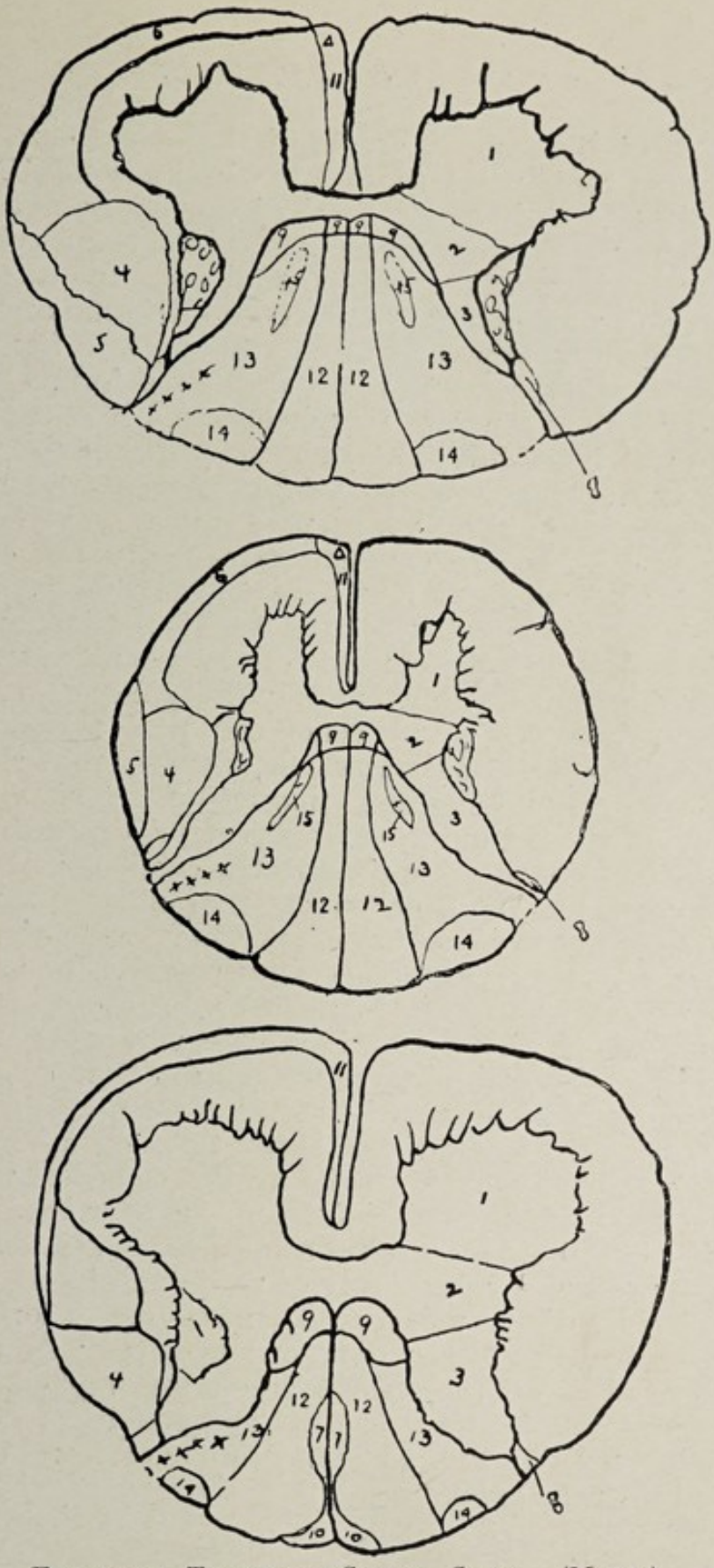

FIG. 217.—TRACTS IN SPINAL CORD. (MOTT.)

1, anterior horn; 2, base of anterior horn; 3, posterior horn; 4, pyramidal tract,; 5, direct cerebellar tract; 6, antero-lateral tract; 7, oval area of Flechsig; 8, Lissauer's zone; 9, cornu-commissural; 10, Gombault and Philippe's tract; 11, direct pyramidal tract; 12, Goll's column; 13, Burdach's column; 14, postero-internal triangle; 15, comma tract; xxxx, root-zone. 7, 9, 10, and 15, are endogenous tracts, and do not undergo degeneration in locomotor ataxy. The ground-fibres situated around the grey matter are commissural, uniting the different segments of the cord.

Destruction of the sensory tracts of the spinal cord or of the posterior spinal roots will lead to loss of sensation. The sensory defects may be loss of sensation (1) of touch (*tactile anæsthesia*), (2) of painful sensations (*analgesia*), (3) of heat and cold (*thermo-anæsthesia*), (4) of muscular sense (*ataxia*).

The posterior roots convey to the cord all forms of sensibility; hence, when the morbid process affects the roots, all forms of sensibility may be affected. But when the fibres forming the roots enter the cord, they separate morphologically into three systems having different functions: (1) "short spinal" ending in the grey matter of the spinal segment, taking part in the reflex arc; (2) "middle length" fibres which pass into the external part of the posterior column and conduct impulses to the cerebellum; (3) "long fibres" which at first line the external portion of the posterior column, afterwards reach the median portion, and conduct kinæsthetic impulses to the opposite cerebral hemisphere.

The path of the sensory (afferent) impulses is not definitely established. It may, however, be concluded that the grey matter conducts painful and thermal sensations, while the posterior columns conduct tactile and muscular sense-impressions. The other afferent tracts in the cord—the antero-lateral (ventral cerebellar) and the direct cerebellar—conduct impulses to the cerebellum. There is a descending cerebellar tract, occupying the anterior border of the lateral column, the fibres of which probably arise from Deiters' nucleus (Fig. 233, p. 575). The accompanying diagram (Fig. 217) represents the various afferent and efferent tracts of the spinal cord. Those tracts which arise from cells within the spinal cord are spoken of as *endogenous*, those which arise from cells outside—*e.g.*, the spinal ganglia—are spoken of as *exogenous*.

Owing to the existence of the separate tracts of fibres noted above, it is possible for one form of sensation to be lost while others are preserved. Thus, in disease of the grey matter (syringomyelia), we have the characteristic symptom of *sensory dissociation*—viz., tactile sense preserved, while sense of pain and of heat and cold is lost. In diseases of the posterior columns—*e.g.*, locomotor ataxy—we may have ataxy either alone or associated with anæsthesia. In general myelitis all the sensory tracts are implicated, and all forms of sensation are affected. In transverse lesions of the cord there is an interruption to the transmission of all forms of sensation from parts below the lesion.

CEREBRAL LOCALISATION.

In the brain, differentiation of function and structure finds its highest development, and morbid processes may be so localised as to lead to derangement or loss of some particular function. Cerebral localisation in *man* is sometimes said to have had its foundation in the discovery, in 1861, of the *speech-centre* by Broca,

after whom is named that portion of the brain corresponding with the third left frontal convolution and its junction with the ascending frontal. The important clinical observation of Hughlings Jackson, who showed that an irritative lesion of the cortex produced epileptiform convulsions affecting representative groups of muscles in a definite sequence, received its anatomical and physiological explanation by the experimental discovery of cerebral localisation by Fritsch and Hitzig in the dog.

The Rolandic Area (Central Convolutions, Motor Area).—There is abundant evidence to prove that the departure-platform of the efferent motor impulses is situated in the central convolutions,

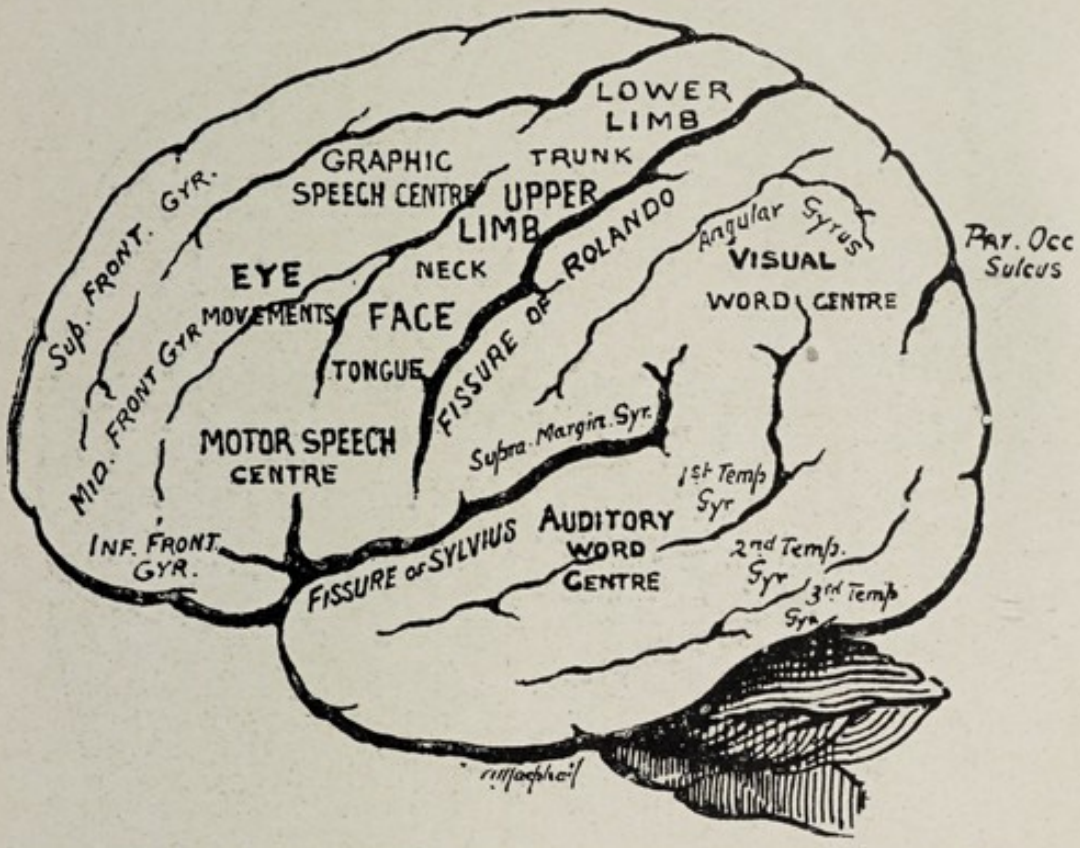

FIG. 218.*—LEFT HEMISPHERE, SHOWING THE SITUATION OF THE CORTICAL PROJECTION-CENTRES.

immediately anterior to the fissure of Rolando (Fig. 218). The neurones of this system are physiologically connected with the terminals of the afferent system, while further communications are effected by the tangential system of fibres in the superficial layer of the cortex, by which co-ordinate action of adjacent systems is maintained.

In every voluntary movement the whole *three nervous circles* (*cerebral, cerebellar,* and *spinal*) are in action (Fig. 233); impulses are ascending the afferent systems and descending the efferent during the whole time. We are conscious of the position of our limbs by the sensations which ascend the afferent system, and this

* Fig. 218 has been reproduced from Monro's "System of Medicine," by permission of the publishers, Messrs. Bailliere, Tindall, and Cox.

consciousness is necessary to, and precedes, volitional movement. *The sense of movement* (*kinæsthesia*) is a combination of the sensations proceeding from skin, muscle, tendons, and joints. *A priori* we should expect the arrival-platform of these sensations in the cortex to be in close proximity to the departure-platform of the efferent system. Flechsig, by the embryological method, has

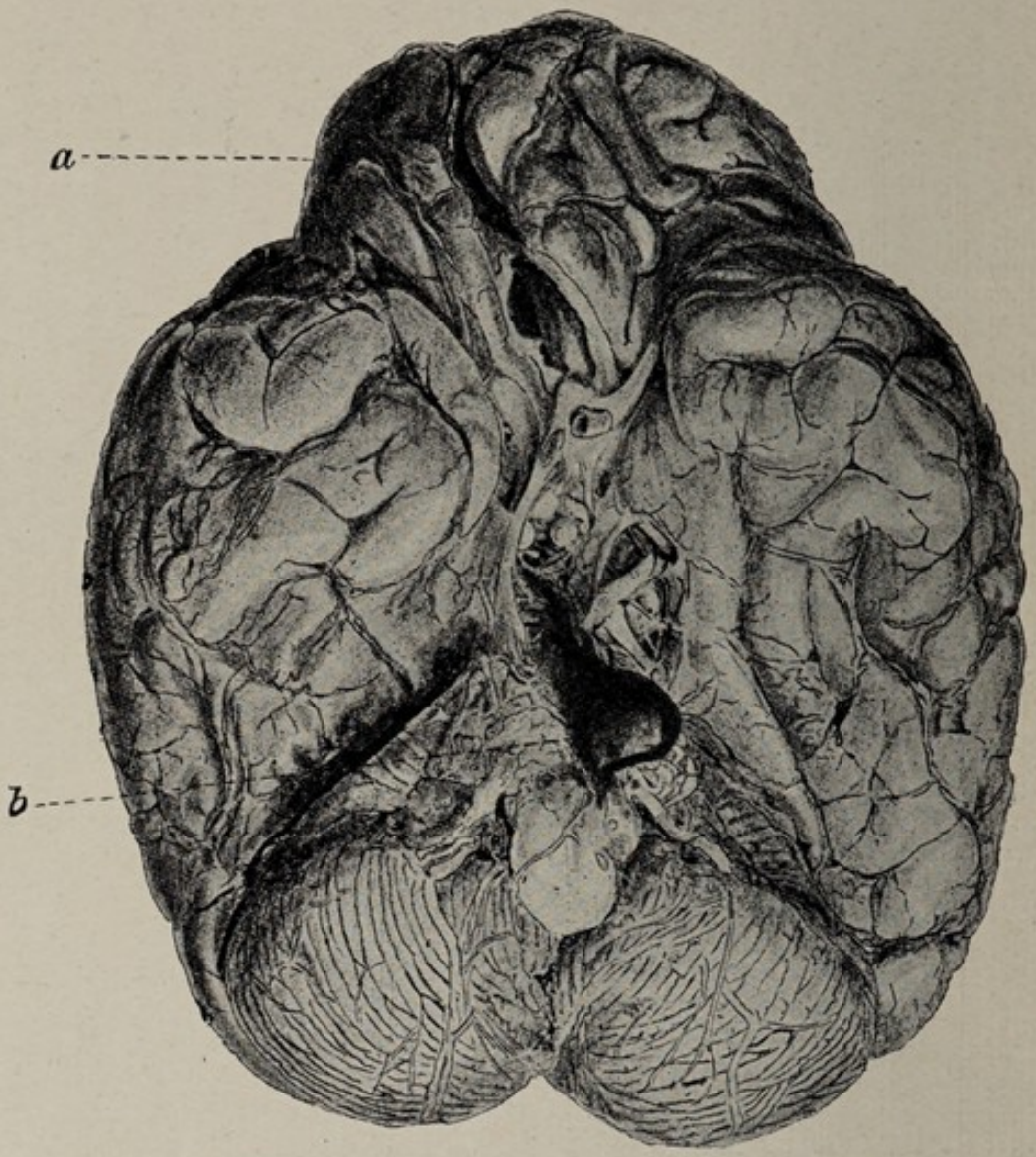

FIG. 219.—PHOTOGRAPH OF BASE OF BRAIN. (MOTT.)

a, atrophy of the right frontal lobe, due to softening; *b*, healed aneurysm of the basilar artery. From a case of post-hemiplegic dementia with epilepsy.

shown that the sensory fibres of the internal capsule terminate in the central convolutions. It must be admitted, however, that *lesions of the cortex do not as a rule produce marked sensory defects.*

Lesions of the brain may be irritative or destructive. If an *irritative lesion* be situated in the excito-motor area, it will cause *fits*, commencing usually with a *sensory aura* in the part which is thrown into convulsions. If it be a *destructive lesion*, there will be a *loss of function*, which may or may not be discoverable, accord-

ing to the side of the brain affected and the part injured. If the lesion be small and localised, there may result a paralysis of a single limb or other part (*monoplegia*). By careful observation of such cases, and by experiments on animals, it has been possible to map out the Rolandic area in man into definite areas (Fig. 219).

Broca's Area.—The part of the brain corresponding with the posterior part of the third left frontal convolution and its junction with the ascending frontal was identified by Broca in 1861 as the centre for articulate speech, lesions in this region being followed by motor aphasia or inability to put ideas into spoken words.

The **angular gyrus** is stated to be the seat of visual word-memory or power of reading, while the posterior third of the **first temporal convolution** is said to contain the centre for auditory word-memory or ability to understand spoken words. Disease of the base of the **second frontal convolution** has been found associated with inability to write words (*agraphia*), power of speech remaining intact. *Loss of speech*, of *visual word-memory*, of *auditory word-memory*, or *agraphia*, only occur when the centres in the *left hemisphere* are destroyed, *unless* the patient be born a *left-handed* person.

The **occipital lobes** are connected with vision. Thus Munk first demonstrated experimentally that removal of both occipital lobes caused blindness, while removal of one only caused blindness of the opposite half of the field of vision (*hemianopsia*).

Frontal Lobes.—It is probable, from observations upon the effects of disease and of extensive injuries, that the frontal lobes are concerned with the higher functions of mind, as impairment of the intellectual, moral, and emotional faculties has been the only result of extensive destruction of the cortex in this region (Fig. 219). Even extensive lesions in the frontal region may in some cases not be discoverable during life—probably owing to want of previous knowledge of the intellectual and moral character of the individual before he was afflicted.

Other parts of the brain, which cannot be shown to possess motor or sensory power, are supposed by Flechsig to consist of *association-centres* (so-called " silent areas ").

Lesions in the **centrum ovale** produce effects according to the size and seat of the lesion. The motor and sensory projection-systems form two funnels, each having its base at the cortex and its neck at the internal capsule (Fig. 232). It requires a large lesion in the region mentioned to interrupt the whole of the fibres belonging to one of these systems.

Lesions of the **internal capsule** are especially common in both softening and hæmorrhage. Both motor and sensory fibres pass through this region, the latter occupying the posterior third of the capsule, the former the central third, while the functions of the anterior fibres are uncertain. The most common effect of a lesion in this region—or of one which causes pressure upon the capsule—is *hemiplegia*, the opposite side of the body being paralysed. This

condition may be accompanied by *hemianæsthesia*, in some cases, on the same side of the body as the paralysis.

