A text-book of general pathology : for the use of students and practitioners / by J. Martin Beattie and W.E. Carnegie Dickson.

A TEXT-BOOK OF GENERAL PATHOLOGY

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A TEXT-BOOK OF
GENERAL PATHOLOGY

FOR THE USE OF
STUDENTS AND PRACTITIONERS

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To

WILLIAM SMITH GREENFIELD,

M.D., F.R.C.P.,

PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF EDINBURGH,

OUR TEACHER, CHIEF, AND FRIEND,

WE RESPECTFULLY DEDICATE

THIS BOOK.

PREFACE

If any excuse were necessary for adding another to the many text-books of Pathology, it would be found in the fact that the present volume is based on the teaching of the Edinburgh school. This school, in which the first chair of Pathology in the United Kingdom was founded, has sent its teachers and students to all parts of the world, and thus of necessity has had a considerable influence in moulding pathological opinion. In spite of this, some fundamental points which have been taught in Edinburgh for years, and which are founded on careful experimental investigations, combined with a very extensive experience in human morbid anatomy and morbid histology, have not, we think, received sufficient attention. To mention only two points—on infarction much is yet taught which is quite in opposition to experimental investigations; and the relation between certain diseases of the kidney and arterial degeneration seems to be very imperfectly understood.

The book is intended primarily as a text-book for medical students and practitioners, and we have, therefore, dealt fully with the more important and fundamental points in Pathology, and have either omitted altogether or dealt very briefly with rare and unimportant conditions. Minute microscopic anatomy of abnormal structures and tissues has been dealt with—though sometimes briefly, for we fully recognise that no descriptive writing can be substituted for the actual specimen and the microscope, and, moreover, the subject is fully dealt with in text-books on Morbid Anatomy and Histology. In dealing with animal parasites, much of the minute morphology

has been omitted. Bacteriology is so well dealt with in the many excellent text-books now published, that, important as it is to, and inseparable though it be from, Pathology, we have omitted it altogether as a separate subject.

We have especially to thank our old teacher and chief—Professor Greenfield, of Edinburgh University—for placing the notes of his lectures at our disposal. At his suggestion the work was undertaken, and without his hearty co-operation and the benefits of his wide experience it would have been impossible for us to overtake it. To acknowledge his help is to us a pleasure, but it is, perhaps, even a greater pleasure to have the opportunity of again bringing forward views founded on the results of careful observation and experiment, which he has previously published and taught for many years, but which have not received the attention and recognition which they merit.

The compilation of a complete bibliography has not been attempted, though reference has been made to some of the more important papers consulted. We have made free use of the standard text-books on pathology and medicine, and would specially acknowledge our indebtedness to the papers on "Inflammation," by Professor Adami; on "Protozoa," by Professor Minchin; and on "Parasitic Worms," by Manson and Shipley, in the "System of Medicine" by Allbutt and Rolleston; and also to Max Braun's "Animal Parasites of Man."

Almost all the illustrations are new, and are from specimens either specially prepared for us, or kindly lent for this work. The great majority of them are the work of Mr Richard Muir, Demonstrator of Pathological and Bacteriological Methods in the University of Edinburgh, and we desire to thank him for the care and trouble he has taken in their selection and preparation, the majority of the microscopical specimens being from his private collection.

We have also to thank Professor Cunningham, Curator of the Edinburgh University Anatomical Museum, and the Fellows

of the Royal College of Surgeons, Edinburgh, for permission to use specimens in their museum collections; Mr Henry Wade, F.R.C.S.Ed., Conservator of the Museum of the Royal College of Surgeons, Edinburgh, to whom we are indebted for the use of several specimens from his private collection, for purposes of illustration; to Mr Wade our thanks are also due for his kind assistance in revising the chapter on Tumours; to Professor T. H. Milroy, of Belfast, for his help in certain parts of the book dealing with problems of chemical physiology; to Dr W. E. Marshall, of the Lister Institute of Preventive Medicine, for suggestions in regard to parts of the chapter on Immunity; and to Dr Ashworth, Lecturer on Invertebrate Zoology, Medical Entomology, and Protozoology in the University of Edinburgh, for revising the chapter on Animal Parasites.

Lastly, it is a pleasure to acknowledge the uniform kindness and courtesy which we have received from our Publishers in connection with this work, and we thank them for the great care which they have bestowed upon its production.

J. M. B.
W. E. C. D.

October 1908.

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GENERAL PATHOLOGY

CHAPTER I

THE CELL IN HEALTH AND DISEASE

"Omnis cellula e cellula."—VIRCHOW.

THE tissues of the animal body, as well as those of vegetable organisms, are composed of **cells** and their products, and it is therefore essential that, for the study of the tissues in health and in disease, the elementary facts concerning cell structure and function should be understood as thoroughly as our present-day optical instruments and knowledge of optics and chemistry will permit. As the methods at our disposal become less imperfect with every advance in biological chemistry and in the construction of the microscope and its accessories, we may hope to penetrate further into the as yet little known mysteries of cell-life.

In the study of all physiological and pathological processes, we must (at all events until our knowledge of the more intimate structure of protoplasm, and of the still smaller units of which it, in turn, is built up, becomes more advanced) regard the cell as the **ultimate biological unit**—at the same time a **unit of structure** and a **unit of function**—however complex the tissue or organ built up of these cell-units may be. This great truth was first put forward by Schleiden in 1838, and by Schwann in 1839, but it was not until after the publication of Virchow's epoch-making work on Cellular Pathology in 1858 that these fundamental facts were generally accepted in the realm of pathology, and it was recognised that all the functions of the body are the result of, and are dependent upon, the sum of the varied activities of the innumerable cell-units of which the body is built up.

GENERAL MORPHOLOGY OF THE CELL

As above indicated, a multicellular organism, whether plant or animal, may be regarded as a vast colony of unicellular units, but it is only in a very limited sense that the individual tissue-cell can be looked upon as an **independent** unit. All grades of independency may be found, from the highly differentiated and fragile nerve or secretory cell, which may die almost immediately after removal from its normal environment where other cells or their products minister to its wants, up to the all but independent leucocyte, which may live for hours, or even days, if kept in suitable surroundings after it has been removed from the living body. But even the wandering phagocyte, which may be thus kept alive experimentally *in vitro*, cannot be truly regarded as an independent unicellular organism, and it soon perishes from lack of suitable nutriment which should be elaborated for its use by other specialised cells of the body, or it is poisoned by effete substances of its own formation which should be removed by the highly endowed cells of the excretory organs, co-operation being essential to the common welfare.

The cell-units of the body differ widely from one another in structure and in function in the different tissues and organs of the body, but in many ways even the most divergent types of cell have much in common, and we may, as it were, picture to ourselves an ideal representative cell which may be studied and discussed as the common type of all.

Such a cell may be defined as an organised mass of living matter forming the morphological and functional unit from which the tissues are built up, the older definition of the cell as a "nucleated mass of protoplasm" being scarcely wide enough in all its applications.

In shape, the animal cell varies indefinitely with such factors as the type of tissue in which it occurs, the density and nature of the surrounding structures, etc. It may be round or oval, spindle-shaped, cylindrical or polygonal, or entirely irregular; and very many types of cell from time to time change their outline, not only with their growth, but with variations in their functions. This is true not only of such cells as muscular fibres or the amœboid leucocyte, where it is a well-established fact,

but it is also characteristic of nerve and endothelial cells and many others where its occurrence is not so widely recognised.

Protoplasm, the essential and primary material of which the cell is composed, and in which the physical manifestations of

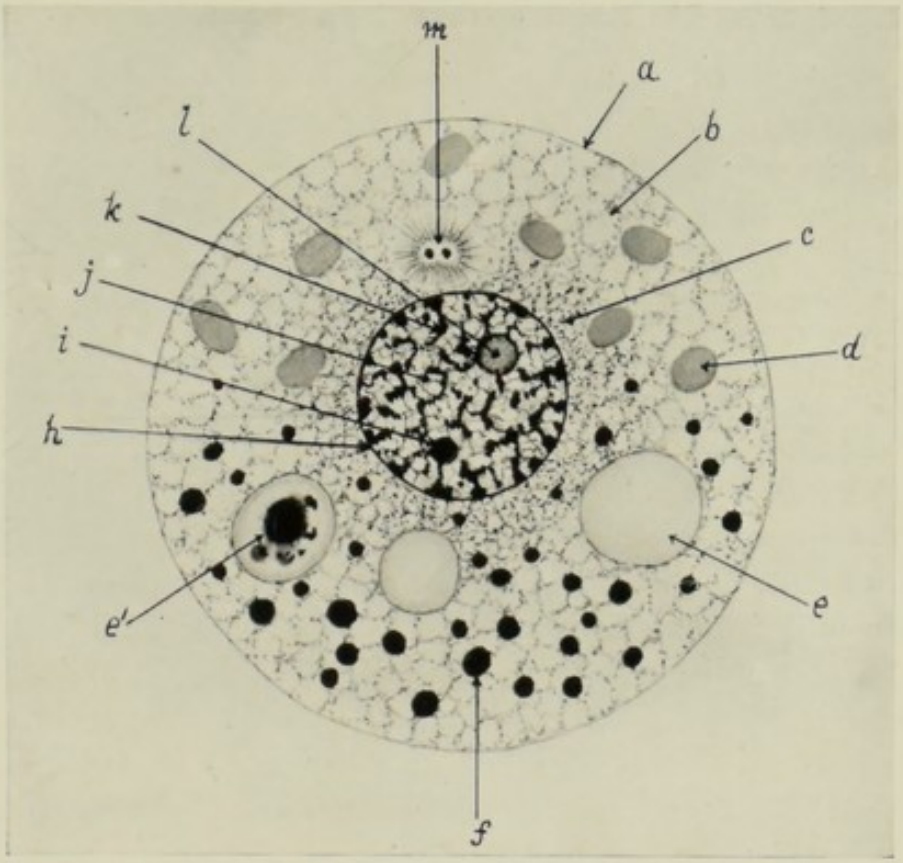


FIG. 1.—Diagrammatic Representation of Cell Structure. (After Wilson.)

a. Cell-wall or membrane.
b. Cytoreticulum or spongioplasm, containing the hyaloplasm in its meshes.
c. Endoplasm.
d. Plastids or protoplasts.
e. "Vacuole." *e'*. Digestive "Vacuole," containing partially digested cell inclusion.
f. Metaplasm (granules of pigment, ingested food, etc.).
h. Nuclear membrane.
i. "Net-knot" or karyosome.
j, *k*. Nuclear Network, consisting of chromatin and linin, and enclosing in its meshes the nuclear hyaloplasm or karyolymph.
l. Nucleolus or plasmosome.
m. Astral system, containing divided centrosome.

the vital processes which are carried on in it occur, is a soft, viscid, colourless, transparent or translucent substance, composed of two distinct structural elements, a delicate fibrillar or thread-like reticulum, the **spongioplasm**, in the meshes of which is contained the **hyaloplasm**, a clear, fluid-like substance,

which is probably a more or less passive nutrient material for the nourishment of the living protoplasmic network. The latter may be rendered much more apparent by the use of certain chemical reagents, such as a weak solution of hydrochloric acid; and it was formerly a much debated question whether the reticulated appearance of protoplasm was not an artefact produced by the various methods of fixation employed in the study of the cell. A few authorities still adhere to the view expressed in 1892 by Bütschli, that the reticular appearance is due to a foam-like structure produced in a mixture of two liquids of different degrees of viscosity, *i.e.* an emulsion; but the majority of cytologists agree that the reticulum actually exists during life, and that it is the most highly organised constituent of protoplasm, in which its vital processes have their physical basis.

This spongioplasmic reticulum is rendered more evident, not only by the use of certain artificial fixatives, but also during some of the changes seen in the process of cell-division by mitosis, and in some diseased conditions such as cloudy swelling. The latter condition is sometimes described as "an increased granularity" of the protoplasm, a term which should be restricted to an increase in the number of true cell-granules such as those found in the granular series of leucocytes, and should not be applied to the condition at present under discussion, where the meshes and nodal points of the network have merely become more evident.

Into the still undetermined question of the ultimate structure of the spongioplasm we cannot fully enter here, and it is sufficient for our present purpose to state that most physiologists hold that the fibrillar substance is not homogeneous, but is composed of clusters or rows of certain minute bodies (variously known as micellæ, microsomes, bioblasts, gemmules, etc.), which cannot as yet be demonstrated by the powers of magnification at our disposal.

The **spongioplasm** is contractile and elastic, and may be the seat of very active movements. Sometimes it may show a definite arrangement in parallel rods or bundles, as in the so-called striation seen in some glandular cells, *e.g.* in the salivary glands, kidney, etc. In other instances it may be developed into special fibrils, such as those seen passing through the

cytoplasm of nerve cells, or into motile, thread-like cilia in ciliated epithelium.

Nucleus.—In the typical cell there is usually a **single** nucleus, the executive centre for the control of the constructive and functional activities of the cell,—a more highly evolved part of the protoplasm found in all except the lowest living forms.

In some cells, for example in those of the liver, especially in some of the lower animals, there are frequently two nuclei present, but this is generally merely evidence of as yet incomplete or imperfect cell-division. In another important series of cells, for example, the osteoclasts, giant-cells and other cells which are most commonly concerned in the local absorption of bone, fibrous tissue, pathological substances, etc., and also in the so-called giant-cells found in morbid conditions such as tuberculosis (tubercle giant-cells), tumours (*e.g.* the myeloplaxes in myeloid sarcomas), etc., enormous numbers of nuclei, sometimes reaching even to several hundreds, may be found.

The shape of the nucleus varies greatly in different cells, not only according to the class of tissue to which they belong, and at different periods of their growth, but also from time to time according to the variations in the state of functional activity of the cell. In some cells, especially after **fixation** by various chemical or physical methods, the nucleus is more or less regularly rounded or oval in outline, and situated approximately in the centre of the cell. In other cases it is indented or kidney-shaped, or, again, it may be highly irregular in its configuration, as in the polymorphonuclear leucocyte of the blood.

One of the most complicated nuclear forms is that found in the megakaryocytes or giant-cells with hollow basket-like nuclei found in the bone-marrow. Change of nuclear configuration in a developmental series of cells is well exemplified in the granular myelocytes or marrow cells, and in the transitional myelocytes formed from them preliminary to the development of the ordinary polymorphonuclear leucocytes of the blood. Or, again, in the development of connective tissue, the younger or so-called "embryonic" actively dividing cells are rounded in shape and possess rounded nuclei large in proportion to the size of the cell. These cells first enlarge some-

what, and then gradually become elongated until they assume a spindle-shaped outline, the nuclei undergoing a parallel series of morphological changes until they finally assume a rod-like shape. An analogous series of changes may be observed during the development of young muscle cells.

The relative position of the nucleus within the cell is of some importance, but it is not sufficiently recognised that, during life, the nucleus may actively move from one part of the cell to another. A beautiful demonstration of this may be seen on watching the behaviour of the large mononucleated leucocytes in a warm-stage preparation of the blood from a case of malaria. In these cells, when they attack one of the malaria parasites, very active movements, both of the nucleus and of the cytoplasm, may be observed; the nucleus may be seen to move about actively with an amœboid motion, from time to time, rapidly changing its position within the cell, whilst in the cytoplasm itself streaming movements, apparently of the spongioplasm, occur, especially in the part of the cell nearest to the parasite which is being attacked. Changes in the position of the nucleus are also of some importance in connection with the process of cell-division, whilst an eccentric position of the nucleus is sometimes characteristic of certain degenerative conditions, *e.g.* in some degenerations of nerve cells. Too much stress, however, should not be laid on such changes, as considerable variations in the position of the nucleus may occur during different phases of cell life and activity.

Structure of the Nucleus.—In the ordinary vegetative condition of the nucleus—sometimes very misleadingly called the "resting" stage—in contradistinction to the changes which will be discussed later under the subject of cell-division or mitosis, the nucleus presents a more or less definite, typical structure, the component elements of which may be described in detail as follows:—

Nuclear Membrane—a thin, very delicate, and usually quite transparent structure surrounding the nucleus, and composed of an **achromatic** substance, that is to say, a substance without special affinity for the dyes or stains used in the study of the cell under the microscope. This achromatic substance is possibly allied to the material composing the spongioplasm of

the cytoplasm, and to linin or achromatin, one of the constituents of the nuclear network referred to below, some authorities regarding all three of these substances as merely special modifications of the same substance.

Nuclear Network.—The body or interior of the nucleus is composed of a **reticulum** or **network**, in the meshes of which lies a substance variously called the **nuclear hyaloplasm**, **ground-substance**, **nuclear sap** or **karyolymph**. In the **nuclear network** the filaments are composed of an unstainable or achromatic substance called **linin** or **achromatin**, along the course of which are attached or embedded granules or small masses of a material which has an intense affinity for certain dyes, and hence is called **chromatin**, a substance of extreme importance, which will be more fully discussed later under cell-division, cell-chemistry, and cell-degeneration. For the present it is sufficient to say that this chromatin or nuclein is a very complex substance compounded of albumin and nucleic acid, an organic acid very rich in phosphorus and nitrogen. At the nodes or junctions of the nuclear network, the chromatin is sometimes aggregated into larger masses which stain deeply, and are termed **net-knots** or **karyosomes.** These are not separate structures; they stain intensely, as does the rest of the chromatin, with the basic or "nuclear" dyes; and must be very carefully distinguished from nucleoli or plasmosomes, the staining affinity of which is for the protoplasmic or "acid" dye.

The **nuclear hyaloplasm**—sometimes also called the **nuclear ground-substance**, **nuclear sap**, or **karyolymph**—is a clear fluid substance, probably chiefly nutrient in its functions, and usually structureless in appearance, though sometimes a very fine fibrillar or granular structure may be seen in it.

The **nucleolus** or **plasmosome** is a structure which is found embedded or suspended in the nuclear network. It is usually single, but frequently two, and sometimes three, four, or even five, of these structures may be found in one nucleus. It has been averred by some authorities that the nuclei of certain cells, *e.g.* the small lymphocyte, do not possess nucleoli, but this is almost certainly an error, as in most cases it is not difficult to demonstrate their presence if suitable staining reagents be employed, though in the case of the erythroblast or nucleated red corpuscle success in this direction has not yet been

attained. As already stated, the nucleolus is essentially an *oxyphil* structure, staining with the acid or protoplasmic dyes. Thus, if the preparation is stained with a suitable mixture of acid and basic dyes, *e.g.* eosin and hæmatin, or eosin and methylene blue, the protoplasm and the nucleoli, being *oxyphil* in their reaction, stain a bright red colour, while the basophil chromatin takes up the basic dye and is stained an intense blue (Plates III. and IV.). The nucleolus, which may be rounded or somewhat irregular in its outline, usually contains towards its centre a minute unstainable spot, the **endonucleolus**, the significance of which, as indeed also that of the nucleolus itself, is as yet unknown.

The **centrosome** is a body of great importance in relation to cell-division, and will be again referred to in that connection. It is occasionally found inside the nucleus, but is more usually situated in the cytoplasm, just outside the nuclear membrane.

The **cell-body** or **cytoplasm** is composed of protoplasm, a brief account of the visible structure of which has already been given (p. 3). In the cytoplasm we may distinguish the **cyto-reticulum** or **spongioplasm**, and the **hyaloplasm** or more fluid substance lying in its meshes.

In some animal cells, more especially in certain of the primitive unicellular organisms, the cytoplasm may show differentiation into distinct, more or less concentric, **zones**: an inner, less highly differentiated zone immediately around the nucleus, termed the **endoplasm**; and an outer zone, the **ecto-** or **exo-plasm**, in which most of the so-called "cell-organs" and other highly differentiated structures, such as cilia, fibrils, etc., are found; though some of the latter, *e.g.* nerve fibrils, have of late been described as passing right through the endoplasm and even through the nucleus itself. This differentiation into cytoplasmic zones is very well seen in the case of the giant-cells or megakaryocytes of the bone-marrow.

Embedded in the cytoplasm, numerous more or less differentiated structures may be found in different varieties of cell. Some of these structures may be "cell-organs" more or less vital to the life and functions of the cell, whilst others may be merely passive bodies such as waste- or by-products, included foreign substances, food and other material stored up for future

use, etc. Reference may here be made to the more important of these structures. (See fig. 1, p. 3.)

Centrosome and **Attraction-Sphere.**—The centrosome has been called the dynamic centre for the reproductive activities of the cell, as it is the structure which leads the way in mitotic division. It is usually situated in the endoplasm or innermost part of the cytoplasm, immediately outside and often towards one pole of the nucleus. Sometimes it is single, but more commonly there are two centrosomes placed close together, and surrounded by a common envelope known as the **centrosphere** or **attraction-sphere**, from which delicate thread-like rays may be seen radiating into the surrounding protoplasm, especially when the process of cell-division is about to begin, forming the so-called **astral system of the centrosome.** In the vegetative condition of the cell, the centrosomes lie passively side by side within the centrosphere; but with approaching nuclear division they diverge from one another, each taking up its position at one of the poles of the dividing cell, and becoming the centre of the aster towards which the dividing elements of the original nucleus are drawn to form the nuclei of the daughter cells. In nerve cells, and possibly also in cells in which the centrosomes have not yet been detected, these bodies are situated **inside** the nuclear membrane. In the giant-cells or megakaryocytes of the marrow, Heidenhain has described the presence of very large numbers of centrosomes, placed in the endoplasm enclosed within the hollow basketwork of the highly complex nucleus characteristic of these cells.

Plastids or **Protoplasts** are structures of some importance in this connection, and may be regarded as localised areas of the cytoplasm in which special function has led to the development of special "cell-organs," *e.g.* for the production or transformation of starch, etc.

"**Vacuoles.**"—In many living cells, *e.g.* in leucocytes, small, clear, apparently structureless areas, often with pulsating walls, may be observed. These are sometimes rather erroneously called "vacuoles," and may be either temporary, especially in very actively functioning cells, or in some cases more or less permanent in their nature. One very important form of "vacuole" is that formed around a foreign body or particle which has been **englobed** or taken into the cytoplasm of the

cell by the process known as phagocytosis. A clear space may be observed round such an "included" object or its remains, and in reality constitutes a little stomach, or **digestive vacuole** as it is called, within the protoplasm, in which the processes of intracellular secretion and assimilation go on in a precisely analogous way to those of extracellular peptic and other forms of digestion. (See under **Phagocytosis**, p. 203.)

Another important variety of "**vacuolation**" of the protoplasm, which occurs not only in the cytoplasm but also in the nucleus, is due to degenerative alterations in the reticulum in disease. This will be more fully dealt with later.

Metaplasm, *e.g.* **products of secretion and excretion**, etc., may be found stored temporarily within the cytoplasm until they are required by the organism, or until they can be got rid of by excretion; whilst in other cases the so-called "**granules**" and other substances appear to be more or less permanent constituents of the cell. In the former of these groups may be placed granules or globules of various fatty substances, glycogen, and other food elements. The secreting cells of practically all glandular organs contain in their cytoplasm numerous granules which may be demonstrated by appropriate staining methods, for example that of Richard Muir.[1] Other cells of importance in this connection are the granular leucocytes of the blood, which owe their present classification to the size and staining affinities of the granules in their protoplasm. The precise chemical nature of these granules has not yet been determined, though many of them are probably compounds of albumin with other substances, *e.g.* in the form of nucleo- or gluco-protein bodies, etc. It is not yet absolutely determined whether these cytoplasmic granules are attached to the cyto-reticulum, or are merely situated in its meshes.

These cell-granules are at present classified very roughly into groups, according to their affinity for various acid, neutral, and basic dyes:—

i. **Oxyphil** (also called **eosinophil** or **acidophil**), with affinity for the acid or protoplasmic dyes.
ii. **Basophil**, with affinity for the basic or nuclear stains.

[1] Richard Muir, "Laboratory Notes," *Journal of Pathology and Bacteriology*, Edin. and Lond., June 1906, p. 373.

iii. **Neutrophil**, with no special affinity for either.
iv. **Amphophil**, with an equal affinity for both acid and basic dyes.

Pigment granules and particles may be present in various forms in the cytoplasm. They may be in the form of **included** or **englobed** foreign particles, or they may be a by- or waste-product of cell-activity, etc. The presence of foreign bodies such as bacteria, and other parasitic organisms, blood and other cells, etc., will be fully dealt with under **Phagocytosis**; and the presence of various degeneration products, such as droplets of colloid or mucoid material, fat and oil, etc., will be discussed in the chapter upon **Degenerations and Infiltrations**. To such lifeless and inert bodies and inclusions in the cytoplasm the term **metaplasm** is applied.

Cell-wall or membrane.—On examining sections of certain vegetable tissues such as pith and cork, one finds them to be built up of innumerable minute empty spaces, surrounded by very definite walls, composed chiefly of cellulose. Erroneously regarding the walls of these empty spaces as the essential components of a living vegetable tissue, the older histologists applied the term **cell** to them, looking upon the protoplasm which they previously contained when the tissue was alive and growing as a mere passing nutrient juice. Later, when it was discovered that the protoplasm, and not the cell-wall, was the essential living element of animal and vegetable tissues, the application of the term **cell**, which had by this time become too firmly established in scientific nomenclature to be dispensed with, was simply transferred from the cell-wall or membrane to its more essential living contents. So far from the cell-membrane being an essential component of the animal cell, it is now known that many cells, *e.g.* leucocytes and nerve cells, etc., have either no cell-membrane at all, or possess on their surface only an exceedingly delicate layer of specially adapted protoplasm representing it in function and position.

In some situations there may be direct structural continuity of the cytoplasm of adjacent cells. This may be incomplete or partial, as in the case of the cells of the Malpighian layer of the epidermis, in which the cell-bodies or neighbouring cells

communicate by means of the **intercellular bridges**, giving rise to the **prickle-like** appearance characteristic of these cells; or, again, this union may be more or less complete, as in the case of the so-called syncytial layers or masses of protoplasm, which possess numerous nuclei, but have little or no differentiation of their protoplasm into separate cell-units.

The cells, however, of certain of the tissues may possess a definite cell-wall, usually formed by direct transformation, chemical or physical, of the outer layers of the cytoplasm, which may come to contain such special substances as keratin, chitin, chondrin, collagen, lime salts, etc. In some situations, for example in the superficial layers of the epidermis, what may be called a physiological exaggeration of this process is seen, whereby the whole cell becomes changed into keratin, *i.e.* is transformed into a structure or material corresponding to cell-wall or membrane, for the analogous purpose of forming a protective layer or covering for the surface of the body. In certain pathological conditions similar changes may occur, either in normal positions but in exaggerated degree, or in altogether abnormal situations. Some of these conditions will be discussed in the Chapter on **Degenerations and Infiltrations.**

CELL-DIVISION

For full descriptions of the highly complex subject of cell-division reference must be made by the reader to special works upon the subject, but the question has such important bearings on certain branches of Pathology that a brief outline of the process must be given at this point, special emphasis being laid upon certain of its abnormal or pathological variations.

Allusion has already been made to the doctrine of "*Omnis cellula e cellula*" established by Virchow, and we have here to consider the process by which one cell, by subdivision of its own substance, gives rise to daughter cells, usually two in number.

Two methods of cell-division, by **karyokinesis**, or movement of the nucleus, are described—**direct** and **indirect**. The former is characterised by the fact that the nucleus divides *without* the preliminary transformation of the nuclear network into the thread or spireme, and its resolution into chromosomes. To the

direct method, therefore, the term **amitosis** has been applied. It is brought about by direct fission of the nucleus and protoplasm, and is so extremely rare in its occurrence that we need not further consider it here, except to remark that it is said to occur in some malignant tumours. It should, however, be carefully distinguished from certain degenerative conditions, especially that known as **karyorrhexis,** with which it might easily be confused, for example in the case of nucleated red blood corpuscles in the bone-marrow, or in the circulating blood, in the latter of which positions erythroblasts undergoing karyorrhexis may be found in some pathological conditions, such as pernicious and other forms of anæmia, myelogenous leukæmia, etc., although in these diseases nucleated red cells undergoing true mitosis may also occasionally be found.

By far the more important, and certainly in the higher animal and vegetable cell the practically universal, method of cell-multiplication is that known as **indirect karyokinesis** or **mitosis**, so named from the essential part which the formation of the spireme and chromosomes takes in the process.

The two chief, if not fundamental, factors in this mode of cell-multiplication are (1) the arrangement of the chromatin into loops or chromosomes, and the cleavage of these into two; (2) the rearrangement of the subdivided chromosomes in the daughter nuclei. To all the phenomena occurring before and leading up to the division of the chromosomes, the term **Prophase** is applied. To the actual splitting of the chromatin loops the name **Metaphase** is given. This is followed by the **Anaphase**, during which the daughter nuclei are built up; and the process is completed during the **Telophase**, in which the cell-body becomes divided into two daughter cells. A tabular scheme of these phases, and the accompanying series of diagrammatic figures, may aid in the explanation of this complicated process.

MITOTIC DIVISION

I. **PROPHASE.**—1. During the **vegetative period** of cell-life there may be only *one* centrosome present, but, as already indicated, division of this body usually long precedes the further processes of mitosis, and may be looked upon as the beginning

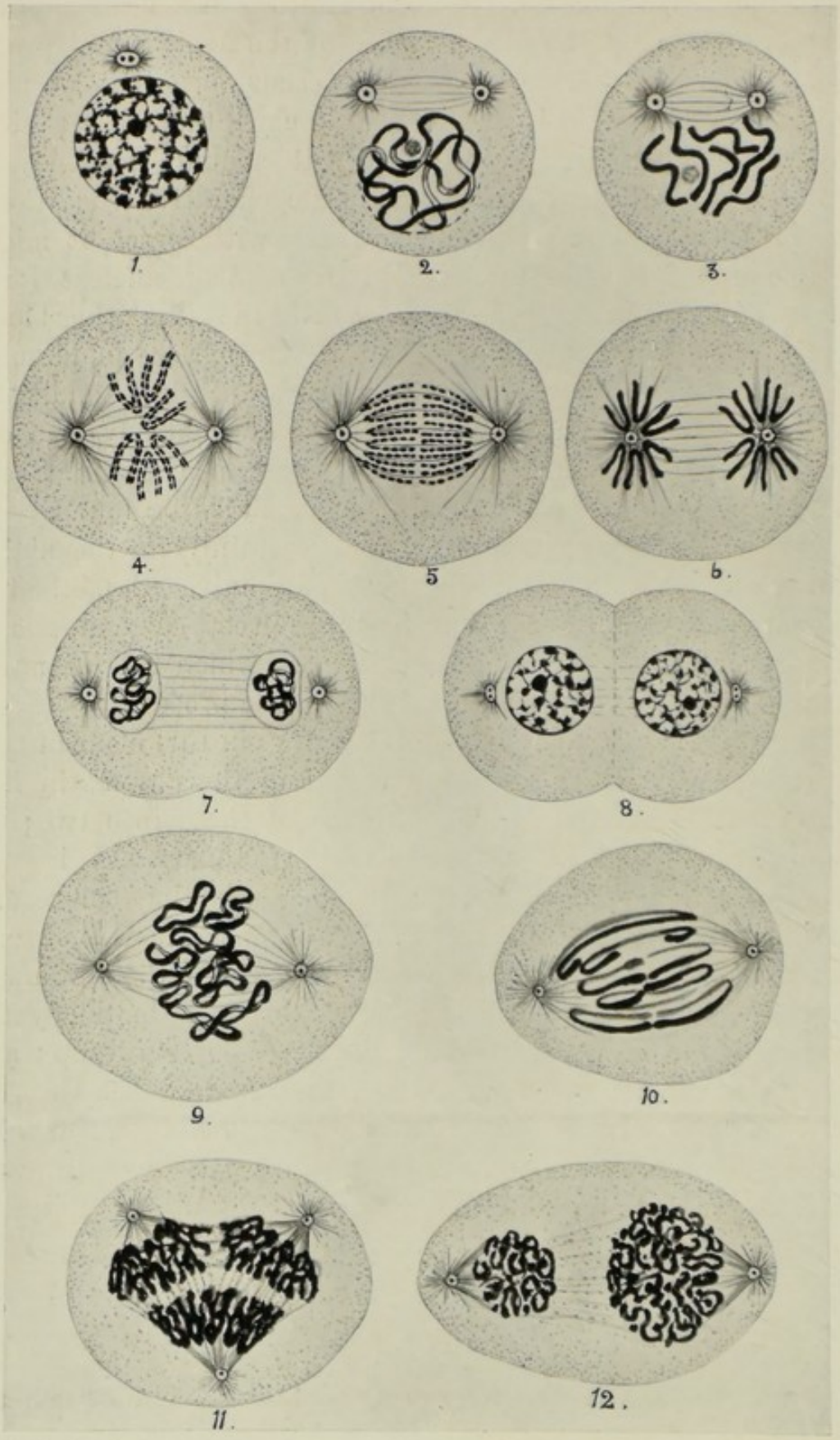


FIG. 2.—Diagrammatic Representation of the Processes of Cell-division.

of a potential division of the cell which may supervene when occasion requires.

2. **Division of the centrosome** within the attraction-sphere. This, as we have just said, may occur during the vegetative period, or even during the later phases (ana- or telo-phase) of the *previous* mitotic division, when the cell now about to divide was itself being produced as a daughter cell.

The presence of *two* centrosomes is therefore quite a normal occurrence during the vegetative state of the cell, and may be found for a considerable period before any further signs of nuclear division supervene. When this is about to occur, the centrosphere usually enlarges somewhat, and the astral rays which radiate into the surrounding protoplasm become much more distinct.

Description of Figure 2.

1–8. Mitosis in Somatic Cells.
1. Cell during *vegetative period*. The Centrosome has already divided.
2. *Prophase.*—Division of attraction-sphere; formation of achromatic spindle and spireme.
3. *Prophase.*—Breaking up of spireme into chromosomes.
4. *Metaphase.*—Splitting of the chromosomes after their arrangement around equator of spindle during prophase.
5. *Anaphase.*—Halves of divided chromosomes passing towards poles of spindle.
6. *Anaphase.*—Chromosomes at poles of spindle.
7. *Anaphase.*—Chromosomes united into spiremes. Formation of nuclear membrane round daughter nuclei. This diagram also shows commencement of Telophase.
8. *Telophase.*—Final stage, with division of cytoplasm. The new centrosomes have already divided.

9, 10. Mitosis in Gametogenetic Cells.
9. Formation of ring-shaped chromosomes in *Heterotype Mitosis.*
10. Their division and passage to poles of spindle.

11, 12. Irregular Forms of Mitosis.
11. *Multipolar Mitosis.*
12. *Asymmetrical Mitosis.*

3. **The attraction-sphere itself then divides into two**, each half possessing a centrosome, centrosphere, and astral rays, *i.e.* each forming a complete astral or attraction system.

4. These attraction-spheres gradually diverge from one another, and a **spindle** composed of **achromatic threads** becomes formed between them in the cytoplasm, these threads appearing to have the function of guiding lines for certain of the subsequent processes. While these phenomena are going on, certain very important changes are also taking place in the nucleus itself. The nucleolus disappears, either by solution within the nucleus or by extrusion into the cytoplasm, where it loses its characteristic staining reactions and becomes lost to view. The nuclear network, with its attached chromatin, becomes condensed, and arranges itself into a long spiral or

convoluted thread, the **skein** or **spireme**, from which the process of mitotic division derives its name (*μίτος*, a thread). This spireme usually breaks up into a number of V- or U-shaped loops, the **chromatin loops** or **chromosomes**, of which there is in each dividing cell a definite number, constant for each species of animal or vegetable organism, and said to be sixteen in the case of the human subject. At or before this stage the nuclear membrane gradually disappears, the process generally commencing on the side nearest to the attraction-systems and spindle. The last-named structure, as above described, is composed of achromatic threads formed in the cytoplasmic network; but at this stage another very important set of thread-like structures, known as the **attraction-fibres**, is formed. These are also achromatic in their staining reactions, and are found growing out towards the nucleus in two distinct sets or systems, each with its point of origin or focus at one of the two attraction-systems. These attraction-fibres penetrate into the nucleus, the chromatin network of which has by this time broken up into chromosomes; and to *each* individual chromosome several attraction-fibres from *both* attraction-systems become attached. The attraction-fibres then progressively shorten and draw the chromosomes towards the spindle, around the equator of which they become arranged between the guiding fibres of the spindle, each loop with its apex pointing inwards. At this stage the chromosomes stain very intensely, and give rise to a single, star-like figure, sometimes known as the **monaster** or "mother-star," or, from the relative position of the chromosomes with regard to the spindle, the **equatorial plate**; whilst to the attraction-systems and the achromatic spindle between them the name **amphiaster** is given. All the preceding complex movements of the nucleus lead up and are preparatory to the next and most essential phase of the mitotic process.

II. **METAPHASE**, or **division of the chromosomes.** — Each chromatin loop splits longitudinally into two, the cleavage beginning at the apex of the V, as is shown in the diagram.

III. **ANAPHASE**, or **the building up of the daughter nuclei.** — The two sets of attraction-fibres then become progressively shortened, and draw the respective halves of the divided chromosomes to which they are attached towards each pole of

the spindle, where they become united into a convoluted thread or spireme, which, in turn, gives rise to the nuclear network of the daughter nucleus, around which a nuclear membrane is then formed, and in which a nucleolus appears.

The centrosome may at once divide and its two halves remain side by side without any further change during the vegetative period now entered upon by the daughter nuclei.

IV. **TELOPHASE.**—This term is applied to the final stage of the process of cell-division, during which the guiding threads of the spindle become divided along the line of demarcation between the two daughter cells; and the cell-body undergoes constriction, the cytoplasm becoming divided from the surface inwards. The process of division of the original cell into two daughter cells is now complete, the remains of the enclosed half of the achromatic spindle disappearing, and each of the resulting cells forming a complete cell-unit.

MODIFICATIONS OF THE PROCESS OF CELL-DIVISION BY MITOSIS

1. One of the most remarkable modifications of the process of cell-division by mitosis, as above described, is that known as **reduction of the chromosomes** during the maturation of conjugating germ-cells. We have seen that the ordinary process of cell-division, as it occurs in the general somatic or body cells, is characterised by the formation of a definite, specific number of chromosomes. Thus, in the case of the human subject there are sixteen of these bodies formed in ordinary **somatic** mitosis. In the case of each of the conjugating germ-cells, or male and female gametes—the ovum and spermatozoon—the number of chromosomes is reduced to one-half the original number, in order that, in the single cell—the impregnated ovum or zygote—formed by the union of these two elements, the number of chromosomes characteristic of the species may be maintained. Were this process of reduction not carried out during the maturation of these conjugating cells, the number of chromosomes would become progressively doubled at each union. To the process of cell-division characterised by this reduction of the chromosomes to half their original number, the term **gametogenetic** mitosis is

applied, in contradistinction to the ordinary somatic variety already mentioned. The pathological importance of this variety of cell-division lies in the fact that its occurrence has been described in some malignant neoplasms; and that certain theories as to the possible origin of tumours have been largely based upon this apparent similarity with the processes occurring in gametogenetic cells from which are derived the mature gametes or conjugating germ-cells.

In the case of the ovum and spermatozoon, this reduction of the chromosomes occurs during the last two cell-divisions immediately preceding the production of the mature male and female gametes or conjugating germ-cells. In the case of the ovum it is brought about during the process known as **extrusion of the polar bodies**, which are in reality themselves small or aborted ova which do not go on to further development, the mature ovum alone giving rise to the somatic layers of the embryo. In the case of the spermatozoon the stages of the process are precisely analogous, except for the fact that, instead of, as in the female, only one of the four germ-cells finally formed (ovum and three polar bodies) going on to maturation, all four, in the case of the male, become fully developed and functioning spermatozoa.

For a full description of the mechanism by which the reduction of the chromosomes is effected, reference must be made to special works on Embryology and on the Cell.

Into the problems concerned with the embryonic origin of the gametogenetic cells of the ovary and testis we cannot enter here; and we merely mention that, at all events in certain of the lower animals, the original cells of the sexual organs appear to be derived, not from cells originating from the impregnated ovum itself, but from cells coeval with it; in other words, from germ-cells which actively migrate into the body of the early embryo and become localised in the Wolffian body or its neighbourhood to form the special cells of the sexual organs. Reference will again be made to this question when the various theories connected with the causation of tumours are under discussion.

Other modifications and varieties of the mitotic process are of comparatively small importance for our present purpose, and do not call for a detailed description. They may be summarised as follows :—

2. **Heterotype Mitosis**, in which the halves of each of the dividing chromosomes at first remain united at their ends, giving rise to a series of *ring-like* bodies. This variety of mitosis is specially seen in gametogenetic tissue during the development of germ-cells. It is important from the fact that its occurrence is described in some malignant tumours (Farmer, Moore and Walker; Bashford and Murray, and others). More recent observations, however, for example those of Bashford and Murray, do not appear to confirm the occurrence of the so-called heterotype mitoses in malignant tumours, and these observers also deny the alleged occurrence of anything of the nature of nuclear fusion or fertilisation which some writers have described as occurring in malignant growths.

3. **Pseudo-reduction** may occur in certain somatic cells, and is probably explained by the fact that two of the chromosomes remain united together.

4. In certain unicellular organisms, the centrosome may remain **inside** the nuclear membrane, and the spindle will then be formed *within* the nucleus. This modification is, however, not found in the higher animals.

5. **Asymmetrical Mitosis**, where the chromosomes are unequally distributed between the two daughter nuclei, or where some of the chromosomes are destroyed after their formation. Such asymmetrical mitoses are common in certain tumour cells, especially in carcinomas, and may be accompanied, and perhaps caused, by an asymmetrical development of the centrosome and spindle. This type of mitosis has also been induced artificially by the application of certain chemical substances. The terms **hyperchromatic** and **hypochromatic** are applied to such cells whose nuclei possess respectively too many and too few chromosomes. (See fig. 2, cell 12, p. 15.)

5. **Multipolar Mitosis**, in which the spindle may possess three, four, or perhaps even more poles, at which corresponding nuclei are built up. This method is said to occur normally in certain vegetable cells; but in the animal cell it is entirely pathological, and is probably due to a premature splitting of the centrosome, or to one or both of the daughter nuclei at once going on to another division. Such multipolar mitotic figures have been found especially at the growing margins in some forms of cancer. (See fig. 2, cell 11, p. 15.)

In this group we may also include certain abnormalities in the impregnated ovum, which may sometimes lead to the production of monstrosities.

THE CHEMISTRY OF THE CELL

Protoplasm, or the substance of which living cells are composed, is usually described as being a soft, colourless, transparent, jelly-like substance; but it must be borne in mind that, on more exact examination, it is found to be possessed of a finely fibrillar structure, in the interstices of which there lies the apparently homogeneous interfibrillar hyaloplasm.

It is an exceedingly complex substance, within which, during life, a constant cycle of chemical changes is going on. For our present purpose, we need not discuss whether protoplasm is composed of one single highly complex substance, built up of molecules of almost infinite complexity; or whether there are in it numerous independent or semi-independent simpler substances.

Whether the molecules of these simple substances are linked together chemically or not, and their exact relationships to one another, are matters of great interest and importance; but the following simplified table of the composition of protoplasm must, for the present, suffice.

COMPOSITION OF PROTOPLASM

Proteins.—The term *protein* is now employed to designate all albuminous substances, whether simple or conjugated. It is highly probable that, in living protoplasm, albumins and other proteins may be directly united with fatty bodies or with carbohydrates. For the convenience of our readers we append here the recommendations made by the Chemical and Physiological Societies of Great Britain as to the nomenclature of albuminous substances:—

RECOMMENDATIONS.

I. The word Proteid—which is used in different senses in this country and in Germany—should be abolished.

II. The word Protein is recommended as the general name of the whole group of substances under consideration. It is at present so used both in America and Germany. It admits readily of the use of such derived words as protease and proteose. If used at all, the term Albuminoid should be regarded as a synonym of protein.

III. The sub-classes should be as follows :—

1. **Protomines.**—These are simple members of the group. They are exemplified by substances like salmine and sturine, which have been separated from fish-sperm.

2. **Histones.**—These are more complex substances: this and the previous class probably pass gradually into one another. The class is exemplified by the histones separated by Kossel from blood corpuscles ; precipitability by ammonia is one of their distinguishing features.

3. **Albumins.**—These are proteins of which egg-albumin and serum-albumin may be taken as typical examples.

4. **Globulins.**—These are proteins which differ from the albumins in solubility ; they are more readily "salted out" of solution than the albumins. They are exemplified by serum-globulin and fibrinogen. The class should also include certain derivatives of globulins such as fibrin and myosin.

N.B.—The carbohydrate radicle separable in small quantities from many members of Classes 3 and 4 is probably not to be considered as a prosthetic group, as it is in the gluco-proteins (see below).

N.B.—It appeared advisable, especially from the teachers' standpoint, to introduce a general term to include proteins coagulable by heat (Classes 3 and 4) ; but a term likely to meet with general acceptance has not yet been suggested.

5. **Sclero-proteins.**—This new word takes the place of the word albuminoid in the limited sense in which the majority of physiologists have been accustomed to use it. It includes such substances as gelatin and keratin ; the prefix indicates the skeletal origin and often insoluble nature of its members.

6. **Phospho-proteins.**—This class includes such substances as vitellin and caseinogen, with its derivative casein. The prefix nucleo- frequently used in relation to this class is incorrect and misleading.

7. **Conjugated proteins.**—These are substances in which the protein molecule is united to a "prosthetic group." The principal subdivisions are :—

(*a*) *Nucleo-proteins.*
(*b*) *Gluco-proteins* (*e.g.* mucin).
(*c*) *Chromo-proteins* (*e.g.* hæmoglobin).

8. **Derivatives of Proteins.**—Of these, the products of protein-hydrolysis (a term preferable to proteolysis [1]) are those which require special attention. These should be classified as follows :—

(*a*) *Meta-proteins.*—This term is suggested in place of albuminate

[1] Although mindful of the unfortunate fact that terms such as proteolysis fail to convey a meaning in harmony with that which is conveyed by the terms electrolysis and hydrolysis (on which they are moulded) of decomposition *by*, the Committee have not ventured to deal with the difficulty ; they recognise, however, that the practice is one to be obviated if possible (compare Armstrong, *Proc. Roy. Soc.*, 1904, **73**, 500.

(acid-albumin, alkali-albumin), which is objectionable because (1) these products are obtainable from both albumins and globulins; also (2) because the termination "-ate" implies a salt.

(*b*) *Proteoses.*—This term includes albumose, globulose, gelatose, etc. The subdivision of these into proto-, hetero-, deutero-proteoses, etc., and the various modifications of Kühne's original classification, have been considered; the whole subject is, however, at present too unsettled for any final nomenclature of these subdivisions to be proposed.

(*c*) *Peptones.*—This term should be restricted to the further products of hydrolysis which differ from the proteoses, inasmuch as they cannot be salted out from solution, and usually resemble them in giving the biuret test.

N.B.—It has been pointed out that certain vegetable products hitherto regarded as peptones do not give the biuret test. It does not appear possible to bring such exceptional substances into any general classification at present. The same difficulty in classifying arises in connection with certain other vegetable proteins; for instance, those which, like gliadin, are soluble in alcohol.

(*d*) *Polypeptides.*—The majority of the polypeptides are synthetical substances. Some, however, have been separated from the products of protein-hydrolysis, and it is therefore advisable to include them in the present classification. They are products of cleavage beyond the peptone stage, and consist of two or more amino-acids in association; the majority of those hitherto prepared do not give the biuret test.

IV. The term caseinogen should be used for the principal protein in milk, and casein for its derivative, which is the result of the action of rennet.

V. The two principal proteins of the muscle plasma should be termed paramyosinogen and myosinogen; the term soluble myosin should take the place of v. Fürth's soluble myogen-fibrin; the term myosin should be restricted to the final product formed during *rigor mortis*.

Fats, *e.g.* neutral fat: lecithin (which contains phosphorus, etc.)—fats being composed of fatty acids and glycerin.

Alcohols, of which group Cholesterin is a member. Recent researches appear to show that this substance, which has hitherto been regarded more or less as an effete product, may possibly play an important part in metabolism.

Carbohydrates, *e.g.* glycogen or animal starch, which may be built up from starch, dextrin, maltose, glucose, etc.

Inorganic Salts, *e.g.* chlorides, phosphates, sulphates, etc. The cells contain more potassium and phosphoric acid than the fluid which bathes them, and the salts play a most important part in cell-metabolism.

Water.

In addition to these more essential components, protoplasm also contains—

i. **Food material** about to undergo, or in process of, absorption.
ii. **Effete substances** resulting from katabolic metabolism, *e.g.* carbon dioxide; cholesterin (*vide supra* under "alcohols"); certain pigments; azotised derivative products formed by the splitting of higher compounds, *e.g.* urea, creatin, creatinin, etc.
iii. **Special products of the vital activity of the cell**, *e.g.* zymogen granules.

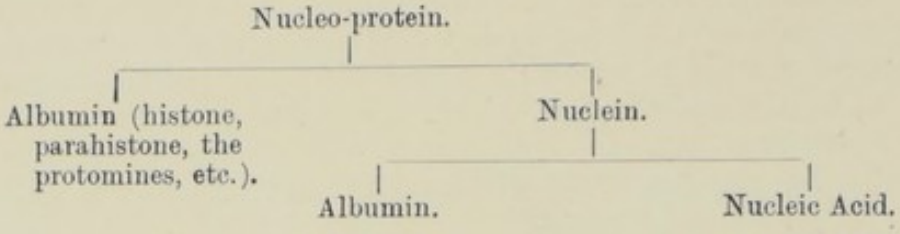
The most important of the above groups is that of the proteins; and a short account may be given here of the changes which these substances undergo, more especially during digestion and assimilation. These proteins are found, not only in cell-protoplasm, but also in the body fluids, *e.g.* in the blood and lymph. They may be **simple**, or they may be **conjugated**, *i.e.* compounds of albumins or globulins with some other organic substances such as the fats, sugars, or certain phosphorus-containing compounds, — for example, nuclein (the phospho-proteins or so-called nucleo-albumins), or iron-containing substances like hæmatin (as in hæmoglobin = globin + hæmatin). During the processes of proteolytic digestion or protein-hydrolysis, proteins are split up into the following series of dissociation products:—

1. Proteins (*e.g.* albumins, etc.).
2. Proteoses (*e.g.* albumoses, etc.).
3. Peptones.
4. Simpler products which may be classified according to their constitution, as follows:—
   (*a*) Monoaminomonocarboxylic acids, *e.g.* glycin, alanin, leucin (fatty); also Oxyamino acids, *e.g.* tyrosin (aromatic); and Thioamino acids, such as cystein and cystin.
   (*b*) Monoaminodicarboxylic acids, *e.g.* aspartic and glutamic acids.
   (*c*) Diaminomonocarboxylic acids ("hexone" bases), ornithin, lysin, histidin, arginin; and diaminoxymonocarboxylic acids, such as diaminotrioxydodecanic acid.
   (*d*) Heterocyclic compounds, such as prolin, tryptophane, indol, skatol, etc.

During this process of proteolytic digestion or protein-hydrolysis, the large, non-assimilable molecules of albumin, etc., are thus broken up into substances with progressively smaller molecules, until they are sufficiently reduced in size to be capable of being taken into or absorbed by the animal cell, in which they are then built up again during the process of assimilation and become constituents of the protoplasm.

The nucleo-proteins are split up by peptic digestion into their constituents, albumin and nuclein. The former of these (histone, parahistone, the protomines, etc.) undergoes the proteolytic changes

described in the preceding paragraph ; and the nuclein is precipitated, and some of its nucleic acid may be freed.



Nucleo-proteins are *completely* digested by tryptic digestion.

Chromatin, which, as we have seen, shows such a special affinity for the basic dyes, and which therefore appears to act as an acid radicle, consists essentially of substances which are either closely allied to, or are identical with, the nucleins, these being also acid substances with great affinity for the basic stains. This apparent identity of chromatin and nuclein is a point of very great importance, especially in view of the fact that, during certain phases of cell and nuclear activity, the nucleins play a very important rôle in the process ; and during these periods there are, *pari passu* with the chemical changes occurring in the nuclein compounds, corresponding variations in the intensity with which the nuclear chromatin "fixes" or is stained by the basic dyes. This is accounted for by the fact that the nucleo-proteins in the nucleus form a **series** in which the relative amounts or relative combining affinities of the albumins and the nucleins vary. The firmer combinations of the two, *i.e.* the lower members of the series, stain less intensely with the basic dyes, whereas the looser combinations stain more intensely. Thus, during mitosis, when the reproductive activity of the nucleus is at its maximum, the chromatin consists of almost pure nuclein, and probably contains little or no albumin, and this stage is therefore characterised by very intense staining, a condition also induced by certain degenerative changes. During periods of great constructive activity, on the other hand, for example during active secretion, the staining reaction of the chromatin gradually becomes diminished, either because of chemical changes occurring in it, or—and this is the more generally accepted view—by its actual transformation in varying degree into secretory or zymogen granules which pass out into the cytoplasm. Here they may give rise to enzymes or ferments which bring about intracellular digestion and assimilation ; or, on the other hand, they may pass out of the cell as an extracellular secretion, the nature of which varies with the organ or tissue producing it, *e.g.* the special secretions of the stomach, pancreas, salivary glands, and so on.

The processes of **extra**-cellular digestion, absorption of the digested food, and intracellular assimilation and storage, may be shortly described here. From the chromatin or nucleo-protein material within the nucleus, the zymogen granules, above described, are formed. From these arise such enzymes as the proteolytic ferments,

e.g. pepsin, trypsin, etc.; the fat-splitting ferments, the sugar-inverting ferments, etc. After their excretion, *i.e.* **outside** the cell,[1] for example in the alimentary canal, these act upon the food molecules, and, as was explained in the case of proteolysis, break them up into molecules small enough to be capable of absorption. These simpler products can then be taken into the cell. Some of them are re-synthetised by other ferments in the cytoplasm in which they may be stored as food, whilst some may be carried into the nucleus to supply it with material and energy for the rebuilding up of the chromatin and the manufacture of the zymogen granules from it—the whole forming, as it were, a cycle of vital processes, the controlling centre of which lies in the nucleus. This cycle of changes is one of extreme importance both physiologically and pathologically, and reference will again require to be made to it when we are considering problems connected, not only with visible changes in the nucleus and cytoplasm, but also with the processes of phagocytosis and intracellular digestion, and many of the more abstruse phenomena involved in the great question of immunity. Such tissue ferments or enzymes — for example erepsin — which break up proteoses and peptones into amino-acids, are of great importance. The ferment just named occurs in all the organs and tissues of the body. Autolysis or self-digestion of such organs and tissues may be brought about experimentally "*in vitro*" by incubating them at body temperature under aseptic conditions; and a further study of these ferments may possibly come to explain certain pathological phenomena, the causation of which is now obscure.

STAINING PROPERTIES OF THE VARIOUS CELL-ELEMENTS

The investigation of the exact nature of the chemical components of **living** protoplasm presents features of almost insuperable difficulty; and our knowledge is practically limited to the study of the chemistry of protoplasm which is **dead**, whether its death precede the application of, or be caused by, the chemical and other reagents which we employ. Again, the isolation and study of component parts of the cell may be, and usually is, impossible; and our knowledge of "micro-chemistry" is largely dependent on the chemical affinity and visible colour reactions of certain dyes and other chemical substances with the various component structures of the cell and its products.

The reagents which are most commonly used for the purpose of staining microscopical sections of tissues may act either

[1] NOTE.—In some cases the enzymes secreted remain inactive until they are acted upon by another enzyme, *e.g.* trypsinogen requires to be "activated" by enterokinase, a ferment present in the *succus entericus*.

physically or chemically. The latter method is that which occurs in the case of the most important group of reagents used for this purpose, viz. the aniline dyes. These are manufactured from coal-tar, and are derivatives of benzene (C_6H_6), or its homologues, toluene (toluol), xylene (xylol), quinone, naphthalene, and anthracene.

Benzene . .	C_6H_6	
Toluene . .	$C_6H_5 \cdot CH_2$	(methyl-benzene)
Xylene . .	$C_6H_4 \cdot (CH_3)_2$	(dimethyl-benzene)
Quinone . .	$C_6H_4O_2$	
Naphthalene	$C_{10}H_8$	
Anthracene .	$C_{14}H_{10}$	

Some compounds of these substances, which have been called the **chromogens**, possess what are known as colour-radicles or **chromophores**, to which their specific colour is due. Certain of these chromophores are basic, whilst others are acid in their reaction, the same being also the case with certain other radicles of the molecule; and, depending on the balance of these, the whole molecule of the dye may act as a base or as an acid, as the case may be; or in some instances they may be neutral, and are then known as the **salt-dyes** (*e.g.* the eosinate of methylene blue, which forms the basis of the Romanowski staining method and its many modifications, such as those of Jenner, Leishman, Nocht, and others).

Under suitable conditions, chemical union of these dyes with the tissue elements can be brought about, some structures possessing a greater affinity for those of the basic and some for those of the acid series; whilst other tissue elements may take up both equally, or have no special affinity for either. The tissue elements may thus be classified somewhat roughly into those which are oxyphil, basophil, amphophil, and neutrophil, respectively.

Oxyphil (sometimes called acidophil: eosinophil).—Cytoplasmic reticulum: centrosome: attraction-sphere and rays: spindle fibres: nuclear membrane: linin network of the nucleus: nucleoli or karyosomes: certain cell-granules.

The more important acid or cytoplasmic stains are eosin and erythrosin, acid fuchsin, light green.

Basophil.—Chromatin and chromosomes, *i.e.* substances rich in the phosphorus-holding nucleic acid: certain cytoplasmic granules.

The more important basic or nuclear stains are hæmatein (combined with alum as "hæmalum"), methylene and thionin blues, gentian violet, saffranin, Bismarck brown, methyl and methylene greens, basic fuchsin.

CELL FUNCTIONS AND ACTIVITIES, AND THE RELATIONSHIP OF NUCLEUS AND CYTOPLASM

The life history of any cell may be summarised by the statement that—except in the case of the fertilised ovum which is formed by the *union* of two cells—it must evolve by the division of a parent cell and grow; it must maintain itself and perform its functions; and after a varying period it must degenerate and die, or it may, either as a somatic or as a gametogenetic cell, transmit its characteristics to another generation.

Sufficient mention has already been made of the processes of somatic and gametogenetic cell-division; the maturation and conjugation of germ-cells; and the part played by the chromatin loops, which are apparently the means of conveyance of hereditary characteristics from parent to offspring. We have also discussed the processes of food ingestion, either by absorption of soluble food substances or by the englobing of food particles by the cytoplasm; intra- and extra-cellular digestion by means of enzymes; and the assimilation of the nutriment so prepared. Along with these we may also class the changes occurring during the processes of respiration. With these processes are also intimately associated the problem of cell-growth, and—when they fail—of cell-degeneration.

There only remains therefore for discussion in this connection the question of **specific** or **specialised cell function.**

In the case of the simple unicellular protozoon—for example, the amœba—all the vital vegetative and reproductive processes are carried out by one individual cell. But in the metazoon or multicellular organism, the carrying out of any one or more of these vital processes may be specially relegated to some special cell or set of cells, which thus becomes endowed with **specialised function.** In this way, movement and contractility specially devolve upon muscle cells; secretion and excretion upon glandular cells; reproduction upon the cells of the

generative organs, and so on. All degrees of such evolution of specialised function are met with in the cells of the animal body; and also all degrees of interdependence upon the specialised functions of the other cells of the organism, from the comparatively independent leucocyte and wandering cell up to the highly complex and delicate nerve cell which is practically entirely dependent upon other cells for everything except its own specialised function. Under abnormal conditions, many cells may take on functions apparently differing largely from their accustomed duties. Thus kidney, liver, and other glandular cells may become actively phagocytic to hostile cells or organisms or to foreign particles. Endothelial cells take on this phagocytic action so readily that it may almost be considered one of their normal functions; and perhaps certain of the so-called metaplastic changes occurring between the cells of closely allied tissues may also be included as examples of this condition.

FUNCTIONAL RELATIONS BETWEEN NUCLEUS AND CYTOPLASM

Due co-ordination between these two elements of the cell is required for the full performance of the cell functions. A cell deprived of its nucleus may live for a varying period, and even carry on certain of the less complex metabolic processes, *e.g.* in the case of red blood corpuscles, which are said to have a normal existence of from fourteen to thirty days. Cells which have lost their nuclei may also react to external stimulation; they may move, englobe food particles, etc., but they cannot perform any of the higher activities of cell-life. They cannot grow or reproduce themselves by division; they cannot digest the food particles which they may have succeeded in ingesting; they cannot secrete or excrete. In other words, their capacity for the performance of the higher metabolic processes and for the co-ordination of these has been lost. The nucleus may thus be looked upon as the **executive** and **co-ordinating centre** controlling most of these metabolic processes, *e.g.* assimilation and growth, etc. It is the formative chemical centre, and perhaps also the seat of the formative energy of the cell. More than a quarter of a century ago, Claude Bernard concluded

that the cytoplasm or cell-substance is the seat of vital expenditure of energy, whilst the nucleus is to be regarded as the executive centre governing this expenditure, and specially concerned with synthetic metabolism. Recent observers go even further than this; and Adami,[1] in a review of the subject, states his belief that—

"this conception does not exactly represent the relationship, for the nucleus is also the seat of expenditure, nay, appears often to determine that expenditure. But clearly the indications are that the higher syntheses, those associated with growth and those governing the specific enzyme actions of the different forms of cell, are determined and initiated by the nuclear matter."

DEGENERATIVE AND ALLIED CHANGES IN THE CELL

As already indicated, any or all of the three great groups of cellular activity, viz. (1) growth and maintenance or nutrition, (2) reproduction, and (3) specialised function, may be influenced or interfered with either temporarily or permanently by certain conditions. Most important among these may be placed alterations in the quality or quantity of the supply of nutriment; and exposure to the action of injurious agencies such as excessive heat or cold, pressure, electricity, and other forms of radio-activity, or of chemical substances, such as organic and inorganic poisons, toxins produced by bacteria, etc. In the histological study of such conditions, the only guides to our knowledge at present available are the actual physical changes brought about in the tissues. The axiom that function and structure are so essentially interdependent that any alteration in the one, however slight, must necessarily mean a corresponding change in the other, is of the utmost importance. From alterations in the functions of an organ during life we may be able to deduce, sometimes with a comparative degree of certainty, the presence of definite changes in the actual structure of the organ or tissue; for example, the presence of certain abnormal substances in the urinary secretion often indicates certain definite structural alterations in the kidney. Conversely, it is often possible, from the consideration of the actual histological changes in an organ or tissue, to infer what

[1] Adami, "The Dominance of the Nucleus," *British Medical Journal*, London, Dec. 22, 1906, p. 1760.

abnormalities were present in its functional activities during life; and hence the correlation of **structure** and **function** is of extreme importance.

The wide range of structural variations possible in the healthy cell during different phases of cell-activity must be constantly borne in mind in this connection, as many of the degenerative conditions affecting the cell are in reality exaggerations of these normal functional variations.

All gradations, from slight stimulation up to total death and destruction of the cell, may be brought about by the **same** injurious agent, the degree of change depending upon such factors as its amount, intensity, length of application, etc., and, of course, also on the capacity of the tissue to resist its attack. Thus the application, say, of some sufficiently dilute toxic substance may cause a stimulation of any or all of the various cell functions. The earlier changes seen in "cloudy swelling" are in many ways analogous to those seen in the cells of an actively secreting gland. An increase in the number of dividing cells in the part, as evidenced by abnormally numerous karyokinetic figures, etc., is often a characteristic feature of such a condition; and many other phenomena, both cytoplasmic and nuclear, may be regarded as analogous to those seen during increased, or in some cases decreased, functional activity.

Again, the irritant may, from its nature or from the method of its application, be able to kill the cell outright, with little or no change in its visible structure—the condition aimed at when we artificially "fix" a tissue for examination—or in other cases it may bring about great changes in, or perhaps even the total destruction of, the normal structure.

The extreme variability of the results produced by the application of the same injurious agent, in different degrees of concentration or in different amounts, in repeated or in single doses, is very well illustrated in the case of certain chemical substances which are used medicinally. Thus, corrosive sublimate in very minute doses is found to stimulate the reproductive and other activities of a tissue; in larger doses it produces marked toxic changes, such as intense inflammation or actual necrosis; whilst, if it is applied locally in concentrated solution, it "fixes," *i.e.* kills, the tissues outright, with but little

apparent alteration in their morphological structure. Similarly, the various salts of mercury, arsenic, lead, etc., when given in small repeated doses, produce at first a very definite stimulation of the reproductive or hæmopoietic activities of the bone-marrow; but if their administration be prolonged, the stimulating effect wears off, the tissue gradually fails to react, becomes worn out, and undergoes an extreme degree of degeneration, accompanied by very profound anæmia. This is well seen in cases of chronic lead or arsenic poisoning.

Thus, in studying the action and results of any particular form of irritant, whether chemical or physical, all gradations between these extremes may be met with, but for our purpose here it will be sufficient to mention some of the more commonly recognised degenerative conditions seen in the cell.

In some cases these degenerative changes may be found specially affecting the **cytoplasm**, while in other instances it is the **nucleus** which suffers most; but if they are found in any marked degree in **one** of these constituents, the **other** part of the cell is also almost invariably affected.

CYTOPLASMIC CHANGES

Probably the commonest degenerative condition affecting the cytoplasm is that known as **cloudy swelling**, which will be again discussed later. The cell-body becomes swollen, perhaps from the imbibition of fluid from the surrounding lymph, and the cyto-reticulum is physically altered in such a way that its meshes appear coarser and more irregular. At first, the reticulum tends to stain more deeply, and perhaps somewhat irregularly, with the acid dye, the outline of the individual strands usually becoming somewhat hazy and indistinct. The meshwork then tends to become progressively more loose and open in its arrangement, and gradually loses its staining capacity. At certain parts of the cytoplasm, clear vacuole-like spaces tend to appear, due to destructive changes and the accumulation of fluid in its meshwork. These so-called vacuoles may increase in size and number until the whole cell-body shows merely as a scanty shred-like network with very slight staining capacity, and finally it becomes broken up and disappears. (See fig. 3, p. 33.)

In other cases, the swollen cytoplasm becomes more homogeneous in its appearance, perhaps owing to the imbibition of lymph, *e.g.* in what is known as **Zenker's degeneration of muscle.** This is rather to be regarded as a "post-necrotic" change, that is, a change supervening **after** the death of the cell; and its occurrence was originally described by Zenker, who observed the condition in the abdominal muscles in cases of typhoid fever. It may also be found in paralysed or in bruised muscle, or in muscle which has been subjected to the action of certain bacterial toxins, *e.g.* in acute infective fevers, or where these act locally around areas of inflammation. The muscle fibres lose their transverse striation, become swollen and homogeneous in appearance, and later undergo fragmentation and absorption.

Although the changes described above as occurring in the cytoreticulum in cloudy swelling appear to be the most important feature of the cytoplasmic changes, reference must be made to certain other phenomena described by some authors. Adami,[1] in a recent discussion on *The Physiology and Pathology of the Nucleus*, holds that—

"In cloudy swelling, which so commonly accompanies the acute fevers and conditions of intoxication, we note, more particularly in the cells of secretory glands, that the nuclei, which in the first stage of irritation may become more intensely stained, rapidly lose their staining property and become indistinct, and the cell-body becomes filled with granules of albuminous nature. Stolnikow was apparently the first to make accurate studies upon the changes that occur in these degenerative processes; many others have since noted the same collection of the chromatin in the region of the nuclear membrane; the discharge into the cytoplasm (well seen in the liver cells in phosphorus poisoning); have described these little masses as first staining like nuclear substances, and later losing the nuclear stain completely, the cell-body becoming filled with shell-like, clear-staining globules."

These globules in all probability correspond to certain of the "albuminous granules," the occurrence of which is described by many authors as characteristic of cloudy swelling. They are to be seen especially in glandular secreting cells, and may be an exaggeration or abnormality in the formation of what physiologists describe as "secretion granules," though in all probability many of the "albuminous granules" may be the result of disintegration of the protoplasm.

[1] Adami, "A Discussion on the Physiology and Pathology of the Nucleus," *British Medical Journal*, London, Dec. 22, 1906, p. 1764.

NUCLEAR CHANGES

In the early stages of irritation, *e.g.* in cloudy swelling, the nucleus may show a distinct preliminary increase in its staining capacity, a condition analogous to that seen in the early stages of mitosis, or in an actively functioning cell before its chromatin has become transformed into the special products of cell-activity.

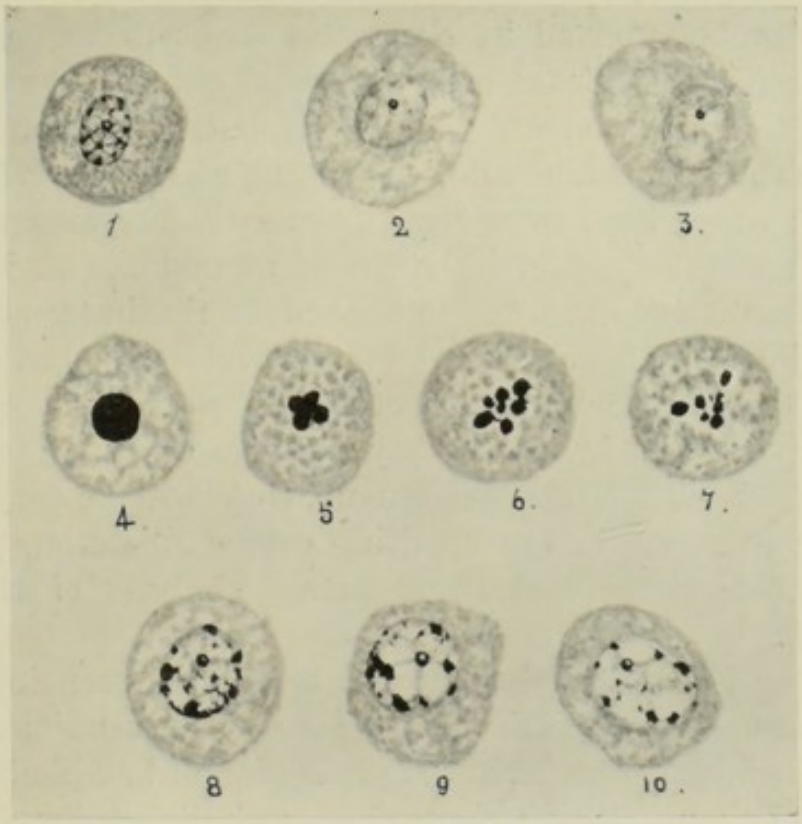


FIG. 3.—Cell-degeneration.

1–3, Karyolysis.
4–7, Pyknosis, Hyperchromatosis, and Karyorrhexis.
8–10, Karyorrhexis.
Cloudy swelling is present in all of these cells.

This preliminary increase in the staining capacity of the nucleus forms a marked feature in some cell-degenerations, and is sometimes known as **hyperchromatosis**.

In the later stages of cloudy swelling, the nucleus usually becomes progressively paler in its staining reactions, the chromatin apparently becoming dissolved, or at all events so changed in its composition that it loses its affinity for the basic dyes. This apparent *solution of the chromatin* in the cell-juice is known as **karyolysis** or **chromatolysis**.

Fragmentation of the nucleus, or **karyorrhexis**, is also a common method of nuclear degeneration, and is usually preceded and accompanied by hyperchromatosis. If the nucleus at the same time becomes more condensed in its structure, the term **pyknosis** is applied to the condition,—hyperchromatosis and pyknosis being evidently closely allied processes, which are frequently found in conjunction with one another. As the process of karyorrhexis advances, the nuclear network becomes broken up, and its chromatin tends to aggregate into irregular particles or masses. These may exhibit no apparent plan in their method of arrangement, but, on the other hand, they are sometimes found dotted very regularly over the whole nucleus; or, perhaps even more frequently, they are arranged in a somewhat symmetrical manner around the periphery of the nucleus, being apparently attached to the inner surface of the perinuclear membrane. The latter may then become dissolved, and the chromatin particles are found scattered in the cytoplasm, in which they undergo solution; or, if the cytoplasm itself has also broken up, they will be found lying free, for example, in the resulting caseous material, pus and other inflammatory and degenerative products of tissue destruction.

Another important phenomenon sometimes seen in connection with nuclear degeneration, and to which allusion is made in a preceding paragraph, is the production of bud-like processes which are extruded from the periphery of the nucleus into the cytoplasm. These little masses containing chromatin at first retain their affinity for the nuclear dyes, but this becomes gradually lost as the chromatin disappears. This phenomenon may be very well seen in the normal development of the erythroblasts or nucleated red blood corpuscles of the bone-marrow which are in process of losing their nuclei and becoming transformed into erythrocytes or ordinary non-nucleated red corpuscles; and it may also usually be well seen in the erythroblasts which have escaped into the blood stream in various pathological conditions.

CHAPTER II

GENERAL RETROGRESSIVE PROCESSES

We have now to consider the application of our knowledge of cellular physiology and pathology, not merely to the case of the individual cell-units themselves, but also to that of various body tissues of which the cell-units are the constituent elements.

Much that has been said with regard to cellular pathology need not be repeated here, but we may again mention that, as was pointed out by Virchow, there may be interference with any of the three great varieties of cell- and consequently also of tissue-activity, namely, **nutrition, reproduction,** and **special function.** Further, we must also bear in mind the various channels or modes of access by which injurious agents may attack the tissues and their component cells. Thus they may act **directly** upon them, for example, on a free surface; they may be carried to them by the blood-stream or by the lymphatics; or they may act **indirectly** through the mechanism of the nervous system, or by impairing some other bodily function which is necessary for the health of some, or perhaps even all, of the tissues, *e.g.* the secretion of the thyroid and other glands.

When an injurious agent brings about the actual death of cells or tissues within the living body, the term **necrosis** is applied to the process. This, together with the closely allied subject of gangrene, will be considered separately in a subsequent chapter; whilst the question of **atrophy**, which may also be classified as a retrogressive change, will be discussed later along with **hypertrophy.**

No distinct line of demarcation can be drawn between the remaining two generally recognised groups of retrogressive

changes known as the **degenerations** and the **infiltrations**, many intermediate forms being found; but for practical purposes, a **degeneration** may be defined as a retrogressive pathological change characterised by the **direct transformation** of the cell protoplasm (or of the tissue elements derived from it) into useless or inert material; whilst in the case of an **infiltration** such useless or inert material may arise elsewhere (though it need not necessarily do so), and is stored up in excessive amount in the cells, or in the other tissue constituents formed from them. Food material, such as glycogen or fat, or products of metabolism, such as pigment, urates, etc., may thus be accumulated, owing either to excess in their amount, abnormalities in their composition, etc., or to the temporary or permanent disablement of the cells preventing the performance of their normal activities, synthetic, katabolic, excretory, or otherwise.

From what is indicated above, it will be easily understood that, the more highly endowed an individual cell is with regard to its special function, the more easily may its very delicate mechanism be thrown out of gear; and hence it is that certain highly complex, and at the same time extremely delicate, cells are more liable to injury than are the hardier and less highly differentiated cells of the body. When so damaged, such highly endowed cells have also, as a rule, much less power of recovery. Thus certain ganglionic, glandular, and other highly specialised cells are much more liable to suffer from injury and disease than are, say, the less differentiated cells of a supporting connective tissue. Again, certain toxic agents have a special selective capacity for certain cells or certain tissues, and may cause their destruction, at the same time leaving other cells and tissues practically unharmed. Thus the toxins of the bacillus of tetanus act specially on certain ganglionic cells, while those of the diphtheria bacillus may act more particularly on some of the secretory cells of the kidney.

DEGENERATIONS AND INFILTRATIONS

I. CLOUDY SWELLING

The condition of **cloudy swelling**, which is also sometimes known as **turbid swelling**, or **parenchymatous** or **albuminoid degeneration**, includes a variety of retrogressive changes which may be due to a large number of conditions interfering with the cell-life or metabolism, and which are characterised, as the name implies, by a swelling of the cell, and the formation of a cloudy "granular" appearance in its protoplasm. This is due partly to coagulation or precipitation of certain of the protoplasmic constituents, *e.g.* proteins or protein-fats, in the form of granules, and partly to changes produced in the cyto-reticulum, whereby it becomes coarser and more irregular in appearance. The granules are, in the earlier stages, soluble in dilute acetic acid or caustic soda, and are probably albuminous in their nature; whilst, if the condition becomes more extreme, fatty granules and globules may also appear, probably from the splitting of the so-called "protein-fat," "albumin-fat," or "soap-albumin."

The swelling of the cell is due to fluid, probably imbibed by osmosis from the surrounding lymph, accumulating in the meshes of the reticulum, and giving rise to the so-called "vacuole-like" spaces. These cellular changes have already been somewhat fully described. They are usually accompanied by softening or loosening of the cement-substance between the cells, as is well seen in what is called **catarrhal** inflammation, where the cells become swollen and separated from one another and from their basement membrane—if this structural element be present. The condition of cloudy swelling was originally described by Virchow, in 1850, as "hypertrophy with a tendency to degeneration."

Ætiology.—Cloudy swelling is most usually produced by the action on the cells of some **soluble toxic substance circulating in the blood.** The most common of these substances are the **bacterial toxins**; for example, those found in the acute infective

fevers, such as pneumonia, diphtheria, typhoid and scarlet fevers, etc., and in other toxæmias or septicæmias. Various **organic poisons**, such as snake venom, the vegetable poisons abrin and ricin, poisonous fungi, etc., and many **inorganic poisons**, such as corrosive sublimate, etc., may also produce the condition, as may, in all probability, certain toxic substances of unknown or little understood nature and origin, for example unexcreted normal or abnormal products of metabolism (*e.g.* in Bright's disease), or certain substances supposed to be generated in and absorbed from the alimentary canal and elsewhere in the case of the so-called "auto-intoxications."

A very considerable degree of cloudy swelling is found in cases of severe internal hæmorrhage, and appears to be due to the action of the extravasated hæmoglobin, which, when free in the blood-serum or lymph, has a distinctly toxic action.

Again, the condition may be produced **locally** by the action of certain chemical or bacterial irritants, and also by the action of heat, for example in burns and scalds.

The precise mechanism by which the change is brought about is still doubtful. The toxin or other poisonous substance may act by entering into direct chemical union with the cell protoplasm, as in the case of corrosive sublimate, which forms an insoluble albuminate of mercury; it may unite with, or in some instances may chemically displace, some important protoplasmic constituent, as in the case of poisoning by carbon monoxide, where this gas firmly unites with the hæmoglobin of the red blood corpuscles, displacing the oxygen, and forming a much more stable compound than the necessary oxyhæmoglobin, and thus destroying the vital oxygen-carrying capacity of the hæmoglobin of the red corpuscles. Or, again, the poisonous substance may act on the cell protoplasm, altering its nutritive selective capacity in such a way that it tends to take up abnormal substances from the surrounding lymph.

The exact chemical nature of the change is not yet understood, but the so-called "granules" are alleged by some observers to be albuminoid in character, as they swell up and disappear on the addition of dilute acetic acid, but are not soluble in alcohol or ether. Fatty globules are often found associated with cloudy swelling, and fatty degeneration is frequently a sequel of the condition.

Effects on the various organs and tissues.—The organs specially affected are the **liver**, **kidneys**, and **heart**, *i.e.* organs containing highly endowed cells, more especially those concerned with the destruction or excretion of the toxin causing the condition; for example, the parenchymatous cells of the liver, or the cells of the convoluted tubules and the ascending part of Henle's loop in the case of the kidney. As already indicated, the chemical or other special affinities of the toxin for special cells may also account for the fact that some tissues

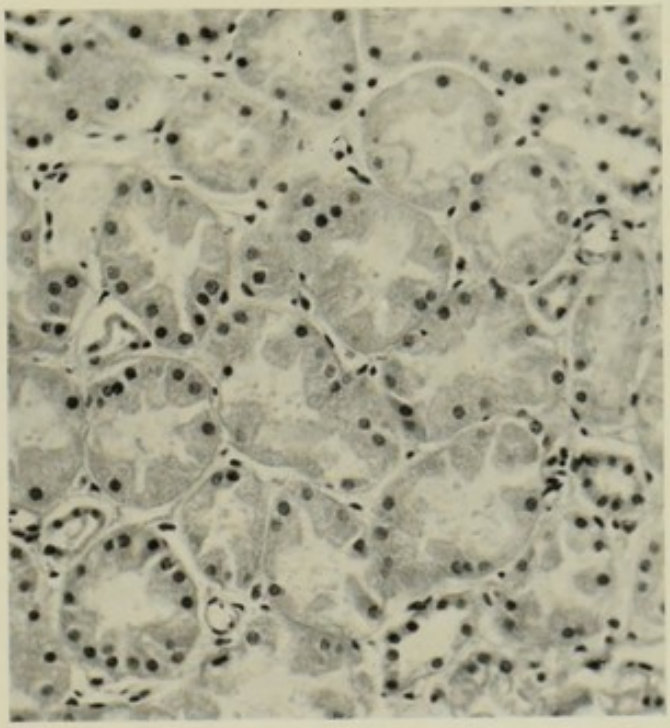


Fig. 4.—Cloudy Swelling in Secreting Tubules of Kidney.

may suffer more than others, *e.g.* nerve cells in tetanus. The effects of the change upon the cell may be anything from slight stimulation up to total destruction of both structure and function.

Naked-eye appearances.—The organs are usually slightly swollen, softer in consistence, and paler in colour. The cut surface loses its transparency and becomes more opaque or cloudy, suggesting the appearance produced by immersing in hot water. In the early stages there may be associated congestion, but soon, owing to the swelling of the parenchymatous cells of the organ, the vessels become compressed and emptied of their blood, the pale colour of the organs being thus due to

the swollen condition of the parenchymatous cells. Owing to this emptying of the blood-vessels which help to map it out, the minuter naked-eye structure of the organs is often considerably obscured; for example, in the case of the liver the outlines of the lobules may be very indistinct and difficult to see.

The microscopical appearances and distribution, and the staining reactions of the change, have already been sufficiently

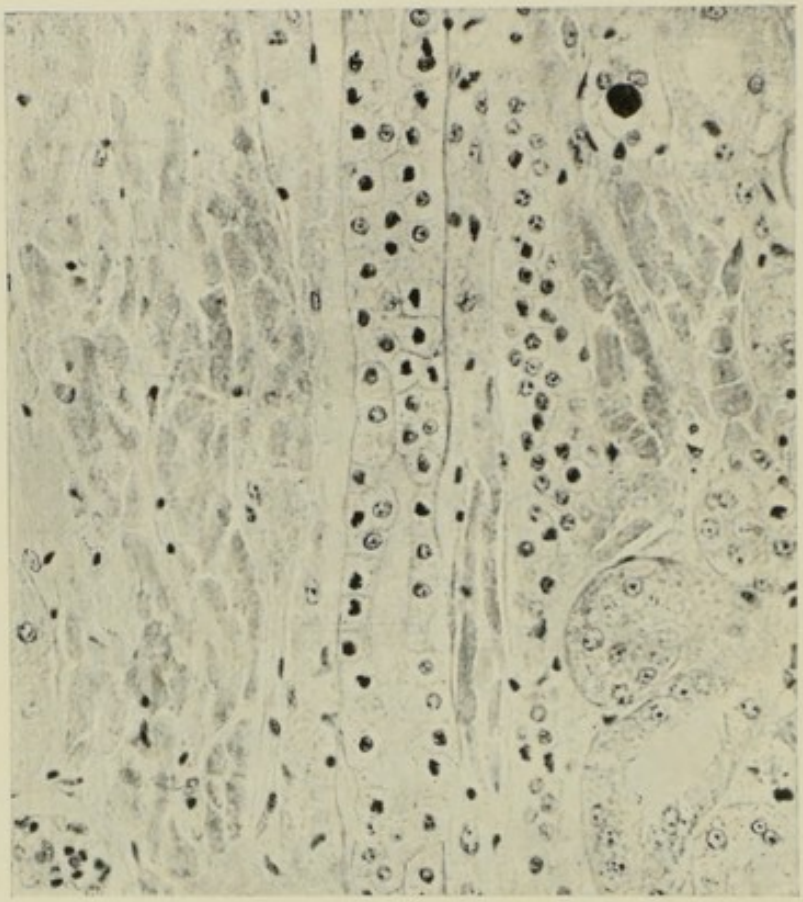


FIG. 5.—Advanced Cloudy Swelling or more correctly Necrosis of Kidney. The collecting tubule (seen in longitudinal section, in centre of field) is less affected than the more highly specialised convoluted tubules and secreting portions of Henle's looped tubules, seen on either side.

described. The typical structure of the affected cell may become obscured or lost, for example, the striation of heart muscle.

Course and Results.—In certain cases the change may be very rapidly produced, *e.g.* in some fevers within six or eight hours. The results may be transient, *i.e.* may pass off with the removal of the toxin, in which case the cells may recover, entirely or partially, according to the extent of the damage to them and

their power of resistance. In the case of partial recovery, a degradation in the type of the cell may occur. Thus, highly endowed columnar secreting epithelial cells, say, in the kidney, may become changed into cubical or even merely flattened lining epithelium. If the irritation is intense and prolonged, the condition may go on to fatty degeneration; or it may go on to cell-death or necrosis without the supervention of fatty degeneration, and the cytoplasm may undergo disintegration into mere granular detritus.

FATTY DEGENERATION AND ALLIED CONDITIONS

The part played by fats and their allies and compounds in normal metabolism is a subject of great difficulty and complexity, and recent papers and text-books must be consulted for information upon the physiological aspects of the question. As, however, the problems connected with the subject in its pathological bearings are best studied and understood by looking upon certain of the abnormal conditions found **as exaggerations or modifications of the normal processes** of the metabolism of fats, a few words must be said with regard to some of the more recent views upon this subject.

The neutral fats are compounds of the fatty acids (stearic, palmitic, oleic) and glycerin. During intestinal digestion they are split up into these two radicles, and the fatty acid thus liberated becomes transformed by union with an alkali, potash or soda, into a diffusible—*i.e.* soluble—soap, in which form it can be absorbed by the intestinal mucous membrane. A large proportion of this soap is then re-synthetised into fat by the epithelial cells, and passed into the lacteals. As to the question of the part played by leucocytes in the transportation of fat through the intestinal mucous membrane, we need not enter here. It is possible that a considerable proportion of the soap passes directly as such into the blood of the portal system, is carried to the liver, and there built up again into neutral fat by the cells of that organ, within which it may either be stored in non-diffusible form till required, or may undergo assimilation proper, *i.e.* become synthetised into an integral part of the cytoplasm, being then no longer recognisable as fat by the

usual staining and other micro-chemical reactions. When required for the nutrition of the various body tissues, the fat temporarily stored in the liver is re-transformed by that organ into soluble soap, in which diffusible form it can be dealt out and carried to the tissues by the blood. In the tissues it may then be assimilated as a food, or, as in the case of the subcutaneous, extraperitoneal, and similar areas, it may again be stored as neutral fat, and from these, in turn, it may be re-absorbed as soap should there be special demand for it, *e.g.* in fevers or starvation, where this reserve store of body fat may be very rapidly used up.