The functions of the **cerebellum** have been determined more accurately in recent years, and Luciani has shown that removal of this organ in animals produces *asthenia*, *atonia*, and *astasia*. It is generally admitted that the cerebellum is an organ concerned with *muscular co-ordination*, and it is probably by the exercise of this function under the guidance of peripheral stimulation that it serves to maintain *steadiness in gait and station*. Each lateral lobe of the cerebellum is connected with the motor cortex of the opposite cerebral hemisphere. Probably the cerebellum has also an important influence upon the *maintenance of tonus* in the *fixation of a joint* by the *correlative action* of the antagonistic muscles. The results of *cerebellar disease—e.g.*, tumour, cyst, or abscess—are *unsteadiness of gait and station;* the ataxy which results is peculiar, *the gait being oscillating*, causing the patient to sway to and fro like a drunken man. As a rule the patient walks and tends to *fall towards the affected side in unilateral lesions*. There is generally *hemiparesis* on the same side as the lesion.

Injury to the **pons Varolii** may be accompanied by hyperpyrexia, by conjugate deviation of the head and eyes, by contraction of the pupils, and by crossed paralysis, the face being paralysed on the same side as the lesion, the arm and leg on the opposite side. This last phenomenon is due to the fact that the fibres from the face-area of the cortex cross to the opposite side in the pons; those from the arm- and leg-areas decussate in the medulla.

AFFECTIONS OF THE MENINGES.

Three membranes enclose the central nervous system, but owing to the intimate connection of the pia mater and arachnoid these two always suffer together. Inflammation of the tough fibrous *dura mater* is termed *pachymeningitis*. Inflammation of the soft *pia-arachnoid* is termed *meningitis*, or more precisely, as the antithesis to pachymeningitis, *leptomeningitis*.

Pachymeningitis.

The dura mater consists of two layers, a thick outer layer which is periosteal in its functions, and a thin inner layer with a smooth epithelial surface. Either layer may be the seat of inflammation, which is usually chronic.

External pachymeningitis is frequently caused by caries or necrosis of the spine or bones of the skull, due to syphilis, wounds, or extension from disease of the middle ear. The dura mater at first is œdematous and congested; later it may be covered with pus, which separates it from the bone and also infiltrates its substance. If the inflammation does not become purulent, the thickened outer layer of dura mater may become firmly adherent to the bone.

Internal pachymeningitis is characterised by the formation of an organised inflammatory exudate, which usually causes adherence of the dura mater to the arachnoid, and extends generally over the greater part of one or both hemispheres. This formation, which is practically a layer of granulation-tissue, consists of several layers, and is usually very vascular. Owing to the rupture of vessels, blood-cysts are found between the layers, known by the name of *hæmatomata* of the dura mater. The condition is rare, and is met with usually in general paralysis of the insane and in chronic alcoholism.

Meningitis or Leptomeningitis.

ÆTIOLOGY.—Inflammation of the pia-arachnoid is in nearly all cases due to infection by micro-organisms. *The most important form is tubercular* (p. 251). A number of other causes of infection exist, which may be considered under the headings *local* and *general.*

Local Causes.—1. Traumatic injuries of the head with direct infection by pyogenic organisms.

2. Adjacent disease outside the dura mater—suppurative otitis, caries of the mastoid or petrous portions of the temporal bone, and occasionally disease of the bones of the nose or orbit. The infection in these cases may spread directly, or along the course of lymphatics or bloodvessels. It is probable that some cases of meningitis in which no visible organic cause is found post mortem may have arisen by the infection gaining access to the middle ear by the Eustachian tubes.

3. Tumours and abscesses of the brain may cause inflammation of the adjacent meninges.

General Causes.—Meningitis may occur in the course of certain infective diseases—*e.g.*, small-pox, scarlet fever, measles, septicæmia, syphilis, gonorrhœa, pneumonia, and acute rheumatism. Cerebro-spinal meningitis, due to a specific diplococcus (p. 120), may also occur in an *epidemic form.* A form of meningitis described by Barlow and Gee, designated *posterior basic meningitis,* is due to the same or to a closely allied diplococcus. It affects infants and young children, and one-half the cases are fatal.

Meningitis in rare instances has followed a blow not causing any wound, and it has been found post mortem in some cases of sun-stroke. Thickening and opacity of the membranes also occur in chronic wasting degenerative processes of the central nervous system; for example, tabes dorsalis and general paralysis: the process is here generally considered to be *secondary* to the atrophy.

MORBID ANATOMY.—When the infection is local, the meningitis may be circumscribed; but when the cause is some infective blood-condition, it is usually generalised, and may in some cases affect the spinal as well as the cerebral meninges—*e.g.*, meningitis occurring in the course of pneumonia may in many ways resemble the

epidemic form. Tubercular meningitis usually affects *the base* primarily and especially, whereas in other forms the *convexities* of the hemispheres are affected. Certain changes are common to all forms of meningitis. The pia mater is intensely hyperæmic and red, as if the vessels had been artificially injected. Soon opacity and thickening of the membranes occur, recognisable most readily in the arachnoid, especially along the course of the vessels, owing to distension of the perivascular lymphatic sheaths. An inflammatory exudation from the bloodvessels of the pia mater occurs; this may be serous, sero-purulent, or purulent, and is most abundant in the sulci of the convexity and in the spaces at the base of the brain. In severe cases pus mixed with fibrin forms a continuous opaque yellowish layer under the visceral layer of the arachnoid. The inflammation usually spreads to the adjacent structures, causing neuritis, myelitis, encephalitis, and, later on, adhesions. The ventricles of the brain and the interpeduncular subarachnoid space may be distended with a turbid serous fluid, and the choroid plexus and the velum interpositum are usually congested and swollen. This fluid, examined microscopically, may be found to contain large granular epithelial cells, leucocytes, or pus-cells.

The suppurative process is extremely marked, and often very rapid in development, in epidemic cerebro-spinal meningitis.

Effects.—The first stage, or *period of excitation*, is characterised by headache, delirium, rigidity, and general or local convulsions: these symptoms can be accounted for by the irritation, in early stages of inflammation, of the cortex, crus, pons and medulla, or of the spinal cord and nerves. The second stage or *period of depression* occurs as the inflammation extends into the cortex and motor nerves, *paralyses* of various kinds appearing. In the final stage, the increasing effusion into the skull causes a rise of intercranial pressure, and thus induces *coma*.

THE CEREBRO-SPINAL FLUID.

The cerebro-spinal fluid is altered in many cases of disease. Thus it is *increased in quantity* in cases in which there are pressure on the veins of Galen and resulting venous hyperæmia, as well as in inflammatory conditions of the membranes. It may exist under *increased pressure* in such conditions, and also in renal affections.

Obliteration of the foramen of Magendie, by preventing the escape of cerebro-spinal fluid from the ventricles of the brain and causing its accumulation in these cavities, produces *hydrocephalus* or distension of the ventricles with fluid: the cerebral substance then atrophies as a result of pressure. In other cases wasting of the brain-substance is followed by increased exudation of fluid to fill up the cranial cavity (general paralysis, senile atrophy).

In meningitis the number of *leucocytes* in the cerebro-spinal fluid

is increased—in tuberculosis the lymphocytes predominating, in most other infective conditions the multinuclear leucocytes. *Infective organisms* may exist in this fluid; as, for example, tubercle bacilli, pneumococci, meningococci, and trypanosomes. The percentage of albumen present is also increased in infective (inflammatory) conditions, and also in spinal tumours, in which case there is usually no increase in the cell-count.

CHAPTER XXXIV

PATHOLOGY OF THE NERVOUS SYSTEM—*Continued*

INFLAMMATION OF THE CENTRAL NERVOUS SYSTEM.

Encephalitis.

INFLAMMATION of the brain may arise from three causes: traumatic injury, inflammation of adjacent structures, and acute infective diseases—erysipelas, typhoid fever, typhus and diphtheria. *Anatomically*, the alteration in the brain-tissue which results from acute inflammation is a process of *red softening*.

A primary inflammation of the grey matter of the brain (*polio-encephalitis*) occurs in some cases of poliomyelitis (p. 557), and may exist without any obvious spinal lesion. The condition may be signalised by temporary blindness, deafness, or paralysis of cranial nerves. If the cerebellum be affected, there may be ataxy.

Cerebral Abscess.

The causes of this condition may be divided into local and distant. By far the most frequent *local* cause of cerebral abscess is *chronic ear-disease*. Inflammation of the middle ear or mastoid cells is often followed by a purulent discharge and by *caries of the bone*; not infrequently arrest of the discharge, owing to defective drainage, is followed by abscess. Occasionally there may be no bone-disease, only suppurative inflammation of the middle ear or mastoid cells; and in such cases the infection probably passes by the perivascular lymphatics along the veins which connect the tympanic cavity and mastoid cells respectively with the superior petrosal and lateral sinuses. Disease of the nose and orbit, syphilitic caries of other bones, tumour of the brain, and injury, are among the rarer causes of cerebral abscess. *Distant causes* are pyæmia, gangrene of the lung, fœtid bronchitis, bronchiectasis, and empyema —all rarely met with—in which the infective agents are carried to the brain by the blood-stream. Streptococci and staphylococci are the micro-organisms most often responsible for the suppuration.

MORBID ANATOMY.—Abscesses are usually solitary, but there may be several, and in pyæmia sometimes many; in size they are

rarely less than that of a walnut, and may even involve the greater part of a cerebral hemisphere. Owing to the frequency with which ear-disease acts as a cause, abscess is met with most often in the temporo-sphenoidal lobe and in the lateral lobe of the cerebellum. In nasal and orbital disease it is usually found in the adjacent frontal lobes. In chronic cases the abscess-cavity is limited by a well-defined capsule: the more acute the abscess, the less tendency is there for it to be circumscribed.

The process of *suppuration* commences with inflammatory softening, cell-infiltration replacing and destroying the normal structure. Pus is formed, which in the case of ear-disease is usually of a greenish colour, and frequently of fœtid odour and acid reaction. The pus is contained at first in an irregular cavity, and there is a tendency for the abscess to increase by necrosis of portions of the limiting tissue; it may thus, by spreading, burst into the lateral ventricles or externally. It may, however, become encapsuled by connective tissue, the pus then becoming thick and viscid. It is thought that pus thus encapsuled may dry up and caseate or calcify, or even be completely absorbed, leaving little more than a scar, but this must be a very rare occurrence. The symptoms produced by abscess depend upon local irritative effects of the infective inflammation, septic absorption, and, in severe cases, increase of intracranial pressure.

Myelitis.

The term *myelitis* has been used for all forms of "degeneration" of the spinal cord, and thus we have the sub-divisions—acute, sub-acute, and chronic; or it may be considered according to its localisation, and then the terms "transverse myelitis," "diffuse myelitis," "leuco-myelitis," "poliomyelitis," and "meningo-myelitis" are used.

The true causes are probably infective organisms or toxic agencies. Cold and injury may operate, as in pneumonia, by lowering the vital resistance. Some forms may be due to vascular occlusion, and analogous to cerebral softening.

Of all the infective diseases which lead to these various forms of myelitis, syphilis is the most important; but tuberculosis (in the production of Pott's disease and meningo-myelitis), epidemic cerebro-spinal meningitis, gonorrhœa, measles, diphtheria, influenza, scarlet fever, small-pox, and typhoid fever offer examples of infective diseases which have been followed by various forms of myelitis. Probably the inflammation is due to the *toxines* produced in the blood by the infective organisms. Other toxic agencies, as in ergotism, pellagra, and lathyrism,* offer examples of *vegetable poisons;* lead and arsenic, of *mineral poisons*, any of which may cause myelitis.

* Poisoning by *Lathyrus*, chick-pea.

Acute Myelitis.—The naked-eye appearances are variable; the spinal tissue is sometimes softened, pinkish-white in appearance, yellowish or brownish-red, according to the condition of the blood-vessels and the amount and change in the extravasated red blood-corpuscles. In an early stage, a large number of granular corpuscles and amyloid bodies appear; the axis-cylinders are either swollen and granular, or destroyed, and the myelin-sheaths of the white matter are rapidly broken up. The ganglion-cells undergo degeneration; their processes are swollen and varicose, or broken off. Stained by Nissl's method, the chromatic substance loses its normal appearance, and the granules are no longer visible in the cell-body or dendrons. The protoplasm is diffusely stained, and the nucleus eccentric or extruded; later, the cells present signs of atrophy, and eventually may completely disappear.

The *vessels*, thrombosis of which appears in many cases to be the determining cause of the above-mentioned changes, are engorged with blood, and their lymphatic sheaths filled with leucocytes; and when the inflammation is very intense, hæmorrhages may be found. There is an increase of nuclei and small round cells in the grey matter, and Deiters' cells are more numerous than normal.

Later the connective tissue undergoes proliferation, and there is rapid progressive softening of the nervous elements owing to granulo-fatty degeneration. The process thus passes into the chronic stage constituting *grey softening*. Hæmorrhages may occur in these foci of softening; and eventually the process ends in a *sclerosis*, an overgrowth of fibrous connective tissue replacing the cells which have been destroyed.

All varieties of **diffuse myelitis** have a common pathological anatomy, but the clinical symptoms will of necessity vary according to the seat, extent, and distribution of the inflammatory process.

Meningo-Myelitis.—Erb has called attention to the fact that in syphilis, very frequently in the early secondary stage of the disease, a *focal myelitis* occurs, the principal features of which are diffuse myelitis of the white matter (not involving definite tracts), local thickening of the meninges, and a *periphlebitis*, with venous stasis or thrombosis, but no syphilitic changes in the arteries.

Transverse myelitis is produced by Pott's disease, aneurysm, tumours, and thickening of the dura mater. The symptoms vary according to the seat of the lesion. The mechanism of the damage to the cord is twofold—viz., *compression* and *inflammation*. The cord may (at the seat of compression) be flattened, indented, or even reduced very greatly in size; on section it has usually a grey appearance. The microscopical appearances of inflammation correspond with those already described, and the changes in the cord above and below the seat of injury are described under *Secondary Degenerations* (p. 576).

The pathological effects may be considered under two distinct headings—*Root-symptoms* and *Cord-symptoms*. The former usually develop first in the form of *shooting pains*, owing to irritation of the

sensory roots involved. With the pain there is usually *hyperæsthesia* of the skin. Irritation of motor roots causes *painful contracture. Cord-symptoms* are: paresis or paralysis below the lesion, *increase of superficial reflexes* and of *myotatic irritability* (p. 541). There may be no loss of sensibility discoverable in the parts below the lesion, although there is complete paralysis; but there may, on the other hand, be delay, and in severe cases absolute loss, of sensation. Paralysis of the sphincters and a tendency to bed-sores accompany lesions affecting the lumbar enlargement. If the lesion be in the lower cervical region, the pupils may be affected from implication of the cilio-spinal centre, and the pulse-rate diminished from damage to the accelerator fibres of the heart.

Poliomyelitis.—An acute inflammation of the anterior cornua is the morbid change found in *infantile paralysis* and in *acute spinal*

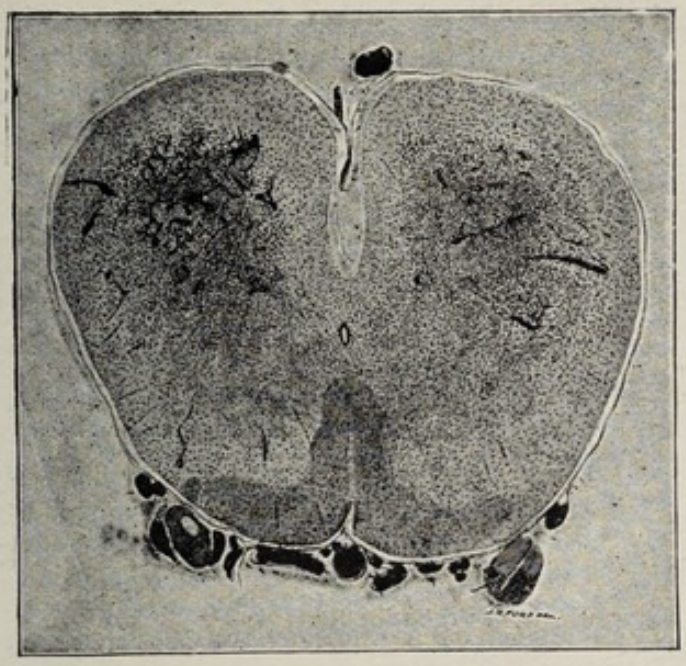

FIG. 220.—ACUTE ANTERIOR POLIOMYELITIS.

paralysis of the adult. Flexner and others have shown that injection into a monkey of ground-up spinal cord from a patient who has died of this disease will reproduce in the animal a condition of poliomyelitis, and that the infection can be similarly passed from this animal to a second. More recently the causal organism has been cultivated, and has been shown to reproduce the disease in monkeys. It is a minute coccus, so small as to pass through the pores of many types of porcelain filters.

The microscopical appearances of the anterior horns in a recent case are similar to those described as occurring in caute myelitis, showing congestion of the bloodvessels, hæmorrhagic foci, perivascular infiltration with mononuclear cells, and degenerative changes in the nerve cells (Fig. 220). When the acute process has subsided, the cells destroyed are replaced by connective tissue, which shrinks

as it grows older (Fig. 221).* Thus, in an old case, the segments of the spinal cord corresponding with the muscular paralyses (usually the lumbar and cervical enlargements) exhibit a more marked translucency of the grey matter of the anterior horns; and if limited to one side, as it often is, a diminution in size of the anterior horn as compared with the opposite healthy side. The anterior-horn cells may be absent, or vestiges of degenerated ganglion-cells, in the form of obtuse or rounded protoplasmic bodies without processes, may be present. The fine nerve-plexus around the cells is either greatly diminished or completely absent, and only neuroglia and Deiters' cells may be visible. The fibres forming the anterior root

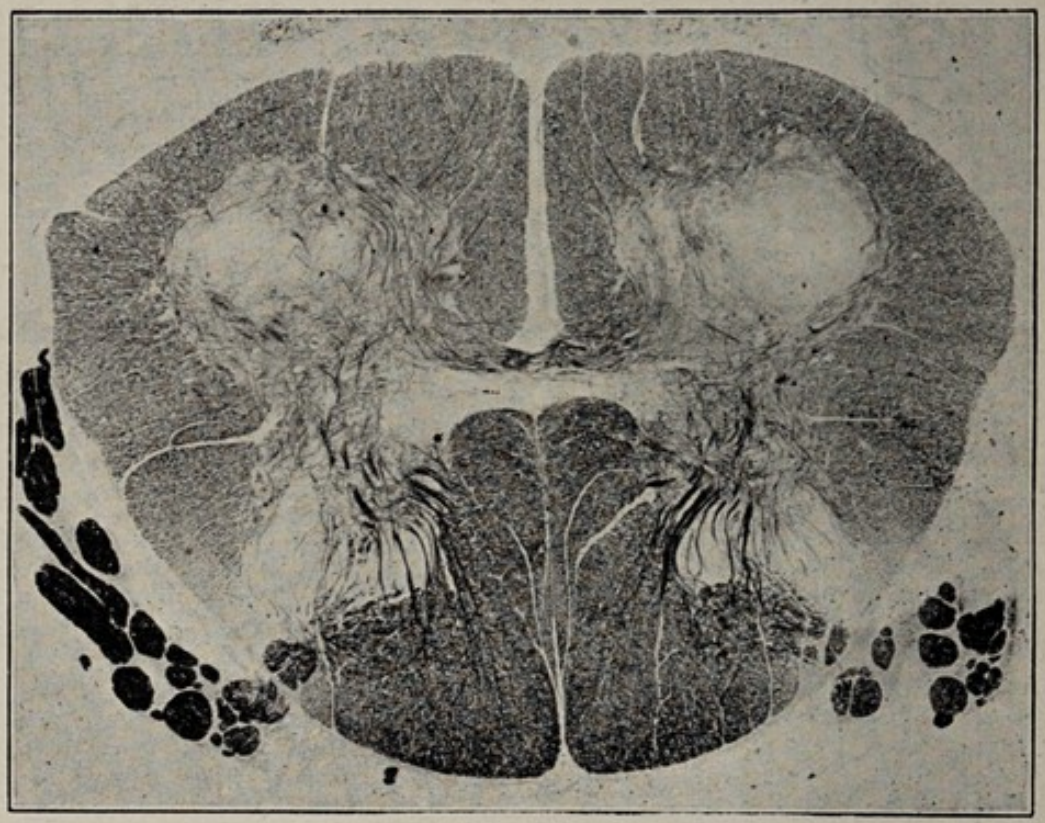

FIG. 221.—ANTERIOR POLIOMYELITIS OF TWO MONTHS' STANDING.

are necessarily destroyed along with the cells from which they originate, and the roots therefore shrink in size. The vessels are thickened. When the lesion is bilateral it is rarely symmetrical; more frequently it is unilateral, and it will then be observed that there is secondary atrophy of correlated structures of the same half of the cord—viz., of the posterior column, antero-lateral column, and posterior horn: some observers have described atrophy of the corresponding motor convolutions of the brain.

Landry's Paralysis (*acute ascending paralysis*).—No definite lesion has been described in this disease; it may be due to the effects of a toxine acting upon the central or peripheral nervous system. *The*

* We are greatly indebted to Dr. F. E. Batten for permission to reproduce Figs. 220 and 221 from his Lumleian lectures of 1916.

absence of troubles of nutrition and sensibility points to the poison acting, like curare, especially upon the motor tract, and serves to distinguish the disease from acute myelitis (p. 556).

CONGENITAL DEFECTS OF THE BRAIN.

Only those defects associated with Congenital Hemiplegia, Diplegia, Epilepsy, and Imbecility, will be here described.

Infantile paralysis of cerebral origin arises from a number of morbid conditions. Some are of vascular origin, some are due to inflammatory conditions, and some to arrested development.

MORBID ANATOMY.—*Cysts*, *areas of sclerosis*, or *patches of softening*, may be found—the result of embolism, thrombosis, or hæmorrhage, usually meningeal. A congenital defect of the convolutions of variable extent, by which a cavity is formed, penetrating a variable distance into the hemisphere, sometimes as far as the ventricles, is termed *porencephalia*. The meninges are intact and present neither thickenings nor adhesions; often the membranes are found adherent to the ependyma of the ventricles. The defect is generally limited to the area of some definite vascular supply. The convolutions around usually present a radiate appearance.

Atrophy and Sclerosis.—Groups of convolutions, an entire lobe, or the whole of a hemisphere may be wasted (Fig. 222), and usually in such cases there is atrophy of the opposite half of the cerebellum. The membranes may appear normal; more often they are thickened and adherent. Sometimes there are little nodular projections all over the surface of the atrophied convolutions. Some of these cases may be the result of polio-encephalitis, others are due to thrombosis of veins. In both conditions multiple hæmorrhages, atrophy of nervous tissue, and overgrowth of glia-tissue are found.

Mention may also be made of a severe form of infantile paralysis, of cerebral origin, associated with blindness, which affects members of the same family. It has been termed by Sachs, who described its pathology, "amaurotic family idiocy." It may be due to hereditary failure of development (*agenesis corticalis*); but in most instances it seems rather to result from progressive degeneration of the cerebral cells. It is characterised by a peculiar form of optic atrophy, in which a greyish patch with a cherry-red spot in the centre is visible in the macular region of the fundus oculi.

TUMOURS.

Cases clinically described as "cerebral tumours" are not infrequent: according to Starr, this condition is the cause of death in one case out of every 120 examined upon the post-mortem table of hospitals. The condition is met with most frequently in early and middle life; it is twice as frequent in males as in females, and of all

the cases of cerebral tumour more than one-half are tubercular. *Secondary* deposits may occur in the brain, arising from malignant

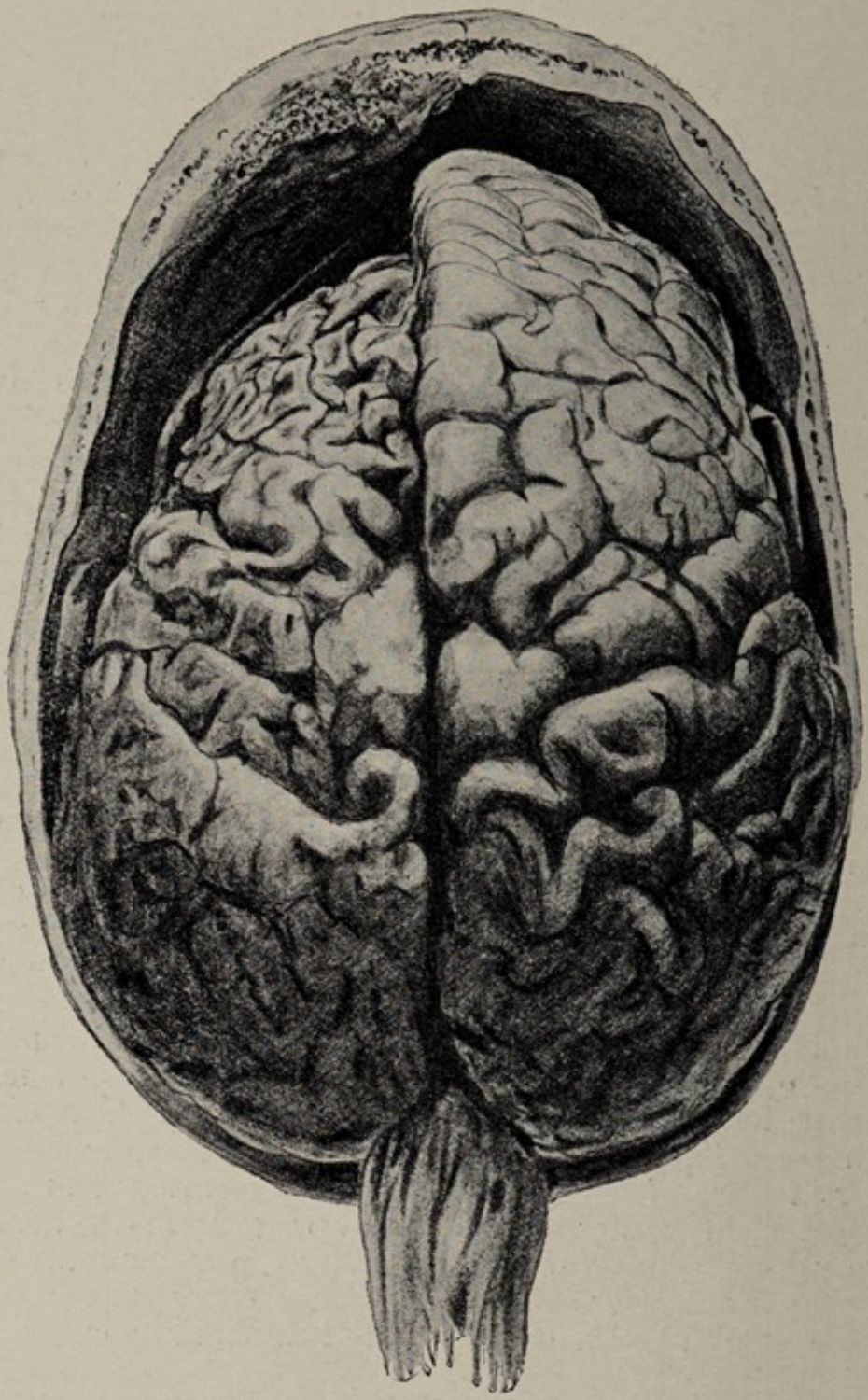

FIG. 222.—HEMIATROPHY OF THE LEFT HEMISPHERE. (MOTT.)

From a case of congenital hemiplegia with epilepsy and imbecility. There was also atrophy of the right half of the cerebellum. It will be observed that the bone is correspondingly thickened where the brain is atrophied. The lesion was probably primarily in the anterior part of the optic thalamus.

growths in other parts of the body. They may then be multiple, whereas a primary growth is single.

1. **Gliomata** (p. 291, Fig. 223).—These growths do not necessarily destroy the brain-substance, for frequently the nerve-

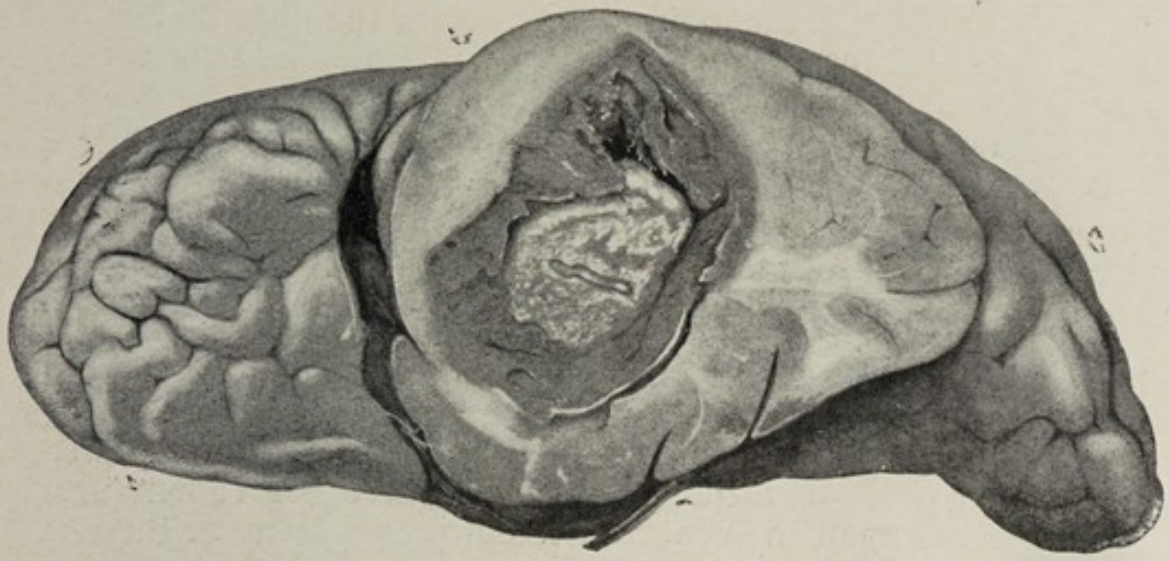

FIG. 223.—GLIOMA OF TEMPERO-SPHENOIDAL LOBE. (FROM A SPECIMEN IN C. C. H. MUSEUM.)

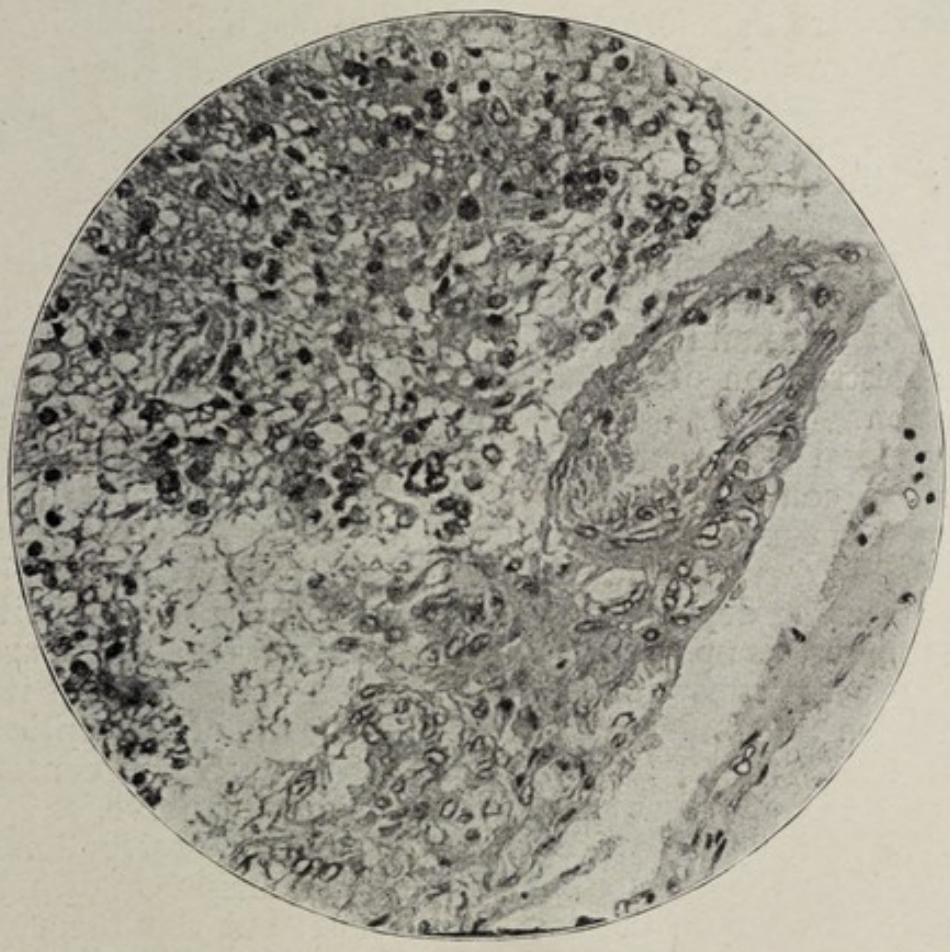

FIG. 224.—MICROPHOTOGRAPH OF A SECTION OF GLIOMA OF THE PONS. (× 300.) (MOTT.)

fibres, being merely pushed aside, retain their conducting power (Fig. 224).

2. **Sarcoma** (p. 304) seldom arises in the substance of the central nervous system, being of mesoblastic origin. Primary sarcoma commences in the fibrous structures of surrounding tissues—for example, in the pia-arachnoid membrane, in the dura mater, in the periosteum of the cranial bones and vertebræ, and in the bones themselves, especially of the base of the skull.

3. **Gummata.** (See Syphilis of the Nervous System, p. 566.)

4. **Tubercular Masses** (p. 253).—These tumours are most frequently met with, according to Gowers, in (1) the cerebellum, (2) the cortex, and (3) the pons. They occur especially in children, and frequently give rise to *hydrocephalus*.

5. **Carcinoma** is nearly always secondary, and the primary growth is most frequently in the mammary gland; this form is multiple and grows rapidly.

6. **Psammomata** (p. 296) as a rule do not produce symptoms of intracranial pressure, although they may give rise to convulsions when pressing upon the central convolutions. Many of these may be seen upon the post-mortem table in cases which were classed as "epileptic dements" in the asylums. The tumours are circumscribed, and indent, but do not infiltrate, the subjacent brain-tissue; they are therefore quite capable of removal.

Parasitic cysts (echinococcus and cysticerci (p. 87), *cholesteatomata, angio-sarcomata, angiomata, dermoid cysts, cysts of the choroid plexus,* and other growths—*e.g., tumours of the hypophysis cerebri*—are met with in rare cases. The morbid anatomy of these tumours is described elsewhere.

Effects.—The pathological effects of tumours are: (1) Increased intracranial pressure upon all parts of the brain, producing compression of veins and hydrops ventriculorum; and (2) direct irritation or destruction of nerve-elements, causing loss or impairment of function.

The **general symptoms of tumour** are headache, vomiting, vertigo, slow pulse, convulsions, stupor, drowsiness, and, most important of all as a means of diagnosis, optic neuritis. All these symptoms are probably due to increased intracranial pressure.

Optic neuritis depends not so much upon the size and situation of the tumour, as upon the rapidity of its growth. There are three views as to the causation of optic neuritis—viz., (1) that it is due to irritation and inflammation of the sheath of the optic nerve, produced either by irritation arising from substances contained in the cerebro-spinal fluid of the sheath of the optic nerve, or by direct extension of meningitis; (2) that it is due to obstruction of the outflow of the venous blood from the ophthalmic vein owing to the increased pressure on the cavernous sinus; but this theory of von Graefe has been discounted by the fact that a free anastomosis occurs between the ophthalmic and facial veins; (3) that the intracranial pressure interferes with the return of lymph along the sheath of the optic nerve, causing œdema and swelling of the disc. Gowers inclines to the opinion that a combination of causes may be in

operation. No doubt simple stasis in the veins would soon be followed by exudation and migration of leucocytes, and all the appearances of inflammation might thereby be produced. In many cases of tumour an ampullary swelling has been observed where the sheath is weak at the entrance to the eyeball.

Regional or focal symptoms are caused by either direct or indirect involvement of structures possessing particular functions. The morbid process may occasion phenomena of an *irritative* character—*e.g.*, tumour situated in some part of the Rolandic region may produce unilateral convulsions: or it may be *destructive*, and produce loss of function (paralysis).

Syringomyelia.

This is a *central gliosis* (increase of neuroglia) of the spinal cord causing destruction of the grey matter and *excavation*. The usual seat is around the central canal in the peri-ependymal tissue, or behind the canal in the grey substance of the posterior commissure; thence it invades the anterior and posterior horns. It is usually a neoplastic formation, but according to Charcot it may arise from a central myelitis. The cause of this active growth of embryonic tissue is unknown. The resulting symptoms are muscular wasting and loss of sensation to heat and cold, and to painful impressions, but preservation of sense of touch. This *sensory dissociation* is peculiarly characteristic of the disease, and affords evidence that Schiff was right in asserting that the grey matter conducts painful sensations, and the posterior columns tactile and muscular sense-impressions. The destruction of the anterior horns produces the muscular wasting; that of the posterior horns the sensory disturbance, and, possibly, the trophic affections that often occur. The distribution of the motor, sensory, and trophic changes will depend upon the segments of the spinal cord affected. There may be unilateral destruction of anterior and posterior horns of the same side; and this has been found associated with motor paralysis and sensory disturbance of the same limb or side of the body.