Klotz,[1] in a recent paper upon Calcareous Degeneration, points out the fact that *in the tissues* sodium and potassium soaps are not nearly so soluble as *in vitro*, and he therefore concludes that in the cell they are probably in combination with some other protoplasmic constituent, almost certainly albumin. This "albumin-soap," as he calls it, being very insoluble in water and alcohol, is capable of being stored within the cell in non-diffusible form until required. As an additional argument in favour of this hypothesis, he cites the result of test-tube experiments in which he found that, on adding some dilute egg-albumin to a weak solution of pure soap, say sodium stearate, a flocculent precipitate was slowly formed, analogous in physical, chemical, and staining reactions to the intracellular soap granules. He therefore thinks that the latter are probably also combined with albumin in the form of a "soap-albumin."

In other situations the soap may be taken into the cells from the blood or lymph, and the fatty acid split off and reunited with glycerin to form a neutral fat, which is then stored until required. This is in all probability chiefly the case in the great storage areas of the body, *e.g.* the subcutaneous tissue, omentum and extraperitoneal fat, bone-marrow, etc., all of which tissues are extremely vascular, and the fat cells of which are in very intimate connection with the circulating blood.

Again, in addition to being thus temporarily stored up in certain cells, either as neutral fat or as a soap-albumin, fat is a food element necessary for the carrying out of the vital

[1] Klotz, "Studies upon Calcareous Degeneration," *Journal of Experimental Medicine*, 1905–6, pp. 1, 322, and 504.

functions of the individual cell; and for this purpose it is assimilated and built up into an integral part of the cytoplasm, and can then no longer be distinguished as fat by the usual tests.

There are therefore several stages of this process at which theoretically it is possible for interference to occur, and for pathological variations to take place. Some of these may be classified as **infiltrations**, others as **degenerations**; but in many cases it is impossible to make this distinction, while in some instances **both** conditions may be present at one time.

1. An excessive amount of fat, or substances capable of being transformed into fat, may be ingested, the excess being accumulated in the usual storage, and perhaps also in other, areas. Into this group cases of obesity or adiposity from overfeeding and similar causes would naturally come, and in some of these cases the ordinary connective tissues may be largely transformed into fat.

2. Abnormal activity of the storage functions of some cells, although the actual amount of fat brought does not exceed the normal supply, *i.e.* an anomalous condition of metabolism, of which the reason is not apparent.

3. Diminished power of the cells to utilise fat brought to them (as soaps)—not necessarily in increased amounts—the cells retaining their power of splitting off the fatty part of the soap, and storing it as fat or as soap-albumin; but being unable, owing to some injury, toxic or otherwise, to utilise these substances after their ingestion. This would be a form of **true fatty infiltration.**

4. Destruction of the cell from some toxic or other cause, accompanied by a disintegration of the cytoplasm, and by a freeing of the fat from its combination in the complex protein molecule in which it was combined as a soap-albumin. Klotz also suggests the possibility of another process in some cases—the absorption by the damaged cell of soaps from the blood or lymph, the vitality of the cell being so diminished that no conversion into neutral fat occurs, the soaps then combining to form a relatively insoluble compound with the albuminous substances derived from the disintegrating protoplasm.

5. An older view, not now held by many modern observers, was that the fat was a dissociation product of proteins—not in the sense of these being in this instance compounds of albumin with some fatty body, but as simple albumin. That this may occur is possible, but it must be remembered that in the so-called classical examples of the formation of fat from casein in the "ripening" of cheese, and the production of adipocere—a fatty material said to be formed from the body tissues after death under certain peculiar conditions—the action of saprophytic organisms must also be taken into account. Another modification of this view is that protoplasm is a compound of protein and carbohydrate—a gluco-protein—and that the fat may be derived from the carbohydrate part of this on its disintegration. The more modern view, however, that the fat in such cases is derived from the splitting off of fat previously combined with albumin, appears to be more likely, and has already been discussed.

Many years ago Quain pointed out that in fatty hearts there was no actual increase of the total fatty material present. Van Noorden found that in cases of phosphorus poisoning the total fat of the body was not only not increased, but actually diminished in amount; and more recently Rosenfeld[1] has shown that in fatty degeneration of the kidney there is usually less fatty material present than there is in the case of the normal organ, in which it is present in combination with proteins, and therefore not stainable as fat.

Some recent writers—for example, Herxheimer and Walker Hall[2]—have expressed the opinion that the term "fatty degeneration" conveys an impression not warranted by the present condition of our knowledge, and suggest the use of the words "degenerative fatty infiltration," as indicating that the fat is brought from outside and deposited in cells whose vitality is so lowered that they cannot use up enough of the fat, and cannot build up the compound of protein and fat. They do not consider that the fat is formed by the splitting of proteins or other substances within the cells, and look upon the process as one of infiltration by fat from outside.

[1] Rosenfeld, *Berlin Klin. Wochenschrift*, 1904, xli. p. 587.

[2] Herxheimer and Walker Hall, "Fatty Degeneration or Infiltration?" *Medical Chronicle*, 1904.

As is so often the case in such controversies, there appears to be justification for both views, and we must in the meantime simply leave the question an open one.

The actual **source** of the fat itself in these conditions is also an unsettled problem, but, for convenience, the most recent views may be summarised as follows:—

1. In true **fatty infiltration**, fat is brought **from outside**, *i.e.* from the food or from the storage areas, and is accumulated within cells which are **not** extensively damaged.

2. In **fatty degeneration** there are two possible sources of the fat, and in any given case it may arise from **one** or **both** of these sources:—

(*a*) Accumulation of fat brought **from outside**, in a **previously injured cell.**

(*b*) Freeing of fat, previously combined with albumin, **within** the cell itself, this previously combined fat now becoming visible and demonstrable by the ordinary specific stains for fat. This process may occur under the influence of toxins; or in other cases it may be due to the action of the natural ferments — the lipases — which are concerned normally with the splitting up of fats. What is known as **autolysis**, or disintegration of tissues brought about by their own ferments, is an analogous process.

THE COMMONER VARIETIES OF FATTY CHANGE

FATTY DEGENERATION may be regarded as a retrogressive change associated with the appearance of fatty granules or globules in the cytoplasm of the cell. It is of great importance, not from the mere fact of the presence of the fat, but because it is a common method of decay in the animal cell. It frequently occurs as a sequel to, or in combination with, cloudy swelling, especially if the toxic agent at work be more prolonged and intense in its action. Fatty infiltration and other degenerative conditions are frequently found associated with fatty degeneration.

Etiology.—Some of the possible causes of the condition have already been discussed whilst dealing with its theoretical

aspects. The condition is found in certain instances as **a physiological process**,—for example, during the involution of such structures as the thymus gland; or, again, in the milk-secreting cells of the mammary gland; and in this category may also be included the fatty degeneration found in the muscle cells of the uterus during its involution after parturition, and various senile changes in the tissues at a period of life when their activities are becoming decreased. Fatty degeneration may also occur in certain tissues at **any** period of life; for example, where there is **diminished functional activity**, as in the case of unused or paralysed muscles; or it may follow hypertrophy of an organ or tissue brought about by increased functional activity, where the excessive strain cannot be kept up and the nutritional power of the overworked tissue fails. **Defective nutrition** is often an important factor in the production of fatty degeneration. This deficiency may be **general**, *e.g.* in old age, starvation, cachectic conditions, grave anæmias, etc.; or it may be **local**, from diminished vascular supply, as in the case of areas in tumours, infarcts, patches of atheromatous thickening in the inner coats of the vessels, etc.

As already indicated, fatty degeneration may be found associated with other degenerative conditions, especially with cloudy swelling; it is also frequently found along with waxy or amyloid disease, and in these cases it is probably caused by the action of the same **toxic agents** which produce these conditions. It is also found in most of the **acute and chronic infective fevers** due to bacterial and other toxins, *e.g.* pneumonia, diphtheria, typhoid and scarlet fevers, puerperal septicæmia, tuberculosis, etc.

Certain **organic poisons** are important causes of fatty degeneration; for example, chloroform, iodoform, alcohol, carbon monoxide, etc. The first named of these substances, **chloroform**, is of special importance in view of the now well-recognised occurrence of what is known as **delayed chloroform poisoning**, occurring after its administration as an anæsthetic. Attention in this country was first drawn to the condition by Dr Leonard Guthrie,[1] although in Germany the dangerous after-effects of chloroform had been described by Casper in 1850. Stiles and

[1] Guthrie, "Some Fatal After-Effects of Chloroform upon Children," *Lancet*, January 27, 1894.

Stuart M'Donald[1] have recently published a paper dealing fully with the subject. Chloroform is a powerful protoplasmic poison, and, when introduced experimentally by subcutaneous injection, it produces profound degenerative changes in highly differentiated cells, and also gives rise to very rapid emaciation, and the presence of acetone in the urine. After inhalation, it may produce the same train of symptoms in certain cases which appear to have some idiosyncrasy, not as yet understood, predisposing the patient to its action in this way. In cases where death occurs from this cause, intense fatty degeneration is usually found in the liver, kidneys, and other glandular organs, as well as in the heart muscle, endothelial cells of the cerebral and pulmonary capillaries, etc.

Many **inorganic poisonous substances** are also important in this connection, especially phosphorus, arsenic, antimony, some of the mineral acids, etc. The action of **phosphorus** has been specially studied, both when given in large single and in smaller repeated doses, the production of very profoundly marked fatty degeneration being possible.

A very extreme degree of fatty degeneration may be found in **pernicious anæmia**, and is probably produced by the action of some toxin of unknown nature, this being also in all likelihood the explanation of the presence of fatty degeneration in certain other diseases in which metabolism is greatly deranged, for example in **diabetes mellitus** and **diabetic coma**, in some cases of which not only the various organs may show extreme fatty change, but a large quantity of free fat may also be found in the blood, a condition known as **lipæmia**. In these diabetic cases, the excess of fat in the blood, in addition to being derived from the pre-formed fat coming directly from the chyle, and perhaps from the storage areas, may possibly also be formed from glycogen which is carried to the cells, but, owing to their impaired state, not sufficiently used up by them.

Fatty degeneration may also occur **in dead tissues**, even outside the body. If **autolysis** of organs after death be carried out experimentally under aseptic conditions, there appears to be no actual increase in the amount of fat present, *i.e.* there is only a freeing of the combined fat, which thus becomes visible.

[1] Stiles and Stuart M'Donald, "Delayed Chloroform Poisoning," *Scottish Medical and Surgical Journal*, August 1904.

Under the action of certain organisms or ferments, however, there may be actual elaboration of fat from the other protoplasmic constituents, and it is in this category that the "ripening" of cheese and the formation of adipocere, already alluded to, would most probably come.

Physical Effects of Fatty Degeneration upon the various Organs and Tissues.—Fatty degeneration, just as in the case

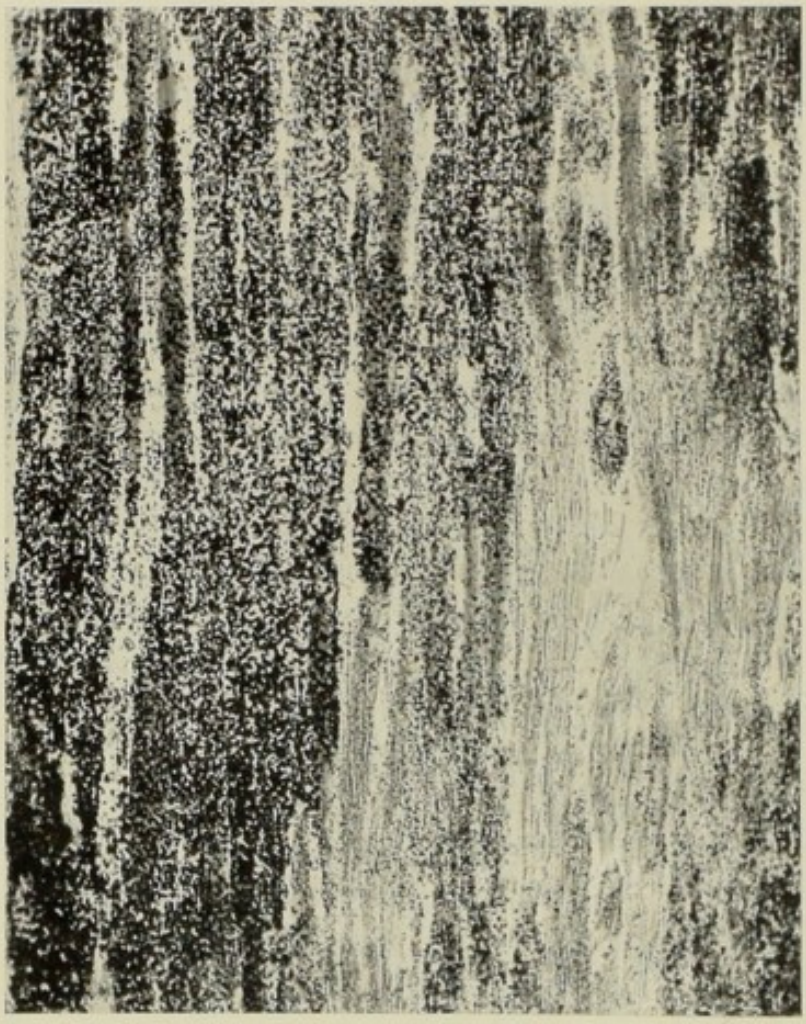


Fig. 6.—Fatty Degeneration of Heart Muscle. Stained with osmic acid. × 200.

of cloudy swelling, specially affects **highly endowed cells,** more particularly those of the glandular organs concerned in the destruction and elimination of the special toxin involved, for example the liver and kidney; and in the case of the latter, it is the highly specialised secreting cells of the convoluted tubules and the thick part of Henle's loop that are principally

DESCRIPTION OF PLATE I

PLATE I

FIG. 1.—*Fatty Infiltration of Liver.* Frozen section stained with Scharlach R. and Hæmatin. The fat is seen in the form of large globules contained in, and distending, the liver-cells towards the periphery of the lobules. × 40

FIG. 2.—*Fatty Degeneration of Kidney.* Frozen section stained with Nile-blue (Lorrain Smith's method). Numerous small, discrete, fatty globules and particles are shown in the cells of the secreting tubules, more especially towards their outer parts, *i.e.* next the basement-membrane. × 300

FIG. 3.—*Fatty Degeneration of Liver* from a case of delayed chloroform poisoning. Frozen section stained with Sudan III. and Hæmatin. The fatty material is stained an orange-red colour, and is arranged in smaller particles towards the centre of the lobule (lower part of section), where the cells show considerable atrophy. The fat towards the periphery is in larger globules which distend the cells. The capillaries between the columns of liver-cells show chronic venous congestion. At the upper margin of the figure is seen a portion of a portal tract, with sections of a bile-duct, hepatic artery, and part of a portal vein. × 200

FIG. 4.—*Atheroma of Aorta.* Frozen section stained with Sudan III. and Hæmatin. Towards the lumen of the vessel (upper margin of section) is seen the laminated thickening of the inner coat. As this is traced outwards, the fatty material increases in amount till, towards the middle coat, it is contained in large necrotic spaces, which also contain calcareous particles stained dark blue with Hæmatin. The internal elastic lamina has undergone degeneration and fragmentation. The middle coat shows slight degenerative changes towards its inner part. Outer coat is not specially affected. × 40

Fig.1. × 40

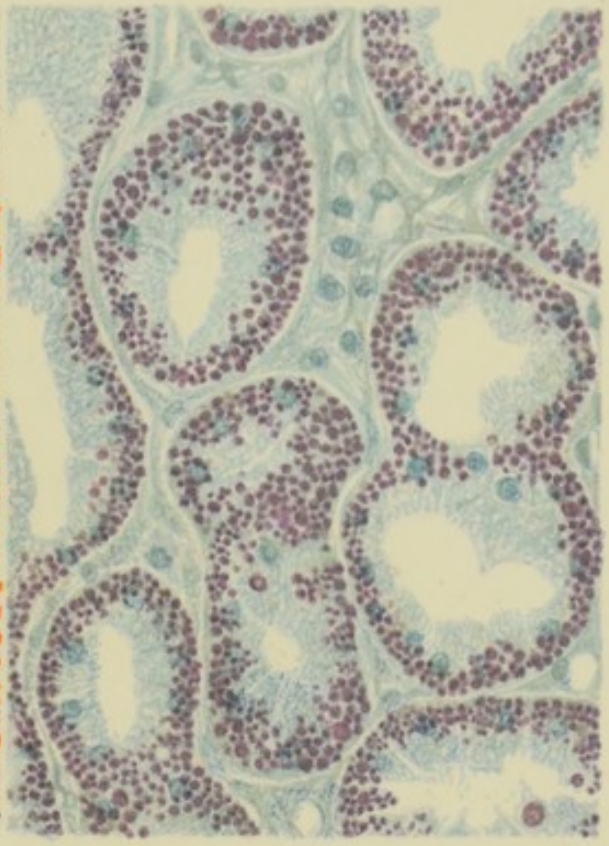


Fig.2. × 300

Fig.3. × 200

Fig.4. × 40

involved. Other examples of highly endowed cells which are very liable to be attacked are nerve cells; endothelial cells lining blood-vessels, pulmonary alveoli, etc.; muscle cells, more especially those of the myocardium.

Naked-eye appearances. — The organ is usually slightly swollen. In colour it may vary from whitish or greyish to a bright, almost canary yellow; the organ is softer than normal in its consistence, and it may be distinctly greasy in appearance and to the touch. The change may be diffuse, or it may in some cases be more patchy in its distribution in any particular organ, for example in the cortex of the kidney. A good example of such patchy distribution is to be seen in the so-called "thrush-breast" appearance often got in the myocardium immediately subjacent to the endocardium, and spreading outwards into the heart muscle, especially in cases of pernicious anæmia. In the liver the change may be more or less uniform throughout the lobule, but in some cases it is found to be more advanced towards the central vein, *i.e.* the change may begin in the centres of the lobules and spread outwards towards the portal tracts, whilst in fatty infiltration the process tends to begin at the periphery and extend inwards. These two conditions are frequently found combined in the same liver.

Microscopical appearances and Distribution.—When the change follows or is associated with cloudy swelling, the individual cells may be increased in size. If the condition occurs alone, however, they are often shrunken and smaller than normal, *e.g.* in the liver or heart. The cytoplasm becomes filled with clear, colourless, highly refractile, rounded globules or granules, at first usually small and scattered, and, except in very acute cases, with only a slight tendency to run together, the nucleus remaining more or less in its normal position, and showing distinct degenerative changes such as karyolysis or karyorrhexis. The fatty particles may be scattered irregularly throughout the cytoplasm, but in some cases they tend to be aggregated in special positions, *e.g.* in the deeper parts of the epithelial glandular cells lining the secreting tubules of the kidney. In degenerating muscle fibres, they are usually arranged in longitudinal rows. The patchy distribution or otherwise of the change in the different organs will also be evident on microscopical examination.

Chemical and Staining Reactions.—As already indicated, fatty substances within the body may be found in the form of neutral fats, fatty acids, soaps, or compounds of any of these with albumins or other substances ("fat-albumin," "soap-albumin," etc.). These bodies differ greatly from one another with regard to their **solubility** in various reagents. Thus, sodium and potassium soaps are freely soluble in water, and are therefore diffusible—calcium soap, however, being insoluble, and possibly playing an important part in the process of calcification. Neutral fats are freely soluble in chloroform, ether, benzole, xylol, etc.; and therefore, in paraffin sections, where any of these substances have been employed during the embedding and staining processes, the positions previously occupied by the fat-globules will appear as clear, colourless, vacuole-like spaces, from which the fat has been dissolved out. Neutral fats are soluble in petroleum ether, but soaps are not, and this forms a valuable differential test for distinguishing between them. Soaps are rendered less soluble by their combination with albumins (Klotz), such compounds being practically insoluble in water and in alcohol. Neutral fats and sodium and potassium soaps are soluble in hot alcohol.

The most generally used stains for the demonstration of fat are osmic acid, Sudan III, and Scharlach R. The first of these (osmic acid) is best used according to Marchi's method, but it must be borne in mind that it only reacts with oleic acid and olein, which are stained an intense black, whilst stearic and palmitic acids and their corresponding fats are not affected. Sudan III stains the neutral fats and fatty acids an intense reddish-orange colour, whilst soaps take on a somewhat lighter pinkish-yellow tint. Scharlach R. closely resembles Sudan III in its reactions. None of these stains is absolutely differential, certain non-fatty granules being also frequently stained. The most reliable results are those obtained with Sudan III.

Lorrain Smith[1] has recently described a method by means

[1] Lorrain Smith, "The Staining of Fat with Basic Aniline Dyes," *Journal of Pathology and Bacteriology*, Edinburgh and London, vol. xi., Jan. 1907, p. 415; and "On the Simultaneous Staining of Neutral Fat and Fatty Acid by Oxazine Dyes," *ibid.*, vol. xii., Oct. 1907, p. 1. (See also "A Reaction of Certain Colouring Matters of the Oxazine Series," by Jocelyn Field Thorpe, *Transactions of the Chemical Society*, 1907, vol. xci. p. 324.)

of which fats may be differentially stained by almost any of the ordinary aniline dyes, his new Nile-blue method giving very beautiful results.

Course and Result of Fatty Degeneration.—The length of time required for the production of fatty degeneration varies indefinitely in different cases. It may be produced in a few hours, for example, by intense septic poisoning. In other cases it may take a much longer period. As already indicated, it may be combined with or may follow cloudy swelling, especially if the toxin be more intense or prolonged in its action.

If the cause be removed in time and the damage to the cells be not too severe, recovery, complete or partial, may occur; or, again, the process may go on to necrosis or death of the cell. If the individual survives, this may, in turn, be followed by absorption, total or partial, of the dead cells, or by the deposition of acicular crystals of the fatty acids, cholesterin, etc., or the damaged area may undergo calcification.

FATTY INFILTRATION is an increase of fat in cells which normally contain some fat or oil globules; for example, the cells of the liver, suprarenal cortex, salivary glands, pancreas, and kidney (the last mentioned especially in the cat and dog). The term **adiposity** or **obesity** is applied to the condition where there is an undue accumulation of fat in the ordinary storage areas, such as the subcutaneous, omental, extraperitoneal, and other connective tissues. It may be noted here that the condition of the heart usually, but somewhat loosely, called "fatty infiltration," should rather be termed "adiposity" of that organ, as the fat is deposited, not in the muscle cells, but in the subepicardial and intermuscular connective tissue, in the former of which positions the presence of a small amount of fat may be regarded as a practically normal occurrence.

As we have already seen, the condition of fatty infiltration is often very closely allied to fatty degeneration, many authorities holding that all cases of the latter should really be regarded as forms of fatty infiltration occurring in previously damaged cells, *i.e.* a "degenerative fatty infiltration," whilst ordinary fatty infiltration is supposed to occur in cells not previously

damaged. Pure fatty infiltration without any accompanying degenerative changes in the cell is probably of rare occurrence, either when the excess is due to an over-abundant supply or to a defective using up of fat, the deposition of fat from outside being favoured by lowering the vitality of the cell, in which case there also naturally tends to be a defective using up of fat by the cell, with less or perhaps no building up of "soap-albumin" (or "protein-fat"), the fat thus remaining in stainable form. A physiological example of the process is found in the tissues of hibernating animals.

Causes of Fatty Infiltration.—In many cases the condition appears to be closely allied to fatty degeneration, and may occur along with it from similar causes, for example in **phthisis**, or after **typhoid fever.** The other possible factors in its causation have already been sufficiently discussed.

Microscopical appearances.—A detailed account of the effects of fatty infiltration in the various organs and tissues need not be given here. In the liver the change is specially seen in the cells around the portal tracts, towards the periphery of the lobule, and it then tends to spread progressively inwards as the condition becomes more advanced. The globules of fat show a tendency to coalesce and push the nucleus towards one side of the cell, giving it the appearance of an ordinary fat cell. The condition is very frequently seen in cases of chronic venous congestion, a combination which, when advanced, produces the characteristic appearance sometimes described as "nutmeg liver."

GENERAL ADIPOSITY or OBESITY, *i.e.* abnormal increase of fat in the usual storage areas, may be brought about by various causes. **Excess of food**, especially if combined with **lack of exercise**, and the consequent defective using up of the ingested food, is a common cause of the condition, as are also **alcoholic drinks**, especially beer. It may follow **castration**, a method employed in the fattening of stock; and an analogous change may occur **after pregnancy**, **during lactation**, or at the **menopause**, and also in certain cases of **insanity.** In some instances of **disturbed metabolism** from unknown causes a similar change may be seen, and sometimes appears to be due to **disease of the thyroid gland.** A **local increase** of fat

may occur in or around atrophying organs, for example around and in the hilus of a chronic granular contracted kidney.

"**Fatty infiltration of the heart**" should, as already indicated, rather be regarded as an increased **adiposity** of the organ, where there is an abnormal increase of subepicardial fat, first in its normal positions, later passing in along the lines

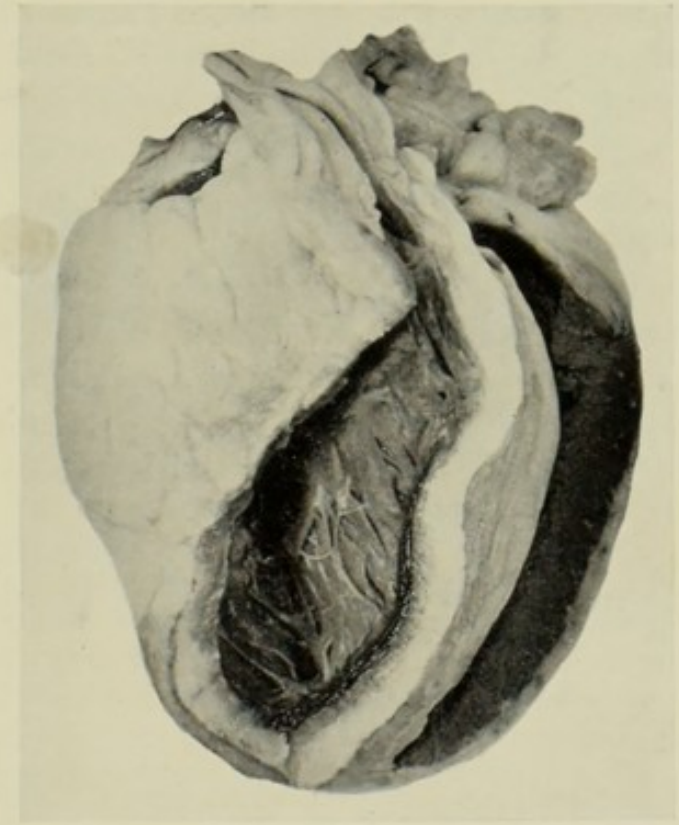


FIG. 7.—Fatty Infiltration of Myocardium of Right Ventricle. The muscular fibres have been almost completely replaced by fat.

of the vessels, and finally passing in between the muscular bundles, and even between the individual fibres, thus interfering with their nutrition, and tending to produce atrophy.

THE MUCINOID (MUCOID AND COLLOID) DEGENERATIONS

Mucoid and **Colloid Degenerations** are by many authorities considered separately. There is, however, no absolute chemical difference or distinct line of demarcation between them, and it is convenient to class them together under the common term

Mucinoid Degeneration, as suggested by Greenfield and Lyon,[1] the essential cellular changes in both being similar, and the chief difference lying in the fact that in the so-called colloid degeneration the colloid substance produced tends to be firmer or more inspissated in its physical characters, like thickened glue, whilst the products of mucoid degeneration are more like thin jelly, or in some cases are even almost fluid in their consistence. In the case of the thyroid gland, in some phases of its activity, for example in catarrhal conditions where there is hyperactivity of its secretory functions, the normal colloid substance may be rapidly transformed into mucoid material. A somewhat analogous change is also seen in the thyroid gland in cases of exophthalmic goître.

Both forms of degeneration are characterised by the presence of gluco-proteid substances, for example the mucins and mucoids, etc., colloid material being said to differ from these only in a few minor points, such as the possession of a slightly higher sulphur-content, precipitation with tannin or tannic acid, etc.

The **Mucins** are complex protein substances containing a carbohydrate radicle, *i.e.* they are gluco-proteins. They are the cause of the sliminess of the mucous secretions of the respiratory and alimentary tracts, and substances closely allied to them are also found in the urine (a mucinoid) and bile (a mucinoid nucleo-albumin). The mucins are also closely allied to the mucinoids or mucoids normally found in the connective tissues.

Mucin, if dried and then added to water, swells and forms a slimy or gum-like mucilage, and is soluble only with difficulty. On the addition of acetic acid it is precipitated in the form of a tough adhesive curd, insoluble in excess, but easily soluble in excess of hydrochloric acid. It is not coagulated on boiling, and is readily soluble in alkalies. With alcohol it is not precipitated unless in the presence of a sufficient quantity of neutral salts, in the absence of which only a pale opalescence is produced. It is precipitated by copper sulphate, mercuric and ferric chlorides, and lead acetate, but not by tannin or potassium ferrocyanide.

The **Pseudomucins**, also gluco-protein substances closely allied to the mucins, are sometimes found in the contents of certain cysts, especially in those of the ovary. They are freely soluble in water, and are *not* precipitated by acetic acid or by the mineral acids. Alcohol produces with them a tough curd-like precipitate, but otherwise they react very much like true mucins. The **Paramucins**, also

[1] Greenfield and Lyon, *Chapters in Pathology*, Edinburgh, 1905, p. 15.

members of the gluco-protein group, and sometimes found in the form of a clear "trembling jelly" in ovarian and other cysts, are insoluble in water, and, except for the fact that they are precipitated by tannin, react like the mucins.

The **Mucoids** or **Mucinoids** of connective tissue are precipitated by acids, and are soluble in dilute alkalies. They do not give any precipitate with tannin. They are gluco-proteins, and do not essentially differ from the mucins, except by the possession of a higher sulphur-content. Members of this group are found in tendon, bone, cartilage, etc., and in certain of the body fluids.

Colloid material resembles stiffened glue in appearance. It is semi-solid, translucent and homogeneous in appearance, and is usually yellowish or brownish-yellow in colour. It does not swell in water; it is precipitated by tannic acid, but not by acetic acid; and it stains a characteristic orange colour with picro-carmine or with van Gieson's picro-fuchsin.

These degenerations are best studied in two groups, as follows:—

I. { (*a*) **Mucoid Degeneration of Cells.**
   { (*b*) **Colloid Degeneration of Cells.**

II. **Mucoid or Myxomatous Degeneration of Connective Tissues.**

I. (*a*) MUCOID DEGENERATION OF CELLS

Mucin is normally secreted by the "chalice" or "goblet" cells of mucous membranes and by the cells of mucous glands. In these cells it first becomes visible as the so-called mucigen "secretion-granules." Towards the free end of the cell these gradually swell and coalesce to form a clear, transparent, colloidal or jelly-like substance, which distends the cytoplasm next the lumen. It is then secreted, there being in this physiological process no disintegration of the cyto-reticulum or injury to the vitality of the cell.

Under certain conditions, a **pathological exaggeration** of this process may be found in these mucus-secreting cells, for example in catarrhal inflammation of mucous membranes, in which condition there occurs a series of changes practically similar to cloudy swelling. Analogous changes may occur in other glandular epithelial cells, for example in those of the kidney, thyroid, etc., or in epithelial tumour cells, *e.g.* in cancers growing from the stomach, intestine, etc., or in compound cystic ovarian adenomata. The cells tend to swell

into a clear, soft, jelly-like mass, containing mucin, pseudo-mucin, or paramucin. If secreted into a closed cavity, these will accumulate; if on a free surface, there will be increased flow of secretion. In this pathological process, unlike what occurs in the case of the physiological secretion of the mucin, the protoplasm of the cells tends to disintegrate, the intercellular cement

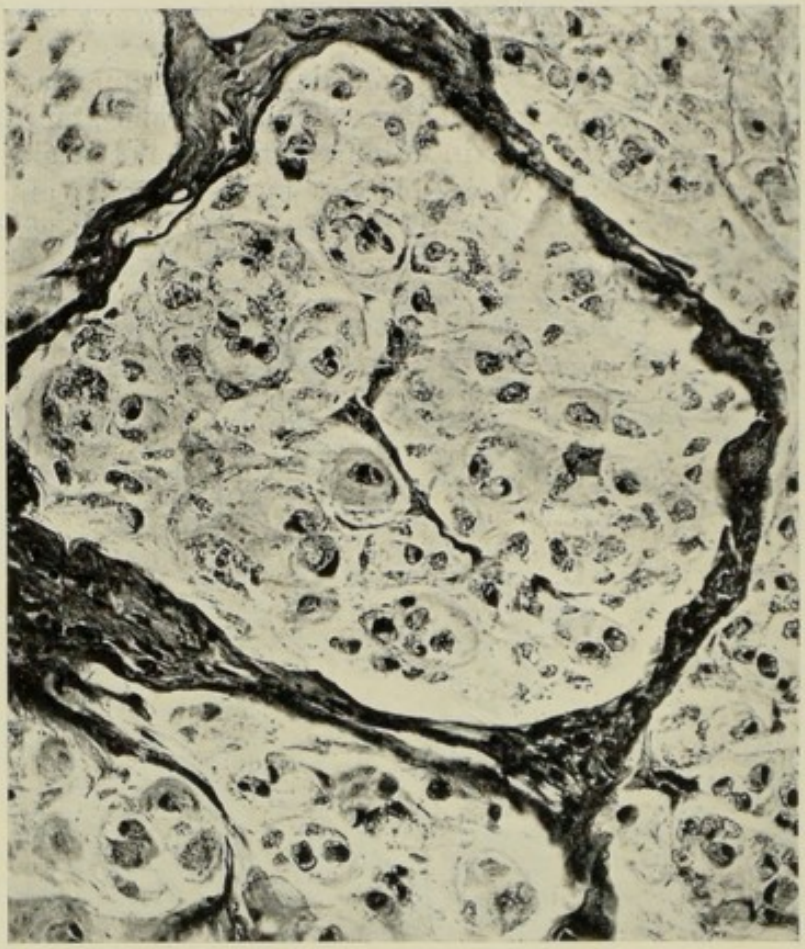


Fig. 8.—Mucoid Degeneration of Cells in "Colloid" Cancer. × 200.

substance may undergo solution, and the cells themselves may pass into and blend with the secretion—a process also well seen in the colloid forms of the degeneration.

I. (*b*) COLLOID DEGENERATION OF CELLS

Colloid transformation of cells occurs as a normal process in the closed glandular spaces of the thyroid, and to a less extent in those of the pituitary and prostate glands. In these the colloid material is produced by the direct transformation of the

protoplasm of the epithelial cells themselves. The cells become swollen, are cast off, and become fused together to form the colloid mass in the lumen. In certain abnormally active conditions of these glands, for example in acute fevers and septicæmias, the colloid may become absorbed, and may be replaced by more fluid mucoid material—a sort of **catarrhal** condition. Similarly, in exophthalmic goître a more active condition of the thyroid gland supervenes, and is characterised by the disappearance of the colloid material, which is in all probability merely a more or less inert "by-product," in which the active substances produced by the gland are dissolved—just as codeia or some such powerful drug may be conveniently dissolved and kept in jelly—to undergo absorption when required.

The thick, colloid character of the material in these cases is probably largely due to the fact that the secretion is poured into a **closed** space, the more fluid part of the secretion being absorbed into the blood or lymph. Owing to the fact that the colloid is formed directly from the cells, a somewhat concentric structure is sometimes observable, corresponding to various layers of cells which have undergone the change. The blocking of ducts or tubules in any gland which secretes mucin or mucinoid substances will give rise to similar accumulation, for example in the case of colloid casts in kidney tubules which have become obstructed from any cause. Such colloid accumulations may later undergo calcification.

In certain positions, for example in the kidney, prostate, lungs, and, perhaps most frequently of all, in the central nervous system, small spherical or ovoid bodies are sometimes seen, which, upon microscopical examination, are found to have an irregularly concentric laminated appearance, somewhat similar to the structure of a grain of starch; hence the name **corpora amylacea** usually applied to them. These bodies have, however, no connection with the process of waxy or amyloid disease proper, though they may give a brownish colour-reaction with iodine. They may also be found occurring in certain tumours, and in old blood-clots and inflammatory exudates. In the case of certain tissues (*e.g.* those of the central nervous system) which have been preserved for some time in spirit, an appearance somewhat resembling these bodies may be **artificially** produced.

In all probability corpora amylacea are formed by the partial fusion of concentric layers of cells undergoing some sort of degenerative process closely allied to or identical with colloid degeneration; and in some, though not in all, instances they appear to be formed around a small vessel which becomes obliterated. These corpora amylacea, in common with other areas of very degenerated tissue, very readily undergo secondary calcification.

II. MUCOID OR MYXOMATOUS DEGENERATION OF CONNECTIVE TISSUES

As already mentioned, the connective tissues normally contain certain members of the gluco-protein series.

In the fœtus, mucoid connective tissue is the normal precursor of all the connective tissues, and it is also found in the umbilical cord ("Wharton's jelly"). It is formed of stellate or somewhat irregular cells with long branching and interlacing processes, lying in a clear homogeneous or slightly granular semifluid matrix containing mucin or mucinoid substances. The only tissues which in the adult body retain their resemblance to the original mucoid tissue are the vitreous humour of the eye and the pulp of the teeth.

Pathologically, a similar appearance may be found as a retrogressive process occurring in any of the connective tissues. A very characteristic form of such myxomatous degeneration may occur in the bone-marrow of old and debilitated patients, and also earlier in life in certain cases of acute or chronic disease, especially in alcoholic subjects, in which that tissue has become exhausted. The blood-forming elements disappear, and the fat of the adipose tissue is absorbed, the protoplasm of the fat cells being transformed—from the periphery of the cell inwards, as the fat disappears—into a fibrillated, or in some instances a somewhat denser homogeneous gelatinous substance, which becomes fused with that formed from neighbouring cells. The process may also occur in cartilage or in the bones of old people, especially if these tissues are undergoing rapid absorption.

In **myxœdema**—a condition due to atrophy of the thyroid gland—a wide-spread form of myxomatous degeneration super-

venes in the connective tissues. The condition here appears to be due to defective nutrition and interference both with the formative and with the absorptive processes, which in the normal state apparently to a large extent depend upon the influence of substances secreted by the thyroid, and perhaps also, but to a less extent, by certain of the other secreting glands. Myxomatous degeneration is not infrequently

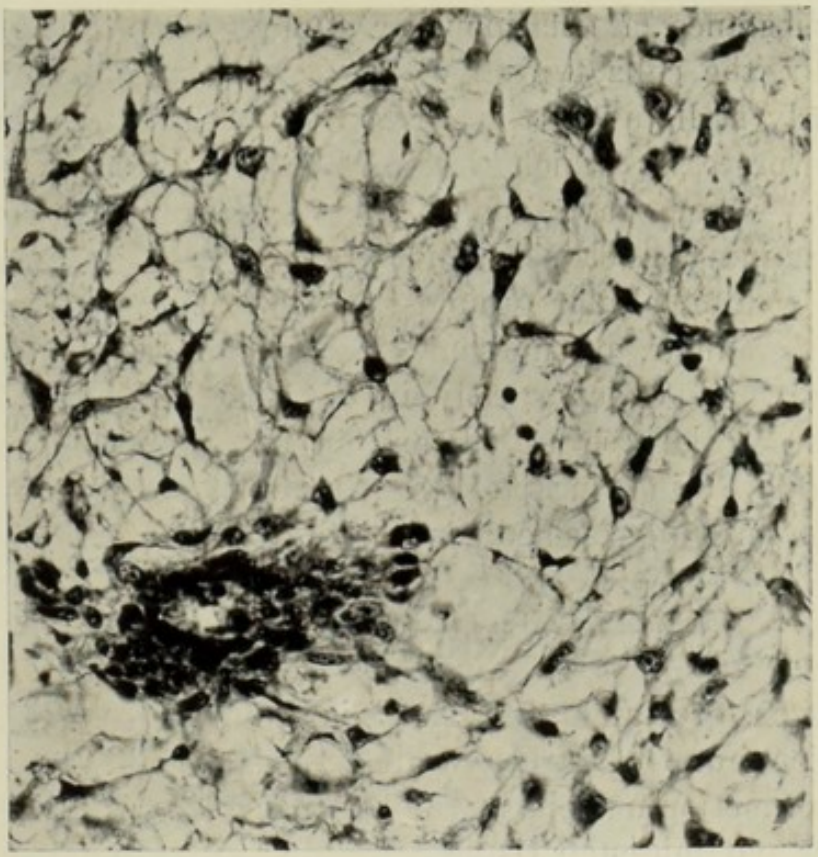


FIG. 9.—Myxomatous Tumour of Breast, showing characters of cells. × 250.

seen **in various inflammatory conditions**, for example in granulation tissue, and in the so-called "mucous polypi" growing from the mucous membranes of the nose or naso-pharynx, intestine, etc. These latter are often described as myxomatous tumours, but they are in all probability frequently not true neoplasms, but rather to be regarded as chronic inflammatory overgrowths, which become polypoidal owing to the constant movements of the contents and walls of the passages into which they project, whereby they are dragged upon and tend to become elongated.

Myxomatous degeneration **occurring secondarily in tumours** is comparatively common, for example in fibromas, chondromas, lipomas, cancers, sarcomas, etc. The so-called "hydatid mole" or myxoma of the chorion may, however, for the present at all events, be regarded as a true neoplasm or new growth.

The Changes produced in the Connective Tissues by myxomatous degeneration.—The tissues become transformed into a transparent or semi-transparent, more or less homogeneous, viscid substance of gelatinous or gummy consistency. **Microscopically**, the cells typical of the condition are found to be irregularly stellate or triangular in outline, and possess long, delicate processes which branch and anastomose with one another. They have somewhat large, rounded or oval, faintly-staining nuclei, which are poor in chromatin. The matrix or intercellular ground-substance may be homogeneous, slightly granular, or in some instances finely fibrillated in structure, and varies greatly in its amount, the cells being sometimes widely separated, and in other cases more closely arranged. All intermediate stages between such a myxomatous condition and fully formed connective tissue may be found.

GLYCOGENOUS INFILTRATION

Glycogen or "**animal starch**," is a member of the polysaccharide group of carbohydrates. It is found in most of the actively functioning cells of the body, and especially in those of the liver and muscular tissue, but also, though to a less extent, in the cells of the kidney, cartilage, and epithelium generally, and in leucocytes. Pathologically, this substance may be increased in any of these situations, and it may also be found in certain tumours. In some diseases, *e.g.* diabetes mellitus, the increase is very considerable. In certain inflammatory conditions, acute fevers (*e.g.* pneumonia), and in some chronic infective diseases and cachexias, especially tuberculosis, there may be considerable increase of glycogen granules in the cytoplasm of the circulating leucocytes and in the blood-plasma.

Chemical Tests and Reactions.—Glycogen is freely soluble in water, and forms a pale opalescent solution. In the tissues after death it is very rapidly converted into glucose, and therefore, for microscopical examination, rapid fixation in alcohol, in

which reagent it is insoluble, is necessary. With iodine the reddish-brown iodide of glycogen is formed. This colour disappears on heating, but reappears on cooling. Similarly, the colour is discharged on the addition of alkalies, and reappears on making slightly acid with hydrochloric acid. Glycogen, if free from glucose, does not reduce cupric oxide. It is precipitated by basic lead acetate.

Microscopically, glycogen appears in the cell in the form of small granules or droplets. In ordinary sections which have been treated with water, these are dissolved out, leaving vacuole-like spaces. In sections fixed with alcohol, the characteristic golden-brown reaction is obtained with iodine.

WAXY DEGENERATION

Waxy, amyloid, or **lardaceous degeneration** is a retrogressive process characterised by a peculiar change in certain of the formed connective tissue elements — especially the delicate fibrillæ and laminæ—whereby they swell and become more translucent, homogeneous, highly refractile and resistant; and whereby the affected connective tissue elements also assume certain very distinctive staining reactions. The change usually affects first the delicate connective tissue lying between and supporting the muscular fibres of the smaller arterioles (*i.e.* the "ultimate arterial distribution") of certain organs; spreading later to the "perithelial" or fine supporting connective tissue of the capillaries, and then to the connective tissue in the coats of the veins. At the same time it also spreads backwards along the walls of the arteries. An **exception** to the more usual form of distribution of the change here described is found in the case of what is known as **diffuse waxy spleen**, where the condition begins in the perithelial connective tissue coats of the venous sinuses and connective tissue reticulum of the pulp; though it is also usually found at the same time in the connective tissue of the arterioles, both in the Malpighian bodies and in the pulp. Another exceptional form of distribution is seen in certain very rare cases where the connective tissue between the collecting tubules towards the apices of the Malpighian pyramids in the kidney is especially attacked.

Etiology.—Waxy degeneration is most commonly found in

chronic cases of **tuberculosis**, especially of bones, joints, and lungs; and in **syphilis**, both in its congenital and in its acquired forms. "**Chronic suppuration**" is also very generally stated to be one of the causes. Many of those cases described as "chronic suppuration" are really tuberculous in origin; and we think it would be more correct to state that certain toxic products, especially those of bacterial origin acting for a prolonged period, may cause waxy degeneration. In cases of tuberculosis, it is, no doubt, the products of the organismal growth which give rise to this peculiar form of degeneration, and probably the same is true of syphilis. It has also been shown that other bacterial or toxic diseases, *e.g.* rheumatism, may give rise to this condition. Beattie [1] records four cases of **amyloid degeneration** following repeated attacks of acute rheumatism, where all other causes were definitely excluded; and this only confirms the observations of Gibson [2] in his thesis upon *Hyaline and Waxy Degeneration*, in which he gives a synopsis of all the cases of waxy disease occurring in the records of post-mortem examinations conducted in the Pathological Department of the Edinburgh Royal Infirmary during the periods 1852–62 and 1870–86.

Out of a total of 430 cases of **waxy disease**, the condition was found associated with:—

Chronic Phthisis	in	193
Chronic Suppurative Conditions of Bones and Joints	,,	46
Chronic Abscesses and Ulcerations	,,	66
Syphilis	,,	75
Enlargement of Heart, Hypertrophy with Valvular Disease following Rheumatism (no history of Suppuration or Syphilis)	,,	20
Malignant Disease (no note of Suppuration)	,,	5
No data given in record	,,	25
		430

From this table it will be seen that a certain proportion of cases occurs where there is no definite evidence of any of the above causes being at work. Further, waxy disease has been

[1] Beattie, "Rheumatic Fever and Amyloid Degeneration," *Brit. Med. Jour.*, Nov. 24, 1896, p. 1444.

[2] Gibson, "Hyaline and Waxy Degeneration," Thesis for the Degree of M.D. in the University of Edinburgh (awarded a gold medal) 1887.

described as occurring occasionally in certain cases of leucocythæmia, lymphadenoma, chronic malaria, chronic dysentery, and cancer. It is true that in most of the cases the details are not sufficient to absolutely exclude syphilis or other of the more common causes; but still, in these cases, toxic products, bacterial or cellular, are being produced, and we must, at any rate, regard them as possible factors in the causation of the condition.

Ultimate nature of the change.—**Amyloid** or **waxy material** is **albuminous** in its nature; not fatty or starchy, as was supposed by some of the earlier observers. In 1840, Rokitansky described the condition as **lardaceous** disease, because of the resemblance of the affected organs to bacon. In 1845, Dr Budd, of Bristol, described it as a "**scrofulous,**" *i.e.* tubercular, disease, and applied the term "**waxy**" to the condition because of the naked-eye appearance of the affected tissues. Seven years later, Budd described this waxy change as occurring **between**, and not **in**, the cells. He had the waxy material analysed by Professor Miller, of King's College, London, by whom it was found to be albuminous in its composition, the contained carbon, hydrogen, nitrogen, and oxygen being present in their protein proportions. In 1853, a discussion on the subject took place at a meeting of the Medico-Chirurgical Society of Edinburgh, and the albuminous nature of the change was on that occasion definitely recognised by Hughes Bennett, Gairdner, and Sanders. Nevertheless, in the following year, Virchow and others of the German school came to the conclusion that the waxy material was an animal cellulose of the nature of starch, because of its brown reaction with iodine, and because of the production of a blue colour with iodine and sulphuric acid. It was for this reason that he applied the misleading but now very generally used term "**amyloid**" to the condition. This view was proved erroneous in 1859 by Friedreich and Kekulé, who confirmed the view of Miller that the change was albuminous or protein in nature. Kekulé also investigated the results upon amyloid material of artificial peptic digestion, to the action of which it is very resistant; and, because of this great resistance to peptic digestion, he claims to have been able to isolate the material—which he terms "**lardacein**"—in a condition of purity. He states that it is

an albuminoid substance, allied to keratin and elastin. After very long peptic digestion, the substance is broken up into the ordinary products of protein-hydrolysis.

Mann,[1] in his *Chemistry of the Proteids*, states that amyloid or waxy material is probably a gluco-protein in which the carbohydrate radicle has not yet been demonstrated. It gives all the usual colour reactions of the albumins (except the lead sulphide test), the albumin being probably in very firm combination with chondro- or chondroitin-sulphuric acid, an observation first made by Oddi in 1894, and confirmed by Krawkow in 1897. Analysis of amyloid material from different organs gives considerably varying results, from which it has been inferred that the protein constituent may vary in the different organs. It is said to possess a greater sulphur and oxygen content than does elastin, to which it appears to be related; and it is in some ways chemically analogous to the nucleo-protein group. Amyloid material is very slowly and imperfectly digested by pepsin; and more completely digested by trypsin and by autolytic enzymes. From these and other data it is extremely probable that amyloid is produced by the transformation *in situ* of the tissue proteins.[2] This waxy material is not, as was at one time supposed, a precipitate from the blood. The change occurs specially in organs in which the profounder metabolic changes occur, or in which excretion is carried on. These organs are very liable to damage in various toxic and organismal diseases, in which they are specially concerned in the destruction or elimination of toxins; and it is most probable that waxy disease is due to some deleterious substance or toxin acting upon the connective tissue elements, and so modifying them chemically or physically that they tend to take up certain normal, or more probably abnormal, protein substances from the surrounding blood or lymph (*cf.* the somewhat analogous changes seen in hyaline degeneration in cases of diphtheria or scarlet fever).

The result of direct experiment appears to confirm the view that the change is due to the action of bacterial or other toxins.

[1] Mann's *Chemistry of the Proteids*, London, Macmillan & Co., 1906.

[2] Note.—For a fuller account of the Chemistry of Amyloid, see *Chemical Pathology*, by Wells, 1907, Saunders Co., Philadelphia and London, p. 347 (from which the above account is partly taken).

DESCRIPTION OF PLATE II

PLATE II

FIG. 1.—*Waxy or Amyloid Degeneration of Spleen* (*Sago waxy form*). Frozen sections stained with Iodine, showing portions of two Malpighian bodies and neighbouring pulp. Upper section seen with *transmitted*, lower with *reflected light*. ×50

FIG. 2.—*Waxy or Amyloid Degeneration of Spleen* (*Diffuse form*). Frozen section stained with methyl violet. The perithelial coats of the venous sinuses and the reticulum of the pulp show waxy degeneration. The endothelium lining the sinuses (which show chronic venous congestion) is not affected by the waxy change. ×300

FIG. 3.—*Waxy or Amyloid Degeneration of Liver*. Frozen section stained with methyl violet. Longitudinal section of a vessel (the Portal vein) showing implication of connective supporting tissue of the muscular coat. In the neighbouring liver tissue, the connective tissue of the capillaries is extensively affected. ×70

FIG. 4.—*Waxy or Amyloid Degeneration of Kidney*. Frozen section stained with methyl violet, to show waxy change in capillaries and afferent arteriole glomerulus. The intertubular capillaries also show slight waxy change. ×70

FIG. 5.—*Similar Preparation*. Transverse section of medulla showing waxy change in the straight vessels. In the large collecting tubule is seen a colloid (sometimes erroneously called a "waxy") cast, which gives *no* reaction for waxy material. ×300

FIG. 6.—*Hyaline Degeneration in Vessels of Spleen*. Paraffin section stained with Hæmatin and van Gieson's Picro-Fuchsin, showing hyaline swelling of walls of arterioles of Malpighian bodies. The hyaline material is stained canary yellow. ×300

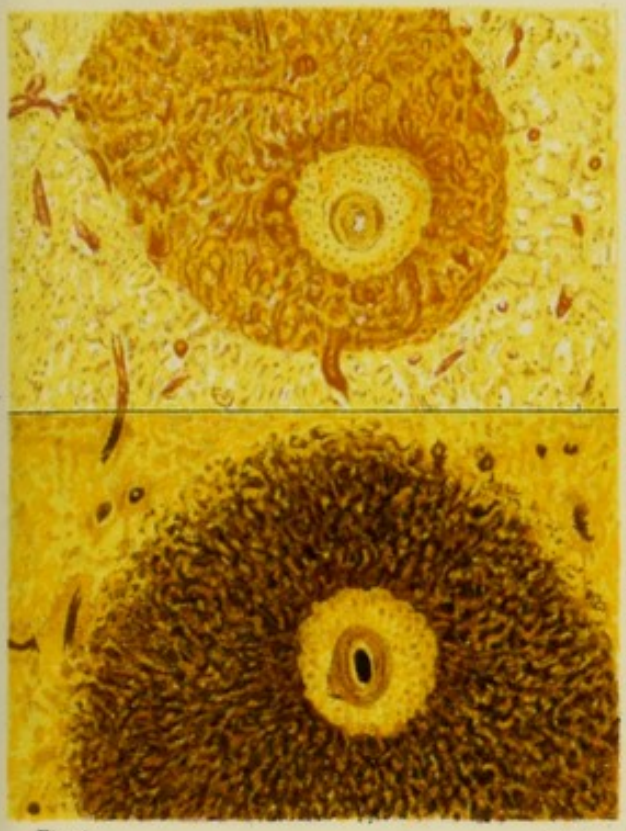


Fig.1. × 50

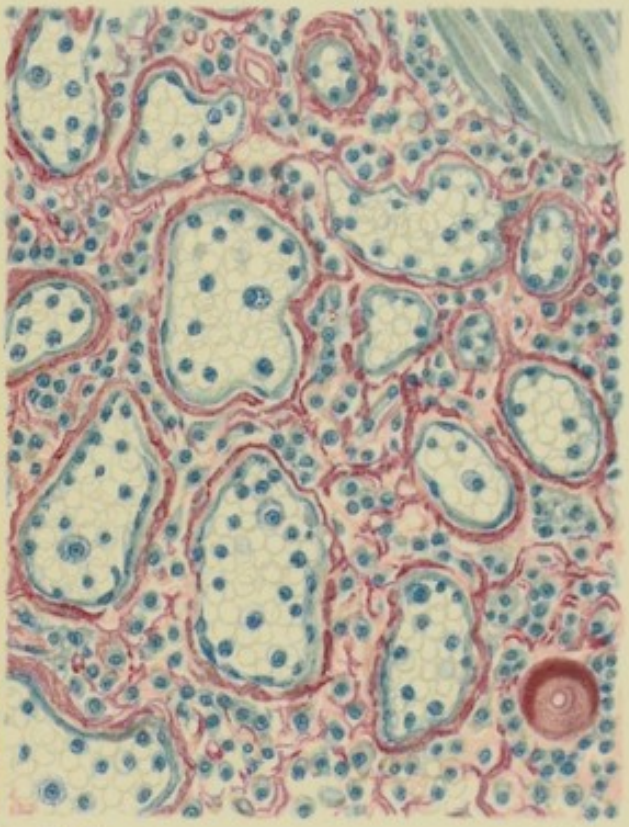


Fig.2. × 300

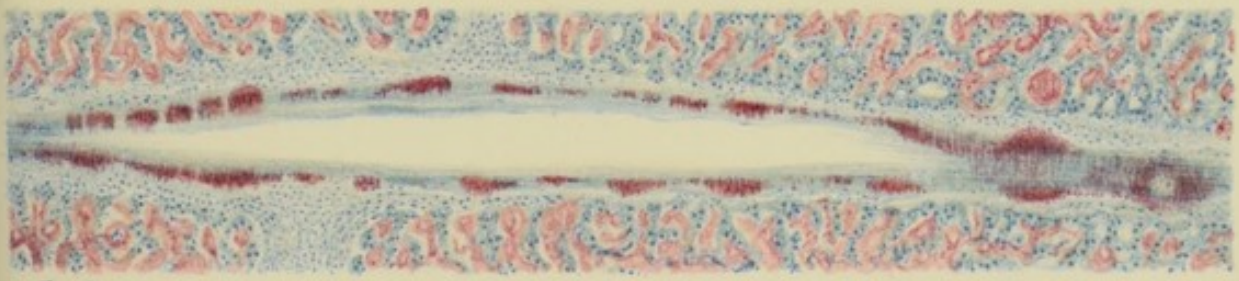


Fig.3. × 70

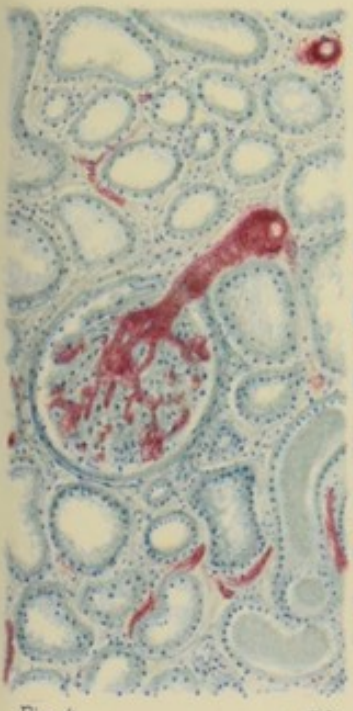


Fig.4. × 70

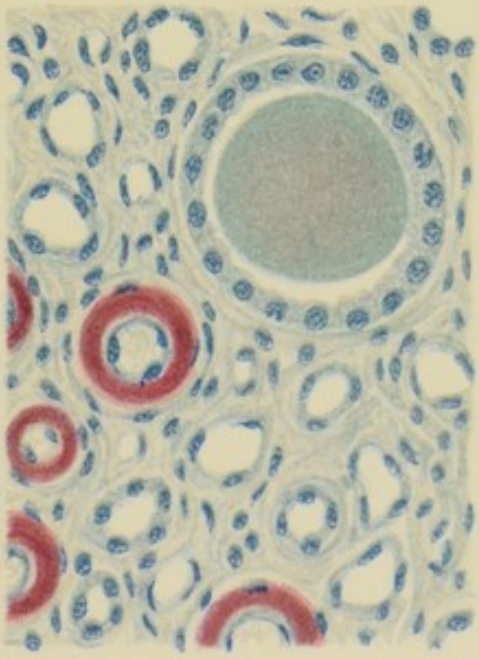


Fig.5. × 300

Fig.6. × 300

For example, Davidsohn[1] produced what appeared to be true waxy disease in animals (chickens and rabbits) after repeated inoculations with *Staphylococci*, especially if these organisms were modified in various ways—for example, if isolated from tuberculous cases. He obtained negative results with *Streptococci*, *B. coli*, etc. The condition also appears to have been produced by repeated injections of the toxins formed by *B. pyocyaneus*. Similar results have been recorded by Krawkow,[2] Maximow, and others, whilst Czerny describes the experimental production of the disease in animals in which he induced chronic suppuration by the repeated injection of turpentine. A point of some interest in connection with Davidsohn's experiments is that he altogether failed to produce the change in animals from which he had previously removed the spleen—an observation suggesting the possibility, at all events, that it is in this organ that the supposed toxin is elaborated.

Staining Reactions, etc.—As already stated, waxy material is a highly resistant substance, practically insoluble in water and in the body fluids, and very slightly affected by acids. It may be partially dissolved by prolonged boiling in water for several days, especially if under increased pressure. It is very slowly digested by pepsin, but is more rapidly broken up into its dissociation products by tryptic digestion. It is readily soluble in strong alkalies such as ammonia. It gives practically all the chemical colour-reactions characteristic of the albumins (except that with lead sulphide).

The most important diagnostic tests for waxy material are those with iodine, iodine and sulphuric acid, and also its metachromatic staining properties with certain of the aniline dyes. (See Plate II. figs. 1–5.)

[1] Davidsohn, *Virchow's Archiv*, 1897, vol. cl. p. 16.
[2] Krawkow, *Archiv f. experiment. Pathol. und Pharmak.*, 1897, xl. p. 195.

These may be conveniently tabulated as follows:—

Reagent or Dye.	Waxy Material.	Normal Tissues.
Iodine:		
(*a*) With reflected light	Dark reddish mahogany brown.	Pale yellow.
(*b*) With transmitted light	Light orange.	Greenish-yellow.
Iodine + sulphuric acid or zinc chloride	Brown colour usually deepened; may become bluish or greenish black; very variable.[1]	Variable.
Methyl violet. . .	Rose-red or pinkish-violet (due to the chondroitin-sulphuric acid).	Bluish-violet.
Picro-carmine or picro-fuchsin	Somewhat variable reaction—faint orange to orange-pink colour.	Connective tissue fibres red.
Osmic acid, Sharlach R., and Sudan III	Not stained.	Typical reaction with fat.

[1] NOTE.—This darkening appears to be due merely to interaction between these reagents when the iodine is dissolved in spirit, or in a solution of potassium iodide in water (Dickinson).

The most valuable and delicate of these stains is methyl violet, which may sometimes give the characteristic rose-red or pinkish-violet reaction when iodine may fail to demonstrate the presence of any waxy material. Gentian violet and methyl green give a similar but less characteristic reddish metachromatic colouration with waxy material.

Organs most frequently affected.—The organs most usually affected by waxy disease are, in order of relative frequency, the kidney, spleen, and liver; the mucous membrane of the small intestine, and the lymphatic glands; and, less frequently, the change is found in the stomach, large intestine, suprarenals, pancreas, bone-marrow, thyroid, etc. It is found only with extreme rarity in the lungs, and practically never in the central nervous system.

It is thus specially found in the organs concerned with excretion, hæmolysis, and the destruction of toxic substances; and it is usually got in a group of several of these organs at the same time, for example in the kidney, spleen, liver, and perhaps intestine. It may in certain cases be found in one organ

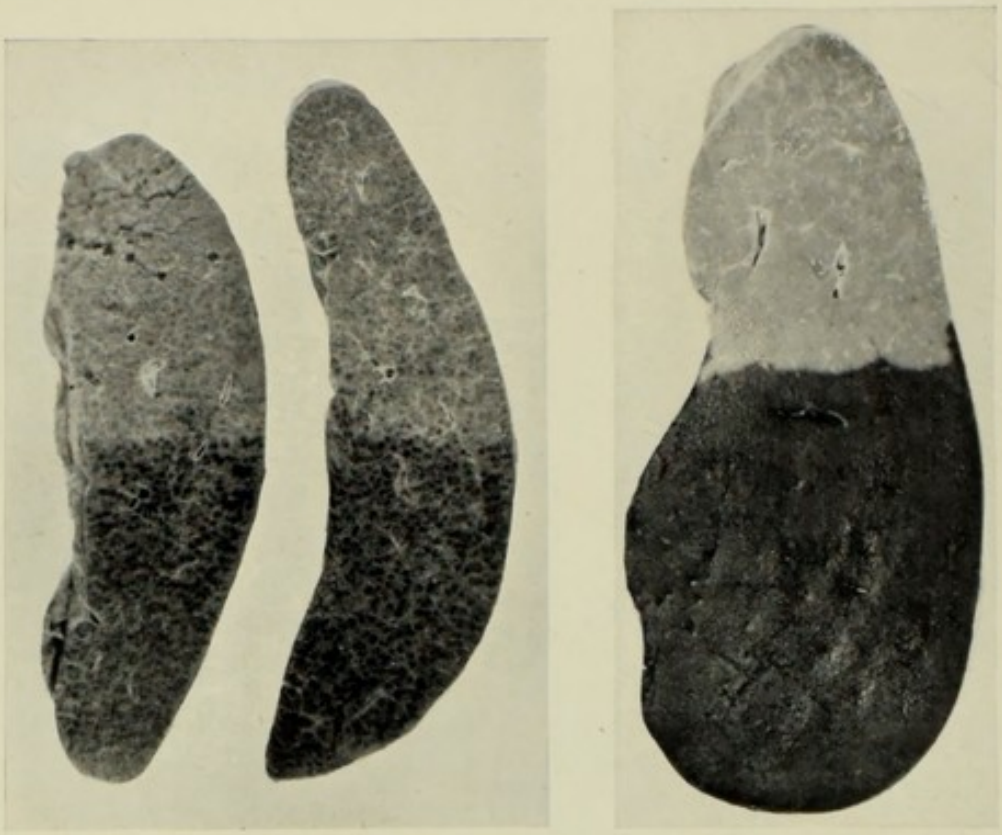
alone, for example in the kidney, but this is an occurrence of extreme rarity.

Changes produced in the organs by waxy disease.—The naked-eye appearances produced by waxy disease vary considerably with the duration of the disease, and according to the organ in which it occurs. If the condition is at all advanced, the affected organs are usually enlarged—sometimes to a considerable degree, for example in the case of the liver. The tissue becomes firmer, denser, heavier, and more elastic,

FIG. 10.—Waxy or Amyloid Degeneration of Liver. The lower parts of each section have been treated with iodine. Three specimens showing different types of distribution of the change.

somewhat resembling india-rubber in consistence. On cutting across a waxy liver or spleen, the edges and corners of the divided organ remain sharp and distinct, and do not collapse or become rounded. The cut surface is usually smooth, dry, and glossy in appearance, the waxy material, which may be present in greatly varying amount, being homogeneous, dark and translucent or wax-like, and usually showing the typical mahogany brown reaction with iodine. With this reagent the naked-eye distribution of the change is rendered more evident (figs. 10, 11);

but in certain cases, for some as yet unknown reason, iodine may altogether fail to show the presence of waxy material, even though present in great amount and easily demonstrable by methyl violet. **In the case of the liver**, the waxy change is often somewhat patchy in its distribution, or it may be widespread and diffuse (fig. 10). Before the change has become very advanced, the lobules may appear to be marked out into three concentric zones, the intermediate of these being that most



A. B.

FIG. 11.—Waxy or Amyloid Degeneration of Spleen. A., Sago waxy type. B., Diffuse waxy type. (Lower portions of sections treated with iodine.)

affected by the waxy disease. **In the spleen**, the change in most cases specially affects the Malpighian bodies, the condition being known as **sago waxy spleen** because of the resemblance of the enlarged translucent Malpighian bodies to grains of boiled sago (fig. 11, A., and Plate II. fig. 1). The organ is usually, though not always, enlarged; whilst in the other variety of waxy change—**diffuse waxy spleen**—in which the pulp is specially affected, the organ may attain a very considerable size (fig. 11, B., and Plate II. fig. 2). **In the kidney**, the naked-eye changes are very often complicated, and perhaps masked, by the presence of other associated

pathological conditions which either may have preceded, or may accompany or follow, the waxy disease itself. The commonest of these associated conditions are fatty degeneration and various inflammatory changes, especially interstitial nephritis. Thus, the appearances of a waxy kidney may vary indefinitely. It may be enlarged, or, if associated with chronic granular contraction of the organ, it may be much diminished in size. Its consistency also varies greatly. For example, it may be firm and hard, but in some cases it may be unduly soft. In more or less uncomplicated waxy disease of the kidney—a condition rarely seen, however—there may be very slight naked-eye alteration in the organ, or there may be a characteristic pale, whitish, translucent appearance in the swollen cortex and in the pyramids. Perhaps the most characteristic appearance is that seen when the disease is associated with fatty degeneration and catarrhal changes. The organ is increased in size; dull yellowish or yellowish-white in colour, with mottled opaque white or yellowish-white fatty and catarrhal patches, intermingled with the more translucent waxy areas. With iodine, the lines of the interlobular arteries and glomeruli of the cortex and the straight vessels of the medulla are stained a dark brown colour.

In the case of the intestine, the mucous membrane usually undergoes catarrhal and atrophic changes; and with iodine the waxy vessels of the mucous and submucous coats can be demonstrated as minute dark brown specks or lines.

Microscopical Distribution of Waxy Disease in the affected Organs.—It has already been indicated that the change is usually seen first in the middle coats of the ultimate arterioles of the organ, the delicate connective tissue **between** the muscular fibres becoming swollen and homogeneous, and exhibiting the typical staining reactions detailed above (Plate II. fig. 3). It then spreads backwards along the larger arterioles to the smaller arteries, and forwards along the perithelial connective tissue of the capillaries to the middle coats of the small veins. It may spread to the connective tissue framework of the affected organ, and to basement membranes if these be present; but it should be carefully noted that the change **never** affects the endothelial cells lining the vessels, the connective tissue *cells*, or the glandular epithelium. In other words, the con-

dition **does not affect cells**, but only the formed connective tissue elements of the organ.

Allusion has already been made to the two exceptions to the usual method of distribution, viz. diffuse waxy spleen, and certain very rare cases of waxy kidney, in the latter of which the change is found in the connective tissue between the larger collecting tubules towards the apices of the Malpighian pyramids, a condition occasionally seen in congenital syphilis, mostly in young subjects. Another point of some difficulty in this connection is the fact that in the liver the change may begin as usual in the smaller branches of the hepatic artery, and then spread to the walls of the capillaries lying between the columns of liver cells, not, however, at the periphery of the lobule, as one would expect, but in the intermediate zone of the lobule—the reason why the outer zone should be passed over by the change not being very apparent, but being probably due to the distribution of the vascular supply.

Course and Results of the Disease.—Waxy degeneration occurs in certain chronic organismal diseases of protracted duration, where there is long-continued action of the resulting toxic substances upon the tissues. This is usually a question of many months, or even years, and it is probable that the condition has never been produced in less than three months. It is a progressive disease; and it is doubtful whether waxy material, when once formed, can be re-absorbed on the removal of the cause of the condition, for example by the excision or amputation of a chronic tuberculous joint. It is difficult to obtain any direct evidence bearing upon the point, but such re-absorption is probably only possible in cases where the disease is in its earlier stages.

The results of the disease upon the organs may be considered under three main heads, viz.—(1) the effects upon the vessels themselves; (2) the effects upon the parenchymatous cells of the affected organ; and (3) the increased liability of waxy organs to undergo inflammatory and degenerative changes, more especially fatty degeneration. The last of these has already been referred to especially in the case of the kidney, in which organ there is also a greatly increased liability to various forms of nephritis—a fact which has led to the erroneous statement that "Bright's disease may sometimes lead to waxy degeneration

of the kidney," a statement for which there appears to be absolutely no foundation in fact.

Effects on the Vessels.—As stated above, the change is usually first seen in the connective tissue supporting the muscular fibres of the middle coat, especially in some of the smaller arteries (Plate II. fig. 3). Because of the enormous swelling of the connective tissue fibrils in this situation, the muscle fibres become compressed and atrophied, and may ultimately be completely destroyed, the controlling influence of the arterioles upon the circulation through the organ thus being to a great extent diminished, or even lost. The walls of the capillaries and veins also suffer. The lumen of the vessels, though often considerably narrowed by the swelling of the walls, is very seldom actually obliterated—a fact which can be demonstrated by injecting the arteries of a waxy organ with, say, carmine, the injection passing with ease into even the smallest vessels. The special selective capacity of the wall—if such exists, as in all probability it does—must, however, be considerably affected; and this, together with the loss of the normal powers of contraction and relaxation of the muscular coat of the arterioles, tends to cause an increased amount of transudation, a fact which may, in part at all events, help to explain the occurrence of the increased excretion of urine and the presence of diarrhœa in cases where the kidney and intestine are affected by the disease.

Effects on the Parenchymatous Cells of the Organs.—Another point of extreme importance is the compression and consequent atrophy of the special cells of the affected organ, which is produced by the great swelling of the formed connective tissue elements, whether in the vessel-walls or in the supporting framework of the tissue. Thus, although the actual size of the organ, *e.g.* the liver, spleen, or kidney, may be increased, there may in reality be an advanced degree of atrophy of its functioning or parenchymatous cells.

Note.—The following conditions, which, from the somewhat misleading names applied to them, or from a superficial resemblance which they may have to true waxy degeneration, have sometimes been confused with that disease, should be carefully distinguished from it:—

1. **Corpora amylacea** (*q.v.* p. 57).
2. "**Amyloid tumours,**" *e.g.* of conjunctiva. These may be inflammatory in origin or not, and appear to have no relation whatever to true waxy degeneration.

3. **So-called "waxy" casts in kidney tubules.** These are really colloid in nature, and are due to degeneration of the tubular epithelium (see p. 57).

4. **Zenker's degeneration of muscle** (*q.v.* p. 111) — really a necrotic or post-necrotic change.

5. **"Localised waxy degeneration," so-called,** — occurring around chronic abscesses and in the walls of old sinuses, etc. It is extremely doubtful whether this condition is in any way related to true waxy disease.

HYALINE DEGENERATION

Under the term **hyaline degeneration**, many diverse conditions have been described by different authors. It is best, however, to restrict the term to certain peculiar changes found in the connective tissue elements in the walls of the smaller arteries and of the capillaries, and in some other positions, and which are produced under the influence of certain toxic substances, whereby the delicate connective tissue fibrils tend to swell and become more homogeneous, refractile, and transparent, and more resistant to the action of digestion and of chemical agents.

We therefore exclude from this group certain degenerative changes occurring in cells; for example, the so-called "hyaline bodies" (Russell's "fuchsin - bodies"), "cancer - bodies," etc., found in degenerating epithelial cells, these being usually either the remains of cell-inclusions or the products of colloid degeneration of protoplasm.

The change is in some ways analogous to, but quite distinct from, waxy or amyloid degeneration. Both are toxic in origin, and both specially attack the formed connective tissue elements; but in staining reactions, distribution, and in many other particulars, the two conditions are essentially distinct. We have already seen that waxy degeneration is specially found in chronic infective toxic diseases, whilst hyaline degeneration usually occurs in some of the **more acute** infective conditions, *e.g.* diphtheria and scarlet fever. It may, however, also occur in certain forms of chronic Bright's disease, and in some other long-standing toxæmic conditions.

Nature and distribution of the change.—The change is essentially a degenerative one in the delicate supporting connective tissue fibrils, especially of the inner, and to a less

extent of the outer, coat of the smaller arterioles, but it may occur, though much more rarely, in the middle coat, and it may also affect the perithelium of capillaries. It is especially found in the spleen and kidney, in the brain, spinal cord, pia-mater, and less commonly in lymphatic glands and other tissues.

In these situations the connective tissue fibrils in the vessel-wall tend to swell and fuse together, and so to form irregularly distributed, clear, homogeneous, transparent, structureless masses, which may encroach upon or even obliterate the lumen of the affected vessel, and may lead to secondary changes such as degeneration or actual necrosis in the area of supply, thrombosis, etc. The hyaline material does not appear to have any very definite chemical composition, though it is said to be allied to elastin and keratin. Its staining reactions are somewhat variable, but it has usually a distinct affinity for some of the acid dyes, taking on a red colour with eosin or with acid fuchsin, especially when the hyaline material is of recent formation. Two of the most convenient stains for the demonstration of the condition are picro-carmine and picro-fuchsin (van Gieson's stain). With the former of these, in the earlier stages it takes on a pinkish tinge, whilst later it stains yellow with the picric acid part of the dye. With van Gieson's stain, recent hyaline material usually shows a bright red colour, but later it tends to stain a characteristic orange-red, orange, or ultimately even a bright canary-yellow colour (Plate II. fig. 6). The change, unlike waxy degeneration, is very irregular and patchy in its distribution. It does not give the characteristic " waxy " reactions with iodine or methyl violet, etc.

On present evidence, we cannot as yet accept the view of some observers that hyaline degeneration is a preliminary stage of waxy change. As already noted, the ætiology and distribution of the two conditions are for the most part distinct.

It has recently been stated that the immersion for several days of fragments of tissue in hæmolysed blood may lead to the artificial production of hyaline degeneration,—a statement which, however, requires further evidence before it can be generally accepted.

The condition of hyaline degeneration leads to no special

naked-eye changes in the organs, microscopical examination being necessary for its detection. It may be followed by calcification, for example in the arterioles of the kidney and spleen.

GOUTY DEGENERATION AND INFILTRATION

Into the general subject of gout and the chemistry of uric acid metabolism we do not propose to enter. The subject is one of enormous extent and does not come within the scope of the present volume, and we refer those specially interested in it to such recent works as Wells's *Chemical Pathology.*[1] It is sufficient to state here that in water, uric acid is comparatively insoluble, but that in the urine it is somewhat less insoluble because of the presence of phosphates, and perhaps of certain other substances. In the blood-serum, uric acid is probably held in solution by combination with some other as yet unknown organic derivative of nucleic acid.

Uric acid is largely derived from the breaking down of the nucleo-proteins both of the food and of the body tissues, being readily produced from the purin bases contained in these substances, probably under the influence of specific enzymes or ferments. Uric acid is eliminated as such in the urine only to a small degree, the larger proportion being oxidised by enzymes in the liver, kidney, muscles, etc., and converted into urea, in which form it is excreted by the kidneys.

The amount of uric acid in the urine and in the blood therefore varies in any given case, and is dependent upon many factors.[2] The amount of uric acid and urate crystals deposited

[1] Wells's *Chemical Pathology*, Saunders Co., Philadelphia and London, 1907, ch. xxi. p. 503.

[2] NOTE.—These are summarised by Wells (*loc. cit.*, p. 510) as follows:—

(1) The amount of purin bodies taken in the food, upon which, chiefly, depends the amount of exogenous uric acid.
(2) The amount of destruction of tissue nucleo-proteins.
(3) The amount of purin bases formed in the muscle tissue.
(4) The amount of conversion of purin bases into uric acid.
(5) The amount of destruction of uric acid occurring in the body.
(6) Possibly upon the capacity of the tissues to synthesise uric acid; and in case such power to synthesise uric acid exists, upon the presence of the precursors of uric acid in the body.
(7) The retention of uric acid in the blood and tissues.
(8) The power of the kidneys to excrete uric acid.

in the urine, depending upon such factors as temperature, reaction, concentration, amount of neutral phosphates present, etc., is probably a matter of comparatively minor importance; and Wells is of opinion that "it may be safely stated that at the present time there exists no good evidence which makes it probable that uric acid is responsible for any pathological conditions whatever, except uric acid calculi, uric acid infarcts in the kidneys, and certain manifestations of gout."

In patients subject to chronic gout, especially during the periods between the acute exacerbations, there appears to be no special abnormality in the amount of uric acid excreted in the urine, although the amount present in the blood is said to be larger than it is in health. Just before an acute exacerbation, the amount of uric acid excreted in the urine is usually diminished, whilst during and immediately after the acute attack the amount may be considerably increased.

Whatever the relationship between uric acid metabolism and gout may be—and from recent work on the subject it appears more than likely that its variations are to be regarded rather as the result than as the cause of the disease—the characteristic lesions produced by the deposit of uric acid, chiefly in the form of mono-sodium or acid sodium urate ($NaH\bar{U}$) in certain situations, may be shortly described.[1] This acid salt of uric acid is deposited in the form of granules or of acicular crystals, more especially in the articular cartilages and ligaments of joints; in bone and in tendons and tendon sheaths; in the cartilages of the ear and eyelids; in the fibrous tissue of the heart valves; in the interstitial tissue of the kidney; and in the subcutaneous fibrous tissue, especially in the neighbourhood of joints. In the last of these situations considerable masses may sometimes be found deposited, forming the so-called chalk-stones or "tophi," which may become exposed by the ulceration and destruction of the skin over them.

[1] NOTE.—The following analysis of such deposits, by Ebstein and Sprague, is given by Wells (*loc. cit.*, p. 391):—

Uric acid	59·70
Tissue organic matter	27·88
Sodium oxide	9·30
Potassium oxide	2·95
Calcium oxide	0·17
MgO, Fe, P_2O_5, S	traces

The condition tends specially to involve first the structures in and around some of the smaller joints, *e.g.* of the foot or hand, more especially the metatarso-phalangeal joint of the great toe. The larger joints, *e.g.* the knee joints, may become involved later. The deposit specially occurs in the cartilaginous and fibrous structures of the joints. The earliest changes

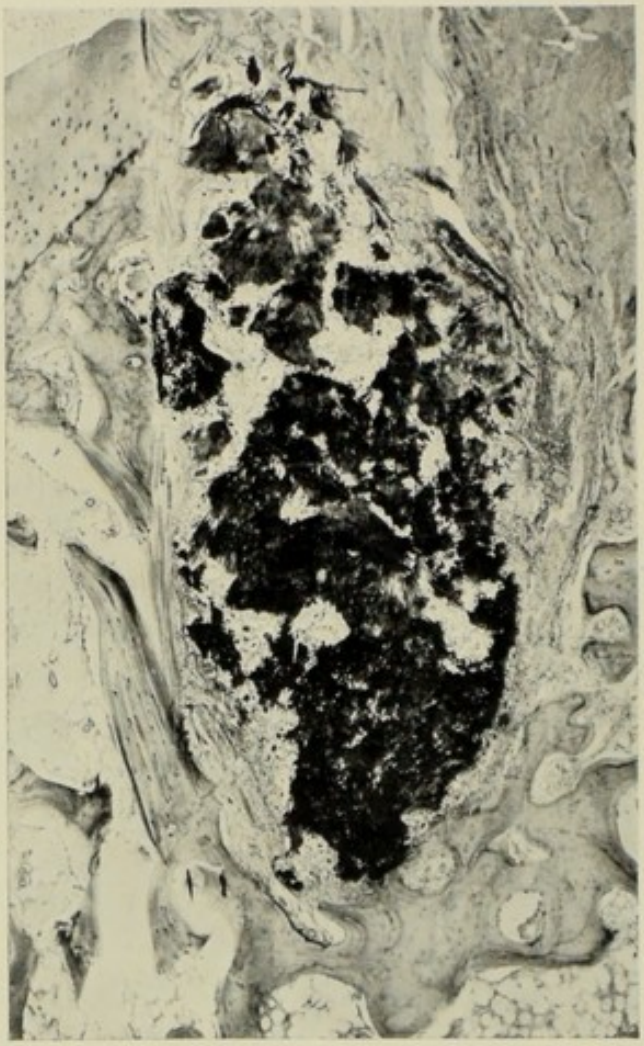


Fig. 12.—Gouty deposit in bone. × 20.

appear to occur in the more superficial layers of the articular cartilages, especially in the cartilage cells, which proliferate, become swollen, and undergo degenerative changes. It is in and immediately around these degenerating cells that the granules and acicular crystals of acid sodium urate are deposited, whilst later they are also found in the intervening matrix. The cartilage, especially towards the surface, becomes opaque white, and has the appearance of having been "smeared

with plaster of Paris," or "streaked with white paint." Later, it may become necrotic and undergo a more or less extensive process of ulceration. Accompanying the phenomena there is usually a varying amount of acute and, later on, of more chronic inflammatory change in the surrounding parts.

The ordinary chemical tests for the presence of these granular particles and crystals of urates are—

1. The addition of a strong acid, *e.g.* hydrochloric. This displaces the uric acid, which then crystallises out and can be recognised microscopically.
2. The murexide test. The substance to be tested is treated with strong nitric acid, and carefully evaporated to dryness on the bottom of a white porcelain dish. Ammonia is then added, and the characteristic purple colour is developed if urates or uric acid be present.

Ætiology.—The cause of gout is still quite unknown. It has long been regarded as a disease due to some "error in metabolism," but what the cause of the error is has still to be discovered. Many recent observers consider that it is caused by the derangement of metabolism by the action of some as yet undiscovered toxic substance or substances, perhaps organismal in origin, a view in support of which much may be said. An almost identical series of changes is found in the joints in the so-called lead-gout found in chronic lead poisoning, which also tends to produce changes in the kidney similar to those found in ordinary gout.

PATHOLOGICAL PIGMENTATION AND PIGMENTARY DEGENERATION

The group of conditions commonly known as the **Pathological Pigmentations** includes many diverse changes, some of which are very obscure in their nature and ætiology. It is convenient to classify them under the following headings:—

I. Abnormalities in the amount, distribution, etc. of the **normal animal pigments**, and of **pigments closely allied to these.**

II. The presence of **hæmatogenous pigment**, *i.e.* pigment derived from the hæmoglobin of the red blood

corpuscles; and along with this we may also consider the so-called **hepatogenous pigmentation** due to the deposit of bile-pigment, which is derived from the destruction of hæmoglobin in the liver.

III. The presence of **extraneous pigmentary substances**, *i.e.* introduced into the tissues from without.

IV. Discolourations of the skin **due to parasites.**

V. Discolourations of the organs and tissues **due to post-mortem decomposition.**

I. ABNORMALITIES IN THE AMOUNT, DISTRIBUTION, ETC. OF THE NORMAL ANIMAL PIGMENTS; AND THE PRESENCE OF PIGMENTS ALLIED TO THEM

The origin and chemistry of the normal pigments of the body are still subjects about which little is known. Some of these pigments, *e.g.* those found in the skin, hair, uveal tract of the eye, and certain other localities, appear to be **allied to the albumins**; whilst those found in the corpus luteum, testes, suprarenals, nerve cells, and in adipose tissue, seem to be of the nature of coloured fats or fatty compounds, and are known as the **lipochromes.**

To the pigments belonging to the former of these groups the general name **melanin** is given. These melanins vary considerably in their composition in the different tissues. They all contain nitrogen, hydrogen, and carbon (usually in the approximate relative proportions 1 : 5 : 5); and many of them have also a comparatively high sulphur-content, although this element is said to be absent in the case of the melanin found in the choroid coat of the eye. In melanotic sarcomas the characteristic pigment present is closely allied to or identical with normal melanin, and may contain a large amount of sulphur—sometimes even as much as 10 per cent. Some, though by no means all, of the melanins contain iron, but usually only in very small amount.

The melanins are the product of the metabolic activity of special cells, *i.e.* they are built up by the living protoplasm, and are not merely the disintegration products of hæmoglobin or of some of its derivatives. In all likelihood they are derived from the complex protein molecule (probably from

its aromatic chromogen molecular groups), possibly under the influence of specific ferments or enzymes.

The melanins are insoluble in most of the ordinary solvents, *e.g.* water, alcohol, chloroform, benzol, ether, etc. They are practically unaffected by even strong boiling hydrochloric acid, but are readily decolourised by strong alkalies, by chlorine and other bleaching reagents, and by the action of sunlight.

These pigments are usually intracellular, and are commonly in the form of minute yellowish-brown, brown, or brownish-black granules, which may be scattered throughout the cytoplasm, or in some cases are so densely packed as to entirely obscure the cell-structure.

Congenital deficiency, or even the entire absence of the normal pigments, is seen in the condition known as **albinism.** In **leucoderma** the cutaneous pigment becomes irregular in its distribution, some patches becoming paler than normal owing to the deficiency, whilst surrounding areas may show an increase of pigment. Again, after the repair of wounds and ulcers, especially if these are of any extent, the scar tissue is frequently deficient in pigment, and may therefore be whiter than the surrounding skin, which contrast may, indeed, especially if there has been any chronic irritation and delay in the healing process, be accentuated by an actual increase of pigment in the skin immediately around the scar. Localised deficiency of skin pigment may also be due to trophic and nervous causes; for example, the white patches in leprosy due to implication of the cutaneous nerves.

Increase of pigment is, however, a condition more frequently met with than deficiency. Such increase may be **physiological,** *e.g.* in the case of the mammary areola during pregnancy. "Sunburn" and "freckles" may also be regarded as a physiological reaction to the stimulation of light, the increase of surface pigment serving to protect the deeper structures against the harmful action of the too powerful actinic and other rays, in the same way as does the pigmented skin of the negro. Localised pigmentation may also result from irritation of the skin, *e.g.* caused by a blister, parasites, certain skin diseases, etc.