DISSEMINATED CEREBRO-SPINAL SCLEROSIS.

(Insular Sclerosis ; Multiple Sclerosis.)

This very obscure disease is characterised by varying symptoms due to the formation of islands of sclerosis *scattered at random* in the brain, spinal cord, and cranial nerves. It usually attacks healthy young adults of both sexes, and nearly always occurs between puberty and middle life. Many morbid influences have been associated with the disease—*e.g.*, grief, worry, and overwork. As a considerable number of cases have followed an acute specific fever, it has been conjectured that the disease is the result of a toxine.

Morbid Anatomy.—Scattered at random through the brain, spinal cord, and nerves, are *islets of sclerosis* varying in size from a hemp-seed to a walnut (Fig. 226). The naked-eye appearance of these patches varies at different stages of the disease. In the early stage, the morbid process only becomes apparent after the tissue has been hardened in Müller's fluid for a few days, and doubtless this may account for some of those cases which have been confounded with hysteria, owing to the absence of any recognisable lesion on the post-mortem table. In the advanced stage the islets closely resemble gliomata, and present a greyish gelatinous appearance, offering, therefore, a marked contrast to the surrounding white matter, in which they are usually situated. Occasionally the process extends to the grey matter of the cord and medulla, but very seldom to the cerebral cortex. The term *sclerosis*, however, is a misnomer, as the patches are usually softer than the surrounding tissue. They are largest in the centrum ovale, but most abundant and smallest in the spinal cord, although in some cases they may extend in a fusiform manner for a considerable distance.

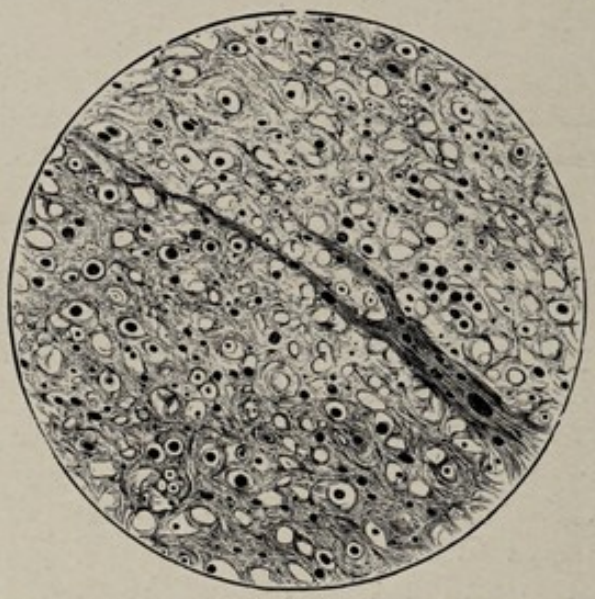

Fig. 225.—Insular Sclerosis: A Small Portion of the Edge of an Island of Sclerosis. (× 180.)

The section shows overgrowth of the neuroglia-tissue at the expense of the white myelin-sheath. The black dots are sections of naked axis-cylinder processes, their myelin-sheath having disappeared.

Microscopically, the islets consist of a feltwork of neuroglia, in the meshes of which are a greatly diminished number of nerve-fibres, presenting for the most part morbid appearances especially affecting the myelin-sheath (Fig. 225). At the edges of the patch a gradual transition into normal tissue can be observed. Where the process is seen in an early stage, the vessels may be found to be dilated. It is uncertain whether this is an inflammatory reaction due to a toxine in the blood, or is only the reaction to injury of the myelin-sheath of the nerve-fibres. It has long been held that although the medullary sheath is undoubtedly absent, the axis-cylinders persist unchanged throughout the islet; only in this way can we account for the fact that *as a rule systemic degenerations are absent above and below the patches*. But cases do occur in which the axis-cylinders also show well-marked changes, and in which they, as well as the sheath, are undoubtedly absent in the sclerosed area. The morbid process appears to begin in the myelin-sheath, which swells up and eventually disappears, its place being occupied by the proliferated neuroglia-tissue. When systemic degeneration occurs,

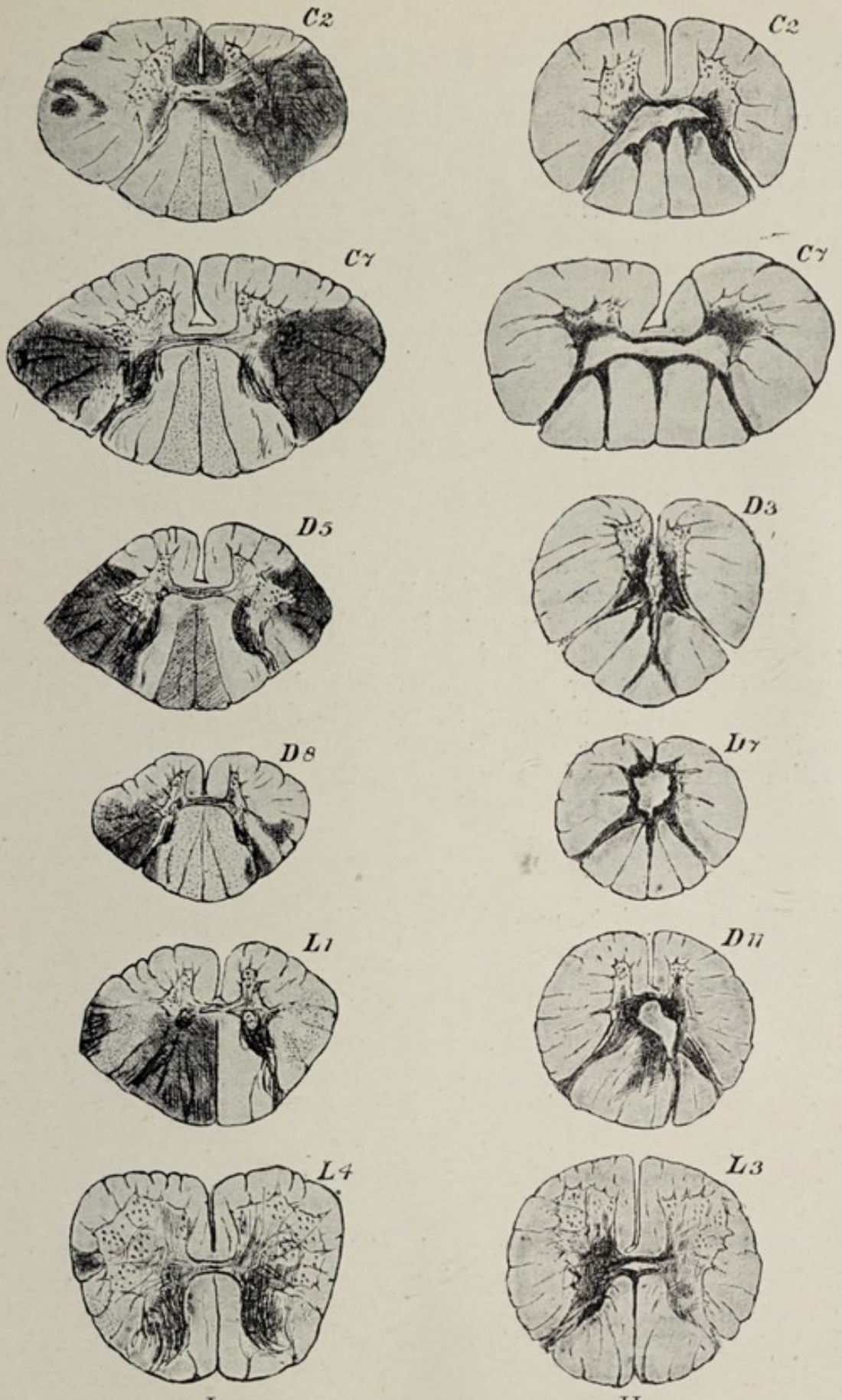

FIG. 226.—A SERIES OF SECTIONS OF THE SPINAL CORD. (A. F. TREDGOLD.)

Drawn to scale from cases of (I.) disseminated sclerosis and (II.) syringomyelia.

The letters and numbers indicate the levels in the cord; thus, C2, 2nd cervical vertebra, etc.

it usually begins in the crossed pyramidal tracts. It has been suggested that the characteristic rhythmical tremors upon intentional movements are due to the absence of the myelin-sheath, so that voluntary impulses are not insulated in their passage along the pyramidal tract.

Syphilitic disease of vessels may produce *single* or *multiple patches* of softening with *secondary sclerosis;* but should these foci of disease be situated in the course of projection-systems, secondary degeneration invariably results.

CEREBRAL ANEURYSM.

The causes of aneurysm of the cerebral arteries are the same as of aneurysm elsewhere—viz., *syphilitic arteritis* and *atheroma;* but besides these an even more important factor is infective embolism. The *arteries of the base* are especially prone to be affected, and the size of the aneurysm may vary from that of a pea to that of a pigeon's egg. The arteries of the left side are more often affected than the right, the carotid system more often than the vertebral. Rupture occurs in rather more than one-half of the cases; the blood most frequently escapes into the membranes at the base of the brain, sometimes into the brain-substance or the ventricle.

SYPHILITIC DISEASE OF THE CENTRAL NERVOUS SYSTEM.

Syphilis is one of the most important factors in the production of disease of the nervous system.

A frequent result of syphilitic disease is an **inflammation of the arteries,** especially about the base, which may result in occlusion of these vessels, either directly by the *endarteritis* produced, or more often by *secondary thrombosis*. Another very common result of syphilis is a local or general **inflammation of the membranes** (*gummatous meningitis*), and the formation of neoplastic deposits (*syphilomata*) on the surface or in the substance of the brain. The meningitis, in severe cases, extends usually to the whole cerebro-spinal axis.

Each of these cerebral forms of this disease may produce most varied symptoms, and the two forms often coexist. Thus, partial or complete occlusion of the vessels may cut off the blood-supply from various portions of the brain, causing *softening* (p. 568) and loss of function (if there is complete occlusion), or disturbance of function, temporary or permanent, if there be some compensatory supply of blood to the part by other vessels. In other cases symptoms of *cerebral irritation* or *increased intracranial pressure* occur. These consist in pain in the head, worse at night, sometimes vomiting and convulsions, and other irritative symptoms, according to the situation of the lesion. Owing to the frequency with which

the *base* of the brain is affected, *paralysis of the cranial nerves* is one of the most common results; a partial or complete paralysis of the third nerve (motor oculi) being present in a majority of cases of cerebral syphilis.

Syphilitic disease of the nervous system may manifest itself at any time from three months after infection to twenty-five or even more years. It was formerly believed that syphilitic brain-disease was essentially a tertiary lesion, but carefully recorded statistics now show that it occurs with greatest frequency in the first or second year after infection, and that the frequency diminishes with each successive year.

Morbid Anatomy.—The virus of syphilis affects the mesoblastic structures of the brain, and produces a round-celled infiltration of the membranes, which may form a superficial colloidal or gelatinous layer, or a deposit in the form of a node or nodule, or multiple nodes or nodules; and this round-celled infiltration may extend from the surface into the substance of the brain along the course of the vessels, or into the fissures, filling them up with a gummy mass. It is probable, as Wilks pointed out, that gummata do not begin primarily in the substance of the brain, but are extensions of the neoplastic formation from the surface along the vessels. The membranes thus affected appear thickened locally or generally, the condition depending upon the age of the process. If it be of recent origin, the inflammatory deposit may be soft and gelatinous, or greyish-red, or of a yellowish colour; if of some standing, the inflammatory process may have gone on to the formation of scar-tissue.

Should the granulation-tissue form a tumour on the surface or in the substance of the brain, a *gumma*, as distinguished from superficial gummatous meningitis, occurs. Gummatous tumours may vary in size from a cherry-stone to a pigeon's egg. Gummata are particularly common about the base of the brain, in the neighbourhood of the optic chiasma, but they may occur in any part, and may even involve the dura mater and erode the skull, projecting through it externally.

Changes in the Arteries.—These vessels present little greyish white nodules, usually on one side, so that, when cut across transversely, the nodules present a half-moon appearance. The vessels themselves feel stiff and cartilaginous between the fingers, and will not collapse on pressure. When there is universal arteritis, the vessels, small as well as large, appear opaque, dirty-white in colour, and their walls are thickened, so that they can easily be cut transversely, owing to the resistance they offer. The vessels about the base are particularly liable to this inflammatory change; possibly it is due to the cerebro-spinal fluid which exists there in abundance, and which possibly contains the toxine.

Microscopically, syphilitic arteritis (p. 271) is characterised by proliferation of the subendothelial cells. It generally affects one side of the vessel, but it may affect the whole of the intima. This

endarteritis is frequently associated with a *periarteritis*. The inner coat is thickened, owing to a development of spindle-shaped and stellate cells. According to Heubner, these do not undergo caseous degeneration, and he distinguishes it thus from atheroma. There is actually nothing specific in the process; but it is strong presumptive evidence of syphilis when one finds a thickening of the intima, which has not undergone caseation. When the arteritis is very acute, a new formation of capillaries in the intima may take place.

Thrombosis of the diseased vessel is frequent; subsequent organisation of the clot may occur, and eventually the vessel may be converted into a fibrous cord.

Vascular rupture is rare, so also is the formation of aneurysm. The important clinical result of endarteritis syphilitica is cerebral softening. The arteries lying in the Sylvian fissures are most frequently diseased, so syphilitic softening of the brain is commoner in the region supplied by the middle cerebral arteries than elsewhere (p. 572).

CEREBRAL SOFTENING.

Thrombosis and embolism are the most common causes of cerebral softening.

Softening from Thrombosis.—This is commonly the result of atheromatous, calcareous, or syphilitic changes in the *cerebral arteries* (p. 566). As a result of the interference with the supply of blood, the cerebral substance undergoes a more or less rapid process of necrosis (p. 16) (Fig. 227).

Thrombosis may also occur in the *cerebral sinuses and veins*. Thrombosis of a sinus may be *primary*, or it may be *secondary* either to (1) disease of some adjacent part, as of the bone in inflammation of the middle ear; or (2) to extension of a thrombus along a vein—as in the case of the orbit—from an inflamed part to the sinus into which it opens. The result is great distension of all veins opening into the sinus, œdema of the area whence they draw their blood, minute hæmorrhages, especially in the vascular cortex, and softening from impaired nutrition (Fig. 229).

Softening from Embolism.—The softening resulting from embolism is, for the most part, entirely dependent upon the obstruction to the circulation caused by the embolus and by the resulting thrombosis. It is rapidly induced, and is often attended by the extravasation of blood in its neighbourhood, when it constitutes one form of *acute red softening*. If the interference with the circulation be slight and there be no extravasation of blood, the softened portions are white in colour. The vessel most frequently blocked is the middle cerebral artery; and in the majority of cases it is that of the left side. In almost all cases in which softening of the cerebral substance results from embolism it is due to arrest of the embolus in one of the vessels *beyond* the circle of Willis, because

here the circulation cannot be readily restored by the collateral vessels (Fig. 230). Softening, however, does not necessarily follow the blocking of a cortical artery, for communication between these branches is freer than is often supposed.

If the detached fragment which gives rise to embolism carries infective organisms, not only is the vessel blocked by the embolus,

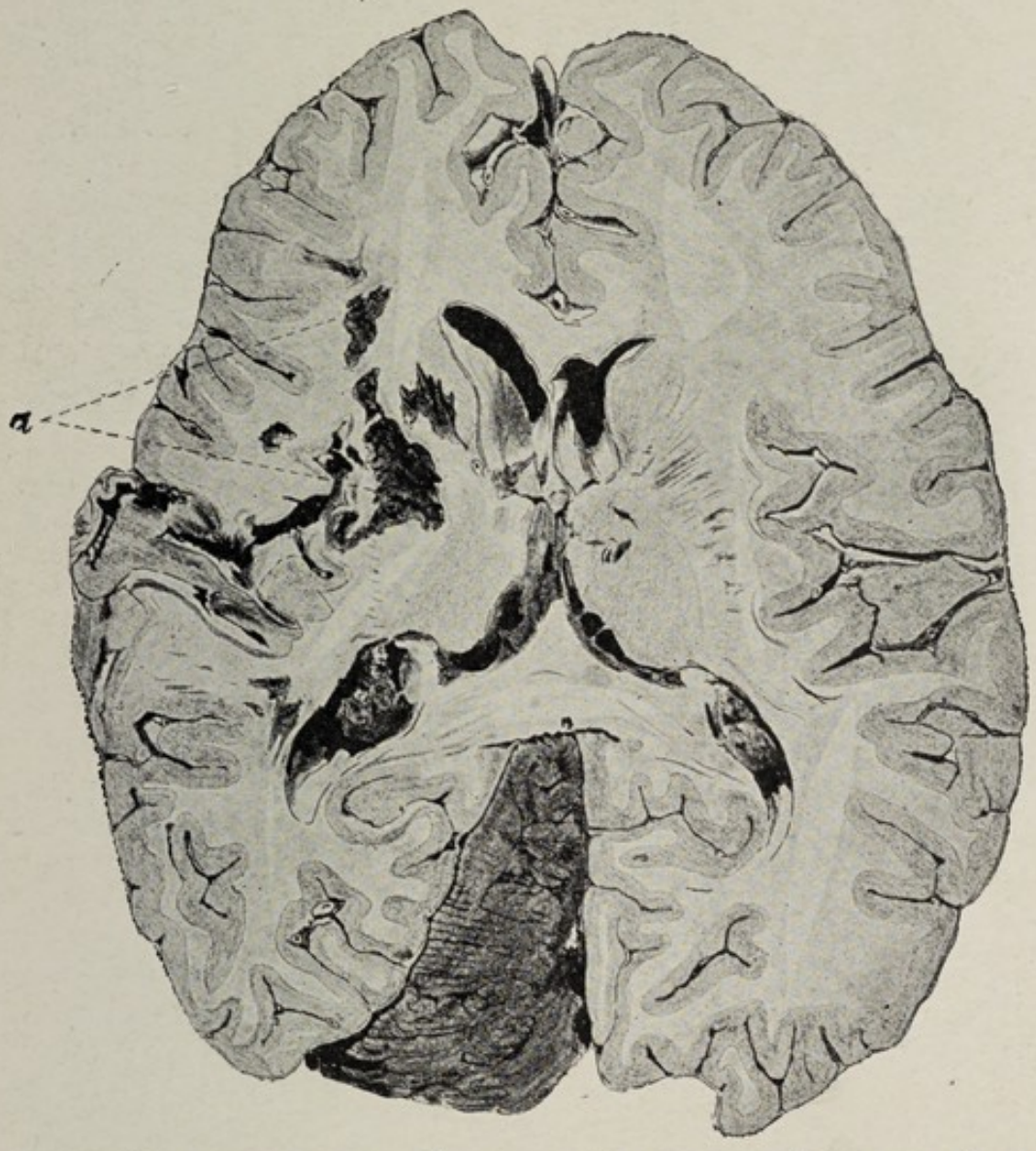

FIG. 227.—SOFTENING OF THE ANTERIOR HALF OF THE INTERNAL CAPSULE, DUE TO SYPHILITIC THROMBOSIS, FROM A CASE DIAGNOSED AS EPILEPTIC DEMENTIA. (MOTT.)