Pigmentation is often, however, an **accompaniment or a result**

of certain retrogressive or degenerative and atrophic processes, occurring sometimes as a senile change, sometimes as the result of disease.

Above the age of forty or forty-five, the fine granules of pigment found in the protoplasm of heart muscle fibres towards the poles of the nucleus tend naturally to increase as age advances, the fibres at the same time becoming smaller in size. This condition may in certain cases be exaggerated in degree, or it may occur at an abnormally early age, for example in cachectic or wasting disease such as cancer, chronic phthisis, etc., and is then known as **Brown Atrophy of the heart** (Plate III. fig. 4). Whether this pigment found in the heart fibres in brown atrophy is a true melanin or a lipochrome (pigmented fat) has not yet been satisfactorily decided. Such senile pigmentary changes may be found not only in heart muscle, but also in the kidneys, liver, suprarenals, muscular coat of the intestine, pia-arachnoid, and elsewhere.

In wasting conditions the skin pigment is often abnormally increased in amount, especially over the flexures and in other parts where there is normally a greater amount of skin pigment present. Abnormal increase of cutaneous melanin pigment is specially found in chronic ovarian and uterine disease (the so-called "**chloasma uterinum**"); and in chronic diseases of certain other glandular organs, more especially of the suprarenal or adrenal bodies, destruction of which may lead to **Addison's disease**, a condition which is characterised by great muscular weakness and wasting, and by marked brownish pigmentation of the skin, particularly where this is exposed to the action of light, friction, or other form of irritation. Irregular patchy pigmentation of certain of the mucous membranes, *e.g.* of the mouth, is also characteristic of this disease. The exact nature of the pigment in Addison's disease has not yet been accurately determined, but in all probability it is identical with or closely allied to the normal melanin pigment of the skin.

Local increase of melanin pigment is also seen in connection with certain tumour growths, *e.g.* in pigmented moles, or more notably still in **melanotic sarcomata** and **cancers.** In these the melanin, which may be in very large amount and often very irregular in its distribution, is mostly contained within the tumour cells. It may, however, be found free in the

DESCRIPTION OF PLATE III

PLATE III

FIG. 1.—*Hæmatoidin crystals,* free and contained in phagocytic endothelial cells in an organised thrombus in a vein Stained with Hæmatoxylin. ×1000

FIG. 2.—*Phagocytic cells* (*from bone-marrow*) *containing blood-pigment.* Stained with Methylene Blue and Eosin. One cell also contains an englobed red blood corpuscle. ×1000

FIG. 3.—*Pernicious Anæmia.* Section of liver stained with potassium ferrocyanide and hydrochloric acid, to demonstrate the presence of *Hæmosiderin* in the liver-cells by the Prussian blue reaction. Counterstained with Safranin. ×1000

FIG. 4.—*Brown Atrophy of Heart.* Longitudinal section of muscle-fibres stained with Alum Carmine. The unstained yellow pigment is seen in the protoplasm, especially towards the poles of the nuclei. ×1000

FIG. 5.—*Obstructive Jaundice.* Section of liver, stained with Alum Carmine, showing masses of dark green *bile-pigment* in the liver-cells, which also contain some yellow *blood-pigment.* Nuclei of liver-cells. ×1000

FIG. 6.—*Large phagocytic cells* (probably endothelial in origin) *containing carbon-pigment.* These cells are from a case of anthracosis, in which they were present in large numbers in the pulmonary alveoli. Stained with Methylene Blue and Eosin. ×1000

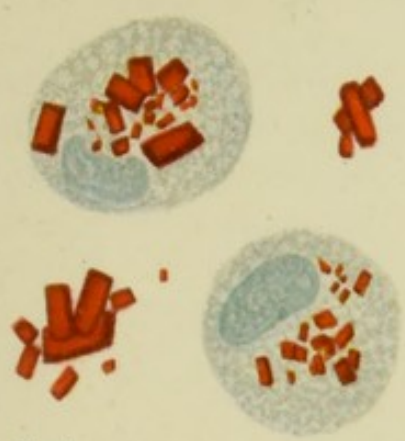


Fig.1. × 1000

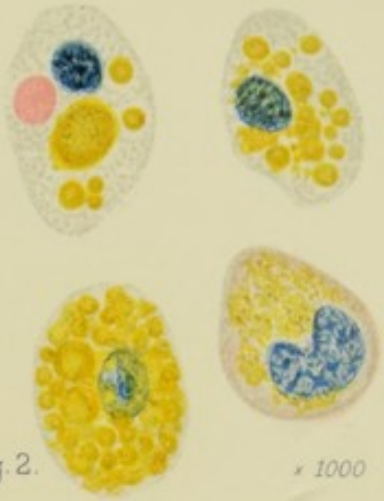


Fig.2. × 1000

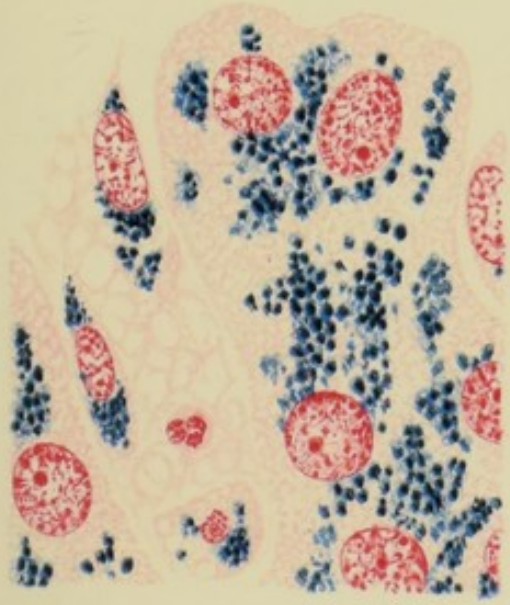


Fig.3. × 1000

Fig.4. × 1000

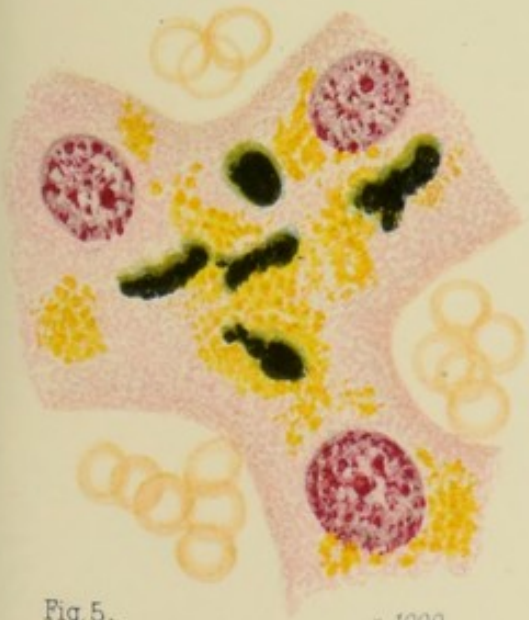


Fig.5. × 1000

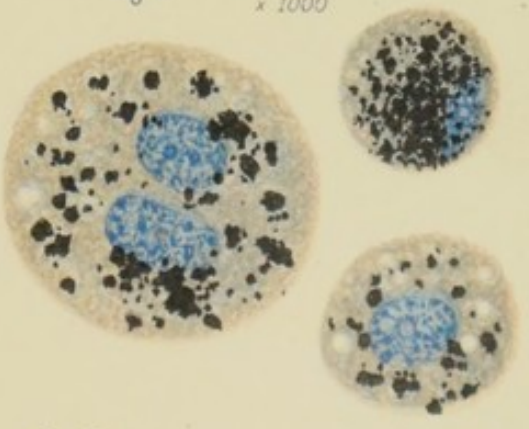


Fig.6. × 1000

lymphatic spaces, and may also be present in the blood and lymph, and in marked cases it may even be excreted in the urine by the kidneys, either as melanin or as the colourless melanogen, the urine containing which may darken on standing or on the addition of oxidising agents, such a case being known as one of **melanuria**.

Reference has already been made to the presence in the tissues of certain pigmented fatty bodies or **lipochromes**, *e.g.* the **lutein** found in the corpus luteum; or the pigment seen in

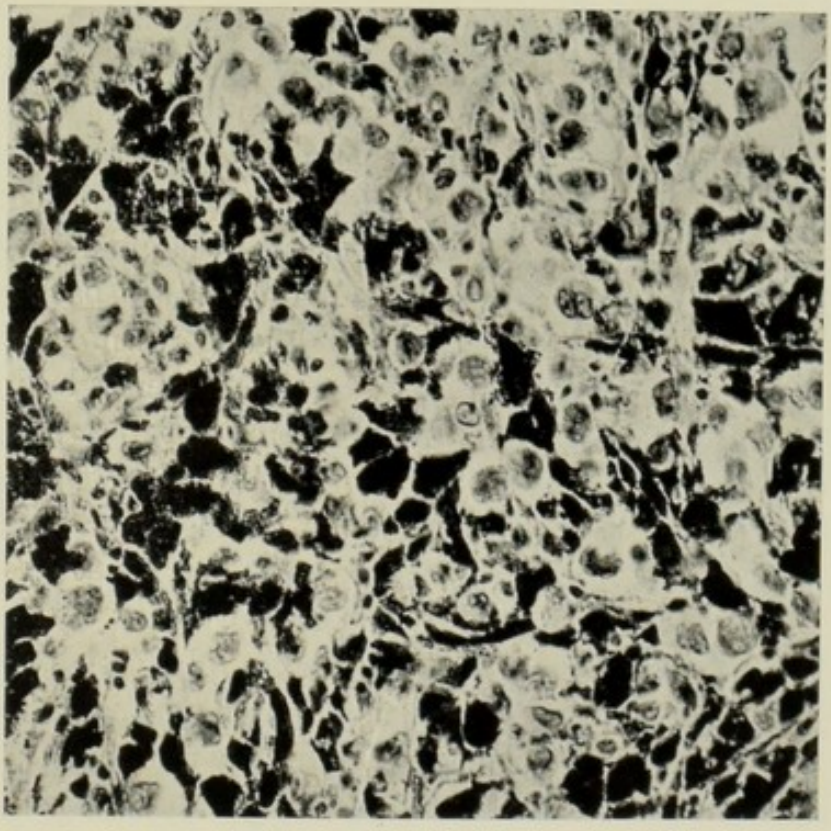


FIG. 13.— Melanotic Sarcoma, showing accumulation of melanin in certain of the tumour cells. × 300.

many ganglionic cells, both normally in certain parts of the nervous system, and abnormally in some forms of degeneration of nerve cells. Lipochromes may be found in some pathological conditions, *e.g.* in **xanthoma** or **xanthelasma**, a condition in which there are developed small yellowish tumour nodules, especially in the skin of the eyelids; and in **chloroma**, a very rare disease characterised by the development of peculiar greenish-coloured lymphomatous or lymphosarcoma-like growths, more especially in connection with the bones. It may

also be of interest to note here that many of the pigments produced by bacteria appear to be of the nature of lipochromes, *e.g.* in the case of cultures of *Staphylococcus pyogenes aureus* or *citreus*.

II. HÆMATOGENOUS PIGMENTATION

Under certain circumstances, pigment derived from the hæmoglobin of the red blood corpuscles may be found in the tissues or elsewhere. The presence of such hæmatogenous pigment may, for example, be the result of a direct attack by organisms upon the red blood corpuscles themselves while circulating in the vessels, *e.g.* in malaria. In this disease the malarial parasites live within the corpuscles, attacking and feeding upon the hæmoglobin, and forming yellowish-brown granules of pigment, to which reference will be made later.

Again, the erythrocytes may be damaged by bacterial and other toxins or poisons, and may break down whilst still circulating in the vessels, their contained hæmoglobin being discharged into the serum. More commonly, however, the damaged corpuscles are, before their disintegration, taken up and digested by leucocytes, and by endothelial and other phagocytic cells: a process which occurs more especially in the organs normally concerned with hæmolysis, *i.e.* the liver, spleen, bone-marrow, lymph and hæmolymph glands, and some other tissues. In diseases such as pernicious and other grave anæmias, hæmoglobinuria, malaria, etc., the amount of pigment so derived may sometimes be very considerable in the cells of these and other organs and tissues.

In some instances such hæmatogenous pigment may be formed from the hæmoglobin of blood which has undergone thrombosis within the vessels, or which has been effused into the tissues or into some natural cavity. Or, again, the occurrence of such pigment may be due to stagnation of the blood, for example in chronic venous congestion. In the case of the lungs in this last-mentioned condition, the abundant pigment found in the large mononuclear phagocytic cells in the alveoli is doubtless due to small hæmorrhages into the air-vesicles. In the case of the liver, the pigment is specially found in the hepatic and also in the endothelial cells towards the central vein of the

lobule. It is probably evidence of increased hæmolysis, a condition favoured by the stagnation of the blood.

Chemical nature of the Hæmatogenous Pigments.—**Hæmoglobin**, the normal pigment of the red blood corpuscles, is a compound of an albuminous basic histone-like substance called **globin**, with a non-albuminous acid radicle, the iron-containing pigment **hæmatin**. The hæmoglobin molecule is one of enormous complexity, its approximate composition being given by Mann as

$$C_{758}H_{1203}N_{195}O_{218}FeS_3,$$

the composition of hæmatin being given as

$$C_{34}H_{34}N_4FeO_5.$$

A trace of phosphorus is found in the hæmoglobin of certain birds, but not in that of man.

Even in health, the red corpuscles are comparatively short-lived, and as they become effete are constantly being destroyed by the hæmolytic organs, more especially the liver, spleen, bone-marrow, kidneys, and hæmolymph glands. The effete corpuscles are taken up and destroyed by the cells of these organs, especially by endothelial and other phagocytic varieties of cells. The albuminous globin radicle is digested and absorbed, whilst the pigment hæmatin is split up into two parts, an iron-free substance called **hæmatoidin**, which is largely excreted by the liver as bilirubin, with which it is apparently identical in chemical composition; and secondly an iron-containing moiety called **hæmosiderin** (or "blood-iron"), which is stored in certain of the tissues, especially the liver, spleen, and bone-marrow, to be built up again into hæmoglobin when required.

An enormous exaggeration of these normal hæmolytic processes may occur in disease, usually under the influence of bacterial or other toxins and poisonous substances, for example in the so-called anæmias, more especially in pernicious, but also in severe secondary cases. Evidence of this increased destruction of red cells in such cases is to be found in the excessive formation and storage of hæmosiderin in the liver, spleen, kidneys, and other organs, a fact which will be again referred to later.

Hæmoglobin, to the chemical composition of which allusion has already been made, is a crystallisable substance. In the case of the human subject it is comparatively soluble, but from the blood of rats or guinea-pigs it may be very easily crystallised out by adding water and evaporating. It is insoluble in glycerin, and microscopical preparations of it may therefore be made in this as a mounting medium. When thus prepared it usually occurs in rhombic prisms or plates.

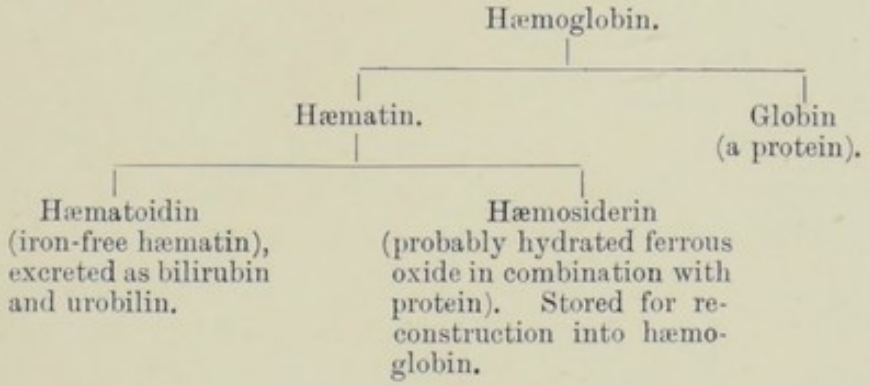
Hæmatin, the iron-holding radicle of hæmoglobin, constitutes about 4 per cent. of the latter substance, which therefore mainly consists of the protein, globin. Hæmatin is a brown, non-crystallisable substance, which may occur either in reduced or in oxidised form. In the tissues it is readily split up into an iron-free constituent, **hæmatoidin**, and an iron-containing part, **hæmosiderin.**

Hæmatoidin, the iron-free constituent of hæmatin, is apparently identical with bilirubin or bile pigment, and is usually excreted by the liver as a waste product. It may, however, if not carried to that organ, slowly crystallise out in the form of very characteristic yellowish or orange-red to dark ruby-red clino-rhombic prisms or needles (Plate III. fig. 1), though it may also be found in the form of irregular masses or granules. Its formation, unlike that of hæmosiderin, occurs independently of cell-activity, and it is therefore specially got where hæmorrhages or thrombi of large size have occurred, and where absorption has been slow and imperfect, for example in old cerebral hæmorrhages, thrombi in large veins, etc. When once formed, these hæmatoidin crystals and granules are extremely resistant, and may be found in the tissues many years after their formation.

Hæmosiderin, the iron-containing part of hæmatin.—In the normal process of hæmolysis, as indicated above, the iron-free hæmatoidin is eliminated in the bile, but the iron-containing part of the broken-down hæmatin is stored up as hæmosiderin by certain cells until it is required for the production of fresh hæmoglobin. This hæmosiderin is probably in the form of hydrated ferrous oxide, more or less loosely combined with some protein substance or substances. The stability of this combination appears to vary in different diseases and in different organs. Hæmosiderin, when the combination is loose, is easily

stained by the Prussian-blue reaction [1] (Plate III. fig. 3). When more firmly united with protein, the colour reaction may be slow in appearing, this union having first to be broken up; or, again, it may be entirely prevented when the combination is sufficiently firm to resist the separation. When unstained, the hæmosiderin series of pigments occur in the form of yellowish or golden-brown granules, which are usually present within the cells, though in some cases they may be deposited in the intercellular lymphatic spaces by phagocytic cells. This pigment is not found in crystalline form.

Hæmosiderin requires for its formation the action of living cells, or ferments derived from them; and the presence of oxygen is also said to be a necessary condition for its elaboration. It is formed and stored in great excess in certain pathological conditions in which hæmolysis is exaggerated, notably in pernicious anæmia, malaria, etc., as already indicated. It is found specially in the cells of the liver, kidneys, spleen, bone-marrow, etc.



"HEPATOGENOUS" PIGMENTATION, ICTERUS, OR JAUNDICE are terms applied to the conditions characterised by the presence of bile-pigment, usually in solution in the body fluids, whereby the tissues are permeated and in a certain sense "stained" by the yellow or greenish-yellow biliary pigments formed by and re-absorbed from the liver. As already stated, bilirubin, the most important of these biliary pigments, is apparently identical, or rather isomeric, with hæmatoidin, and is derived from the destruction of effete red blood corpuscles in the process of hæmolysis. Such biliary pigment is always

[1] NOTE.—The tissues are treated alternately with a 20 per cent. watery solution of potassium ferrocyanide and with dilute hydrochloric acid (not stronger than 5 per cent.).

found in the liver, and true general jaundice is said not to occur experimentally if the liver has been previously removed or thrown out of action. Bile-pigment, being soluble in alkaline watery media, is, in such cases of jaundice, for the most part in solution in the blood and lymph, the tissues being thus permeated, as it were, but not necessarily actually stained, during life at all events, by the yellow or greenish-yellow solution; though certain of the tissue elements, *e.g.* connective tissue fibres, do become bile-stained during life, others, for example muscle cells, fat cells, etc., undergo staining only after death.

When jaundice becomes more advanced, however, the pigment may be deposited in granular form, a condition which is specially well seen in the liver, and to a less extent in the kidney cells, *e.g.* in cases of severe obstructive jaundice. In the skin in old-standing cases of jaundice, the original yellow or greenish-yellow tinge may gradually be replaced by a dark olive-green or even by a dark brownish-green colour, produced apparently by a slow oxidation or other change in the bilirubin.

Part of the excess of bile pigment and bile acids in cases of jaundice is excreted in the urine by the kidneys, and these organs are specially liable to be extensively damaged, albuminuria being a frequent accompaniment of severe attacks. The commonest cause of general jaundice is obstruction to the outflow of bile from the liver, *e.g.* caused by an impacted gall-stone in, or by a tumour pressing upon or infiltrating, the larger bile-ducts or common bile-duct; or, again, by catarrhal swelling of the mucous membrane of these passages. In the so-called "hæmatogenous" forms of jaundice found in various toxic conditions, for example in the septicæmias, cases of snake-bite, etc., although the hæmoglobin freed by the disintegration of the red corpuscles may be in sufficient quantity in the serum to produce a distinct yellow discolouration, nevertheless the jaundice produced in such cases is rather to be regarded as due to simultaneous implication of the liver. The hæmoglobin in the blood is carried to that organ and transformed into bile pigment. In the liver, owing either to increased viscosity or increased toxicity of the bile, or perhaps also owing to the direct action of the original toxic substances which cause the hæmolysis acting at the same time upon the cells lining the bile capillaries and smaller bile-ducts, these passages become

readily blocked, a condition probably aggravated by pressure upon them from without by the liver cells which have undergone cloudy swelling. Egress of bile from these channels is thus prevented, and absorption of it occurs by means of lymphatics, and perhaps also of blood-vessels, the general jaundice so produced being thus really due to **obstruction and stasis of the biliary flow**, though in this case it is in the smaller and not in the larger biliary passages that the process occurs. In all probability, in such instances of toxic hæmolytic jaundice, there is usually also some actual **breaking down of liver cells**, leading to disorganisation of the bile-capillary system, and to the consequent absorption of the bile by the other available channels, viz. the lymphatics and blood-vessels. The extreme jaundice found in acute yellow atrophy of the liver and in phosphorus poisoning is in all likelihood largely of this nature.

Although it appears to have been proved that true jaundice is caused only by the resorption of bile formed in the liver, it is possible that a **slight** yellowish tinge may in some cases be produced in the tissues by the breaking down of red cells while still in the circulation, and the extrusion of their hæmoglobin into the serum. Such hæmoglobin is, however, rapidly broken up by the spleen and liver, etc., its hæmatoidin constituent being excreted as bilirubin.

The profound toxic effects of jaundice are to be regarded as due, not so much to the presence of bile pigment, as to the action of the accompanying bile-salts, which produce cloudy swelling, hæmorrhages and other cytolytic phenomena, bradycardia, coma and death.

Bile-pigment may be found accumulated, sometimes in considerable quantities, in the cells of the liver and elsewhere, in the form of small greenish or greenish-yellow granules. The most convenient test for the presence of bile-pigment, known as "Gmelin's reaction," is the play of colours obtained on the addition of impure nitric (*i.e.* nitric + nitrous) acid, a test also applicable for the detection of hæmatoidin, which, as has already been pointed out, is isomeric with bilirubin.

Note on Malarial Pigmentation.—It is impossible to enter into this important subject in detail, and the following résumé of it must suffice.

At least **three** varieties of pigment may be distinguished.

1. A very dark brown pigment, often described as being "black" in colour, elaborated by the parasites from the hæmoglobin of the red cells which they infest. This occurs in granules, and is the specific pigment which gives the characteristic naked-eye and microscopical peculiarities to malarial organs and tissues. By some observers it is regarded as being albuminous in nature, and is therefore classified by them as belonging to the melanin series of pigments. Ewing,[1] however, doubts the truth of this view, and is inclined to regard it as being of the nature of a blood-pigment. It appears probable that the parasite, in the process of its growth, feeds upon the protein globin radicle of the hæmoglobin of the corpuscles, the hæmatin part not being assimilated, but altered in some way, and left as a by-product, which may or may not have any special function in the life of the parasite. Whatever be its nature, this pigment formed by the specific activity of the parasite may be found, sometimes in enormous quantities, within phagocytic cells, especially the large mononuclear leucocytes and the endothelium of vessels, and in the phagocytic cells of the spleen, liver, and bone-marrow ; and less frequently, lying free in the lymphatic spaces. It is insoluble in strong acids, is altered by treatment with alkalies, and is readily dissolved by ammonium sulphide.

2. Yellow pigment formed from the hæmoglobin of broken-down red cells. This is a product of hæmolysis, and occurs in the cells of the various organs and tissues. When freshly formed, although containing iron, it usually does not give a positive reaction with the ammonium sulphide or the ferrocyanide tests. Later, however, the pigment is split up or altered, and the typical iron reaction is developed, the pigment so produced being indistinguishable from the hæmosiderin found in other conditions characterised by great destruction of red cells and their contained hæmoglobin.

3. Bile-pigment and urobilin. The excessive amount of freed hæmoglobin is transformed by the liver into bile-pigment, and also by the kidneys into urobilin. If the elimination of the bile-pigment so formed is deficient, jaundice will result.

Hæmoglobinuria.—In certain diseases characterised by rapid and extensive destruction of red cells, more hæmoglobin may be freed into the blood than can be dealt with and transformed into bilirubin by the liver. In such cases the kidneys may excrete part of the hæmoglobin, the resulting urine being dark brown or even almost black in colour—the condition of hæmoglobinuria. This condition is typically seen in **hæmoglobinuric** or "**black-water**" **fever**, and also in the so-called **paroxysmal hæmoglobinuria**. On spectroscopical examination of the urine from such cases, the typical absorption bands of hæmoglobin, and sometimes of methæmoglobin, are found.

[1] Ewing, *Journal of Experimental Medicine*, 1902, vol. vi. p. 119.

Hæmatoporphyrinuria, the presence of hæmatoporphyrin or iron-free hæmatin in the urine in excessive quantities, is a rare condition, most typically found in certain individuals after the administration of large doses of sulphonal or trional, the urine becoming of a dark port-wine colour, and showing the absorption bands of hæmatoporphyrin spectroscopically.

Hæmochromatosis is a very rare condition, characterised by wide-spread pigmentation of the organs and tissues of the body, accompanied or preceded by cirrhotic and atrophic changes in the liver and pancreas. The disease of the latter organ may or may not give rise to glycosuria. The skin in such cases may also be the seat of extensive pigmentation, a phenomenon which, combined with the presence of glycosuria, led to the application of the term "diabète bronzé" being applied to such cases.

The following are the conclusions of a paper by one of the authors upon this subject:[1]—

1. The condition known as **hæmochromatosis** is a distinct entity, and the diabetes associated with it is but a late manifestation, due to a very considerable destruction of the cells of the pancreas and an increase of fibrous tissue.
2. The degeneration in the cells of the liver, pancreas, and other organs, and the cirrhosis, in part, are due to a toxic agent possibly derived from the intestine by way of the portal circulation.
3. The pigmentation is due partly to the degenerated cells not being able to perform their metabolic processes properly, and partly to transportation from the liver and pancreas.
4. The cirrhosis is due, mainly, to the toxic agent causing the cell-degeneration, but one must admit that it may be due, in part, to the irritation caused by the pigment.

CHANGES OCCURRING IN EFFUSED OR EXTRAVASATED BLOOD.—Hæmorrhage, or the escape of blood from the vessels, may occur into the tissues or cavities, or from the surface of the body, and is due to injury of the vessel-wall, which may be either traumatic or toxic in origin. Hæmorrhage may also occur from the heart, *e.g.* from rupture or injury. Hæmorrhages, varying in size from those visible only by means of the microscope, up to large effusions, may be found. Among the toxic causes of hæmorrhage may be mentioned the bacterial toxins; certain chemical poisons such as phosphorus; phytotoxins or vegetable poisons such as ricin and abrin; zoötoxins or animal poisons such as snake-venom, which contains a specific substance, an

[1] J. M. Beattie, "Hæmochromatosis with Diabetes Mellitus," *Journal of Pathology and Bacteriology*, 1903, vol. viii. p. 117.

endothelio-toxin or **endothelio-lysin**, which specially attacks the endothelium of the vessels. In the latter category may also be placed certain other specific toxic substances discussed later in the Chapter on Immunity. The hæmorrhages occurring in pernicious and other anæmias, leucocythæmia, Bright's disease, etc., are probably also due to toxic substances of, as yet, unknown nature and origin, present in the blood; and it has already been mentioned that the hæmorrhages which may occur in jaundice are in all probability due to the toxic action of the re-absorbed bile-acids.

The secondary changes occurring in such hæmorrhages vary considerably with their size and locality, and may also be influenced by the presence of the toxic substances in the blood, or by organisms.

When of small size, they are usually readily absorbed, but when large, such absorption may be very gradual, and may be partial, and in some cases very slight. The sequence of the changes to be observed in effused blood may be readily studied by injecting, with aseptic precautions, varying quantities of blood into, say, the peritoneal cavity or elsewhere. Coagulation may or may not occur, depending on the presence or absence of the necessary ferments, and on the amount and nature of cell-damage in the part, and also on the variety of cells present. Small hæmorrhages may be rapidly absorbed, the fluid of the effused blood being carried off by lymphatics, and perhaps also by blood-vessels. Some of the red blood corpuscles may also directly pass into the lymphatics. If the effusion is of large size, however, these processes may be very imperfectly carried out, and other changes then occur in the remaining mass. This may gradually become more inspissated by absorption of fluid. Coagulation need not necessarily occur, but the red corpuscles usually run together into homogeneous masses, their hæmoglobin being largely extruded. This hæmoglobin may soak into and stain the surrounding tissues, and a large part of it may be absorbed into the lymphatics and blood-vessels and carried to the liver, and excreted as bile-pigment. If large quantities of hæmoglobin are freed, the kidneys will also take part in its excretion, and in such cases the hæmoglobin or its derivatives appear to act as powerful cell-poisons, and may produce marked cloudy swelling and other degenerative

changes in the organs and tissues, and may also cause considerable local inflammatory reaction.

Chemical and physical changes also occur locally in the pigment of the effused blood. The hæmoglobin is split up, probably by enzyme action, into its components, globin and hæmatin. The former is readily digested and removed, whilst the latter is further split up by enzymes into the iron-free hæmatoidin and iron-containing hæmosiderin. The granules of the latter are very slowly removed, carried to the liver and elsewhere, and stored until they can be utilised for the formation, in the bone-marrow, of fresh hæmoglobin. The hæmatoidin not removed to and excreted by the liver, and therefore especially that part of it in the deeper portions of the effused blood, slowly crystallises out to form the characteristic ruby-red prisms, etc., as already described earlier in this chapter. In large hæmorrhages, where the absorptive changes are very slow or imperfect, hæmatin, or even the original hæmoglobin, may remain intact, and may crystallise out. Hæmatoidin is, however, of very much more frequent occurrence, and, as already noted, may persist for many years in the remains of old blood-clots. Another important and very insoluble constituent of the red blood corpuscles, viz. cholesterin, may also crystallise out, and its characteristic rhomboidal plates, with a notch out of one corner, may be found in old hæmorrhages.

Phagocytosis in and around blood-effusions is a subject which is to some extent dealt with elsewhere. Both red blood corpuscles, and the granules and crystals of pigment derived from their disintegration, may be extensively taken up by various phagocytic cells, more especially by the macrophages or large mononuclear cells, fully described in the section on phagocytosis. Ingested red corpuscles rapidly disappear within the digestive vacuoles of these cells, leaving some pigment granules in their protoplasm as a residue. These phagocytic cells may then migrate and deposit their contained pigment elsewhere. They specially tend to pass along the lymphatics, and are arrested in the lymphatic glands, where they may deposit their contents; or, perhaps more commonly, are themselves englobed by the actively phagocytic endothelial cells which line the lymph sinuses of the glands, often leading to extensive pigmentation of these organs. The pigment particles

may also be found in the endothelial cells lining lymphatics, and in the connective-tissue and other cells in the neighbourhood, or they may be carried even to distant parts of the body. This pigment may persist for very long periods; and ultimately the remains of such a hæmorrhage may show as brownish or brownish-red pigment granules or crystals and débris, surrounded by proliferated fibrous tissue.

Blood effused into certain organs or tissues may undergo special changes. For example, in gastric hæmorrhage the blood may become brownish from the action of the gastric juice; or it may be blackened by the action of sulphuretted hydrogen upon it, *e.g.* in the stomach, and especially in the intestine, leading to the condition known as **melæna**, or the presence of black altered blood in the stools.

III. PIGMENTARY SUBSTANCES OF EXTRANEOUS ORIGIN

Substances introduced into the body from without may produce alterations in the colour of the tissues, either because of these substances themselves possessing definite colour, or because they may stain, or may form coloured compounds with the tissues or with certain of the tissue elements.

Such substances may obtain entrance into the body by means of the respiratory passages or the alimentary canal, or through the skin.

(*a*) **Pneumonokoniosis, or Pigmentation due to inhalation of foreign particles.**—The lungs of newly-born infants, and also those, it is said, of persons who live in regions where dust and smoke are absent—*e.g.* Laplanders—are pale in colour, and do not show the presence of particles of carbon, stone-dust, etc., so commonly seen in these organs as almost to be regarded as a normal condition, more especially in city dwellers or in workers exposed to dust by the nature of their occupation. Minute particles of soot, coal, stone, etc., suspended in the air in the form of dust, are inhaled into the respiratory passages. The greater part of this dust comes in contact with and adheres to the moist mucous surfaces of the nose, pharynx and trachea, and larger bronchi, and is carried out by the secretions of these passages. If in excessive amount, however, some of the particles may be carried further into the lungs, and perhaps even as far as the ultimate

air-vesicles, though most of them are probably caught on the moist walls of the smaller bronchi. The particles are then englobed by phagocytic cells—leucocytes, epi- and endo-thelial cells—and these, if not carried out by the ciliary movements of the cells lining the bronchi and expectorated in the sputum, may migrate into the lymphatic spaces and along the lymphatic channels of the fibrous tissue framework of the lungs, carrying with them their contained pigment. This they may deposit in the lymph-spaces of any part of the fibrous framework, for example in the peribronchial and perivascular tissue, and in the interlobular septa, especially where these join the deeper layer of the pleura, thus tending to demarcate the outlines of the lobules, and producing a somewhat polygonal network of pigment which may be seen shining through the transparent serous layer of the pleura. Some of the pigment is also usually carried to the bronchial and perhaps to other groups of lymphatic glands, which act as filters for the lymph stream. Such pigment, especially if in excessive quantity, acts as a chronic irritant, and produces a gradual proliferative increase of the fibrous tissue of the lung.

In the case of coal-miners and others exposed to an excessive amount of coal-dust in the air they breathe, this pigmentation and chronic proliferation of the fibrous tissue of the lungs may become very extreme, and is known as **Coal-miners' Lung**, or **Anthracosis**, from the black colour of the organs. The bronchial glands of such cases usually become deeply pigmented, and the pigment may also be found in more distant groups of glands, and even in the spleen and liver, and lymphatics of the peri- and epi-cardium, diaphragm, and elsewhere.

The inhalation of fine particles of stone-dust produces similar but usually more marked and severe results, the irritation and proliferative changes being more pronounced. The condition is known as **Silicosis**, or **Stone-masons' Lung**, and frequently though not necessarily, is combined with or leads to invasion of the diseased tissues by the tubercle bacillus.

Other forms of these **pneumonokonioses**, or lung-dust diseases, as they are called, may be produced in iron or steel grinders (**siderosis**), workers in vermilion, feathers, etc.

(*b*) **Pigmentation produced by substances introduced by the alimentary canal.**—In this instance the substances may be

absorbed in solution; and later, on being carried to the tissues, may become altered in such a way as to produce pigmentation, for example in **argyria**, or **chronic silver-poisoning**, which may supervene in cases where soluble silver salts are administered for a prolonged period. Particles of the insoluble albuminate of silver are deposited in the skin, especially in the connective tissue around the sebaceous and sweat glands; and also in the liver, bone-marrow, and kidneys, more particularly in the glomeruli, and in and around the straight tubules and elsewhere. In the case of the skin, the pigment may, under the action of light, assume a slate-grey or even a dark bluish-purple colour.

In like manner, the prolonged ingestion of small quantities of **arsenic**, either medicinally or as an impurity in beer or other article of diet, may lead to marked pigmentation of the skin. In **chronic lead-poisoning**, the characteristic "blue line" on the gums along the roots of the teeth is due to the formation of lead sulphide, and is most marked where attention is not paid to cleanliness of the teeth.

(*c*) **Pigmentation due to foreign particles introduced through the skin.**—Perhaps the best example of this is in **tattooing**, where insoluble pigmentary substances such as carbon (*e.g.* in the form of gunpowder, or Indian or Chinese ink), Prussian-blue, vermilion, etc., are intentionally introduced through small punctured wounds in the skin. In such cases some of the pigment may be carried by phagocytes and deposited in neighbouring lymphatic glands. Similar pigmentation may follow from the penetration of unburned grains of gunpowder in explosions, or from the firing of blank cartridge. In persons following certain occupations, *e.g.* miners, chimney-sweeps, engineers, etc., from lack of proper attention to cleanliness, dirt particles may become rubbed into or "ingrained" in the skin.

POST-MORTEM CHANGES

Under this heading may be classified the occurrence of *rigor mortis*; softening of the tissues from autolysis and from putrefaction; *post-mortem* discolouration of the tissues, gas-production, etc.

RIGOR MORTIS is a stiffening of the dead body, due to the

hardening and shortening of its muscular tissues. It is said to supervene first in the muscle of the heart, but the earliest superficial evidence of it is usually to be found in the muscles of the face, the rest of the body becoming involved, roughly, from above downwards, and the condition tending to pass off again in the same order. The cause of the phenomenon is the coagulation of certain protein substances—the globulins **myosinogen** and **paramyosinogen**, which are present in the muscle-plasma—perhaps under the influence of an enzyme, which, however, has not yet been isolated. These two substances become coagulated to form **myosin** or **muscle clot**, a reaction which is hastened by the presence of lactic acid in the muscles. The period after death at which *rigor mortis* may supervene is extremely variable, and depends upon many factors, such as the duration, rapidity, and nature of the illness preceding death. It usually appears in from one to seven hours after death, and may pass off in a day or two. In cases of tetanus, or of strychnine poisoning, and in some of the acute infective fevers, it may supervene almost immediately after or even before actual death has taken place. It also occurs very rapidly in individuals dying after severe muscular exertion, owing to the large amount of lactic acid present in the muscles; and it is usually more marked in muscular individuals than in those who are ill-developed or wasted. In other conditions, *e.g.* death from hæmorrhage, its appearance may be greatly delayed, or it may be very slight, or even absent. As a general rule, the more rapid its onset, the more quickly does it disappear, and *vice versa*. In all probability its disappearance is due to the softening of the myosin clot under the action of autolytic ferments, which will be discussed later.

POST-MORTEM SOFTENING OF THE TISSUES.—This process may be brought about by two sets of substances, viz. the bacterial and the autolytic tissue ferments or enzymes; and it may be inhibited by destroying or preventing the development of these substances, *e.g.* by heat, or by chemical preservatives, such as formalin, corrosive sublimate, alcohol, etc.

The normal process of putrefaction occurring in organic matter consists in the splitting up of the more complex into simpler chemical substances, by the agency of the bacteria of putrefaction. These act upon the tissues by means of proteo-

lytic and other digestive ferments, the processes being in many ways similar to those occurring during animal digestion.

Such putrefactive processes may occur with great rapidity after death, and are aided by warmth, moisture, and the ready access of putrefactive organisms. They occur early in cases of death from septicæmia, and where the organisms enter the blood-stream and tissues before death. Such organisms are always present on the surfaces of the body and in certain parts of the alimentary canal, especially the mouth and intestines; and putrefactive changes are generally found first in these regions, and particularly in the abdomen.

Putrefaction is usually accompanied by the production of gases such as sulphuretted hydrogen, which may act upon the blood present in the tissues, and produce certain colour phenomena referred to in the next section. Gas bubbles are also frequently found in the vessels, for example on the surface of the brain. These are due to decomposition products, and should not be mistaken for air embolism (*q.v.*).

Softening of the tissues after death also occurs from the action of certain ferments which are developed from the tissues themselves, quite apart from the presence of bacteria. Thus, if pieces of tissue are incubated under aseptic precautions, they become softened and disintegrated from the action of these so-called **autolytic ferments**, the earlier stages of the process very much resembling what is seen in cloudy swelling and in necrosis. The phenomenon known as the "ripening" of meat, and also the disappearance of *rigor mortis* in muscle, appear to be due to the action of these autolytic ferments, and occur even if bacterial action is prevented, *e.g.* by suitably lowering the temperature.

While discussing these *post-mortem* autolytic phenomena, mention may also be made of what is known as **post-mortem digestion** of the stomach, the wall of which organ may, after death, become extensively thinned and even perforated by the action of the gastric juice, especially if death has occurred during active digestion. A similar *post-mortem* auto-digestion by means of the normal ferments of its own secretion is specially liable to occur in the pancreas.

The naked-eye and microscopical alterations produced in the tissues by these bacterial and autolytic ferments must be

constantly borne in mind in the examination of *post-mortem* specimens, and it is sometimes extremely difficult to differentiate between these alterations and the changes produced by bacterial and other toxins in disease, both conditions being usually combined in varying degree.

For descriptions of the putrefactive changes which occur in the intestines during life, *e.g.* the production of indol, skatol, sulphuretted hydrogen, etc., reference should be made to works on Physiological Chemistry; similarly, the series of decomposition changes which occur at various periods after death will be found in text-books on Medical Jurisprudence.

GAS-PRODUCTION IN THE ORGANS OR TISSUES.—Reference has already been made to the production of sulphuretted hydrogen by putrefactive bacteria in the alimentary canal. Gas may also be produced in the tissues by the action of special gas-forming organisms, e.g. *Bacillus aerogenes capsulatus*, the *Bacillus of malignant œdema*, etc.

POST-MORTEM DISCOLOURATION OF THE TISSUES.—When blood-pigment is extensively liberated from the red corpuscles by putrefaction, it may soak out through the vessel-walls and stain the neighbouring tissues. After death from septicæmic diseases this usually occurs very early, and the cutaneous veins may frequently be seen marked out on the surface of the body as reddish or greenish-red lines. Similarly, the tissues and organs, *e.g.* the liver, spleen, kidneys, etc., may show a diffuse red staining; and a like phenomenon may be observed in the endocardium and inner coats of the aorta, pulmonary and other vessels. It should be noted, however, that such diffuse blood-staining may occur from blood destruction in toxic and septicæmic cases, quite apart from *post-mortem* decomposition.

Again, the greenish *post-mortem* discolouration so frequently seen in the skin, usually commencing over the abdomen, is due to the action of the sulphuretted hydrogen, liberated during putrefaction, upon the still undecomposed hæmoglobin of the blood. Similarly, the dark slate-blue, dark greenish, or almost pure black discolouration (**Pseudomelanosis**) so frequently seen on the surface of the abdominal organs, and even penetrating their substance for a considerable depth, especially in the case of the liver and spleen, is due to sulphuretted hydrogen generated in the intestines, acting upon the iron of the

hæmoglobin after that pigment has been broken up, the black sulphide of iron being formed. In certain circumstances this black or greenish-black discolouration may occur during life, *e.g.* round inflammatory, and especially round and in gangrenous foci or areas.

Pigmentation, or, more accurately, **discolouration** of the skin and mucous membranes, may be produced **by certain coloured parasitic fungi**; for example, one of the black moulds, *Mucor niger*, which causes a black discolouration of the lingual papillæ. Some of the coloured *aspergilleæ* are also sometimes pathogenetic in man; for example, *Aspergillus niger*, the cause of **aspergillar mycosis**, which may attack the outer and middle ear, nose, mouth, etc. The *Microsporon furfur*, which causes **pityriasis** (or **tinea**) **versicolor**, produces a brown or brownish-yellow discolouration of the skin, and has not yet been definitely classified.

CALCIFICATION

(*Synonyms.*—**Calcareous Degeneration, Calcareous Infiltration, Petrifaction.**)

Calcification is a process characterised by the deposit in the tissues of insoluble salts of calcium and magnesium, more especially calcium phosphate and carbonate, the process being usually **a consequence of other degenerative conditions.**

The changes found in calcareous degeneration must be carefully distinguished from the process of ossification in normal growing bone, and even in pathological bone formation, processes in which the laying down of the calcium salts is carried out as a special function of the bone-forming **cells** of the part, and in which, as pointed out by Klotz,[1] there is nothing to indicate any connection between this process and the formation of the fatty substances, the presence of which he considers an essential preliminary to pathological calcification.

The process of calcification is of extremely common occurrence in dead or degenerated tissue within the living body, not only in man, but in most of the lower animals, especially the herbivora. In old age, calcification of the costal and

[1] Klotz, "Studies upon Calcareous Degeneration," *Journal of Experimental Medicine*, 1905, vol. vii.

laryngeal cartilages and of the coats of the arteries is very common, and to a certain extent may almost be regarded as a normal senile change; but in some individuals, as the result of increased strain or from chronic inflammatory or other causes, the process may take place abnormally early, or to an excessive degree. It may occur at any age in a weakened and damaged tissue—especially in fibrous tissue—which has been the seat of inflammatory or degenerative changes, for example in the coats of blood-vessels which have been attacked by atheroma or other form of arteriosclerosis; and similarly, it may be found in heart valves which have been subject to long-continued and abnormal strain, or which have been the seat of chronic endocarditis. In these situations, it is almost certain that the deposit of lime and other salts always **supervenes upon some other degenerative change**, most commonly **fatty degeneration**, though in the vessels it may also follow **hyaline degeneration.**

Calcification may also be found in old hæmorrhages; thrombi (*e.g.* as "phleboliths," etc.); in the remains of inflammatory exudations, for example in the pleura or pericardium, where these have undergone incomplete absorption. One of the commonest sites of the process is in old tubercular lesions, for example in old caseous foci in the lungs, old caseous tubercular glands, etc. It may be found in any area of degenerating and dead tissue within the living body, for example in old infarcts; in the dead and retained fœtus *in utero* ("lithopædion"); in some tumours (*e.g.* in myomata, as the so-called "womb-stones"); in dead parasites, and even in portions of living ones (*e.g.* in the capsule of *Trichina spiralis*); and in and around included foreign bodies. Calcification is an important agency in the production of **calculi** in various situations, for example in gland ducts, or in hollow organs, *e.g.* in the case of Vesical, Biliary (Gall-stones), Renal, Intestinal, Salivary, and Pancreatic Calculi. Many of these calculi start originally as small collections of inspissated mucus, degenerated cells, inflammatory products, etc., these becoming first infiltrated and then surrounded by consecutive layers of lime or other salts. In the same way, urinary or other crystals, foreign bodies, etc., may act as "nuclei," around which calculi may be formed by accretion of lime, often mixed or alternating with other sub-

stances, *e.g.* with uric acid, urates, etc., in the case of urinary calculi; or with cholesterin, bile-pigment, etc., in the case of gall-stones.

Effects of Calcification on the tissues.—Heart valves, arteries, tendons, etc., affected by the change, become more rigid, and may show a loss of elasticity and an increased brittleness which may render them liable to rupture. The affected parts become hard, white or whitish-yellow, and opaque in appearance; the lesions are often rough and gritty or nodular to the touch, and arrest the knife on section. In the case of calcification of old tubercular areas in the lung, or of old caseous bronchial glands, there is often deeply pigmented fibrous tissue mingled with or surrounding the calcified areas.

Chemical and Staining Reactions in Calcareous Degeneration.—Calcium and magnesium phosphates are soluble in dilute acetic or hydrochloric acid **without** the evolution of carbon dioxide gas; whilst the corresponding carbonates are also freely soluble in these acids, **with** the production of this gas.

Microscopically, when unstained, the deposit usually shows as an aggregation of small refractile granules or masses, dark by transmitted, and white by reflected, light.

Hæmatoxylin produces with calcium salts, if these be present in sufficient amount, an intense bluish-black colour, the salts being usually in the form of fine dust-like granules.

Klotz finds von Kossa's silver impregnation method the most delicate test for calcium salts; but, as the reaction is chiefly limited to the calcium phosphate, he recommends the preliminary conversion of the calcium salts into chromate, the calcium being then replaced by silver, and the silver chromate thus obtained blackened by exposure to sunlight.

Mechanism of the process.—Among the older theories as to the method by which the process of calcification is produced, may be mentioned that of Virchow, who thought that in old age, and also in certain diseases, there occurred a solution or absorption of lime salts from the atrophying bones, and a consequent excess or over-concentration of these in the blood, followed by their deposition in the calcifying areas—a process of "metastatic calcification." Lancereaux believed that this supposed supersaturation of lime salts in the blood was due to defective excretion of these by the kidneys. There is no

experimental evidence that any such "supersaturation" actually occurs, and, in 1881, these theories were superseded by the views of Litten, who pointed out the predilection which certain tissues and substances, for example dead or degenerating tissues, possess for lime salts; and he cites, as an example, the calcification which may occur experimentally in necrotic secreting cells, and in casts formed by the fusion of these in

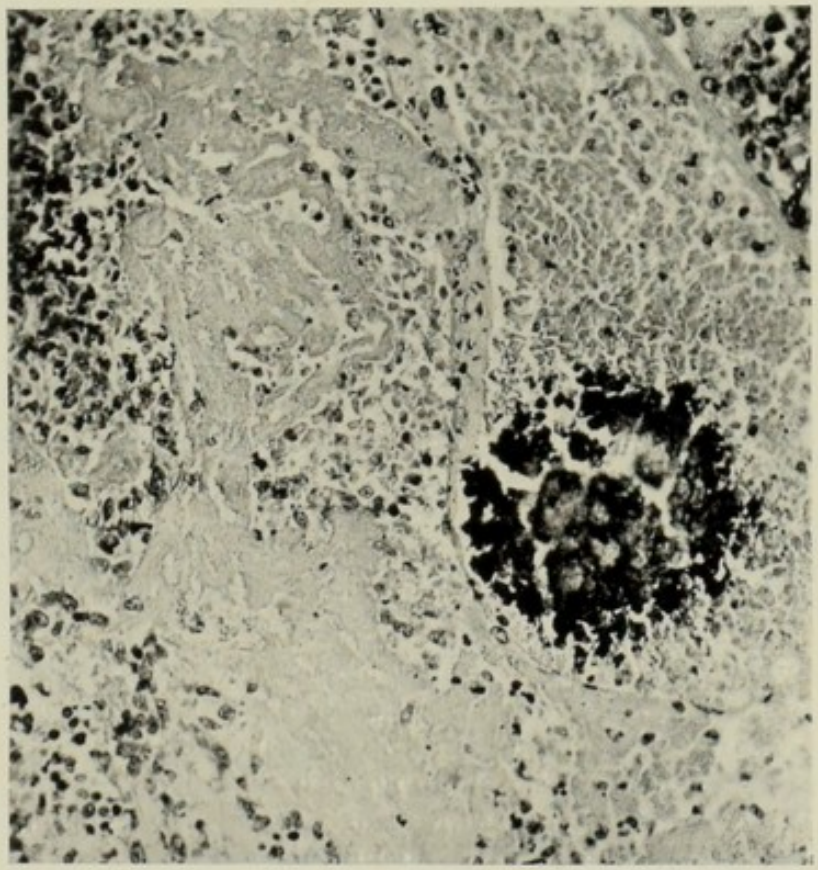


FIG. 14.—Area of Calcification occurring in a necrotic area in a sarcoma. The calcareous particles are stained very dark with hæmatoxylin.

the tubules of the kidney—a process which may occur in chronic renal disease, but which is specially found in connection with corrosive sublimate poisoning, a point confirmed by Lyon and other observers.

Litten believed that a "coagulation necrosis" of the cells forms a necessary preliminary to calcification, the dead and altered protoplasm possessing a special affinity for, and fixing in insoluble form, the soluble lime salts of the blood and lymph.

That some degenerative condition of the tissue is a necessary

preliminary to calcification is practically certain, as even a large excess of lime salts in the food or blood will not produce the calcification of healthy tissues. Greenfield and Lyon [1] state that "the old view, that an antecedent fatty degeneration was necessary, cannot now be maintained, as it is not essential that any such degeneration should precede the deposition of lime salts." The most recent work on this subject has been done by Klotz, whose investigations were undertaken to determine, histologically and experimentally, the organic substance present in degenerating tissues with which lime salts entered into combination; and the general conclusion to which he comes from his experimental work on animals, and from the analysis of degenerating human tissues, is that calcareous degeneration is preceded or accompanied by the deposit in them of fatty material, usually in the form of soaps. This soap, he states, exists in chronically inflamed tissues, or, if lime is already to be found in the tissues, the soap appears in the peripheral zone of the calcareous infiltration. The stages of the process, according to Klotz, appear to be as follows:—

1. Calcareous infiltration is preceded by a degeneration of the affected tissue, characterised by the presence of neutral fats, fatty acids and soaps, which stain with Sudan III.
2. By employing appropriate methods, *e.g.* on treating with petroleum ether, the microscopic fat and fatty acids can be removed, and the soaps remain behind, the last named being detected by reason of their differential staining with Sudan III.
3. The granules in certain regions which give the soap reaction with Sudan III, give also the calcium reaction with silver nitrate.
4. As the process of calcification advances, many of the masses deposited in the part no longer stain with Sudan III, but only react for calcium salts.

From the above data Klotz makes the following deduction as to the sequence of events:—

(*a*) The occurrence of degeneration in the affected region, with deposit of **fatty globules**; (*b*) the splitting off from these of the **fatty acids**, which then combine with alkalies to form **potash** and **soda soaps** (these being probably in combination with albumin as "**soap-albumins**"); (*c*) the gradual replacement of the potash and soda by calcium, and the formation of **insoluble calcium soap**, still

[1] Greenfield and Lyon, *Chapters in Pathology*, 1905, Green & Sons, Edinburgh, p. 23.

probably in combination with albumin (or in some instances it is possible that the fats may be attacked directly by the calcium salts); and (*d*) the gradual absorption and disappearance of the fatty moiety of the calcium soap-albumin, owing to the interaction of this with substances in the blood and lymph containing phosphoric and carbonic acids—highly **insoluble calcium phosphates** and **carbonates** (still perhaps in combination with the albuminous element of the original compound) being formed, and the soluble sodium and potassium soaps being liberated.

We give the above *résumé* of the views of Klotz upon this important subject in some detail, as his work has recently attracted considerable attention. Until these views have been confirmed by further research, however, it is impossible to definitely affirm that his deductions are accurate.

NECROSIS AND GANGRENE

In studying these subjects, it is of the greatest importance to remember the part played, not only by the active causal agent, but also by the tissue acted upon. Both necrosis and gangrene may be brought about in perfectly healthy tissues by some powerful physical, chemical, or toxic agent; but they are most frequently seen, and much more readily occur, in tissues whose resisting power is lowered from any cause. Further, certain tissues are more resistant than others. Causes which give rise to marked destructive changes in the brain or in highly functioning secreting cells, would have little or no effect on such tissues as skin, connective tissue, or bone. In order that a tissue, the cells of which are well nourished and possessed of an average functional capacity, may die, the causal agent must be an active one, and one of no inconsiderable strength; but, on the other hand, a very slight cause may bring about extensive destruction in a tissue imperfectly nourished, the resisting power of which is in consequence much diminished.

NECROSIS

Virchow applied the term **necrobiosis** to the gradual death of individual cells or groups of cells in the living body, this death being the result of retrograde and degenerative processes; while the term **necrosis** was applied to conditions in which the

death was more rapid, and directly followed some definite cause. The term **necrosis** is now commonly used for both conditions, and we may define it as the death and degeneration of single cells or of larger or smaller groups of cells together with corresponding changes in the intercellular elements within the living body. This death is indicated by the cessation of function, or by some structural or chemical alteration, visible, it may be, to the naked eye, or only with the aid of the microscope.

Causes of Necrosis :—

1. **Arrest of the Circulation.**—For the healthy nutrition and for the growth and development of any tissue, it is essential that its blood-supply should be satisfactory; and therefore any factor which interferes with the normal circulation in a part will be a cause of degenerative processes; and if that factor brings about an absolute arrest of the blood-supply, **necrosis** may follow. This will certainly be the result if the arrest of the circulation be permanent; but even with temporary arrest, extensive necrotic changes may be produced. Litten has shown that, in rabbits, ligature of the renal artery, for from one and a half to two hours, is sufficient to produce a necrosis of the greater part of the highly functioning epithelium of the secreting tubules, although the circulation afterwards becomes perfectly re-established. Highly functioning and delicate tissues suffer more rapidly and more severely from alterations in the arterial supply than do the more resistant, supporting and other tissues. Temporary arrest of the circulation may cause extensive necrotic changes in secreting cells or in the brain tissue, whereas it would have no appreciable effect on the skin, on connective tissue, or on bone. The degree and extent of the necrotic change depend upon the amount of collateral circulation, and on the rapidity with which it is set up. In organs, *e.g.* the lung, where there is an extensive anastomosing blood-supply, necrosis from obstruction of an artery is rare; whereas in organs, *e.g.* the spleen, where the anastomosis is feeble, and where we are dealing with the **end-arteries**, necrosis invariably follows.

The arrest of the circulation may be brought about in various ways, *e.g.* by thrombosis; embolism; pressure from without by ligature, tumours, aneurisms, or inflammatory exudations; or

by spasmodic contraction of the vessels produced by chemical agents or by nervous influences.

Thrombosis.—The effects of this are well illustrated in the condition of senile gangrene, where, with a feeble circulation, there are extensive degeneration and narrowing of the arteries. But similar results may follow thrombosis from other causes.

Embolism.—Necrotic areas, following the impaction of emboli in the arteries, are seen frequently in the spleen and kidney in cases of cardiac disease, especially in those cases in which there are loose, easily detached vegetations on the valves, or where there are thrombi in any of the chambers of the heart.

Spasmodic Contraction of the Arteries.—A symmetrical necrosis of the fingers and toes occasionally follows the spasmodic contraction of the arteries in chronic ergot-poisoning and in Raynaud's disease.

2. **Physical and Chemical Agents.**—Necrosis may undoubtedly be caused directly by prolonged or excessive pressure, especially if the vitality of the part be lowered. Bed-sores in debilitated people or in those suffering from nervous diseases, *e.g.* acute myelitis or hemiplegia, are the most familiar examples. No doubt, in most of these cases lowered vitality and diminished sensation play a very important part, but it is certainly the pressure which is the ultimate cause of the necrosis, for it is over the parts that are exposed to its action, *e.g.* the sacrum, the iliac crests, the trochanters, the internal condyles of the femur, and on the heels, that bed-sores develop; and by careful attention in minimising or preventing the pressure, the sores may be avoided. It must also be admitted that necrosis of healthy tissues may be caused by severe crushing injuries, but, in the great majority of cases of necrosis following pressure, the principal factor is interference with the blood supply by laceration or thrombosis of the vessels. Much of the necrosis following severe crushing injuries is secondary to damage of the arteries of the part. In the necrosis following tight bandaging, the obstruction of the arterial supply is the principal, if not the only, cause.

Chemical Agents.—Mineral acids, carbolic acid, and other caustics and corrosives act directly upon the tissue cells, causing their degeneration or death; while other chemicals

such as ergot act on the arteries, causing contraction; and, if this is prolonged, necrosis results.

Temperature.—Extreme degrees of heat and cold are in themselves directly injurious to cell-life, and may therefore cause necrosis; but in the great majority of such cases, the high or low temperature acts by causing contraction of the arteries, or by injuring the tissues to such a degree that arterial thrombosis takes place, and the necrosis is, in part at any rate, a secondary result of the vascular alterations. The time of exposure, the intensity of the heat or cold, and the condition of vitality of the tissues, are all important factors in determining the degree of the resulting destructive changes.

By direct experiment, Cohnheim has shown that if the ear or the leg of a rabbit be plunged for a comparatively short time into water at a temperature of 54° to 58° C., or into a freezing mixture at −16° to −18° C., the part perishes irrecoverably. On the other hand, these parts may be kept at a temperature of 42° C., or in a freezing mixture at −1° to −2° C. for several minutes, without any permanent change taking place. There may be slight hyperæmia, which soon passes off; but if, on the other hand, they be kept at these more moderate temperatures for several hours, more or less extensive necrosis will follow. Again, moderate degrees of heat or cold, while not in the least injuring healthy tissues, may cause necrotic changes in tissues whose vitality is lowered. This is seen in the bed-sores which sometimes follow the application of hot bottles to the limbs of patients suffering from myelitis or other diseases where the nutrition of the skin and other tissues is lowered.

Electricity and Radio-active bodies.—These probably act directly upon the tissue elements. Necrosis of the skin is not infrequently seen after undue exposure to Röntgen rays, or after the prolonged application of the electrode of the galvanic current. Exposure to the action of radio-active substances may produce a similar result.

3. **Bacteria and their Products.**—These play a very important part in the production of necrotic changes. Sometimes the poison generated is so intense that the cell is killed outright, but in other cases the degenerative and necrotic process is more gradual, and the tissues affected undergo very obvious altera-

tions in their chemical characters and in their staining reactions. The area of necrosis may be comparatively large, or the effect of the toxin may be seen throughout the tissues and organs of the body, and may affect specially the more highly functioning cells. The latter condition is seen in the necrosis of the cells of the secreting tubules of the kidney or in the liver in many infective diseases, while the former is illustrated in the wide-spread necrosis of the epithelial cells of the pharynx

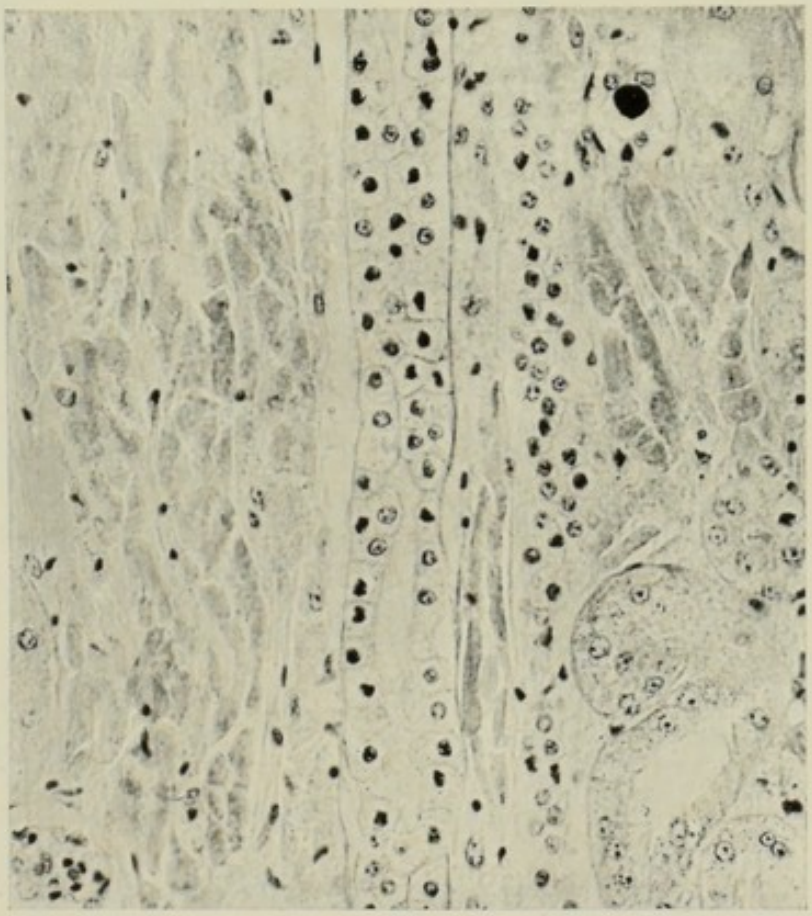


Fig. 15.—Necrosed tubules in the Kidney, showing absence of nuclei in the majority of the cells of the secreting tubules. ×300.

brought about by the action of the diphtheria bacillus and its toxins. In many cases there are multiple areas of necrosis—**focal necrosis**—in various organs. These are best studied in the liver, but they may be found in the kidney and the spleen, and sometimes in certain of the supporting tissues. These areas may be visible to the naked eye, or may be microscopic in size. They are of common occurrence in typhoid fever, but are also found in diphtheria, in puerperal septicæmia, and

probably in most bacterial infections. They may result in consequence of the direct action of bacteria, but probably are most commonly caused by certain soluble toxic substances produced by the bacteria. In many cases the most careful examination fails to demonstrate the presence of any bacteria in these areas. Welch and Flexner have shown that they may be produced by the injection of diphtheria toxin. On the other hand, it has been shown by Mallory[1] that the areas in the liver in typhoid fever may be due to a thrombosis of

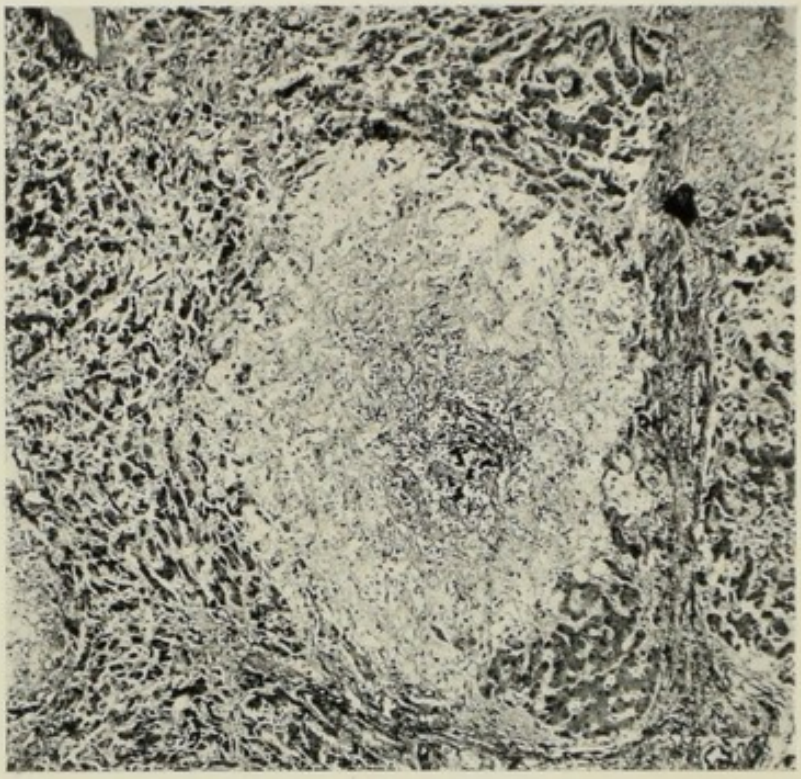


FIG. 16.—Liver, showing a pale area of focal necrosis. ×150.

capillaries, caused by the formation of fibrin round intra-vascular phagocytic cells derived from the endothelium of the vessels.

4. **Vegetable Toxins and Ferments.**—Necrosis, similar to that produced by bacterial toxins, may be brought about by certain vegetable poisons such as **ricin** and **abrin**.

Fat-Necrosis, which is specially seen in the pancreas, the omentum, and the mesentery, is caused by the direct action of the fat-splitting ferment of the pancreas. Langerhans and others have produced the condition experimentally by the

[1] Mallory, *Jour. Exp. Med.*, iii., 1898.

injection of pancreatic extract into the peritoneal cavity; whilst Flexner[1] has isolated the fat-splitting ferment from the necrotic areas, and has produced typical fat-necrosis by the introduction of steapsin into adipose tissue.

5. **Nerve Lesions.**—Brief reference has already been made to the production of bed-sores by pressure, in cases where there is diminished vitality of the part and loss of sensation. Though, in such cases, the ultimate cause of the necrosis is pressure, yet the nerve lesion is a very important causal factor; and in some cases of acute transverse myelitis, the necrosis develops so rapidly that it can hardly be the result of pressure alone, and we must look for the direct and ultimate cause in the disturbance of the trophic and vasomotor innervation. This condition is known as **acute decubitus.** Section or disease of the peripheral nerves may lead to necrosis. The **perforating ulcer of the foot** in locomotor ataxy is a familiar example, as is also the ulceration of the cornea which follows paralysis of the fifth cranial nerve. **Anæsthetic leprosy** leads to extensive necrosis and ulceration, but this cannot be attributed to the nerve lesion alone. The anæsthesia exposes the parts to all forms of external injury and to organismal infection, which must play a considerable part in the production of the necrotic process.

Intense Inflammation.—In some cases of intense inflammation, a part may be cut off from its nutrient supply. The sloughing of large portions of the mucous membrane of the intestine in dysentery, or the separation of areas of the mucous membrane in typhoid fever, are examples of this, and the same condition is seen in the necrosis of the subjacent bone where the periosteum is separated from it by inflammatory exudations. In these forms of necrosis, there are probably at least two of the causes already stated working together, viz. (1) the obstruction of the arteries by thrombosis, and (2) the direct action of bacteria and their products upon the tissues.

All these causal agents in the production of necrosis may act directly on the healthy tissues, but they are undoubtedly greatly aided by a condition of lowered vitality, such as is produced in some acute diseases, *e.g.* typhoid or typhus fevers, or which may follow degenerations in the nervous system, or which are the

[1] Flexner, *Jour. Exp. Med.*, ii., 1897.

result of senile changes in cases where the heart is weak and the vascular system degenerated.

Variations in the resisting power of different individual tissues must also be considered. If the blood-supply of a part is permanently cut off it inevitably dies, but if the obstruction is only temporary, one portion of an organ may undergo extensive necrosis, whilst another may be wholly unaffected. Ligature of the renal artery in rabbits, for from one and a half to two hours, causes extensive necrosis of the secreting epithelium, whilst the connective tissue structures may remain uninjured. Portions of the brain and of the intestine undergo very rapid degenerative changes, with loss of function, soon after their blood-supply is interfered with; while the skin, fibrous tissue, and muscle may be wholly deprived of their nutrient supply for many hours without any interference with the performance of their metabolic processes.

Changes which occur in the necrosing tissue.—Different tissues suffer from these necrotic changes in varying degrees. Highly functioning cells, such as those of the secreting tubules of the kidney or those of the liver, undergo the necrotic changes much more readily than do the less highly organised fixed connective tissue cells, the cells lining the collecting tubules of the kidney, or the cells lining the capillaries.

In necrosing tissue, the most characteristic changes are those occurring in the cell; but as these have already been fully described in a previous chapter, only brief reference will be made to them here. The chromatin substance of the nucleus may undergo a gradual solution (**karyolysis** or **chromatolysis**), and eventually it completely loses its reaction to nuclear stains. In other, and perhaps the majority of cases there is a preliminary fragmentation (**karyorrhexis**). In this form of cell-degeneration, the chromatin breaks up into a number of irregular granules, which, after the destruction of the cell-body, may become scattered in the necrotic focus, eventually undergoing solution and disappearing. The cytoplasm of the cell becomes swollen and homogeneous, and loses its normal reticulated appearance. This is apparently due to an absorption of fluid from the surrounding lymph, the substances absorbed being probably certain of the coagulable albumins. In some cases the cytoplasm becomes swollen and vacuolated, and shows

a more reticulated structure. One of the commonest changes is a gradual loss of the sharp contour of the cells, and a blending and obliteration of the cell-boundaries. The **fibrous** and **muscular** tissues, though not suffering so rapidly as the more highly functioning cells, also undergo the necrotic change. They become swollen and homogeneous in character, and present the appearance of tissues undergoing hyaline degeneration, although they may not give its characteristic reactions. The muscle-fibres soon lose their striation and may become fragmented. Depending to a considerable extent upon the site at which these changes take place, the cause of them, and the

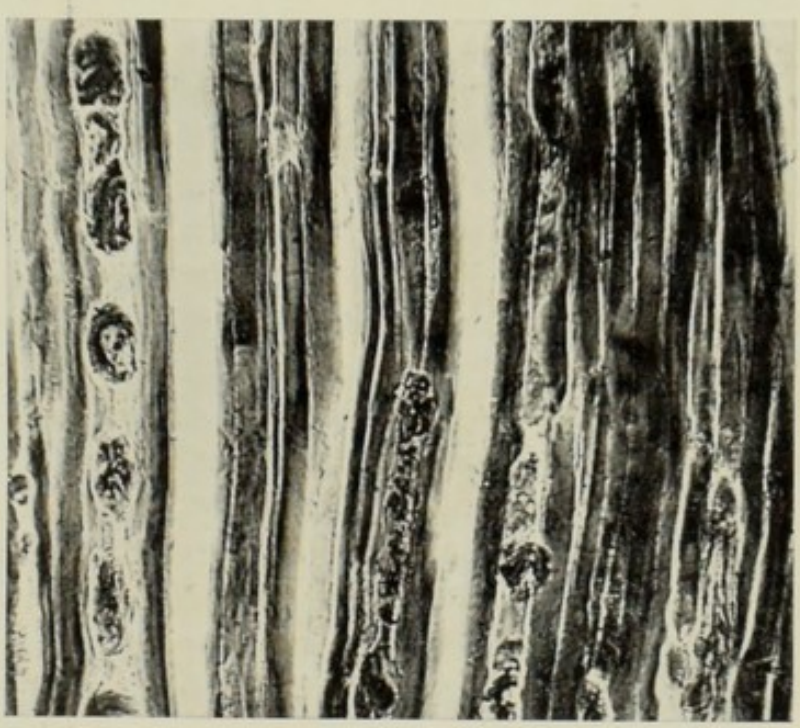


FIG. 17.—Zenker's degeneration of Muscle, showing the homogeneous character of the necrosing muscle fibres. × 50.

condition of the tissues at the time, different appearances are presented. These have been divided into three main groups :—

(1) Coagulation Necrosis.
(2) Colliquative Necrosis.
(3) Caseation.

Coagulation Necrosis.—Zenker's degeneration of muscle-fibres is a form of coagulation necrosis, but the condition is more typically illustrated in the degeneration which takes place in infarcts in the kidney and spleen. The same change is pro-

duced by various toxins, and is illustrated in the necrosis of the epithelial cells of the pharynx in diphtheria. The affected part is usually dry and more or less homogeneous or granular. It is opaque in appearance and of a pale-greyish colour. These characters are well shown in the small areas of necrosis seen in the fatty tissue of the mesentery, following some cases of acute pancreatitis.

The chemical processes by which this form of necrosis is brought about are still far from being satisfactorily explained, but in many cases, as stated by Alex. Schmidt and by Weigert, a true coagulation takes place. There appears to be formed, during the necrotic process, and probably from the degenerating cells, a nucleo-protein substance of the nature of a fibrin ferment. This unites with fibrinogen normally present in the surrounding lymph, and gives rise to the formation of fibrin, or at any rate to a coagulable albuminous substance, which in many cases gives a positive reaction to Weigert's fibrin stain. Cohnheim states that necrosis with coagulation occurs only — (1) when the dead part contains an abundance of coagulable material, and (2) where it is everywhere intimately bathed with lymph.

Colliquative Necrosis. — In this form the necrotic tissue undergoes softening and liquefaction, a process certainly occurring primarily in tissues that are deficient in the coagulable albumins which are concerned in fibrin formation. The brain and spinal cord are particular seats of this form of necrosis, infarcts in these tissues regularly undergoing softening, and the dead tissue becoming converted into a soft semi-fluid mass. The colour of this softened area, at first pale, may become red or brown or yellow, from the admixture with it of pigment from the blood or from the bile. Such secondary softening may also occur in areas of coagulation necrosis. Polymorphonuclear and other leucocytes may secondarily invade the softened area, especially if it become infected by micro-organisms, and thus pus may be formed; but the primary condition is degenerative and non-inflammatory, and must be carefully differentiated from suppuration.

Caseation.—Both coagulation necrosis and colliquative necrosis are really **secondary** changes in the degenerated tissue, and are therefore, strictly speaking, **post-necrotic**. Caseation is, however, still more definitely a **post-necrotic** change. The affected

tissue becomes more or less firm, dry, and of a greyish-white or pale-yellowish appearance, resembling various forms of cheese. The original structure of the tissue is entirely lost, cell outlines cannot be detected, nuclei have lost their capacity for taking up basic stains, and all the affected tissues are converted into a granular amorphous mass.

Caseation occurs especially in tuberculous areas, and is the classical form of degeneration caused by the *Bacillus tuberculosis*

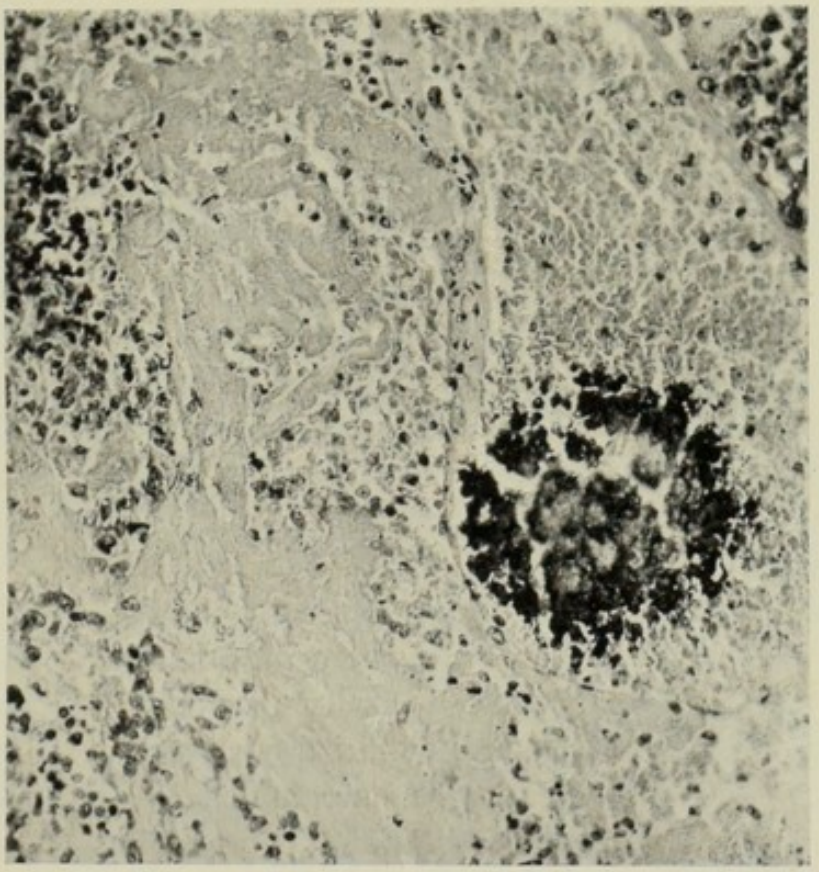


Fig. 18.—Necrosis in a Sarcoma, showing loss of nuclear staining power, indefinite outline of cells, and a rounded area (dark) of calcification.

and its products. It also occurs in *syphilis*, and is common towards the central parts of rapidly growing tumours. It may also follow coagulation necrosis.

Sequelæ of the Necrotic process.—If the necrosed area is on a skin or mucous surface, it becomes separated from the living tissues, is cast off as a slough, and leaves an irregular ulcerated area. This is well seen in ulceration of the leg accompanying varicose veins, and also in typhoid and tuberculous ulceration of the intestine. The sloughing is in many cases aided by septic

organisms which have secondarily gained access to the necrosed part. If the area is in the interior of a solid organ or in a position where separation cannot take place, there follows an attempt at absorption, more or less successful according to the nature and size of the area of necrosis to be removed. The dead part acts as a foreign body. Leucocytes, both polymorphonuclear and mononuclear, migrate from the adjacent vessels and invade the dead tissue. Many of these die, and their remains, as well as many still active leucocytes, form a zone round the area of necrosis. Later, these dead leucocytes, etc., become absorbed. New vessels, formed by budding from the adjacent vessels, grow into the necrosed area. These are accompanied by connective-tissue and other cells, which arise by proliferation of the endothelial and fixed connective-tissue cells of the part. The dead area, if it be small, may be completely absorbed and replaced by fibrous tissue, or there may be actual regeneration even of highly functioning and specialised cells. This regeneration seems to take place by the multiplication of the surrounding cells. If the dead area is larger, the absorption is generally incomplete, a central whitish or yellowish, caseous-looking area, surrounded by a zone of well-formed fibrous tissue, persisting—a condition well illustrated in some infarcts in the spleen and kidney. In these caseous-looking areas, lime salts may be deposited, or in them fatty acids, cholesterin, blood-pigments, triple phosphates, etc., may be found. If the necrosed area becomes secondarily infected by septic organisms, or if pyogenic bacteria are introduced by the causal agent, *e.g.* by an embolism following the detachment of a portion of a vegetation in ulcerative endocarditis, purulent softening and abscess formation may follow. In some cases where absorption fails, the dead part may be

FIG. 19. — Necrosis of bone, showing sequestrum (pale) in centre, surrounded by the "new case."

completely cut off from the living tissue, and, if the necrosed tissue is specially resistant, it may remain for a very considerable time practically unaltered in its structure, though around it a marked proliferation of the adjacent structures may be observed. The most typical example of this condition is seen in necrosis of bone, where the separated and dead part or **sequestrum** still retains to a large extent its normal microscopic structure, and is surrounded by a bony capsule—**the case**—which is a product of a formative periostitis.

GANGRENE

Gangrene may be defined as that condition of any of the tissues of the body in which there is **necrosis combined with putrefactive changes.** In many cases, the tissues undergo a primary necrotic change, and the bacteria which cause the putrefaction are introduced, generally from without, into the dead or dying tissue. On the other hand, there are cases in which the infective agent is the cause both of the necrosis and of the decomposition. In these latter instances—the forms of **primary gangrene**—we have to deal either with specific gangrene-producing bacteria, or with ordinary bacteria acting on devitalised tissues. Most writers have described two forms of gangrene—the **moist** and the **dry**; and though this is convenient, and practically essential from the clinical stand-point, the distinction has, we think, led to erroneous statements being made. Dry gangrene is regarded by many as a form in which bacteria are not present, and which is caused mainly, if not wholly, by arterial obstruction, while the moist form is held to be due to the action of infective agents. The difference between the two forms is in reality one of degree and of situation rather than of kind. Bacteria are found in *both* forms. If the tissues are devoid of moisture, or are in a situation where evaporation can readily take place, or, in some cases, if the degeneration and death be slowly produced, the form of **dry gangrene** is most likely to occur. Bacteria are present, but are, in the absence of moisture, in an unsuitable environment, and do not rapidly multiply. The classical example of this form of gangrene is the **senile gangrene** of the foot, in which the tissues become hard and dry, shrivelled, and **mummified.** The hæmoglobin in

the dead part is diffused through it and stains it a dark-brownish or black colour. If, on the other hand, the tissues contain abundance of moisture, or are in a situation in which evaporation cannot readily take place, or if the area be large and the gangrene rapidly produced, the **moist** form is found; and, as a natural result of the condition of the tissues, bacteria which were originally present, or which have been subsequently introduced, grow rapidly and produce secondary changes. The decomposition leads to the production of gases of various kinds, which often have a very foul odour. These, acting on the hæmoglobin or other pigments in the part, produce green or greenish-black discolouration. Poisonous products of various kinds are also formed, and very great destruction, with softening and complete disintegration of the tissues, results. The toxic products are absorbed into the general circulation, and may give rise to very marked degenerative changes in various organs of the body, or may cause the death of the individual. Moist gangrene usually occurs in tissues or organs naturally exposed to infection by saprophytic micro-organisms, *e.g.* the cutaneous surface generally, the lungs, the intestine, the mouth, and the external genitals.

Primary Gangrene.—In this form of gangrene, the infective agent is the primary cause both of the destructive and of the putrefactive changes. Certain bacteria, *e.g.* the *Bacillus of malignant œdema*, the *Bacillus aerogenes capsulatus*, and probably some other allied anaerobic organisms, produce direct death of the tissues, with abundant serous exudation and excessive gas production. The condition may spread very rapidly, and large areas may become converted in a very short time into a dark-greenish emphysematous mass, which is infiltrated with blood-stained serous fluid. If the nutrition of the tissues is impaired, this form of gangrene is more liable to occur. **Cancrum oris**, **gangrenous vulvitis**, and **hospital gangrene** are most probably due to some of the more common bacteria acting in very much devitalised tissues. The first two of these diseases are rapidly-spreading forms of gangrene, which are seen usually in ill-fed, unhealthy children who are living under bad hygienic conditions, or in children who are convalescent from some acute infective fever; whilst the third is a similar condition which sometimes attacks recent or granulating wounds.

The tissues at the seat of infection become swollen and very much inflamed, and in the centre an ash-grey slough appears. This soon separates from the surrounding inflamed tissue, and leaves an irregular, excavated, and foul ulcer. The sloughing spreads very rapidly; and, if the patient lives long enough, large areas of tissue are completely destroyed, the adjacent parts becoming involved to a greater or less extent.

In Secondary Gangrene there are putrefactive changes secondary to or consequent upon necrosis. In many cases, a primary obstruction of the arterial supply causes the necrotic change; and the bacteria which are present or which may be introduced from without, bring about the gangrenous condition. A good illustration of secondary gangrene may be found in strangulation of the intestine, where the arterial supply is obstructed. If the tissues be examined in the early stage, all the changes which have already been described under necrosis are found. Bacteria multiply very rapidly in the dead portion, and these or their products cause alterations in the blood-pigment, and consequent dark staining of the part. In the late stages, sloughing and gas-production, especially if the tissues are infiltrated with fluid, or the dry form of gangrene may occur. In the majority of cases, there is no difficulty in differentiating between the primary and the secondary forms of gangrene, but not infrequently it is almost impossible to make the distinction.

In certain acute infective fevers, *e.g.* typhoid, gangrene is occasionally a sequel of a disease in which the tissues have become devitalised, and in which the circulation may be very feeble. The typhoid bacillus may settle down in bone, periosteum, or elsewhere, and necrosis with gangrene may be the result; but in these cases, it must always be remembered that a very slight injury may have caused certain destructive changes which preceded the invasion of the bacteria, or that there may have been thrombosis in some of the smaller vessels, with consequent death of, it may be, very small areas of tissue.

Gangrene of the lung sometimes follows pneumonia. It may, however, appear independently and without previous consolidation, in which case we believe the gangrene to be always directly due to the invasion of dead or dying tissue by putrefactive or other organisms. In the brain, gangrene is always the result of the introduction of infective organisms generally from

the nose or ear ; and it may be quite impossible, in a given case, to say whether it is to be classified as primary or secondary.

The gangrene which sometimes occurs at the free ends of the nose, fingers, or toes must be regarded as almost always secondary. The tissues of the part have undergone degeneration owing to the impairment of the blood-supply, or because some of the vessels have become thrombosed, or because there has been injury to, and consequent destruction of, a tissue which is already very feebly nourished. This degenerated tissue becomes secondarily invaded by bacteria, and, dependent on the conditions present, either the dry or the moist form of gangrene may result.

Causes of Gangrene.—All those agents which bring about necrosis may also be the cause of gangrene, if organisms, especially those which produce putrefaction, gain entrance to the dead part. Bacteria may of themselves, however, be the cause of both the necrosis and the gangrene. As in necrosis, tissues whose vitality is lowered from any cause are most liable to become gangrenous. The gangrene occurring in old people is in many cases the result of thrombosis in vessels which have become much degenerated as a result of general senile changes; but there is present, in addition, a lowered resistance of the tissue, brought about by imperfect nutrition, partly, at any rate, in consequence of the arterial degeneration.

The gangrene which occurs in patients with **diabetes mellitus** may, in part, be due to some special factor of which we are at present ignorant, but there seems no reason to doubt that the abnormal metabolism which brings about such wasting of the tissues must, of itself, so weaken the tissue cells in general as to render them very susceptible to destruction by slight mechanical, chemical or other form of injury, and thus allow the occurrence of the necrotic and gangrenous processes.

Changes in the gangrenous part and in the surrounding tissues are of great importance. The gangrenous area may spread and gradually involve a progressively larger extent of tissue; or an inflammatory reaction on the part of the healthy tissue may be set up at its junction with the dead tissue, and thus there may be established a protective barrier of developing or newly-formed connective tissue—the so-called **line of demarcation.**

The spreading or diffuse form of gangrene is very commonly, if not always, due to an infective agent, is of the moist variety,

and develops very rapidly. Gangrenous, gas-containing bullæ are developed at various places, and a foul, penetrating odour is evolved. The diffuse spread of gangrene is also, however, not uncommonly seen in the dry, senile form. This must be attributed to the imperfect nutrition and consequent defective metabolism of the parts of the body affected. In fact, it may be taken as a general rule, that all necroses which are brought about in a healthy individual by causes other than by infective organisms, have a tendency to become circumscribed. The inflammatory zone may completely shut off the dead area, which may, if small, be finally absorbed or become enclosed in a well-formed fibrous envelope. Even in spreading forms of gangrene, this inflammatory zone develops, but it does so more or less imperfectly, and fails to act as a barrier to the rapidly-spreading destructive processes.

ATROPHY

The expression **atrophy** is a somewhat indefinite one, and is applied, occasionally rather loosely, to conditions where there is wasting of the organs and tissues, generally preceded or accompanied by certain retrograde processes in them, and usually characterised by diminution in their size, or even by their complete disappearance. It should be noted, however, that the special functioning tissue of an organ may undergo very extensive atrophy without a corresponding diminution in the actual bulk of the whole organ itself. This may, on account of other changes occurring in it, in some cases remain practically normal, or may even become increased in total bulk, *e.g.* in "waxy" or amyloid disease of the liver or spleen, where the swelling of the waxy connective-tissue elements leads to pressure-atrophy of the intervening parenchymatous cells.

The term **atrophy** must not, of course, be applied to conditions of arrested development (**hypoplasia**), or to complete congenital absence (**aplasia**) of an organ, *e.g.* of the thyroid gland in cretinism, or of one kidney. Nor should it, as is sometimes done, be made to include the active destruction of an organ by bacterial or other organisms or their toxins, *e.g.* such a case as the condition somewhat erroneously termed

Acute Yellow "Atrophy" of the liver, in which the hepatic cells are destroyed by the action of some as yet unknown, but highly virulent, toxic agent.

Atrophy may, in some instances, be wide-spread throughout all or nearly all the tissues of the body; but in other cases a single organ or tissue, or a special group of these, may be affected. In the latter case the condition is known as **local atrophy**, whilst to the former class of cases the term **general atrophy** is usually applied, though it should be noted that in such cases the various organs and tissues may, and generally do, undergo wasting in very varying degrees. Thus the central nervous system, the heart, and the kidneys are most resistant, and, as a rule, suffer least, though the two latter organs may in some diseases undergo very extensive atrophy; whilst, on the other hand, adipose and muscular tissue, the lymphatic glands, spleen, etc., are often affected more severely and at an earlier period. The bones are usually regarded as very resistant structures; but, though their hard surface-shell of compact bone may often show little change in shape and size, yet the contained bone-marrow and cancellous tissue sometimes exhibit a very extreme degree of atrophy, and there may even be considerable wasting of the compact bone itself.

Although the causes and results of general and of local atrophy are in the main similar, it is convenient to discuss them to a certain extent independently.

General Atrophy.—During the period of development and growth of the body, the anabolic or constructive processes are in marked excess over the katabolic or destructive ones. In the metabolism of adult life there should be a more or less approximate balance of these two sets of processes, whereby the nutrition of the tissues is as far as possible maintained *in statu quo* In old age, there is a natural and progressive diminution in the activity and vitality of the tissues, and a gradual falling off in their capacity for building up and maintaining themselves; the balance between the anabolic and katabolic processes gradually failing, not so much from an increase of the *latter*, as from the slow and progressive decrease in activity of the *former* set, whereby the reparative capacity of the tissues to make good the waste due to metabolism is diminished or lost. As a result, the condition of **senile atrophy**

or **wasting** supervenes. It is probable that, coincident with these changes, there is also, in old age, some diminution in the activity of the cells whose special function it is to regulate the development, and check or remove any overgrowth of the less highly endowed supporting tissues, and these may thus become abnormally increased in their relative proportions.

In some instances, what is known as **premature senility**, characterised by the abnormally early appearance of these atrophic and other senile changes, may supervene. In certain individuals this may be due to definite, ascertainable causes, such as intemperance, prolonged physical or mental strain, present or previous disease, etc.; but, again, its cause may be obscure; and, indeed, in some individuals and families there appears to be a hereditary predisposition towards its occurrence.

Certain factors, some of which have already been dealt with in the Chapters on the Physiology and Pathology of the Cell, are needful for the maintenance of tissue nutrition and for preserving the balance of the metabolic processes. Thus the **functional activities** of the various organs and tissues must be normal, and neither deficient nor excessive in degree or nature. **Nutriment** must be sufficient in amount and quality, and there must be no interference with its ingestion, digestion, and absorption. The alimentary canal and the digestive organs and secretions must be normal. Lymphatics, blood-vessels, and the blood itself must be healthy; and the trophic power of the tissues themselves must be sufficient to allow of their taking up and assimilating suitable nutriment when brought to them, discarding what they do not require, and excreting waste products,—subjects which have already been discussed when dealing with cellular metabolism and degeneration. An extreme degree of emaciation or general wasting may follow **starvation**, and may be due to actual deprival of food or of some essential food elements; it may occur from inability to swallow, *e.g.* in stricture of the œsophagus, or obstruction at the cardiac orifice of the stomach; or it may be produced by inability to digest and assimilate the food which has been ingested, *e.g.* in cases of gastric ulcer or carcinoma. Stricture of the pylorus, tubercular disease of the intestines, lacteals, or mesenteric glands, preventing the occurrence of intestinal absorption, etc., may also bring about very much the same results. In cases of

death due to actual starvation from absence of food, in addition to the general emaciation from lack of nourishment, there may also be the occurrence of a profound degree of wasting in the walls of the stomach and intestines, owing to the cessation of their normal functional activities.

Intestinal parasites may lead to the general emaciation of their host, not only from the digestive disturbances and irritation due to their presence and absorptive activities, but also, in some cases at all events, owing to the production by them of certain toxic products of their metabolism.

In cholera and in severe cases of prolonged diarrhœa, an extreme degree of general wasting occurs, and is due to a combination of the gastro-intestinal disturbance, toxic absorption, and the draining away of the body fluids.

In cases of chronic suppuration, albuminuria, glycosuria, etc., the long-continued loss of albumin, sugar, etc., may aid in producing degeneration, emaciation, and atrophy.

Nerve-control must be normal and its pathways intact, the central nervous system not only exerting a direct "trophic" influence upon the other body tissues, but also affecting their nutrition indirectly by regulating the amount of blood reaching them through the blood-vessels—the muscular coats of which are under the control of the vasomotor nerves and nerve centres—and also by regulating the actual functions of the tissues themselves. To take an example, paralysed muscle, *i.e.* muscle cut off from its nerve-supply, wastes, not only from loss of function, and consequent diminution in its blood-supply, but also from loss of neurotrophic influence.

The special secretions of certain glandular organs, *e.g.* the thyroid and the pituitary body, and also the subsidiary or "internal" secretions of the testes, ovaries, pancreas, etc., have a very important influence upon the general nutrition of the body tissues, as is well seen in cases where the thyroid secretion is absent, diminished, or perverted.

Age and **sex** are important factors in the problem of general nutrition, the atrophy of the sexual glands at the menopause in the female, and climacteric in the male often leading to marked changes, sometimes in the direction of an increase, sometimes of a diminution of the body-weight.

The presence or absence of disease, either local or general,

must also be borne in mind in dealing with the subject of atrophy. Certain bacterial and other toxins and poisons are a frequent cause of emaciation; and an extreme degree of bodily wasting may be found in cases of severe or long-continued fevers, tuberculosis, syphilis, diabetes, and in many other similar diseases. In patients suffering from, say, one of the acute infective fevers, emaciation may be due to a combination of (*a*) the direct injurious action of the toxin upon the organs and tissues, and the consequent impairment of their function and vitality; (*b*) the increased "combustion" or tissue waste and high temperature; and (*c*) the inability of the patient to take in, digest, and assimilate sufficient nourishment.

A certain degree of general emaciation may follow the exhibition of certain organic medicinal preparations, *e.g.* anti-toxic sera, thyroid extract, etc.

To some cases of general atrophy and emaciation, when these are not due to specific fevers, tuberculosis, or other obvious cause, the term **Marasmus** is sometimes applied. Such cases are of frequent occurrence in infancy, and are probably often due to the absorption of toxic substances generated in the alimentary canal.

Local Atrophy.—In some instances the condition of local atrophy may be found affecting an **individual** organ or tissue in whole or in part, whilst in other cases a **group** of similar or allied tissues may undergo atrophic changes. The latter of these conditions may in some instances be regarded rather as part of a more generalised process; for example, the atrophy of the lymphatic glands and lymphoid tissue generally, which is usually found in old age. In the former case, however, *i.e.* where the atrophy is restricted to a single organ, or to adjacent organs and tissues, a definite, localised cause may be demonstrable in some, though not in all instances.

Local atrophy may occur in the **physiological involution** of certain organs and tissues, examples of which process may be found at all periods of life. Sufficiently familiar instances are the disappearance of the yolk-sac and vitelline duct, the left superior vena cava, the thyroglossal duct, and very many other structures during intra-uterine development; the involution of the thymus gland during childhood, and of the uterus, etc., after parturition; the atrophy of the female generative organs

at the menopause; senile involution of many tissues and organs, *e.g.* of certain parts of the osseous skeleton, such as the neck of the femur, lower jaw, etc.

Local atrophy in disease is also common, and may arise from various causes, many of which are essentially similar to those which bring about some of the degenerations discussed in the preceding chapters; or which, if more severe, may result in necrosis.

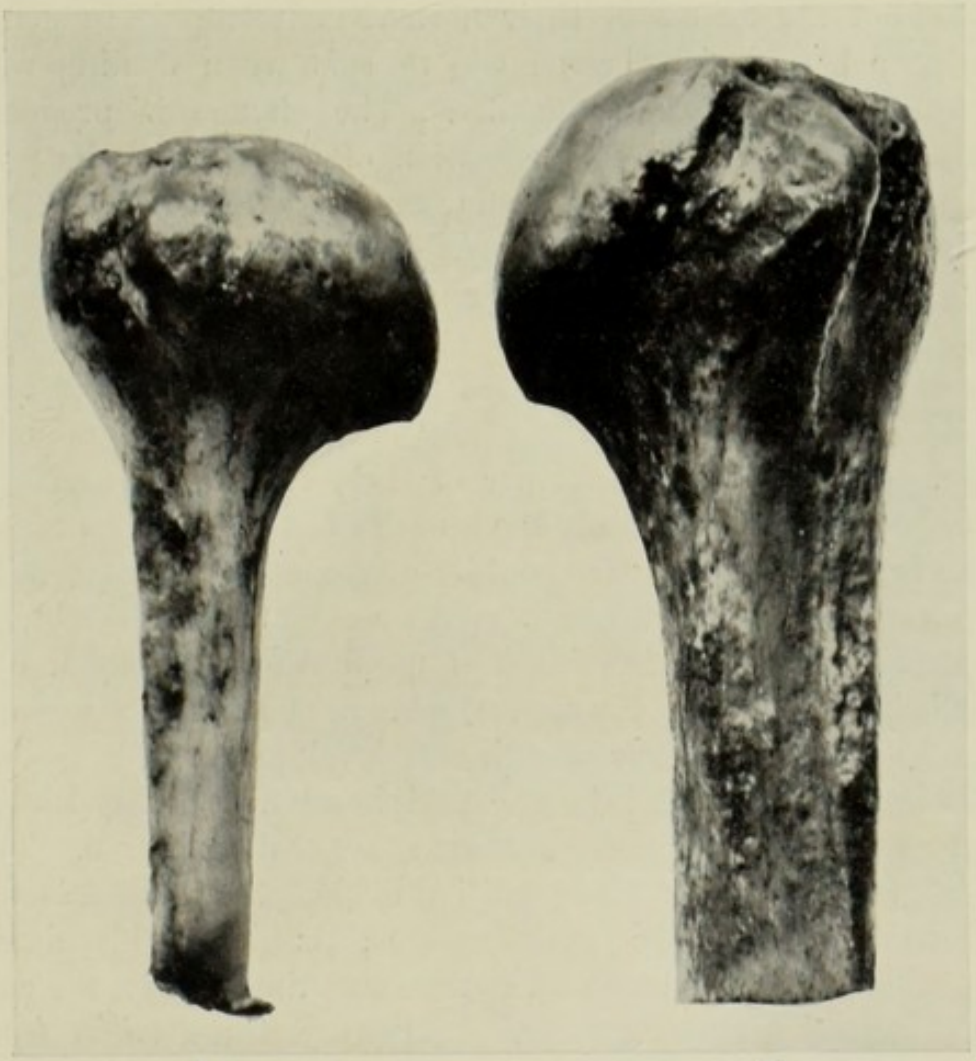
Thus **defective nutriment**, or the prevention of its free access to the part, especially if such obstruction be gradually produced, *e.g.* by disease of the arteries, is a common cause of local atrophy. Narrowing of the coronary arteries of the heart may lead to extensive degeneration and atrophy of the myocardium. Thickening of the walls and diminution in the lumen of the renal vessels, or obstruction to the blood-flow through the glomeruli, may produce extensive atrophic changes in the various structures of the kidney.

Impaired nutritional capacity.—As already stated, the tissues, in order to maintain a healthy state of nutrition, must possess sufficient vital capacity for assimilation; and this may be impaired in many ways; for example, by disease, old age, nervous derangement, abnormal temperature, pressure, etc.

The amount of blood supplied to a given part is largely governed by the degree of its functional activity, and therefore **diminution or arrest of function** necessarily leads to a corresponding diminution or arrest of the blood-supply. Muscles and muscular organs waste from disuse. The left ventricle may become considerably atrophied in cases of mitral stenosis, where only a small and feeble stream of blood is projected into it from the auricle; and where, in consequence, it has less work to do in expelling its diminished contents. Similarly, the stomach becomes atrophied in cases of œsophageal obstruction; and the intestine becomes thinned and wasted below a malignant or tuberculous stricture. The muscles in the neighbourhood of an ankylosed joint undergo marked atrophy from disuse; and the same condition supervenes in the muscles, bone, and other tissues in the stump of an amputated limb (fig. 20). In the animal kingdom, interesting examples of the atrophy of an organ from disuse are to be found in the almost complete disappearance of the organs of sight in fishes and other animals living in the darkness of the Mammoth Cave of Kentucky, or

at great depths in the sea where little light ever penetrates; whilst many parasitic animals have come to depend so entirely upon their hosts for nutriment that they have lost almost all specialised organs except those of reproduction.

Excessive use, especially if of prolonged duration, may also



A. B.

FIG. 20.—(A.) Atrophy of head of Humerus following upon amputation; (B.) Head of opposite bone for comparison. (Specimens kindly lent by Mr Henry Wade.)

ultimately lead to atrophy, for example in the case of muscles, or even of glandular organs. Thus, in the expanded, immobile chest produced by emphysema, breathing has to be carried on by means of the extraordinary muscles of respiration. These, more especially the sterno-mastoids and scaleni, may at first become considerably hypertrophied; but as time elapses, the additional strain upon the vitality and nutritive capacities of

the muscles cannot be maintained, and atrophy supervenes. A similar condition of atrophy, usually accompanied by degenerative changes and dilatation, may be seen in the myocardium of heart-chambers which have been previously hypertrophied.

Disease or injury of the central nervous system or of the peripheral nerves may lead to local atrophy of tissues thus deprived of the effects of their normal neurotrophic influence. Reference has already been made to this when dealing with the question of general atrophy. The change is produced partly by the diminution or cessation of function in the part, partly by changes in the vascular supply, and partly by the cutting off of trophic nerve energy. Thus in infantile paralysis (**poliomyelitis anterior acuta**), and in progressive muscular atrophy (**poliomyelitis anterior chronica**), where the motor cells of the anterior cornua in certain parts of the spinal cord are destroyed by disease, the corresponding muscles gradually waste. Especially in the former of these diseases, occurring as it does early in life, not only the muscles but also the bones, *e.g.* of the lower limb or of the shoulder-girdle and upper extremity, are often considerably diminished in size, partly, no doubt, an arrested development from lack of use, but also largely due to their being deprived of the neurotrophic influence of the nervous system necessary to their growth and development.

Similarly, disease or injury of peripheral nerves may lead to great wasting of the tissues in their areas of distribution. This is seen, for example, in the condition of **peripheral neuritis** due to alcohol, lead-poisoning, diabetes, etc.; though in this disease the toxic agents probably also, at the same time, act on the cells of the central nervous system. In leprosy, the *Bacillus lepræ* may specially attack and destroy nerve trunks, with the result that, in addition to the production of wasting of the skin and other tissues, the bones—for example, of the hand, especially the phalanges—may become extremely thin and small. In locomotor ataxia, a disease characterised by degeneration and sclerosis of the posterior columns of the spinal cord, there may be extensive nutritive changes in the bones and joints.

Influence of pressure.—It was long ago pointed out by John Hunter that **continuous pressure causes atrophy**, whilst **intermittent pressure, on the contrary, tends to produce hypertrophy or overgrowth.** An example of the latter condition is well seen

in the overgrowth of skin epithelium to form a "corn," following upon the intermittent compression of a tight boot. Continuous pressure causes gradual atrophy from interference with the function and vitality of the tissue itself, and more especially of its cellular elements, cell-division and function being diminished or arrested. It also acts partly by interfering with the local blood-supply from compression of the vessels and lymphatics of the part. Examples of such wasting resulting from continuous pressure may be seen in the atrophy of tissues around an aneurism or tumour. Such pressure-atrophy may even occur in bone; and the sternum or vertebral bodies may undergo extensive erosion in cases of pressure upon them by aortic or other aneurisms. This absorption seems to be to a large extent carried out by means of multinucleated and other phagocytic cells which appear at the surface of the bone in the neighbourhood of such an aneurism or tumour. Abnormal and long-continued increase of pressure **within** an organ may similarly lead to atrophy and distension of its component tissues; for example, in the case of the lungs, where prolonged coughing and other causes may produce pressure-atrophy of the alveolar walls and capillaries, etc., *i.e.* the condition known as emphysema.

Similarly, the abnormal pressure of one tissue constituent upon another within the same organ may lead to atrophy of the more delicate constituent. Thus, in chronic venous congestion, the parenchymatous cells of the liver become atrophied, and may even ultimately disappear, in the areas where they are compressed between the distended capillaries. Or, again, the special cells of an organ may similarly undergo atrophy from compression between the swollen and altered fibrous tissue elements, as occurs in waxy or amyloid disease.

Changes occurring in atrophying organs.—As a general rule, the more highly endowed special cells are first affected, and usually exhibit certain retrograde or degenerative changes, which have been discussed in previous chapters. The cells themselves may diminish in size and lose their more specific characters, and there is usually a diminution or loss of the power of cell-division and reproduction, and hence a defective formation of new cells to take the place of those which are degenerated and atrophied. In some cases the more highly specialised cells may show a degradation in type, or there may even be a degradation

in the type of the entire tissue; for example, connective tissue may be replaced by fatty or myxomatous tissue, cartilage may be transformed into myxomatous tissue, and so on. In some cases, active phagocytosis may assist the other destructive processes at work. The supporting connective tissue framework of the tissue or organ usually exhibits proliferative changes and becomes more fibrous—the condition known as **fibrosis**, or **fibrous atrophy**, which may be met with as a senile, a degenerative, or a chronic toxic, irritative process. Many of the blood-vessels of the affected area may become thickened and narrowed, or even completely obliterated, and may ultimately disappear, although in some cases, where there is much increase of connective tissue, it may become vascularised by the proliferation of pre-existing vessels.

The term **Metaplasia** was introduced by Virchow to denote the transformation of one tissue type into another: for example, mucoid tissue into cartilage, and *vice versa*; cartilage into bone; formative or hæmopoietic bone-marrow into fatty or mucoid, or even into osseous tissue; and so on. It is necessary to note, however, that these metaplastic changes can only occur between members of the **same** group, *e.g.* among the connective tissues themselves, but **not** from a connective tissue to an epithelium, or the reverse. Virchow originally applied the term to changes occurring between members of the connective tissue group only, but there is no reason why it should not also be used to denote a change from one to another epithelial type, *e.g.* from a higher to a lower, or *vice versa*, as may frequently be observed in glandular and other epithelial tumours.

As we have seen, such metaplastic transformation may be due to the deterioration of nutrition, or to degradation of function, but it may also be reparative; or in other instances it may be brought about by an **alteration** in the character of the function required of the tissue. Thus, active blood-forming bone-marrow may be substituted for the more inert fatty marrow, when such a change is demanded by the needs of the organism, or cartilage may appear in the fibrous tissue of a false joint. Similar metaplastic changes, but apparently serving no useful purpose, are of extremely common occurrence in very many varieties of tumour growth.

CHAPTER III

DISTURBANCES OF THE CIRCULATION

In order to maintain the nutrition of the whole or of any part of the body at its highest level, various physiological functions must be perfectly performed, and the chief of these is the **circulation**. Any disturbance of this leads to nutritive changes; and, if the disturbance be prolonged, the changes may be very marked, and permanent damage be done to the cells and the various tissues of the body. For carrying on the circulation in its normal state, at least three factors are necessary, viz. a normally functioning heart, healthy blood-vessels, and blood which is normal in quantity and quality. The relation between these three factors is so intimate that a disturbance of one very commonly leads to more or less alteration in the others; but it will be convenient to study each separately.

The Heart.—Various degenerations and inflammations of the pericardium, myocardium, and endocardium give rise to disorders of the circulation, and the heart either acts so feebly that it cannot send on the blood with sufficient force, or, on account of various obstructions, more blood is received than can be sent out. As a result, the arterial supply is diminished and the venous system engorged. The venous engorgement increases the work of the heart, and this increase tends to exaggerate the existing pathological conditions. An increased pressure develops in the dilated veins, and is followed by an increased transudation of lymph and the production of dropsy. The diminished arterial supply leads to deficient oxygenation of the blood, the accumulation of carbon dioxide, and a bluish discolouration of the skin—**cyanosis**. It also has a devitalising effect on the tissues of the arterial wall, and this, in itself, favours accumulation of blood in the veins and

capillaries, especially in dependent parts, the condition of **hypostasis** or **hypostatic congestion** being thus produced.

The Blood-vessels.—The elasticity of the walls of the arteries is the principal factor in regulating the rate and the amount of blood flowing through them. If this elasticity is diminished or lost, a dilatation of the lumen follows, which, according to Thoma, is compensated for by a thickening of the inner coat, and a consequent still further diminution in elasticity. The propulsion of the blood is not now aided by the contraction of the arterial walls, and the result is stagnation and hypostasis. Further degeneration takes place in the walls of the arteries, and this, by increasing the work of the heart, leads to hypertrophy and other compensatory changes in that organ.

The Blood.—Morbid alterations in the composition of the circulating fluid have a deleterious effect on cell-nutrition in general; and though in some cases this is a very important factor in producing pathological changes, it may, for our present purpose, be almost neglected. Again, alterations in the quantity of the blood passing into a part is of very considerable importance, and it is obvious that this must be largely influenced by the two former factors, viz. impairment in the function of the heart or of the blood-vessels, or of both.

For convenience of study, the circulatory derangements may be divided into two groups:—

1. Those in which the changes are due to mechanical impediments to the flow of blood through a part of the body.
2. Those due to the reaction which the tissues and vessels undergo in response to irritation, these being classed under the general term **Inflammation**.

Changes dependent on Mechanical Obstruction.—Mechanical obstruction to the flow of blood may affect either the veins or the arteries, or both. If the obstruction is venous, interference with the outflow of blood and consequent engorgement of the part take place; if arterial, there is a diminished supply of blood, with resulting impaired nutrition of the part. To the latter condition the term **Anæmia** is commonly applied; and to the former, **Congestion** or **Hyperæmia**. Both of these names are used somewhat indiscriminately. The term **Anæmia** is used to indicate that a part of the body has a lessened arterial

supply, but it is also applied to certain morbid conditions of the blood itself; whilst **Hyperæmia** is used for conditions where the blood accumulates in a part, either from an increased afflux or from a diminished outflow. It is true that the term **active hyperæmia** or **active congestion** is applied to the condition produced by an increased flow of blood to a part, and **passive hyperæmia** or **passive congestion** to that produced by a diminished outflow; but this distinction cannot be strictly maintained, for, under the term **active hyperæmia** are included those conditions in which the engorgement is due merely to a local dilatation of the minute vessels of the part, and in which there is neither increased afflux nor obstructed outflow. Though these terms must be retained, we agree with Greenfield and Lyon that "for conditions due to dilatation of the minute vessels of the part—the venules and capillaries especially—the term **congestion** would be convenient; whilst those due to venous obstruction might well be called **venous engorgement**, and those associated with increased afflux of blood **active hyperæmia.**"

VENOUS ENGORGEMENT, OR VENOUS OBSTRUCTION

If the veins of a part become obstructed from any cause and the inflow of blood still continues, the venous channels dilate and the part becomes blue from defective oxygenation of the blood. These **cyanosed** parts are usually cold, and sensation in them is more or less interfered with. The obstruction may be central in origin, *i.e.* in the heart or in the lungs, and the resulting **engorgement** is then **general**; or, on the other hand, the **engorgement** may be more **local** in its distribution, where it is due to changes in or around the vessels.

General Engorgement.—This is most commonly due to structural alterations in the heart itself. If the mitral valve is diseased, so that there is accumulation of blood in the left auricle, and consequent obstruction to the free inflow from the pulmonary veins, venous congestion is produced in the lungs. The onward flow being thus diminished brings about obstruction in the right side of the heart, and engorgement of the whole of the systemic veins. The parts nearest the source of obstruction, the organs from which the venous return is more or less indirect, *e.g.* the spleen, and the vessels in which gravity plays

an important part, *e.g.* the long veins in the lower limbs or the left spermatic vein, give greatest evidence of the engorgement. The obstruction in the lungs causes a deficient aeration of the blood, and a general condition of cyanosis follows. Such general cyanosis may also be produced by a mixing of venous with arterial blood, and may take place in consequence of abnormalities in the heart, *e.g.* a patent foramen ovale. General venous engorgement may also occur in cases in which the obstruction is in the lungs themselves.

Local Venous Congestion may be brought about by many factors:—

1. Obstruction by ligature, tight bandaging, or by pressure from without by tumour or aneurism.
2. Thickening of one or more of the coats of the vein, sometimes with marked degenerative changes and deposits of lime salts, leading to narrowing of the lumen or to dilatation. The result will be a retardation of the blood-flow and consequent obstruction.
3. The obstruction may take place in the lumen of the vein by the formation of a thrombus, and, in many cases, this thrombosis has followed and is consequent upon pre-existing degenerative changes in the wall of the vein.
4. Foreign bodies, portions of new growths, or parasites may be found in the lumen, as rarer causes of obstruction.

The phenomena and effects of the local venous congestion vary with the character and position of the obstructed vein, the rapidity of its production, and also with the degree of obstruction. Obstruction of veins, where the collateral venous supply is good, may lead to no serious results, because new channels are at once opened up to replace the old and obstructed ones. On the other hand, if some of the larger trunks or the main vein from an organ be obstructed, the anastomosing channels are not sufficient to carry on the work, and very important derangements in nutrition, etc., take place. Where the collateral supply is not sufficient, and where a single vein carries out most of the venous return, considerable changes result from its obstruction. Examples of such veins are the renal, the ophthalmic, the pulmonary, and the external iliac. The immediate effects will, of course, vary with the suddenness

and completeness of the obstruction; for, if the obstruction occurs suddenly, and especially if it be complete, considerable changes may take place before the collateral supply is established; whereas, if the obstruction occurs slowly, the likelihood of a complete collateral supply being established is greatly increased. Thus in some cases of obstruction slowly produced by tumours, large venous channels may become completely blocked without producing any serious results to the circulation. The portal vein may become completely obstructed, and yet the blood may find its way by collateral channels into the systemic veins in such a quantity that, during life, no evidence of obstruction can be detected. The degree of obstruction is of necessity an important factor; for, when the lumen of a vein becomes considerably narrowed from any cause, thrombosis is liable to occur. The thrombus causes a complete block in the blood-flow, and may produce all the changes associated with acute venous engorgement.

ACUTE VENOUS ENGORGEMENT.—This condition may arise from rapidly developed thrombosis of some of the larger veins or sinuses, *e.g.* the renal, the splenic, or the ophthalmic veins, or one of the cerebral sinuses; but it is best studied experimentally, by ligature of either a superficial vein, or of the renal or the splenic vein. Immediately following ligature, there is distension and engorgement of all the minute veins and capillaries of the area to which the ligatured vein belongs. The area, if superficial, becomes swollen, livid, cold and numb. The distended capillaries may rupture, especially those which are feebly supported, and larger or smaller hæmorrhages may cause further swelling and discolouration of the part. Ligature of the *whole* renal vein causes marked engorgement throughout the kidney, with numerous hæmorrhages from rupture of smaller vessels. If only a *branch* of the vein is ligatured, the engorgement and hæmorrhages are confined largely to the special area which this branch drains, but there is also a certain amount of engorgement in other parts. This latter soon passes off, and is possibly accidental, and due to interference with the other branch of the vein during the operative procedure. In the engorged area, the hæmorrhages are best seen in the glomerular capsules and between the tubules in the boundary zone. They occur almost immediately

after the ligature has been applied, and result from the rupture of the distended and feebly supported capillaries, but they become more marked some hours later. This late hæmorrhage is no doubt due to the occurrence of degenerative changes in the walls of the capillary channels, which render them more liable to rupture. The degeneration is, of course, caused by the impaired nutrition brought about by the ligature. In disease, such hæmorrhages are an important, though not very common, result of acute congestion. They occur naturally in the vessels whose walls are thin and feebly supported. In obstruction of the ophthalmic vein, hæmorrhages are seen in the retina; while hæmorrhages in the lung occur as a result of thrombosis of branches of the pulmonary veins; and hæmorrhage into the pia mater, over the vertex of the brain, is sometimes observed as a result of sudden thrombosis of the longitudinal sinus. The hæmorrhages are more likely to occur if there has been previous damage to the vascular endothelium by toxic or chemical substances, which may also have played some part in causing the obstruction. The distension of the veins of the part soon causes **swelling**, which becomes more marked at a later period, and is then due to an accumulation of transuded lymph in the tissue. This secondary swelling or **dropsy** must now be considered.

DROPSY OR ŒDEMA.—In certain cases of venous obstruction, accumulations of clear watery fluid are found in the tissue spaces or body cavities, and to this condition various names have been applied. If the accumulation is in the tissue lymph spaces, it is called **dropsy** or **œdema**, whereas, if there is a general infiltration of all the subcutaneous and muscular connective tissues, the name **anasarca** is used. Accumulation in the peritoneal cavity is called **ascites**, in the pleural cavity, **hydrothorax**, in the pericardial sac, **hydropericardium**, and in the ventricles of the brain, **hydrocephalus**.

Part of the process of nutrition of the various tissues of the body is carried on by lymph, which in a normal individual transudes from the capillaries. This transuded lymph, altered, it may be, in composition, is absorbed by the lymphatics and the veins, and is thus carried back into the blood-stream. It has been shown by experiment, that if the pressure in the capillaries is increased, transudation takes place to a greater degree. The veins and the lymphatics may still be efficient

channels of absorption for this increased transudation, and no pathological accumulation of fluid may arise. If, however, there is considerable venous obstruction, one of the paths of absorption is interfered with, and the obstruction causes a further increase of pressure in the capillaries, and consequently a further increased transudation of lymph. If mere physical pressure were the cause of abnormal increase of lymph in the tissues, there should always be found, in cases of increased transudation with diminished absorption, an accumulation of fluid in those tissues which are drained by the obstructed vein. In certain cases of venous obstruction this dropsy is found, but in other instances it is entirely absent. Where the femoral vein is obstructed, there may be very considerable œdema of the tissues of the corresponding lower limb; and, on the other hand, in some cases, on *post-mortem* examination, complete obstruction, even of the inferior vena cava, may be found without a trace of dropsy. It is thus quite clear that mere increase of pressure and diminished absorption by the veins are not in themselves the sole causes of the dropsy which frequently follows obstruction of veins. It has also been shown by experiment that even extensive obstruction of lymphatic channels need not give rise to œdema. Other causal factors must therefore be considered, and, in doing this, we propose studying the condition in its most frequently occurring forms.

Cardiac Dropsy.—This occurs in cases of venous engorgement where there is central obstruction to the circulation from valvular disease of the heart, or from general cardiac weakness. The œdema shows itself first in the feet and legs, if the patient is in the upright position, or in the tissues of the back or in the dependent parts of the lungs, if he is lying down. This at once suggests that gravity must play some part in the process, and that increased pressure has also an important causal relation to it. But, in these chronic cases, there is very often a long-continued increase in the venous and capillary pressure, which must act deleteriously on the vascular walls. To a considerable extent they lose their contractile power; for, though the walls may become thickened, the newly formed tissue is mainly of the nature of non-contractile fibrous tissue. On the much debated question of the selective secretory or excretory capacity of the vascular endothelium in this connection, it

need only be said, that if the lining cells perform such functions, these must become deranged, as a result of pathological changes in the endothelium itself. In addition, the tissues round the dilated vessels, partly from pressure and partly from malnutrition, undergo a certain amount of atrophy and degeneration. Their elasticity, and consequent onward driving power, are much diminished. The perivascular lymphatics, and probably also the small venules and capillaries, are to a considerable extent interfered with, and the vasomotor control may also, to a certain degree, be lost. All these factors will favour the accumulation of lymph in the tissues.

The Œdema of Anæmia or Cachexia.—Considerable accumulations of fluid are often found in the serous cavities or in the subcutaneous tissues, when there is neither general heart disease nor special venous congestion. In many of these cases there are considerable disturbances of nutrition, frequently due to some chronic infective condition which produces marked alterations in the cellular and fluid elements of the blood; and many authors hold that the so-called "hydræmic" condition of the blood is the sole cause of the dropsy. In other cases where there are similar very grave alterations in the blood, dropsy or œdema does not occur; and it has been shown experimentally by Cohnheim and Lichtheim that "hydræmic plethora" may be produced by injecting large quantities of a 0·6 per cent. saline solution into the vascular system of animals, without producing œdema. Further, the fact that in many cases there may be a unilateral œdema, *e.g.* in one pleural cavity, seems definitely to negative the idea of the condition of the blood itself playing any very important part in the process. Cohnheim attributes the whole of the œdema of anæmic or cachectic conditions to an increased permeability of the vascular wall. This may be brought about by the hydræmic condition of the blood, the protein elements being relatively diminished, the vascular endothelium not receiving its normal nutrient supply and undergoing degeneration. In cases where the hydræmic condition of the blood and the nutritive disturbances are due to some infective condition, the probability of a toxin or a metabolic poison of some kind acting directly on the vessels must be considered. It is abundantly proved by experiment that vascular endothelium

undergoes both proliferative and degenerative changes during the course of an infective disease, *e.g.* in typhoid fever, and these changes must considerably influence the transudation of lymph. As we have mentioned above, Cohnheim finds the whole explanation of the cachectic œdema in the modification and increased permeability of the vascular wall. For "the injured vessel-wall is more permeable than normal, and when this is the case the normal or less than the normal blood-pressure is sufficient to produce an increase of lymph flow, or, in other words, to produce œdema."

Renal Dropsy.—In certain cases of renal dropsy, and more particularly in those which are consequent upon acute nephritis, the accumulation of fluid is especially found in the loose cellular tissues about the eyelids, whereas in others, the distribution resembles more that seen in cardiac dropsy. In the former, the accumulation is certainly independent of gravity; but in renal dropsy there are many factors at work. There is usually an increase of pressure in the blood-vessels, and often a very profound alteration in the walls of the vessels themselves. Further, a hydræmic condition of the blood is very commonly found; and, what is perhaps the most important factor, an accumulation in the blood of waste products of various kinds, which must have some influence on osmosis. The relative part which each of these factors plays in the process it is impossible to estimate.

Œdema due to vasomotor disturbance.—The œdema which occurs in the paralysed limb in cases of hemiplegia, or that following spinal paralysis, is apparently due to a vasomotor disturbance, which no doubt causes both an increased transudation of lymph and a diminished absorption; and here it would seem that the main cause is disturbance of vascular innervation, and probably also an increased permeability of the vessel wall. Richard Lower, in 1860, ligatured the inferior vena cava in animals, and described the occurrence of œdema in both hind limbs. Ranvier repeated the experiments with quite different results—no œdema being produced. After section of the sciatic nerve on one side and ligature of the vena cava, œdema appeared on the side on which the sciatic nerve had been divided, but not on the other. Further, it was shown experimentally that division of the sciatic nerve alone did not

produce œdema. Ranvier, at first, concluded from these experiments that the vasomotor nerves controlled the output of fluid from the blood-vessels, but at a later period he modified his view, and attributed the dropsy to an increased tension produced by the dilatation of the arteries, and an increased supply of blood to the part. This œdema may, of course, be attributed to the increased arterial flow combined with the venous obstruction; but we feel that here also we are justified in suggesting that an increased permeability of the vascular wall, on account of degenerative changes which would necessarily follow the operative interference, may have played a considerable part.

Inflammatory Œdema.—Of this, very little need be said here. There is undoubtedly increased pressure, but the most important factor seems to be an alteration in the vascular endothelium. The vessels become much more permeable, and proliferative and degenerative changes can be readily demonstrated in their lining endothelium.

Lazarus Barlow,[1] in his experimental investigation of the results of venous engorgement, has shown that an increase in venous pressure does not **of itself** lead to an increased output of lymph. If, however, a ligature is placed round a limb tightly enough to completely arrest the circulation, and is kept on for an hour, and if afterwards the blood-pressure be raised, there is a rapidly-formed and well-marked œdema in the tissues. We do not propose discussing the problems raised by these experiments, but must merely refer our readers to the original papers. Barlow's conclusions are that the œdema is mainly due to two factors: (1) the starvation of the tissues by the loss of the nutrient blood-supply; and (2) the accumulation of the waste products of their own metabolism. He points out that the amount of lymph which escapes from the vessels is determined by the needs of the tissues rather than by the condition of the blood-vessels. "When the tissues are starved, or when the products of functional activity are stored up in the tissues, an arterial congestion (active) occurs, which is accompanied by an increased flow of lymph. One portion of this increase flows away by the lymphatics, and is recognised by an increased flow

[1] Lazarus Barlow, "Œdema," *Phil. Trans. Roy. Soc.*, vol. clxxxv. B, 1894, p. 779; "Osmosis—Lymph-formation," *Jour. of Physiol.*, vols. xiv.–xix., 1893–1896 (various papers); *General and Experimental Pathology*, 1904.

from the lymphatics; another portion, if special methods are adopted, can be shown to remain in the tissues. Now, if a sufficient amount of this lymph remains in the tissues, the clinical condition of œdema is produced" (Lazarus Barlow).

On this view, the accumulation of fluid in the tissues or cavities of the body is simply an exaggeration of the normal physiological processes. In health, even with accumulation of metabolic substances, the reserve power of the heart and vessels is so great that they are able to meet the increased demands upon them, and œdema does not occur. But when there is some failure of the heart, or some pathological condition of the vessels or of the blood, then the equilibrium is disturbed. The lymph poured out is not absorbed, further starvation of the tissues and further accumulation of waste products take place, and, in consequence, a greater demand for lymph is made, and the tissues become bathed in it. The lymphatic system is unable to cope with the increased work thus thrown upon it, and of necessity much of the fluid must remain in the tissues and cavities.

At present, there does not appear to be sufficient evidence in support of the view of Hamburger and Heidenhain that the vascular endothelium has certain secretory functions, to justify us in dealing with this aspect of the question. We must refer our readers who desire more information on the point to the original papers,[1] and to the criticisms of Starling[2] and others.

From what has been said above, it will be seen that in the causation of dropsy the following factors at least must be considered:—

1. Alteration in the vascular walls, brought about by disease, prolonged dilatation, vasomotor paralysis, toxic or metabolic poisons in general, these causes leading to an increased permeability.

2. Increased pressure in the capillaries, due to obstruction of the veins by thrombosis or by pressure of tumours, etc.

3. Vasomotor paralysis, causing increased arterial flow and diminished absorption by the veins and lymphatics.

4. Alterations in the heart, due to valvular disease or

[1] Hamburger, *Zeigler's Beit.*, vol. xiv. p. 444; and *Virch. Arch.*, vol. cxli., 1895, p. 398. Heidenhain, *Pfluger's Arch.*, vol. xlix., 1891, p. 209.

[2] Starling, Leathes, etc., *Jour. Phys.*, vol. xiv.–xix., 1893–1896. Starling, *Lancet*, 1806, vol. i.; *Trans. Path. Soc.*, 1901.

general weakness. These may act by causing increased pressure on account of the venous stasis.

5. Alterations in the blood itself, brought about by an increase in the watery elements and a relative diminution in the proteins, or by the introduction of some toxic substance.

6. Starvation of the tissues, and the accumulation in them of metabolic products which demand from the vessels, in some unknown way, an increased flow of lymph.

In some cases, one of these factors may be sufficient to bring about the œdema, but, in the great majority of instances, two or more of them are acting in conjunction, and it is generally impossible to accurately assign the relative share of each in the process. We consider, however, that, though increased pressure must play a very considerable part, it cannot be allotted the important rôle ascribed to it by some of the older writers. One of the chief factors is, we believe, the presence in the blood and in the tissues of substances which, in default of a better term, we may call "poisons"—*e.g.* metabolic products, toxins, ferments, lysins (endothelial and other), antibodies, etc. These act by causing degeneration and increased permeability of the vascular endothelium, by interference with lymphatic absorption, by disturbance of the normal osmotic properties, both by alterations in the fluid and in the osmotic membrane, and also by degenerative and other effects in the surrounding tissues.

Composition of Dropsical Fluids.—The amount of proteins and salts in transuded fluids corresponds approximately with that in the blood-plasma. Certain substances found in excess in the blood-plasma, *e.g.* sugar, bile, uric acid, etc., are also present in the transuded lymph. The transuded fluid is always more dilute than the blood-plasma — the latter containing about 91 per cent. of water, the former about 96 per cent.

The composition of dropsical fluids varies in different forms of œdema, and also according to the situations in which the fluid is found. In inflammatory œdema, the specific gravity of the fluid is higher and the amount of proteins greater than in the œdema following venous engorgement. Schmidt has pointed out that, as a general rule, the proteins in a hydrothorax or an ascites are greater in amount than in an œdema of the subcutaneous tissues.

The following tables will best illustrate these points:—

1. **Composition of various Dropsical Fluids removed simultaneously from the body of a person who had died of Albuminuria.** (C. Schmidt, Hoppe-Seyler's *Physiol. Chemie*, p. 607.)

	Fluid from			
	Pleural Cavity.	Peritoneal Cavity.	Subarachnoid Space.	Œdema of Extremities.
Water in 1000 parts	963·95	978·91	983·54	988·70
Solid matter ,, ,,	36·05	21·09	16·46	11·30
Organic ,, ,, ,,	28·50	11·32	7·98	3·60
Inorganic ,, ,, ,,	7·55	9·77	8·48	7·70

2. **Specific Gravities and Percentages of Albumin in certain Transudates.** (Thoma, *Text-book of General Pathology*, 1896, vol. i. Translation by A. Bruce.)

	Specific Gravity.	Percentage of Albumin.
Peritoneal effusion in nephritis . . .	1·006	0·56
Pleural ,, ,, . . .	1·007	
Peritoneal effusion in general venous engorgement	1·012	1·96
Pleural effusion in general venous engorgement	1·012	1·30
Transudates of mixed origin from subcutaneous tissue of lower limbs	1·007–1·011	0·05–1·1

CHRONIC VENOUS CONGESTION

Obstruction to the outflow of blood from a part may be **local** owing to blocking of some of the larger veins, but this rarely leads to any serious pathological changes. If the main vein of an organ or the superior or inferior vena cava becomes blocked, destructive and degenerative changes may follow; but even in such cases compensation may take place after some time, and no serious permanent damage occur. If, on the other hand, the obstruction to the circulation is "**central**," and causes a general slowing of the venous flow, gradual changes occur

in all the organs of the body, which may lead to very serious derangement of their functions. The causes of general venous congestion are usually to be found in the heart itself or in the lungs, and the most important **central** cause is disease of the mitral valve. If this valve becomes incompetent or its orifice stenosed, the blood will tend to accumulate in the left auricle, free exit of blood from the pulmonary veins will be prevented, and thus the whole vascular system of the lung will become engorged. The right ventricle has to work against this increased pressure in the pulmonary vascular system, and cannot empty itself completely. The right auricle becomes distended with venous blood, and this distension tells back on the great veins which open into it. Venous return is thus hindered, and a general distension of the systemic venous system results. The right heart becomes hypertrophied in its attempt to overcome the resistance in the vessels of the lung, and it may, to a certain extent, especially if the mitral valve is only stenosed, and not incompetent, be able to compensate for and reduce the circulatory disturbance in the lungs to a minimum. The hypertrophy of the left auricle which results from the mitral stenosis, will exert during systole a certain amount of "**backward pressure**" on the blood in the pulmonary veins; but this backward pressure will be exerted to a greater degree if the left auricle is kept full of blood, as is the case in regurgitation brought about by incompetence of the mitral valve. The result in such cases is the production of **chronic venous congestion** in the lungs. The whole of the pulmonary vessels become dilated and their walls much thickened, and hæmorrhages may occur into the pulmonary alveoli. Degenerative changes, sometimes very advanced in degree, are very commonly seen in the branches of the dilated pulmonary vessels. Of the systemic veins, the hepatic, splenic, and renal are most affected. In such cases, the liver always shows chronic venous congestion in a marked degree. This is due to the very direct and close connection between the hepatic veins and the inferior vena cava, aided by the low pressure in the portal veins and by the comparative absence of valves in the hepatic veins. The wide and open network of sinuses in the spleen, its circulatory relationship with the liver, and the length and tortuosity of the splenic vein, explain the readiness with which venous

engorgement takes place in this organ. The kidneys also tend to show chronic venous congestion in a marked degree, probably owing to the relatively large size of their veins, and also to the complexity of the arterial circulation of these organs. Chronic venous congestion may, of course, occur in other organs and tissues, and in these its degree may vary considerably. This variation is generally dependent on the presence or absence of

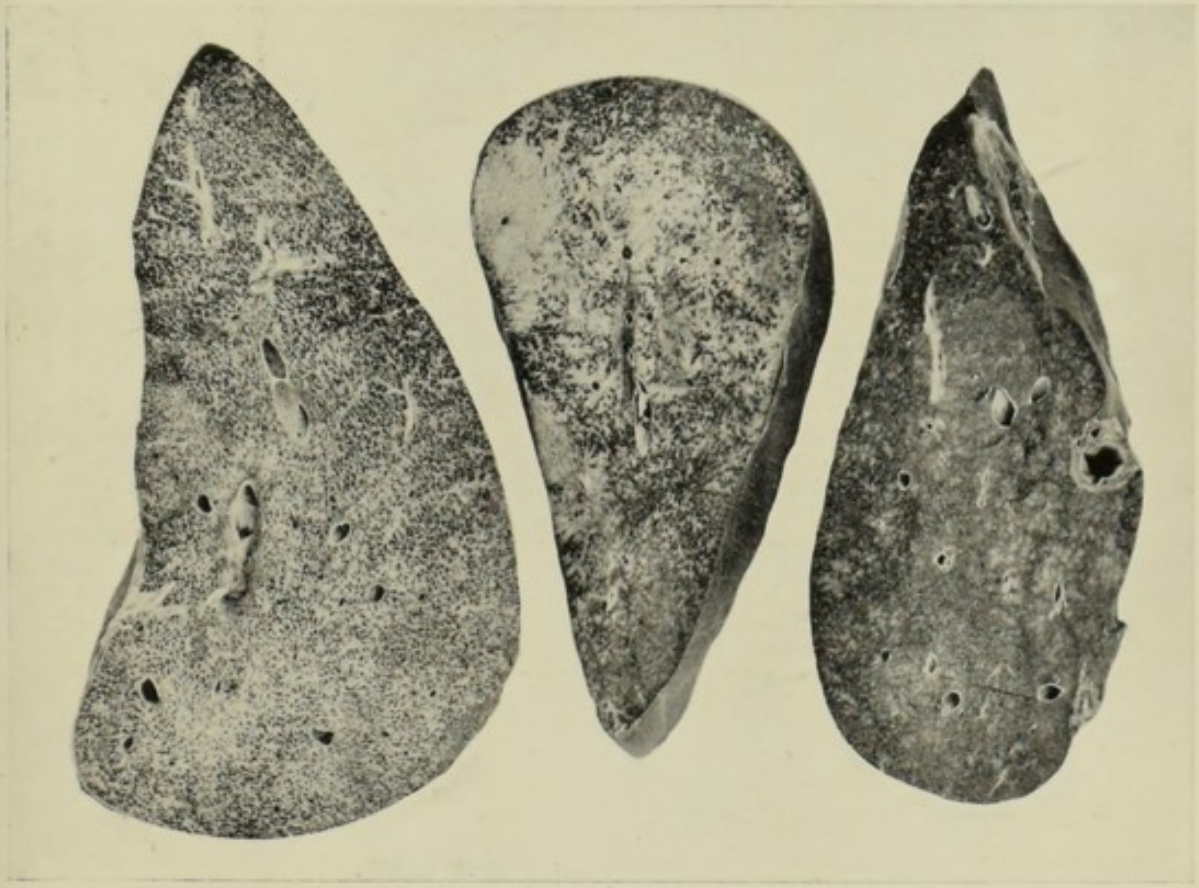


FIG. 21.—Liver, chronic venous congestion. Section on left—early stage, showing dilated central vein surrounded by engorged capillaries. Other sections show more advanced stage with a greater extent of vascular dilatation.

factors which act as accessory aids or hindrances to the venous return. Of these the most important is **gravity**. In addition, however, the **position** of the vessels, the **condition of their walls**, and the nutrition of the general muscular system of the body must be considered. If the vessels are poorly supported, and if their walls, and especially their muscular coats, are degenerated, dilatation and also a varying degree of elongation, are very liable to occur. Muscular movement is an important factor in aiding the flow of blood through the veins, and hence

the value of moderate exercise in conditions leading to local stagnation. Further, **the driving power of the left ventricle** is a very important factor, for the force of the arterial determines to a large extent that of the venous flow. Respiratory movements also act by drawing the blood into the large venous trunks, and thus aiding the circulation through the lungs, so that if the respiration is embarrassed, venous congestion is more liable to occur.

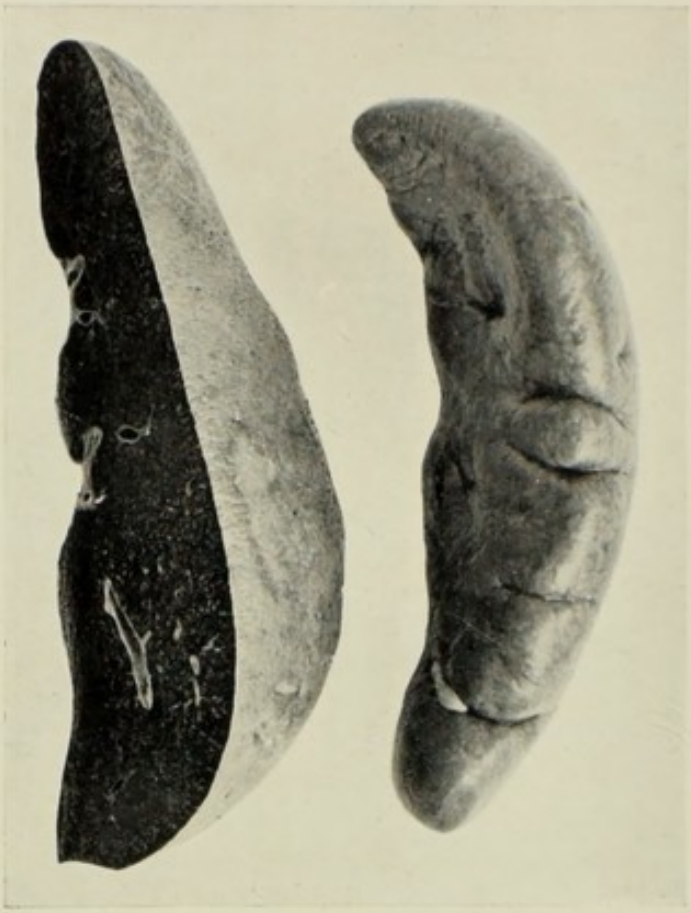


FIG. 22.—Spleen—chronic venous congestion.

The Effects of Chronic Venous Obstruction :—

(1) **On the larger veins.** — Collateral circulation is very slowly set up in the venous system, but when it does occur it is almost always excessive in amount. The newly opened-up channels, as well as those originally present, become dilated and tortuous, especially where the veins are not well supported —and a condition of **varicosity** is produced. This is well seen in the limbs. The distension of the veins is always irregular, and this distension produces incompetence of the valves, which

further increases the dilatation and obstruction. The action of gravity aids this to a considerable extent. In the larger veins, the walls become much thickened, usually irregularly so. The muscular coat may become hypertrophied, and later fibrous, and the inner coat thickened and degenerated. The thickened and degenerated areas of the inner coat may show fatty degeneration and calcification. Inflammatory reactions and thrombosis are more liable to occur in these damaged

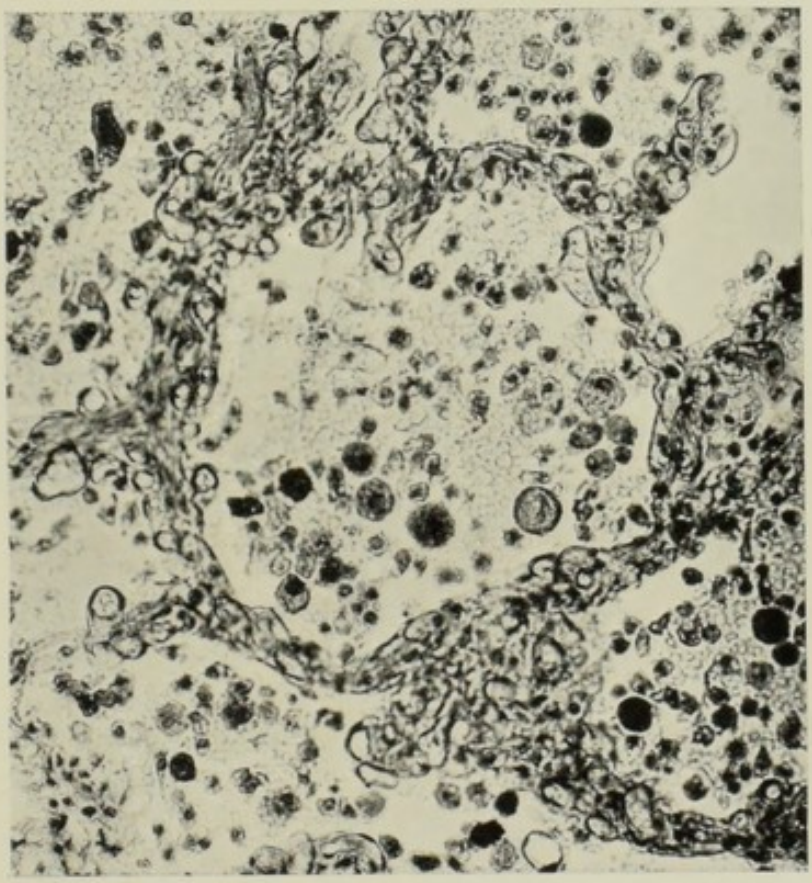


FIG. 23.—Lung, showing varicosity and thickening of alveolar capillaries, in chronic venous congestion. × 200.

veins, and it is not uncommon to get chronic dropsy as a result of the increased pressure combined with the vascular changes.

(2) **On the smaller veins and capillaries.**—The thickening of the smaller veins is more general and more uniform than that usually seen in the larger ones, and is mainly confined to the inner coat. In the capillaries, the thickening is in the form of fibrous laminæ around the endothelium. This is in all probability a proliferation of a very delicate pre-

existing layer of fibrous tissue, which becomes much thickened in some advanced cases.

(3) **On the nutrition of the tissues.**—The pressure of the distended vessels may cause atrophy of the surrounding tissues, especially if these tissues are of delicate structure and highly developed functionally. To some extent the defec-

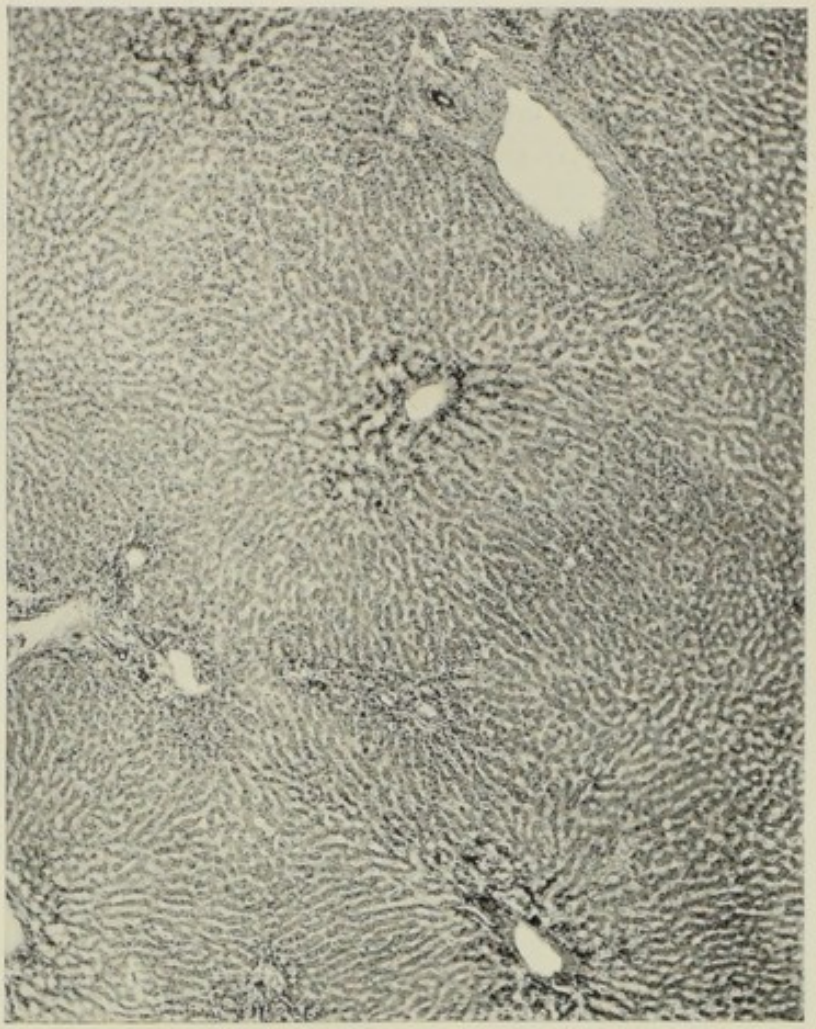


FIG. 24.—Liver, early stage of chronic venous congestion, showing dilatation of central vein and capillaries, with deposit of blood-pigment. ×50.

tive nutrition aids in this wasting, but there cannot be the least doubt that **the important factor** in many cases is direct **mechanical pressure.** This is well illustrated in the case of the atrophy of the liver cells in a "cardiac" liver, where the cells waste and disappear in the centre of the lobules first, owing to the fact that the central veins and their immediate tributaries from the lobule suffer to the greatest degree from

engorgement of the hepatic veins. In the skin over varicose veins, destructive changes frequently occur, causing the so-called **varicose ulcers.** Mechanical pressure is here again the primary agent, though alterations in nutrition and the presence of micro-organisms also play a very important part.

In the spleen, the larger veins in the trabeculæ, the venules, and the venous sinuses become greatly distended, and, as a result of the pressure thus produced, atrophy of the lymphoid

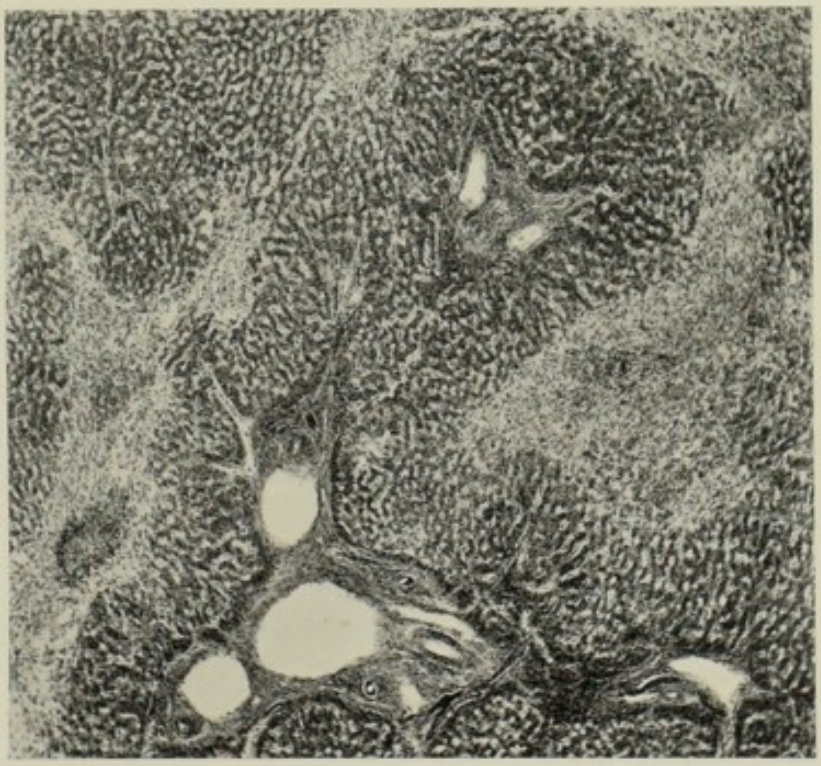


Fig. 25.—Liver, chronic venous congestion—advanced stage—showing atrophy of liver cells at the centres of the lobules. Cells round the portal spaces are healthy. × 30.

cells of the splenic pulp, and even in some cases, though to a less degree, of the cells of the Malpighian bodies, takes place. In the kidney the distension is specially seen, and its effects are observed in the venæ stellatæ, the venulæ rectæ, the interlobular veins, and the glomerular capillaries, in which thickening of the walls is often very evident. It is the dilated straight venules which give the characteristic dark-red striated appearance to the Malpighian pyramids in such a case. Changes in the renal epithelium, though present, are not a marked feature.

Hæmorrhage from the dilated veins is apt to occur, especially in places where they are not well supported. These hæmor-

rhages are frequently seen in the lung, *e.g.* into the alveoli from the distended alveolar capillaries, or into the bronchi from the capillaries in their mucous membrane. In the kidney, also, small hæmorrhages may occur from the glomerular capillaries, and the blood may accumulate between the glomerular tuft and Bowman's capsule, small quantities being found clinically in the urine.

Organs which show chronic venous congestion are usually moderately enlarged, dark in colour, and firm in consistence, and generally contain yellowish pigment derived from the blood. All pathologists are agreed that the enlargement and the dark-red colour are due to an overfilling of the venous and capillary channels with venous blood. It is very commonly taught, however, that the firmness is due to overgrowth of fibrous tissue, and this overgrowth is attributed to the increased lymph supply favouring the growth of connective tissue. Microscopical examination shows that in certain cases, and especially in certain organs, *e.g.* the lungs, there is an increase of fibrous tissue; but this is by no means common in the other organs in which chronic venous congestion, even in an extreme degree, exists. In the liver, in the majority of cases of "**cyanotic induration**," fibrous overgrowth is confined almost entirely to the walls of the vessels. In the spleen, fibrous thickening is also mainly in the walls of the venules and venous sinuses, though there usually is, in addition, some thickening of the trabeculæ, but not more than would necessarily be produced by the increased strain on these structures. In the lungs, fibrous overgrowth frequently occurs in the indurated areas, and especially along the lines of the lymphatics. This overgrowth is generally in proportion to the amount of blood-pigment and carbon particles in the lymphatics, and may be explained by the chronic irritation caused by the pigment. It is analogous to the fibrous overgrowth seen in anthracosis, silicosis, etc. Thus, to a large extent the hardness and firmness of the organs must be attributed to an overfilling of the venous and capillary channels.

It has already been stated that atrophy of the parenchymatous or special functioning cells of the organ occurs in long-standing chronic venous congestion. This is especially seen in the liver in the condition known as "**cyanotic atrophy**," where

the majority of the cells are destroyed, and the organ shrinks irregularly and becomes much smaller than natural. This atrophy may also be seen in the capillary system; but in this case it is the atrophy of disuse rather than the atrophy due to pressure.

Hypostatic congestion.—This term is specially used for a condition in which certain dependent regions of the body, particularly the bases of the lungs, become engorged with blood, œdematous, and partially collapsed. Frequently, patches of consolidation, broncho-pneumonic in type, are associated with these changes, and then the term **hypostatic pneumonia** is applied to the condition. These changes are seen in debilitating conditions of all kinds, especially where the patient is confined to bed. The production of the condition is aided by gravity, but there are many other factors at work. Deficient expansion of the lungs, combined with weakened action of the respiratory muscles, is an unavoidable consequence of the recumbent position, and congestion and collapse are therefore liable to occur. The collapse is aggravated by catarrhal secretions, which gravitate to the lower lobes of the lungs, especially if bronchitis is present. Distension of the stomach and intestine may interfere with the proper action of the diaphragm. The congestion is helped by a weak circulation in cases where the heart is acting feebly. All these agencies play their part in the production of the condition.

THROMBOSIS

Under the name **thrombosis** we include all forms of coagulation of the blood in the heart or vessels **during life**, the resulting mass being known as a **thrombus.**

The occurrence of thrombosis depends on several factors, the principal one, however, being the presence of any inequality or irregularity in the walls of the heart or vessels; or, what amounts to very much the same thing, the presence of any foreign body in contact with the blood. This factor is aided by a slowing of the blood-stream from any cause, and also by alterations in the blood itself, or by the presence in it of abnormal substances, as, for example, certain toxins, *e.g.* those of the pneumococcus.

Under normal circumstances, *i.e.* with healthy vessels, a normal rate of blood-flow, and with blood in a normal condition, no coagulation takes place within the vessels or the heart; but, if there is an upsetting of this balance by one or more of these factors getting out of order, thrombosis may then occur. If the vessel-wall is injured, or if irregularities are produced in it by disease, the blood-flow is impeded, and, in addition, certain formed elements of the blood tend to adhere to and accumulate on these damaged parts. Again, irregularities in the vessel-wall may cause eddies in certain places, and in these, coagulation is very apt to occur. Further, if there is disturbance of the normal blood-flow from disease of the heart, or on account of narrowing of the vessels by pressure from without, *e.g.* by tumours, coagulation may occur. This, however, is more likely to take place if there are, in addition, irregularities caused by disease in the walls of the vessels, especially in the inner coat. Coagulation in the vessels or heart, due solely to a pathological condition of the blood itself, or to the presence in it of abnormal substances which aid coagulation, may also occur.

Varieties of Thrombi.—Thrombi are usually divided into two varieties, the **red** and the **pale** or **white**, which differ not only in colour, but also in their mode of formation.

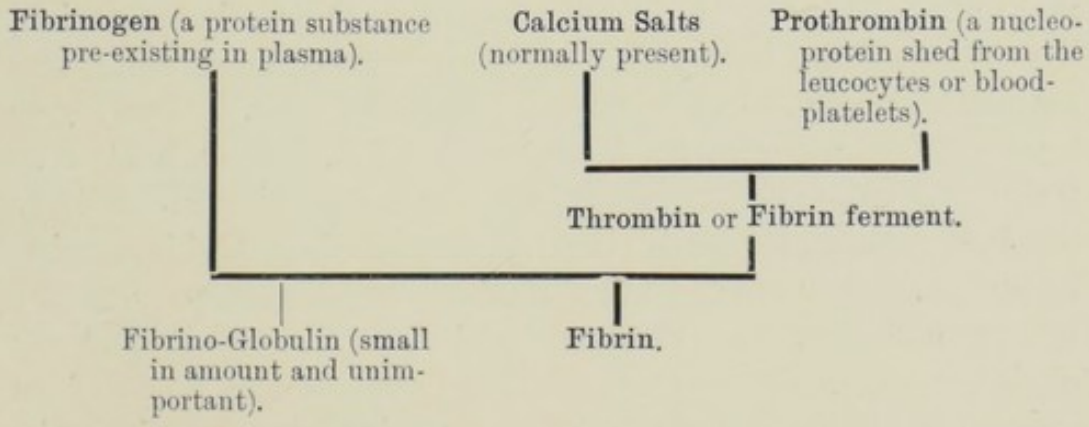
Red Thrombi.—These are formed in cases where there is rapid coagulation of the blood from any cause; and in their method of formation they are, for all practical purposes, identical with the clotting which takes place outside the body. They are formed, *e.g.*, in the heart immediately after death, or, it may be, even in the process of dying, where the circulation is in an extremely feeble condition. In the blood-vessels, where there has been sudden arrest of the blood-stream, they may also be seen as an extension of a pale thrombus. These clots are usually large, and may completely fill the chamber of the heart or the lumen of the vessel in which they have been formed. They are composed of masses of fused red corpuscles, with leucocytes entangled among them, and with fibrin threads very irregularly arranged.

Pale Thrombi.—In speaking of pale thrombi, it must be clearly understood that we refer to those which are pale from the beginning, and which have been slowly formed; and we must distinguish between these and the red thrombus which, by

decolourisation, has become pale some time after its formation; and also the pale, often yellowish-coloured, translucent, soft clot that is met with very frequently in the heart at a *post-mortem* examination, and which is formed by a coagulation of the serum after a partial separation of the erythrocytes.

The **true "pale" thrombus** is usually of an opaque, dull-white colour, firm in consistence, and very often more or less adherent to the wall of the vessel or to the endocardium. It is now generally accepted by pathologists that these pale thrombi are primarily and essentially composed of blood-platelets. We do not propose entering into the controversy which has been waged about the question of the origin and nature of these blood-platelets. We are not specially concerned here as to their mode of formation, but that they are definite formed elements of the blood seems beyond dispute. They are minute, discoid bodies, measuring from 2 to 2·5 μ in diameter, highly refractile, and having, in blood withdrawn from the body, a great tendency to run together into irregular masses. In these masses the outlines of the individual platelets are very soon lost. In their staining reactions they resemble the **nucleoproteins**, and it is quite possible that they may be, in part, the source of the **nucleoprotein (prothrombin)** which, acting in conjunction with the fibrinogen and calcium salts normally present in the circulating blood, brings about the formation of fibrin and produces coagulation.

Scheme (after Halliburton, *Handbook of Physiology*, p. 414).



Whatever be their source, and whatever be their special function, it is beyond dispute that they play the most important part in the formation of thrombi. Zahn has shown experi-

mentally that if the wall of a vessel be injured, certain of the formed elements, especially the leucocytes, fall out into the peripheral stream, which, in the normal condition, is free from these elements; and further, that these leucocytes adhere to the vessel-wall at the site of the injury. On these experiments, he based the view that the leucocytes were the principal factors in thrombus formation.

Bizzozero introduced a bundle of glass threads into a stream of blood which was allowed to flow freely from a severed artery, and he found that the threads became covered with a mass of fused platelets, which had all the appearances of a pale thrombus.

Eberth and Schimmelbusch showed that if a vessel be compressed in such a way that the endothelium is injured, or if the endothelium be injured by chemical means, and at the same time the blood-flow be retarded, an accumulation of blood-platelets takes place on the injured area. They showed that, with retardation of the blood-flow, the leucocytes, as Zahn and Cohnheim had demonstrated, pass from the axial to the peripheral stream, but that, on further retardation, the blood-platelets fall out, while many of the leucocytes return to the more central part. With still further slowing of the stream, the blood-platelets accumulate in great numbers towards the periphery. To any roughened or injured part of the lining of the vessel these platelets adhere in great numbers, and become fused together, or "conglutinate." This process, according to these observers, is the basis of thrombus formation. They maintain that the blood-platelets, by their disintegration, liberate a fibrin ferment; and, as a result, fibrin and more platelets are deposited upon the primary mass. Thus, layer by layer, the thrombus increases in size. They hold that the leucocytes and the red blood corpuscles play an entirely passive part, and merely become entangled in the increasing thrombus. In support of the blood-platelet, as opposed to the leucocyte theory, the experiments of Kemp and Calhoun[1] are of importance. They removed a portion of the blood of an animal, partially defibrinated it, and reintroduced it into the vessels of the same animal. This they repeated from six to ten times till the blood no longer coagulated. They found that

[1] Kemp and Calhoun, *British Med. Jour.*, 1901, vol. ii. p. 1539.

the platelets diminished progressively with each defibrination, and disappeared entirely when the blood was no longer coagulable. On the other hand, leucocytes were always present. There seems to be little doubt that the view of Eberth and Schimmelbusch is the correct one. The various changes can be seen in vessels after ligature, and we have ourselves observed the various stages of the process as it occurs in the

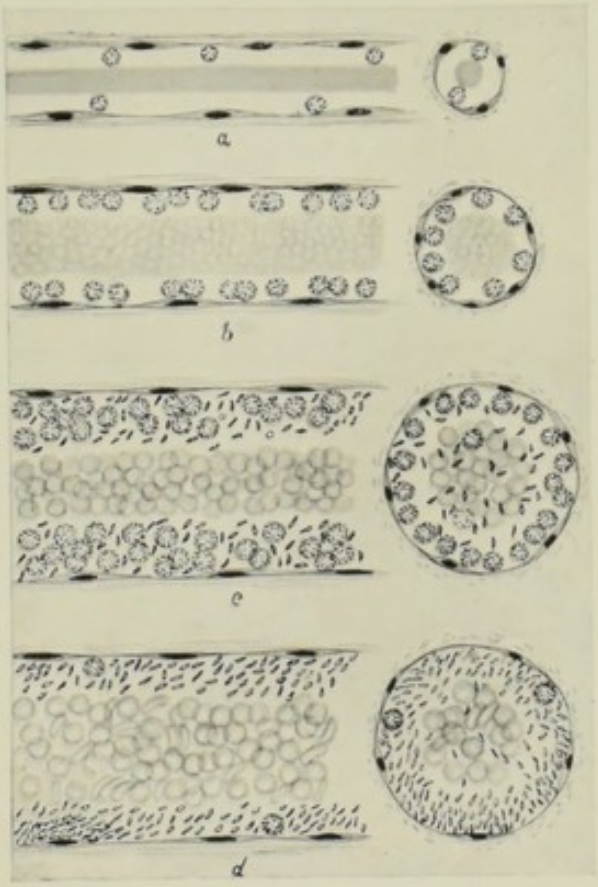


FIG. 26.—Diagram of Thrombus formation.

a. Normal blood-stream.
b. Slowing of stream—Leucocytes at periphery.
c. ,, Leucocytes and blood-platelets at the periphery.
d. ,, Blood-platelets accumulating in great numbers.
The increasing dilatation of the vessels is also shown.

thrombosed veins of experimental infarction of the kidney. In some of the vessels the thrombus consists wholly of fused blood-platelets, and in others, where the thrombosis is well advanced, the leucocytes can be seen practically unaltered. These observations were made on numerous specimens which we have been enabled to examine through the kindness of Professor Greenfield of Edinburgh, and we have fully confirmed the observations which he himself has made on this subject.

The characters and situations of thrombi, and the conditions under which they occur, will be most conveniently dealt with if the three important sites—the heart, the veins, and the arteries—are treated separately.

The Heart.—Clotting of blood in the various chambers of the heart is, of course, a usual occurrence after death, and it is important to distinguish between these **post-mortem clots** and those formed before death, or even during the period of dying. The *post-mortem* clots are either dark in colour, or they may be combined with pale or yellowish-coloured clot. This latter is most commonly found lying on the surface of the dark clot, and is due, as already stated, to coagulation of the serum from which the red blood corpuscles have been separated. The **post-mortem clots**, of whatever colour, are very easily broken down; the **ante-mortem thrombi** are pale in colour, tough, and very stringy, and may be adherent to or entangled in the muscular columns of the heart wall. In some cases, *e.g.* the **ball-thrombi**, they may lie quite free in the cavities of the heart. During the act of dying, especially if the period of heart failure has been prolonged, clots may form in various chambers of the heart, and especially on the right side. These are pale or yellowish in colour, and somewhat opaque; they are fairly tough, and also somewhat stringy. They may be loosely attached to or entangled with some part of the heart. These are very commonly continuous with definite *post-mortem* clot on the one side, and on the other with firmly adherent *ante-mortem* thrombus, either in the auricular appendices, or in the auricles or ventricles behind a flap of a valve, or entangled between the columnæ carneæ. It is often difficult to definitely classify these so-called "agony" clots. They differ to a certain extent in different cases, and appear to be stages in the formation of true *ante-mortem* thrombi. They are, as has been already stated, probably formed during the act of dying, and the more prolonged the period of heart failure is, the nearer they are in structure to the true *ante-mortem* thrombus. These "intermediate" clots are most commonly seen on the right side of the heart. They are frequently attached to some *ante-mortem* thrombus in the right auricular appendix, and tend to spread downwards through the tricuspid orifice towards the apex of the right ventricle, where they are frequently entangled in the

muscular bands. They may then pass upwards for a varying distance into the pulmonary artery. They are well seen in cases in which death has been caused by pneumonia. These clots, on microscopical examination, are found to consist largely of fibrin threads and entangled leucocytes. The true *ante-mortem* thrombi of the heart are most commonly found at sites where there is slowing of the blood-stream or where eddies form. The auricular appendices, especially the right appendix, are by far the commonest sites. They are also found entangled in the columnæ carneæ of the ventricles, more particularly towards the apex. They are specially well seen if there has been previous damage to the heart wall, *e.g.* over the endocardial surface of an infarction of the heart which has not proved immediately fatal. Sometimes large **ball-thrombi** are found in the left auricle in cases of mitral stenosis. *Ante-mortem* thrombosis frequently occurs on valves which are the seat of inflammatory changes or of chronic fibroid thickenings. These so-called **vegetations** are composed almost wholly of fused blood-platelets, firmly adherent to the diseased valve. The superficial parts may be very friable, and are often crowded with micro-organisms.

Veins.—*Ante-mortem* thrombosis is very common in the veins. It results from two main causes: (*a*) slowing of the blood-stream; and (*b*) dilatation, tortuosity, and other diseased conditions of the vessels. The thrombus very commonly commences, as an accumulation of blood-platelets, in the pouch of one of the valves, or at a part of the wall which has been injured. By the gradual accretion or conglutination of platelets, the mass increases in size until it blocks the lumen. Then follow rapid coagulation and formation of red clot, this latter extending up to the junction of the first large vein. At this point the clot causes obstruction, further coagulation follows, and extensive progressive thrombosis may result. Thus, thrombosis commencing in one of the superficial veins of the foot, may extend so as to fill the whole femoral vein, and may even be prolonged through the iliac veins to the inferior vena cava. In these cases of extensive thrombosis, the starting-point may have been a slight injury to the vein; but the spread is very often due to a weakened condition of the heart's action, favoured, no doubt, by general debility, and, it may

be, by a pathological condition of the blood itself. The uterine veins may be the starting-point of very extensive areas of thrombosis. The thrombi formed in cases of general debility are called **marantic** thrombi. We believe, however, that many of these so-called **marantic** thrombi are really due to the presence in the blood of abnormal products of metabolism or toxic products from bacteria, which act, not merely by damaging the vascular walls, but also by causing alterations in the coagulative power of the blood. It has been shown experimentally that the injection of peptone, of various tissue extracts, and of some animal poisons, brings about coagulation. Bacterial toxins, especially the toxin produced by growth of the *Pneumococcus*, may also cause coagulation. How exactly these bodies act we do not know, but we are strongly of opinion that this aspect of the thrombosis problem is of very considerable importance, and has been too much neglected, because of the emphasis which has been laid on the more simple **mechanical** view.

Arteries.—Local thrombosis on roughened or degenerated patches in arteries is not uncommon, but complete obstruction is rare. Where the lumen of the artery has been very much narrowed, as in some cases of atheroma, the obstruction to the blood-stream may be so great that complete thrombosis may occur. This is sometimes seen in the cerebral arteries. Thrombosis most frequently occurs in arteries where there has been complete obstruction by means of an embolus, and in these cases the thrombus usually spreads to the first collateral branch. Even after ligature of an artery, the thrombus formation may be very slight, a small, pale, conical thrombus being seen on the proximal side of the ligature. On the distal side, the clot, if present, is of the red variety. Further, in arteries, the thrombus formed may be to a considerable extent absorbed. It may become adherent at one side, and the lumen may be quite open on the other. Such thrombi are described as **parietal**.

Capillary thrombosis is frequently seen in inflammatory conditions, and is most commonly toxic in origin.

Thrombosis in aneurisms and the formation of **laminated** clot will be dealt with under **Diseases of Vessels** in a later volume on Special Pathology.

Subsequent Changes in a Thrombus.—A thrombus, as has

already been indicated, may become wholly or partially absorbed. This is brought about mainly by an invasion of it by young vessels and connective tissue cells, which gradually absorb and replace the coagulum. The process is the same as that which takes place in the healing of a wound, and will be fully described under **Repair**. The thrombus may soften and break down, especially if bacteria are present, and in this way it may give rise to emboli in various parts of the body. Further, a thrombus may become calcified and produce in the veins the so-called "**phleboliths.**"

ARTERIAL OBSTRUCTION

If an artery is obstructed, either partially or completely, anæmia of the area supplied by the artery is produced. This local anæmia is usually designated by the term **ischæmia.** If the obstruction is partial, or more especially if it is temporary, very slight nutritive changes may be produced. More serious results follow from complete obstruction, and it is to these especially that reference will now be made.

The obstruction may be caused in various ways, and it will be convenient, at this point, to deal with these.

1. **Changes in the wall of the artery itself.**—The lumen of the artery may become much narrowed by excessive contraction of its muscular coats, or by proliferative or degenerative changes, especially in the inner coat. The former may be brought about by excessive stimulation of the vaso-constrictor nerves. This rarely gives rise to serious nutritive disturbances. Sometimes, however, as in Raynaud's disease, where the vaso-constrictor irritation is constantly repeated, gangrene may ensue.

Contraction of the muscular coat may also be brought about by the direct action of electrical stimulation upon the muscle cells, by excessive heat or cold, and also by certain poisons, *e.g.* lead, ergot, and suprarenal extract. The prolonged administration of ergot sometimes gives rise to very serious damage; but, apart from this, muscular contraction caused by these agents is not commonly sufficient of itself to bring about complete obstruction, though some of them—*e.g.* lead—by causing

prolonged partial obstruction, may be directly the cause of atrophy and necrosis.

The proliferative and degenerative changes in the walls of the arteries, such as are found in atheroma or in syphilitic disease, rarely, of themselves, give rise to complete obstruction; but the narrowing and the degenerative changes combined are very frequent causes of thrombosis, and thus the partial obstruction may be made complete.

2. **Compression of the artery from without**, *e.g.* by a ligature or by a tumour; or **infiltration of the wall** by new growth.

3. **Obstruction of the lumen** by a thrombus formed locally, or by a thrombus, clot, or foreign body carried from some distance. This is by far the commonest cause of complete arrest of the arterial supply. Obstruction by a clot or foreign body carried from a distance is known as **Embolism**, and the obstructing body as an **embolus**.

EMBOLISM

The commonest emboli are those composed of **vegetations** or thrombi which have become detached from the aortic and mitral valves of the heart. Sometimes portions of a thrombus in a chamber of the heart or in an artery or vein, or fragments of clots formed on atheromatous patches in the aorta or other large artery, become detached and give rise to emboli. The embolus, from whatever source it comes, is carried by the blood-stream until it reaches an artery whose diameter is less than that of the embolus, and there it becomes impacted, such impaction often occurring at the bifurcation of a vessel. After impaction, it may be broken up and the smaller pieces carried further into the vessels, and thus one form of **multiple embolism** may result. This is specially the case if the embolus is **septic**, *i.e.* contains bacteria. The obstruction in the artery may be at once complete; or if not, it usually soon becomes so by the occurrence of thrombosis, which may spread for a considerable distance forwards in the artery, and also backwards to the first collateral branch.

In addition to the emboli formed from vegetations or thrombi, sometimes, though much more rarely, embolism results from the blocking of arteries by air, by fat, tumour or other cells, and by animal or vegetable parasites.

AIR EMBOLISM.—This is extremely rare. Sometimes, during a surgical operation, when large veins in the neck, near the thorax, are opened, considerable quantities of air may be aspirated into the heart, and death from **air embolism** may occur. In such cases, air-bubbles are found in the large veins near the heart, in the right auricle and ventricle, and in the pulmonary capillaries.

Hill and Macleod[1] showed that if animals were subjected to the action of compressed air for varying periods and quickly decompressed, bubbles of gas could be seen in the blood-vessels, heart, liver, etc. They deduced from this that the symptoms of **caisson sickness** are caused by air embolism, and based this conclusion on the fact that, during compression, the gases in the blood greatly increased in amount, and that during decompression, if this was too rapid, the gas quickly escaped in the form of bubbles.

The presence of air-bubbles in the blood and in the viscera, *e.g.* the liver, sometimes seen *post-mortem*, is due, in the great majority of cases, not to air embolism, but to the production of gas in the body by some of the bacteria specially concerned in the processes of decomposition. Even in cases where the air-bubbles have been found within an hour after death, careful examination has proved the presence of these bacteria. One of the chief members of this group is *B. aerogenes capsulatus*.

FAT OR OIL EMBOLISM.—Some writers maintain that this is a common form of embolism. Fractures of long bones with laceration of the bone-marrow, forcible manipulation of bones in the attempt to break down adhesions, lacerations and contusions of adipose tissue, and injuries to the liver, etc., are all stated to be causal factors. That embolism does occur in these instances, and especially after fractures of long bones, must be admitted; but we believe that these cases are very rare. The fat gets into the veins, is carried to the right side of the heart, and thence to the pulmonary capillaries, where it can be demonstrated.