There was only slight paresis of the right side, but epileptic fits indistinguishable during life from idiopathic epilepsy. *a*, softened area.

but an infective inflammation of the arterial wall at the seat of obstruction occurs with softening of the coats and formation of an aneurysm, which may subsequently burst; so that a patient suffering from ulcerative endocarditis may die from hæmorrhage a short time after embolism of a cerebral artery.

MORBID ANATOMY.—The results of embolism and thrombosis

are essentially the same—the arterial blood-supply is cut off, and there is anæmia of the area supplied by the artery. For the first twenty-four hours there is only a slight change in the appearance and consistence of the part, although the neurones may show

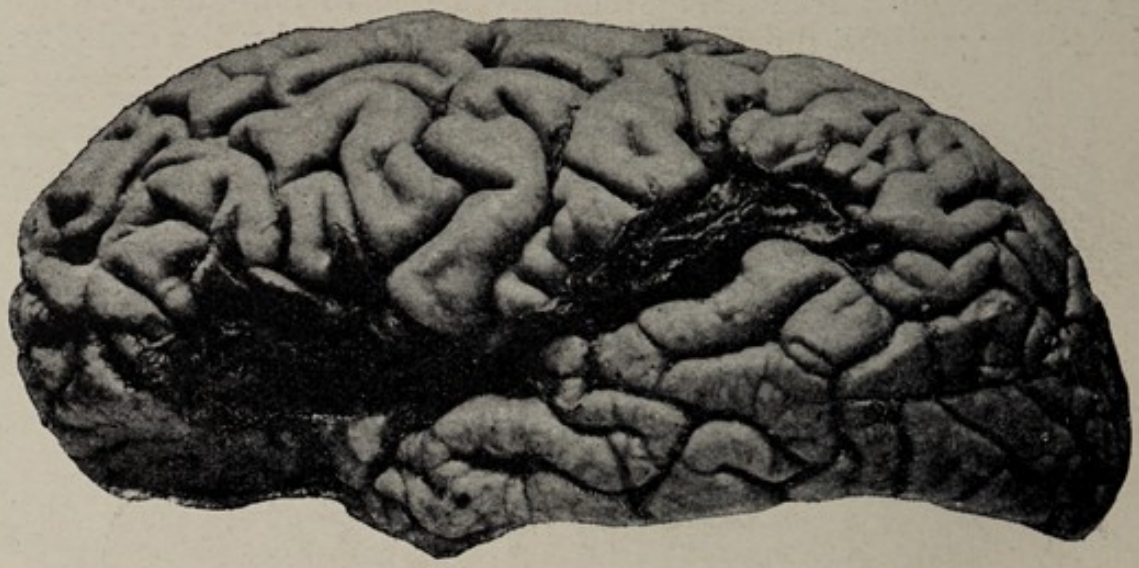

FIG. 228.—AREA OF SOFTENING AROUND THE LEFT SYLVIAN FOSSA, DUE TO EMBOLISM. (F. BATTEN.)

From a patient of Dr. Ormerod's, who had suffered from right hemiplegia two years previously, with motor aphasia and word-blindness. Owing probably to collateral circulation by the anterior cerebral artery, the upper part of the central convolutions was not destroyed; therefore the hemiplegia was due to softening of the internal capsule.

microscopically well-marked histo-chemical changes. The affected area has generally a pale appearance; sometimes the capillaries may become distended by a backward flow of blood from the veins, and, giving way, produce small hæmorrhages into the perivascular

FIG. 229.—CORTEX CEREBRI, SHOWING RED SOFTENING.

The condition resulted from thrombosis of the great anastomotic vein extending into the longitudinal sinus. The grey matter is deeply stained, owing to effused blood, and vascular puncta can be seen in the white matter; but it is especially the cortical grey matter which is affected.

lymphatics. Later on, the tissue breaks down and softens, owing to imbibition of cerebro-spinal and serous fluids by the dead tissues. When very little blood returns from the veins to the capillaries, the area of softening remains *white;* it is *red* when blood does regurgitate

from the veins, especially when the walls of the capillaries give way, allowing the red corpuscles to escape (Figs. 227, 228, 229).

Since the grey matter is far more vascular than the white, *red softening* is generally seen in the cortex and basal ganglia. *Yellow softening* is merely a later stage of the red, owing to alterations in the blood-pigment.

Microscopically, the softened mass consists of myelin-drops, swollen and degenerated nerve-fibres, altered nerve-cells, and granular corpuscles of Glüge with free fat-granules. These granular corpuscles, which may measure as much as 30 μ in diameter, are leucocytes distended with fatty débris.

If the circulation be re-established within a short time, the nervous structures do not necessarily die; but regeneration is

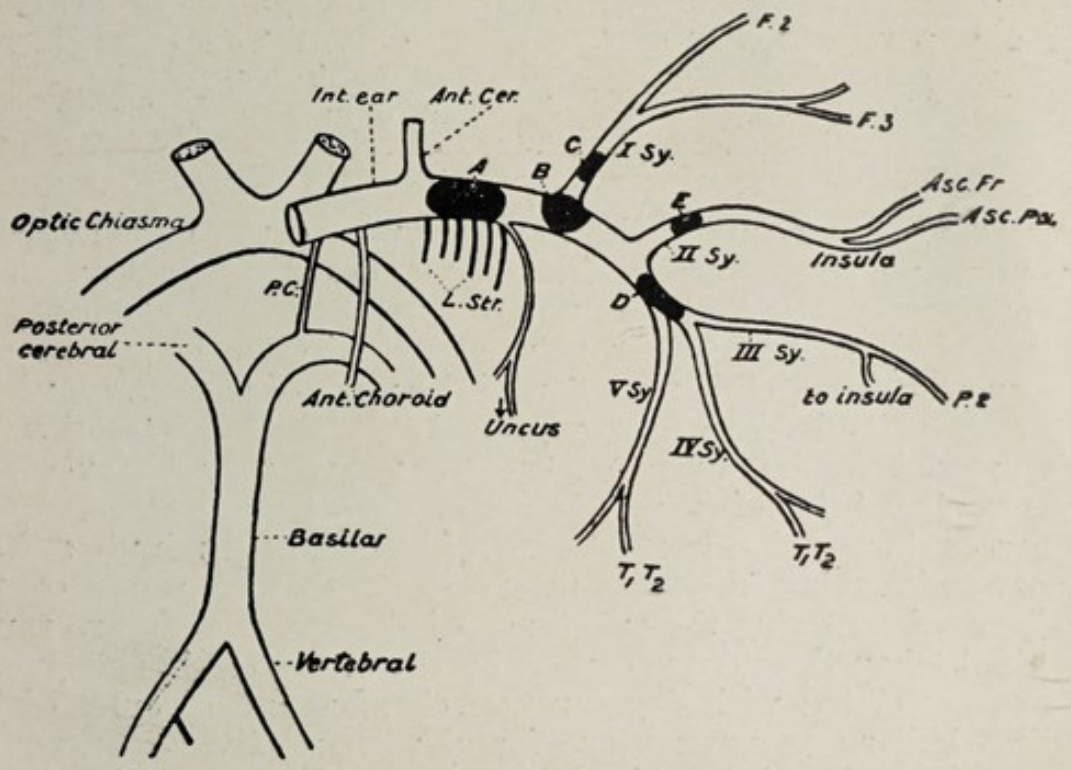

FIG. 230.—DIAGRAM TO SHOW THE EFFECT OF EMBOLISM OF THE MIDDLE CEREBRAL ARTERY. (AFTER VON MONAKOW.) (SEE TEXT.)

impossible, if necrosis has commenced. Resorption of the dead tissue is gradually brought about, with eventual formation of a *cyst*. If the area be small, a *scar* of fibrous tissue may be the sole indication of the destruction that has taken place. The convolutions of the cortex may sometimes be seen atrophied and sclerotic, especially in senile atheroma; and on tearing off the thickened pia-arachnoid, they present little erosions of a rusty-yellow colour. Sometimes portions of the convolutions, or even a whole lobe, may have entirely disappeared, and the space be occupied by a serous fluid, enclosed by the thickened pia-arachnoid membrane.

EFFECTS OF SOFTENING.—Vascular lesions usually effect extensive areas of the brain simultaneously. Thus, if the **middle cerebral**

artery be blocked at its commencement, there will not only be softening of the whole cortical area supplied by this vessel, but also of the internal capsule and basal ganglia (Fig. 230, *A*), resulting in *hemiplegia ;* and, if on the *left side,* there will be *aphasia, word-deafness,* and *word-blindness.* If the artery be blocked at *B* beyond the basal arteries, there is a possibility of some collateral circulation being restored by the anterior cerebral. If the *first* Sylvian branch be blocked (*C*), there will be *softening* in *Broca's convolution and aphasia.* If the *second* (*E*), there will be softening of the Rolandic area and *hemiplegia ;* while blocking of the *posterior main division* (*D*) of the middle cerebral artery on the left side will cause *word-blindness* and *word-deafness,* frequently accompanied by dementia, but not by motor aphasia or hemiplegia. The effect of occlusion of the *posterior cerebral artery* is lateral homonymous *hemianopsy,* often only partial in character.

CEREBRAL HÆMORRHAGE.

Cerebral hæmorrhage is the most frequent cause of hemiplegia in persons who have passed forty; and, according to Gowers, it seldom occurs under that age, unless Bright's disease or aneurysm exists. The latter may be produced by infective embolism and subsequent infective inflammation of the walls of the artery, which may eventually lead to its rupture. In Bright's disease there is high arterial tension due to increased peripheral resistance and hypertrophy of the left ventricle.

Charcot showed that in most cases of hæmorrhage minute *miliary aneurysms,* varying in size from $\frac{1}{100}$ in. to $\frac{1}{25}$ in., existed on the small vessels entering the substance of the brain; they are round or spindle-shaped, and are caused by degenerative changes in the intima, associated with degenerative changes and atrophy of the media. Miliary aneurysms are found with relative frequency in those regions where hæmorrhage is most generally met with. There is, however, one artery in particular, the left lenticulo-striate artery, which is especially liable to disease and rupture, and which has therefore been called "the artery of hæmorrhage" (Fig. 232).

The small arteries which supply the basal ganglia come off directly at right angles from the large arteries at the base of the brain—they are terminal arteries, and, like all the intracerebral vessels, they are not supported by the substances of the brain, being surrounded by a perivascular lymphatic sheath. Probably these facts explain the frequency of hæmorrhage in this situation. Hæmorrhage may occur in the cortex, pons (Fig. 231), cerebellum, centrum ovale, peduncles, and medulla oblongata.

Other conditions which predispose to cerebral hæmorrhage are plumbism, alcoholism, syphilis, and inherited tendency to arterial disease. It may occur also in tumours. In children *meningeal hæmorrhage* may occur, and a frequent cause of birth-palsies is

rupture of a vessel (usually a vein) during parturition. Subpial, subarachnoid, and subdural hæmorrhage is frequently seen in general paralysis and senile dementia. Cerebral or meningeal hæmorrhage may occur in various blood-diseases. Primary ventricular hæmorrhage occurs in rare instances from rupture of a vessel of the choroid plexus or velum interpositum.

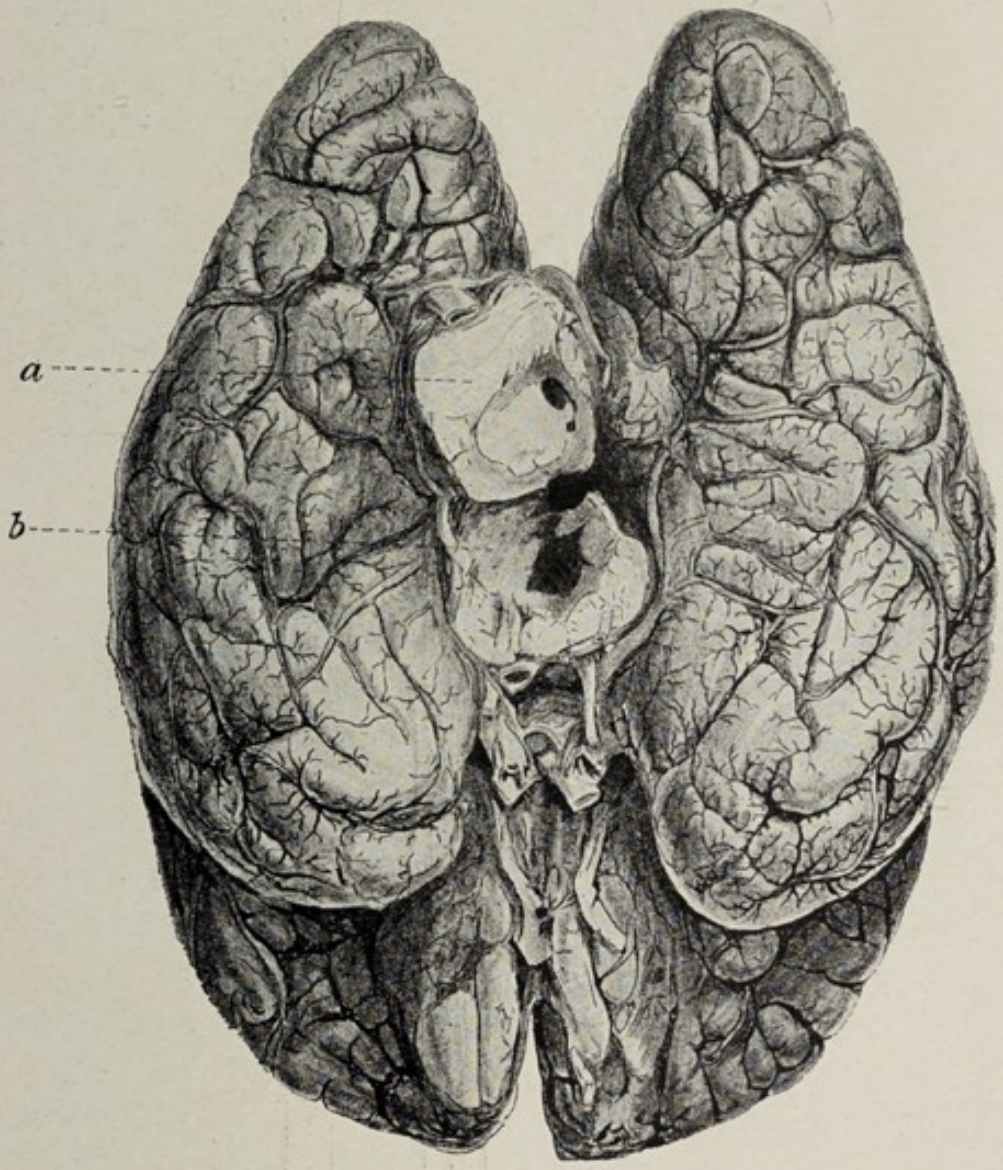

FIG. 231.—HÆMORRHAGE INTO PONS VAROLII. (MOTT.)

From a case of chronic Bright's disease with miliary aneurysms, one of which had ruptured into the upper part of the pons, giving rise during life to alternate hemiplegia. The pons (lower part, *a*; upper part, *b*) is seen cut transversely to show the hæmorrhage.

The hæmorrhage is usually single; but when small, there may be more than one. Sometimes evidence of a previous hæmorrhage is found in another region in the form of a cyst with orange-yellow staining of the walls and adjacent brain-substance; or there may be a scar of connective tissue formed. In severe cases of hæmorrhage causing death, irruption of blood may take place not only into the lateral ventricle of the same side, but also through the foramen of

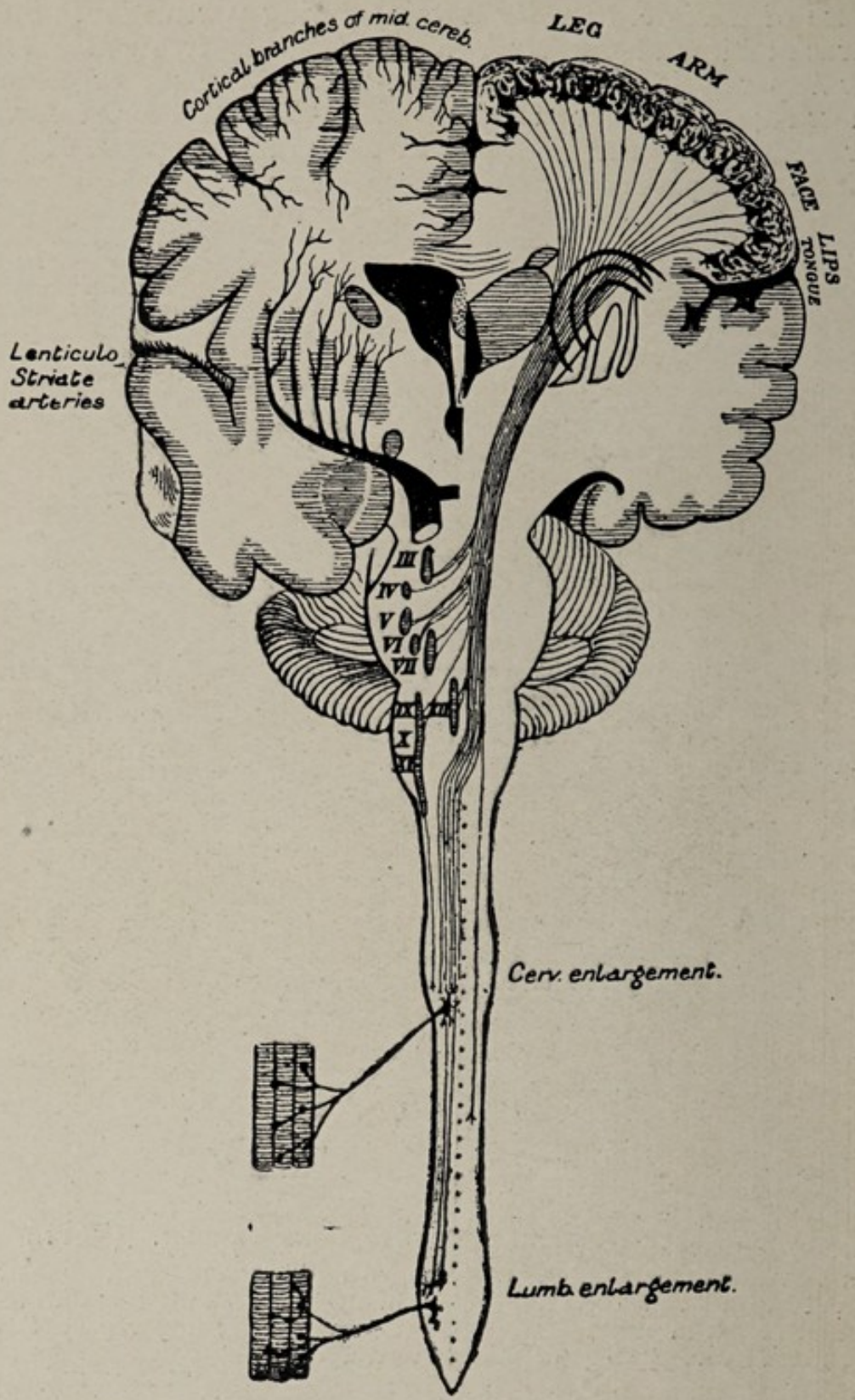

FIG. 232.—DIAGRAM TO SHOW THE DISTRIBUTION OF THE LENTICULO-STRIATE ARTERIES. (MOTT.)