Accumulations of fat filling capillaries in the lung, and more rarely in the kidneys, are sometimes found in diabetes mellitus; and in this disease minute oil globules may appear in the blood-plasma. In very advanced fatty degeneration of the

[1] *Journal of Hygiene*, vol. iii., 1903, No. 3, p. 401.

liver cells, *e.g.* in delayed chloroform-poisoning or in phosphorus-poisoning, the occurrence of masses of fat in the capillaries of the lung has been described. Though it is quite certain that, in these very advanced cases, fatty degeneration takes place in the endothelial cells of the capillaries in the various organs of the body, yet the larger accumulations seen in the lungs cannot, we think, be wholly attributed to the local production of fat, but much of it must be brought in the form

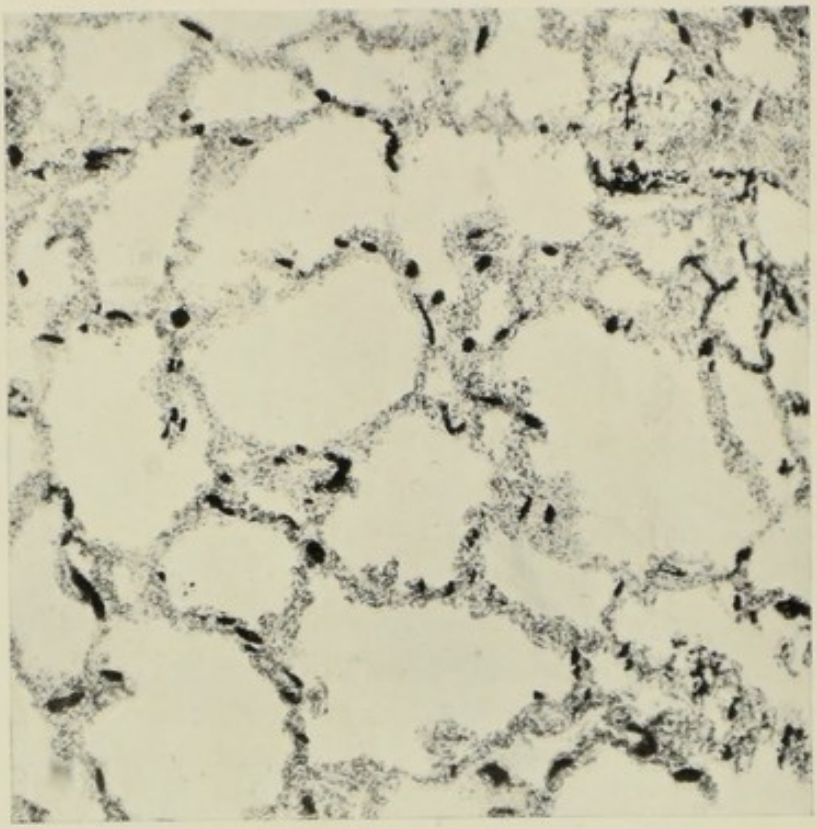


FIG. 27.—Fat embolism of Lung—showing fat globules (black) in the capillaries. × 60.

of emboli from elsewhere, and we consider that the liver is the main source of supply. The lung in **fat embolism** shows small, irregular, pneumonic patches and multiple small ecchymoses both in its substance and immediately under the pleura. The appearance is very similar to that seen in early acute septic infection of the lungs.

EMBOLI OF TUMOUR-FRAGMENTS, OR OF FRAGMENTS OF TISSUE derived from the liver in rupture or degeneration, from the bone-marrow in leukæmia, or from the placenta, are very uncommon, except those consisting of tumour cells which gain

entrance to the circulation by erosion of the wall of an artery or a vein. Usually these are very small, but occasionally tumour-fragments of larger size are found impacted in some of the arteries. Such larger emboli are sometimes seen in branches of the portal vein in the liver. After impaction, these tumour cells may undergo proliferation and give rise to metastatic new growths.

Emboli composed of Animal and Vegetable Parasites.—The most important of these are the **septic** emboli which contain pathogenetic bacteria. They most commonly arise from the breaking up and detachment of vegetations on the valves of the heart in ulcerative endocarditis, and of infective thrombi in the veins. Both emboli and thrombi of this nature are soft, and tend to undergo disintegration. The fragments become widely distributed, and often give rise to multiple emboli in various parts of the body. It is in this way that multiple pyæmic abscesses are commonly produced.

The Sites of Emboli.—As a rule, emboli from the valves or chambers of the heart are carried by the blood-stream, and become arrested merely because the lumen of the artery is too small to allow them to pass. Thus there seems no special reason why they should occur in one organ more than in another. Judging from records of the *post-mortem* room, the commonest sites are the kidney, spleen, and brain. Probably many of the other vessels, *e.g.* those of the limbs, receive the emboli; but the vessel which is obstructed is—owing to the free anastomosis present in these regions—of comparatively little importance, and no symptoms or signs follow the impaction. Emboli coming from the large veins, *e.g.* varicose veins of the limb or the pelvic veins, or from the right side of the heart or pulmonary artery, become impacted in the branches of the pulmonary artery; those coming from the pulmonary veins, the left side of the heart or its valves, or from the arteries themselves, lodge in the systemic arteries; while those coming from radicles of the portal system become impacted in the portal vein in the liver.

The commonest source of the emboli found in the pulmonary artery is a thrombus in the right auricle in chronic heart disease. Thrombosis occurs particularly in the right auricle, and more especially in the dilated right auricular appendix.

Portions or the whole of such thrombi easily become detached, are carried through the right ventricle and pulmonary artery, and so give rise to **pulmonary apoplexy** or infarction.

We have already stated that, as a rule, emboli are carried **with** the blood-stream, and follow its **normal course**, but there are some rare exceptions:—

1. **"Crossed" or "Paradoxical" Embolism.**—This is produced by emboli which pass from the systemic veins, with the blood-stream through a patent foramen ovale into the left auricle, and so into the systemic arteries.

2. **Retrograde Embolism.**—This very rare condition occurs only in veins, and the emboli are carried in a direction **opposite to that of the blood-stream.** This is usually explained by a temporary reflux of the blood in the vein, owing to some obstruction to the return of blood to the right heart. Ribbert suggests that in those cases of obstruction, where there is complete or almost complete venous stasis, pulse waves occur which gradually force the embolus backwards. In this way, an embolus of the inferior vena cava may be carried into the renal or hepatic vein. Welch[1] notes that liver cells have been met with in the cerebral and renal veins in cases of hepatic cirrhosis. This he explains on Ribbert's hypothesis.

Effects of Embolism.—It must be clearly understood that we are here dealing with so-called "**bland**" or non-septic emboli. The obstructive results are the same whether the emboli be "**bland**" or **septic**; but in the latter form there is, in addition to the degenerative changes, the softening action of the bacteria and their products. In the "**bland**" or non-septic embolus which produces complete obstruction of an artery, the general effects are the same as those brought about by thrombosis or by compression of the vessel; and in discussing the subject, we have based our statements on the results both of ligature of the artery, and on artificial obstruction produced by means of tobacco or other seeds, and we have further controlled these results by comparison with the effects of embolism as seen in disease. When an artery is obstructed, certain **circulatory changes** almost immediately become pronounced. These are very soon followed by **nutritive** disturbances, and later both

[1] Welch, "Embolism," Clifford Allbutt's *System of Medicine*, vol. iv. p. 228, 1905.

processes go on side by side. It is convenient, however, to take the earlier pronounced changes first and deal fully with them, leaving the nutritive disturbances for consideration later.

Circulatory Phenomena following complete obstruction of an important Artery, *e.g.* the superficial femoral :—

These are best studied experimentally by ligature of the artery. At first, the limb becomes cold, numb, and blanched, and pulsation in the artery beyond the ligature ceases. If special care is taken to avoid damage to the limb, and if the vessels and heart are healthy, the limb, after a few hours, again becomes warm and red—even warmer and redder than the opposite limb. It may also become slightly swollen, and pulsation returns in the peripheral vessels. After a time, the circulation in the limb appears to have resumed its normal condition. The explanation of these changes is that anastomosing channels are gradually opened up, and in a short time a sufficiently complete **collateral circulation** is established. The anastomosis between vessels in most parts of the body is very extensive. The channels may be large and very easily seen; but, on the other hand, they may be extremely minute or very scanty, and may not be demonstrable until an obstruction has called them into use. Though there are some possible exceptions, *e.g.* the **end-arteries** of Cohnheim (which will be referred to later under **Infarction**), still it may be said that there is scarcely any part of the body where some communications do not exist. These existing communications, often very abundant and very tortuous, are enlarged and opened up. Not only do the vessels dilate, but their coats become thickened and strengthened. If the newly opened up channels are not well supported, they may become varicose. There is practically no evidence that **new** vessels are formed in cases of acute arterial obstruction. The collateral supply is established in a greater or less degree in all cases; and, where it is imperfect, some special or abnormal condition of the vessel or tissue is the cause. For the perfect and rapid establishment of collateral circulation, certain factors are essential.

1. **The arteries must be healthy.**—If any of the coats of the vessel have undergone degenerative changes, proper expansion and contraction are interfered with, and the channels of communication are not properly opened up.

2. **There must be sufficient blood-pressure.**—Whatever explanation be given of the cause of the opening up of these collateral branches, it is quite definitely proved that, if the heart is weak, and is not capable of driving the blood with sufficient force, the anastomosis will be incompletely established.

3. **The vitality of the affected area must be sufficient to allow of its surviving till the collateral supply is established.**—In cases of debility, where the nutritive processes are imperfect, the cutting off of the blood-supply, even for a very short time, may be sufficient to cause degeneration and death of the tissues before the available channels can be opened up.

4. **There must be available channels of collateral supply.**—As has been stated, these exist in almost all parts of the body; but they may have become altered in such a manner by disease, or so many arteries may have become obstructed at the same time, that no sufficient collateral supply can be established. Further, the obstructed artery may be one of the **terminal** or **end-arteries** of Cohnheim. Even between some, if not all, of these and other vessels there are collateral channels; but they are very few, and not sufficient to compensate for the obstruction, even if they enlarge rapidly and to their full capacity.

The following are the most important **end-arteries**:—

i. The renal artery and its branches, especially the interlobular cortical branches.

ii. The splenic artery and its branches.

iii. The larger branches of the coronary arteries of the heart.

iv. The arteries supplying the basal ganglia of the brain, and those supplying the grey matter of the spinal cord. The collateral supply of the cortical arteries of the brain and the spinal cord is more abundant, but yet imperfect.

v. The superior mesenteric artery, and some of the coronary branches to the stomach.

vi. The central artery of the retina.

vii. The branches of the pulmonary arteries, especially those distributed to the surface and free margins of the lobes.

viii. The branches of the portal vein—practically an artery in its distribution—within the liver have very few anastomoses.

Obstruction of a branch of one of these arteries, especially in organs such as the spleen or kidney, may lead to certain important changes in the part whose artery is blocked. These changes are classed under the term **infarction**, and the affected area is called an **infarct**.

INFARCTION.—As has just been stated, obstruction to an **end-artery** leads to changes in the area of tissue supplied by that artery. It becomes swollen, and often engorged with blood, and on microscopical examination every part of the tissue seems "stuffed" with red blood corpuscles. To this condition, Virchow applied the term **infarction** or **stuffing**, and to the area he gave the name **red** or **hæmorrhagic** infarct. In many cases, however, *e.g.* in the spleen and kidney, the area is pale and bloodless, and shows some reddening only at its periphery. These areas have been called **pale** or **anæmic infarcts**. Both red and pale infarcts are commonly seen, and, naturally, pathologists sought an explanation of the difference. Virchow regarded the pale infarct as a later stage of the red. He maintained that the pallor was due to alterations taking place in the blood corpuscles during the process of necrosis. Other authorities still hold that infarcts in the kidney and the spleen, at any rate, are always pale at the beginning; and that the red colour is due to the re-entry of the blood into the bloodless area, or to hæmorrhage from the rupture of degenerated vessels. Others, again, hold that pale infarcts always result from **arterial**, and red or hæmorrhagic infarcts from **venous** obstruction. On account of these marked differences of opinion, much confusion exists; and we propose, therefore, to deal fully with the subject. The views we put forward are not new, but they are based on actual experiment and observation. They correspond in the main with the observations of Bernard Cohn, Cohnheim, and Litten, and have been taught for many years by Professor Greenfield in the University of Edinburgh. The experiments on which this teaching is based were originally carried out by Professor Vulpian and Dr Carville in Paris in 1874, and the specimens were demonstrated by Hardy, the Professor of General Pathology. At a later period, the experiments were repeated by Dr George Mackay in Berlin, and the specimens were sent to Professor Greenfield for examination. More recently, one of the writers had the opportunity of following

closely an extended series of experiments and observations conducted by Dr Duncan Forbes in the Pathological Department of the University of Edinburgh, on the suggestion and under the direction of Professor Greenfield.

In these experiments, mainly carried out on rabbits and dogs, obstruction of the artery was brought about by compression, by ligature, and by the injection of tobacco, begonia, and mustard seeds into the arterial circulation. In some animals the organs were exposed and the ligature applied, or the seeds injected, so that the whole process could be carefully watched. These observations were controlled by killing the animals at varying periods, and examining the organs which had not in any way had their natural positions disturbed. Controls were made by ligature of vein and artery, vein alone, and artery alone. Experiments were also made by detaching the capsule, ligaturing the ureter, etc. In these experiments, the changes observed corresponded in all important details with those seen in the human subject in disease.

We propose dealing, in the first place, with the main experiments, together with the conclusions to be drawn from them.

Obstruction of the entire Renal Artery.—The changes are identical whether the obstruction be produced by ligature or by embolism, but the appearances vary with the length of time the obstruction has lasted. Almost immediately after the obstruction, areas of congestion appear on the surface of the kidney. Two hours after the ligature is applied, the kidney has become distinctly enlarged, and there is marked congestion, especially in the region of the pelvis and about the apices of the pyramids. The enlargement of the organ and the congestion increase, and attain their maximum in a period of from sixteen to twenty hours. During this period, there has been a considerable increase in the weight of the kidney. Forbes[1] states that in four hours the increase is 4 per cent., and in eleven hours it is 39 per cent.

Sections of the kidney in the earlier stages of this hyperæmic period show that the congestion of the vessels is most marked in the medulla, especially in the parts adjoining the pelvis and

[1] Forbes, "A Study of Experimentally-produced Infarcts of the Kidney," Thesis, Univ. Edin.

calyces, and also in the superficial parts of the cortex. The deep part of the cortex is pale. During the later stages of this period, the congestion becomes more marked and is more widely spread. Microscopical examination indicates in a general way the order in which the dilatation proceeds. First, there is engorgement of the larger veins, the stellate veins under the capsule, and the branches of the vessels just as they approach the renal arches ; then, in a few hours, the vessels of the medulla and some of the glomerular tufts near the boundary zone are much engorged ; and later, the remainder of the glomerular tufts and the vessels of the intertubular plexus. Hæmorrhage is frequently seen arising from the dilated vessels in the medulla, but very rarely from the cortical vessels. From twenty hours onwards, the congestion becomes lessened and the size of the kidney gradually diminishes. Degeneration and death of the tissues follow, and a small pale necrotic mass, which may become partially or completely calcified, is produced.

Obstruction of Branches of the Renal Artery.—Areas of congestion of a purplish colour appear on the surface of the kidney a very short time after obstruction. These vary in size, number and position according to the size, number and distribution of the branches obstructed. Examined *in situ*, a few hours after obstruction, purplish areas are seen on the surface. On removal of the kidney from the body, these purplish areas, which appear distinctly raised above the surface, are found to be wedge-shaped, the base of the wedge being at the free surface of the kidney. At a later period after the obstruction, *e.g.* from twenty-four to thirty hours, there is marked change in colour; the originally purplish areas have now become pink, especially at their periphery, and are surrounded externally by a pale boundary layer. On section, these pink areas are seen to be wedge-shaped, and are sharply marked off by the pale boundary line already noted. There is also a very characteristic narrow pale zone immediately under the capsule, and this is sharply separated from the wedge-shaped infarct. At a later period—forty-eight hours—the surface may still show purple or pink irregular areas raised above the surface. All these irregular areas are on section seen to be wedge-shaped infarcts. Centrally, in the larger ones there is a pale area surrounded by

a broad red band, whilst in some of the very small ones only pale depressed areas may be found.

Microscopical examination of these early infarcts shows that the capillaries in the central part are engorged with blood, and that the tubule-cells, as well as the connective tissue cells, are undergoing necrotic changes. The blood corpuscles stain imperfectly, the tubule-cells are very granular, and many of their nuclei have completely lost their power of taking up nuclear stains. Leucocytes of various forms may be found in and

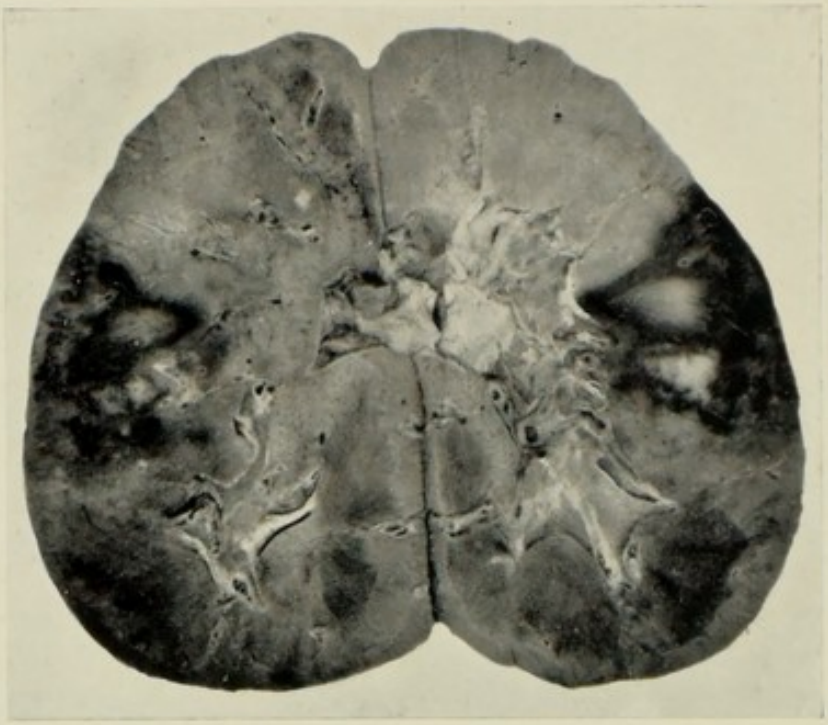


FIG. 28.—Infarcts in the Kidney, showing raised wedge-shaped area, with pale centre and congested periphery.

between the tubules, and also in the glomeruli. In the paler areas, coagulation necrosis is very marked. Immediately under the capsule, and at the periphery of the infarct, the degenerative changes are less evident, and the cell-nuclei may stain perfectly.

In the later stages, the whole infarct is pale, is depressed below the surface, and is surrounded by a reddish congested area. On microscopical examination, the whole pale area shows advanced necrotic change, and at the periphery there is an inflammatory reaction, with dilatation of the vessels and commencing connective tissue formation.

It will be convenient to summarise briefly the main changes in an infarct due to obstruction of a branch of the renal artery in the rabbit and in the dog, as these correspond with those which are found in the case of the human subject.

The infarct in the early stages is of a dark venous colour, firm in consistence, and raised above the surface. The marginal part becomes pale in colour, and in a few hours is slightly depressed below the level of the central part. On section at

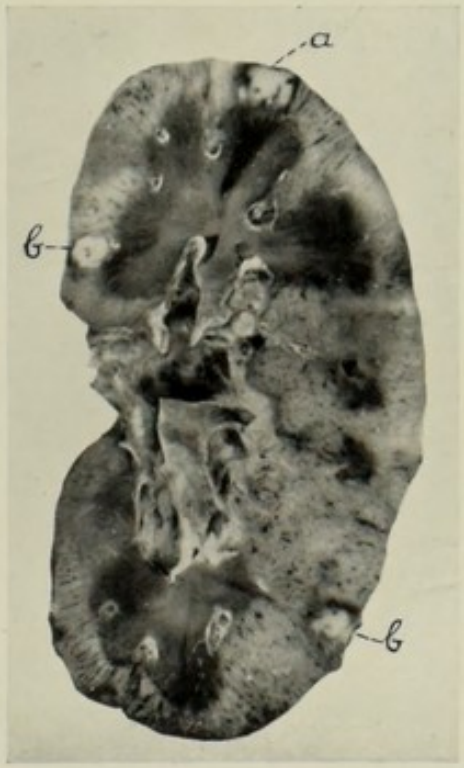


FIG. 29.—Infarcts in the Kidney, showing the pale centre and congested periphery. Note that the surface of the infarct is depressed below the general surface of the kidney. *a.*, Infarct extending into medulla. *b.b.*, Smaller infarcts confined to cortex.

this stage, a central reddish or purple area surrounded by a pale margin is seen. Then follow a decolourisation of the necrotic tissue and contained blood in the central part and a dilatation of vessels at the inner part of the pale area, the infarct thus becoming divided into three zones:—

1. A central pale area of necrosis.
2. A reddish zone, in which the capillaries are much dilated and congested.
3. A pale outer zone, where the circulation is still active.

Even the smallest infarcts are reddish and raised at first, but

they very soon become pale; and, unless examined *in situ* within four or five hours after obstruction, this red colour has disappeared, and they are described as pale infarcts. In the late stages, necrosis has extended throughout the infarct, which often becomes infiltrated with leucocytes, and invaded to a certain extent by connective tissue corpuscles and young blood-vessels. In this way the infarct, if small, may become completely absorbed; or, if of larger size, a definite capsule of fibrous tissue may be formed round it, and the central part may undergo calcification. Very commonly in an infarct two areas in which

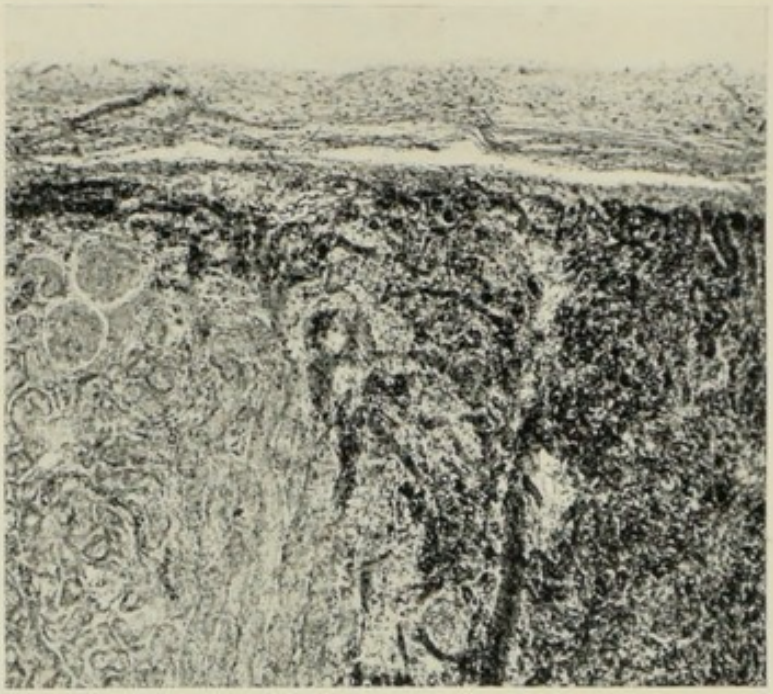


FIG. 30.—Margin of an infarct in the Kidney, showing dark (congested and cellular) and paler (necrotic) area. ×40.

the necrotic changes are not so advanced are seen — one immediately under the capsule, and the other forming, as it were, a bridge between the cortical and medullary part of the infarct, in the region of the boundary zone. These are parts where the collateral supply is sufficient to maintain the nutrition.

Infarction of the Spleen.—The effects of arterial obstruction are well seen in the spleen. In the dog, the spleen, still attached by its vessels, can be lifted from the abdomen with practically no disturbance of its vascular arrangements, and the results of obstruction carefully observed. Within five

minutes after the obstruction of a branch of the splenic artery, dark, livid, raised areas are seen, running transversely to its long axis, and extending very often completely across the organ. These gradually become more swollen and more definitely raised above the surface. On microscopical examination, the whole area is found to be filled with red blood corpuscles, and it is quite impossible to distinguish the condition from one of hæmorrhage into a localised area. This marked hæmorrhagic condition is, no doubt, dependent on the special structure of the organ—the blood easily penetrating the meshes of the splenic pulp. Decolourisation is a later process, and is mainly due to changes in the hæmoglobin, though necrosis also takes place, and necrotic Malpighian bodies may be made out in the pale area. These pale areas are usually surrounded by a more or less narrow congested band, and in this band new fibrous formation takes place. As in infarction in the kidney, the degenerated area becomes cut off from the surrounding part by a definite fibrous capsule, and absorption of the dead and degenerating area may occur with varying degrees of completeness.

FIG. 31.—Infarct in Spleen—showing raised surface, transverse arrangement, and pallor.

From these experiments, it is established that infarcts in the kidney and spleen, at any rate, are at first always **red**. If the infarct is very small, pallor supervenes in a few hours; and, even in a congested infarct, the pallor may appear almost immediately after the organ has been removed from the body. **What, then, is the explanation of this vascular engorgement?** From the experiments of Litten, Cohn, Vulpian, and others, there can, we think, be no doubt that the engorgement in the kidney is due to the opening up of pre-existing collateral channels, and to the afflux of blood through minute communications which normally exist between the vessels supplying

the ureter and pelvis of the kidney and those of the medulla, and between branches of the lumbar arteries which supply the perinephric tissue and the vessels in the capsule of the organ. Cohnheim attributed the engorgement to a reflux through the veins. He argued that the blood was driven through the veins largely by pressure communicated from the arteries. If, therefore, an end-artery were blocked, the pressure in the veins draining the area which it supplies would be practically negative, whereas the pressure in neighbouring veins and in the inferior vena cava would still be sufficiently high to force the blood back into the veins of the infarct, and thus its capillary system would be filled up. This was a very simple explanation, and one which, at first sight, seemed likely to be correct; but Litten and others showed that if **both artery and vein were ligatured,** the engorgement was **greater** than if the **artery alone** were obstructed. Cohn, Litten, and Vulpian found that if, after ligature of the renal artery, the renal vein were cut, blood continued to flow from the severed vein. It was further demonstrated by Litten and others that if, after ligature of the renal artery, a cut were made in the kidney, bleeding occurred; but that, if the collateral supply were then cut off by stripping the capsule and ligaturing the ureter, the bleeding at once stopped. Further, it was shown that if all sources of collateral supply were cut off and the artery was then obstructed, no engorgement took place. The more important of these results were confirmed by Greenfield, and afterwards by Forbes, working under his direction. Thus, Cohnheim's reflux theory cannot be maintained, and the inevitable conclusion from these experiments is that the hyperæmia is due to the collateral supply. Further investigation has shown that the collateral supply is unable to maintain the outflow through the veins, and, in consequence, thrombosis is apt to occur, and thus to increase the engorgement.

In infarcts produced by obstruction of a branch of the renal artery, the capillaries and smaller vessels become distended with blood, and, in the boundary zone, rupture and hæmorrhage into the collecting tubules or into the subcapsular region take place. At the margin of the infarct, the glomerular capillaries often become very much distended, and the intertubular capillaries which are nearest the collateral supply become

rapidly filled with blood (fig. 30). Hæmorrhage may occur into the space between the glomerular tuft and Bowman's capsule. This filling of the capillary system is rarely complete, for many of the vessels become blocked by swelling of, and degenerative changes in, their lining epithelium, and by pressure and

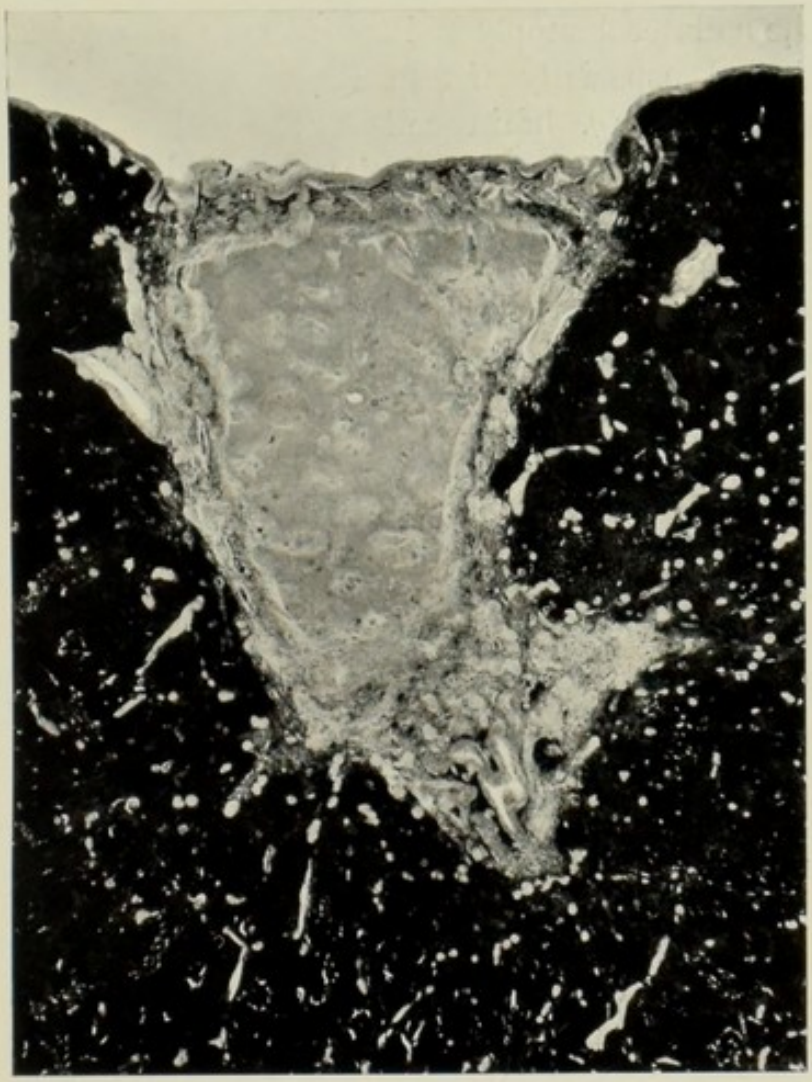


Fig. 32.—Old infarct in the spleen, showing pale caseous mass surrounded by a fibrous tissue capsule. Note depression below the surface of the spleen. ×5.

swelling caused by the transuded lymph. There is no evidence of a refilling of the capillaries from the veins; and if the collateral supply is well established, the engorgement goes on after the veins have become blocked by thrombi.

The secondary pallor is due largely to necrotic changes and to blocking of the capillaries, but in part also to the process of obliteration of vessels when their function is at an end. When

the active process of absorption ceases, or when the dead area is enclosed by fibrous tissue, no engorgement is found.

Nutritional Changes following Arterial Obstruction.—These vary in amount, according to the rapidity and the degree of completeness with which the collateral supply can be set up, and also according to the vulnerability of the tissue affected. Where the collateral supply is imperfect, or where it is slowly produced, and especially if the tissue involved be a highly functioning one, *e.g.* brain cells or secreting cells, **necrosis** follows (*vide* Chapter on **Necrosis**). Ultimately, in infarcts, the vascular engorgement passes off, and the necrotic mass, which is opaque white or yellowish-white in colour, becomes partially or completely absorbed by means of leucocytes and other phagocytic cells, and by new blood-vessels which are projected into the dead areas from the vessels of the surrounding living tissues. If the infarct is not completely absorbed, it becomes a caseous mass, enclosed by a capsule of fibrous tissue. (See fig. 32.)

Obstruction of Arteries of the Brain.—The result of obstruction of the cerebral arteries, whether by embolism or thrombosis, is the **softening** of a portion of the area supplied. Hyperæmia is usually not a marked feature. The softening, as has been already indicated, does not usually involve the **whole** area supplied by the obstructed artery, unless there is in addition a wide-spread general arterial degeneration — a condition in which a collateral supply is not readily available. The infarct often becomes **liquefied**, and in great part absorbed, leaving, it may be, only a cavity or pseudocyst containing some milky fluid.

Infarction of the Heart Wall.—This is usually the result of thrombosis in diseased coronary arteries. The commonest sites are certain parts supplied by the left coronary artery, viz.—

1. The anterior wall of the left ventricle near the apex.
2. The anterior part of the interventricular septum, towards the apex of the heart.
3. The posterior part towards the apex or other portion of the interventricular septum.

The areas of infarction are irregular in shape and firm, and

the central part is either yellowish or dull white. They are surrounded by a dark reddish area of hyperæmia. If extending to the endocardium, thrombosis takes place over them, and, at a later period, aneurism of the heart may result. On microscopical examination, the muscle fibres are necrotic, and are seen to be in process of absorption, their place being taken by fibrous tissue.

Pulmonary Infarction.—Infarcts of the lungs, or **pulmonary apoplexies**, are very commonly multiple. They are wedge-shaped, with the base of the wedge at the surface, dark-red in colour, raised above the surface, and very firm. They are usually situated near the free surface, and especially at the margins of the lung, though they may sometimes be found deeper in the lung substance. They are more common in the lower than in the upper lobe. Unless they are septic, the pleural surface shows no signs of inflammatory reaction. On microscopical examination, the air-alveoli are filled with red blood corpuscles, and the alveolar capillaries are much distended with blood. Necrosis is usually entirely absent, probably owing to the very complete collateral circulation through the bronchial arteries, and therefore the comparatively slight impairment of nutrition. Decolourisation may take place by alterations in the hæmoglobin, and there may result a localised increase in fibrous tissue, which may contain pigment derived from the broken-down red corpuscles.

Causes of Pulmonary Infarction.—The condition of pulmonary infarction in the human subject is most commonly associated with great venous engorgement in the lung, due very often to disease of the mitral valve of the heart. In this condition of venous engorgement, thrombosis in and hæmorrhage from the distended vessels might very readily occur; and some regard the infarctions as due to this thrombosis and hæmorrhage. Most probably, in some cases this is the actual explanation of the condition. **Embolism** as a cause must, however, also be considered. In cases of mitral disease with dilatation of the right side of the heart, thrombosis almost invariably occurs in the dilated right auricular appendix. Portions of this thrombus very easily become detached, are carried into branches of the pulmonary artery, and may give rise to infarction, as do emboli in other arteries; but even in these cases the previous

congestion of the vessels of the lung is a contributory cause. Portions of such thrombi are frequently found in the pulmonary vessels. Hæmorrhages from the bronchi or into the air-cavities, as causal conditions, need not be considered. There is abundant evidence that during respiratory movements such blood becomes scattered and produces areas of collapse, which are surrounded by areas of distension of the air-cavities, conditions which are not seen in pulmonary infarction. Dilatation of the collateral channels takes place in the lungs, but the engorgement cannot be explained wholly on the ground of this dilatation. Further, in all cases in which pulmonary infarctions occur, there is a pre-existing greatly engorged state of the capillaries and a high venous pressure, conditions which favour hæmorrhage; and all facts point to the venous dilatation and the hæmorrhage as important causal factors in their production.

ACTIVE HYPERÆMIA

Active Hyperæmia of any part of the body is due to an increased afflux of blood to it. The part, if on the surface, becomes of a dark-red colour, the local temperature is raised, and there may be some swelling. A more detailed examination shows that the arteries and capillaries of the hyperæmic area are dilated, and that the blood-flow is more rapid. There may also be an increase in the normal lymph transudation, though this increase is not usually marked, and is not an important factor in the process. The essential change in all cases is the arterial dilatation, and this may occur under a variety of circumstances.

I. **Physiological.**—When special organs are called into functional activity, the arterial supply is increased. This is physiological, and is necessitated by the extra nourishment required by these organs. Among the commonest examples of this is the increased blood-supply of the uterus during pregnancy, and of the mammary glands during lactation.

II. **Pathological.**—In studying pathological dilatation of arteries, it is often very difficult, or even impossible, to determine the ultimate cause. There are many factors to be considered, and these interact on one another in almost all cases.

Alterations in the walls of the arteries may be caused by interference with the nerve-supply, or pathological conditions of the innervation may be due to degenerative conditions of the vascular walls. Again, interference with the blood-supply may cause both damage to the nutrition of the vascular walls and derangement of the nervous control. Still, for convenience, it is necessary to study each group of cases separately.

(1) **Hyperæmias caused by the direct application of mechanical, chemical, thermic, or other analogous forms of irritant.**—Exposure of the frog's mesentery to the air, or to irrigation by a 1·5 per cent. salt solution, is sufficient to set up an active hyperæmia in it. So, the application of alcohol, ether, ammonia, mustard, cantharides, etc., to the skin or mucous membranes is followed by a local arterial hyperæmia. Nitrites cause arterial dilatation by a relaxation of the non-striped muscle of the arterial wall.

Ligature of the finger produces anæmia of the part, and is followed, on removal of the ligature, by active hyperæmia. Cold acts in the same way. The application of moderate heat immediately gives rise to active hyperæmia. In most of these cases, and certainly where there has been previous anæmia, even for a short time, the nutrition of the vascular walls is damaged, though the causal agents also exert part of their dilating influence through the vaso-motor nerves. This dilatation of the arterioles can be brought about by the application of moderate heat to the skin, even when the nerves to the arteries have all been cut. The arterial dilatation must therefore, in some instances, be capable of occurring independently of the vaso-motor centres. The hyperæmia may be very marked, and the distension so great that rupture of badly supported capillaries may take place. This is sometimes seen when a distended bladder is too quickly emptied by a catheter. The ill-supported vessels in the mucous membrane become rapidly distended with blood, are ruptured, and produce extensive hæmorrhage into the bladder.

(2) **Those due to vaso-constrictor paralysis and vaso-dilator stimulation.**—Section of the sympathetic nerve in the neck in animals is followed by arterial dilatation and redness in the corresponding half of the head and neck. The same

result is sometimes seen in the human subject, as a consequence of pressure upon the nerve by tumours, enlarged glands, etc. Reflex vaso-motor influence also leads to hyperæmia, *e.g.* in blushing. The stimulation of vaso-dilator fibres probably also plays some part in certain cases; and the erythemas of the skin—seen in the area of distribution of an injured nerve—the erythemas in other conditions, the rashes in fevers, and the wheals in urticaria, may be in part due to this stimulation. In the infective conditions above noted, the toxins may act as vaso-dilators, but, undoubtedly, damage to the vascular walls by these toxins plays a very important part in bringing about the active hyperæmia.

CHAPTER IV

INFLAMMATION AND REPAIR

INFLAMMATION

We do not think it advisable to enter into the discussion as to what special reactions of the tissues should be included under the term **inflammation**, and what should be excluded. For all practical purposes, it is sufficient to consider, under the term, that series of reactions which follows irritation or injury, and which has for its special purpose the prevention or repair of damage. Thus we include both the effects of the injury, and that series of changes which nature exhibits in her attempt to remove or oppose the cause, and to remove and repair its results. From the time of the injury until complete healing takes place, the various reactions co-operate with, and are often dependent upon, one another; and it is generally impossible to draw an absolute line between the end of the one and the commencement of the other. For the study of the reactions, it is necessary to make definite lines of separation; but it must be clearly understood that these are more or less arbitrary, and that the processes may go on side by side.

Causes of Inflammation.—Among the most important of the causes must be placed **bacteria and their toxins.** Other irritants — mechanical, chemical, and thermic — which cause tissue damage will excite the reactions for the prevention and repair of that damage. Even though the injury be extremely slight, protective action and repair are necessary; and all the inflammatory reactions will exhibit themselves in a more or less pronounced degree. Thus it may be stated broadly, that anything which causes damage or irritation to the tissues may excite these reactions which are classed under the term **inflammation.**

The character of the reaction and the degree of its manifestation will, of course, depend on the nature of the irritant and

the intensity of its action. Thus, the majority of pathogenetic bacterial irritants will call forth a greater leucocytic response than will a foreign aseptic body; and certain bacteria will cause a greater reaction than others. Again, the vitality and the power of response on the part of the tissues are of considerable importance. A slight injury may give rise to serious inflammatory phenomena in tissues the vitality of which is low, whereas in healthy tissues the reaction would be very slight. A similar variation is seen in individual tissues under different conditions. If a tissue is exhausted from any cause, its reactive power may be almost destroyed. For example, in cases of pneumonia, there is usually a very pronounced leucoblastic reaction in the bone-marrow and a resulting protective leucocytosis; but in certain cases, and especially in alcoholic subjects, this reaction may be practically absent; and in such cases the protective power of the leucocytes is lost, and the prognosis much more serious.

Phenomena of Inflammation.—These can be well studied during life in a transparent vascular membrane, such as the mesentery of the frog or the omentum of the guinea-pig. If these are exposed and irritated, after a short preliminary stage of transitory anæmia, the blood-vessels dilate, the blood-flow becomes accelerated, and a condition of **active hyperæmia** is set up. Soon, however, the blood-stream becomes sluggish, and the venules show irregular dilatation. Actual arrest of the circulation with thrombosis may occur in certain areas, especially if the vessels or tissues have been previously diseased. During this so-called period of **stasis**, there is an increased transudation of lymph through the vessel-walls, leading to swelling of the inflamed area and to the production of **inflammatory œdema**. The membrane is now red, swollen, and usually opaque. The opacity is increased by accumulations of leucocytes, which are seen to leave the dilated vessels and to emigrate to the focus of infection or to the point of injury. Red blood corpuscles may also be seen in the tissues.

If, now, the irritant is removed and the resulting damage be very slight, these phenomena gradually subside; but if the irritant has caused degenerative or necrotic changes in the tissues, the inflammatory processes continue until repair is effected. The damaged and necrotic tissues are absorbed and

removed by phagocytic cells, and are probably also acted upon by certain ferments which may be produced by these cells. New capillaries are formed from pre-existing capillaries, and these, together with proliferated connective tissue, and perhaps other cells, pass into the damaged area, and eventually effect repair. These phenomena must now be studied in detail.

I. VASCULAR PHENOMENA INCLUDING BOTH THE CHANGES IN THE VESSELS THEMSELVES AND IN THEIR CONTAINED BLOOD.

Omitting the unimportant stage of **transitory anæmia** which may occur in certain cases, there is at first an **acceleration of the blood-stream** with a dilatation of the minute vessels, especially the capillaries and venules. The dilatation of the arterioles is very slight, and seems to play no important part. Some, indeed, hold that it does not occur at all. Even if we deny the occurrence of arterial dilatation, the acceleration of the blood-flow is quite well explained by the dilatation of the capillaries and venules, and the consequent diminished peripheral resistance. The dilatation of the vessels can only be explained by the action of the irritant *directly* upon the vascular walls, or through the intervention of their **local** vaso-motor apparatus; for dilatation of the vessels occurs even when all connection with the cerebro-spinal vaso-motor centres has been severed. Lister showed that the diameter of the capillaries may be increased by only one-fifth to one-quarter; but this means a very considerable increase in their sectional area, and consequently in the amount of blood flowing through them. The period of active hyperæmia, which may last for only a few hours, is succeeded by the period of **stasis**, in which there is further dilatation of the vessels and a **slowing of the blood-stream.** This slowing may become very marked, and, in certain parts, **complete** arrest may take place, with consequent thrombosis. When the stream becomes sluggish, a rearrangement of the relative position of the fluid and the formed elements of the blood is observed. The leucocytes and the blood-platelets fall out into the clear plasmatic peripheral stream; but, just before actual stasis, the leucocytes tend to return to the centre, and a mixing of all the elements takes

place, though there is generally found in the outer part of the peripheral stream an excess of blood-platelets. The rearrangement of the corpuscular elements is merely a physical phenomenon. The velocity of the axial is always greater than that of the peripheral stream, and the corpuscles circulate in the axial stream so long as the velocity is sufficient. As the blood-flow becomes sluggish, the leucocytes, which are of less specific gravity than the red blood corpuscles, tend first of all to fall out into the peripheral stream. If the rate of flow is still further

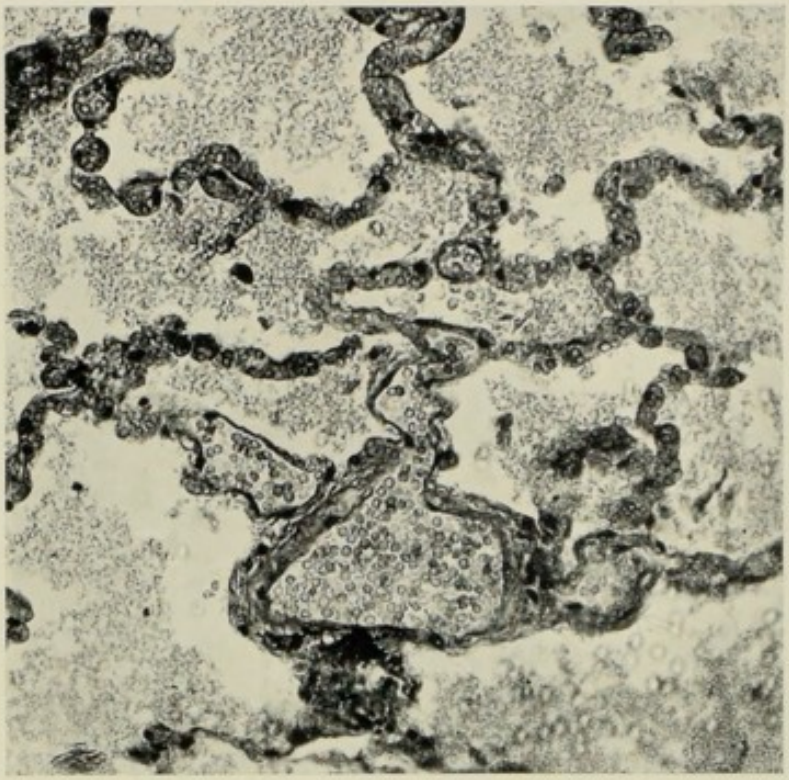


FIG. 33.—Lung. Acute congestion, showing dilatation of vessels in the alveolar walls and œdema in air-spaces. × 200.

diminished, the red corpuscles also get into the peripheral stream, and a mixing of all the elements takes place. Complete stagnation may be a later phenomenon, and then the vessels appear to be filled with a mass of fused red corpuscles. Further, it is observed that the leucocytes in the peripheral stream become adherent to the wall at various points, and begin to migrate through the coats of the vessels into the surrounding tissues.

The slowing of the blood-stream depends on several factors. As a result of the inflammatory process, and from the direct action of the irritant, the endothelial cells lining the vessels

become swollen, the cement substance becomes loosened, and the cells project into the lumen. Thus a greater frictional resistance to the flow of blood is set up. This friction is probably increased by the adhesion of leucocytes to the walls, and by the greater viscidity of the red blood corpuscles which are in contact with the walls. Lister showed definitely that these red blood corpuscles became more viscid, and in consequence more difficult of circulation. In addition to the alteration in their endothelium, the vessels undergo other structural and functional changes. In consequence of the damaged nutrition, their normal elasticity is impaired, and they become unduly stretched. This is more marked in the venules than in the capillaries. The dilatation and loss of elasticity lead to an increased intravascular pressure and further dilatation; the blood cannot escape freely from the veins, and tends to accumulate in them. Possibly, also, alterations in the plasma play some part. The transudation of lymph has increased considerably during this period of stasis, and, as a result, the blood-plasma may become more inspissated.

2. **Transudation of Lymph.**—The increased transudation of lymph is observed very early in the process, and becomes marked during the first two hours. This **inflammatory œdema** (fig. 33) may supervene very rapidly; and its amount is dependent on the situation in which it occurs, on the nature and intensity of the causal irritant, and on the condition of the patient.

In situations where the degree of external pressure is small, or the external support feeble, *e.g.* in the pleural sacs, large accumulations may take place, whereas in solid tissues or organs the exudation is comparatively scanty. Some bacterial irritants cause a very abundant transudation, while with others the amount is quite insignificant. Again, in debilitating disease, where there is pronounced anæmia, with grave alterations in the condition of the blood and changes in the vessel-walls, transudation occurs with greater facility. The transudation is in part due to a greater porosity of the vessels, owing to degenerative changes, and to the increased pressure in the engorged and dilated vessels. There is also the possibility that an alteration in the selective capacity of the endothelial cells of the vessels may have some influence on lymph transudation.

Characters and composition of inflammatory Exudates.—The

characters and composition of the inflammatory exudates in different positions and in different cases vary considerably. The exudate in one cavity may differ greatly from that in another, both in specific gravity and in coagulable power; and the exudate produced by one toxin may show great differences from that produced by another. To a certain extent

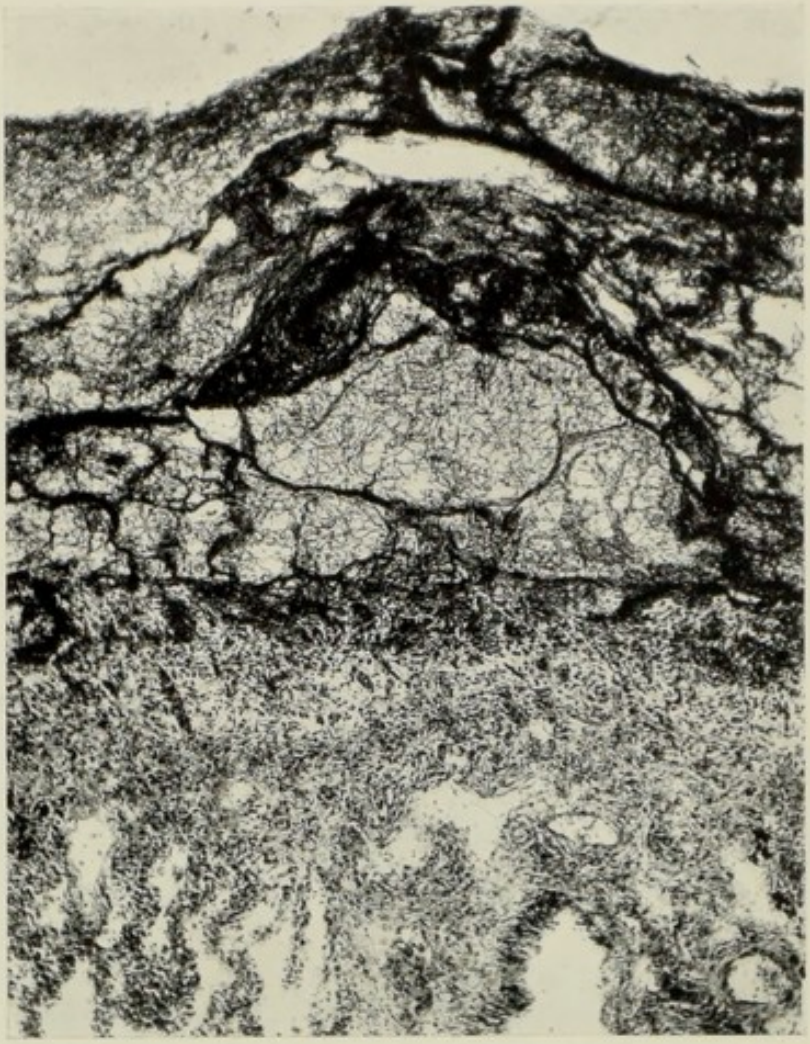


FIG. 34.—Acute pleurisy, showing deposit of fibrin and leucocytes on the surface of the pleura. ×60.

this may be explained by physical causes, *e.g.* an increased porosity of the vessel-wall favouring a more copious, or it may be a more viscid, transudate; or various changes in the endothelium modifying its selective capacity; but such causes are in themselves not a sufficient explanation of the observed phenomena. The inflammatory exudates are always richer in protein constituents than ordinary lymph and dropsical transu-

dates, but the amount of these never reaches that of the blood-plasma. Coagulation very commonly occurs, and depends on the amount of fibrin ferment produced; but in certain situations, *e.g.* in abscesses, coagulation may not take place. This is probably due to the softening or ferment action of bacteria. The exudates may contain special antitoxic, antibacterial, or other substances.

Function of Exudates.—It is quite probable that in the process of repair, where there is a stimulation of the local tissue cells, and, in consequence, an increased local metabolism, the exuded lymph may serve for purposes of nutrition; but we do not consider that this is an important function of the exudate. Much more important is its action in diluting toxic substances, and thus minimising at any rate their local destructive action. Further, it must act as a **flushing-out** agent, carrying the poisons which may be locally produced either to the surface, to glands where possibly they may be destroyed, or to serous cavities. It must be recognised that this mere **flushing-out** action, though beneficial at the region of irritation, may be harmful to the organism as a whole; for the locally acting poisons may be carried into the general circulation, and thus cause wide-spread poisoning effects. This **flushing**, however, acts also by carrying **antibodies** or protective substances in general, which may be locally produced, to various parts of the system; by carrying those which are in the plasma into the tissues, and thus thoroughly infiltrating them with these protective substances. The success of Bier's method of treatment, and no doubt, also, some of the success gained by Wright in the **flushing** aid to his **opsonic treatment**, are to be attributed to this dilution of the toxic products and carriage of antibodies, including the so-called opsonins, to the centres of infection. The exudates also loosen and separate the tissues, and thus aid the passage of the leucocytes in their protective work. By separating inflamed surfaces, *e.g.* the costal and visceral layers of the pleura, they aid the healing process. Further, the fibrin which is formed, coats over inflamed surfaces (fig. 34), protects them, and tends to localise the area of inflammation. It also brings about a temporary union between opposed surfaces, and forms a kind of scaffolding for the processes of repair.

The Solid Constituents of the Exudates.—It has been stated

already that in inflammatory exudates there is more protein than in ordinary lymph. The damage to the vascular endothelium and the more easy passage out of fluid are, in part, an explanation of this fact. But besides the proteins from the plasma, there must be others derived from the breaking down of leucocytes and other cells. The inflammatory exudate contains, in addition, ferments, remains of bacterial bodies, and various products of the growth of bacteria. There may also be glycogen, fats, and, as Klotz[1] has recently stated, a definite

FIG. 35.—Acute pericarditis, showing irregular masses of fibrin with entangled leucocytes. × 40.

amount of soaps. The quantities of these substances vary within wide limits, and this variation depends to a certain extent on the intensity and character of the inflammation, though other factors, *e.g.* the site of exudation, the character of the blood, etc., are also of importance.

Of the ferments present, that concerned in the formation of fibrin is of special importance. This fibrin is deposited in more or less thick layers, especially on endothelial or epithelial surfaces where there has been some damage to the cells

[1] Klotz, O., *Jour. Exp. Med.*, 1905, vii., No. 6.

(figs. 34 and 35). There is a distinct relationship between fibrin-formation and the breaking down of the leucocytes; but for details and discussions in regard to its exact method of formation we must refer our readers to text-books of Physiology.

3. **Escape of Red Blood Corpuscles.**—This is not an essential phenomenon of the inflammatory process, but it is one of very common occurrence. Small accumulations of red blood corpuscles may be scattered over the inflamed area, or the exudation may be hæmorrhagic,—the result of some constitutional

Fig. 36.—Omentum of a healthy guinea-pig. ×200.

condition, or of a wide-spread degeneration in the walls of the blood-vessels caused by the special action of some toxin or other irritant. The more common condition of small areas of hæmorrhage seems to be due to the rupture of over-dilated vessels, no doubt to a certain extent aided by the alteration in and degeneration of the vascular endothelium. Their extremely common occurrence in general septic poisonings supports the view of vascular degeneration being a causal condition. The red blood corpuscles appear in the form of small clumps near the engorged vessels, and are often found in the early stages of the inflammatory process. Some authorities maintain that they pass out either between the epithelial cells, on account of the

softening of the cement substance, or through the apertures left by the migrated leucocytes; but though this method is possible, most evidence seems to point to rupture of the vessels as being the main means of escape.

4. **Emigration of Leucocytes.**—The emigration of the leucocytes is regarded by Metchnikoff and his pupils as the essential feature of all inflammatory processes. It is certainly a constant feature, and plays an extremely important part. It is not

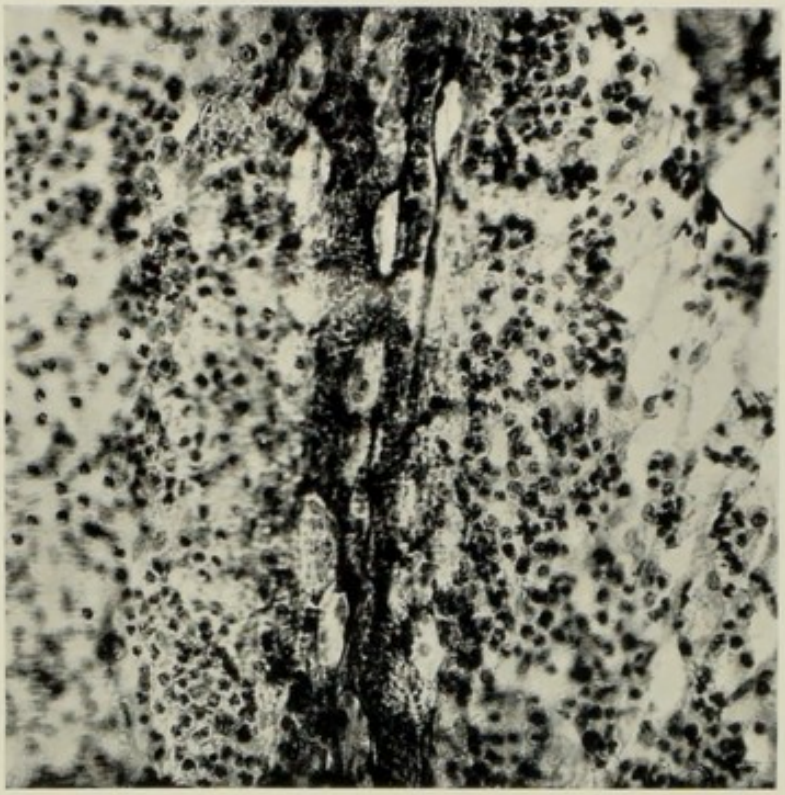


FIG. 37.—Acute inflammation of the Omentum of a guinea-pig, showing a dilated vessel in the centre, filled with leucocytes. Great numbers of emigrated cells are also seen. × 200.

necessary to deal with the discovery of the migration of the leucocytes by Addison and others. It is now generally agreed that most, if not all, varieties of leucocytes have the power of migrating from the blood-vessels, and that this migration occurs in virtue of the amœboid properties which they possess. If a transparent vascular membrane which has been irritated be observed, the leucocytes, after they have come into the peripheral stream, are seen to adhere to the walls of the vessels and then to send out pseudopodic processes, which in a short time project through the wall. Thus gradually the leucocytes escape,

and make their way through the tissues towards the noxious agent or to the site of damage (*cf.* figs. 36 and 37). This passage through the vessel-wall occupies a varying amount of time, depending on the species of animal under observation, on the velocity of the blood-stream and on other factors. The migration is more rapid in warm-blooded than in cold-blooded animals, and this rapidity is more marked if the blood-stream is very slow. The passage is mainly through the capillaries and venules, and very commonly it is specially marked at the junction of

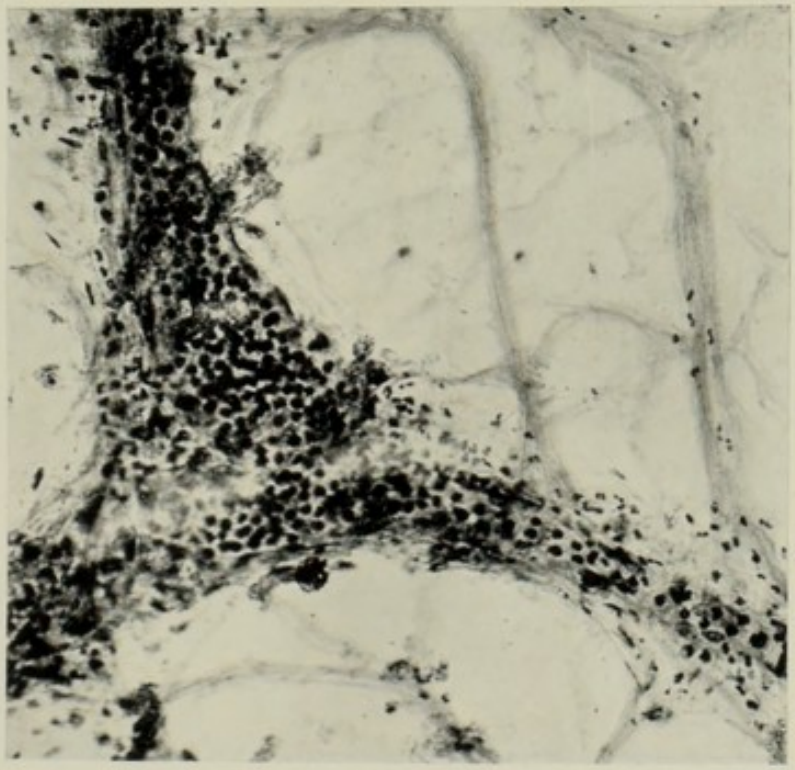


FIG. 38.—Acute inflammation in the Omentum of a guinea-pig, showing the marked emigration of leucocytes at the junction of tributaries of the vessels. × 200.

tributaries (fig. 38). It is doubtful whether the leucocytes ever migrate from arterioles. In most cases, the migration occurs from the delicate vessels composed mainly of endothelium, and the leucocytes make their way between the endothelial cells; and in this process are, no doubt, aided by the softening which has taken place in the cement substance there. At the same time, it is an established fact that the leucocytes can penetrate thick layers of epithelium and other tissues; and, in their passage from some of the larger veins, which undoubtedly does take place, there must be definite migration through the fibrous and

muscular walls. The time taken by the leucocytes to pass out of the capillaries and venules, as has been stated, varies. In the human subject, if the blood-flow is very slow, they may escape in from eight to ten minutes; if more rapid, they may take from one to two hours.

II. THE CELLS OF ACUTE INFLAMMATORY EXUDATIONS AND THE TISSUE CHANGES

The facts recorded are founded on the work of Metchnikoff and his school, Councilman, Adami, Maximow, Marchand, and

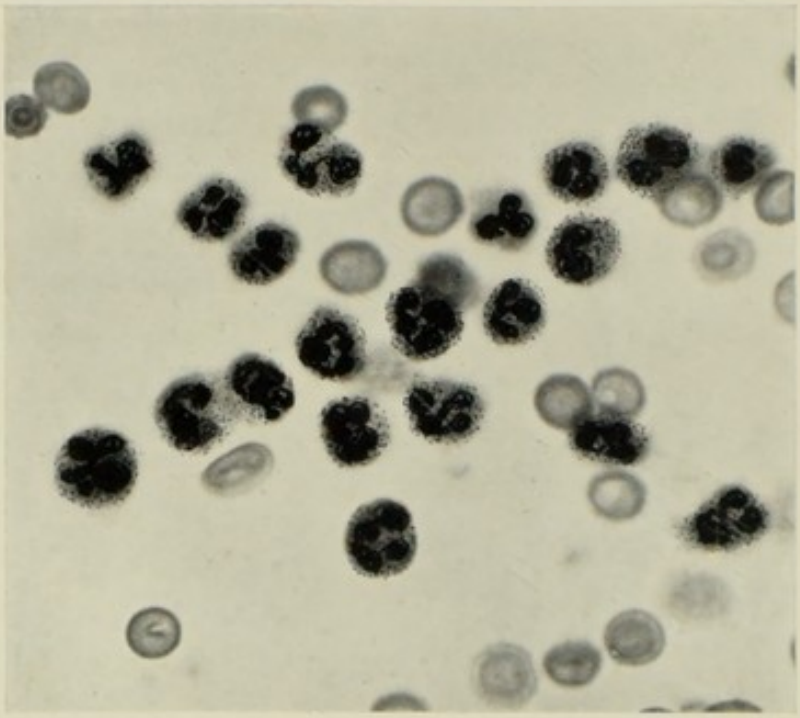


Fig. 39.—Inflammatory exudate of twenty-four hours' duration, showing polymorphonuclear leucocytes. × 1000.

others, and on experimental observations made by one of the writers.[1] In these latter experiments, active cultures of *Bacillus coli* and other organisms were injected into the peritoneal cavity of guinea-pigs, and fluid was removed by means of capillary tubes, at intervals of five minutes up to seven days after the injection. Controls were made with normal guinea-pigs, and by killing injected animals at various times and examining their tissues. Comparisons were also

[1] Beattie, *Jour. of Path. and Bact.*, Edin. and Lond., June 1902.

made with peritoneal exudates in the human subject, cases being employed in which the time of the onset of the peritonitis could be accurately determined.

1. **Polymorphonuclear Leucocytes.** — These leucocytes are the commonest variety in the blood, where they constitute about seventy per cent. of the total leucocytes. They have a nucleus which is divided into segments or **lobes**, each segment being connected by means of a delicate filament of chromatin. The cytoplasm contains irregularly scattered fine granules,

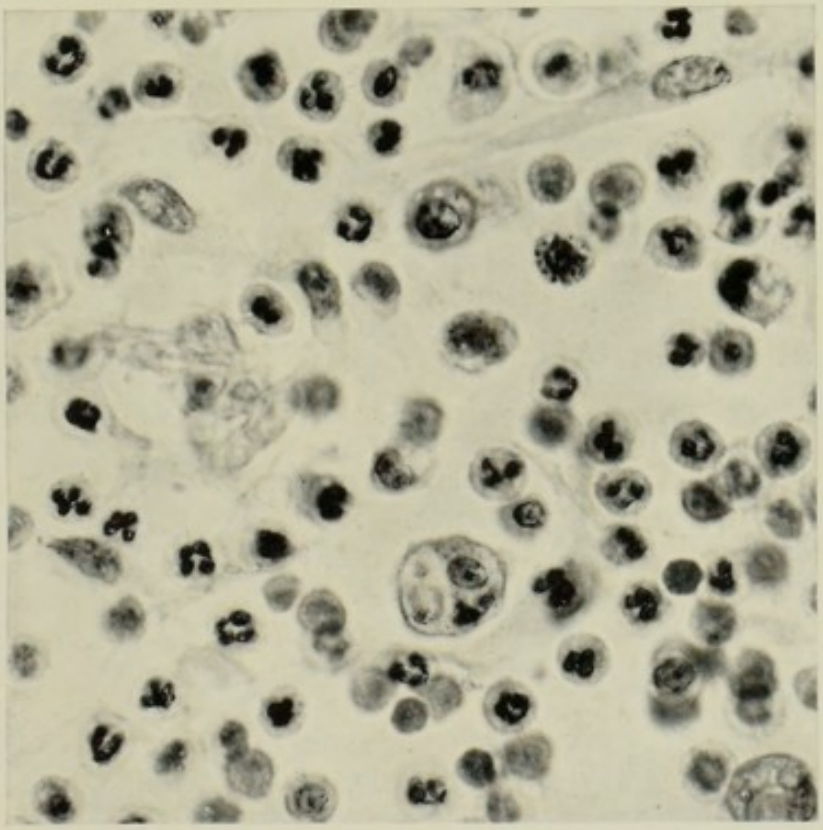


FIG. 40.—Inflammatory exudate of forty-eight hours' duration, showing polymorphonuclear and mononuclear leucocytes; also phagocytosis. × 1000.

which stain faintly with eosin. These leucocytes are numerous in an inflammatory exudation about three hours after inoculation, and they become more abundant in from **eighteen to twenty-four hours** (fig. 39). If they are able to overcome the irritant, they begin to diminish in from **thirty-six to forty-eight hours**, and this diminution is very marked in from **sixty to seventy-two hours**. In from **eighty-four to one hundred and fifty hours** they may have disappeared from the exudate. If, however, they are not able to overcome the irritant, a progressive

increase takes place; and it may be said that the polymorphonuclear leucocytes will continue to migrate in enormous numbers as long as the need for defence exists, and as long as the strain of increased production can be borne by the blood-forming tissue—in this case the bone-marrow. In all of our experiments where the injection produced a fatal result, these leucocytes were always in enormous numbers, even in cases where death was delayed as long as **ninety-six hours**. These results apply to almost all forms of inflammation. With certain organisms, e.g. *Bacillus tuberculosis*, however, the polymorphonuclear response may not be very great; and in the early stages, other cells, which will be referred to later, play the leading part.

Summary of Time Results

(Experiments by J. M. Beattie, M.D., *Jour. Path. and Bact.*, June 1902.)

Non-Fatal Cases:—After intraperitoneal injection of *B. coli*—

Ten to twenty minutes.—Very few polymorphonuclear leucocytes found.

One hour.—Very slight increase in number.

Two to two and a half hours.—Increase very definite.

Three hours.—A considerable number present.

Four and a half to six hours.—The increase becoming marked.

Six to thirty hours.—The increase goes on during these hours.

Thirty to thirty-six and forty-eight hours.—The numbers begin to diminish.

Fifty-four hours.—A very pronounced diminution in numbers.

Sixty to seventy-two hours. — Diminution becomes more marked.

Seventy-eight hours.—Very few polymorphonuclear leucocytes present.

Eighty-four to ninety-six hours.—A few still present.

They may persist for some days, but from the fifth to the seventh day they entirely disappear.

Fatal Cases:—The times at which the various cells appear is practically the same as in non-fatal cases; but the increase in numbers, especially of the polymorphonuclears, is maintained till the death of the animal.

2. **Coarsely Granular Eosinophils.**—From **one to four per cent.** of the white corpuscles of normal blood show, when stained with eosin, brilliantly-coloured pink granules in their protoplasm. These are much larger and more highly refractile

than the granules in the polymorphonuclear leucocytes. The lobed character of the nucleus is not so marked, and it stains less intensely with the basic dyes. These cells are very fragile, readily break down, and discharge their granules. In the experimental work referred to, these leucocytes were found in very small numbers, and did not appear to play any very important part. In certain conditions, however, and especially in diseases due to animal parasites, they

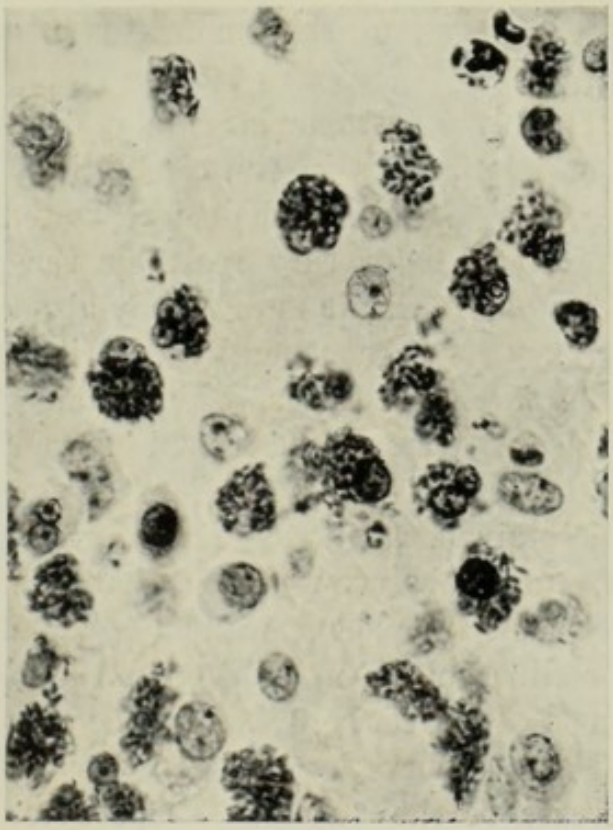


FIG. 41.—Inflammatory exudate, showing eosinophilia. ×1000.

may be very markedly increased in the blood, and may form large collections in inflammatory foci. Opie[1] has shown experimentally by intraperitoneal injections of, among other bacilli, *Bacillus pyocyaneus*, that the eosinophil leucocytes are abundant in the venules of the mesentery at the end of four hours, and migrate freely into the surrounding tissues. They evidently, in special conditions, thus act like the polymorphonuclear leucocytes. This agrees with the view of Ehrlich, Goldmann, and others.

[1] Opie, *Trans. Assoc. Am. Physicians*, 1904, xix. 136; *Johns Hopkins Hosp. Bull.*, 1904, p. 15.

3. **The Mononucleated Cells.** — There is comparative agreement as to the varieties of mononucleated cells in the blood. They may be divided thus:—

(*a*) **Lymphocytes**, which are cells with a relatively large, darkly-staining nucleus, and with very scanty cytoplasm, in which granules can be seen near the periphery, and, according to some observers, larger cells similar to those described, but having more abundant cytoplasm (**large lymphocytes**). These together constitute about twenty-five to forty-five per cent. of the colourless corpuscles of the blood.

(*b*) "**Hyaline**" **leucocytes**, or large mononucleated cells, are present in small numbers in the circulating blood, but are more abundant in certain pathological states, *e.g.* malaria. In their general character they resemble the large lymphocytes, and it is very difficult to draw any absolute distinction between them. They are generally described as having an oval or kidney-shaped nucleus, which stains less intensely than that of the lymphocytes, and cytoplasm which is devoid of granules. This distinction, however, cannot be definitely maintained, as intermediate forms are frequently present. Certain observers hold that transition forms between the small lymphocytes and the larger lymphocytes and these hyaline cells can be seen in the blood, and that one is derived from the other. This certainly is not in accord with our observations. In malaria, where there is a great increase of the "**hyaline**" leucocytes, the ordinary lymphocytes may not be proportionally increased; and in other cases where the small lymphocytes are greatly increased in number, there need not be any increase in these large mononuclear cells. This would certainly suggest that the two kinds are distinct in origin. It is, we think, not improbable that some of these large mononuclear cells may originate from vascular and lymphatic endothelium. In regard to migration, there is now abundant evidence that the lymphocytes can migrate. The large mononuclear cells show well-marked amœboid movements on the warm stage, and there seems no reason why they should not be able to pass out of the vessels in virtue of this property.

(*c*) **Mastzellen** or **Mast-cells**, about a half per cent. of the

leucocytes, are characterised by the presence of irregularly scattered larger and smaller basophil granules, or granules which show metachromatic staining. These cells are more frequent in some pathological conditions of the blood, *e.g.* myelogenous leukæmia.

In inflammatory exudates produced experimentally, various kinds of mononuclear cells are seen in three hours after inoculation, but for the first twelve hours they are scanty. In from eighteen to twenty-four hours the number becomes greater,

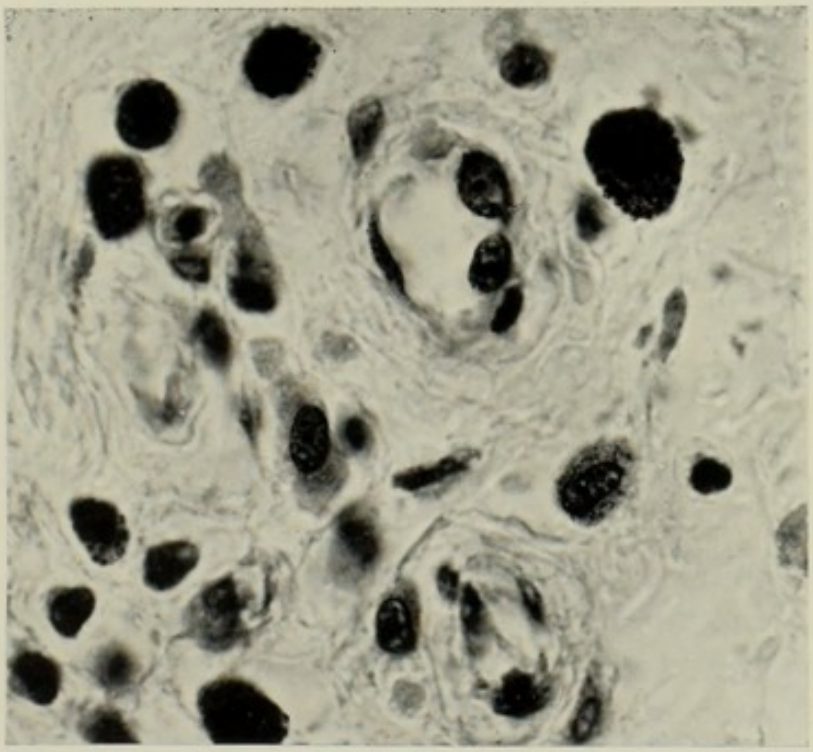


FIG. 42.—Mastzellen—showing basophil granules. ×1000.

and this increase continues *pari passu* with the diminution of the polymorphonuclear leucocytes, until, after the lapse of from fifty-four to eighty-four hours, most of the cells present are of the large mononuclear type. This increase is maintained until one hundred and fifty hours or longer.

Origin and Function of the various Cells found in Inflammatory Exudates.—Adami has classified these leucocytes into the following three groups:—

1. **The hæmatogenous**, viz. those derived from the blood, the polymorphonuclears, the eosinophils, and the mastzellen.
2. **The histo-hæmatogenous**, which include the lympho-

cytes, the hyaline cells, and other forms which may resemble these and may be derived from them. These may either have passed into the inflammatory focus from the blood-stream, or may arise by local proliferation of cells already in the tissues.

3. **The histogenous cells**, which are locally produced cells, and arise by proliferation of the fixed tissue elements.

1. **The hæmatogenous cells**:—

(*a*) **The polymorphonuclear leucocytes** have as their main function the destruction of the irritant. They appear very early in the process of inflammation, ingest inert irritant material, and ingest and digest organised irritants, *e.g.* bacteria. Inert material such as carmine or vermilion is taken up by these cells very soon after it is injected. Bacteria are also ingested in a very short time, but in the experiments referred to above, the ingestion of motile bacteria was a much later phenomenon than the ingestion of particles of carmine. This at least suggests that the bacteria are injured in some way before the cells are able to seize upon them. Metchnikoff maintains that the cells can ingest uninjured living bacteria, but most observers hold that the organisms are first altered in some way by substances contained in the plasma. We agree that substances inimical to bacteria are present in the plasma, and that they are produced by the cells, but we do not think there is sufficient evidence to determine which of the various groups of cells is responsible for their production.

(*b*) **The eosinophil leucocytes** are, we believe, definitely phagocytic to bacteria; and in response to certain chemiotactic stimuli they may, as Ehrlich holds, take the place of the polymorphonuclear leucocytes and perform the same functions. They may possibly also have important, but as yet little understood, relations to the formation of certain ferments.

(*c*) **The mastzellen.**—These need not be discussed, as there is very little evidence that they take any part in the active processes of inflammation. It is, we think, not improbable that these cells are simply degenerative products of other cells.

2. **The histo-hæmatogenous cells.**—With regard to the **small**

lymphocytes, they probably take little part in the acute inflammatory processes; but it is generally held that in the more chronic conditions, and in those in which the cell reactions are delayed for some days, such as that produced by *Bacillus tuberculosis*, or where toxins have been acting over a fairly long period, as in prolonged cases of scarlet fever or in subacute inflammation of the kidney, etc., these cells migrate in considerable numbers from the blood-vessels. Certainly, in the above

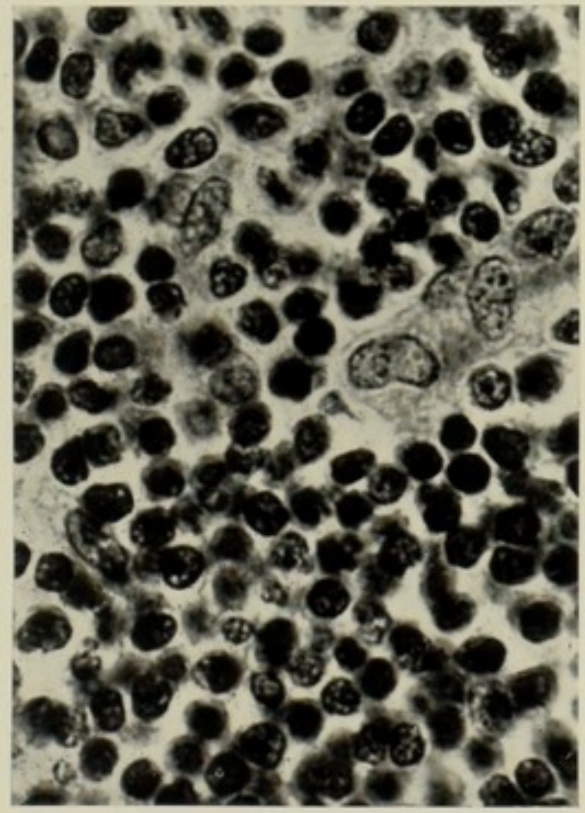


FIG. 43.—Lymphocyte-like cells from a chronic inflammatory focus. × 1000.

conditions, collections of small cells possessing all the characters of lymphocytes are seen in the tissues.

We strongly support the view of Adami and others, that the lymphocyte-like cells seen in the tissues and exudations during the inflammatory process may be derived by proliferation from the lymphoid cells normally present to a greater or less extent in various situations, but especially in the perivascular tissue. These lymphocyte-like cells undoubtedly migrate from the lymph-nodes and from the lymphatic vessels, but we must also accept the view that some of them migrate from the blood-vessels. According to Schridde, the granules of those cells

derived from the perivascular lymph tissue are larger, fewer in number, and of a more pronounced red colour than those of the blood-lymphocytes. With ordinary aniline stains it is quite impossible to distinguish the one form of cell from the other, and it is very doubtful whether Schridde's[1] modification of Altmann's stain will enable us to distinguish them.

Plasma Cells.—The only other form of mononuclear cell that comes into this group is the so-called "**plasma**" cell. The literature on the subject of the plasma cell is most confusing. The differentiation of this from other cells was originally founded on a definite staining process. Later observers base the differentiation on the structure, position, and staining reaction of the nucleus; and now many authors describe cells which have one or more of these differential characters as plasma cells. We shall not attempt to reconcile the conflicting views, but shall content ourselves by giving Adami's description of the plasma cell:[2]—"It has a relatively small, round or oval, not indented nucleus, coarsely granular, rich in chromatin, and, further, staining darkly; the nucleus is situated eccentrically. The cell-body stains deeply with Unna's methylene blue; the shape within the tissues is liable to considerable variation—often rounded or oval; the cells may be polygonal or even drawn out into a spindle; they are obscurely amœboid. . . . As they grow larger and older, the cytoplasm tends to become vacuolated and the nucleus to be less deeply stained." This author holds that they are formed from the proliferating perivascular tissues, though he admits that some of them may be derived from the normal lymphocytes. Maximow, however, derives them principally from the lymphocytes. We believe that, in their differentiation into groups, too much stress has been laid on staining reactions of dead cells, and on the shape and position of the nucleus. With amœboid movement of the cell, the nucleus alters its position in the cytoplasm, and staining reactions differ in relation to age and functional activity; and it seems

[1] Schridde, *Anat. Heft.*, 1905, xxviii. p. 2; *Münchner. Med. Wochenschr.*, 1905, Nos. 26, 29, and 39, and *ibid.*, 1906, No. 4; and *Verhandl. der D. Pathol. Gesellsch. Meran.*, 1905.

[2] Adami, *Inflammation*, Macmillan & Co., 1907, p. 64.

that no very useful purpose is served by this differentiation. These so-called **plasma cells** are amœboid and phagocytic, though some observers deny the latter characteristic; and they correspond in all respects with the mononucleated phagocytic cells of inflammatory exudations, which probably arise from lymphocytes, and the cells of vascular and lymphatic endothelium, endothelium of serous surfaces, etc.

Histogenous Leucocytes:—

(i) **The Cells derived from serous, vascular, and lymphatic endothelium.**—These vary considerably in size. They may be small, and have a scanty amount of cytoplasm, and a nucleus, rich in chromatin, which practically fills the cell; or there may be abundant cytoplasm which may be vacuolated, and a nucleus—oval or indented—which does not take on the nuclear stains very intensely. All transitions may be made out between these two varieties. As has been already stated, these cells are present in the inflammatory exudate in the early stages, but no great increase takes place till from the **eighteenth to the twenty-fourth hour**, and then, in non-fatal cases, they preponderate, until eventually the exudate contains very few cells of other types. They are actively phagocytic and **may** take up bacteria, though in this respect the polymorphonuclears are usually much more active. If, however, tubercle bacilli are injected into the peritoneal sac, the mononuclears are found to be their principal phagocytes, whilst in non-tuberculous inflammatory lesions, the mononuclear cells are phagocytic chiefly to other cells, taking up and destroying polymorphonuclears, eosinophils, and red blood corpuscles, and certain animal parasites, if these be present. Between these mononuclear cells of endothelial origin and the large mononuclears which have emigrated from the blood-vessels, we are not able to differentiate. All we can assert is, that transitional forms between the actively germinating endothelial cells and free mononuclears which resemble lymphocytes can be distinguished. There seems, however, very little doubt that a considerable proportion of the large mononuclear cells of inflammatory lymph are produced by proliferation of endothelial cells, though some may also be

derived from cells which have migrated from the blood-vessels.

(ii) **Cells derived from other tissues.**—In inflammation of the cornea, the corneal corpuscles swell and undergo division. The newly-formed cells are of the mononuclear type, and become actively phagocytic to other cells. When separated from their normal position and relation, these cells cannot

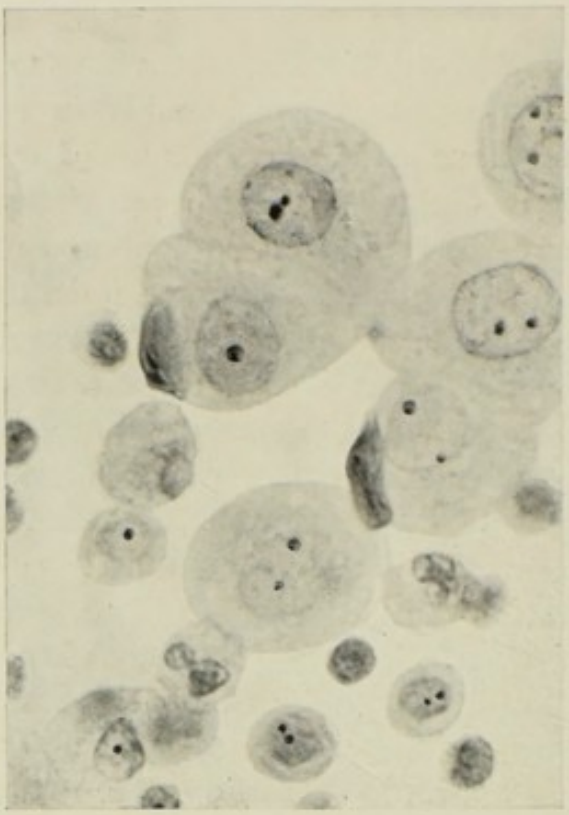


FIG. 44.—Inflammatory exudate from a case of acute pleurisy of several days' duration, showing the preponderance of mononucleated cells, the majority of which are derived from the serous endothelium. Transition forms are seen. ×1000.

be distinguished from those derived from endothelial structures.

Clasmatocytes.—Ranvier described as **clasmatocytes** certain large, apparently wandering cells, elongated or much branched, and possessing an oval nucleus. The cytoplasm contains granules which he regarded as a stored-up secretion. He claimed that they originate from leucocytes, and are derived from the blood. Marchand and others hold that they are "primitive wandering cells" in the tissues. They resemble the modified corneal tissue corpuscles described by Senftleben

and Councilman, and come into the class of the mononucleated cells of the inflammatory process, the evidence seeming to point to their being histogenous in origin.

Polyblasts.—We can deal only very briefly with the group of cells called by Maximow **polyblasts**. These are amœboid, wandering, mononucleated cells which are phagocytic; and in the group are included the various forms of mononuclear

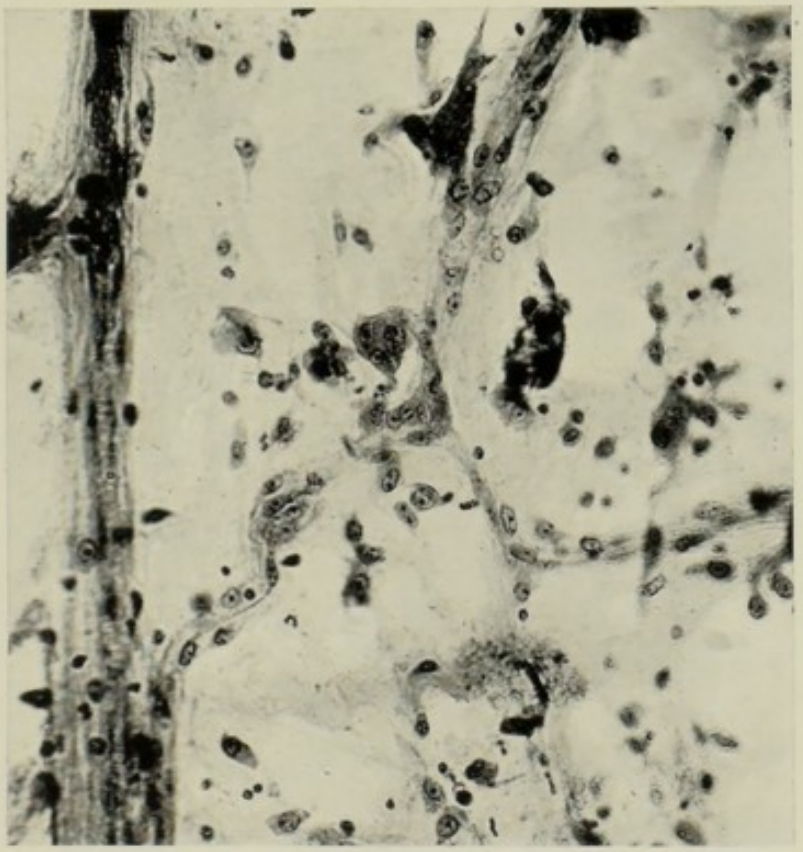


FIG. 45.—Omentum from a case of peritonitis following rupture of the liver. Death in three days. Cells are mainly mononuclear in type, and some have branching processes. These correspond with the clasmatocytes of Ranvier. ×200.

cells we have described. Maximow derives these from three sources:—

(1) A small proportion from wandering cells pre-existing in the connective tissue.

(2) A small number from pre-existing clasmatocytes and clasmatocyte-like adventitial cells (*e.g.* perivascular lymphatic tissue, endothelial cells, serous membranes, etc.).

(3) The principal part from lymphocytes which have emigrated from the blood-vessels.

All these cells are capable of developing into large amœboid, irregularly-shaped cells, with a very definite centrosome apparatus, situated most commonly in the cytoplasm close to the nucleus.

Fibroblasts.—These cells, formed from fixed connective tissue cells, are a later production, and will be discussed under **Repair.**

Giant-Cells.—Some of these are formed by **aberrant** cell-

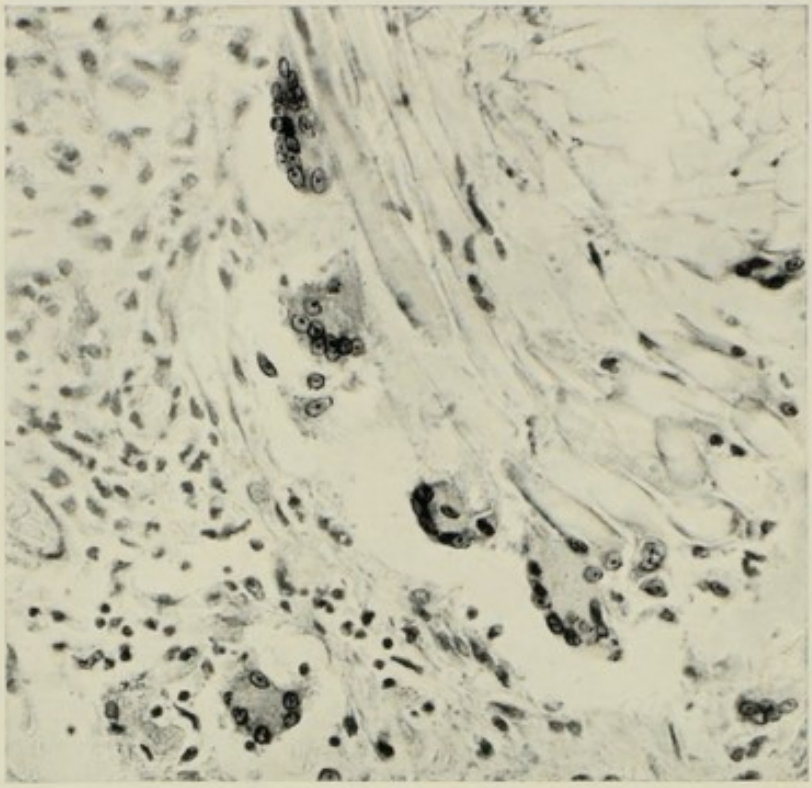


FIG. 46.—Giant-cells bringing about absorption of muscle and a foreign body —a piece of catgut. ×300.

growth, where the nuclei undergo division without the protoplasm following suit. But the majority are formed by fusion of endothelial and perhaps of other forms of mesoblastic cells into plasmodial masses. They are amœboid, and actively phagocytic. They may be found quite early in the acute stage of the inflammatory process, but are more commonly a later production. They are generally well developed where resistant tissues, *e.g.* bone, have to be absorbed, and they are a special feature of certain chronic inflammatory conditions, *e.g.* tuberculosis, syphilis, etc.

PHAGOCYTOSIS

(See Coloured Plates III. and IV.)

Reference has already been made in various places to the ingestion of bacteria, foreign particles, red blood corpuscles, and other cells by the leucocytes, but the subject is of such importance that special consideration of it is necessary. The brilliant work of Metchnikoff and his pupils has given to the subject of phagocytosis an extremely prominent place, not only in the study of the processes of inflammation, but in the much wider sphere of immunity against disease. We may not agree altogether with his conclusions, but about the extreme accuracy of his observations there can be no doubt. They have stood the test of time, and in spite of all opposition are now almost universally accepted. Metchnikoff has studied the subject in all parts of the animal kingdom, and has shown that phagocytosis is an almost universal endowment of cell-life; that it is the most important defensive agent against disease or disease-producing products, and that it is an essential factor for the carrying on of cell-life. Much of the moulding of the body tissues (*e.g.* the bones) is performed by phagocytic cells; waste products and damaged tissues are removed by them; and they are the producers of secretions of various kinds which play important parts in protection against, and in the cure of disease.

The leucocytes project pseudopodia or processes of their protoplasm, by which they grasp or surround, and thus incorporate, their prey. After ingestion, a clear space containing fluid forms round the foreign material, this being probably a digestive secretion of some kind, the reaction of which can be shown to be definitely acid in most cases. Under ordinary circumstances, gradual digestion of the foreign material takes place, and eventually, unless the material is very resistant, it entirely disappears, and the phagocytic cell resumes its normal condition. The parts of the englobed foreign material which resist digestion may be extruded. Numerous vacuoles (digestive) may appear in one cell, and some of the large mononuclear cells may ingest and digest a dozen or more polymorphonuclear leucocytes.

In the human body, probably most of the cells which are actively engaged in nutrition possess phagocytic properties. This is certainly true of the majority of the hæmal leucocytes;

of vascular and lymphatic endothelium; of liver cells; of certain renal cells, especially those of the secreting and collecting tubules; of cells lining the pulmonary alveoli and bronchi; of the cells of mucous membranes, and of many of the fixed connective tissue cells.

In the processes of inflammation, the phagocytic properties of the cells become more pronounced. In the early stages, the polymorphonuclear leucocytes are the first to act. They ingest foreign particles, but are apparently specially concerned in the ingestion of most of the infective bacteria. The polymorphonuclear leucocytes may also ingest red blood corpuscles, and particles of dead or necrosing tissues, as well as foreign particles, such as carbon, blood-pigment, etc. *Living* bacteria are undoubtedly taken up by them, and the process of digestion may be very incomplete—so incomplete indeed that after some time the bacteria may still be capable of growth. In many cases the polymorphs simply carry their ingested material to the surface, as in an ulcer, where it may be cast off, or into the lymphatic channels and glands, where it may be deposited. These polymorphs have been termed **microphages** by Metchnikoff, to distinguish them from the more active and probably more important mononucleated phagocytes, the **macrophages**, which certainly have the large share in the removal of dead or degenerated material. Within the macrophages, a clear space containing fluid surrounds the ingested material, and in these "*vacuoles*," which may be very numerous, there is a gradual disappearance or digestion of the included bacteria, and of the polymorphonuclear leucocytes or other cells. The nuclei of the included cells become fragmented, and a gradual solution or digestion of the chromatin takes place, and this is followed by a disappearance of the cytoplasm. The bacteria lose their staining reaction and are gradually dissolved. The red corpuscles shrink, and their hæmoglobin may either be absorbed or may remain as pigment within the phagocyte. In some cases, and especially with certain bacteria, e.g. *B. tuberculosis*, *B. lepræ*, *B. mallei*, and *M. gonorrhœa*, the organisms may remain in the cells for a long time with little or no destructive changes taking place in them. In some cases it would appear as if they were capable of **actively proliferating**, and in this respect they resemble some of the parasites

infesting unicellular organisms. There also seems to be some relation between the virulence of the organisms and the amount of phagocytosis. As a general rule, it may be stated that the more virulent the organism, the less is the amount of phagocytosis, and the later is it in making its appearance. The phagocytic action appears to be aided, as has been stated previously, by substances in the blood-serum and lymph which have an injurious action on living organisms. These agglutinins, antitoxins, opsonins, etc. are probably produced by the various cells of the body, and not specially or exclusively by the leucocytes.

Fate of the various Cells in the absorption of the exudate and in repair.—Many of the **polymorphs** are cast off or destroyed as **pus-corpuscles**, others are ingested by the mononucleated phagocytes, while some enter the lymphatics and possibly also the blood-stream. They probably take no part in the formation of new tissue. The **mononucleated cells** may migrate into the lymphatics and pass to the lymphatic glands, where the foreign matter they contain may be deposited. Others apparently enter the blood-stream and are carried to the spleen, bone-marrow, and various other organs and tissues, where their contents are deposited, and where the cells undergo disintegration. The part they play in the formation of new tissue will be discussed under **Repair**.

Causes of Leucocyte emigration.—We have seen that the leucocytes are actively amœboid, and that, when the blood-stream is slowed, they pass to the periphery and attach themselves to the walls of the vessels. It has been pointed out that they may move backwards and forwards in the vessel before finally attaching themselves to it, as if seeking a suitable place of exit. If watched, protoplasmic processes are observed projected through the vessel-wall, the nucleus with a small ring of cytoplasm being the first part of the cell to project. Finally, the whole cell is seen to escape and to migrate to the definite centre of irritation. It has also been pointed out that, as a result of the inflammatory process, the endothelium of the dilated vessels becomes swollen and the cement substance between the cells loosened. The swelling of the endothelium, the slowing of the stream, and the dilatation of the vessels must aid the accumulation of the leucocytes at the periphery. The loosening of the cement substance must render the walls of the

capillaries more pervious, and thus make the passage of the leucocytes more easy; but the essential point in this emigration is the active amœboid power of the leucocyte itself. This emigration is determined by some attractive force outside the vessel. It has been definitely shown by experiment that certain products of bacterial activity and tissue metabolism, as well as certain chemical and physical agents, attract wandering cells, while others have no attractive power. Leber[1] studied this subject very carefully by introducing

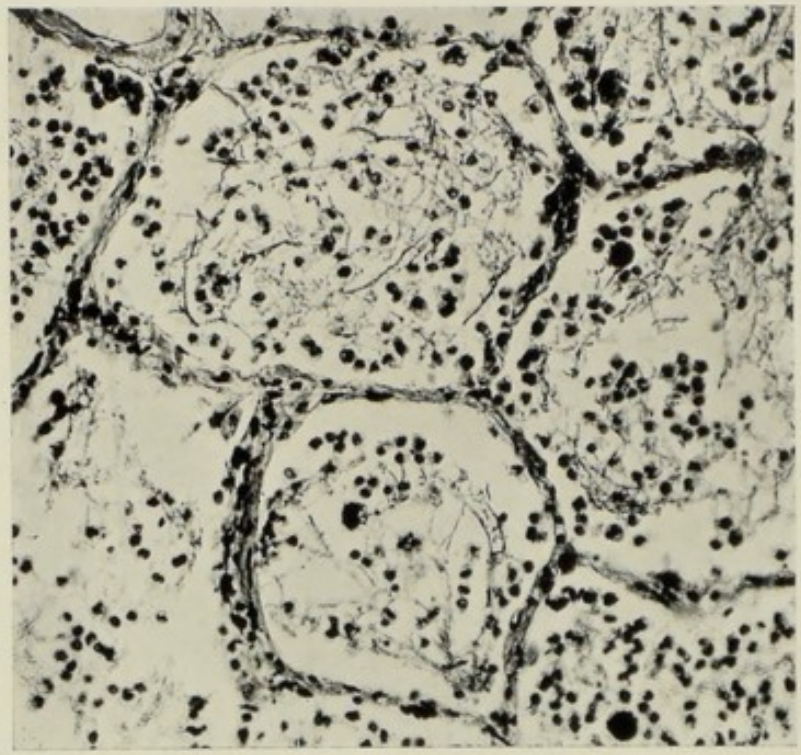


Fig. 47.—Acute Pneumonia, showing fibrin and leucocytes in the air-spaces of the lung.

glass tubes, closed at the outer end and containing chemicals, into the blood-vessels. He and other observers found that certain chemical substances, *e.g.* various compounds of mercury, finely powdered copper, turpentine, etc. exert a **positive** attraction; whilst quinine, chloroform, glycerine, alcohol, etc. act **negatively**; that weak solutions sometimes act positively, while strong ones have a negative action. The toxins of most of the septic bacteria and the toxin of diphtheria, if not too concentrated, attract leucocytes in great numbers, whereas, if

[1] Leber, *Die Entstehung der Entzündung*, Leipsig, Engelmann, 1891.

they are concentrated, the leucocyte emigration is not marked. To this force the name **chemiotaxis** has been given.

If the mesentery of a frog is exposed and irritated, even with normal saline solution, the leucocytic changes described are seen. The saline solution, or even the mere exposure to air, exerts a **positive chemiotactic** action. If, however, the exposed mesentery be washed with a weak solution of quinine, as first pointed out by Binz,[1] the leucocytes remain globular and do not become adherent to the wall of the vessels. Binz thought that the quinine paralysed the leucocytes, but Disselhorst[2] showed that if the leucocytes were removed from the vessels, their amœboid movement was still quite evident. Apparently, the only explanation of this fact is that the quinine has neutralised the previous **positive** attraction, and a **negative** chemiotaxis is set up. Besides the attractive force of chemical agents and bacterial products, there are other possible forms of stimuli which may produce leucocytic emigration. In fact, these blood-leucocytes probably respond to stimuli in the same manner as amœbæ and other unicellular organisms, and therefore the reactions to light, heat, electricity, and various tactile stimuli must be regarded as forces which influence the leucocytes in their movements.

Summary

Before dealing with the subject of Repair, it will be convenient to give a brief summary of the part played by the various cells in the inflammatory process.

Polymorphonuclear Leucocytes.—In acute inflammation of bacterial origin, these are the cells which in the early stages play the most important part. They migrate in enormous numbers, and often for considerable distances, to the site of irritation. They are actively phagocytic to bacteria, and may produce a ferment, which is liberated either during the life or after the death of the cell, and which may have some deleterious influence on living organisms. After they have performed their functions, they may wander back into the lymphatics or blood-vessels; may undergo dissolution or disintegration *in situ*; may be cast off as pus cells, or may be englobed and digested by the proliferating tissue-cells and mononuclear leucocytes. In tissue formation they probably take no part.

Eosinophil Leucocytes.—These, unless in special circumstances,

[1] Binz, *Virchow's Archiv*, 1874, lix. p. 293; 1878, lxxiii. p. 282; 1882, lxxxix. p. 389.

[2] Disselhorst, *ibid.*, 1888, cxiii. p. 198.

take very little part in the inflammatory process. Under the influence of certain irritants, especially those produced by certain animal parasites, they become abundant in the blood and migrate to the inflammatory foci. They are phagocytic to bacteria, though perhaps in a minor degree. They are very fragile, and many of them become disintegrated in the inflammatory tissue. Their function is quite unknown. The secreting activity associated with an alleged active discharge of their granules has not been confirmed.

Mast-Cells.—These may be present in less acute inflammatory foci. They are slightly amœboid. According to Maximow, they degenerate and disappear during the inflammatory reaction. They may be simply degenerative products of other cells, and therefore without any function.

Lymphocytes.—These are slightly amœboid, and do not migrate very actively during the process of **acute** inflammation. In some **chronic** inflammations, however, they appear to be the predominant cell present. They may give rise to the larger lymphocytes or large mononuclear hæmal cells and to the so-called **plasma cells**; and, according to Maximow, they form the greater part of the **polyblasts**, or the wandering amœboid mononuclear cells of inflammatory exudations. They may possibly take some part in the formation of fibrous tissue, but at present our information on this point is not satisfactory. We are not prepared to accept the view that the majority of lymphocyte-like cells of chronic inflammatory conditions have migrated from the blood. Many of them are, we believe, formed by proliferation of pre-existing lymphoid tissue.

Histogenous Wandering Cells.—These are derived from endothelial cells of serous surfaces, etc. They are amœboid and very actively phagocytic, especially towards cells, foreign material, and certain bacteria. Some of these cells, especially those derived from vascular endothelium, may migrate from the vessels. They may undergo necrosis and degeneration in the inflammatory focus, or they may pass into glands by way of the lymphatics. In some cases they may fuse together to form plasmodial masses or giant-cells. Their share in the formation of new tissue is disputed.

Fibroblasts.—These are formed from pre-existing connective tissue cells, and, according to Maximow, are the only ones concerned in the formation of new fibrous tissue.

INFLAMMATION IN NON-VASCULAR AREAS.—This is best studied in the cornea, which in health is a transparent non-vascular membrane, composed of parallel laminæ of fibrous tissue. Between these laminæ are numerous lymph spaces and channels, and also somewhat flattened connective tissue cells—the **corneal corpuscles.** The lymph channels communicate freely with one another and with lymphatics at the periphery of the cornea. It is difficult to produce damage to the cornea

without so injuring the conjunctiva that the conjunctival inflammation set up obscures the corneal changes. By restricting the damage to a very small area, Senftleben,[1] and more recently Councilman,[2] have studied the condition of interstitial keratitis very carefully. Where damage was produced without exciting inflammatory changes, as in Senftleben's experiments with solutions of chloride of zinc, there was no sign of leucocyte emigration within twenty-four hours, and no sign of peripheral congestion. The corneal corpuscles at the centre of the injured area, however, showed degenerative and destructive changes, while those nearer the periphery were enlarged. Later, proliferation took place in the peripheral healthy corneal corpuscles. These sent offshoots into the necrosed area, and thus complete repair was brought about—the only factors taking part in the process being the fixed connective tissue cells. If the damage were more extensive, and especially if bacteria were present, there was produced an area of opacity around the focus of injury. Polymorphonuclear leucocytes were found in abundance in this area, and also migrating along the surface from the conjunctival vessels, though there may have been, as yet, no congestion of the peripheral vessels. With still more severe irritation, in addition to the production of the central opacity, the vessels at the periphery of the cornea became dilated and engorged with blood, and leucocytes were seen migrating from them along the lymph spaces between the various layers of the cornea to the site of irritation. There was also a transudation of lymph, with which the lymph spaces became distended, and by absorption of which the connective tissue fibres became swollen and œdematous. The corneal corpuscles underwent proliferative changes early in the process, and during the second day after the injury they could be seen as wandering cells in the damaged area. These cells acted as phagocytes. Adami[3] states that the "lymphocytes are not visible till the fourth day, and they do not so much pass out of the vessels as from the sheath of lymphoid tissue surrounding them." New capillaries, arising from the vessels at the

[1] Senftleben, *Virchow's Archiv*, 1878, lxxii. p. 542.
[2] Councilman, *Boston Jour. Med. Sc.*, 1898–99, iii. p. 99; *Am. Jour. Med. Sc.*, 1897, cxiv. pp. 22–25.
[3] Adami, *Inflammation*, Macmillan & Co., London, 1907, p. 26.

periphery, penetrated the corneal structures, and were accompanied by proliferated corneal corpuscles. Thus repair was brought about. From the results of these experiments, it will be seen that the changes in a non-vascular area correspond with those seen in any vascular part. The dilatation of the vessels, the lymph transudation, and the leucocyte emigration take place in both; and the character of the migratory leucocytes and their time reactions also correspond.

SEQUELÆ OF THE ACUTE STAGE OF INFLAMMATION

Phenomena following the Inflammatory Process.—If the irritant be removed, the process may at any period become arrested and all the phenomena subside, unless the tissues have suffered great damage. The condition may, however, spread very widely by way of the lymphatics or blood-vessels, and, from a very slight infection, there may arise wide-spread **diffuse inflammation** and general septicæmia; or the condition may be more localised, and **abscesses** or **ulcers** may be formed. Several factors may determine the localising or the spread of the processes. Among these are the nature of the irritant, the vitality and the nature of the tissues involved, the situation of the inflammatory focus, the resisting power of the individual, etc.

In all situations and in all forms of inflammation there is some degeneration of the tissues, especially if highly endowed. In many cases the degenerative and necrotic changes are extensive, and abscesses and ulcers result.

SUPPURATIVE INFLAMMATION is usually caused by the pyogenetic or pus-forming organisms, and in most of such cases the causal bacteria can be demonstrated in the pus or discharge. In not a few cases, however, the pus is **sterile**, but this sterility is really due to the death and destruction of the bacteria by the products which they themselves have produced, either in virtue of their own multiplication or by their action on the cells and tissues of the body. The formation of pus *may* take place without the intervention of bacteria. It has been shown conclusively that certain chemical substances—toxins, sterilised cultures, etc.—have a positive chemiotactic power for polymorphonuclear leucocytes, and may produce definite abscesses. These abscesses, however, are always localised and heal rapidly.

Among the substances which produce them are turpentine, petroleum, silver nitrate, zinc chloride, mustard, oil of cloves, compounds of mercury, etc.

Suppurative inflammation, however, is best studied experimentally by injecting into the subcutaneous tissues small quantities of bacterial cultures. The usual inflammatory changes, dilatation of vessels, transudation of lymph, and emigration of leucocytes, are seen after a few hours. In about

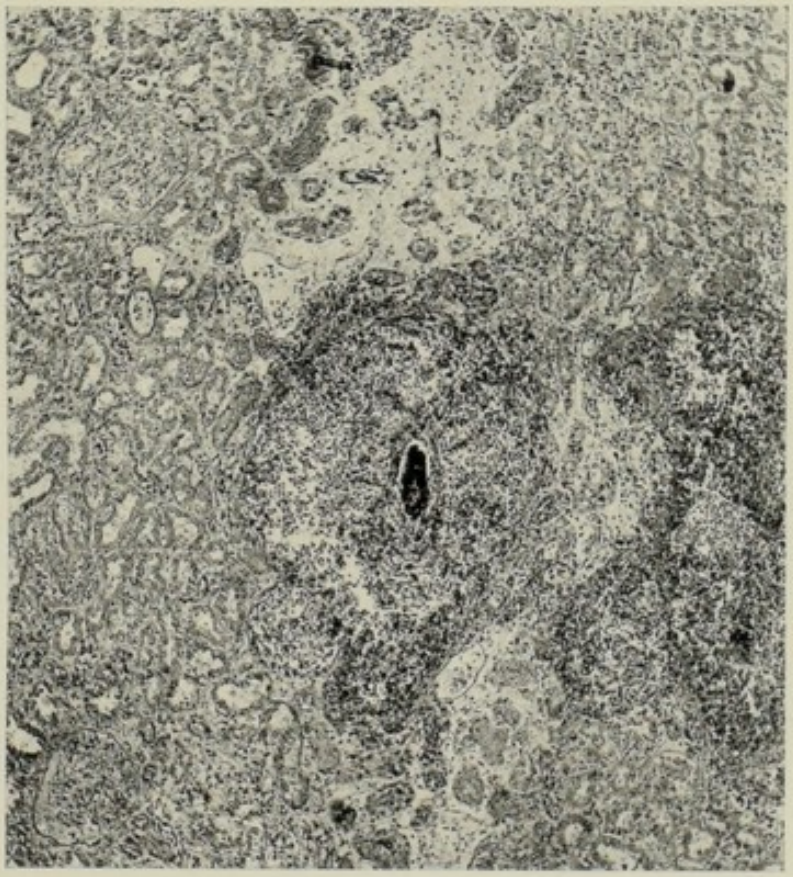


Fig. 48.—Abscess in the Kidney, showing central plug of bacteria, with surrounding mass of leucocytes. × 50.

twenty-four hours after the injection there may be great multiplication of the bacteria, and the polymorphonuclear leucocytes are seen in great numbers in all parts of the infected area, separating the fibrillæ of connective tissue. The vessels are much congested, and the connective tissue becomes swollen and œdematous. Near the marginal zone there are usually numerous mononucleated cells. In about **forty-eight hours** a well-defined **abscess** is seen. The centre of this shows densely packed leucocytes, mainly of the polymorphonuclear type,

some of which show definite karyolysis and karyorrhexis; and mingled with these are the bacteria, many of them free, many lying in the cytoplasm of the leucocytes. Fragments of broken-down and degenerating tissue (*e.g.* muscular, fibrous, etc.) may be found in this central degenerated cellular area. At the periphery of this **pus** or central mass of cells, necrotic tissue, and debris, the capillaries are congested; and, surrounding them, are very numerous leucocytes, both of the polymorphonuclear and mononuclear type. At a period of from four to six or ten days, the degenerative changes in the leucocytes and the necrotic changes in the original tissues become much more marked, and a definite wall of granulation tissue is in process of formation. This wall contains many new capillaries, and newly formed connective tissue with numerous fibroblasts and other mononucleated cells. If the area of irritation be near the surface, either of the skin or of a mucous membrane, the superficial layers may become necrosed, the dead tissue being cast off as a **slough**, and an **ulcer** may thus be produced. The nature of the minute changes in the abscess and in the ulcer are really identical, and the floor and edges of the ulcer and the wall of the abscess show a similar formation of granulation tissue.

Pus is usually alkaline in reaction, and contains not only the proteins normal to blood-serum, but also other derivatives from these proteins, viz. peptones and other albumin-containing bodies. Fatty acids and cholesterin, as well as pigment derived from red blood corpuscles, or produced by chromogenetic bacteria are frequently found. The cells are very abundant, and are mainly of the polymorphonuclear type, in various stages of degeneration and necrosis. In addition to these, however, mononucleated cells, derived from endothelial structures, and connective tissue cells are also present. Fibrin may be found, but not in any considerable quantity. It seems to undergo peptonisation by the ferments which are present. Portions of muscular, fibrous, or elastic tissue, in various stages of necrosis, may also be found.

CATARRHAL INFLAMMATION.—This term is specially applied to that form of inflammation in which there are proliferative changes in the functioning epithelium. The cells may merely be shed, or they may divide and form new cells, which become detached and lie free in the lumen of the tubules or ducts or

on superficial parts. This change is found, often in an intense degree, in mucous membranes. The vessels are usually engorged, the basement membranes become swollen from absorption of transuded lymph, and there may also be a considerable degree of leucocyte emigration; but the essential changes are the proliferation, desquamation, and degeneration of the epithelial secreting cells. The secretion of the cells is usually increased in amount, watery and mucous, rather than serofibrinous in character, and the cells often contain pigment particles, especially altered blood-pigment.

INTERSTITIAL INFLAMMATION. — Although interstitial inflammation may be acute, by this term is generally understood a condition in which there is more or less subacute or chronic fibrous overgrowth along the lines of normal supporting fibrous tissue. This is very commonly the result of chronic infective or other irritants, but it may be caused by some special strain, or it may occur as a sequel of chronic degenerative and absorptive processes. It is thus rather of the nature of a hyperplasia than of an inflammatory reaction.

PARENCHYMATOUS INFLAMMATION.—This term has been applied to acute, subacute, and chronic changes which affect the special functioning cells of a part. These changes are largely degenerative, and not specially inflammatory in character, and may be brought about by the direct action of toxins, by impaired vascular supply, or by altered metabolic processes. They are practically always associated with changes in the supporting tissues and in the vessels.

REPAIR

REPARATIVE CHANGES IN INFLAMMATION.—The fixed tissue elements in inflammation undergo both degenerative and proliferative changes. Reference has already been made to many of the **degenerative changes** in the cells. In severe inflammation, the cells undergo cloudy swelling, fatty and mucoid degeneration, etc.; the connective tissue fibres become swollen, or may undergo mucoid, hyaline, or waxy change. Necrosis is a very common result, and is seen in some bacterial infections, in burns, etc., and also as a result of the application of caustic. The changes produced by bacteria or their toxins are mainly

microscopic in character, and specially affect highly functioning tissues, *e.g.* the secreting cells of various organs.

The **proliferative changes** are extremely important, and are best studied in the **healing of a wound**, in the **organisation of a fibrinous exudate**, or in the **absorption of a thrombus in a vessel.** Wherever the changes take place, the same series of reactions is seen, and these have for their object the absorption or removal of the damaged tissue or the inflammatory exudate; or, if this cannot be effected, the enclosing of it in a capsule of fibrous tissue, so as to shut it off from the healthy parts, and bring about the union of separated surfaces. Repair of an injury may be **direct**, that is, may take place without the essential phenomena of inflammation being present. Thus, an injury of the cornea, as has been stated, may be completely repaired merely by a proliferation of existing corneal corpuscles. Similarly, direct union of nerves, tendons, or even of epidermis may take place. Usually, however, the damage will have caused some degree of reaction, and as a result there will be deposit of inflammatory products and destruction of tissue; and before the healing can take place there must be removal or absorption of the exudate or of the damaged tissue.

We shall study the condition (1) in the healing of a wound, and (2) in the organisation of an inflammatory exudate; and then shall refer to any changes which are peculiar to special tissues.

(1) **WOUND HEALING:—**

(*a*) **In an incised wound.**—The processes are best studied in the case of an incised wound which is not thoroughly aseptic, and where the edges are not accurately in apposition. During the first **twelve hours**, the edges of the wound become glued together by blood and by coagulated lymph which has exuded from the dilated peripheral vessels. The margins of the wound are red and slightly swollen. This is due to the dilatation of the minute vessels and to the transudation of lymph. Leucocyte emigration is also seen at this stage—the leucocytes passing into both the lymph and the surrounding tissues for some distance. The vascular endothelium and the connective tissue corpuscles show swelling and distinct proliferative changes even during the first **twenty-four hours**, and these changes become much more marked later. At about the

same period after the infliction of the wound, vascular buds are given off from the minute vessels at the periphery. At first these buds are conical solid masses of protoplasm with nuclei. The nuclei and the protoplasm segment, and thus endothelial cells are formed. These endothelial cells separate from one another, and open out a new channel continuous with the lumen of the vessel. From the distal end of these buds, long protoplasmic processes are sent into the coagulated fibrin and

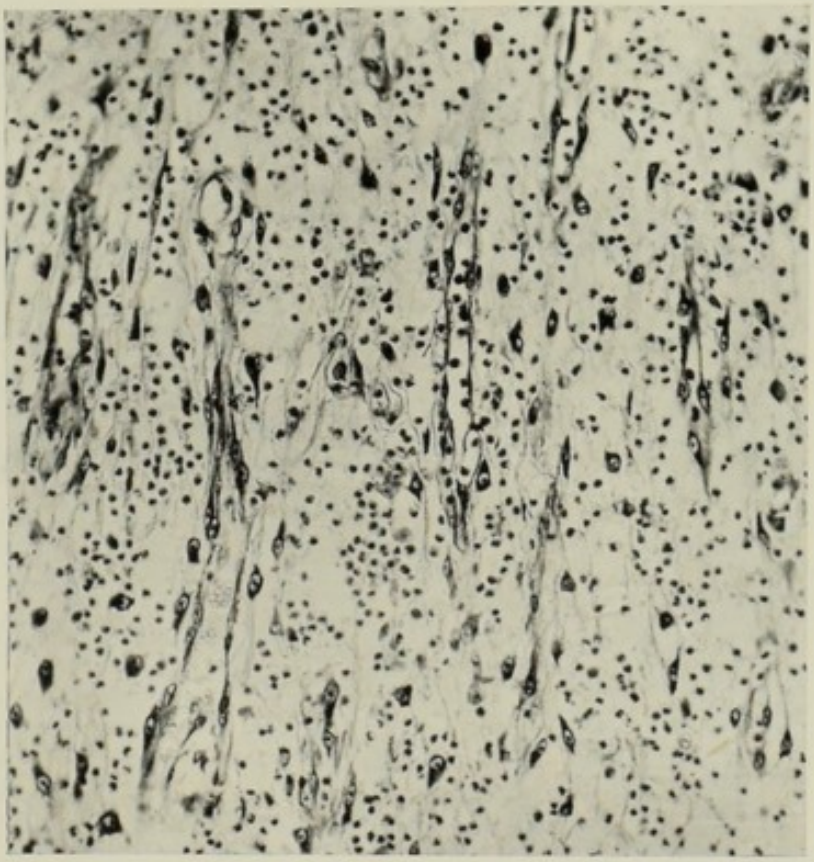


FIG. 49.—Healing wound, showing granulation tissue, with thin-walled vessels, leucocytes and proliferated connective tissue cells. ×200.

blood, and these anastomose with other processes, so as to make a network in the fibrin. These protoplasmic processes give off branches, and eventually open up by segmentation of the protoplasm and the formation of lining endothelial cells. This new capillary network may be well developed in **thirty-six hours**, and even in **twenty-four hours** there is abundant evidence of the formation of vascular buds, and of swelling and mitosis of the endothelium of the developing vessels. Round the new vessels the exudate of lymph undergoes solution and absorption.

As the capillaries develop, they become surrounded by an adventitia probably largely derived from the proliferation of connective tissue corpuscles, which arrange themselves alongside the capillaries (fig. 49). Much of the exudate is removed by this branching capillary network, and replaced by the newly formed connective tissue cells. Thus a **temporary granulation tissue** is formed. In this the vessels are always thin-walled, composed merely of endothelium, or of endothelium with a few adventitious cells, and in consequence dilatation and rupture are common.

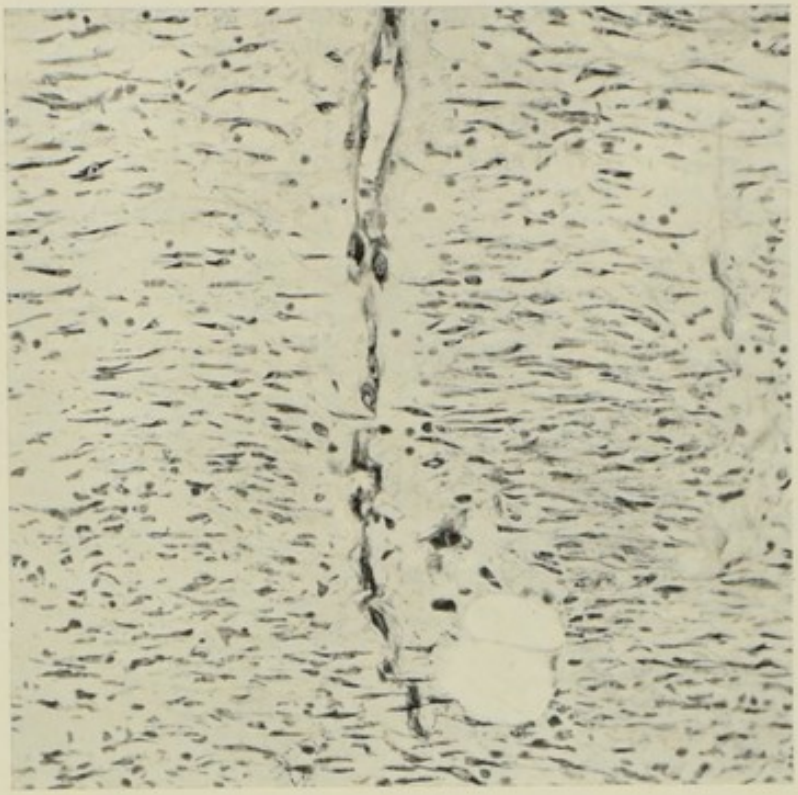


FIG. 50.—Healing wound, showing new vessel with slight adventitial coat, and parallel layers of spindle-shaped cells. × 200.

In most cases these early formed capillaries are not persistent, but when the lymph and the blood have become absorbed they waste and disappear. About this period a new set of vessels is being formed. These arise from the pre-existing vessels by a process of budding similar to that seen in the formation of the primary capillary network. They are formed specially in the deeper parts of the wound, and pass directly upwards towards the surface. These vessels are more regular in their order of development, and are generally better supported than the primary set (fig. 50). They are well seen in from **thirty-six to**

forty-eight hours. About the same period, spindle-shaped cells are formed, which run at right angles to the vessels, and soon form definite parallel layers, beginning in the deeper parts of the wound (fig. 50). By means of these, the opposing surfaces of the wound are, as it were, "sewed" together. The spindle-shaped cells possess long processes, and have a vesicular nucleus and abundant cytoplasm. Some of them may be developed from lymphocyte-like cells or from larger mononuclears; but the majority are formed by a proliferation of pre-existing fixed connective tissue cells, and are termed **fibroblasts**, from the fact that they are the progenitors of fibrous tissue. At

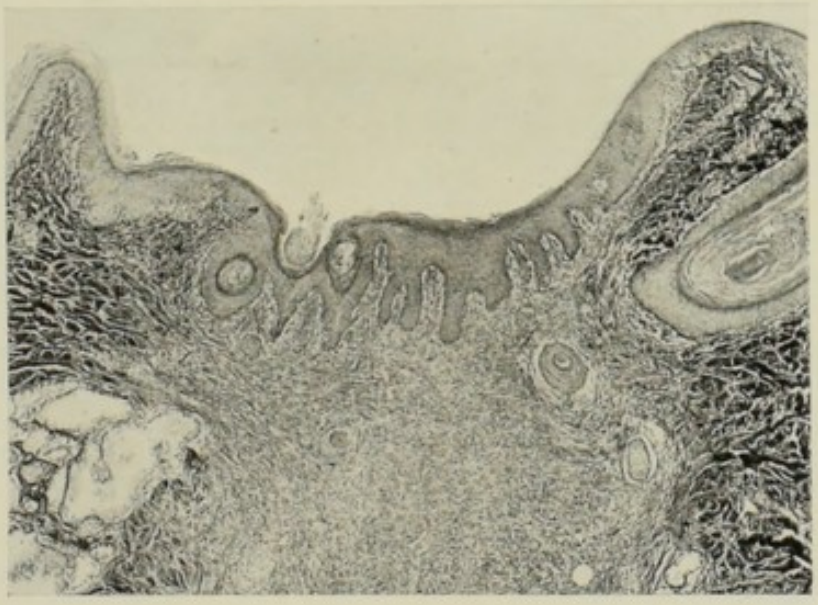


FIG. 51.—Healed wound, showing dense fibrous tissue (scar tissue) with epithelial covering. ×35.

a later period, this second set of vessels shows thickening of the inner coat and gradual shrinkage and disappearance. In from **three to five days**, definite fibrils are seen running parallel with the long fibroblasts. The most recent work seems to show very definitely that these fibrils are formed in the fibroblasts, especially in the peripheral layer, by a transformation of the cytoplasm of this area. Gradually the cellular character diminishes, and in from **three to four weeks** cells and vessels have disappeared, and are replaced by dense white fibrous tissue—**Scar tissue** (fig. 51).

Epithelial Cells.—Even at an early period, *e.g.* in from **twenty-four to forty-eight hours**, a proliferation of the epithelial cells

at the edges of the wound takes place, and these new cells grow over the surface. At first they become entangled in the lymph and blood, and, becoming swollen and œdematous, they perish. As soon, however, as a supporting structure is formed, they grow over the surface as a thin pellicle, and from this, if the wound is not too extensive, a complete covering of epithelium is developed.

(*b*) **In an ulcer.**—The healing process is essentially the same

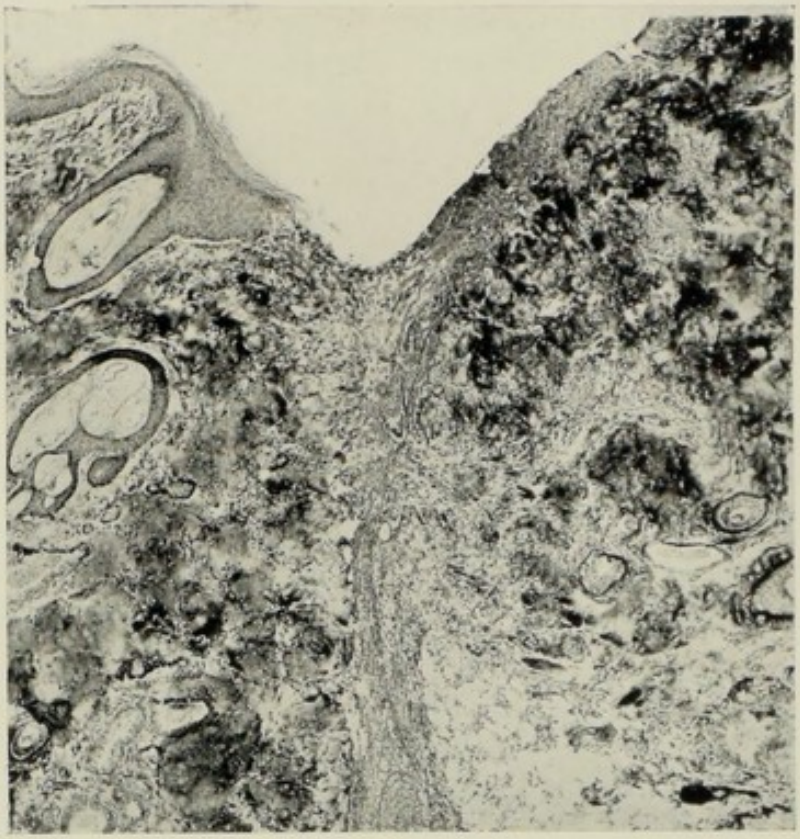


FIG. 52.—Incised wound of four days, showing preliminary repair of epithelium, cellular infiltration of tissues, etc. ×35.

as that just described for an incised wound. The differences are mainly that, in the healing of the ulcer by granulation, there is a large gap to be filled up by the new tissue, and frequently a considerable amount of damaged tissue to be removed. The process, therefore, is much slower, and many degenerative changes are going on side by side with the proliferative ones. The connective tissue is formed in larger quantities and in a more irregular fashion. Leucocyte emigration and transudation of lymph are much more pronounced, and last for

a longer period. The granulation tissue, however, consists of young newly formed capillaries surrounded by newly developed connective tissue cells; and thus corresponds with the new tissue formed in the healing of an incised wound. Further, there occur the formation of definite fibroblasts, the obliteration of the newly formed vascular loops, and eventually the production of scar tissue.

The granulation tissue varies in character in different situations, according to the nature of the tissue to be repaired, and also according to the nature of the irritant and the length of time during which it acts. In cases where bone or other specially resistant tissues have to be removed, and therefore where preparatory softening must take place, cells of a special type are frequently brought into the field. These are multinucleated masses of protoplasm, resembling osteoclasts, and are probably formed by the fusion of several mononucleated phagocytes. These cells are common in granulation tissue in any situation, but are specially abundant where, as we have said, masses of degenerated structures or foreign bodies, especially of a resistant character, have to be removed (fig. 46). In wounds infected by *Bacillus tuberculosis* or by the organism of syphilis, certain special characters, *e.g.* the presence of **giant-cells** and **caseation**, are usually found in the granulation tissue; and the growth of the fibrous structures may be modified considerably. Further, where the healing is much delayed on account of the prolonged action of the irritant, the newly formed tissues are apt to become swollen and œdematous from the absorption of lymph, or they may undergo myxomatous degeneration. In these cases, too, the more acute changes—leucocyte emigration, cellular degeneration, and the formation of pus—predominate over the proliferative ones, and hæmorrhage is a common occurrence on account of rupture of the ill-supported capillaries.

(2) **THE ORGANISATION OF AN INFLAMMATORY EXUDATE**, *e.g.* the fibrinous exudate on the epicardium in a case of acute pericarditis.

If a section of the exudate, with the adjacent heart structure, be stained with hæmatin and eosin, and examined a few days after organisation has commenced, several distinct layers can be demonstrated in it:—

i. An external, darkly-stained zone, varying in thickness,

composed of a network of unaltered or granular fibrin, in which is entangled a varying number of polymorphonuclear leucocytes.

ii. Immediately under this layer is a second zone which stains less intensely. In this, the cells are more abun-

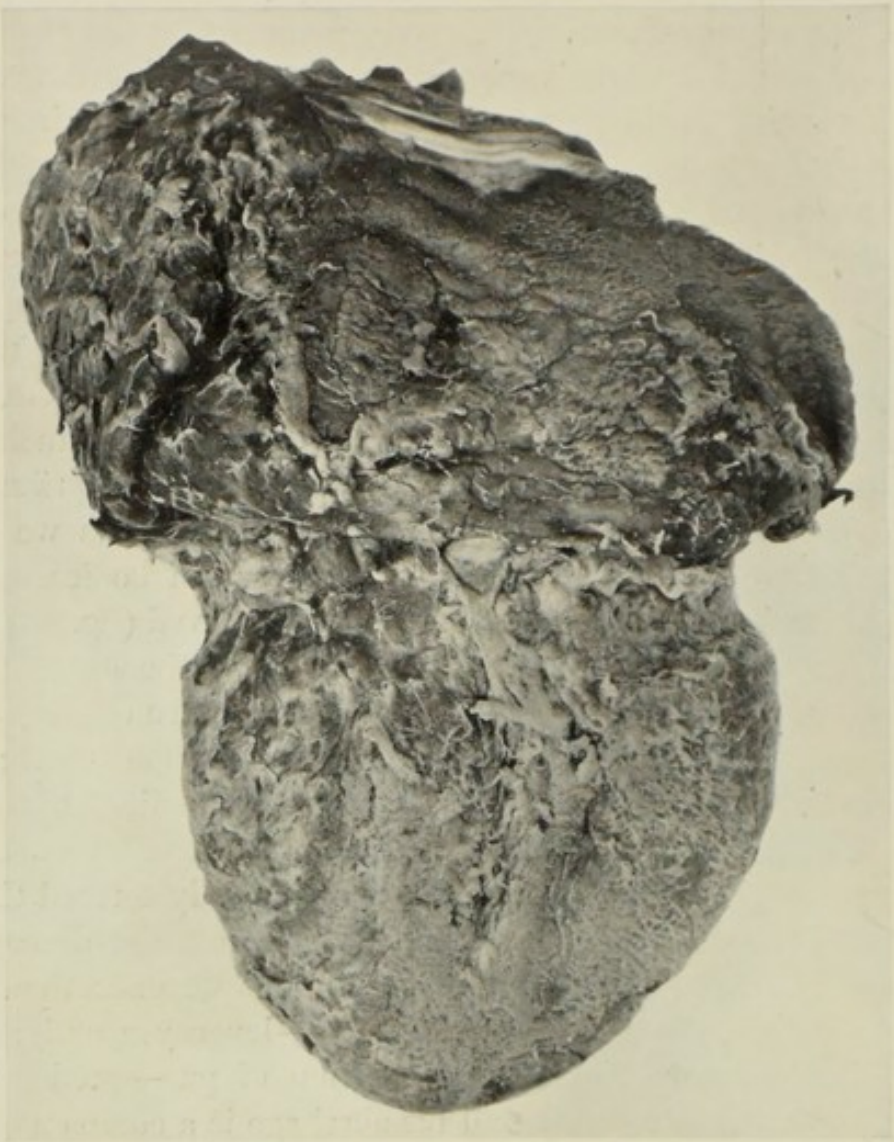


FIG. 53.—An inflammatory exudate on the surface of the heart and pericardium. (Acute pericarditis.)

dant and the fibrin is distinctly granular. There are a few capillaries, and round these, where the absorption is taking place, the fibrin appears somewhat homogeneous and stains very faintly. The cells are mainly polymorphonuclears, but some mononucleated cells may also be present.

iii. Deeper still, the capillaries are much more abundant, and the fibrin has to a large extent disappeared, although remains of it may be seen between the capillaries at certain parts, as small, homogeneous, pink-stained areas (fig. 54). The cells surrounding the vessels are more abundant, and the mononucleated variety predominates. These cells are irregularly scattered, but some more

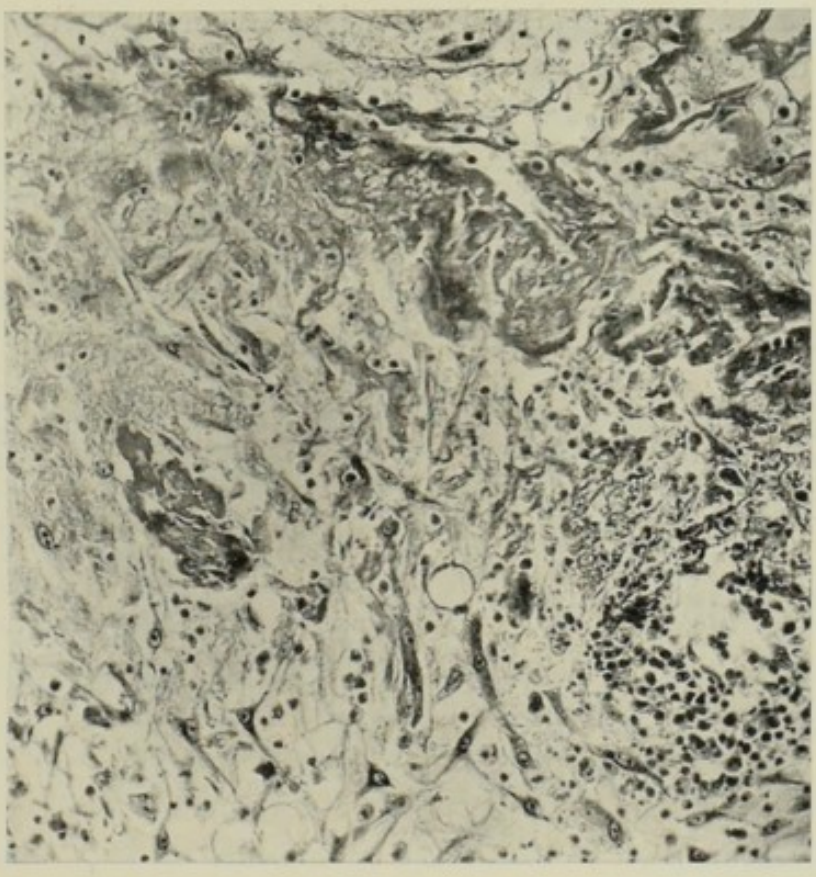


Fig. 54.—Organisation of an inflammatory exudation, showing absorption of fibrin, and the presence of rounded and spindle-shaped cells. × 200.

flattened ones are seen lying parallel to the capillaries. Multinucleated cells are also usually present.

iv. At a deeper level, the fibrin has completely disappeared, and the capillaries in many parts show very distinctly an outer supporting coat of flattened cells lying parallel to their endothelial lining. Between the capillaries there are numbers of cells irregularly arranged, some of which are rounded or oval with granular cytoplasm, others spindle-shaped and showing branching processes

(fig. 49), while others again are large and multinucleated. Fibrils are also seen in varying numbers.

v. Nearer the surface of the heart, *i.e.* at the deepest part, the new tissue becomes denser. The capillaries are less numerous; the great majority of the cells are flattened, and are arranged in layers parallel with the surface of the heart (fig. 50). These cells are the **fibroblasts**, and between them fibres are seen, which in the deeper parts become more abundant, with a corresponding gradual diminution in the size and numbers of the cells. The blood-vessels in this layer, as has been indicated, are scanty, and those that are present have a very definite adventitia, and in some of them proliferation of the endothelium is seen. This proliferation goes on, and at a later period the capillaries are to a large extent obliterated. The newly-formed tissue becomes firmly adherent to the epicardium, invading it to a certain extent, and no definite line of demarcation between the one and the other can eventually be detected. Fat cells, nerves, and blood-vessels of the superficial epicardial layers can be made out in this deeper part. Here and there, however, some of the pericardial endothelium may remain, and at a later stage this, in some cases, proliferates and grows over the surface. Thus, the normal endothelial covering may to a large extent be replaced, and, in consequence, adhesions between the two layers of the pericardium may be absent, or present only in certain areas. Very commonly, however, anastomosis takes place between the newly-formed vessels in the peri- and epi-cardial layers of exudate, leading to the formation of definite fibrous adhesions.

There seems to be no doubt that, in the early stages of the inflammatory process, some of the endothelial cells of the pericardium proliferate, pass into the exudate, and act as phagocytes, just as do the endothelial cells of other serous surfaces.

What has been described applies to the organisation of an inflammatory exudate on any other serous membrane, though the processes may be more irregular, and the distinction into separate layers may not be so definite. In all cases the capillary formation is an early process, and the capillaries are

always formed by budding from pre-existing vessels. The cells, too, are generally of the same types in every case, though one or other of these types may predominate in any individual instance. Much discussion has arisen as to their origin and function; and although we have already, in dealing with the more acute processes, discussed this subject, it will be well at this stage to again refer to some of the more essential points. The cells found entangled in the superficial portions of the fibrin are emigrated leucocytes. These are most commonly of the polymorphonuclear type; though in certain conditions, *e.g.* tubercular exudates or exudates in lymphatic leukæmia, large numbers of lymphocytes may be found. The cells in the **granulation tissue**, where organisation is more advanced, are of various kinds. Some have a rounded nucleus which is very rich in chromatin and almost completely fills the cells, so that only a very small ring of cytoplasm can be differentiated, these cells morphologically resembling the small lymphocytes of the blood. Others are larger, rounded, oval or irregularly polygonal cells, possessing a varying amount of cytoplasm, with a nucleus oval or reniform in shape, and usually showing less chromatin than the cells of the former type. This class includes a considerable group of cells—the larger mononucleated cells of inflammatory exudates, plasma-cells, etc.—which are derived from various sources, and the origin of which has already been discussed. These, together with the lymphocytes and lymphoid cells, are grouped by Maximow as the **polyblasts**. According to this observer, they include the pre-existing free, wandering cells of connective tissue, **clasmatocytes**, and **clasmatocyte-like adventitious cells**; but he maintains that the large majority is derived from the lymphocytes which have migrated from the blood-vessels. In addition to these cells, there are also present irregularly oval or flattened cells, with branching processes, and with a rather faintly-staining nucleus, which in all their characters closely resemble connective tissue corpuscles. These are the **fibroblasts**. There may, in addition, be present, multinucleated or giant-cells. These however, are more commonly seen, and are certainly more abundant, when resistant substances—*e.g.* bone or cartilage, or foreign material, such as ligatures—require absorption; or where special organismal irritants are present—as in tuberculosis or syphilis. The

functions of these various cells in the acute inflammatory processes have previously been discussed; and the part they take in the formation of new tissue is much disputed. It is, however, generally agreed that the principal cells concerned in this process are the **fibroblasts.** They are derived by proliferation from pre-existing connective tissue corpuscles, and are found at first lying parallel with the new capillaries; but at a later period they are seen in layers at right angles to the

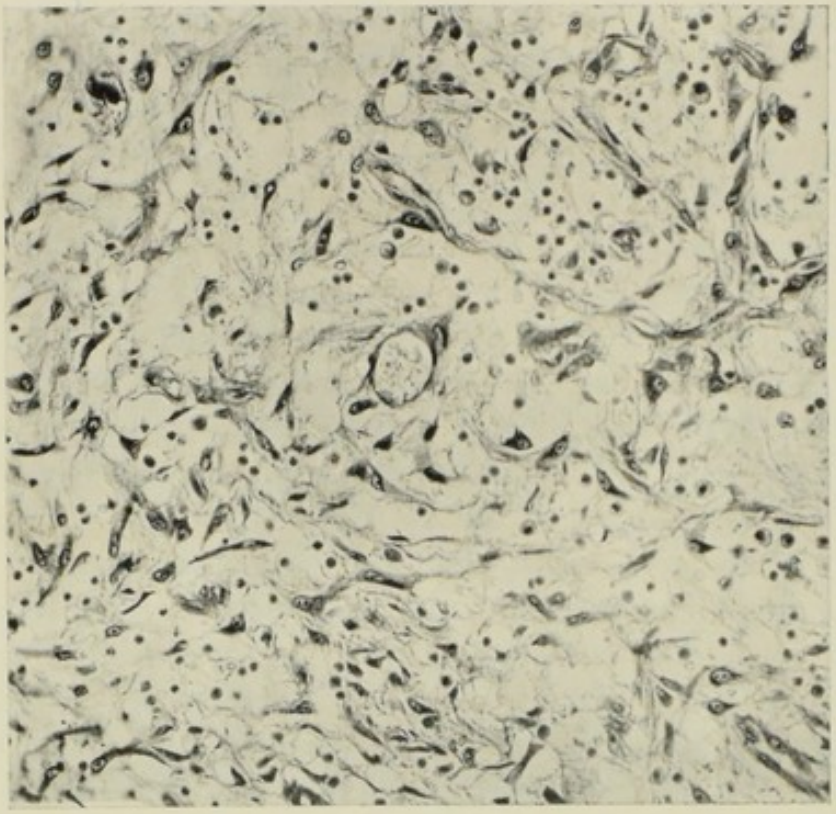


FIG. 55.—Granulation tissue from a healing wound, showing capillaries, and the various kinds of cells. ×200.

vessels. In their earlier stages they are oval, or even rounded, and are difficult to distinguish from other mononucleated cells; but at a later period they become more elongated and spindle-shaped, and send out protoplasmic processes (fig. 55). Proliferation and mitosis in them are seen, in experimental incised wounds, after about **twelve hours**, but are not very pronounced till about the **thirty-sixth hour.** The layers of spindle-shaped cells are well developed in from **three to four days**, and between them, and apparently formed from them, are seen connective tissue filaments. These filaments become more marked; and in from

six to seven days very distinct fibrils of fibrous tissue can be differentiated. It is still commonly held that these connective tissue fibrils are formed as a sort of excretion from the fibroblasts; but the more recent work on the subject points to the view that they originate in the cells, apparently by some change in the peripheral cytoplasm. Masses of these fibrils are formed, become pressed together, and constitute bundles of white fibrous tissue.

The share taken by the **polyblasts** in the processes of fibrous tissue formation is much disputed. Maximow, in his recent able work on the subject, maintains that few, if any, form fibroblasts or fibroblast-like cells, or participate in the development of fibrous tissue. Metchnikoff gives an important place to the wandering cells of connective tissue, and in the tadpole's tail he has traced from day to day the transitions between these wandering cells and definite connective tissue corpuscles. The plasma cell is regarded by many as a progenitor of connective tissue; but Schridde has pointed out that, though it may elongate and in some respects resemble a connective tissue corpuscle, it maintains its specific granularity, and comes to rest within the tissues, but does not take part in the formation of true fibrous tissue. The part played by the lymphocytes or lymphocyte-like cells is still more uncertain. Maximow admits that some of them may become transformed into cells which cannot be distinguished from fibroblasts. Collections of lymphocyte-like cells, the so-called **small-celled infiltrations**, are common in interstitial inflammations where persistent irritation is kept up, and are often a very pronounced feature in the early stages of slowly developing fibrous hyperplasias. These cells, we think, must be regarded as possible sources of fibrous tissue formation; though we accept fully the view that the larger proportion of the fibroblasts is derived from the pre-existing connective tissue cells of the part.

HEALING IN VESSELS.—In the organisation of a thrombus in a vessel, the changes are essentially the same as those described in the healing of wounds, but the endothelial lining of the vessels may show special proliferative changes. It may grow over the thrombus, forming a complete covering; but it is very doubtful whether it actually penetrates it and aids in absorption, and still more doubtful whether it forms new

capillaries, as is maintained by some authors. If the thrombus only partially fills the vessel, its covering endothelium and the portion of the endothelial lining of the vessel opposite the thrombus may be separated by a distinct space from one another, or may be in contact; and, with contraction of the thrombus, a definite channel, lined by endothelium, may be opened up. Eventually, the only result of the thrombus may

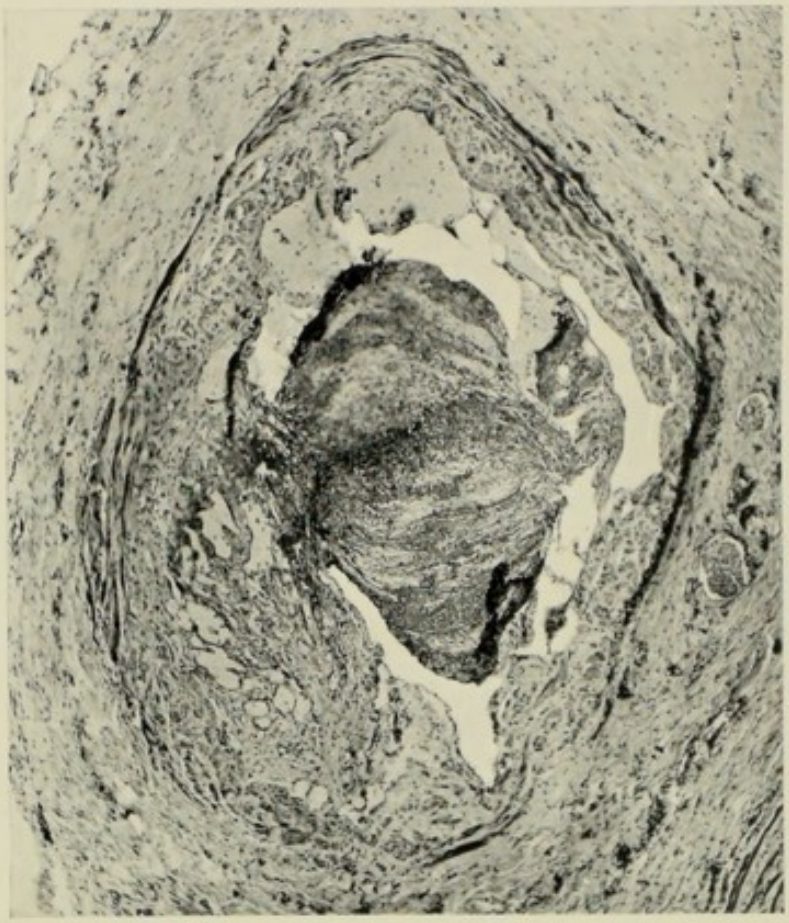


Fig. 56.—Thrombus in a vein, showing partial opening up of the lumen and organisation. Note the dilated vessels in the organising area (left side).

be a thickened patch at one side of the vessel. Restoration by this means is, however, not common. The usual course is for organisation of the thrombus to take place, and its absorption to be brought about by cells and young vessels, as in the healing of an ordinary wound. In thrombosis brought about by ligature, there is, after a few days, a very definite local proliferation of connective cells of the intima, and these cells project into the thrombus in the form of small buds. At a later period, young vessels are seen, and can be traced to

the vasa vasorum, from which they undoubtedly arise. The vessels from opposite sides and at different levels come to anastomose, and the thrombus, if not too large, may be absorbed, or the granulation tissue which is formed may become fibrous and undergo contraction. The fibroblasts formed during this process are usually smaller and more branched than those seen under ordinary conditions in wound-healing. When the clot is large or is formed in a large vessel, the process of vascularisation is usually incomplete, and the more central part of the thrombus tends to degenerate and become fatty, or even calcareous.

HEALING IN SPECIAL TISSUES

As we have already indicated, the essential changes are identical in all forms of repair; but in individual instances there may be certain differences, dependent upon the nature of the tissue, and also on the extent of the damaged area. Reference has previously been made to repair of the cornea, of tendon, and of nerve fibres by direct proliferation of corneal corpuscles, connective tissue cells, and nerve fibres respectively, without the intervention of inflammatory reactions.

ELASTIC TISSUE.—This can be re-formed to a certain extent by offshoots from the pre-existing elastic fibres—possibly through the agency of cells not yet satisfactorily demonstrated. This re-formation is a slow process, and the new tissue is somewhat ill-formed, and may not function so perfectly as the original elastic tissue.

FATTY TISSUE.—In healing wounds, the fat cells remain unaltered for a considerable time, but, as absorption goes on, the fatty tissue undergoes a mucoid degeneration and becomes converted into myxomatous tissue. According to Maximow, some of the polyblasts, especially the clasmatocyte-like cells and the adventitious cells, may become transformed into fat cells. There can be no doubt that large numbers of lymphocyte-like cells make their appearance in the areas of fatty tissue which are undergoing reparative changes.

MUSCULAR TISSUE.—Unstriped Muscle.—In some of the lower animals, regeneration of **unstriped** muscle takes place by division of pre-existing muscle cells; and in the middle coat of arteries, in repair, a new formation of muscle must occur; but, as a general rule, in wounds, union of unstriped muscle is brought

about by the formation of fibrous tissue, and we cannot definitely trace any muscle regeneration. In enlargement of organs composed of non-striped muscle, *e.g.* the uterus, recent work seems to show that there is an enormous enlargement of the individual fibres rather than a formation of new ones.

Heart Muscle.—Wounds in the heart are healed by the formation of fibrous tissue, though there can be no doubt that

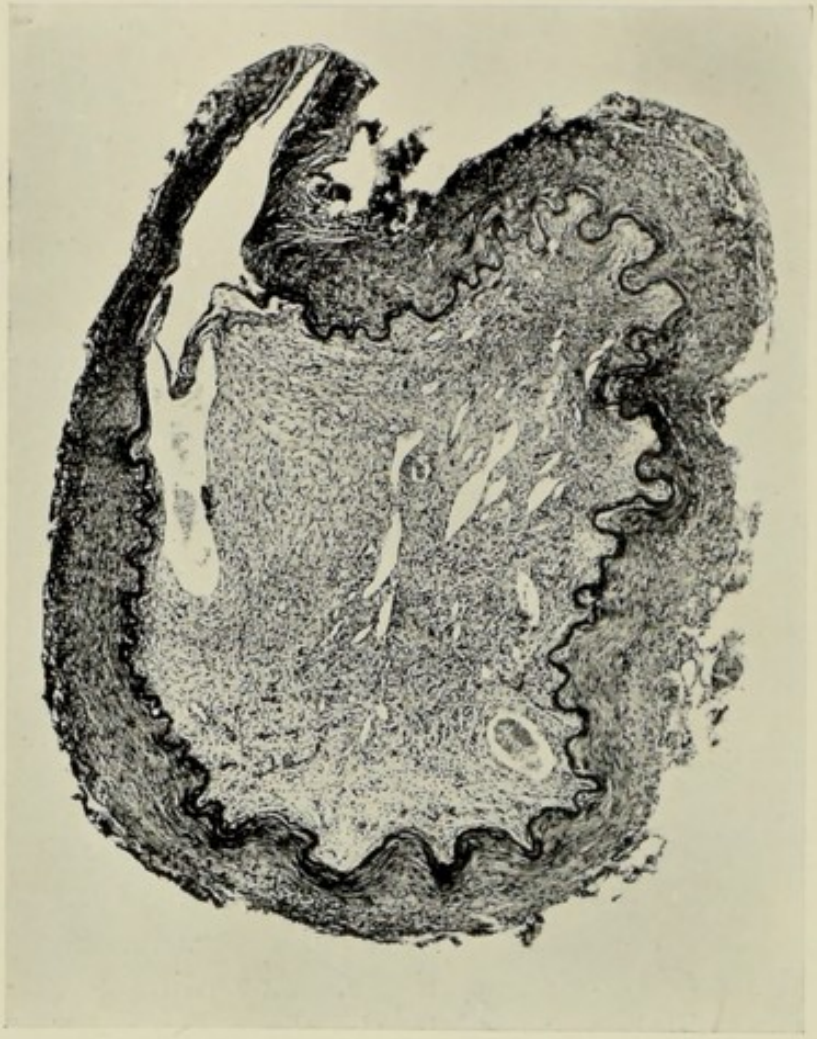


FIG. 57.—An organised thrombus in an artery, showing that the organised tissue (granulation tissue) is wholly internal to the elastic lamina. × 40 diam.

multiplication of muscle fibres by division of the nuclei and subdivision of the fibres in a longitudinal direction may take place.

Voluntary Muscle.—In wounds, union by fibrous tissue is invariable; though some regeneration of muscle may occur, the new fibres being developed probably from the sarcolemma cells.

During absorption of muscle fibres, there is a marked proliferation of the sarcolemma nuclei.

EPITHELIAL TISSUES.—New epithelium is always formed by proliferation and growth of pre-existing epithelium. Squamous epithelium shows very pronounced capacity for repair in this way; but even with some of the more highly specialised epithelial tissues, *e.g.* ciliated epithelium and glandular epithelium, there is considerable power of regeneration. Thus, after recovery from acute bronchitis there may be complete restoration of the ciliated epithelium, so in wounds of the liver the possibility of repair by proliferation of existing liver cells is considerable. In some cases, however, the power of repair is extremely limited, and, where it does occur, the epithelium formed may be of a lower type than that which was destroyed, and, thus, highly functioning columnar epithelium may be replaced by a low, cubical, lining variety.

BONE.—Here a considerable part of the granulation tissue undergoes special changes. The cells are transformed into osteoblasts, and the intercellular substance becomes impregnated with lime salts. This special, imperfectly ossified granulation tissue or **callus** is subsequently absorbed, and replaced by more regularly formed bone with definite Haversian systems —the method of formation being that seen in normal ossification.

CARTILAGE.—Union is most commonly by fibrous tissue, but development of hyaline cartilage from newly formed fibrous tissue may occur. This transformation of periosteal tissue to cartilage is not infrequently seen in certain pathological conditions.

CHAPTER V

PROGRESSIVE TISSUE CHANGES

HYPERPLASIA AND HYPERTROPHY

VIRCHOW defined **hypertrophy** as an **increase in the actual size** of the individual tissue elements, and **hyperplasia** as an **increase in their number**; but there is no general agreement among pathologists as to this use of the terms, nor is it in any way a practicable or useful method of classification, for in most cases of excessive growth there is an increase both in the size and in the number of the individual tissue elements concerned. It is better to reserve the term **hyperplasia** for proliferative changes in a tissue—not being an actual tumour growth—where no useful purpose is served by such proliferation; whilst the term **hypertrophy** should be used to denote the condition where there is a disproportionate increase of an organ or of some of its essential component elements, to **meet a demand for increased functional activity**. In other words, hypertrophy must be looked upon as a **physiological** process or reaction, whereby the tissue adapts itself to meet the increased requirements produced, it may be, by certain **unphysiological**, *i.e.* abnormal, conditions.

The condition of **hyperplasia** is frequently seen in repair, in cases where the reparative processes have been carried out in excess of the actual requirements. Thus, in the repair of a fractured bone, the scaffolding of imperfectly formed osseous tissue or **callus**, which acts as a temporary means of union and support, may be formed in considerable excess; and if this tissue persists, instead of undergoing absorption as it should normally do, the condition may be regarded as one of **hyperplasia**. Similarly, such hyperplastic phenomena may be seen in the repair of connective tissue, squamous and other forms of epithelium, etc.

In the consideration of the subject of **hypertrophy**, we must

exclude all developmental aberrations in the mere size of organs and tissues, *e.g.* inequality in the relative size of certain of the paired organs. It must be borne in mind, however, that during fœtal as well as in extra-uterine life, true hypertrophy may occur in certain organs when such is necessitated by increased functional demand. All forms of new growth or neoplasm must be carefully differentiated from hypertrophy, and such conditions as abnormal enlargements, say of bone, due to defective absorption; and also any thickening of the tissues due to diseases such as syphilis, chronic tuberculosis, osteitis deformans, acromegaly, myxœdema, etc., none of these conditions being really hypertrophies in the strict sense of our definition.

Similarly, we cannot regard as true hypertrophy the increase in certain of the tissues which results from the cessation of the accustomed friction and rubbing away, or other mechanical means whereby their overgrowth is, under normal circumstances, prevented. Instances of such abnormal thickening are seen in the case of the epidermis, especially in that of the soles of the feet, which occurs in bedridden patients; or in the growth of the nails or hair when these structures are not properly trimmed; or, again, in the remarkable tusk-like elongation, usually combined with curving, which is sometimes seen in the incisor teeth of rodents when, on account of malformations of, or injuries to the jaws, accurate apposition between the incisors of the upper and lower jaws is not obtained, those teeth in these animals continuing to grow indefinitely. Such instances are, of course, to be regarded as due to imperfect removal rather than to true hypertrophy of these structures.

Fig. 58.—Transverse section through ventricles near apex, to show "*concentric hypertrophy*" *of left ventricle* in Bright's Disease.

The commonest examples of true hypertrophy to meet increased functional demands are to be found in the case of the hollow muscular organs, *e.g.* the heart, bladder, muscular wall of the stomach and intestine, etc. In these viscera the condition may occur—usually along with a varying degree of dilatation—in order to overcome increased

resistance to the passage or expulsion of their contents. Familiar examples of such a condition may be seen in the hypertrophy of the muscle of the left ventricle in cases of increased peripheral resistance to the passage of the blood-

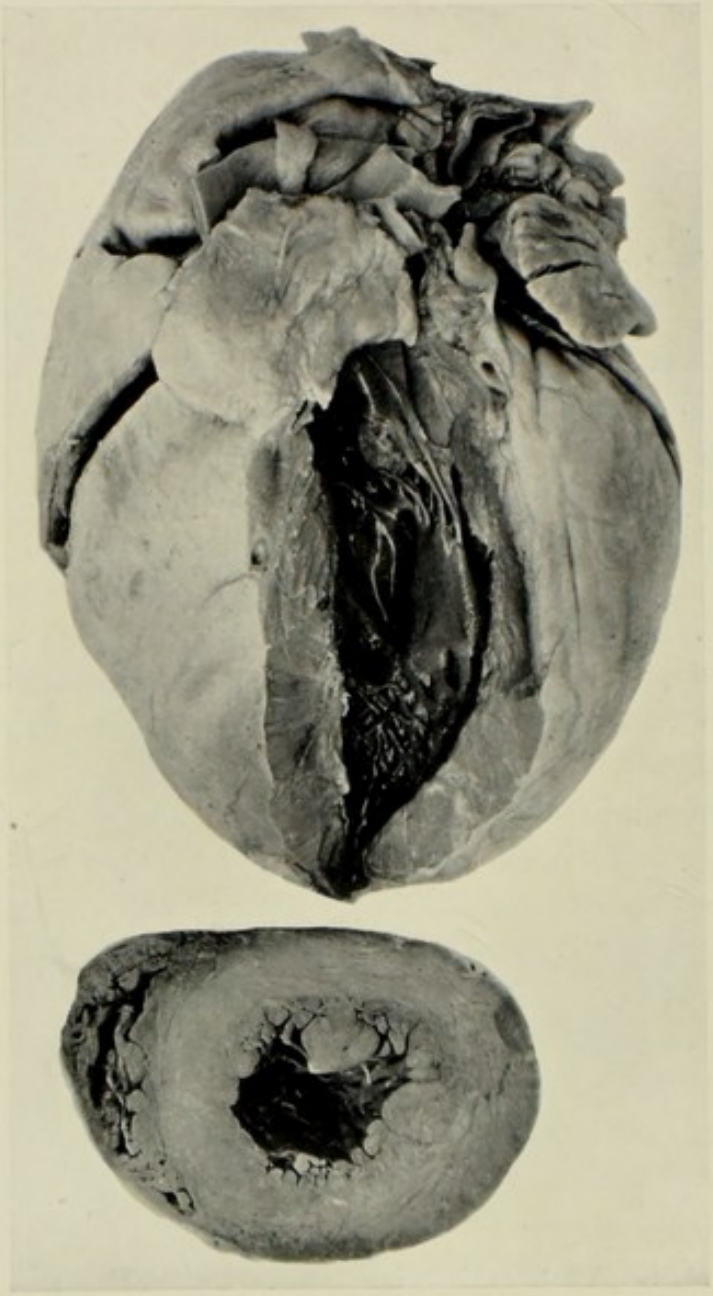


FIG. 59.—*Hypertrophy and Dilatation of Left Ventricle* in Aortic Disease. Below is a transverse section (near the apex of the ventricles) of a similar specimen.

stream, *e.g.* from prolonged spasm of the minute arterioles, arterio-sclerosis, or from narrowing of the aortic orifice; enlargement of the right ventricle in certain obstructive lung conditions or in mitral disease; hypertrophy of the muscular walls of the

alimentary canal above an obstructive narrowing in any part of its course, or hypertrophy of the bladder above a urethral stricture. As a general rule, the better the general and local nutrition and the more gradual the production of the obstructive lesion, the greater the degree of hypertrophy possible, and usually also the less marked the dilatation; and *vice versa*; although in some instances there may be a very extreme degree

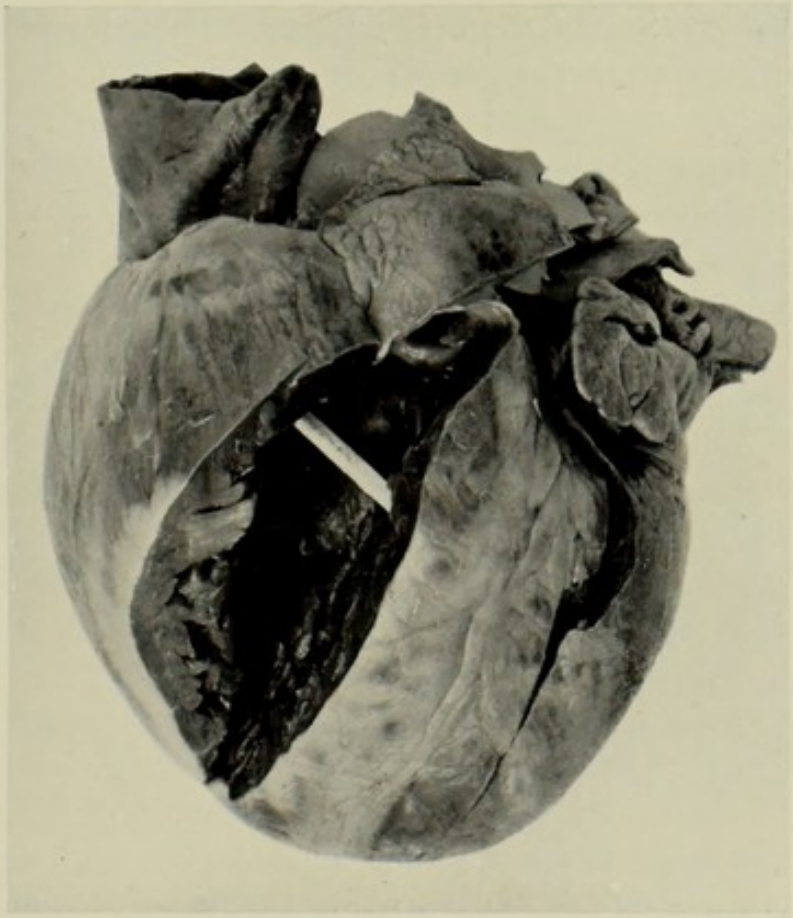


Fig. 60.—*Great Hypertrophy* (combined with Dilatation) *of Right Ventricle* in Mitral Stenosis. Note the comparatively small size of the left ventricle.

of both conditions present, *e.g.* in the left ventricle in some cases of aortic disease, more especially in slowly produced aortic regurgitation.

Physiological examples of increase in the size of organs for the performance of increased function may be seen in the enlargement of the uterus and mammary glands during gestation, etc.; and an analogous enlargement of these organs may occur under certain abnormal circumstances, *e.g.* in some cases of ovarian and uterine disease.

Theories as to the mechanism of production of Hypertrophy.—The various theories as to the mechanism by means of which hypertrophy is produced are little more than approximate conjectures, as the information which we possess concerning the intimate nature of the process is as yet extremely imperfect. In any one given instance it is probable that several factors may be at work, our knowledge of some of which may be summarised as follows:—

1. **By nervous stimulation.**—The neurotrophic influence of the nervous system upon the tissues has already been touched upon in the preceding chapter; and it has been thought by some, that the enlargement of the mammary glands before lactation and in certain cases of uterine and ovarian disease—and also the enlargement of the uterus which occurs during ectopic or extra-uterine gestation—might be explained by the influence of reflex nervous action. This is probably, at all events, partly true, but it must be remembered that tissue enzymes and internal secretions have an important bearing upon these questions. Similarly, the overgrowth—or "hypertrophy," as it is sometimes rather loosely called—which occurs in the tissues involved by the section, say, of the cervical sympathetic in animals, is largely to be explained by vasomotor paralysis, and the consequent increased vascular supply.

2. **The effect of local stimulation.**—The hypertrophy of the skin which results from friction or intermittent pressure—a condition which is well seen in the formation of "corns"—may be regarded as a true functional increase of the tissue, *i.e.* an increase due not only to the friction or pressure, but to the increased functional activity of the skin in its capacity as a protective covering. Also in the case of the connective tissue generally, for example in bones, the tissue is specially adapted to the particular functional strain which it has to bear. The bones show specially developed thickenings and ridges at the points to which muscles are attached. These are more marked in muscular individuals; and in cases of paralysis, etc., where the muscles cease to act, these muscular ridges and prominences tend to diminish in size, or even to disappear. Occasionally, where certain muscles are used to excess, such bony thickenings at their attachments may become very large in size. In the so-called "Rider's Bone" a very pronounced

osseous thickening occurs at the insertion of the tendon of the adductor magnus. This overgrowth is in some instances so much in excess of what is functionally required, that it has been considered by some authorities to be of the nature of a hyperplasia rather than a true hypertrophic overgrowth.

3. **Excess or abnormal character of nutriment.**—An adequate supply of nutriment, oxygen, and the necessary salts, are essential to the production of hypertrophy, but these factors cannot of themselves bring about the condition. Over-feeding in the case of the human subject certainly tends to produce adiposity or overgrowth of the fatty tissues of the body ; but this is rather to be regarded as an increased passive storage of fat by cells which cannot redistribute or use it up with sufficient rapidity. At the same time, certain very interesting and important changes may be brought about in the various organs of the body by the use of special articles of diet, as has been demonstrated lately by the suggestive work of Chalmers Watson on the influence of abnormal elements of diet upon the organs and tissues of certain animals. For example, he describes, in rats fed exclusively upon a meat diet, the occurrence of increase in size and apparently also in functional activity of the thyroid gland, as evidenced by proliferation and the more active character of the glandular epithelium. Some of the changes described by Watson appear to be degenerative in their character, whilst others are of the nature of functional and structural alterations of the tissues, and seem to be for the purpose of meeting the changed nutritional conditions ; and in some instances may even be regarded as true functional hypertrophies. His series of experimental observations are of sufficient importance to call for further investigation of the subject.

John Hunter's famous experiment of the transplantation of the spur of a cock to its comb led to an extraordinary growth of the transplanted structure, a circumstance probably accounted for, firstly, by the changes in its nutrient supply, the comb being a highly vascular structure; and secondly, by the fact that the spur in its new position was not worn away by friction, as it would have been in its normal position (*cf.* the curling, tusk-like overgrowth of rabbits' incisor teeth, already referred to above).

The influence of certain glandular extracts and other substances—for example, thyroid secretion—on the nutritive capacity of the tissues and on metabolism generally, may also have an important bearing upon the subject of hypertrophy. Similarly, disease of certain organs or perversion of their secretions may lead to changes in the body tissues of the nature of hyperplastic, or even—apparently, at all events, in some cases—of hypertrophic overgrowth. Some diseases of the pituitary gland, associated usually with abnormal changes in other glandular organs, may lead in the adult to wide-spread hyperplastic changes in the tissues, especially of the extremities, *i.e.* the condition known as **acromegaly**. When this disease occurs in a child or in an adolescent, it may lead to the condition known as **gigantism**; and although in many cases such "giants"—in spite of the excessive development of their bones especially—may be weak and ailing, yet in a few instances their muscular development may also correspond to their increase in size, and we must then regard the condition as one of hypertrophy.

4. **The effects of chemical stimulation, and the action of certain drugs**, *e.g.* phosphorus, may in some ways be classed along with the changes produced by abnormal food constituents. For example, small repeated doses of phosphorus may lead to thickening of the bones, especially in young subjects; but the conclusions of observers who regard this result as a true hypertrophy are open to criticism. For example, the fact that young animals were used in such experiments, leads to the suggestion that the phosphorus administered to them may bring about these results by modifying the conditions of nutrition and development of the bones; and, moreover, it is probable that, in such cases, the proper **removal** of bone which should occur in normal development may be prevented or interfered with, thus leading to thickening or hyperplasia rather than to true hypertrophic increase of the bones.

5. "**Compensatory**" **Hypertrophy**, *i.e.* one organ or tissue taking on the work of another, or one part of an organ taking on the work of the whole, is of comparatively frequent occurrence, and is due to increased functional demands being made upon the surviving organ or part of an organ. Thus, if a large part, say, of the liver or of the thyroid gland, be experimentally removed in animals, the remaining part may enlarge and do the

work of the whole. If one of two paired organs becomes diseased or injured, the other may possibly enlarge and take on increased function; or one set of muscles may take on the function of another weakened or paralysed set, *e.g.* the extraordinary muscles of respiration may come into play when the action of the intercostals or of the diaphragm is impaired; or the muscles of one limb may become greatly hypertrophied when the opposite limb is amputated or thrown out of action by accident or disease. Of the former group, *i.e.* the complementary hypertrophy of one of two paired organs, the kidney is usually cited as an example, but authentic cases of one kidney enlarging to supply the place and function of its damaged fellow are not so common as is generally maintained, though, of course, the condition may occur, especially in young growing subjects. On the other hand, it is also true that in many cases the so-called "compensatory" hypertrophy does not occur, even though no pathological change can be detected in the surviving kidney. Further, in cases where the unilateral enlargement of one kidney is found, the condition of the organ may be, and often is, **pathological** and not hypertrophic in nature.

The power of compensatory hypertrophy, however, which is said by some to exist between the thyroid and pituitary, thymus and thyroid, spleen and lympathic glands, etc., is a subject still requiring further elucidation and research. The functions of these organs are certainly closely correlated; and their respective secretions probably possess nutritive and other influences by means of which they act upon each other, and the absence of which may bring about certain pathological, or in some instances possibly true hypertrophic, changes in their structure and function. Frequently, however, **several** of these glandular organs may be simultaneously implicated by disease; for example, the thymus and thyroid in exophthalmic goître, the pituitary, thyroid, and other glands in acromegaly, and so on; and these changes, being frequently of the nature of pathological enlargements, are liable to be mistaken for compensatory hypertrophy. In the case of the thyroid and parathyroid glands, however, the latter may, after thyroidectomy, become to all appearance morphologically identical in structure with the normal thyroid gland.

6. "**Complementary Hypertrophy**" is a better term for certain

conditions which are sometimes described as instances of "compensatory hypertrophy"; for example, when one lung or part of a lung becomes expanded to fill up the increased space produced by the collapse or destruction of the other, or of another part of the same lung. This is not really a true hypertrophy for increased function—the expanded lung being often extensively emphysematous—but is merely a physical expansion complementary to the collapse of another part of the contents of the thoracic cavity.

Results of Hypertrophy.—Hypertrophic changes in an organ may enable it so to carry out its functions that the effects of the disease are "compensated for" or neutralised. For example, hypertrophy of the cardiac muscle in valvular lesions or in arterial disease may enable the heart to successfully carry on the circulation in spite of the increased difficulties in the way of its doing so. In such cases of hypertrophy of the cardiac, or, in fact, of any other muscular structure, where there is excessive strain put upon the hypertrophied tissue, the increased nutrition necessary for the continuance of such increased functional activity may fail to be kept up, leading, in the case of the heart, to dilatation and "failure of compensation," to degenerative changes in the muscle, or even to the cessation of its function, and consequently to death. Again, in respiratory obstruction, the excessive strain put upon the hypertrophied sterno-mastoids, scaleni, etc., may ultimately lead to their atrophy.