Hæmorrhage from one of these small branches of the middle cerebral artery is a frequent cause of apoplexy. It will be seen that as the blood effuses and lacerates the brain-tissue, to escape into the lateral ventricle, it will destroy successively the axons of the cortical pyramidal neurones as they descend downwards to the motor nuclei in the pons, medulla, and cord, giving rise thereby to hemiplegia.

Monro into the opposite lateral ventricle. Occasionally it may find its way from the third ventricle through the aqueduct of Sylvius into the fourth ventricle; and, in rare cases, thence through the foramen of Magendie into the subarachnoid space.

If the lesion be not severe enough to cause death, various changes occur in the effused blood and damaged nerve-tissues. For the first few days the clot fills the whole cavity, and does not undergo shrinking; then a fatty degeneration takes place, with absorption of the products. In recent cases the effused blood is dark in colour, generally clotted, and often mingled with lacerated brain-substance. As changes take place in the blood, the colour alters first to a chocolate-brown, and later to a brownish-yellow.

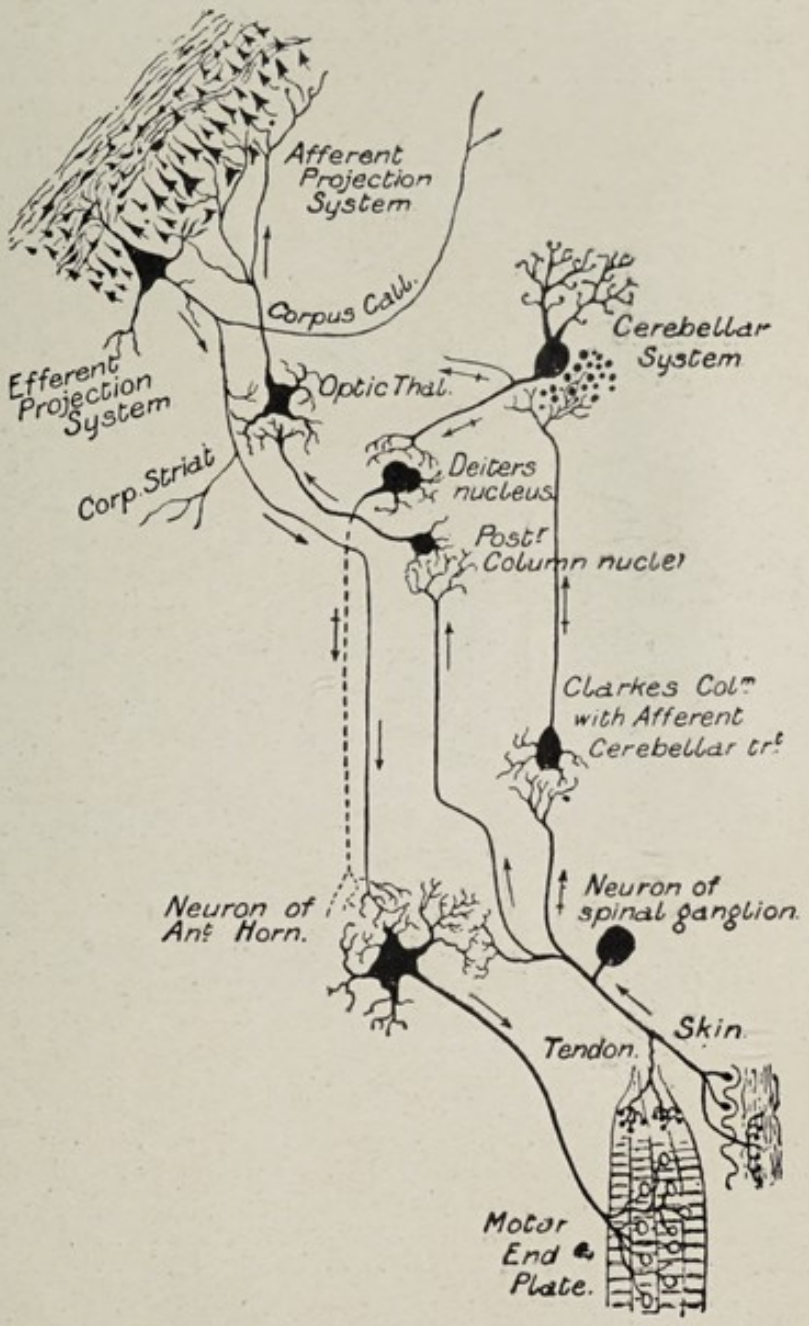

FIG. 233.—DIAGRAM TO ILLUSTRATE THE SENSORI-MOTOR NEURONES CONCERNED IN CONSCIOUS VOLUNTARY MOVEMENT. (MOTT.)

Microscopical examination reveals blood and degenerated nervous, tissue, fibres with their myelin-sheaths breaking up, granule-cells, and phagocytes containing products of degeneration. If the hæmorrhage be more than a few weeks old, *hæmatoidin*-crystals will be found.

The *effects produced* by hæmorrhage depend upon its situation and size. The most frequent seat is the anterior part of the optico-striate mass in the external capsule; but when paralysis occurs, as it usually does, the cause is damage to or pressure on the pyramidal fibres of the hinder limb of the internal capsule.

SECONDARY SYSTEMIC DEGENERATIONS.

As a result of destruction of brain-substance, secondary degenerations arise, the most characteristic of which is the secondary **descending degeneration** arising from destruction of the pyramidal cells of the motor area, or of their fibres in the anterior two-thirds of the posterior half of the internal capsule, such as occurs in cerebral hæmorrhage. A similar degeneration may arise as a result of softening due to embolism or thrombosis of the middle cerebral artery or its branches; of meningeal hæmorrhage and tumours, or, in fact, of any lesion which causes destruction of the pyramidal cells of the cortex of the central convolutions, or which cuts off the connection of the nerve-fibres from the cells of which they are the outgrowths (Fig. 232).

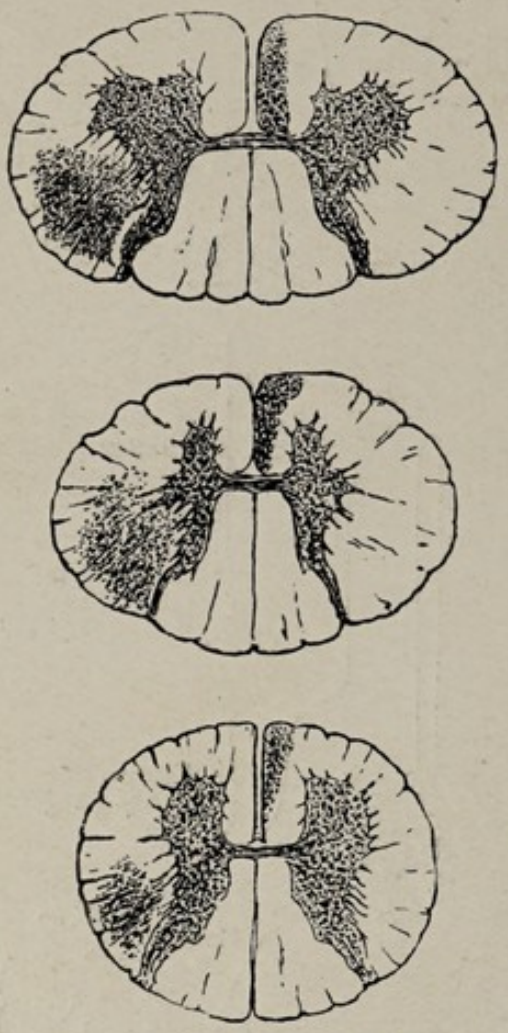

FIG. 234.—DESCENDING DEGENERATION IN THE PYRAMIDAL TRACT FOLLOWING HÆMORRHAGE INTO THE INTERNAL CAPSULE. (MOTT.)

The direct tract is well marked, and is represented at a lower level than it is usually seen.

As a rule, *cerebral lesions leading to secondary degenerations are unilateral.* Hence in these cases only one set of pyramidal fibres is degenerated in the spinal cord—viz., those proceeding from one hemisphere by the internal capsule, the middle portion of the crus cerebri, the pons and the medulla. Here the greater number decussate in the anterior pyramid to form the crossed pyramidal tract of the opposite side; some (about one-tenth) pass in the direct tract down the cord, decussating at lower levels. Both these last tracts will show degeneration (Fig. 234).

On the other hand, *secondary degenerations arising from lesions of the spinal cord are, in nearly all cases, bilateral,* and affect not only the *descending* tracts, which have their centres of nutrition in the cortex cerebri, but also the *ascending* tracts, which have their centres of nutrition in the posterior spinal ganglia and grey matter of the cord. The ascending and descending *ground-fibres,* which unite the different segments of the crus, pons, medulla, and cord together in co-ordinate reflex action, degenerate both above and below the lesion for a variable distance; and, besides, there are two

tracts in the posterior column, which degenerate downwards in transverse lesions of the cord in the dorsal region; they are termed respectively the *comma-shaped tract* and *the median oval area of Flechsig.*

The **ascending degenerations** come under two classes:

1. *In the Posterior Columns.*—Short, medium, and long fibres exist, having their origin in the central portion of the T-shaped process of the posterior spinal ganglion-cells. The short fibres form Lissauer's tract, at the base of the posterior horn; the medium fibres enter the postero-external column, and, after a short course, disappear in the grey matter; and the long fibres, after entering the posterior column, are directed backwards and towards the median line to form the posterior median (Goll's) column. Secondary degeneration limited to the posterior column indicates a root-lesion, as from tumour of the cauda equina, or injury of posterior spinal roots (Fig. 235).

2. *In the Antero-Lateral Column.*—There are three sets of fibres occupying the periphery. They all arise from cells in the grey matter. One tract, consisting of large fibres derived from the cells of Clarke's column, is termed the *direct or dorsal cerebellar* tract. Another, consisting of two sets of fibres, in all probability arising from cells of the grey matter of the opposite horns (the decussation taking place in the anterior commissure), has several names—viz., Gowers' tract, antero-lateral tract, and *ventral cerebellar* tract, because most of the fibres can be traced by a curious course to the middle lobe of the cerebellum. The less numerous fibres enter into the fillet, and probably end at the corpora quadrigemina (Fig. 217).

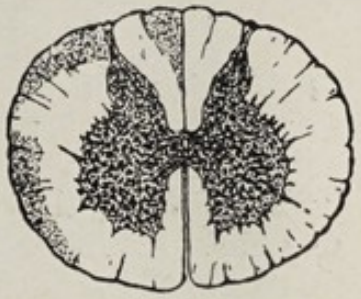

FIG. 235.—THE ASCENDING TRACTS OF DEGENERATION IN THE CERVICAL ENLARGEMENT AFTER EXPERIMENTAL HEMISECTION OF THE SPINAL CORD IN THE MID-DORSAL REGION.

The section shows well-marked degeneration of Goll's column, of the direct cerebellar tract, and of the antero-lateral tracts on the same side as the lesion.

At one time it was thought that all sensory impulses, except those of the muscular sense, decussated immediately on reaching the cord, and this view was held because in most cases of hemi-lesion of the spinal cord a group of symptoms occurs termed *Brown-Séquard paralysis,* which briefly is *hyperæsthesia and paralysis of the side of the lesion, and anæsthesia on the side opposite to it.* Latterly Brown-Séquard gave up the theory of immediate decussation of sensory impulses, but maintained justly that as a means of diagnosis the Brown-Séquard phenomenon was most valuable. Hemisection of the spinal cord in monkeys and other animals is followed by paralysis on the side of the lesion, but most recent observers have been unable to find either hyperæsthesia of the same side or anæsthesia of the opposite side.

The common causes of ascending and descending secondary

degenerations of the spinal cord are focal lesions produced by fracture or dislocation of the bones (Fig. 236), pachymeningitis in Pott's disease, meningitis, and tumours, all of which cause a *focal transverse myelitis*.

PRIMARY SYSTEMIC DEGENERATIONS.

Primary systemic degenerations may affect either the *afferent* sensory paths or the *efferent* motor paths, and not infrequently the two combined.

I. DEGENERATION OF AFFERENT TRACTS.

Locomotor Ataxy or Tabes Dorsalis.

Tabes dorsalis is a primary progressive degeneration of the first afferent (sensory) projection-systems of neurones, by which peripheral sensations are cut off from various parts of the central nervous system; the commonest and most obvious *anatomical change being degeneration of the posterior spinal roots and of the posterior columns of the spinal cord*. The clinical phenomena characteristic of this disease depend upon the systems of neurones which are undergoing degeneration, and on the extent, as well as on the rapidity, of the process.

The disease is the result of syphilitic infection, as is shown by the actual demonstration of spirochætes in cases of the affection, and by the frequent existence of the Wassermann reaction in the cerebro-spinal fluid.

Morbid Anatomy.—The pia-arachnoid is thickened over the posterior surface of the cord, which is flattened, and presents a greyish or greyish-red aspect; moreover, the posterior roots are thin, flattened, and atrophied, although the degree of wasting is not necessarily uniform; they also present a grey appearance like the posterior surface of the cord. The cord, cut transversely, shows degeneration limited to the posterior columns, which are considerably shrunken, and of a greyish or greyish-red colour, contrasting strongly with the white antero-lateral columns. This degeneration is usually much more obvious and advanced in the lumbo-sacral region; the posterior roots entering into the formation of the cauda equina are also, as a rule, atrophied to a greater degree than elsewhere.

The degeneration of the posterior columns of the spinal cord is a *systemic degeneration of exogenous* origin precisely similar in anatomical distribution to that produced by section of the posterior roots*; or, in the case of the lumbo-sacral region, to that produced by a tumour of the roots of the cauda equina.

* Nerve-fibres in the spinal cord are said to be *exogenous* when they arise from ganglion-cells situated outside the cord (posterior-root ganglia), *endogenous* when they arise from cells within the cord itself.

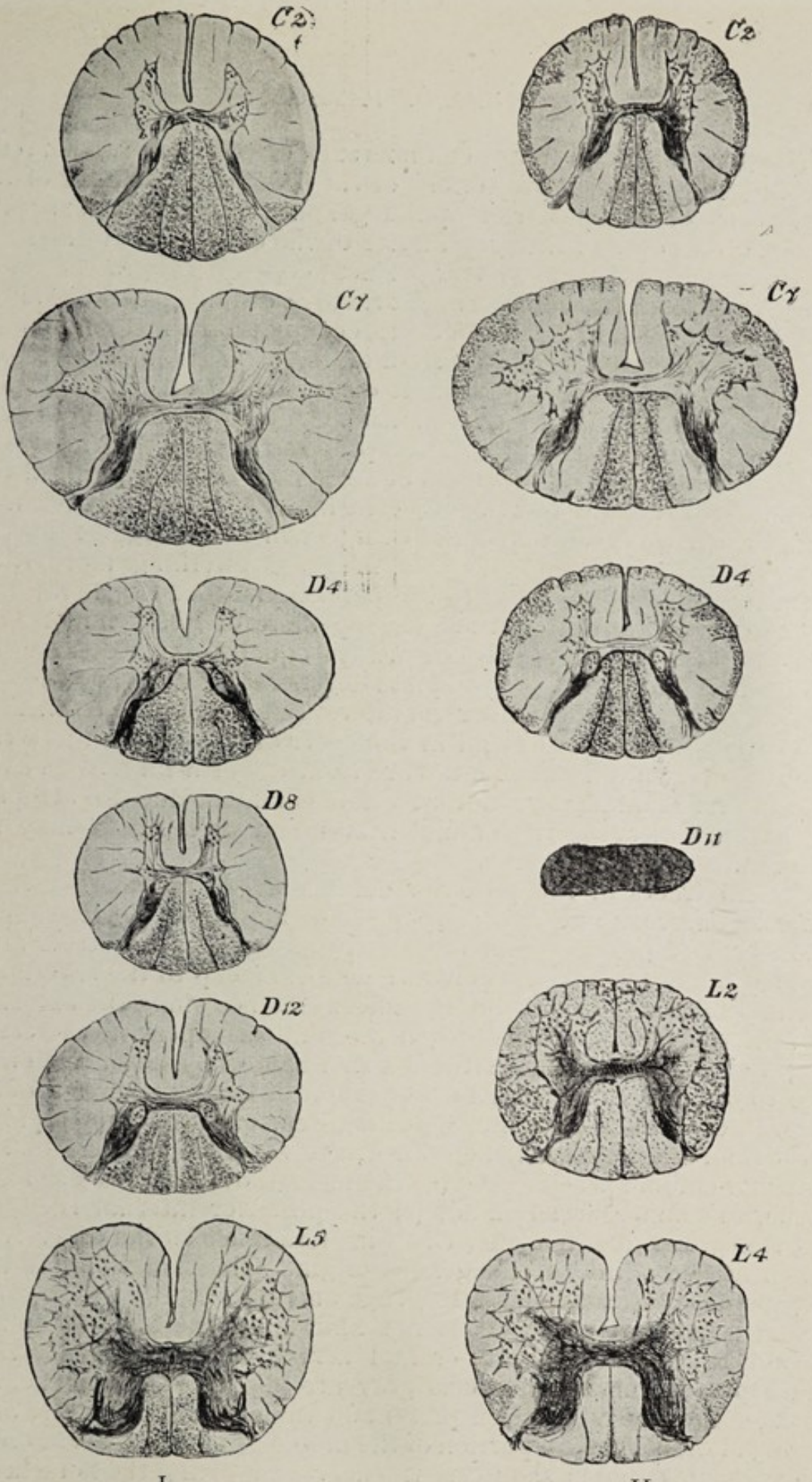

FIG. 236.—SECTIONS OF THE SPINAL CORDS FROM CASES OF (I.) TABES DORSALIS AND (II.) TRANSVERSE LESION, DUE TO FRACTURED SPINE. (A. F. TREDGOLD.)