The microscopical changes occurring in the various individual tissues in hypertrophy require only very brief reference. It is sufficient to say that in true hypertrophy there should be little or no deviation from the normal. The special structural elements of the tissue may become increased in size, *e.g.* in the case of the muscular fibres of the hypertrophied uterus. Or, again, there may be a disproportionate increase in one special histological element of a compound tissue. In actual practice, the microscopical examination of the tissues of hypertrophied organs may often reveal the presence of various concomitant degenerative changes. These, however, may be due to other **antecedent**, to **accompanying**, or to **subsequent** or **supervening** morbid processes, and are not to be regarded as characteristic of hypertrophy.

NEOPLASMS, TUMOURS, OR NEW GROWTHS

In the whole realm of pathology, there is practically no subject presenting for solution more obscure and difficult problems than does the question of the ultimate nature and etiology of new growths; and until we obtain more accurate information as to their causation, any attempt at a general definition of their nature can be regarded as only temporary and provisional. With this reservation, therefore, a neoplasm or tumour may be defined as a new growth arising from pre-existing tissue, independent of the needs of the organism, and subserving no useful purpose, but, on the contrary, often acting deleteriously. It is **autonomous**, *i.e.* it follows its own laws of growth, and is not regulated by those governing the tissues of the body in which it is growing. As distinguished from hypertrophy, it is usually devoid of function, but may occasionally possess very imperfect and usually aberrant functional activities. There is practically always deviation from the normal structure of the original tissue, and nerve control seems to be absent. Further, the **life-history**—if one may be permitted to use the term when speaking of a neoplasm—appears to have no typical termination, the tumour cells being endowed with the power of apparently continuous and unlimited proliferation.

A tumour is not formed for purposes of repair (although in some cases it may supervene in or be implanted upon tissues undergoing, or which have undergone, reparative processes); nor is it the result of continued irritation or stimulation by any **known** bacterial or other organism. It is sometimes an extremely difficult task to differentiate true tumour growths from certain of the lesions produced by bacterial and other parasitic diseases; from the osteophytic overgrowths of bone in connection with the attachments of muscles; from cheloid of the skin following upon burns, etc.; as well as from the appearances sometimes found as the result of excessive overgrowth or hyperplasia in repair.

All tumours arise by the proliferation of pre-existing tissues. These pre-existing tissues may be fully developed, they may be actively growing, or may be still fœtal or even embryonic (*e.g.* in the case of included "germ-cells," *fœtus in fœtu*, true der-

moids, etc.); and they do not, under ordinary circumstances, seem to be the product of something introduced or transferred from without, although in certain exceptional instances the transplantation of what appear to be true tumours has been successfully carried out between animals of the same species; for example, in certain epithelioma-like tumours in the mouse, and also in the case of an adeno-carcinoma in the same animal. Further reference to these experiments will be made later, and it is sufficient at this point to mention that the cells of the experimental new growths obtained by such implantation are in all probability the "lineal descendants" of the tumour cells originally introduced. In the case of the so-called "infective sarcoma" occurring in the dog, and easily transplantable from one to another animal of that species, there appear to be reasonable grounds for the opinion, held by many authorities, that this condition is to be regarded rather as one of the infective granulomatous diseases.

MORPHOLOGY AND HISTOLOGICAL CHARACTERS OF TUMOURS.—As already pointed out, all tumours arise from the proliferation of pre-existing tissues, but may show great diversity from the original type of tissue from which they grow or into which they should develop; for example, they may tend to become **more cellular**, and in some cases **more vascular**, than the original tissue; or, again, in tumours growing from an acinar gland, the tumour cells may become arranged in gland-like spaces, as in adenomas and adeno-carcinomas, or in solid masses, as in scirrhus and encephaloid cancers.

Other diversities from the original tissue type may be found; for example, overgrowth of one special tissue element, as is seen in the proliferation of the fibrous tissue in fibromas, fibro-adenomas, scirrhus cancers, etc.; or transitions from one type of tissue to another within an allied group (metaplasias), as is common among the various forms of connective tissue—for instance between fibrous tissue, cartilage, bone, myxomatous tissue, etc. In a similar manner, one type of epithelium may be changed into another—a flattened epithelium may become cubical or columnar, or *vice versa*; a layer of epithelium which is normally single may become two, three, or more layers deep, and so on. Again, the blood-vessels may be imperfect in their structure, and may by their rupture lead to hæmorrhage.

In the tumour itself, or in secondary growths from it, certain of the peculiarities and characteristics of the original tissue tend to reproduce themselves—usually, however, with easily recognisable variations. Thus, the prickle cells of the stratum Malpighii which proliferate in epitheliomata growing from the skin, etc., are also found in the secondary growths in lymphatic glands, liver, etc. Saccular spaces, closely resembling those of the normal thyroid, may be found in secondary growths following malignant disease of that gland; and similarly, adenomatous spaces lined by columnar epithelium are common in metastatic growths, *e.g.* in the liver, or in the bones or elsewhere, when these follow malignant adenomata of the stomach or intestine. Imperfect attempts at milk secretion and the reproduction of the structure of the mammary gland may be observed in tumours secondary to cancer of the breast. The typical columnar cells so characteristic of compound cystic ovarian adenomata are found in the secondary growths which frequently arise from the malignant forms of these tumours, and innumerable other individual instances of the same general law might be cited.

GROWTH AND METHOD OF SPREAD OF TUMOURS.—All tumours are primarily local, and tend to increase in size, the rapidity varying indefinitely in different cases. Unless in such instances as where the tumour tends to reproduce some of the peculiarities in shape characteristic of the tissue from which it grows (*e.g.* in papillomata), the commonest method of growth is by comparatively uniform enlargement in every direction, as is well seen in the development of the more or less rounded nodules which form in the substance of a solid organ such as the liver. Or, if not growing among more or less homogeneous surroundings, they may grow in the direction of least resistance, for example along certain planes in the organ or tissue; and they may thus, especially in the case of malignant tumours, become extremely irregular in shape, particularly if growing on a free surface. Such irregularity in shape may be further increased by the coalescence of neighbouring foci of new growth; for example, in the case of malignant metastases in any of the organs or tissues. Although the line of least resistance is to a large extent followed, the more resistant tissues, *e.g.* the bones, may undergo absorption from pressure, or may become

extensively infiltrated by malignant growth. The general form of tumours is also largely influenced by the occurrence in them of certain secondary changes. The central parts of nodules may become **necrotic**, and may then undergo **partial absorption**, a condition which leads to the so-called **umbilication** or dimpling of the centres of tumour nodules, as is very commonly seen in growths, say, on the surface of the liver. **Inflammatory changes**, more especially the process of **ulceration**, may also produce great alterations in the shape and size of tumours in certain situations. Thus, in some surface epitheliomata, necrosis and ulceration may proceed so rapidly that the term "malignant ulcer" has been somewhat appropriately applied to such tumours, the base of the ulcer being formed by necrotic tumour tissue, immediately beneath which is the spreading and infiltrating margin of the new growth—the part which would have formed the body of the tumour having completely disappeared.

The **rapidity of growth** of different tumours varies very much, not only with the nature of the tumour, but with its site, and also with other as yet imperfectly understood general factors, such as the special resisting power of the patient, etc. Many of the simple tumours are extremely slow-growing, but even these may at any period, in whole or in part, suddenly take on more active growth, and perhaps become definitely malignant. Thus, some old-standing warts, pigmented moles, atheromatous cysts about the face or elsewhere, compound ovarian cystomas, true dermoid cysts, and probably many other originally simple tumours, may become malignant, invading the surrounding tissues locally, and perhaps also giving rise to secondary growths. The reason for their doing so is very obscure, and may partly depend upon altered nutritional conditions, for example, increased vascular supply, or possibly upon general or reflex nervous influences. Uterine fibroids frequently grow more rapidly at the menstrual periods, and less rapidly, or even appear to recede, during the intervals, and also especially at the menopause. In certain instances, mammary cancers have been said to diminish in size or even to disappear after oöphorectomy—whether from nervous reflex causes, or from general nutritional changes due to the removal of the internal secretion of certain enzymes by these glands, it is extremely difficult to say. Again, such increased rapidity of

growth, and perhaps also the occurrence of metastases in other organs and tissues, may be brought about by factors which lower the resisting power of the patient's tissues.

These changes in the activity of tumour growth may be associated with metaplastic changes, *e.g.* an apparently simple fibroma may "**recur**" after incomplete surgical removal, and may become progressively more cellular, and perhaps also more myxomatous, and less and less fibrous, after each surgical interference—such a tumour being sometimes known as a "**recurrent fibroid**" or **fibro-sarcoma**, the so-called "recurrence" being more accurately regarded as a re-growing of the tumour from fragments of the original neoplasm not completely removed by the operation.

Another phenomenon in connection with tumour growth which has given rise to much speculation is the apparently spontaneous retrogression or, in some instances, even complete disappearance of tumours clinically and histologically conforming with our present ideas of malignant neoplasms. Some of these cases are seemingly well authenticated; but as yet no explanation of such a phenomenon has been discovered, though the possibility of its occurrence must be carefully borne in mind in relation to all cases of so-called "cancer cures."

DEGENERATIVE CHANGES IN TUMOURS are extremely common. Nutrition is often locally deficient, leading to **fatty** or **mucoid degeneration**, **glycogenous infiltration, calcification, necrotic changes**, etc. **Hæmorrhages** are of frequent occurrence in many varieties of new growth, and may be due to rupture or injury, and to the imperfect structure of the newly formed vessels, as in sarcomas and gliomas: to infiltration and ulceration of the tumour cells into pre-existing vessels: or to secondary inflammatory processes from bacterial infection.

SPREAD OF TUMOURS.—Simple tumours merely grow in size, and push aside the surrounding tissues. Malignant tumours may spread:—

(1) **Locally by infiltration**, the tumour cells passing in among the elements of the surrounding tissues, especially by way of the lymphatics, *e.g.* in the case of cancers. They may also spread along serous surfaces, *e.g.* pleura or peritoneum, etc. As they spread in among the surrounding structures, they cause destructive changes by pressure, or possibly by means of

toxic substances or ferments produced by the tumour cells, which destroy the tissues and bring about their absorption.

(2) **By metastatic** or **secondary spread to distant parts.**—Metastases are probably due to the **direct dissemination** of the cells of the original or primary tumour, and not to the action of a virus, or to any so-called "spermatic influence" of the tumour cells on the cells of the surrounding tissues where the secondary growths occur; *i.e.* secondary growths are the **direct offsprings of the primary tumour.** There is, as already pointed out, almost always, in those metastases, persistence of **some** of the characteristics of the original tumour, either in the type of cell or in general structure; but there may, however, be considerable deviation from the original type found in the primary growth; *e.g.* the cells may be larger in size and show deviations in structure, or they may grow much more rapidly. The metastatic growths may in some instances be more vascular, or in others they may be less pigmented than the primary tumour; *e.g.* in some secondary growths in melanotic cases pigment may be almost absent, and so on.

Mechanism of Secondary Spread.—The secondary spread of tumours is essentially a **physical phenomenon**; *e.g.* a fragment of tumour may become detached and sink down in the peritoneal or pleural cavity from the action of gravity or from the movements of the organs; or in some cases the spread may occur **by contact** (as has been specially urged of late by Butlin[1]), *e.g.* of opposite sides of a serous cavity, of the lips, labia, etc.; or **by carriage along lymphatic trunks**, as in some sarcomas (especially in melanotic varieties), and in the majority of cancers, *e.g.* in epithelioma of the tongue spreading to the glands of the neck, etc. In some cases, it is not the nearest but more distant groups of lymphatic glands that are infected *e.g.* the cervical glands in some cases of cancer of stomach. The walls of lymphatic trunks may themselves become extensively affected. In other instances the tumour may be disseminated by the **blood-vessels**; for example, by the **veins**, especially in the case of tumours, the vessels of which are very imperfect, *e.g.* sarcomata; but this method of spread is also common in cancers from the invasion of the vessel-walls, fragments of the

[1] Butlin, "On the Contagion of Cancer in Human Beings: Auto-inoculation," *British Medical Journal*, London, Aug. 3, 1907, p. 255.

tumours being carried away and giving rise to secondary growths in distant parts, especially in the lungs. Spread by means of the **arteries**, *i.e.* an embolic spread, is not by any means uncommon, and probably explains the wide-spread multiple new growths sometimes found in the bones and in other tissues. Myxo-chondromata may spread by direct growth along the interior of blood-vessels, especially of the veins, which may thus become filled by the tumour like a thrombus.

In all instances **multiple tumours** need not necessarily be secondary to some other primary growth, and in some cases seem to be all primary or of similar age; *e.g.* multiple simple tumours, such as lipomata, fibromata of skin, dura mater, etc.

Law of "Homologous Growths."—In tumours of very great malignancy—for instance in melanotic sarcoma—secondary growths may occur in any, and sometimes even in every, tissue of the body. In many cases, however, where the malignancy is not so extreme, such secondary growths may tend to occur especially in tissues similar or allied to that in which the primary growth was found. For example, secondary growths following upon a primary tumour of bone are most frequently also found in bone; whilst the little nodules which may sometimes develop in the skin in such a case tend to disappear spontaneously by a species of abortion, as it were, probably owing to their not obtaining in their new environment suitable nutriment, and also owing to the absence of other factors necessary to their growth and development. In a like way, some lymphatic tumours tend to produce metastases in other parts of the lymphatic glandular system. New growth in one kidney may lead to a similar new growth in the other kidney; and similarly, both suprarenals or both ovaries may become affected when one of these organs has been the seat of a primary malignant neoplasm — probably because the tumour cells have acquired a special proclivity and capacity for growing in a certain soil where the nutriment is specially suitable for their growth; and partly, perhaps, because these allied organs or groups of tissues may have, for some unknown reason, lost their power of resisting the attack. It is a very interesting point to note that certain organs which are comparatively rarely the site of primary tumours are, probably on account of

their relations to the blood and lymphatic circulations, extremely liable to the occurrence of metastases. Thus, the liver is exceptionally liable to become infected from primary carcinomas or sarcomas occurring in the other parts of the abdominal cavity which drain their blood into the portal vein, or the lymphatics of which are closely connected with those passing out at the hilus of the organ. Similarly, the lungs, from their intimate association with the circulation, act as it were as filters for the venous blood coming from all parts of the body, through the right side of the heart; and hence these organs are specially prone to infection by sarcoma cells which may have found their way into the blood-stream. In the same manner, the lymphatic glands are specially liable to be invaded by cancer cells, which most frequently become disseminated by way of the lymphatic channels. Some organs, on the other hand, are remarkably immune from tumour growths, both primary and secondary; for example, the heart and spleen, although these organs are both very freely supplied with blood. The nature of this relative immunity is by no means clear, though in the case of the spleen it is possibly due to the extremely active phagocytic activities of its cells, and perhaps also to the presence of special cytolytic enzymes.

COMPONENT STRUCTURAL ELEMENTS OF A TUMOUR.—In the examination of the histological structure of any given tumour, our attention must be directed more especially to the characters of the **cells**, the **intercellular material, blood-vessels** and **lymphatics**. The tumour cells are the most important, and in fact are the essential elements; and in the consideration of the other component parts, it is sometimes a matter of much difficulty to determine in how far they are to be regarded as concomitant rather than as essential elements.

Cells.—Very great variations are necessarily found in the nature and appearances of the cells of different tumours. As already noted, they in many cases tend to reproduce the characters—imperfectly and aberrantly it may be—of the cells of the original tissue. Thus, prickle cells may be found in growths from a squamous epithelium; glandular cells in those from glands; cells of connective tissue type in those from the connective tissues, and so on. The term **metaplasia** has already been defined as the transformation of one tissue into another

member of the same group, and examples of this type of change are of very frequent occurrence in tumours. Another characteristic frequently exhibited by the cells of new growths, more especially in the malignant varieties, is the tendency to "revert," or to become transformed into cells of a more primitive type developmentally; and, as a general rule, the more malignant the tumour, the more "primitive" or undifferentiated do the cells become. To take a concrete example, the simple tumour arising from fibrous connective tissue is a **fibroma**. In the so-called "**hard**" **fibroma**, a very slow-growing tumour, the cells are indistinguishable from those of any fully formed fibrous tissue, whilst the fibrils are dense and thick, and the blood-vessels have fully formed walls. In the "**soft**" **fibroma**—still a simple tumour, but one the growth of which is not quite so slow as is that of the hard variety—the spindle-shaped cells may be somewhat broader or "plumper"; their nuclei more oval than rod-shaped; the protoplasm more abundant; and the interstitial fibrous tissue rather more scanty, the vessels still possessing well-formed walls. Again, in certain fibro-cellular tumours of very slight malignancy — the so-called "**recurrent fibroids**," or **fibro-sarcomata**—these characteristics may be rather more marked, and the blood-vessels thin-walled and poorly supported. Then, passing back through the series of **sarcomas**, as the type of cell becomes more primitive, *i.e.* as we pass from the **large spindle-** and **round-celled varieties** to the **mixed** and to the **small spindle-** and **round-celled tumours**, the intercellular substance and blood-vessels at the same time become progressively more and more imperfect, and the relative malignancy of the tumour increases. This malignancy reaches its greatest degree in the case of the extremely undifferentiated or primitive **lympho-sarcoma**, in which the cells are small and rounded, the intercellular substance extremely scanty, and the vessels represented by channels passing between the tumour cells, in some cases even apparently without an endothelial lining. In other words, just as the individual human embryo may be regarded as recapitulating the developmental history of the race, and just as we may now and again find a "throw-back" or reversion of the fœtus to a more primitive ancestor, so, in tracing back the character of the connective tissue cells through this complete series of

connective tissue tumours, we find, as we pass from the simpler to the more malignant members of the series, a reversion, as it were, to an earlier type of connective tissue cell. It is to this tendency that the name **anaplasia** has been applied.

Tumour cells may show not only great deviation from the cell-type of the original tissue from which the tumour is growing, but they may also in the same tumour show great diversity individually among themselves. Thus, there may be great variations in the shape and size of the cells, and in the characters and method of division of their nuclei. Multipolar and other irregular and unequal forms of mitosis are of frequent occurrence; and direct or amitotic division is alleged to occur in some malignant growths. There is still very considerable doubt as to the question of the occurrence of heterotype mitosis in malignant tumours, which has been affirmed by Farmer, Moore and Walker, and others, but which is strongly denied by some observers. For example, Bashford and Murray, who were at first strong supporters of the occurrence of heterotype mitosis in tumours, have reconsidered their previous views, and now deny its probability. Further investigation is required before it can be definitely stated whether heterotype mitosis does or does not occur; and the same view must be taken with regard to the conjugation of the nuclei of cancer cells which has been described by some authors.

Tumour cells may show not only very rapid and aberrant vegetative activities, but they may also exhibit rapid and excessive degenerative changes, more especially in their nuclei (karyolysis, karyorrhexis, etc.), and also in their protoplasm, *e.g.* fatty, colloid, and mucoid degeneration, glycogenous infiltration, calcification, etc. (*q.v.*).

Blood-vessels and Lymphatics.—In addition to the tumour cells proper (*e.g.* epithelial cells, non-striped muscle cells, sarcoma cells, etc., according to the variety of tumour), new growths of necessity contain other elements which may not be constituents or parts of the tumour proper, but are rather to be regarded as **a consequence** of its growth.

Tumours, for their growth and maintenance, require a sufficient blood- and lymph-supply, and this they obtain by means of **new**

vessels formed from those in the neighbourhood of the tumour.[1] These newly formed vessels are sometimes very imperfectly developed, *e.g.* in sarcomata, in which they may consist merely of a single layer of endothelium, or even of apparently unlined spaces and channels among the tumour cells. In the latter case, the tumour cells may very easily break off and pass into the circulating blood, and be carried to distant parts—a fact which explains the general tendency of sarcomas to be disseminated by the blood-stream. This imperfect character of the blood-vessels in sarcomas also explains the extreme liability to the occurrence of hæmorrhage, and of various degenerative and necrotic changes in these neoplasms. In other tumours, again, the blood-vessels are well formed and, it may be, fully developed. In the case of cancers, for example, the vessels of the tumour are to a large extent those of the tissues amongst which the cancer cells are infiltrating, but such tumours also contain new vessels formed by a process apparently identical with that which occurs in inflammation and repair. Hæmorrhages are also of frequent occurrence in cancers, but are usually due to the erosion of the walls of the vessels by the infiltrating cancer cells. Degenerative and necrotic changes are common in cancerous tumours, especially in those of rapid growth.

Newly formed lymphatics are very abundant in some tumours, for example in cancers, and it is by the lymphatic stream that these tumours are specially liable to be disseminated, although it should be noted that the spread of cancers by the blood-vessels is not by any means an infrequent occurrence. In some special cases, the newly formed lymphatics are themselves the essential elements of the tumour, *e.g.* in **lymphangiomata.** It is sometimes very difficult, and indeed frequently impossible, to determine whether the lymphatics of a given tumour are newly developed, or are pre-formed in the original tissue in which the tumour is growing.

The intercellular substance varies greatly in its amount and nature in different tumours. Thus, in new growths of connective tissue type, it may vary from the clear, homogeneous, jelly-like matrix seen in some myxomata or the very scanty and

[1] NOTE.—In the case of the *hæmangiomata*, or neoplasms composed of *blood-vascular tissue*, the blood-vessels are, of course, the essential constituents of the tumour, and not merely a consequence of its growth.

imperfect fibrillation of the more malignant types of sarcoma, up to the fully formed dense fibrous tissue of the hard fibroma. In these tumours the cells are separated from one another by the intercellular material; whilst in the carcinomata and other varieties of epithelial tumour, and also in some types of endothelioma, the neighbouring cells of each cell-group remain in contact with one another, the whole group being surrounded by a stroma derived from the pre-existing connective tissue of the part. Certain tumours give rise to very great irritation and proliferation of this pre-existing connective tissue—for example the "scirrhus" varieties of cancers, which indeed owe their name to the hard and dense character of the tissue thus produced.

In the case of the simple tumours there is usually, around the tumour, a condensation of the proliferated connective tissue of the organ or tissue in which the tumour is growing. As such a simple growth increases in size, it pushes aside the surrounding tissues, and usually possesses a distinctly demarcated margin, outside which the proliferated fibrous tissue above referred to may form a definite **capsule**, as it were, enclosing and separating the tumour from the surrounding tissues. Though the presence of such a capsule is very characteristic of the simple tumours, it is not invariably found around them; and, conversely, although malignant growths usually possess margins which are very indefinite owing to the infiltration of the surrounding tissues by the tumour cells, yet one may occasionally meet with examples of encapsulated malignant tumours.

In the general definition of a tumour given on page 239, it was stated that a new growth is devoid of nerve control, *i.e.* is "autonomous." **Nerve fibres** are found in certain tumours, but they are probably those that pre-existed in the original tissue, and which had merely become surrounded and incorporated in the neoplasm, and are therefore not of new formation. Whatever view be taken on this subject, the fact remains that tumours are not under the normal control of the nervous system, as are the tissues in which they grow. This is well exhibited in the cases where patients suffering from lipomata or fatty tumours are attacked by some disease which produces general emaciation and absorption of the body fat, the fat of the tumours remaining unaffected.

The presence of leucocytes and other wandering cells, more especially of small lymphocyte-like cells, in tumours, especially near the spreading margin, is probably a secondary phenomenon due to the irritation of the tumour, and is in all likelihood to be regarded as an attempt at repair. In other cases, such leucocytic infiltration may be due to the secondary inflammatory changes produced by invading bacteria, this being especially common in tumours growing at the surface of the body or in

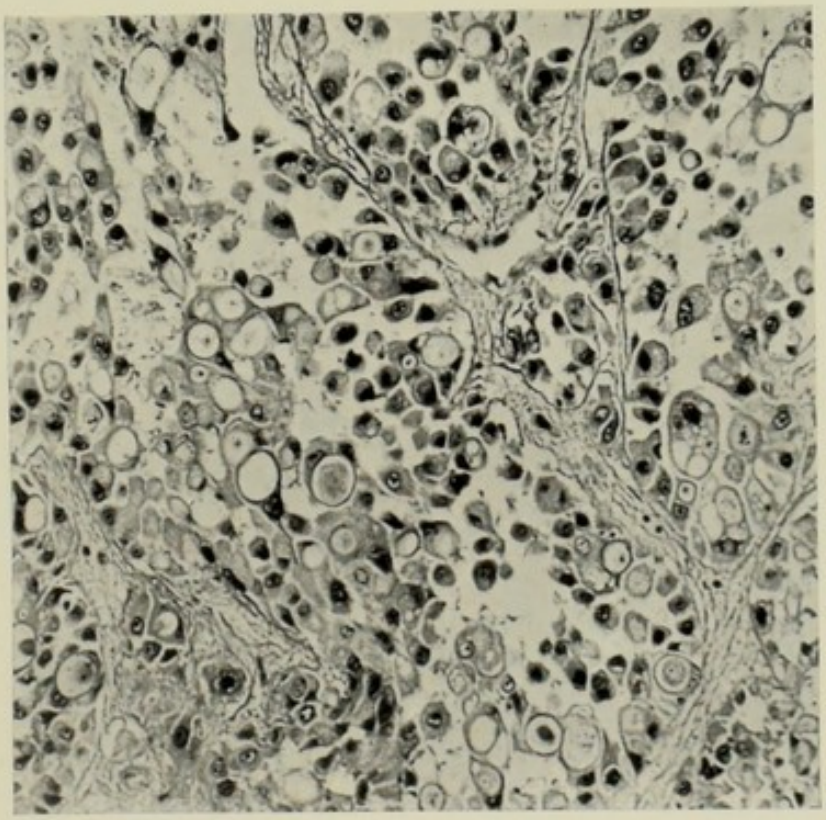


FIG. 61.—*Phagocytosis in Tumours.* Infiltration of pleura by scirrhus tumour of breast. The cancer has assumed a softer type, and the majority of the tumour cells contain cell-inclusions around which clear digestive vacuoles are developed. × 150.

the wall of the gastro-intestinal canal, etc.; *i.e.* in positions specially liable to the attack of micro-organisms. In such inflamed tumours, polymorphonuclear leucocytes are often very numerous.

PHAGOCYTOSIS IN TUMOURS.—Tumour cells are frequently actively phagocytic, and may englobe and digest red blood corpuscles, leucocytes, and other cells, sometimes in considerable numbers. The erosion of the tissues caused by malignant new growths is due in part to this phagocytic activity; though

other factors, such as the action of certain digestive enzymes produced by the tumour cells, pressure, etc., probably play a very important part in this process. Leucocytes and other wandering cells, especially of the large mononuclear variety, are also very commonly seen attacking and destroying the tumour cells, especially where these are degenerated or necrotic.

ETIOLOGY OF TUMOURS IN GENERAL

In spite of the enormous amount of research which has been and is now being carried out on the subject, the essential cause of new growth is still entirely unknown; but certain hypotheses have been advanced to account for their direct causation, and many of the **indirect** or **predisposing** causes are well recognised, and may be summarised as follows:—

1. **Age.**—It is an established fact that the liability to cancer tends to increase as life advances, though children and young adults are not by any means immune. There is also with advancing years, according to the statistical investigations of Bashford and Murray, a similar increased liability to sarcoma, although this variety of malignant disease is much commoner than cancer in the earlier periods of life.

This increased liability to cancer with advancing age may be due to various factors, such as—(i) Progressive lowering of the vitality of the tissues, with a consequent diminution of the power of resistance to invasion. (ii) Loss of control over the formation of new tissue. (iii) Differences in the vegetative vitality or power of reproduction and growth of the different tissues, *e.g.* one tissue retaining more power than another, and so tending to invade the other. It is a well-established fact that malignant disease is specially prone to occur in organs at periods when their proliferative activity begins to decline; for example, during the involution of the thymus gland, the mammary gland, uterus, etc. Bashford and Murray[1] have put forward the somewhat plausible suggestion that this unbounded growth, following on the terminal phases of normal cell-multiplication and at a period when it should naturally subside,

[1] Bashford and Murray, *Scientific Reports of the Imperial Cancer Research Fund*, No. 2, Taylor & Francis, London, 1905.

might possibly indicate the occurrence of the process of conjugation whereby the animal cell naturally renews its youth and vegetative activity; and they and several other writers have recorded certain appearances in malignant tumours, which they have interpreted as possibly pointing to the occurrence of some such nuclear conjugation between tumour cells. The evidence as yet brought forward in support of this contention appears, however, to be insufficient to warrant its acceptance.

2. **Sex.**—Malignant disease is relatively commoner in the female, largely on account of the comparative frequency of mammary, uterine, and ovarian tumours.

3. **Family Predisposition.**—Heredity appears to play a definite part; though whether this is due to a decreased family resistance, or to an actual predisposition to the disease, or, again, to the presence of some possible infective cause, is as yet quite unknown. Members of some families may show a tendency to die of cancer or other forms of malignant disease at a certain age; and, again, some simple tumours, *e.g.* osteophytes, are occasionally found in several members of the same family.

4. **Race.**—Some races of mankind are more liable than others to certain forms of tumour; and the same is proved of the lower animals. For example, white horses are said to be more liable to the occurrence of melanotic sarcoma than are those of other colours; and experimental inoculation with **Jensen's tumour** has been more successful in some strains of mice than in others.

5. **Occupation.**—There is in some trades an increased liability to cancer; for example, among chimney-sweepers, paraffin workers, and others exposed to the influence of special irritants (see later, under **Irritation**).

6. **Environment.**—Certain countries, districts, and even certain houses (the so-called "cancer-houses") are frequently spoken of as predisposing their inhabitants to malignant disease, but in the individual cases usually cited, it is quite possible that there may be other predisposing factors at work, such as heredity, longevity, weakened resistance produced by other disease, etc.

Many other alleged causes, often but little supported by evidence of any value, have been brought forward from time to time, as, *e.g.*, over-feeding, special articles of diet, etc. etc.; and

there is almost no food element which has not at some time or other been suspected of producing malignant disease.

Certain more direct causes probably have some influence in the causation of tumours, and we may now consider some of these more fully :—

1. **Local Irritation** either physical or chemical, seems in some instances to have a very important causal relationship to the disease, and appears in such cases to stimulate tumour growth, perhaps in a way somewhat analogous to that by which it may produce excessive reparative processes. It is impossible at present to say whether prolonged irritation may of itself produce new growth in suitable subjects; or whether it merely prepares the way by weakening the resistance of the tissues locally, and so produces a suitable soil in which some other specific agent may then the more easily cause tumour formation.

Be this as it may, chronic irritation certainly does appear to possess some definite causal influence upon the growth of tumours, as in the case of "**Chimney-sweeper's cancer**," already referred to above, where the long-continued irritation, especially of the scrotum and neighbouring parts, by the accumulated soot particles, may ultimately lead to the development of an epithelioma. Similarly, epitheliomata of the lip and tongue are said to arise from the long continued use of a short clay pipe—the so-called "**smoker's cancer**"; and certainly the enormous preponderance of the disease in this position in the male seems to lend support to such a view. Cancer may also follow prolonged irritation caused by a sharp or jagged tooth, or by the plate supporting artificial teeth. Chronic ulcers in any situation, and scar tissue or cheloid, may ultimately become the seat of new growth; but in some of these cancers, the inclusion of pieces of epithelial tissue in the granulations of the ulcers or in the scars may be the starting-point of the new growth.

Again, cancer of the liver frequently arises from or near a gall-bladder containing gall-stones, and the chronic irritation may be regarded as a causal factor, though here again it may be equally affirmed that both conditions arise from a common cause. Similarly, in cancer of the liver associated with cirrhosis, it is as yet impossible to determine whether both of these conditions are brought about by a common cause, or whether the cancer results from the irritation produced by

the aberrant attempts at repair of the liver tissue, so commonly associated with cirrhosis.

The production of osteophytes at the point of attachment of muscles to bone may possibly be due to chronic irritation; and there seems little doubt that certain chemical irritants, for example paraffin, may, by their prolonged application to the skin, *e.g.* in the case of workers who use these substances in their trades, lead to epitheliomata of the skin.

The close resemblance to true tumours exhibited by certain lesions produced by known bacterial or other similar irritants, such as gonorrhœal or syphilitic warts, is very striking, and certainly suggests the possibility that some, at all events, of what we now regard as true tumours, may ultimately be found to be produced by other as yet undiscovered organisms. Thus, in the past, syphilitic gummata, tuberculous "tumours" of the brain, actinomycotic and other lesions produced by members of the streptothriciæ, etc., were considered and classed as tumours; and at the present time opinion is greatly divided as to whether the so-called "**infective sarcoma**" of the dog is to be classified among the true neoplasms, or as one of the infective granulomatous diseases, the condition having very close analogies with both of these groups.

2. **Direct Mechanical Injuries** may also predispose the tissues to tumour growth, possibly owing to the laceration and consequent intermingling of the different tissue elements; or perhaps by merely lowering their vitality and power of resistance. Patients suffering from tumours of the breast, brain, testicle, etc., when they consult their medical adviser, almost always come with a definite history of injury; and though it is, of course, possible that such an injury may have been the cause of the condition, it must not be forgotten that such a tumour may have previously existed in the tissue, and the accident might only have served to draw the patient's attention to it for the first time.

The laceration caused by some injuries may possibly produce displacement or intermingling of the tissues (*cf.* the intermingling of tissues during the involution of certain organs such as the uterus or the mammary gland); and certain of the elements so displaced and cut off from their normal environment may possibly give rise to tumour growth, perhaps on account of the changed nutritional conditions.

Sarcomatous tumours of bone are sometimes described as following upon fracture, but in this connection it must be borne in mind that the sarcoma may possibly have been **previously** present, and may have thus **predisposed** to the fracture. The occurrence of epitheliomata and of sarcomata arising from the margins of old ulcers and from scars has already been mentioned, and may conceivably be due either to chronic irritation or to actual displacement and intermingling of the tissue elements. Similarly, cystic tumours of the iris have occasionally been recorded as following punctured wounds of the eye, and have been regarded by some writers as possibly due to transplantation of corneal epithelium or other structure at the time of the accident.

It is convenient in this connection to discuss briefly the results of the experimental **transplantation of healthy tissues**. As is well known, "skin-grafting," or the transplantation of pieces of skin epithelium, is frequently carried out with success in the human subject; and, similarly, pieces of bone, nerve, etc. may sometimes be successfully transplanted, a sufficient amount of vitality and proliferative power being retained by some tissues, enabling them, after removal from their normal position, to survive and adapt themselves to their new surroundings, provided these are capable of supplying them with suitable nutriment. The usual fate, however, of such pieces of transplanted tissue is necrosis, and then either absorption by phagocytosis and enzyme action, or the casting off of the dead tissue after the manner of a slough. The more divergent the varieties of animal used in such experimental transplantation, the less likelihood, as a rule, is there of the "grafts" being successful. It is important also to note here that embryonic tissues, when transplanted, appear to perish **more** readily than those of the adult, in spite of their greater vegetative activities, and especially if young animals are used for the implantations.[1]

Whilst the experimental transplantation of healthy tissues has been in many instances successful, there is at present no proof that, even when implanted in abnormal or dissimilar sites, they may give rise to tumour growth. In this connection, the experimental work of Dr Lack is usually cited. This observer, in a series of rabbits, transplanted fragments of

[1] Milne, "Liver Regeneration," *Jour. Path. and Bact.*, Oct. 1908.

apparently healthy ovary intraperitoneally, and in one instance obtained what appeared to be the growth of an adenomatous tumour. This result, although numerous similar experiments have since been carried out, both by Dr Lack himself and by others, has never again been obtained; and it is highly probable that, as the tumour obtained in this single instance is found naturally in rabbits, the animal used for the experiment contracted the disease in some other way.

THE EXPERIMENTAL TRANSPLANTATION OF TUMOURS has until recently been attended with little success, death and absorption of the transplanted portion of tumour usually resulting. It has been clearly shown, especially by Bashford and his colleagues, that malignant disease is very widely spread, and may occur in any member of the vertebrate group. In the vast majority of cases, the experimental transplantation of these tumours has failed. In no case has a tumour from the human subject ever been successfully inoculated into any of the lower animals; and, similarly, practically all attempts at transplantation between animals of different species have completely failed. Even between members of the same species little success has been attained in experiments with the vast majority of tumours, but in a few instances positive results have been obtained. Thus Jensen[1] has succeeded in transplanting what he regards as a variety of epithelioma (Jensen's Tumour) occurring sporadically in white mice; and Borrel[2] has similarly described the successful transplantation of a species of adeno-carcinoma, also among mice. These results have been confirmed and amplified by Apolant and Ehrlich, Bashford and Murray, and numerous other observers, who are of opinion that the lesions dealt with are of the nature of true malignant neoplasms. Even if Jensen's tumour is by some authorities not admitted to be a true malignant growth, a position which appears to be untenable, Bashford and Murray, by their successful transplantation of an epithelioma in mice, have shown conclusively that at all events some definitely malignant tumours can be transplanted in animals of the same species.

[1] Jensen, "Experimentelle untersuchungen über Krebs bei Mäusen," *Centralblatt für Bacteriologie*, Bd. xxxiv., 1903.

[2] Borrel, "Epithélioses infectieuses et epithéliomas," *Annales de l'Institute Pasteur*, Tome xi., 1903.

In these experiments, the cells of the resulting growths appear to be the direct lineal descendants of the tumour cells originally introduced, and may indeed be regarded as artificial metastases produced in the tissues of another animal of the same species, the stroma of the tumour and its blood-vessels being supplied by the tissues of the host.

Allusion has already been made to the so-called "**infective sarcoma**" occurring in dogs, and a considerable amount of experimental work has been carried out in connection with its transplantation. By the majority of pathologists, however, this condition is not regarded as a true tumour growth, but rather as belonging to the infective granulomatous diseases.

HYPOTHESIS OF WALDEYER AND THIERSCH.—These authors recognised the fact that the cells of a carcinoma are derived from those of covering and secretory epithelium. Under normal circumstances, according to their hypothesis, there is a state of equilibrium or balance between the epithelial and the connective tissues with regard to their respective proliferative capacities, each holding the other in check. Overgrowth of the epithelium is thus, they say, prevented by the influence of the connective tissues. With advancing age, however, they postulate a progressive weakening and loss of this restraining power on the part of the connective tissues, with a consequent freeing, as it were, of the epithelium, which can then proliferate and give rise to tumour growth, reversion to a more primitive type of cell at the same time occurring. They thus endeavour to explain the increasing liability to cancer with advancing age. The main objection to this theory appears to be that, were this the true explanation of cancer, the occurrence of multiple primary foci should be the rule, instead of, as is actually the case, the exception, in malignant disease.

COHNHEIM'S EMBRYONAL HYPOTHESIS, or **THEORY OF "EMBRYONIC RESIDUES"** or "**RESTEN**," is grounded on the view that, early in development, some tissue rudiments—embryonic cells, or portions of embryonic or fœtal structures—may become caught or be intermingled in other tissues, where they remain dormant, but retain in latent form their inherent embryonic capacity for unlimited proliferation, and are thus, under favourable circumstances, capable later of taking on new growth, and so leading to tumour formation. This theory

cannot be made to account for the growth of all tumours, but it is certainly a possible explanation of the **mechanism** by which some neoplasms arise, though it affords no clue as to the nature of the factors which stimulate the new growth of the latent "residues." This hypothesis is in many ways analogous to the "**Heterology**" hypothesis of Virchow, who similarly suggested that a portion of one tissue might become entangled in another by a process of intermingling during development, or from injury or disease.

"**TISSUE-TENSION**" **HYPOTHESIS OF RIBBERT.**—Following the arguments of Waldeyer and Thiersch, Ribbert accepts the view that the vegetative capacity or proliferative power of the various component cells of a tissue is regulated by what he calls the "tissue-tension" of the part, there being in health a condition of equilibrium, as it were, or balance among the various tissues and tissue elements, whereby any over-activity on the part of one cell or set of cells is held in check by the restraining influence of its neighbours. Consequently, any pathological disturbance of such an arrangement might conceivably lead to the weakening of such inhibiting power on the part of the less resistant tissue elements, and this weakening might allow abnormal growth of and invasion by certain of the other tissue elements, whose vegetative capacity is not only greater, but is now allowed free scope for proliferation. The displacement or "dislocation" of cells, singly or in groups, during development, or from traumatic, irritative, or other causes, may lead to their isolation, and to their being freed from the inhibitory influences of their fellows—a sort of "growth-liberation," as it were, taking place. Thus epithelial cells, when isolated and deprived of the normal inhibitory influence of the neighbouring epithelial cells and connective tissue, and being endowed, according to Ribbert, with latent capacity for unlimited proliferation, may multiply and give rise to the formation of new growths. Ribbert's hypothesis is thus a combination of both the foregoing theories.

Many examples of such intermingling might be cited, but the following must suffice:—

i. **Developmental Intermingling.**—Part, or even in some cases the whole, of one organ may be embedded in another; for example, the suprarenal gland or a part of it in one kidney, or

less commonly in the liver; or, again, parts of the Wolffian duct may be included in the kidney. These "residues" may remain dormant or latent for many years, and in some cases may remain so for the whole of the patient's life; but in other instances some, as yet unknown, influence may stimulate them to proliferate and become new growths.

Cystic and other tumours—the so-called "false dermoids," "wens," or "atheromatous cysts"—are of common occurrence at the lines of closure of the branchial and facial clefts, and are in all probability due to infoldings of the surface structures, or perhaps to the persistence of small areas of the epithelium originally lining the clefts. Similar cystic tumours may be found along the median line, where imperfect closure and incomplete coalescence of the body-wall of the fœtus may also lead to such conditions as meningoceles, meningo-encephaloceles, etc. Developmental intermingling may also occur where one tissue meets or passes into another; for example, at the junction of skin and mucous membrane.

This theory serves to explain certain cartilaginous tumours of secreting glands (which sometimes tend to be highly malignant). Thus, **in the testicle** such tumours may arise from the inclusion, early in development, of misplaced fragments of vertebral cartilages. Similarly, the cartilaginous tumours sometimes found in the parotid and submaxillary glands may be due to the inclusion of certain of the cartilages of the developing ear or lower jaw.

Birth-marks, moles, or **nævi** growing in the skin may also be caused by this embryonic intermingling of tissues early in development; and they may later in life give rise to tumours, some of which may be highly malignant, *e.g.* melanotic sarcoma. These **moles**, and the tumours sometimes arising from them, may exhibit increased pigmentation, development of hair, abnormal vascularity, etc.

ii. **Intermingling of Tissues from Disease or Injury** may afford a similar explanation of the mechanism by which certain other tumours arise, as, for instance, the multiple chondromata of bones, more especially of the hand, which sometimes develop in rickety subjects. These may be due to tumour growths supervening in islets of cartilage, detached from the epiphyseal or other cartilages, and enclosed in the growing bone during the

abnormal processes of ossification in this disease. Traumatic intermingling may possibly occur in fracture of bone, or, as already suggested above, in punctured wounds of the eye; and the displaced fragments of tissue may later give rise to new growth. A somewhat analogous explanation has also been suggested to account for the frequent occurrence of tumours in organs such as the ovary and breast, in which intermingling of tissues may take place during the periodic enlargement and involution to which these organs are subject. A similar intermingling may occur in chronic inflammatory lesions, in which some of the cells may be cut off by fibrous tissues from their accustomed environment and nutritive conditions. It must, however, be again emphasised that these hypotheses merely explain the possible mechanism and nidus of tumour growth in such cases, and do not give us any information as to the nature of the stimulus which causes these isolated cells or cell-groups to take on an excessive and abnormal growth.

THE INCLUSION OF ONE "INDIVIDUAL" WITHIN THE TISSUES OF ANOTHER, giving rise to the **teratomata**. These tumours appear to result from the inclusion of one ovum or germ-cell, as the case may be, within the tissues of another individual; and from the after proliferation of this included cell many conditions may arise, varying from the most rudimentary true teratomatous dermoid cysts, through the series of those containing skin, hair, sebaceous glands, teeth, etc., and even bones and organs, up to parasitic or adherent twins in all stages of development. Into a full discussion of the ætiology of double-headed and other monsters, and as to whether their formation is due to double-yolked or to binuclear ova, to incomplete fission of the germinal area of one embryo, or to the partial fusion of the germinal areas pertaining to twins, it is not possible to enter here.

The question has been much discussed of late as to whether aberrant germ-cells may give rise, not only to these teratomata, but to many other forms of tumour growth; and a few ardent supporters of this theory even go so far as to assert that all forms of tumour growth are due to their agency. The theory is founded on the well-known view that the direct genealogical continuity of any given species is vested in certain specific cells called **germ-cells**; whilst the body of the individual is, as it

were, merely the bearer or carrier of these cells for a generation, and is an offshoot formed by the proliferation of one special germ-cell. The fertilised ovum or zygote divides and subdivides a given number of times, by a process corresponding in some ways to a larval stage of development, giving rise to a large number of cells—the germ-cells—only one of which should, under normal circumstances, proceed to form the embryo or body of the new individual, whilst the others form the trophoblast around the segmenting ovum. According to Beard, these germ-cells, when the growing embryo attains a sufficient stage of development, migrate into the area where the generative organs are developed; and their function is to give rise to the gametogenetic cells of the ovary or testis of the new individual. While these cells are thus migrating, it is possible that some of them, instead of reaching their proper destination, may lose their way, as it were, and wander into other parts of the embryo, where they may settle down in the tissues and remain quiescent; and then, later, if any abnormal conditions arise which liberate them or stimulate them to proliferate, they may give rise by their proliferation to new growths, imitating the structure, it may be, of the tissue in which they are growing. This wandering of germ-cells has been demonstrated only in certain of the cold-blooded animals, *e.g.* the frog and the skate. The whole question is as yet extremely problematical.

THE REVERSION OF SOMATIC CELLS TO THE CELL-TYPE CHARACTERISTIC OF GAMETOGENETIC TISSUE is regarded by Farmer, Moore and Walker, and others, as the explanation of some of the phenomena described as occurring in malignant tumours, for example the much discussed heterotype mitosis; and Farmer also suggests that the vacuoles so often seen in cancer cells are perhaps the remains of the archoplastic vesicle seen in the normal development of germinal cells.

HANSEMANN'S THEORY OF "ANAPLASIA" IN TUMOUR CELLS.—All cells possess two classes of activity:—

i. The faculty of multiplication.

ii. The capacity of individual growth, and the development of specialised function, with specialised structural peculiarities to correspond.

The former of these—the faculty of cell-multiplication—is found in its most active form early in life, and more especially

in the tissue of the embryo, in which the vegetative activities are far in excess of those connected with specialised function; whilst, as age advances, the reverse is the case, the capacity for specialised function becoming emphasised at the expense of the more primitive faculty of multiplication. Now if, for any reason, the reproductive activity (the so-called "embryonic" character) of the cells should be re-established, the condition may be regarded as a reversion to the more primitive type of cell; and it is to this process of reversion, which appears to take place in the formation of neoplasms, that Hansemann has applied the term **Anaplasia**, already referred to on p. 248. The greater the degree of anaplasia and the more primitive and undifferentiated the type of cell, the more malignant, as a rule, is the resulting neoplasm. The less marked the anaplasia of the cells, the more "benign" or "simple" is the resulting new growth. Between these two extremes there may be found, as is pointed out on p. 247, tumours exhibiting all gradations of "innocency" and "malignancy," and completely bridging over the gap. That this is the case is a fact well recognised by all pathologists, and seems to indicate, as is strongly urged by Cathcart,[1] of Edinburgh, that, in endeavouring to discover the ultimate cause of tumour growth, attention should be directed, not only to the malignant, but also to the simple neoplasms.

PARASITIC HYPOTHESES OF TUMOUR FORMATION. — All the foregoing hypotheses have dealt rather with the mechanism than with the intimate cause of tumour growth; and innumerable attempts have been made to demonstrate the presence of some organismal cause for the disease, and, as a result, numerous "cancer parasites" have from time to time been described, but none of these has had its claim as a causal agent established. Of these "cancer parasites" may be mentioned various bacteria, Russell's "fuchsin bodies," yeasts, and supposed "protozoa." Many of these alleged parasites have been shown to be cell-inclusions or degeneration products, while others have been proved to be associated bodies without any relation to the ætiology of the disease. It must, however, be recognised that lesions very similar to tumour growth may be caused by known

[1] Cathcart, *The Essential Similarity of Innocent and Malignant Tumours*, London, Simpkin, Marshall, Hamilton, Kent & Co., 1907.

parasites, *e.g.* the cystic growths produced in the livers of rabbits by *Coccidium oviforme*; and therefore, although the present tendency is to abandon the parasitic theory of tumour growth, and to look for the ultimate cause of the disease in the potentialities—"embryonic" or otherwise—of the cell itself, our knowledge both of tumours and of pathogenetic parasitic organisms is much too meagre and imperfect to make such a sweeping assertion as that such a parasitic hypothesis is an impossible one. The non-discovery of an organism is not by any means a proof that it does not exist; and even the failure to reproduce the vast majority of tumours in the same species of animals does not disprove the possibility of the organismal hypothesis; for it is quite possible that, in addition to other factors, a specially acquired susceptibility on the part of the animal may be required before the tumour can grow in its tissues. Gaylord[1] reports the endemic occurrence of tumours in small animals, *e.g.* rats, confined in cages previously used by Loeb for the confinement of rats which he had inoculated with what he believed to be a true spindle-celled sarcoma, and not an infective granuloma, as was thought by other authorities. Gaylord and Borrel also report a similar occurrence with adeno-carcinoma in mice. Butlin[2] has recently published a series of cases in which he is of opinion that auto-inoculation has occurred by the direct contact of one part of the body with another part which is the seat of malignant disease, *e.g.* the opposite sides of the vulva, larynx, the upper and lower lips, etc. He thinks that such cases "are too many and too constant in the circumstances of their occurrence to be explained on the theory of coincidence"; and he also believes that cancer may be communicated to other individuals by direct contact with the ulcerated surface of the tumour.

[1] Gaylord, "Evidences that Infected Cages are the Source of Spontaneous Cancer developing among small Caged Animals," *British Medical Journal*, London, Dec. 1, 1906, p. 1555.

[2] Butlin, Addresses in Surgery delivered before the British Medical Association, "On the Contagion of Cancer in Human Beings: Auto-inoculation," *British Medical Journal*, London, Aug. 3, 1907, p. 255.

GENERAL CONCLUSIONS REGARDING THE ÆTIOLOGY OF TUMOURS

We thus have as yet no accurate information as to the ultimate cause of new growths, but it is highly probable that all tumours are not necessarily due to the same cause, and one or more of the above ætiological factors may play a part in the causation of any one given case. Some conditions now classed as tumours will in all likelihood be found to be due to some as yet undiscovered animal or vegetable parasites. Some are certainly produced by special and prolonged kinds of irritation, though this may only **predispose** the tissues to invasion by a special organism. Some tumours, again, are undoubtedly due to the inclusion of "blighted" or aborted ova, *e.g.* teratomatous dermoids; but the part played by germ-cells in the production of tumours is still very doubtful. Intermingling of tissues, developmentally or otherwise, also appears to be a well-established cause, though it may be only a predisposing one. Anaplasia and reversion to gametogenetic tissue give us no explanation as to the direct cause of such a process.

RELATIVE DIFFERENCES BETWEEN SIMPLE AND MALIGNANT TUMOURS.—As has already been emphasised, these differences are only a matter of degree; and in certain cases, lying as it were on the borderland between the two great groups, it is sometimes very difficult or even impossible from the histological examination alone to determine whether a given tumour is or is not malignant. This important fact, well recognised by every pathologist, **cannot be too strongly emphasised**; and for the diagnosis and prognosis of such cases, the **microscopical** and **naked-eye characters** of the tumour, the **site of origin**, the **rapidity of growth**, and the **known proclivities of similar tumours growing under similar conditions**, the **age** and **sex of the patient**, and **other clinical data**, must be carefully considered. The more important points to be attended to in this connection may be summarised as follows:—

Microscopical Examination.—In "**simple tumours**," there is usually a comparative simplicity and definite character in their structure, which resembles more or less approximately that of an "adult" or fully developed tissue. There is absence of infiltration at the margin, and there is usually, though not always, definite encapsulation of the growth by fibrous tissue derived

from the surrounding structures; and in some of the simple adenomata each glandular acinus has a definite basement membrane. This capsule is sometimes entirely absent, *e.g.* in some chondromata and angiomata. If the tumours are multiple, as in the case of multiple uterine "fibroids," lipomata, fibro-neuromata, etc., they are usually all primary, *i.e.* are not due to the occurrence of metastasis.

In "malignant" tumours, the histological structure **may** be more complex, for example, the papillomatous ingrowths seen in some cysts where the epithelium is very rapidly proliferating; but, on the other hand, some malignant neoplasms may possess a comparatively simple, and some simple ones a very complex, structure. There are usually, however, definite, and sometimes very marked, aberrations in general structure, size, shape, and type of cell (*e.g.* the so-called anaplastic tendency already described), this tendency towards such aberrations being more pronounced than in simple tumours. Yet it may, without other information, be impossible to distinguish the cells of some mixed- and spindle-celled sarcomata from those of granulation tissue, or the cells of an extremely malignant lympho-sarcoma from those of normal or of hyperplastic lymphoid tissue; and, similarly, the pigmented cells of a melanotic sarcoma and of an ordinary simple pigmented mole closely resemble each other in general character and arrangement. The occurrence of **infiltration** at the margin of the growth is extremely important. Some tumours which may have little tendency to produce metastatic growths elsewhere, may nevertheless exhibit extreme malignancy, and rapidly infiltrate and destroy the surrounding tissues, as is the case with some gliomas and glio-sarcomas. And, again, some malignant tumours may appear to be surrounded by a definite fibrous tissue capsule, and yet may give rise to extensive secondary growths.

The structural characters of the blood-vessels are often of great importance, for example in the case of sarcomas; but even here it is sometimes difficult or often impossible to distinguish, say, the simple primitive characters of the vessels of some sarcomata from those of the simple granulation tissue seen in repair or in some of the infective granulomatous diseases.

Naked-eye Examination.—The shape, consistence, and general appearance of the tumour may give us valuable information;

and the presence or absence of hæmorrhages, necrosis, umbilication, ulceration, etc., as well as any naked-eye evidence of infiltration and of metastasis, must be noted. In some instances the information so obtained may be completely negative, and yet the tumour may ultimately prove to be malignant; and therefore our attention must also be directed towards the following points:—

The site of origin and the known proclivities of similar growths in other previously observed cases.—In some situations, the possible malignancy of a tumour may be partly determined by such factors as the amount of the **vascular supply**, or by exposure of the part to **irritation**, *e.g.* in the case of the gall-bladder containing gall-stones, the tongue or lips from the presence of a jagged tooth, and so on.

Some malignant adenomas of the **sigmoid flexure** or **rectum** may have little tendency to cause secondary growths, whereas other apparently precisely similar tumours growing from the **stomach** or **duodenum** may increase rapidly and give rise to numerous metastases. Thyroid tumours rarely cause secondary growths. A slow-growing tumour of the stomach may, when it reaches and invades the liver, grow much more rapidly, take on a softer form of growth, and become highly malignant. Some round-celled sarcomas are, when growing from bone, only slightly malignant, but when growing from connective tissue, *e.g.* in subcutaneous tissue, may be highly so. Secondary growths are rare in cystadenomas of the ovary, even though these tumours are very complex in structure, but they may occur, *e.g.* in the peritoneum.

The rapidity of growth is also a valuable guide; and although some malignant neoplasms are extremely slow in their development, yet if the tumour grows rapidly and is highly cellular, and if there is rapid and perhaps aberrant mitotic division and production of cells, the evidence is in favour of malignancy.

THE NOMENCLATURE AND CLASSIFICATION OF TUMOURS

For the complete and satisfactory classification of tumours, further knowledge is required as to their ultimate nature; and until this is obtained, our methods of classification must needs be imperfect and temporary.

The classification of tumours into the two groups **simple** and **malignant**, though of great importance clinically, is by no means sufficient; and, as already pointed out, these two groups are united by a complete intermediate series. In the absence, therefore, of a classification based on the nature of the causal agents in the formation and development of tumours, the most scientific method of dealing with the subject must be founded upon their **histogenesis**, *i.e.* upon the nature of the tissue from which they spring; upon their **histological characters**; and perhaps also to a certain extent upon any special tendency they may exhibit of developing into a definite variety of tissue.

The provisional classification adopted by most authorities is founded to a large extent upon that originally suggested by Virchow, and is histogenetic and embryological in its basis:—

1. **TERATOMATA.**—Tumours which arise from the inclusion of one individual, or the germ-cell or the products of the germ-cell from which that individual would in ordinary circumstances have been developed, within the tissues of another individual of the same species (see p. 261).

2. **HISTIOID** and **ORGANOID TUMOURS** composed of a single definite tissue, simple or complex respectively, as the case may be, and named after the tissues from which they arise, *e.g.*:—

Histioid—fibroma, myoma, chondroma, etc., arising from fibrous, muscular, and cartilaginous tissues respectively.

Organoid—adenoma (containing epithelium connective tissue, blood-vessels, lymphatics, etc.), arising from glandular tissue. These may be either innocent or malignant in nature.

3. **PURELY CELLULAR TUMOURS**—the **sarcomata**, giving rise to no definite fully formed tissue, and essentially malignant in type.

Other pathologists have endeavoured to divide tumours into:—

1. **Connective Tissue Tumours**—including Virchow's histioid or single-tissue tumours; and their anaplastic or atypical analogues, the sarcomas.

2. **Epithelial Tumours**—including Virchow's organoid tumours; and their anaplastic or atypical analogues, the carcinomas.

3. **Teratomas and Cysts.**

The most complete and scientific classification, compatible with our present knowledge, is that advocated by Adami,[1] whose method we therefore propose to adopt practically in its entirety.

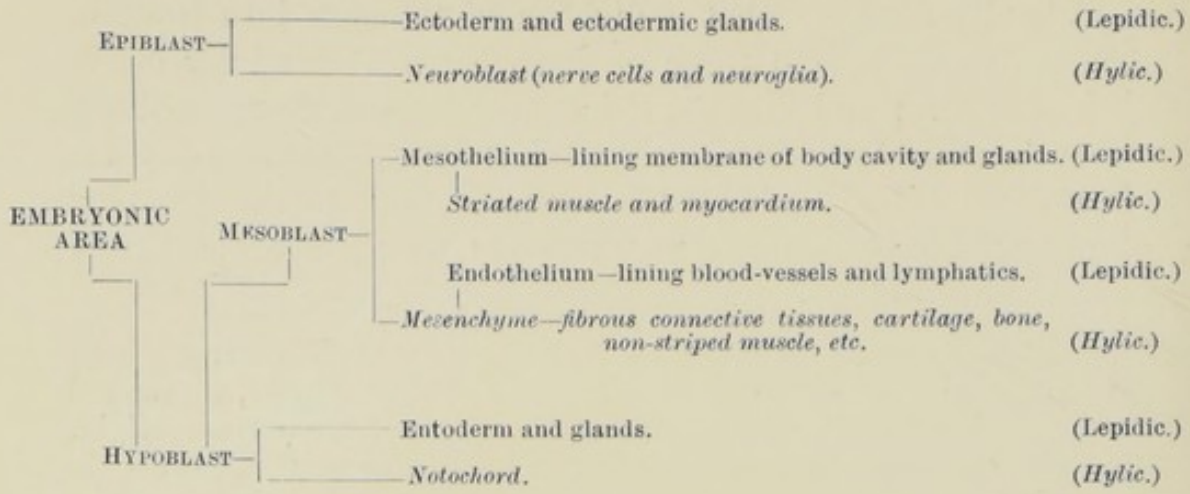
[1] Adami, "On the Classification of Tumours," *Journal of Pathology and Bacteriology*, Edin. and Lond., 1903, vol. viii. p. 243

Adami points out that a division of tumours into those of connective tissue and those of epithelial and glandular origin is insufficient; and that the theory that these arose respectively from the mesoblastic and from the epi- and hypo-blastic embryonic layers has led to considerable confusion, and to the grouping together of certain tumours which are widely divergent from one another in type.

Thus it is now established that "the specific and characteristic cells of several tissues of the glandular type—of the kidneys, suprarenal bodies, ovaries, testes, and uterine mucosa—are of mesoblastic origin, but these, nevertheless, give rise to tumours which may and often do resemble most closely those of hypoblastic and epiblastic origin. . . . And thus the cancer-like tumours which originate in these organs must be accepted as mesoblastic" (*loc. cit.*, p. 243). Adami also points out that gliomata, though resembling sarcomata, take origin from the epiblast; whilst new growths arising from the remains of the notochord, which is hypoblastic in origin, may resemble myxomatous connective tissue-like tumours. These difficulties have done much to discredit attempts at an embryological classification; and Adami then proceeds to show how those apparent exceptions may be reconciled with such a true embryological method.

After the differentiation of the cells of the embryo into the primitive epiblast and hypoblast, the latter gives rise by the proliferation of its cells to the mesoblast, but itself remains as a distinct **lining membrane**. At the same time, the epiblast gives rise to the mass of cells which dips in and becomes detached to form the central nervous system. Similarly, the notochord is formed by a mass of cells which becomes detached from the hypoblast. Mesoblast, neuroblast, and notochord are therefore all "derived from the two primitive cell-layers, and the first two, at least, **lose the lining-membrane characteristics of these two earliest layers, and take on a less differentiated condition prior to farther evolution**" (*loc. cit.*, p. 247). Later, the mesoblast becomes further differentiated, growing out between the epiblast and hypoblast to form or enclose the primitive body cavity, there being now two structures of mesoblastic origin—the **mesothelium** or lining-membrane portion of the mesoblast, and the **mesenchyme** or mesoblastic pulp. From the mesothelium is derived another group of cells on either side of the embryo which becomes the "mother-tissue" of the striated muscle and myocardium; whilst the other tissues derived from the mesothelium are of the nature of lining membranes, *e.g.* the cells lining the pleura, pericardium, peritoneum; or go to form the special glandular cells of the suprarenals, kidneys, and genital glands.

From the mesenchyme are developed the endothelial cells lining blood-vessels and lympathics; but the bulk of tissues derived from the mesenchyme are of the nature of pulp tissues, *e.g.* connective tissue, cartilage, bone, etc. (see table).



Thus epiblast, hypoblast, and mesoblast become each differentiated into two sets of tissues:—

(1) **Lining-membrane tissues** (including the specific cells of glandular organs).

(2) **Pulp tissues.**

The former, from whichever embryonic layer they originate, may either remain as functional covering or lining membranes, *e.g.* the pleura, pericardium, peritoneum, skin, mucous membranes, etc.; or

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Explanation of Figure 62.

I. *Embryonic Area*, showing differentiation into *Epiblast* and *Hypoblast*.
II. *Embryonic Area*, showing differentiation into *Epiblast*, *Mesoblast*, and *Hypoblast*. Dipping in of Epiblast to form *Neural Canal* (N.C.).
III. *Neural Canal* (N.C.) almost complete. Differentiation of Mesoblast into *Mesenchyme* ($Mes^{cm.}$) and *Mesothelium* ($Mes^{th.}$). Formation of *Cœlom* or *Body-Cavity* (B.C.) in the latter. Formation of *Notochord* (N.) from Hypoblast.
IV. *Neural Canal* or *Neuroblast* (N.C.), completely separated from surface epiblast or Ectoderm (Ect.). Formation of *Vascular Endothelium* ($End^{thm.}$) from Mesenchyme. Differentiation of Mesothelium int› *pulp layer* and *lining layer*. Complete separation of *Notochord* (Ncd.) from lining hypoblast or *Entoderm*.
V. Schematic Transverse Section of Embryo, showing the derivation of the body tissues from the three embryonic layers (modified from Adami).[1]

Primitive layer.	*Lepidic Tissues.*	*Hylic Tissues.*
Epiblast.	Ectoderm and derived glands (Ect.).	Neuroblast (Nbl^{t}).
Mesoblast.	Mesothelium lining body-cavity (B.C.) and derived glands. Endothelium lining vessels ($End^{thm.}$).	Mesenchyme ($Mes^{cm.}$). Striated muscle formed from Mesothelium ($Mes^{th.}$).
Hypoblast.	Entoderm and derived glands (Ent.).	Notochord (Ncd.).

[1] *Loc cit.*, p. 248.

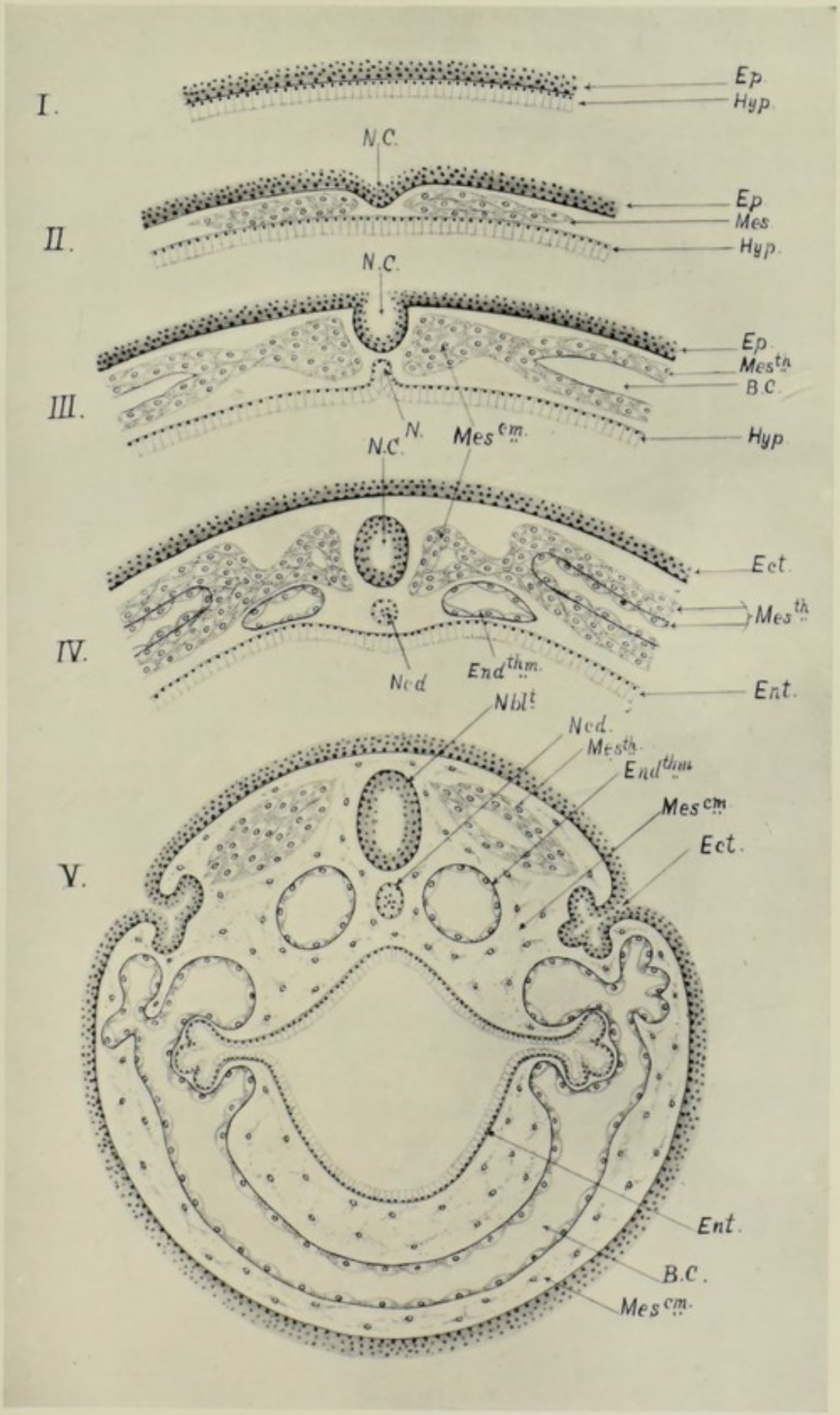

FIG. 62.—*Schemes to show Embryogenetic relationship of the various body tissues.*

they may become developed into the highly specialised parenchymatous constituents of various glandular organs, *e.g.* the sebaceous and sweat glands, digestive glands, and genito-urinary glands, lining membranes of the lungs, etc. etc. These special constituents dip down, as it were, into the mesenchyme, and thus acquire a stroma of connective tissue. They themselves, however, form layers or groups of cells into which the vessels do not penetrate, and in which there is an absence of stroma between the members of the cell-groups. In tissues derived from the embryonic pulp, on the other hand, **the individual cells are separated by an intercellular substance, either homogeneous or fibrillated.**

Adami therefore divides the various tissues of the body into two great groups :—

Lepidic (from λεπις, λεπιδος, a rind, skin, or membrane)—the lining-membrane group.

Hylic (from ὑλη, crude or undifferentiated matter)—the body-pulp group.

The tissues in each of these main groups he further subdivides according as they are epiblastic, hypoblastic, mesothelial, mesenchymatous, or endothelial in origin ; and on this basis he gives the following classification of normal tissues :—

I. LEPIDIC, OR LINING-MEMBRANE TISSUES

in which the blood-vessels do not penetrate the groups of specific cells, and in which there is an absence of definite stroma between the individual cells, although such stroma, of mesenchymatous origin, may be present between the groups of cells.

1. **Epiblastic.**—Epidermis. Epidermal appendages—hairs, nails, enamel of teeth, etc. Epidermal glands. Epithelium of the mouth—salivary glands. Epithelium and glands of—nasal tract and associated spaces. Epidermal portion of hypophysis cerebri. Lens of eye. Epithelium of—membranous labyrinth of ear, anus, male urethra (except prostatic portion).

2. **Hypoblastic.**—Epithelium of—digestive tract and glands connected with it. Specific cells of—liver, pancreas, tonsils, thymus, thyroid. Epithelium of—trachea, lungs, bladder, female urethra, male urethra (prostatic portion).

3. **Mesothelial.** — Lining cells of — pleuræ, pericardium, peritoneum. Specific cells of — suprarenals, kidneys, testes, ovaries (Graafian follicles). Epithelium and glands of—Fallopian tubes, uterus, vagina, vasa deferentia, vesiculæ seminales, etc.

4. **Endothelial.**—Lining endothelium of—blood-vessels, lymphatics.

II. HYLIC, OR PRIMITIVE PULP TISSUES

Organs and tissues in which the special characteristic is that the specific cells lie in, and are separated by, a definite stroma, homo-

geneous or fibrillar, in which there may or may not be blood- and lymph-vessels.

1. **Epiblastic.**—Nerve cells, neuroglia.
2. **Hypoblastic.**—The notochord and its remains.
3. **Mesenchymatous.**—Fibrous connective tissues, cartilage, bone, reticulum of lymph glands, bone-marrow, fat cells, involuntary muscle tissue, spleen, blood-vessels, blood corpuscles.
4. **Mesothelial.**—Striated muscle, including cardiac muscle.

Adami divides tumours or "autonomous neoplasms" into the two great orders **Teratomata** and **Blastomata.** The former of these he defines as "tumours composed of the products of growth of one individual within the tissues of another individual of the same species." Blastomata he defines as "tumours composed of the products of aberrant growth of cells and tissues of the individual in whom they are developed."

Next, he subdivides the **Blastomata** or body-tissue tumours into two main genera—the **Lepidomata**, originating from the lining-membrane tissues enumerated above; and the **Hylomata**, originating from tissues developed from the embryonic pulp.

I. LEPIDOMATA, OR "RIND" TUMOURS

A. Primary Lepidomata

1. **Epilepidomata.**—Tumours whose characteristic constituents are overgrowths of tissues derived directly from the epiblastic lining membranes, or true epiblast.
   - (*a*) **Typical.**—Papilloma, epidermal adenomata (of sweat, salivary, sebaceous, and mammary glands, etc.).
   - (*b*) **Atypical.**—Epithelioma proper, carcinoma of glands of epiblastic origin.

2. **Hypolepidomata :—**
   - (*a*) **Typical.** — Adenoma and papilloma of digestive and respiratory tracts, thyroid, pancreas, liver, bladder, etc.
   - (*b*) **Atypical.**—Carcinoma developing in the same organs and regions.

B. Secondary Lepidomata

3. **Mesolepidomata.** — Tumours whose characteristic constituents are cells derived in direct descent from the persistent **mesothelium** of the embryo.

(*a*) **Typical.**—Adenoma of kidney, testicle, ovary, urogenital ducts; adenoma of uterus and prostate; adenomas originating from the serous membranes, "mesothelioma" of pleuræ, peritoneum, etc.

(*b*) **Atypical.**—Cancer of the above-mentioned organs; squamous endothelioma, so-called, of serous surfaces, epithelioma of vagina.

4. **Endothelial Lepidomata.**—Tumours originating from the endothelium of the blood- and lymph-vessels; endothelioma, perithelioma.

II. HYLOMATA, OR "PULP" TUMOURS

1. **Epihylomata.**—Tumours whose characteristic constituents are overgrowths of tissues derived from the embryonic pulp of epiblastic origin.

(*a*) **Typical.**—True neuroma, glioma.

(*b*) **Atypical.**—"Gliosarcoma."

2. **Hypohylomata.**—Tumours derived similarly from embryonic pulp of hypoblastic origin.

(?) Chordoma.

3. **Mesohylomata.**—

A. **Mesenchymal Hylomata.**—Derived from tissues originating from the persistent mesoblastic pulp or mesenchyme.

(*a*) **Typical.**—Fibroma, lipoma, chondroma, osteoma, myxoma, leiomyoma.

(*b*) **Atypical.**—Sarcoma (derived from mesenchymatous tissues), with its various subdivisions, fibro-sarcoma, spindle-cell sarcoma, oat-shape-cell sarcoma, chondro-sarcoma, osteo-sarcoma, myxo-sarcoma, melanotic sarcoma, etc.

B. **Mesothelial Hylomata.**—Tumours which are overgrowths similarly of tissues derived from embryonic pulp of definitely mesothelial origin.

Rhabdomyoma.

According to Adami, **Teratomata**, in their mode of development and characteristics, follow, with variations, the lines laid down with regard to the Blastomata. **Deciduoma malignum (chorio-epithelioma, placentoma,** or **syncytioma)** being now regarded by most authorities as derived from the

fœtal, and not from the maternal part of the placenta, is classed among this group of tumours, *i.e.* is looked upon as being derived from the cells of another individual of the same species, in this case the fœtus.

Adami points out that, in this method of classification, the difficulties previously experienced by those endeavouring to classify tumours according to their embryological origin are overcome. Thus, gliomata are placed near tumours of mesenchymatous tissues, which they so closely resemble; and adenomata of mesoblastic origin are not isolated from similar gland-like tumours of epiblastic and hypoblastic origin.

In this classification, the terms "sarcoma" and "carcinoma" are used in their original and purely **histological** sense, and **not** as implying that they arise from mesoblast and epiblast respectively, *i.e.* they are not employed with any embryogenetic limitations.

Another point of importance illustrated by the above method of classification is the fact that, in the case of malignant, anaplastic, or atypical tumours, the earlier in development the differentiation of the embryonic layer from which they were derived, the less likely are they to depart in any way from the type to which they belong. Thus epilepidomata and hypolepidomata, being derived from the primitive epiblast and hypoblast respectively, always show evidence of their lepidic origin; but some of the mesolepidomata, *e.g.* certain mesotheliomata and endotheliomata, are not so definite in this respect, and may exhibit a marked tendency to assume more sarcomatous characters. This is explained on the ground that the mesenchyme and the mesothelium from which these tumours originate are derived from the mesoblast; and this being a less primitive differentiation than that into epi- and hypo-blast, the mesenchyme and mesothelium have their characteristics, as it were, less firmly impressed upon them, and tumours derived from them are therefore liable to show a reversion to that more primitive type of mesoblast seen before its differentiation into these two great subdivisions.

It is for this reason that Adami separates Lepidomata into two main groups:—

(i) **Primary Lepidomata**, including tumours derived from

tissues descended directly from the primitive epiblast and hypoblast.

(ii) **Secondary or Transitional Lepidomata**, which include tissues **indirectly** descended from these through the mesoblast and its later differentiations, the mesothelium and the mesenchyme, and which therefore possess the latent capacity of a still further reversion.

THE CHEMISTRY OF TUMOURS

The chemical examination of tumours affords an important field of work for the future; but we have as yet little definite information as to the highly complicated chemical processes which occur in living tissues, whether normal or abnormal. A résumé of our present knowledge of the subject is given by Wells[1] in his recent book on Chemical Pathology.

Only comparatively slight differences have so far been discovered between the chemical constituents and metabolic products of tumours and those of normal tissues. These variations may be summarised as follows:—

Inorganic Constituents:—

Phosphorus—in tumours, as in normal tissues, is found in quantities proportionate to the amount of nuclear material.

Iron—is similarly proportionate in quantity to the amount of nucleo-proteins and of blood. It is therefore abundant where hæmorrhages have occurred.

Potash—is specially increased in rapidly growing tumours, this being one of the most important facts yet discovered in the chemistry of tumour growth; whilst

Calcium—tends to be increased in tumours of slower growth, more especially when degenerative conditions are present.

The ratio of these two elements in the most rapidly growing tumours has been found to be

$$\text{Potassium} : \text{Calcium} = 2 : 1 \mid \text{or} \mid 3 : 2.$$

Hydrochloric acid—in the gastric juice is found to be

[1] Wells, *Chemical Pathology*, Philadelphia and London, Saunders Co., 1907, ch. xvii. p. 411. From this chapter most of the above information has been taken. We would refer those interested in the subject to the original book, which forms a valuable contribution to the literature of Pathology. Full references to the original papers are given.

diminished in cancer of the stomach, and also, it is said, in cases of cancer occurring in other parts of the body.

Organic Constituents:—

Proteins.—In the cell-juice expressed from normal tissues, the proportionate amounts of albumin and globulin are usually approximately equal; whilst in tumours, the albumin is relatively increased in amount, the proportion being about one part of globulin to three or four parts of albumin. In cancerous ascitic fluid, the albumin is stated to be more abundant than in cases of ascites due to other causes.

Nucleo-proteins are specially abundant in richly cellular tumours, especially cancers.

The **melanin pigment** of melanotic sarcomas appears identical in composition with this pigment when found in its normal sites.

Many of the products of protein-hydrolysis (proteolysis) are found in tumours, *e.g.* the **amino-acids, leucin, tyrosin,** etc.

With regard to **other organic constituents,** tumours frequently contain substances specially characteristic of the tissues from which they arise; and these substances, in most cases, show no ascertainable variation from those normally present in the body. Thus, the fat of a lipoma appears identical with that of ordinary adipose tissue. Tumours arising from the suprarenal bodies contain much fat, as do these organs themselves; the secondary growths following malignant disease of the thyroid gland contain iodothyrin, those from the breast may show some attempt at the secretion of milk, and so on.

Glycogen.—The presence of this substance in tumours has been by some writers regarded as of great importance. Glycogen is found in considerable quantity in tumours arising from tissues normally rich in it, *e.g.* cartilage, squamous epithelium, striped muscle, etc. It is also found in increased amount where the nutrition of the part is impaired; a condition which, however, is also observed under similar circumstances in ordinary tissues.

SPECIFIC CYTOTOXIC SERA IN MALIGNANT DISEASE.—Only a very partial degree of success has attended the majority of investigations on the subject of immunity against cancer. Many investigators, working along lines suggested by the results obtained in bacterial and other parasitic diseases, have

studied the results of experimental inoculation of animals, and have described the presence of specific or partially specific antibodies, *e.g.* precipitins, hæmolysins, etc.; but it has not yet been sufficiently demonstrated that these essentially differ from the analogous substances produced by the injection of normal tissues. The result of the work of the various writers which has been hitherto published is so contradictory that further research is required along these lines before any definite opinion can be hazarded on the subject.

SPECIAL VARIETIES OF TUMOURS

THE "SIMPLE" OR "TYPICAL" HYLOMATA (MOSTLY MESOHYLOMATA)

FIBROMA.—In structure, fibromata closely resemble ordinary fibrous tissue. They vary in consistence, not only in the case of different individual tumours, but frequently also in different parts of the same tumour. **Hard fibromas** are usually slow-growing, and are composed of dense fibrous tissue with few cells and well-developed fibrils. **Soft fibromas,** on the other hand, are more cellular and less fibrous, and tend to grow more rapidly. The blood-vessels of fibromas are usually well supported and possess definite walls, the muscular coat, however, being somewhat deficient. Occasionally, the vessels may be represented by thin-walled, dilated, endothelial spaces, *e.g.* in fibromata growing from the cerebral membranes.

Chronic inflammatory thickenings of fibrous tissue, *e.g.* the chronic irritative overgrowths often seen in the capsules of certain organs such as the spleen or liver, and chronic inflammatory lesions in glandular organs, *e.g.* chronic mastitis, often closely resemble fibromas or fibro-adenomas, but must be carefully distinguished from true tumours.

Sites.—Fibromata may arise from connective tissue in any position, but are found specially in the skin, fasciæ, and such fibrous tissues as the dura mater, periosteum, fibrous septa, tendons, nerve-trunks, cicatricial tissue, and in the stroma of some glandular organs, *e.g.* the kidney, in which the tumours are generally situated in the pyramids.

Tumours of yellow elastic tissue are practically unknown, though elastic fibres may be found in some neoplasms. These

are probably in most cases pre-formed, though they may be occasionally of new formation.

Degenerations and **metaplastic changes** are common, and all intermediate varieties between other members of the "pulp" tissue tumours of the same series (mesohylomata) may be found, *e.g.* fibro-myxomas, fibro-sarcomas, etc.

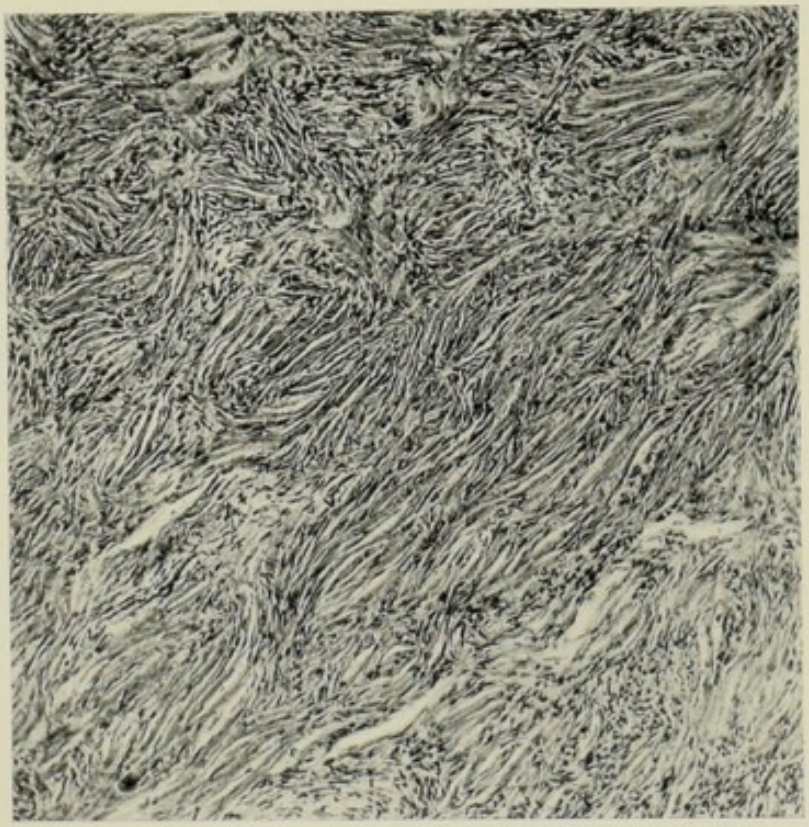

FIG. 63.—*Soft Fibroma*, showing young fibrous tissue arranged in irregular bundles. ×75.

LIPOMAS, macro- and micro-scopically, resemble ordinary adipose tissue in their structure (see fig. 64), and are probably the most innocent and chronic variety of tumour growth known. They are frequently multiple, and may grow from the subcutaneous tissue, especially about the neck, shoulder, back, or buttock; from the extra-peritoneal fatty tissue, omentum, or appendices epiploicæ; or from certain of the viscera. They are occasionally found in muscle and in bone.

Lipomata are usually very slow-growing, and may occasionally attain a large size. They sometimes appear early in life. Transitions between lipomata and myxomatous and fibrous tumours are common.

CHONDROMAS, or tumours composed of cartilage, form a somewhat variable series, and frequently exhibit metaplastic changes. They most commonly grow in connection with the osseous system, and only rarely from pre-existing normal cartilage, being most frequently formed in the substance of the bone, or under the periosteum. They are said to occur more especially after rickets, and may be due to new growth supervening in islets or groups of cells, perhaps derived from

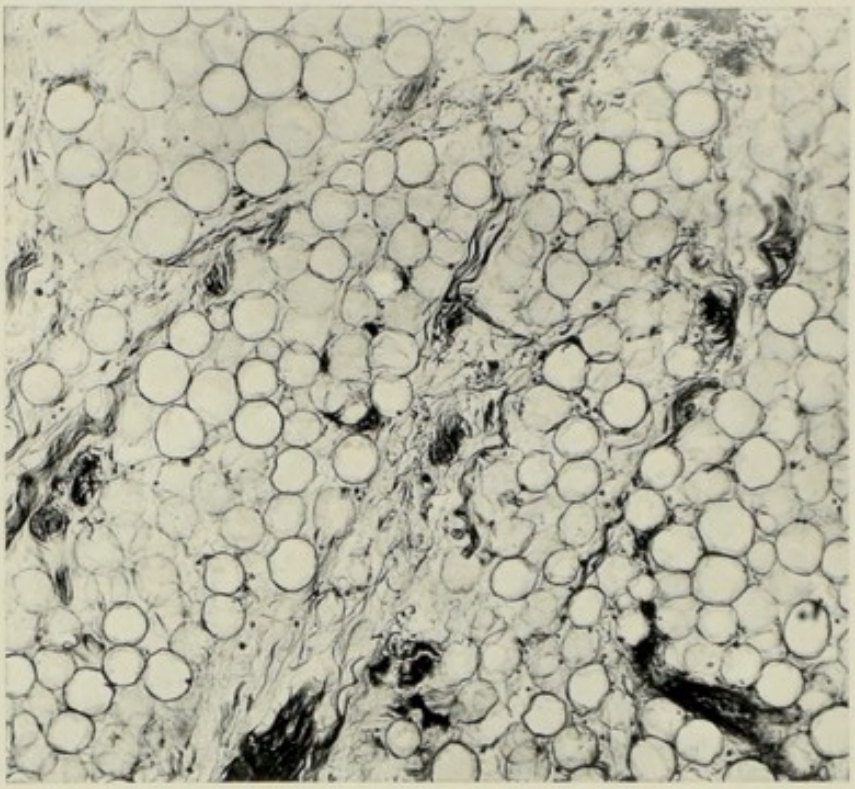

FIG. 64.—*Lipoma*, showing structure closely resembling that of ordinary adipose tissue. ×60.

epiphyseal or other cartilages which have become isolated and enclosed in the growing bone during the abnormal processes of ossification occurring in that disease. In such cases they are often multiple, and are specially found growing from the bones of the hands and the feet.