In the former the degeneration is limited to the exogenous tracts of the posterior columns of the spinal cord; in the latter there is ascending degeneration above and descending below the lesion.

The fibres of the posterior columns are derived from two sources: (1) Exogenous central projections of the T-shaped processes of the nerve-cells of the posterior spinal ganglia; (2) endogenous projections from cells of the grey matter of the cord. The former are degenerated in tabes, the latter are not; consequently in the lower lumbar region of the cord, a small oval area of undegenerated fibres may be seen, even in advanced tabes, occupying the median portion of the posterior column; also a tract of fibres, *the cornu-commissural* (Fig. 217). Now, it is impossible to conceive that vascular changes, or impaired nutrition owing to an insufficient supply of blood, could produce in such a small area as the posterior columns of the spinal cord a degeneration of the fibres of exogenous origin, sparing those of endogenous origin and the adjacent fibres of the lateral column. Neither can we believe that the overgrowth of neuroglia-tissue at the expense of the specialised elements is anything more than secondary and proportional to the parenchymatous degeneration.

The changes in the cord are usually more or less symmetrical; but the posterior roots are not always equally affected, and the localisation and extent of the spinal degeneration will vary accordingly. As a rule the lumbar roots are first affected; but in rare cases the mischief may begin in the cervical region and leave the lumbo-sacral intact. Such cases are termed "arm-tabes." Visual defects and blindness are not at all uncommon, due to atrophy of the optic nerve. The cranial nerves and their nuclei may be affected.

Certain tracts in the posterior column degenerate earlier than others. *Charcot's root-zone* is very early the seat of degeneration. The fibres of *Goll's column* are nearly always degenerated. The *zones of Lissauer*—the fine fibres which form a cap to the extremity of the posterior horn, extending a short distance along the external and internal borders of it—degenerate and disappear in the early stages of tabes. Another situation in which early degeneration is said to occur is the terminal arborisation of the root-fibres around the cells of Clarke's column. Certain groups of fibres enjoy a particular immunity, and can be seen intact when all the rest of the posterior column is sclerosed; (*a*) the median oval area of Flechsig; (*b*) cornu-commissural bundle; (*c*) the posterior internal triangle; but this group does not offer the same resistance as the other two, which are certainly of endogenous origin. The situations of the degeneration are indicated in Figs. 236 and 237.

The degenerative process is not limited to the afferent spinal projection-systems; various cranial nerves may be degenerated, and especially characteristic is grey atrophy of the optic nerve. Changes are also very often present in the cutaneous nerves, and in long-standing cases a portion of the muscular nerves are sclerosed. In cases exhibiting bone-disease the nerves supplying the bone have been found degenerated, and, in the neighbourhood of perforating ulcers and similar *trophic disturbances*, extensive degeneration of the nerves has been observed. The degeneration of the nerves is

more marked at the periphery; and the nearer to the cord the point at which the nerve is examined, the fewer degenerated fibres are found. Slight changes in the cerebral cortex have been described, corresponding with those of general paralysis, but less in degree.

Microscopical examination of the spinal cord shows the myelin-sheaths of the nerve-fibres diminished or destroyed; the axis-cylinder processes may be swollen in one place, attenuated in another, and generally irregular in thickness or completely atrophied; the neuroglia is increased at the expense of the parenchyma, and

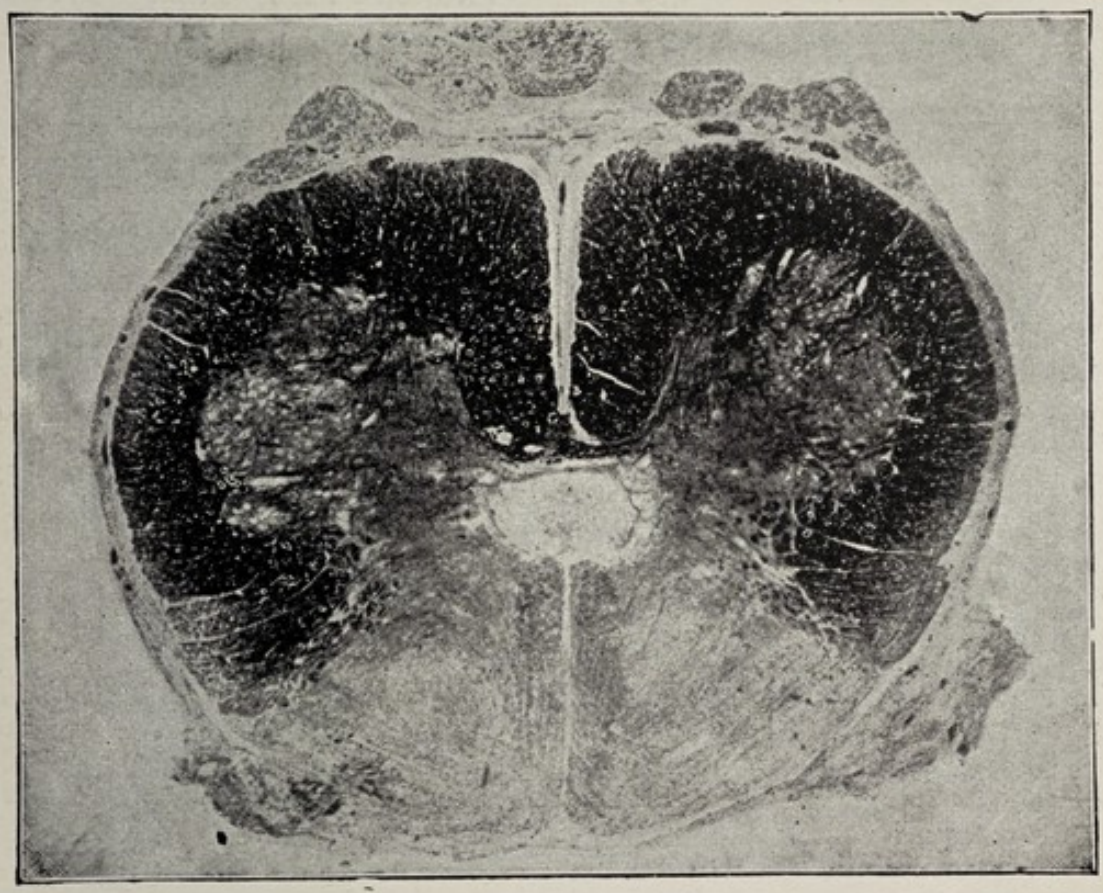

FIG. 237.—PHOTOMICROGRAPH OF SECTION OF LUMBAR ENLARGEMENT OF SPINAL CORD IN A CASE OF VERY ADVANCED TABES, SHOWING EXTREME SCLEROSIS OF POSTERIOR COLUMNS. (× 10.) (MOTT.)

There is complete atrophy of all the fibres except in the median oval area of Flechsig.

there are a large number of Deiters' cells visible. Nearly the whole of the posterior columns in the lumbo-sacral region may be destroyed, leaving only the cornu-commissural and oval areas of endogenous fibres. The walls of the arteries are often thickened, and there is hyaline degeneration of the media; sometimes the vessels are so much thickened by this degenerative process as to become almost obliterated, especially when the sclerosis is advanced. The affection of the vessels may be present only in the sclerosed area, not elsewhere; this change is secondary to the degeneration, and not the cause of it. The pia-arachnoid membrane is also

thickened, and often presents the appearances of chronic inflammation. By some authorities this meningeal thickening about the entrance of the posterior roots (Fig. 238) has been considered to have a causal relation to the atrophy of the fibres in the cord; but the fact that the vessels of the retina are unaltered, even in advanced grey atrophy, shows that tabes is a widespread process of degeneration, primary in origin, and not secondary to vascular change or meningitis.

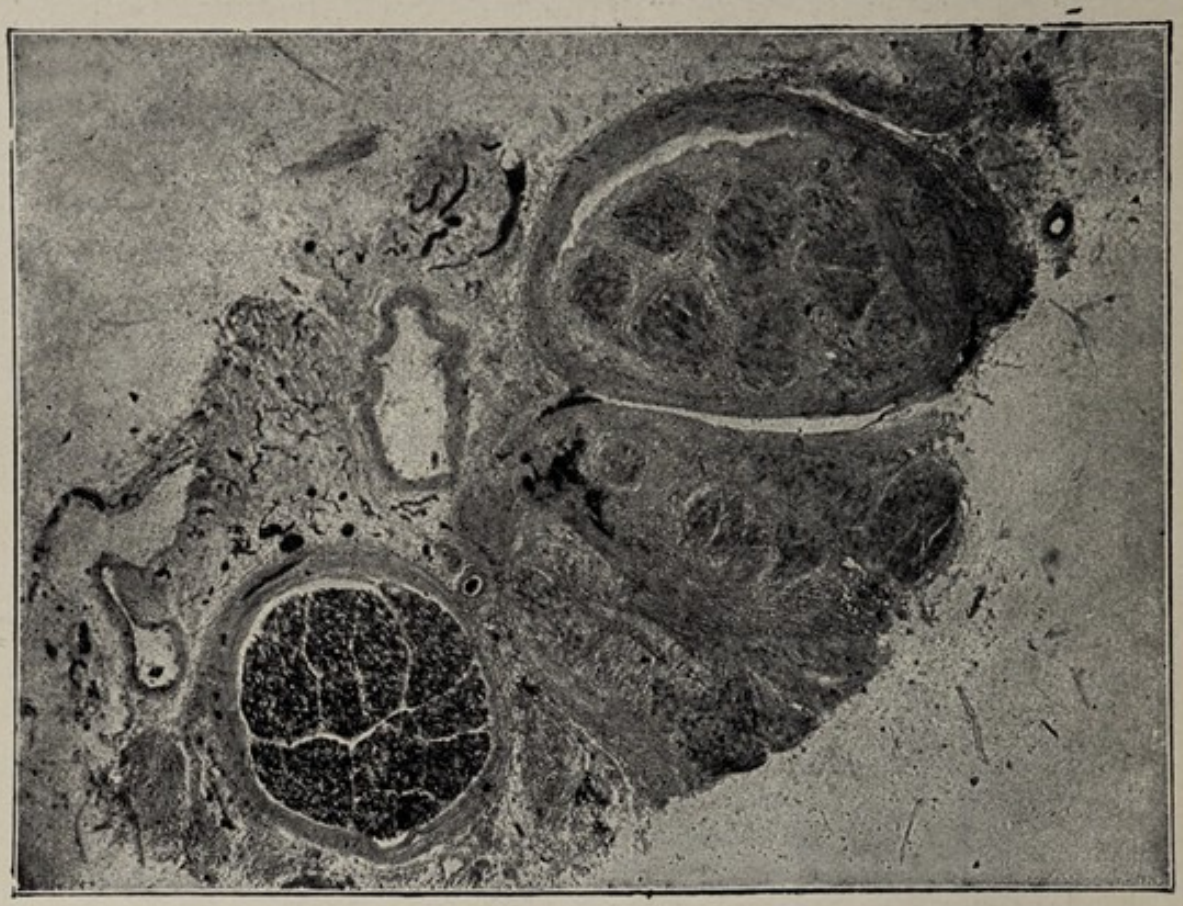

FIG. 238.—SECTION OF ANTERIOR AND POSTERIOR ROOTS CLOSE TO THE GANGLION FROM A CASE OF TABES. (× 30.) (MOTT.)

The figure shows the small anterior root with medullated fibres (normal), and the sclerosed posterior root much larger in size, but almost denuded of medullated fibres; there is a great overgrowth of fibrous tissue around and between the constituent bundles.

As a rule changes in the posterior spinal ganglion-cells are not obvious; but the cells may be shrunken and pigmented, and exhibit chromolytic changes in advanced cases

PATHOLOGY.—Reference to the diagram (Fig. 233, p. 575) will help to explain some of the phenomena of tabes—namely, the *diminution of tonus in the muscles*, the *incoördination*, the *absence of the knee-jerk*, the *ataxic gait*, *Romberg's symptom*, and the *various disturbances of sensation*.

All the three nervous circles described on p. 546—spinal reflex, cerebellar, and cerebral—are more or less interrupted in tabes by the degeneration of the fibres in the posterior column. Hence the

forms of anæsthesia and paræsthesia met with in this disease are readily explained. Closely connected with these are the *trophic disturbances*—Charcot's joints and perforating ulcers—which seem to depend on disorders of sensory nerves. The exact nature of the trophic influence is uncertain—whether the nervous system directly controls the nutritive processes of the tissue-cells, or whether the lesions in question are merely due to alterations in the vascular supply to the affected parts.

The true motor neurone, which controls the muscle, is situated in the anterior horn. In tabes this is unaffected; therefore the muscle does not waste, nor is there, except in the late stages, any paralysis or loss of strength of voluntary movement. There is, however, a loss of tonus. This is due, like the loss of myotatic irritability and the consequent *absence of the knee-jerk*, to the break in the reflex spinal arc, occasioned by the degeneration of the spinal roots, and of those fibres which run forward through the root and the base of the posterior horn, terminating in an arborisation around the anterior-horn cell. By this degeneration the motor neurones in tabes are deprived of the normal stimuli which serve to maintain the reflex spinal tonus and myotatic irritability (p. 543).

Incoördination or Ataxy.—For the maintenance of bodily equilibrium in the erect posture, while standing, or during the successive changes that occur in the trunk and limbs in progression, a proper adjustment in the contraction of correlative antagonistic muscles is necessary. In standing erect the joints are fixed by the tonic contraction of the antagonistic muscles of the lower limbs. The motor neurones of the anterior horn which preside over the muscles are excited by impulses from the periphery. Unequal and imperfect transmission of sensory impulses will lead to unequal and imperfect excitation of those motor neurones, and to a correspondingly unequal and imperfect innervation of the muscles, whereby their normal equable tonic contraction is disturbed and lowered. Seeing that in tabes there is a progressive degeneration of the afferent spinal neurones, we can easily understand that there will be a progressively lowered and unequal tonus in the muscles.

Again, the degeneration of the fine plexus around the cells of Clarke's column, met with early in the disease, is sufficient to explain the loss of power of balancing the body when the basis of support is narrowed by placing the feet together or standing on one foot, even though there be no anæsthesia of the soles of the feet. Reference to Fig. 233 shows that atrophy of this fine plexus leads to interruption of the sensory afferent impulses to the cerebellum, and puts this organ, which is concerned in maintaining bodily equilibrium in the erect posture, at a great disadvantage. On closing the eyes another guiding sensation is removed and the instability is increased.

The *lightning-pains* may be explained by the degeneration of the root-fibres; but their paroxysmal character is difficult to understand. The partial nature of the *anæsthesia* may be accounted for

by the partial degeneration of the roots. Sherrington has shown that at least three roots overlap one another in a skin-area, and in order to produce complete loss of sensation in a part all three roots must be divided. If there is pronounced analgesia or anæsthesia, the peripheral nerves are probably affected. With regard to the *visceral crises* nothing is definitely known.

The *Argyll-Robertson pupil* is the most constant objective symptom of tabes, as it is of general paralysis. No very definite anatomical facts have been brought forward to explain this remarkable phenomenon; but it is asserted that it is due to a break in the junction between the terminal arborisation of optic nerve-fibres in the corpora quadrigemina and the dendrites of the sphincter iridis nucleus.

Friedreich's Disease.

Friedreich's disease, or *hereditary ataxy*, is a rare disease affecting several members of the same family, the great majority of cases beginning between the fifth and fifteenth years. It is unconnected with hereditary syphilis.

There is degenerative atrophy and sclerosis of the posterior columns and posterior roots, but less marked than in tabes; in addition the lateral columns are affected. Frequently there is atrophy of the cells of Clarke's column and sclerosis of the direct cerebellar tracts. Lissauer's tracts, which are always affected in tabes, are in this disease usually unchanged. The affection of the cerebellar tracts is of interest in connection with the typical reeling gait.

Combined Scleroses.

Ataxic paraplegia is a condition in which there is a combination of the symptoms of lateral sclerosis and of ataxy. Little or nothing is known as to the cause of the disease. The appearances of degenerative atrophy in the posterior columns of the cord closely resemble those of tabes; but the lateral columns are also affected, especially the crossed pyramidal tracts. The *combined sclerosis* in these regions quite accounts for the combination of symptoms peculiar to this disease. There is usually no history of syphilis, and the Argyll-Robertson pupil is, as a rule, absent.

In *pellagra*, *pernicious anæmia*, and certain grave forms of *anæmia*, a degenerative atrophy and sclerosis of the posterior and lateral columns may occur. All the long tracts of the spinal cord may be affected (Fig. 239).

II. DEGENERATION OF EFFERENT TRACTS.

The diseases known as Primary Lateral Sclerosis, Progressive Muscular Atrophy, and Amyotrophic* Lateral Sclerosis are probably all due to one and the same pathological process affecting

* "Accompanied by wasting of muscles" (Greek ἀ, not; μῦς, a muscle; τρέφω, I nourish).

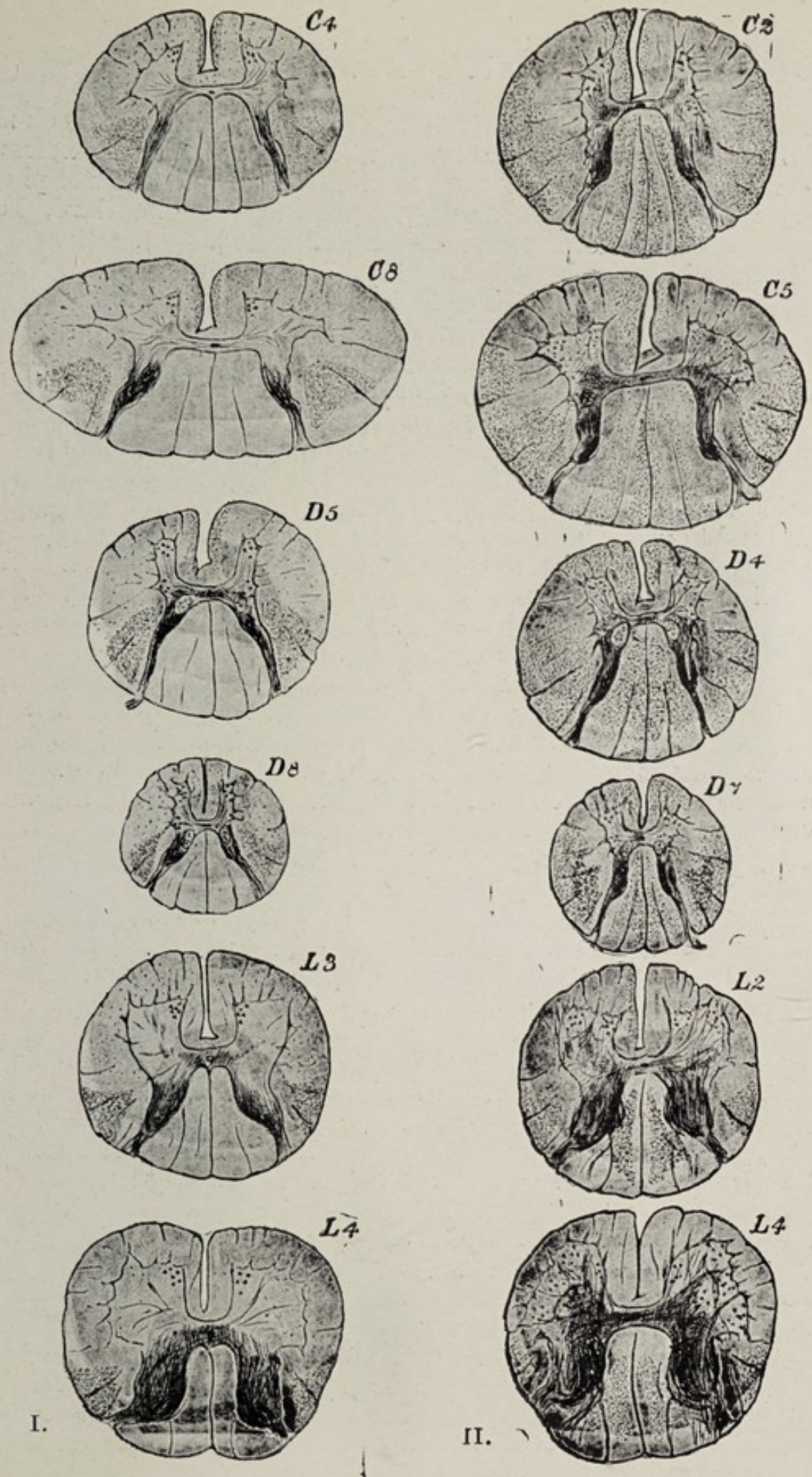

FIG. 239.—SECTIONS OF THE SPINAL CORDS FROM CASES OF (I.) AMYOTROPHIC LATERAL SCLEROSIS AND (II.) COMBINED SCLEROSIS OF GRAVE ANÆMIA. (A. F. TREDGOLD.)

In the former there is atrophy of the anterior-horn cells and degeneration of the direct and crossed pyramidal tracts; in the latter there is degeneration of all the long afferent and efferent tracts of the cord.

different parts of the motor tract. In the first, the lateral columns of the spinal cord (upper motor segment) are alone affected; in the second, only the cells of the anterior cornua and the peripheral nerves derived from them (lower segment); in the third, both segments of the motor path suffer together (Fig. 239).

Primary lateral sclerosis is in all probability due to retrogressive nutritional changes in the cells of the motor area of the cortex, owing to which the *pyramidal tracts degenerate.*

In **progressive muscular atrophy** and **amyotrophic lateral sclerosis,** which may be considered together, the lesion of the lower segment is usually most marked. In the former the change begins in the cells of the anterior cornua, usually in the arm-region, and remains confined principally to these cells. The upper segment of the motor tract, however, usually suffers to some extent, the signs of this condition being often masked by the preceding wasting of the muscles. In amyotrophic lateral sclerosis the upper-segment lesion is well marked from an early stage of the disease, rigidity of the legs and increased knee-jerks being often present along with progressive wasting of the muscles of the arms.

In progressive muscular atrophy we find several different types of the disease according to the initial seat of the degenerative process. Sometimes it will begin in the muscles of the shoulder-girdle, sometimes in the small muscles of the hand: the same distinction can be made in the lower limbs. Sometimes the degenerative process will commence in the nuclei of origin of cranial nerves, giving rise to affection of deglutition, phonation, and articulation (*bulbar paralysis*).

Morbid Anatomy.—Examination of the spinal cord shows that the grey matter of the anterior horns is wasted and greatly deficient in fibres and cells. The large multipolar cells that remain are shrunken, and their processes broken off: in some cases only a little mass of pigment remains. The glia-tissue is increased, and Deiters' cells are very numerous. The regions of the cord affected vary in different types of cases—*e.g.*, when the small muscles of the hand are wasted, the anterior horns are atrophied in the lower cervical and upper dorsal regions. The peripheral nerve-fibres corresponding with the atrophied spinal motor neurones also degenerate. The muscles are much wasted, and in extreme cases can hardly be distinguished from the surrounding fat; but in slight cases they are only pale. Examined microscopically, the fibres are seen to have lost their striation, and many show fatty degeneration. In the amyotrophic form the process commences in the upper pyramidal segment of the motor path. There is atrophy and sclerosis of the crossed pyramidal tracts and of the anterior root-zone. There are, therefore, exaggerated deep reflexes, accompanied or followed by a progressive and characteristic wasting of groups of muscles, owing to degeneration of the anterior horn.

These cases of amyotrophic lateral sclerosis strongly support the view that there may be a primary retrogressive nutritional change

in the neurones, followed by a progressive wasting of their axons, commencing at the terminals, and gradually spreading up the pyramidal tracts; because in some cases the degeneration has been found to extend only as high as the medulla, in others to the pons or crus; while in others, again, the internal capsule and the cortex have been affected.

Bulbar paralysis is the same disease as progressive muscular atrophy, and is due to a degeneration affecting the motor nuclei of the medulla, particularly a group of cells known as the glosso-labio-laryngeal nucleus. It often forms the final stage of progressive muscular atrophy.

GENERAL PARALYSIS OF THE INSANE.

Ætiology.—The syphilitic nature of general paralysis (dementia paralytica) has now been definitely proved by the demonstration of spirochætes in the cerebral cortex (Fig. 240). Krafft-Ebing has

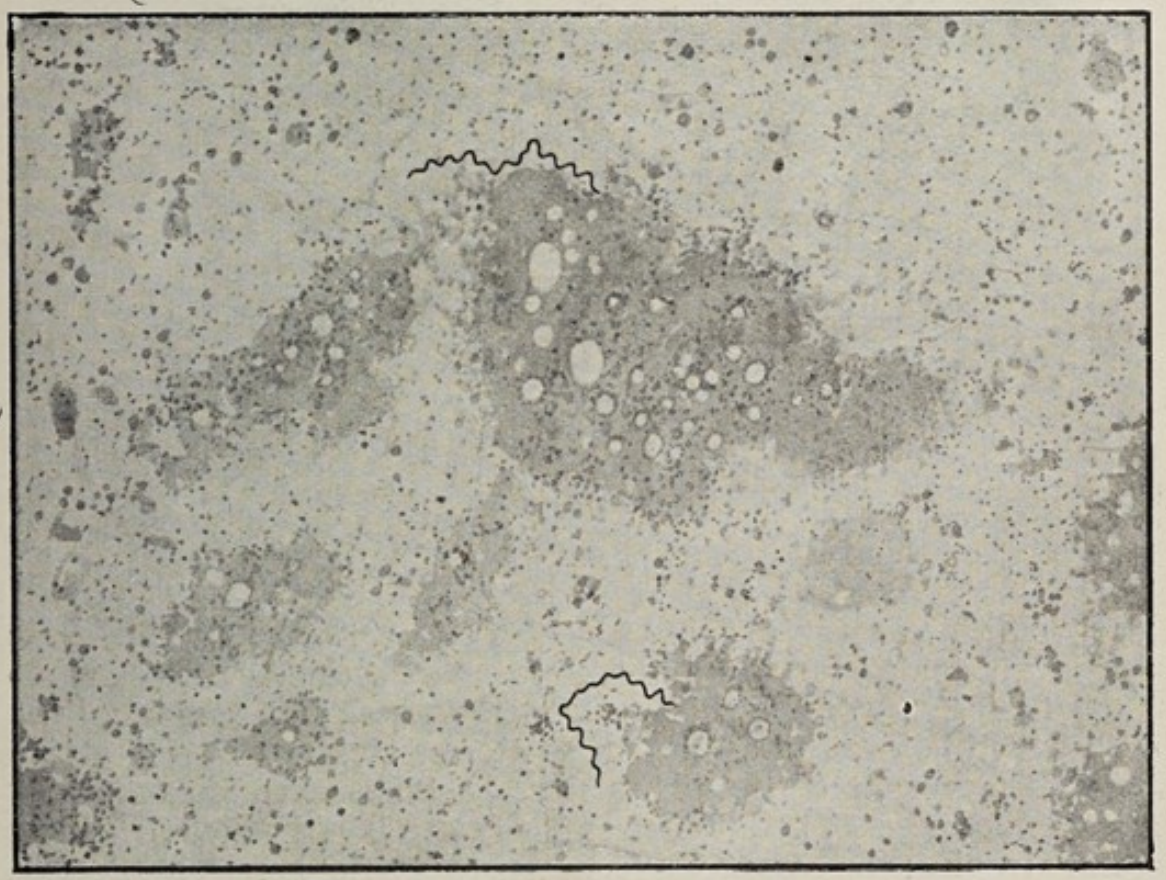

Fig. 240.—Smear Preparation from the Cortex Cerebri of a General Paralytic, showing the Presence of the Spirochæta Pallida (Stained by Fontana's Method). (× 750.)

shown that eight general paralytics, who exhibited no external signs of syphilis, possessed an immunity to the disease, for they could not be inoculated with the syphilitic virus. Finally, Wasser-

mann's reaction (p. 176) is almost always positive in patients suffering from this disease.

It appears probable that general paralysis and tabes dorsalis are, pathologically speaking, the same disease, affecting different parts of the nervous system; in the former the brain is affected, in the latter the spinal cord.

General paralysis affects especially men in the prime of life, in the thirties—the average age of death is forty. It is rare after fifty; it may commence (excluding the juvenile form) at twenty-five; but the most common period is between thirty and forty. The disease runs a slower course in women, and is relatively rare in this sex.

MORBID ANATOMY.—The dura mater is often found thickened and adherent. Upon opening the dura mater there is obvious atrophy of the brain, especially of the frontal and central convolu-

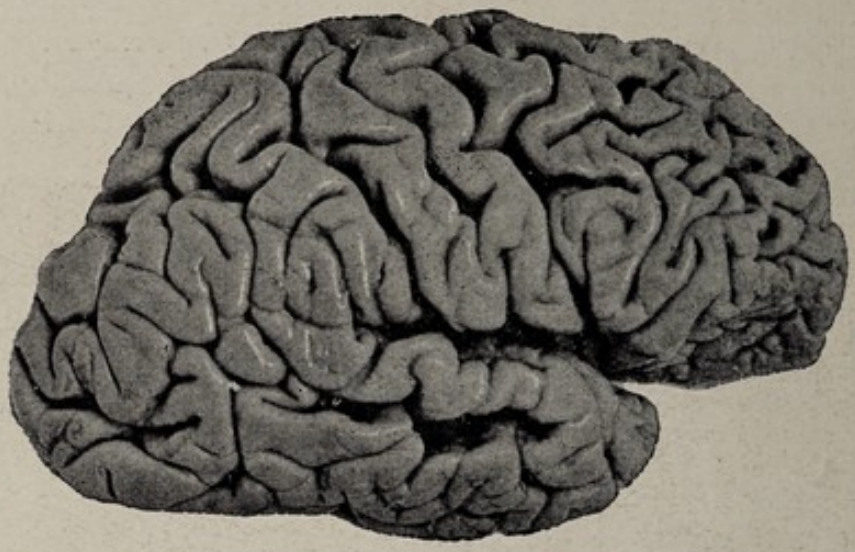

FIG. 241.—PHOTOGRAPH OF BRAIN FROM A CASE OF ADVANCED GENERAL PARALYSIS. (MOTT.)

The membranes have been stripped off. The atrophy of the frontal and central convolutions is very evident, as shown by their small size, and by the depth and width of the sulci.

tions, with *thickening and opacity of the pia-arachnoid*; the sulci present an opalescent, gelatinous appearance, due to the cerebro-spinal fluid beneath the thickened membranes. On removing the brain it will be noticed that there is *a great excess of cerebro-spinal fluid*. The weight of the organ may be diminished by one-third in extreme cases. The lateral ventricles are greatly dilated, owing to the atrophy; the atrophy affects especially the hemispheres, and the *ependyma* of all the ventricles, especially the fourth, is *thickened* and *granular*. If the membranes be stripped from the hemispheres, it will be observed that, especially in the frontal region, the brain-substance tears away with the membranes, leaving a characteristic worm-eaten appearance (Figs. 241 and 242). The atrophy also affects, but to a less degree, the spinal cord; and there may be obvious naked-eye systemic degeneration, the commonest form of

which is similar to that of tabes, although, when examined microscopically, it is generally found that the pyramidal tracts are degenerated. Hæmorrhagic pachymeningitis is not uncommon.

Microscopical examination of portions of the brain stained by Nissl's method shows marked thickening of the pia-arachnoid and an overgrowth of the neuroglia-tissue, at the expense of the nervous tissue. The regular layers (forming Meynert's columns) of nerve-cells of the cortex are destroyed, the cells being in all stages of dissolution, from initial swelling with chromatolysis to complete destruction, leaving only the nucleolus recognisable (Fig. 243). Some cells are swollen and no longer retain their pyramidal form; their processes are atrophied and appear broken off; others are almost globular, owing to swelling of the nucleus; while others, again, pre-

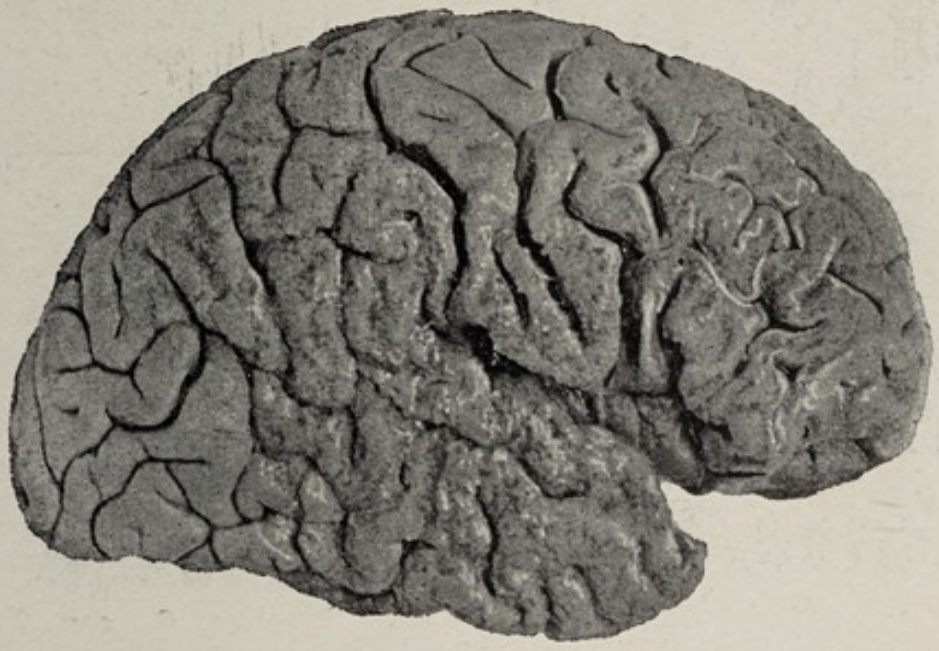

FIG. 242.—PHOTOGRAPH OF BRAIN OF A MORE RECENT CASE OF GENERAL PARALYSIS. (MOTT.)

A little time was allowed to elapse before stripping the membranes. They were then removed, and a worm-eaten eroded surface has been left, due to the adhesions of the thickened membranes.

sent a shrivelled, atrophied appearance. The motor pyramidal cells do not present the normal Nissl granules, and a single healthy-looking cell in a section of the central convolutions is hard to find. There is a great increase in the *spider-cells* of the neuroglia in those situations of the cortex where the atrophy of the nervous elements is most marked—namely, in the frontal and central convolutions and in the island of Reil. The vessels are especially visible, owing to dilatation of the perivascular lymphatics and cellular proliferation in the sheath. Numbers of leucocytes also are said to be present; the blood contained in the vessels, however, does not usually contain excess of leucocytes. By the Marchi and Marchi-Pal methods two important observations can be made—namely, the existence of a large number of degenerated fibres, in various

stages of destruction, and the *absence of the tangential system of fibres.*

The **effect** of the lesions just described is a gradually progressing dementia, owing to atrophy of the association-fibres of the brain.

FIG. 243.—PHOTOMICROGRAPH OF SECTION OF CEREBRAL CORTEX, GENERAL PARALYSIS. (× 150.) (MOTT.)

The columns of Meynert are destroyed; the cortical cells are undergoing destructive changes or are destroyed. There is an overgrowth of glia-cells, and a vessel is seen surrounded with cells lying in a dilated lymphatic sheath. This vessel terminates in the thickened pia-arachnoid membrane.

In the early stages tremor of lips, tongue, and hands is generally present; the speech is slurring, and the handwriting unsteady. Delusions are often present. In the final stages of the disease all mental power is lost; consciousness is in abeyance; and voluntary movement is impossible.

PRIMARY PROGRESSIVE MYOPATHIES.

The ætiology of this group of muscular atrophies is still obscure. Heredity plays a prominent part, especially through the maternal side. No definite pathological lesion of the central nervous system has been observed, and the disease is said to be a primary atrophy of the muscle-fibres. *Pseudo-hypertrophic paralysis* (p. 71), and Erb's *juvenile paralysis*, are the best-known types.

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N.B.—Heavy figures denote the most important reference.

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