Chondromata frequently undergo incomplete calcification or imperfect ossification, and exostoses are frequently developed as cartilaginous tumours, which become ossified later, the ossification occurring in the central part, and the surface being occupied by a layer of proliferating cartilage. Such

cartilaginous tumours are usually composed of rounded or irregular islets of translucent or semi-translucent, white or bluish-white hyaline cartilage, separated and surrounded by a framework of connective tissue containing the nutrient blood-

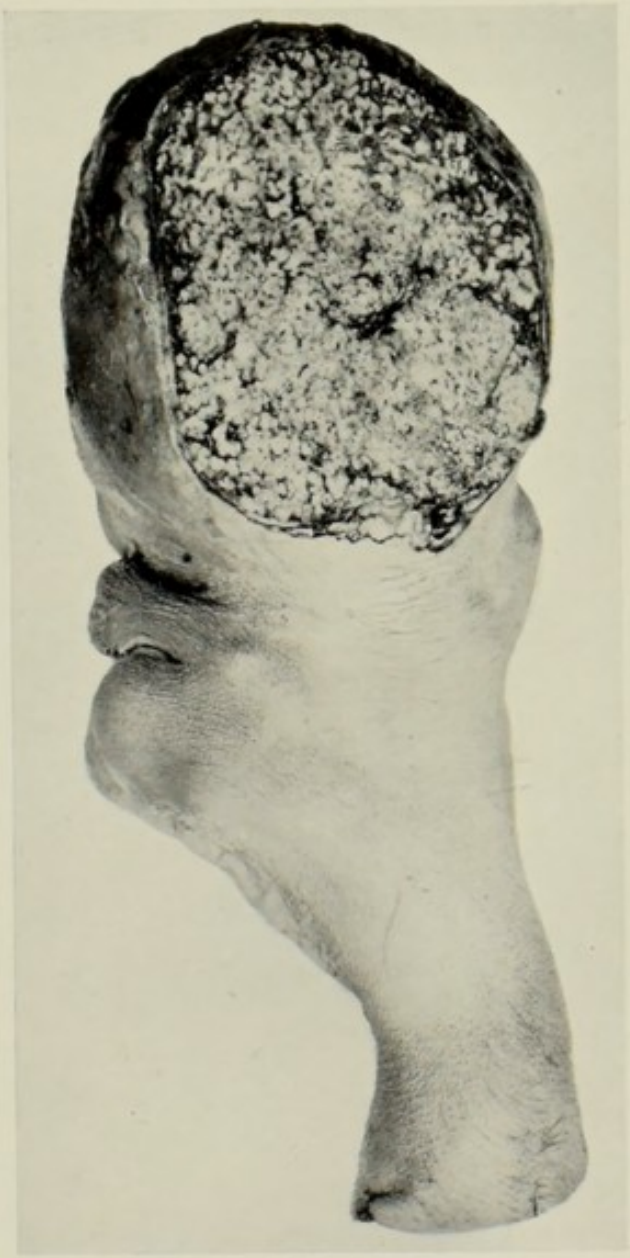

FIG. 65.—*Chondroma* growing from bones of hand.
(Edinburgh University Anatomical Museum. Catalogue, No. Os. D. p. 6.)

vessels, and acting as a formative perichondrium. A gradual transition between this connective tissue and the fully formed cartilage in the interior can usually be traced. The cartilage cells towards the central parts of the islets frequently show degenerative changes, irregularity in size and shape, myxo-

matous transformation, etc.; whilst the matrix may stain more faintly and show fibrillation in these central areas. This myxomatous change may lead to such marked softening as to give rise to cavities, in the so-called cystic varieties of chondroma. Intermediate forms are common, *e.g.* chondro-lipomas, myxo-chondromas, etc.

Cartilage may also be found in mixed tumours arising from certain glands, *e.g.* the testicle, the mammary gland, the

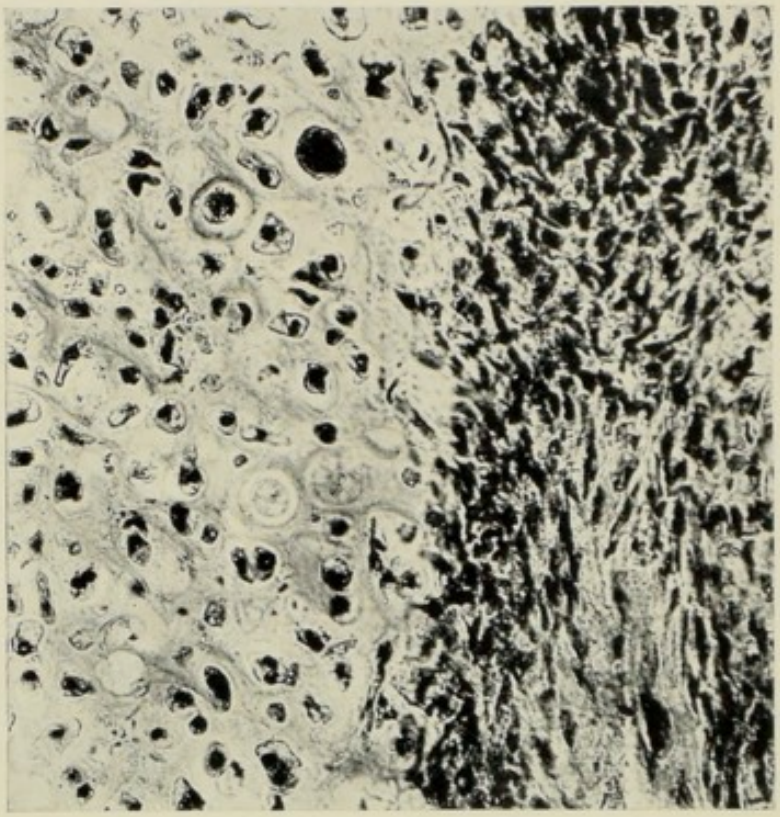

FIG. 66.—*Chondroma*, showing irregular formation of hyaline cartilage. The darker tissue to the right of the field is the fibrous framework of the tumour, which also acts as a perichondrium. × 200.

parotid and the submaxillary glands. Such mixed tumours are probably due to embryonic intermingling of tissues, and are occasionally highly malignant. They are usually of the nature of chondro-adenomas or chondro-sarcomas, in which myxomatous degeneration is very common.

Chondromas growing from the cartilages of the larynx, trachea, ribs, etc (ecchondromas) are very rare.

Tumours bearing a somewhat close resemblance to chondromata may arise from the remains of the notochord or chorda dorsalis. Such **chordomata** are specially found about the basi-

sphenoid and basi-occipital bones (*i.e.* the region corresponding to the anterior end of the notochord), and in connection with the intervertebral discs.

OSTEOMA.—Bony tumours may be composed of compact bone (**osteoma eburneum** or **ivory exostosis**), or of spongy bone (**osteoma spongiosum**). The former are usually small, and occur especially about the bones of the skull. Spongy osteomas may attain a larger size; and often, especially where they are multiple, originate as ossifying chondromata.

Outgrowths of bone or **exostoses**, when growing in connection with the attachment of muscles, are sometimes partly of the nature of hypertrophies and partly hyperplastic in character, and it is sometimes difficult to determine whether a given case should be classified along with these conditions or among true neoplasms.

Bony tumours arising in the **interior** of a bone are called **enostoses**; whilst the term **odontoma** or **dental osteoma** is applied to tumours arising in connection with the teeth, either from the tooth structures as a whole, or from one of the elements, *e.g.* the dentine, the enamel, etc. They may in some cases be due to mal-development of the embryonal tooth-follicles.

MYXOMA—a tumour composed of mucoid or myxomatous tissue, similar in character to the tissue which in the fœtus precedes the other connective tissues, and which persists in the umbilical cord. Such tumours are usually soft and jelly-like or translucent, and present great variations in their microscopical appearances. They usually show somewhat rounded or irregular, or frequently triangular or stellate, branching cells, whose processes form a delicate interlacing network, in the meshes of which there is a clear homogeneous, or sometimes finely fibrillated, intercellular material, containing a large proportion of mucin or some mucinoid substance (fig. 67).

Pure myxomata may be found in the subcutaneous or submucous tissues, in nerve sheaths and elsewhere. The "Hydatidiform Mole," occasionally found in the uterus in place of the normal products of conception, is by some authorities regarded as a myxomatous degeneration of the chorionic villi (fig. 68). Many tumours, sometimes classed as myxomata, are in reality fibromas, lipomas, chondromas, sarcomas, etc., undergoing myxo-

matous degeneration; a condition which may also be found in glandular tumours, *e.g.* in the so-called colloid cancers, myxo-adenomata, etc.

Some so-called "mucous polypi" growing from the nasal or the intestinal mucous membranes are probably to be regarded as chronic inflammatory overgrowths rather than as true tumours; and their polypoidal character results from the

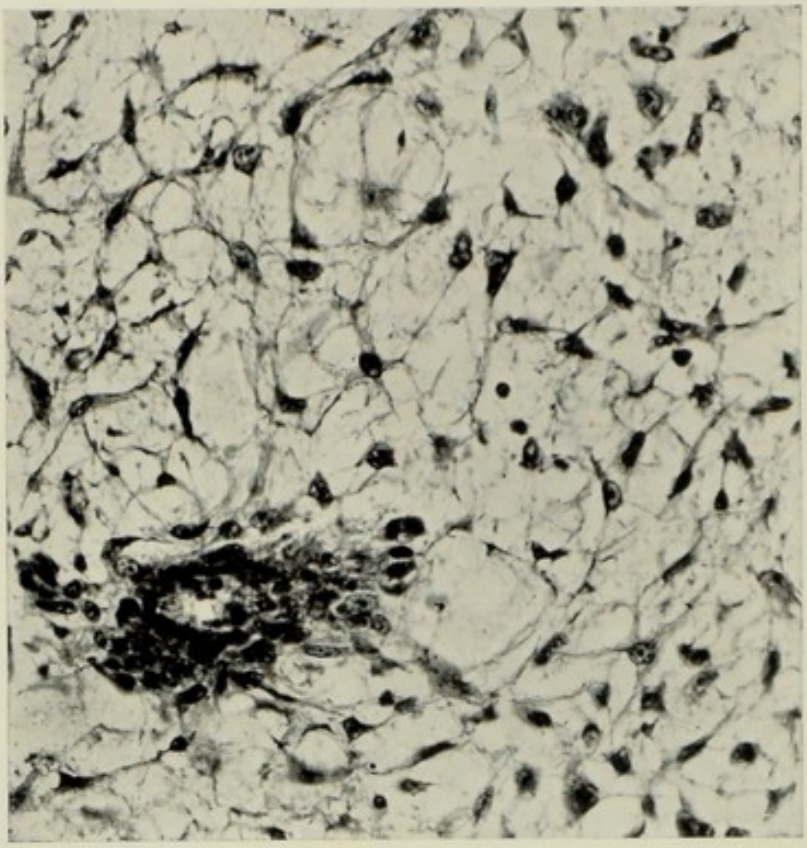

FIG. 67.—*Myxoma of Breast*, showing the characteristic branching cells. The walls of the blood-vessel, seen in section, are deficient in muscular fibres, and are somewhat cellular, there being a condensation of tumour cells immediately around it, forming a supporting adventitial layer. × 250.

traction exercised upon them by the contents passing along these channels.

Though usually simple tumours, myxomata are sometimes very diffuse and may spread very widely. They seldom give rise to secondary growths; and when these occur, it is extremely probable that the primary tumour is in reality some malignant neoplasm which has undergone myxomatous degeneration.

MYOMA. — Tumours of muscle may originate either from smooth or from striped muscular tissue, and are termed Leiomyomata and Rhabdomyomata respectively.

Leiomyomata are very common, and their principal site is the uterus, where, though true muscle tumours, they have unfortunately been named uterine "fibroids." They are composed of irregular bundles and whorls of non-striped muscular fibres, supported by a varying amount of fibrous tissue stroma con-

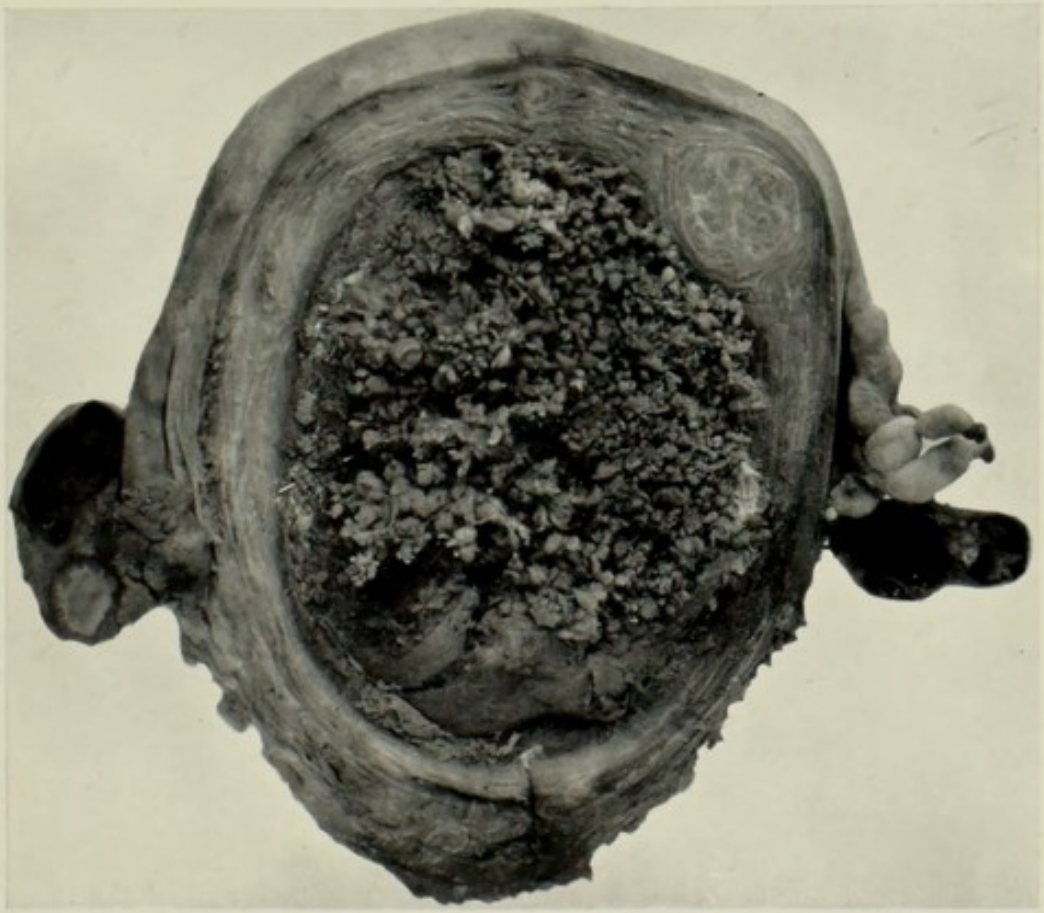

FIG. 68.—"*Hydatidiform Mole*" *in situ*, in uterus. There is also seen in section in this specimen a small leiomyoma embedded in the muscular wall, towards the fundus. (Sheffield University Pathological Museum.)

taining blood-vessels (from the muscular coat of which it is believed by some authorities that these tumours are derived). The intermingling of the somewhat translucent grey muscle fibres with the glistening white bundles of fibrous tissue gives to a section of these tumours an appearance somewhat suggesting that of "watered-silk" (figs. 69 and 71).

Leiomyomata may also occur in the ovary, prostate, alimentary canal, and more rarely in the skin, originating in the last-mentioned locality, it is said, from the erector pilæ muscles.

Uterine myomata may occasionally attain a very large size, and are commonly multiple (figs. 71 and 72). They may be embedded in the muscular coat of the uterus, or they may project from the outer or inner surface, and they frequently become pedunculated. Œdema and myxomatous and other degenerative changes are common. They may become calcified, forming the so-called "**womb-stones.**" If they contain a large amount of fibrous tissue they are called fibro-myomata.

Rhabdomyomata, or tumours of striped muscular tissue, are

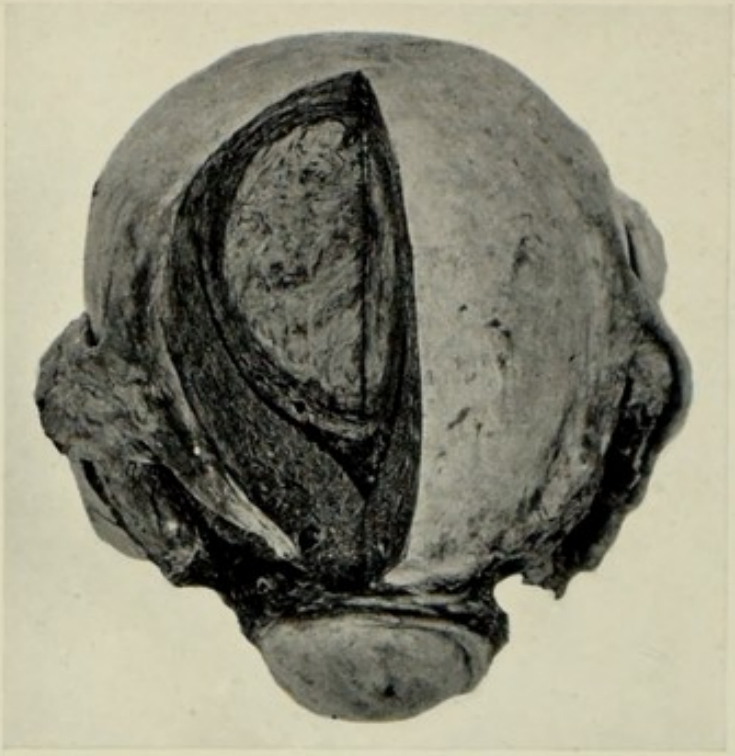

FIG. 69.—Large simple *Leiomyoma* embedded in muscular wall of the fundus uteri. The specimen has been injected, and shows the comparatively poor blood-supply of the tumour as contrasted with the darker uterine muscle, into the numerous vessels of which the injection has freely passed. (Edin. Univ. Museum Catalogue, No. Gen.-U. N. g. 24.)

extremely rare, and are usually "congenital." They may occur in the kidney or in the testicle, or some other part of the uro-genital system, and are probably due to the inclusion in these organs of some fibres of the lumbar muscles. They are sometimes found in the muscles of the lumbar or gluteal, or, though very rarely, in other regions. They have also been described as occurring in the myocardium. The muscle fibres of such tumours are usually imperfectly developed; the early cellular

characteristics of developing tissue may be very pronounced, and the tumours can then hardly be separated from the sarcomas. When mixed with cartilage, bone, fat, etc., they are most probably teratomatous in nature.

LYMPHOMAS. — Lymphadenoid tissue reacts with extreme readiness in many diseases, more especially in those of a septic and infective nature. Thus, many chronic glandular enlargements are produced by known infective agents such as the organisms

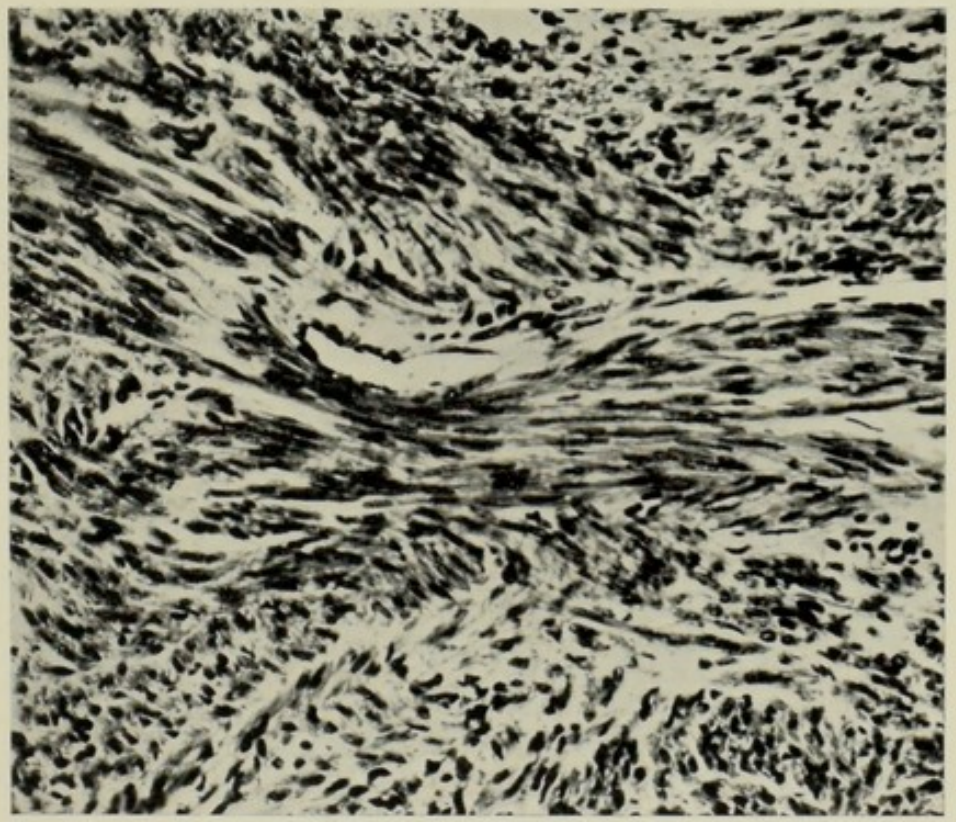

FIG. 70.—*Leiomyoma Uteri*, showing non-striped muscular fibres running in bundles cut in various directions. ×200.

of tuberculosis or syphilis; others, *e.g.* the enlargement found in Hodgkin's disease or lymphadenoma, or that in the leucocythæmias, are more obscure in their ætiology. Between some of these enlargements, especially certain of those seen in the leucocythæmias and true tumour formation, it is almost impossible to differentiate.

True lymphomatous tumours probably do occur quite apart from hyperplasias and from lympho-sarcomas. Such lymphomas may be found in the mediastinum, arising from the thymus or from lymphatic glands, or in the abdomen, where they may form

large masses. Histologically, they closely resemble normal lymphoid tissue, the reticulum and endothelium being well developed, and the lymphocytes being normal in numbers. In lymphosarcomata, on the other hand, there is an enormous increase in the lymphocytes and a marked deficiency in the endothelium and

FIG. 71.—*Multiple Leiomyomata of Uterus*, showing "watered silk" appearance on section.

reticulum, these tumours being practically small round-celled sarcomata of very primitive type.

ANGIOMA.—Tumours composed of vascular tissue may arise from blood-vessels (hæmangiomas), or from lymphatics (lymphangiomas), the endothelial lining of these being apparently the essential constituent of such tumours. Both varieties of angiomata are probably "congenital" in origin.

Hæmangiomata, or **Angiomata** as these tumours are usually designated, may be composed of proliferated and dilated vessels —arteries, veins, or capillaries, as the case may be—and are then known as **plexiform angiomata**; or they may be composed of irregular intercommunicating spaces, the **cavernous angiomata**. The commonest variety of plexiform angioma, the so-called

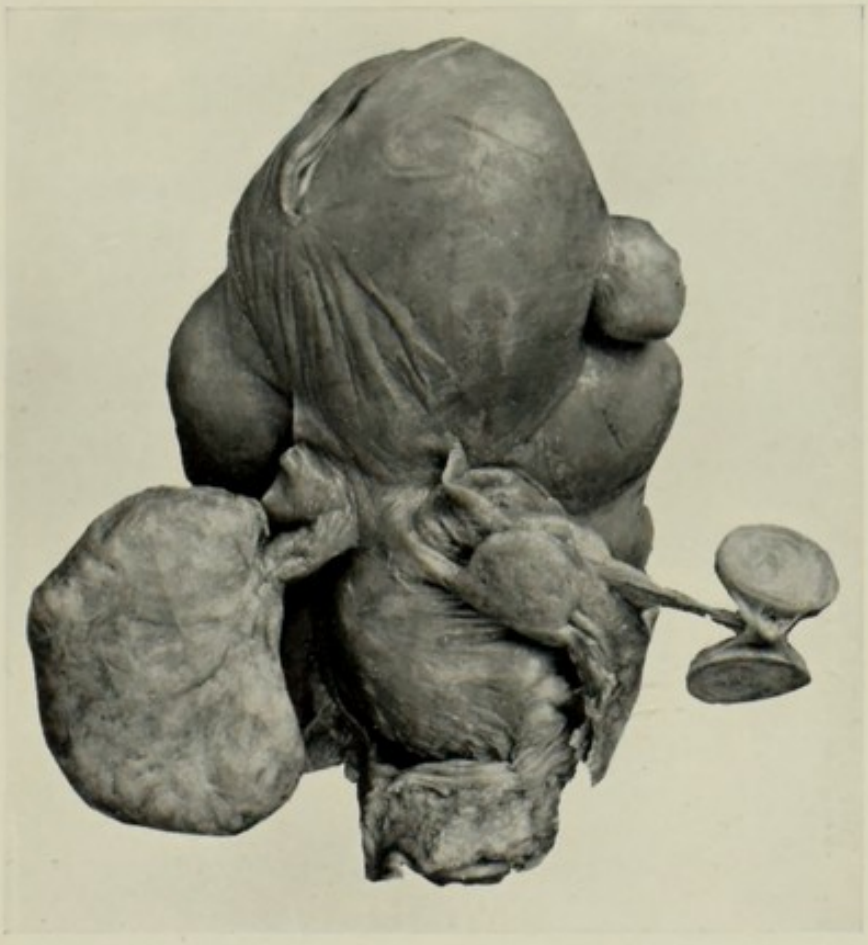

FIG. 72.—*Multiple Leiomyomata of Uterus.* Some have become pedunculated.

congenital nævus, is formed of dilated, thin-walled capillaries. Its most common situation is the skin.

One very characteristic variety of angioma occurs as a projecting, rounded, red or bluish-red, pulsatile mass, usually situated on the scalp, and from which hæmorrhage from ulceration or injury is extremely liable to occur. It is congenital in origin; and histologically, such a tumour may be composed of dilated endothelial capillary spaces, or of very imperfectly formed vessels resembling thin-walled veins.

Arterial or **Circoid Angiomata** are less common, and are usually found as congenital tumours about the scalp.

Cavernous Angiomata are somewhat commoner than the foregoing varieties. They may be found in the skin or subcutaneous tissues, in the membranes of the brain, and sometimes in or on the surface of certain of the internal organs, especially immediately under the capsule of the liver. By some authori-

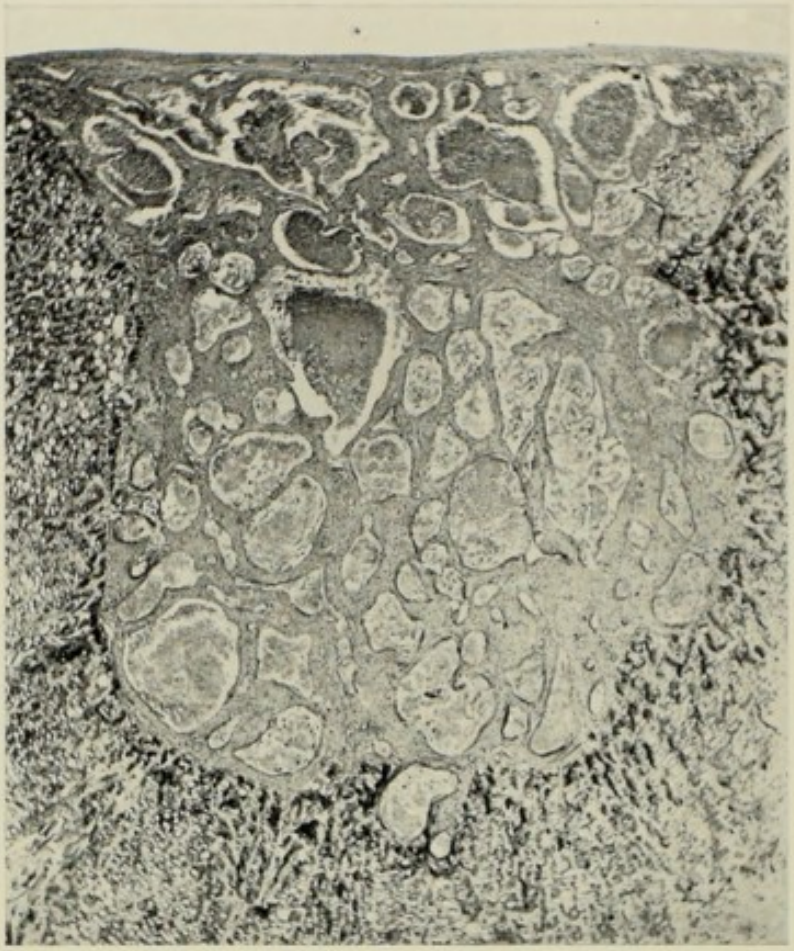

Fig. 73.—*Cavernous Hæmangioma* on surface of liver, showing vascular spaces surrounded by connective tissue stroma. ×28.

ties these are regarded as fibromas containing dilated intercommunicating vascular channels; whilst others are inclined to deny that they are of the nature of true tumours, considering them rather as dilatations of normal blood-spaces or channels. It is sometimes difficult to determine whether some cavernous angiomata do or do not possess an endothelial lining, or whether the spaces are lined directly by connective tissue.

Certain mixed vascular tumours, *e.g.* those originating from the pituitary and pineal bodies, or from the suprarenal, parotid, etc., are probably due to embryonic intermingling. The angio-sarcomata sometimes observed in the parotid, or more rarely in the subcutaneous tissues, have probably a similar origin.

Lymphangioma.—As in the case of blood-vessels, mere dilatation and varicosity must be differentiated from true tumour

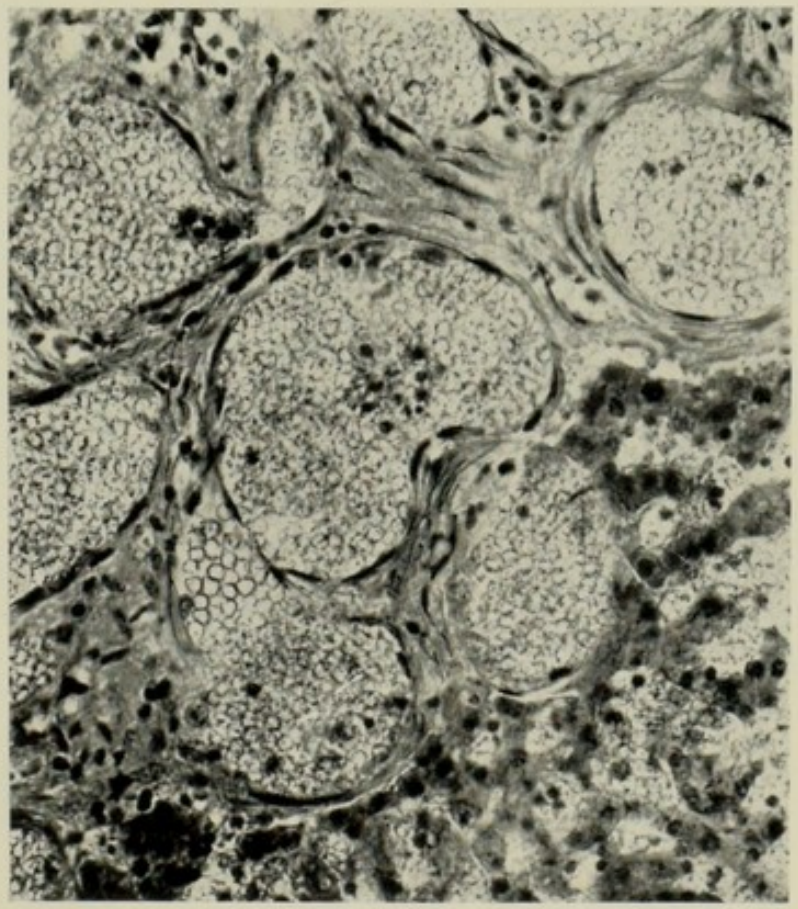

FIG. 74.—*Cavernous Hæmangioma* of liver, showing thin-walled vascular spaces lined apparently with endothelium, and filled with blood. Liver tissue is seen at lower part of section. ×250.

growth. Thus, the lymph-angiectatic swellings due to the presence of *Filaria bancrofti*, and the retention cysts so frequently seen in the lacteals of the intestine and mesentery, must be excluded. It is very doubtful whether the diffuse congenital enlargement of the lymphatics of the tongue (macroglossia) or of the lip (macrocheilia) should be included as tumours. True lymphangiomas are probably always "congenital," and are usually of the cavernous variety. They may be found on the

skin and subcutaneous tissue, or more rarely in the ovary or in the hilus of the kidney.

GLIOMA.—Neuroglia, although of epiblastic origin, is, as Adami points out, a hylic or "pulp" tissue, and consequently tumours arising from it (epihylomata) may be considered along with the other hylomata or "pulp" tumours. Gliomata may be found in the brain, cord, and retina, and may be slow-growing and fibrillar, resembling ordinary neuroglia in structure

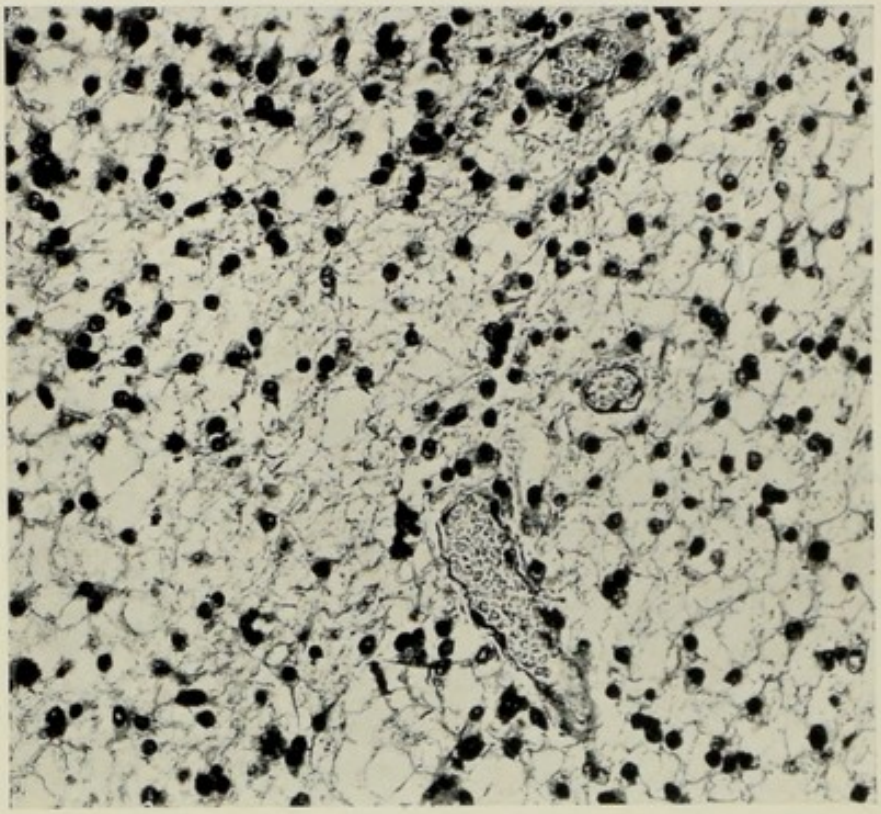

FIG. 75.—*Glioma of Brain*, showing numerous branching cells resembling those of neuroglia. Several thin-walled blood-vessels are seen in the section. × 250.

or they may be large, soft, rapidly invading, malignant tumours which are highly cellular, and possess numerous very imperfectly formed vessels, from which hæmorrhages are extremely liable to occur. Such **glio-sarcomata** (following Adami's example, we use the term "sarcoma" here **without** any embryogenetic significance) may attain a considerable size, infiltrating widely, but not usually tending to produce metastases in other organs.

Gliomas of the retina are usually small in size. They may be present in both eyes, and generally occur in young subjects.

NEUROMA.—True neuromata, *i.e.* new growths of nerve elements proper, are extremely rare, but do occur. In this group should not be included "false neuromas," which are in reality fibromas of the nerve sheaths; nor "amputation neuromas," which are due to reparative processes. Apparently true ganglionic neuromata, *i.e.* tumours containing nerve cells, have been described as occurring in the skin in young children, and also, in some cases, as developing from the sympathetic ganglia and plexuses.

SARCOMATA, OR MALIGNANT HYLOMATA OR PULP TUMOURS

The structure and other general characters of the sarcomata, which may be regarded as the atypical or malignant representa-

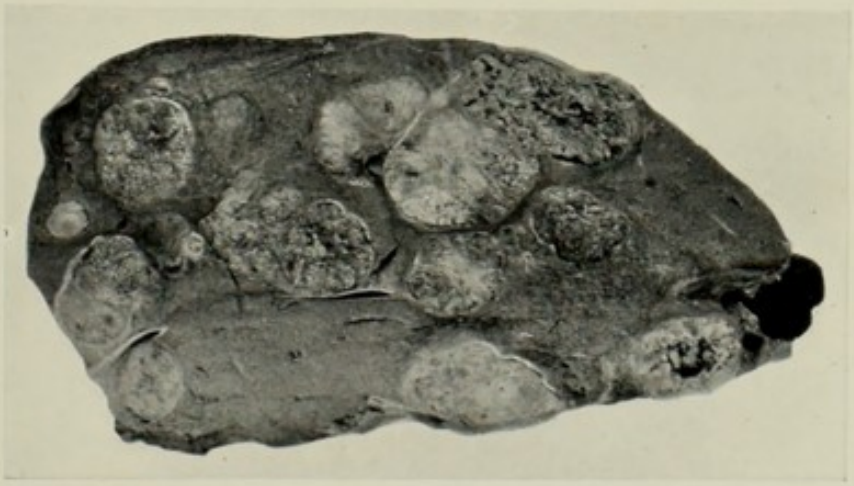

FIG. 76.—*Sarcoma.* Secondary nodules in liver.

tives of the group of tumours which has just been considered, have already, to some extent, been discussed. We may again emphasise the fact that we do **not** use the term "sarcoma" in an embryogenetic sense, *i.e.* we do not restrict it to the malignant **meso**-hylomata only, but in this group we include all malignant or atypical hylomata—whether epi-, meso-, or hypoblastic in origin.

Sarcomata are "pulp" tumours which remain cellular in type, with absence, or only slight and imperfect development, of definite tissue. Most of them are mesoblastic in origin; but the glio-sarcomata are epiblastic; and the very rare malignant chordomata arising from remnants of the notochord are hypoblastic in origin.

Classification of Sarcomata.—Sarcomata may be classified according to—

i. **The variety, size, and arrangement of cells** present, *e.g.* small or large, round-celled or spindle-celled, mixed, myeloid, alveolar, etc.

ii. **The tissue towards which they tend to develop**, usually very imperfectly, *e.g.* osteo-, chondro-, lympho-, fibro-sarcoma, etc.

iii. **The presence of degenerative changes**, *e.g.* myxo-sarcoma showing myxomatous change.

iv. **Admixture with other tumours**, *e.g.* with adenomas, endotheliomas, etc.

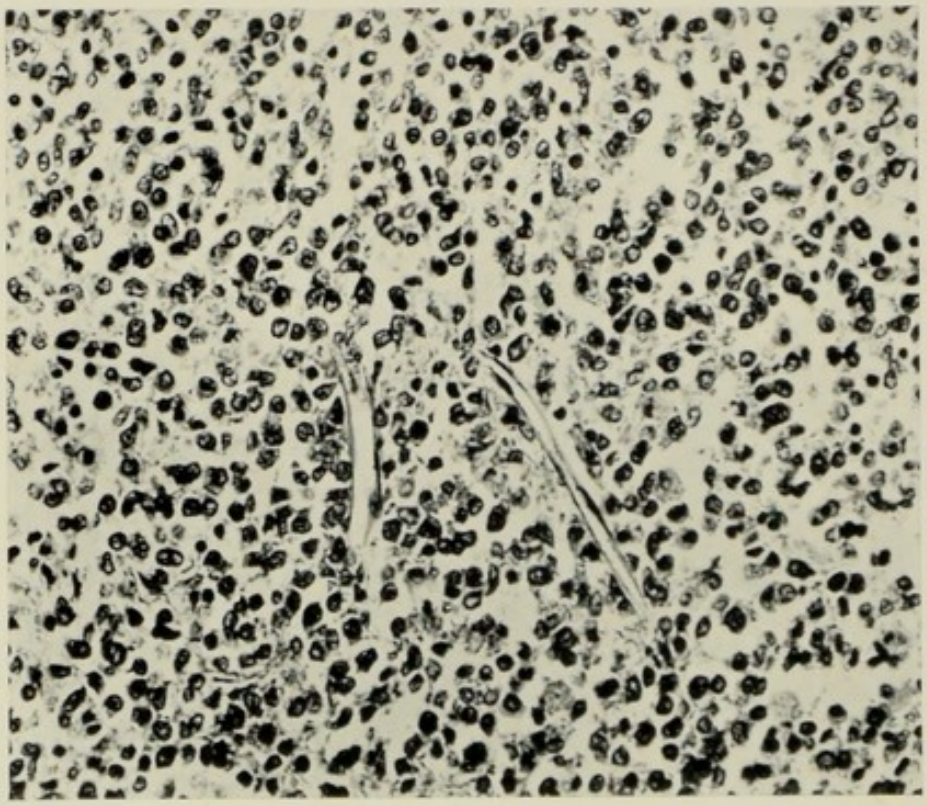

FIG. 77.—*Small Round-celled Sarcoma* with thin-walled blood-vessels. × 300.

ROUND- and **SPINDLE-CELLED SARCOMATA** roughly correspond with the stages to be observed in the development of ordinary fibrous tissue. Thus—

(*a*) In **small round-celled sarcomata**, the cells are small and round, with scanty protoplasm and darkly staining nuclei. The intercellular substance is very scanty, granular, or only slightly

fibrillated. The blood-vessels are numerous, very imperfectly formed, and badly supported. The most undifferentiated and most malignant of this group are the lympho-sarcomata.

(*b*) In **large round-celled sarcomata**, the cells have enlarged, but have not become elongated into spindle-shaped cells. The protoplasm is more abundant, and the nucleus stains less deeply. The intercellular substance shows rather more fibrillation, the fibrils being somewhat more numerous and greater in thickness;

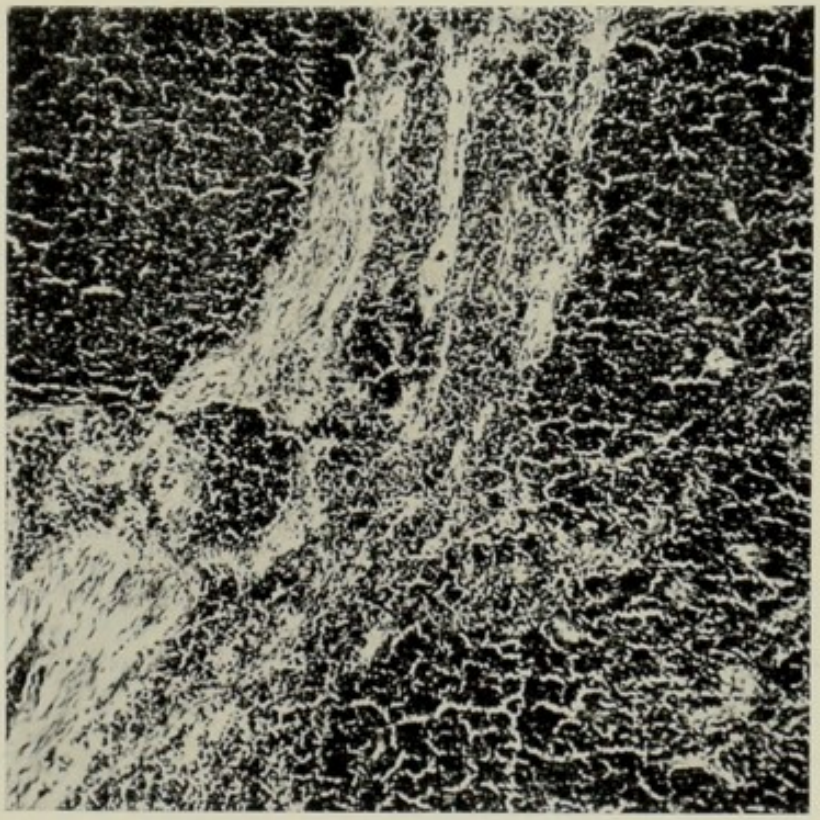

FIG. 78.—*Lympho-sarcoma of Lung*, a tumour composed of densely packed small round cells. Note the pre-existing fibrous tissue undergoing infiltration by the tumour cells. ×90.

and the vessels are somewhat less numerous, and distinctly better supported.

(*c*) In **small spindle-celled sarcomata**, the cells have become elongated and arranged in irregular bundles, but have otherwise remained in a comparatively primitive condition. There may be only very slight fibrillation, and the vessels are very imperfect.

(*d*) In **large spindle-celled sarcomata**, the cells are arranged in bundles, the fibrils are more numerous and thicker, and the vessels may be fairly well supported, *i.e.* the tumour is not so

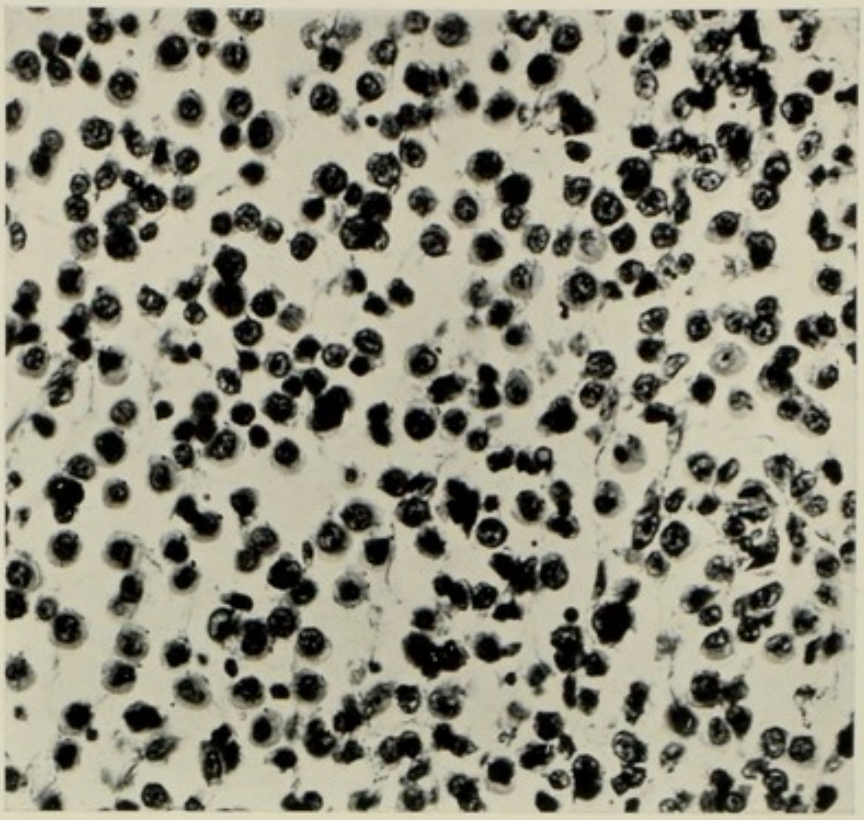

FIG. 79.—Large Round-celled Sarcoma. ×300.

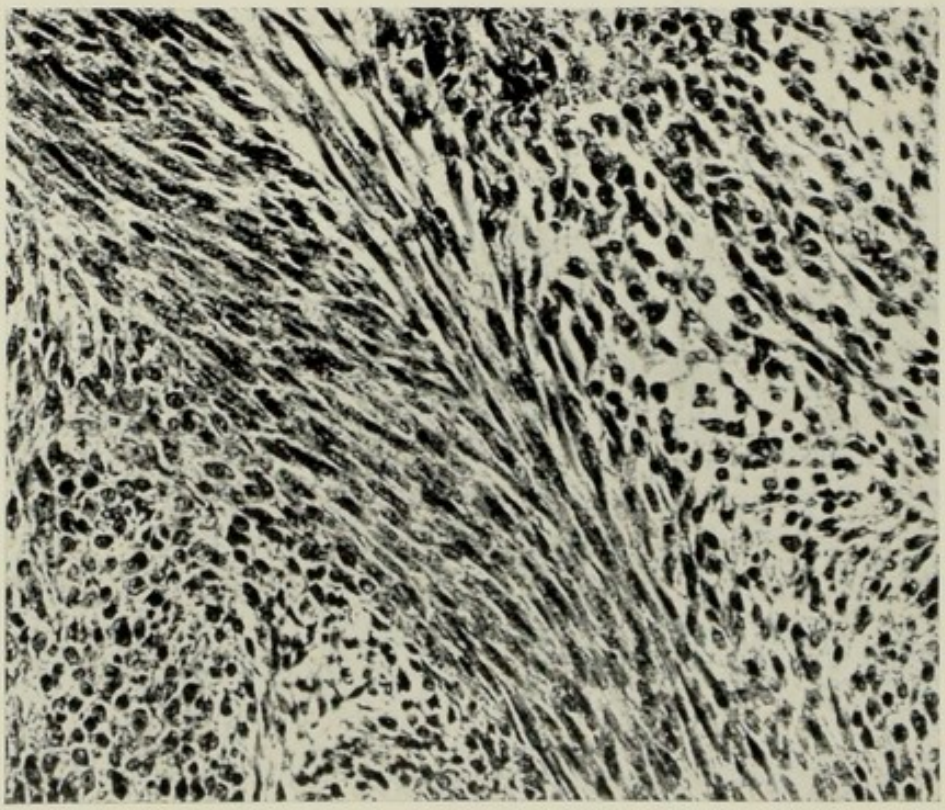

FIG. 80.—Small Spindle-celled Sarcoma, showing bundles of cells cut longitudinally and transversely. ×300.

rudimentary or anaplastic as the foregoing. All intermediate grades may also be found between spindle-celled sarcomata and soft and hard fibromata, the latter corresponding with fully formed connective tissue. These intermediate fibro-sarcomata include the so-called "recurring fibroids," which are tumours of very slight malignancy, whereas the small-celled sarcomata are generally very malignant. It is often, however, not possible to tell the degree of malignancy of a sarcoma from microscopical

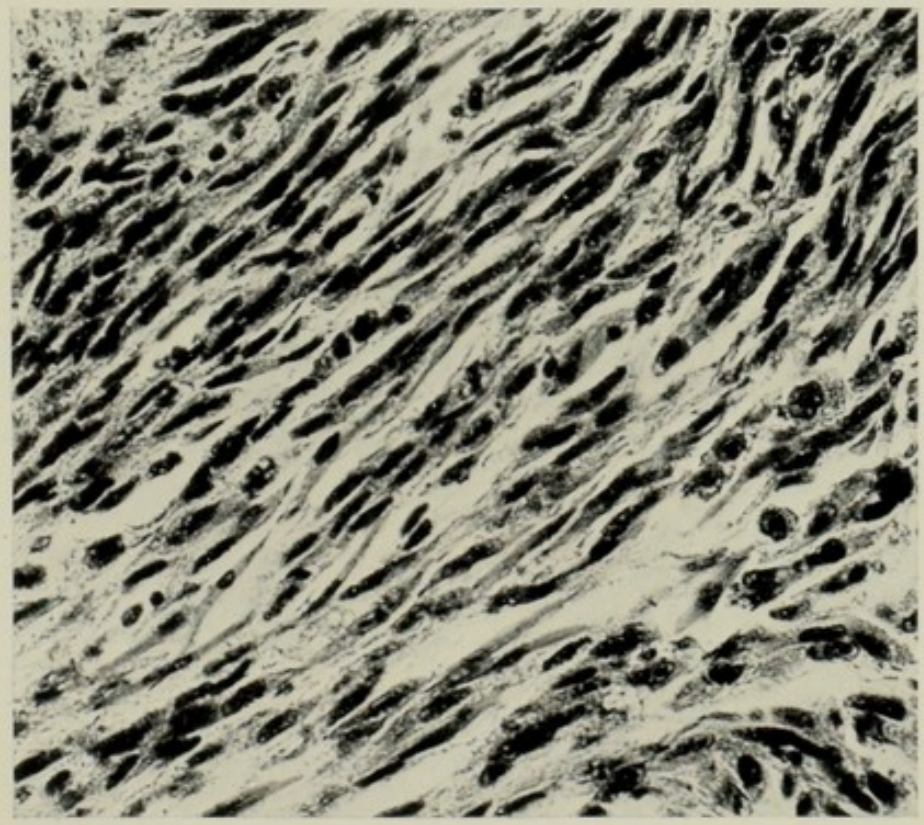

FIG. 81.—Large Spindle-celled Sarcoma, showing cells cut for the most part in longitudinal section. ×300.

examination alone, and account must also be taken of their site and rate of growth, and the presence of other changes, *e.g.* pigmentation, as in melanotic sarcoma, which is one of the most malignant tumours known. It is also sometimes a matter of great difficulty to differentiate certain sarcomata from granulation tissue.

Sites of Origin.—These round- and spindle-celled and also mixed-celled sarcomata may arise in almost any tissue, but especially from bone, fascia, and fibrous membranes.

Mixed-celled Sarcomata are tumours in which several of the

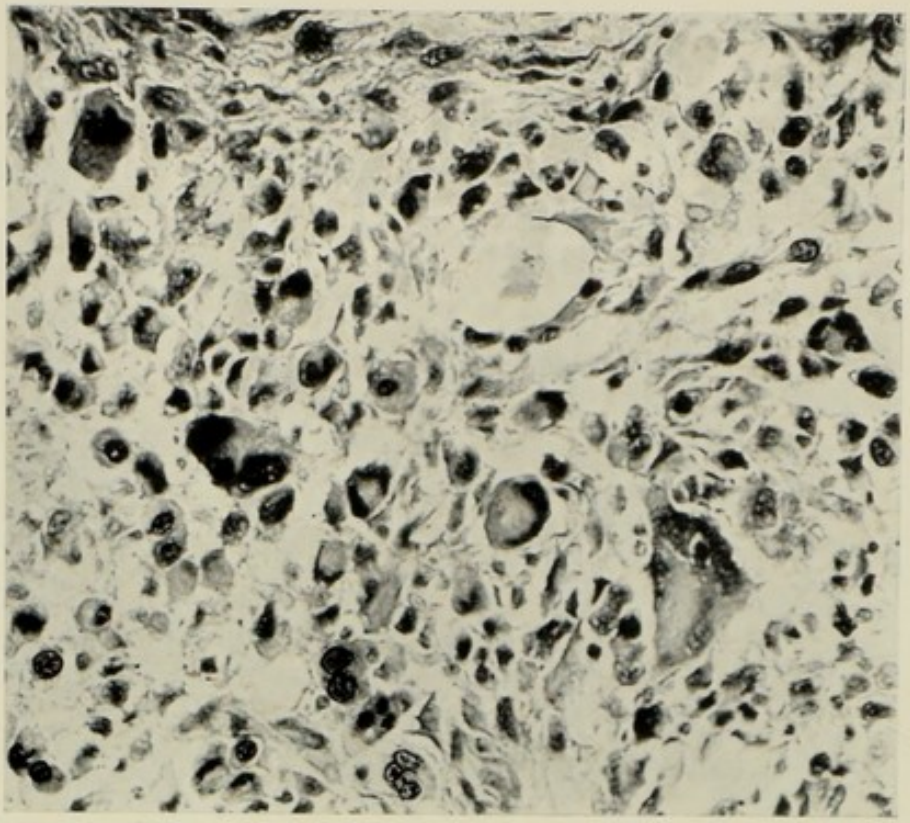

FIG. 82.—Mixed-celled Sarcoma, containing small and large round cells, a few spindle cells, and several small multinucleated giant-cells. ×300.

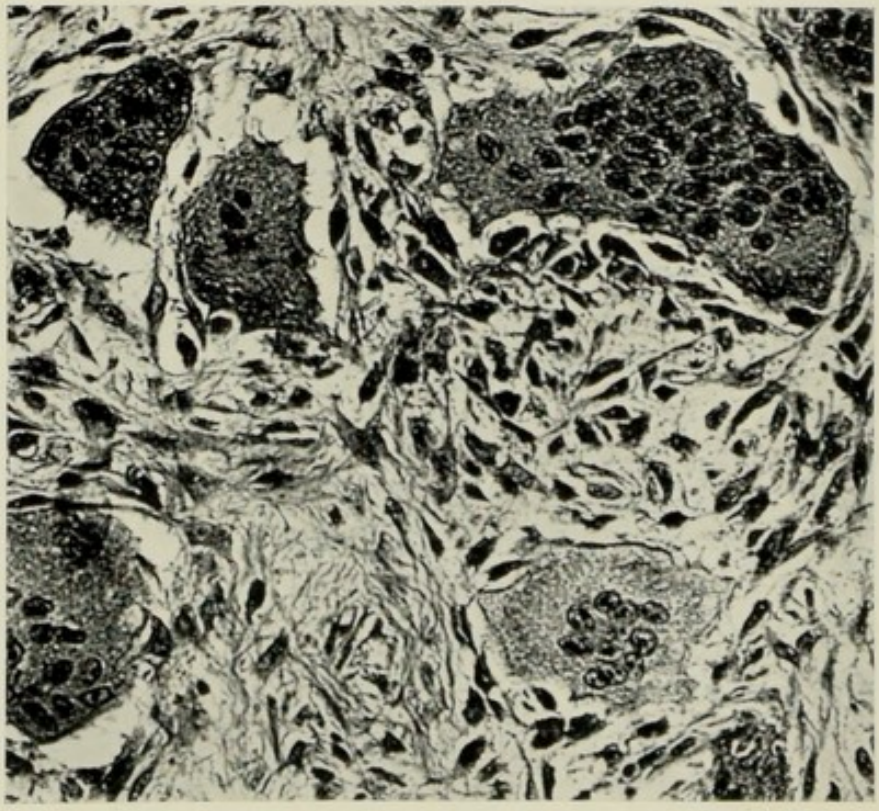

FIG. 83.—Myeloid Sarcoma from Jaw. The tumour consists of spindle-cells, amongst which are embedded numerous large multinucleated giant-cells or myeloplaxes. ×300.

above-mentioned variety of cell-types may occur together. They sometimes also contain multinucleated giant-cells of various sizes. The intercellular fibrillar material is scanty, and the vessels usually rudimentary in type.

MYELOID OR GIANT-CELLED SARCOMATA may be regarded as a variety of mixed-celled tumour. They are usually spindle-celled growths arising from bone, and are specially characterised by the presence of numerous very large, irregularly shaped, multinucleated giant-cells or **myeloplaxes.** Such tumours are commonest in young subjects, and are most frequently found at the lower end of the femur, the upper end of the bones of the leg, and in the lower jaw. In the last-named situation, a tumour of this description constitutes one form of "malignant epulis."

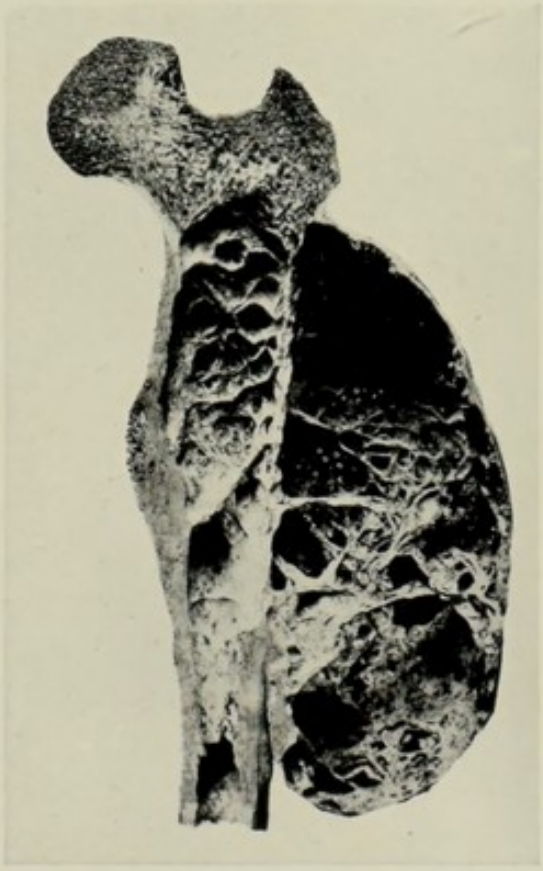

FIG. 84.—Myeloid Sarcoma of shaft of femur. Macerated and dried specimen showing expanded shell of bone.

MELANOTIC SARCOMA.—This is a variety of sarcoma in which some of the cells become pigmented and contain melanin, an albuminous pigment which is elaborated by the tumour cells. The presence of this pigment, the amount of which varies greatly in different cases, gives to melanotic sarcomata their typical sooty, brownish-black appearance. In some cases the pigment may be diffuse, and in others distributed in irregular patches, the remaining portions of the tumour being colourless (fig. 86).

The primary growth usually occurs from some area which contains melanin pigment, *e.g.* the uveal tract of the eye, pigmented moles of the skin, etc. Melanotic sarcomata are extremely malignant, and metastases may occur in practically any and every tissue of the body. Such secondary spread appears to be mainly by means of lymphatics; and this fact,

together with certain resemblances which the tumour cells have to cells of epithelial type, has led to the view held by some pathologists that these tumours should rather be classed as cancers than as sarcomas.

In some pigmented tumours of the skin, the cells are epi-

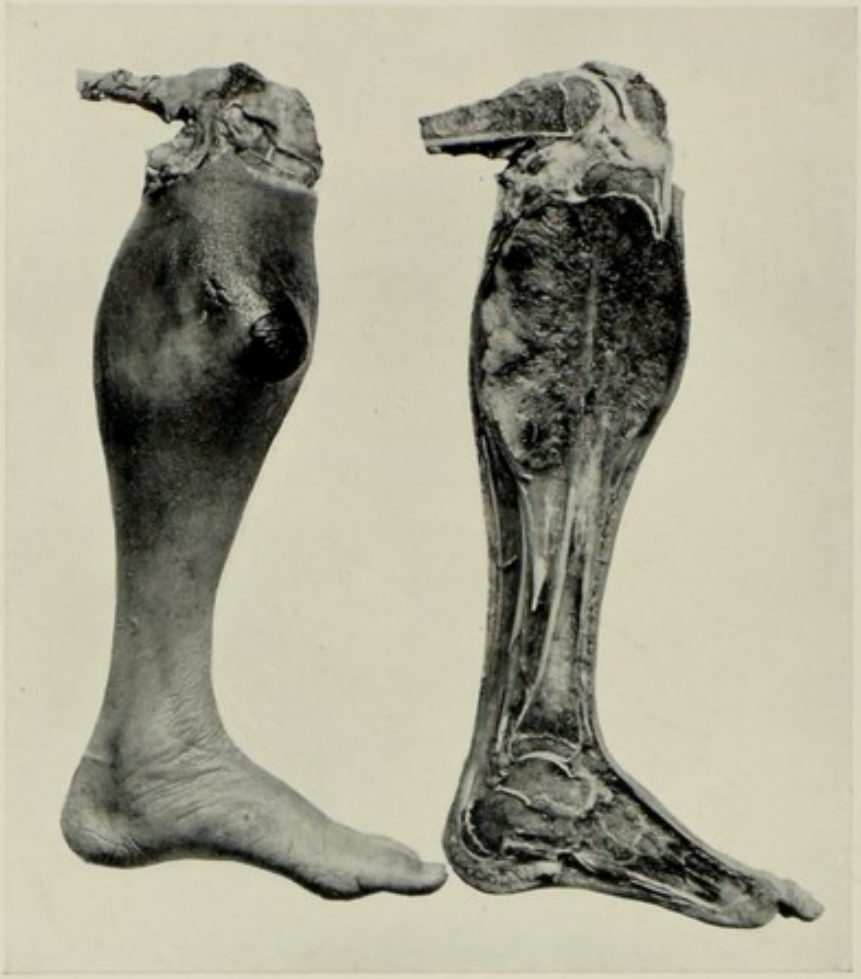

FIG. 85.—Myeloid Sarcoma of head of Tibia.

A. Surface view, showing tumour ulcerating through skin surface.
B. Antero-posterior section, showing large irregular malignant mass, originating from the head of the tibia, and infiltrating and replacing the tissues in the upper part of the leg. (From the Royal College of Surgeons Museum, Edinburgh.)

thelioid in type, and are arranged in definite alveoli. These tumours are probably carcinomata, and not sarcomata.

The characters of the cells of melanotic sarcomata vary very considerably. Some are pigmented spindle-celled tumours which may originate from pigmented skin moles. Others are small round- or oval-celled tumours which are extremely malig-

nant, and the starting-point of which may be the pigmented parts of the eye, or pigmented moles of the skin. In other varieties the cells may vary greatly in size, and may sometimes be of considerable dimensions. The nuclei are usually poor in chromatin, and show a very distinct nuclear membrane and network. The amount of pigment in the cytoplasm varies

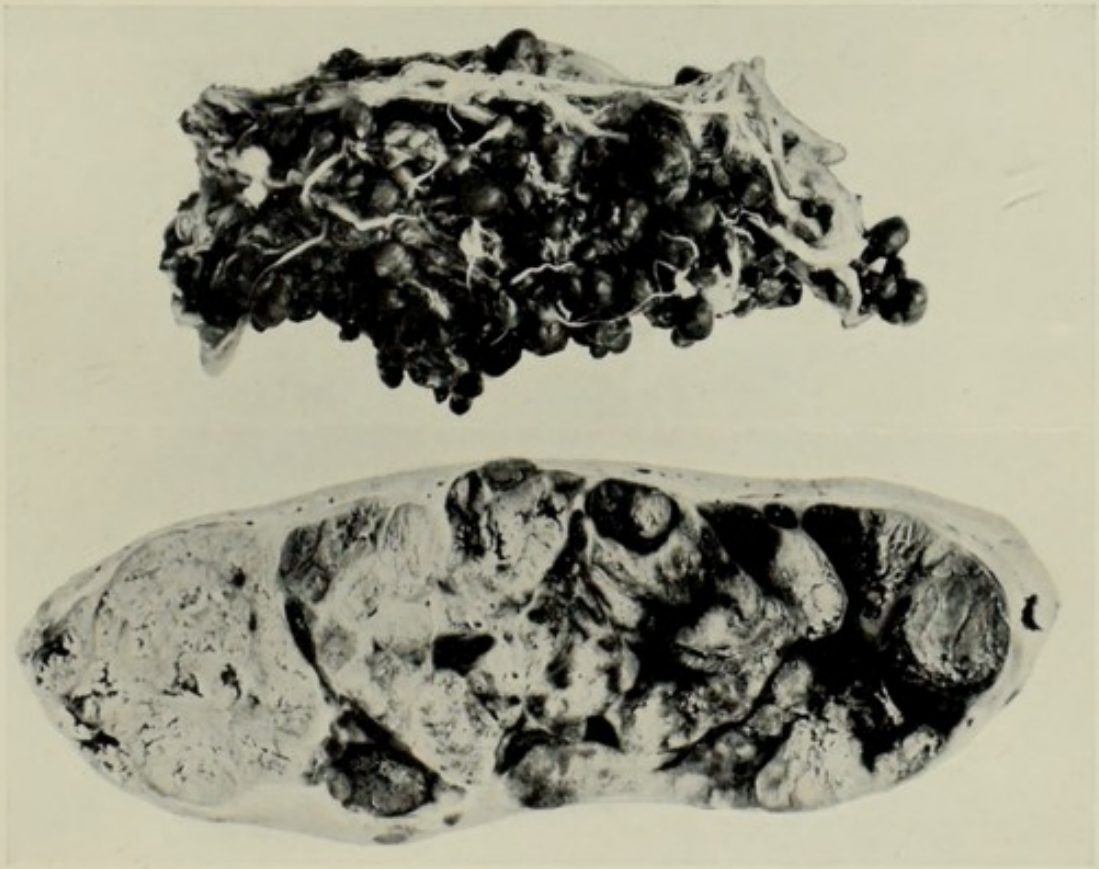

FIG. 86.—*Melanotic Sarcoma.*

Upper specimen.—Numerous secondary nodules of deeply pigmented tumour occurring in omentum. (Edinburgh University Anatomical Museum. Catalogue No. Al. F. c. 3.)

Lower specimen.—Large secondary nodule in subcutaneous tissue. The melanotic pigment is irregularly distributed, considerable areas of the tumour remaining unpigmented. (Edinburgh University Anatomical Museum.)

greatly, from a few scattered granules up to granular masses completely obscuring the cell-structure.

CHLOROMA.—This tumour is one of great rarity. It usually occurs in the form of multiple greenish or greyish-green growths in connection with the bones, especially in relation to the periosteum. Similar growths may also occur in the bone-marrow, kidney, liver, and elsewhere. Microscopically, these tumours resemble lympho-sarcomata in structure.

MESOTHELIOMA, ENDOTHELIOMA, and **PERITHELIOMA.**—These tumours are classified by Adami as "secondary Lepidomata," *i.e.* "rind" tumours, the characteristic constituents of which are derived in direct descent from the **mesothelium** of the embryo. As already explained, such tumours, when malignant, are histologically more allied to the cancers; but in them a still further reversion may readily occur, and they may take on the characters of pulp tumours. **Mesotheliomata,** *i.e.* malignant tumours of this group arising from serous membranes, *e.g.*

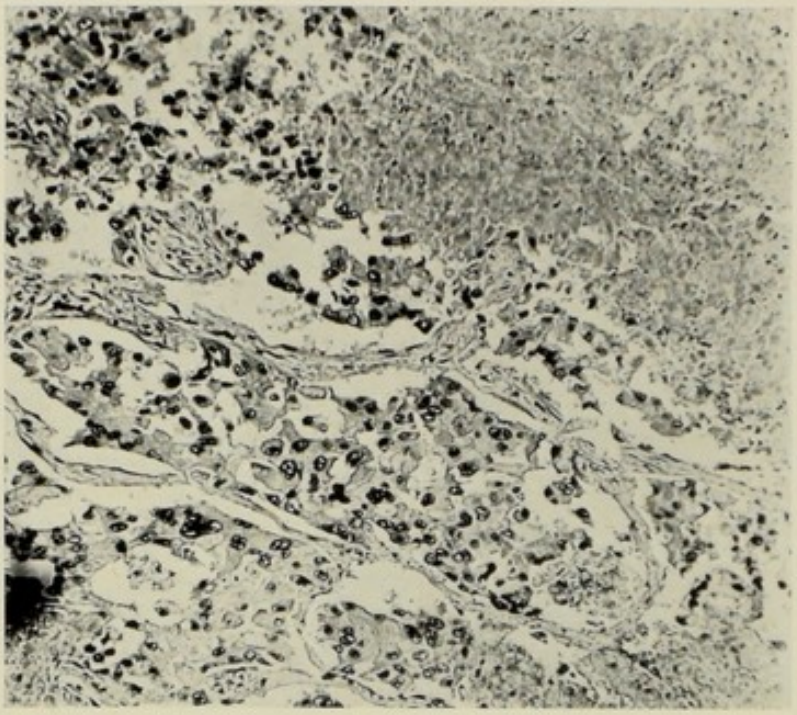

FIG. 87.—Mesothelioma ("Endothelioma") of Lung. Groups of endothelial cells invading the pre-existing tissue. A necrotic area is seen at the upper right corner. ×100.

peritoneum, pleura, tunica vaginalis, etc.; **endotheliomata**, arising from the endothelium of blood-vessels or lymphatics; and **peritheliomata**—a sub-variety of the latter arising from the endothelium of peri-vascular lymphatics — may show an "alveolar" or even an acinus-like arrangement, suggesting the structure of a cancer; whilst in other specimens, and sometimes even in different parts of the same tumour, a typically sarcomatous arrangement of the cellular and intercellular elements may be seen. These variations have given rise to many rather cumbrous names, such as "cylindroma," "carcinoma sarcomatodes," "sarcoma carcinomatodes," "alveolar

sarcoma," etc., under which terms members of this group have been variously described.

In this group may also be included the rare **Angio-sarcoma,** a new growth of blood-vessels which retain their simple or primitive characters, and the endothelium of which may be

FIG. 88.—Mesothelioma ("Endothelioma") of Lung. Large malignant tumour infiltrating and destroying the lung tissue.

several layers deep, and often showing an endogenous process of proliferation by budding.

The **Angiolithic Sarcomas,** or so-called **psammomas**, or **brain-sand tumours,** growing from the membranes of the brain and cord, and also, it is said, from the pineal body and choroid plexuses, are also members of this group. In structure, they exhibit concentric layers of somewhat flattened cells, with, in the centre of each group, a hard, rounded, calcified, sand-like

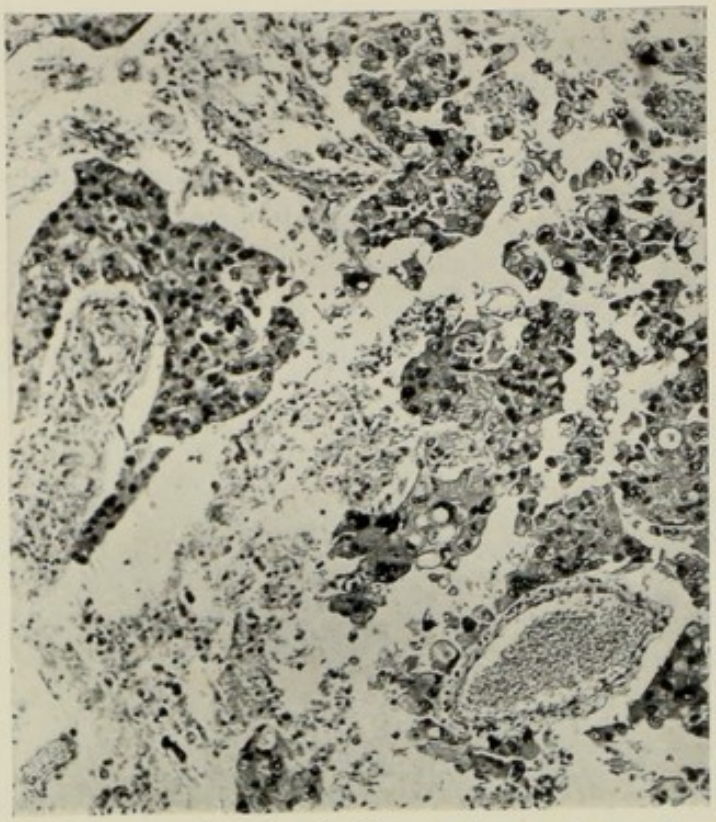

FIG. 89.—Endothelioma of Brain, similar to the specimen shown in fig. 87. The tumour cells are actively phagocytic, and contain digestive vacuoles and cell-inclusions. ×75.

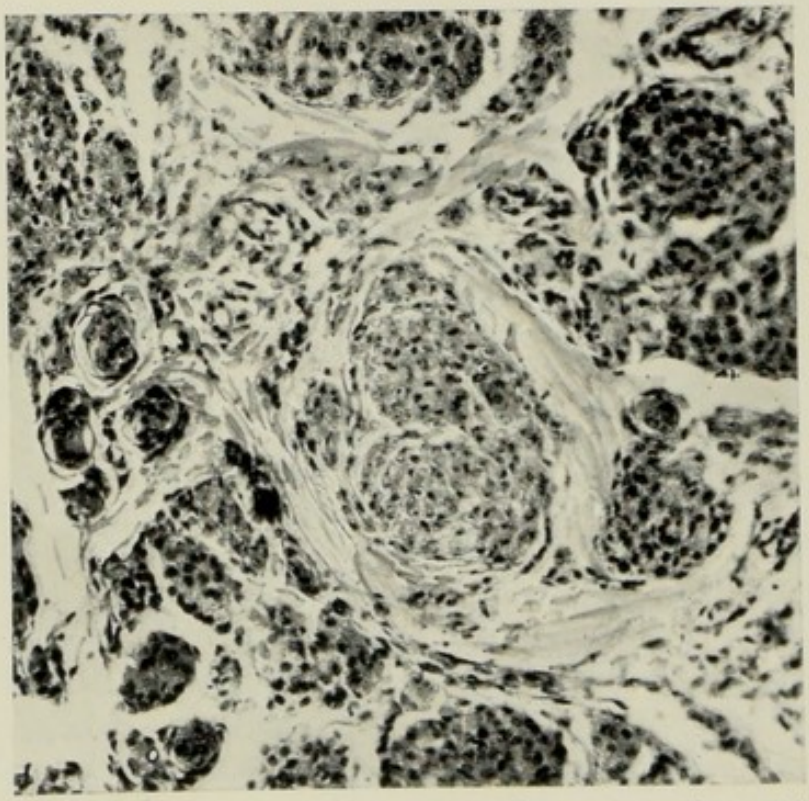

FIG. 90.—Angiolithic Sarcoma or Psammoma of dura mater. Concentric "nests" of cells, constituting probably a variety of perithelioma. Sections of vessels may be seen in some of the smaller cell-groups. ×200.

particle. The latter is not the essential or most important feature of these growths, but is, as it were, an accidental result of the degeneration of the central parts of the nests of cells which are formed around the small blood-vessels by these flattened, concentrically arranged layers of endothelial cells.

GLIO-SARCOMA, OSTEO-SARCOMA, CHONDRO-SARCOMA, and **MYXO-SARCOMA** have already been briefly referred to when

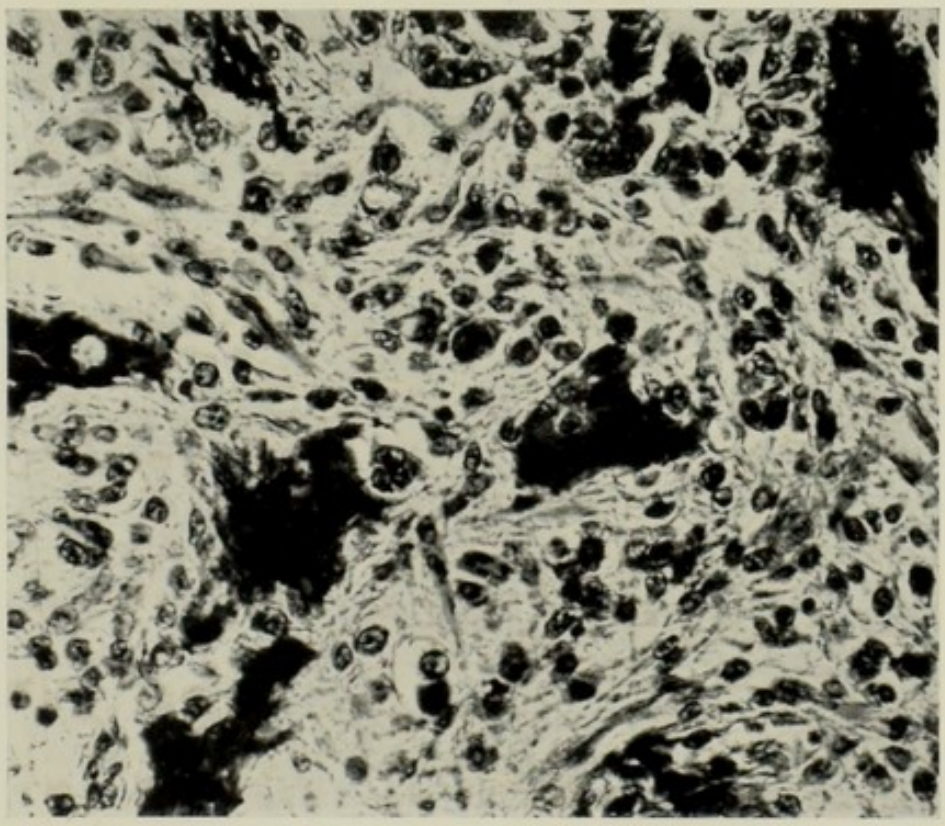

FIG. 91.—Osteo-sarcoma of head of tibia. The dark areas are imperfectly formed spicules of bone, and are embedded in a spindle-celled tumour. ×300.

dealing with the analogous simple tumours, and do not call for further remark.

SARCOMATOUS TRANSFORMATION IN CANCERS

Formerly, a very definite separation was made between the sarcomata and the carcinomata; and though this, for purposes of classification, must still be maintained, it must be recognised that certain tumours which are classed among the sarcomata show a histological structure resembling that of the carcinomata; and further, and more important, certain experimental evidence

seems to indicate that one type may be transformed into the other. Thus, Apolant and Ehrlich,[1] Bashford and Murray, and other workers, on making a long series of consecutive transplantations of carcinomata in mice, found that the character of the tumours gradually became changed. Thus, in one case, an "alveolar adeno-carcinoma" at the tenth sub-inoculation began to show numerous actively growing spindle-cells of sarcomatous type. On further sub-inoculations, the carcinomatous cells were progressively replaced by these spindle-cells, and at the fourteenth generation the tumour had apparently become a pure sarcoma, a character which was thenceforth preserved on subsequent inoculations, the experiment being carried as far as the fortieth generation. Analogous results were obtained in two other series of inoculations, in one of which the tumour became practically a pure sarcoma after the sixty-ninth generation. Apolant also found that this sarcomatous transformation may be aided by heating the inoculation material at 44° C. for varying periods, the development of the inoculated tumour cells being at the same time much delayed.

LEPIDOMATA OR "RIND" TUMOURS—SIMPLE OR TYPICAL AND MALIGNANT OR ATYPICAL

This group includes tumours such as papillomas, adenomas, cysts or cystomas, etc., both typical and atypical.

SIMPLE OR TYPICAL LEPIDOMATA

ADENOMAS OR TUMOURS ARISING FROM GLANDULAR STRUCTURES.—In some respects it appears to be merely an accident of growth, as it were, whether the proliferating glandular tissue forms a papilloma or evagination, or gives rise to an adenoma or invagination of the epithelium. In connection with all covering and lining membranes, whether epi-, meso-, or endothelial in nature, there are certain structural characters which must be borne in mind in considering the tumours which arise from them. Thus, in addition to the essential and specific covering or lining cells, such structures in normal circumstances also possess a basement membrane, supporting connective tissue

[1] Apolant and Ehrlich, *Berl. klin. Wchnschr.*, Jan. 8, 1906.

stroma, blood-vessels and lymphatics, derived from the mesoblast. In all true lepidomata, the lining or covering cells appear to be the essential proliferating elements of the tumour, whilst proliferation of the supporting connective tissue and vessels is to be regarded as a result rather than as an essential feature of the new growth. But it is extremely difficult, in certain instances, to determine whether the primary overgrowth is not one of the subjacent connective tissue elements, and the epithelial proliferation merely, in these special cases, a result produced in order to preserve the continuity of the covering layer of cells. To avoid this difficulty, such tumours, containing both proliferated epithelium and connective tissue stroma, have been classed together by Ribbert and other writers under the common term **Fibro-epithelial Tumours.** We shall, however, content ourselves with merely mentioning this difficulty, and shall follow the classification given by Adami. Such conditions as chronic inflammatory overgrowths of fibrous tissue occurring in glands, and accompanied by irritative overgrowth of the glandular epithelium such as occurs in cases of chronic mastitis, and which often simulate a fibro-adenoma in structure, must be carefully distinguished from true lepidomata. Similarly, cystic dilatations due to the blocking of tubules or ducts by inflammatory products or by compression from without must not be confused with true adenomatous tumours.

Histology of Adenomata (including Cysts)

Epithelium.—The proliferation of the glandular cells may, in the case of the tumour, lead to greater complexity of structure than is found in the original gland. Thus, the cells may be several layers deep instead of single; or papilliform ingrowths or infoldings may occur, especially in cysts lined by rapidly growing glandular cells. Alteration in the type of cell is common; for example, flattened or low cubical may replace columnar cells, or *vice versa*. The individual cells may also show great variations. They may be larger than those of the normal gland, may show different staining reactions, alterations in their minute structure, *e.g.* ciliated cells may lose their cilia, and so on. Degenerative changes are very common.

In the case of tubular glands, the new formation of acini usually occurs as a process of budding from the pre-existing

glandular tubes. In some cases, duct-like structures are the first to appear, from which the tubules may form, and then enlarge in size. In some instances, the lumen may be very imperfect or entirely absent, as in the scirrhus and encephaloid forms of cancer, which are composed of solid clumps of cells filling spaces surrounded by the fibrous tissue stroma. In other cases, the proliferating cells may be arranged in closed

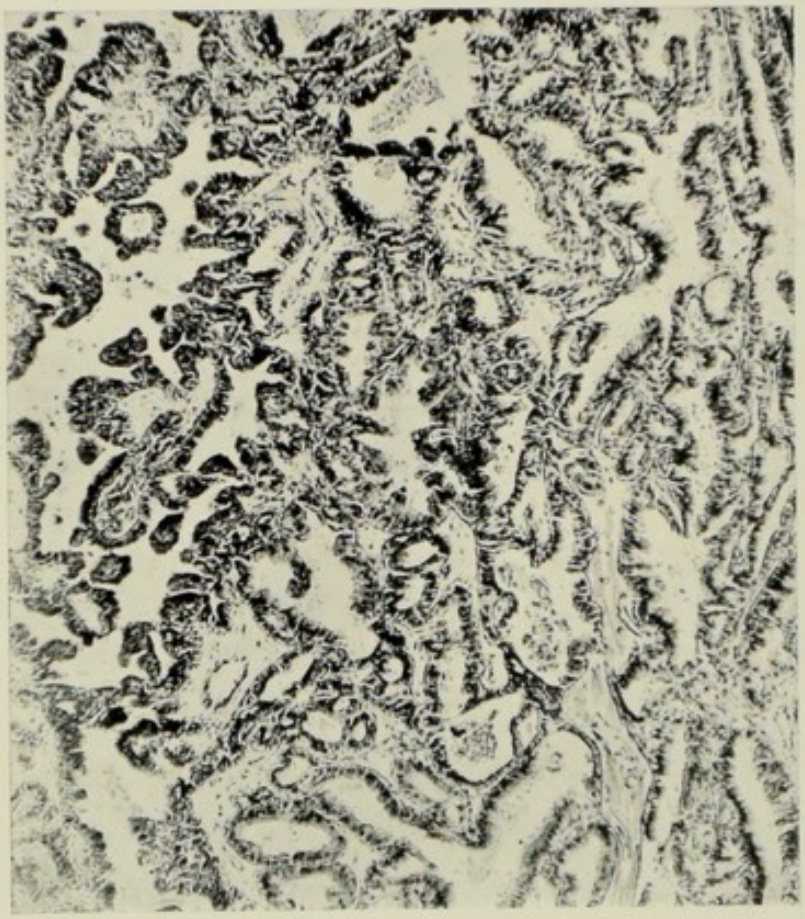

Fig. 92.—Complex Adenoma of Breast The acini are dilated and show numerous papilliform ingrowths or infoldings. × 50.

compartments, which may become dilated and form cyst-like spaces.[1] In some cases, multiple cysts may be produced in this way, or by a further process of endogenous formation within the first cyst as it enlarges.

Contents of Cystic Tumours.—These tumours, consisting of hollow closed spaces, usually possess fluid or semi-fluid contents

[1] Note.—For a synopsis of **Varieties of Cysts**—including both those due to tumour growth and those due to other causes—see appendix at the end of this chapter (p. 328).

of the nature of a secretion. This secretion is generally not of the normal type produced by the cells, and appears to form a necessary accompaniment of the growth of a tumour. It may consist of a fluid containing various mucin-like compounds of proteins and carbohydrates (see pp. 54–5); or it may become thick and inspissated, and undergo various physical and chemical changes, may contain cholesterin, fatty crystals, etc. In other instances, the secretion may consist of altered cells or their

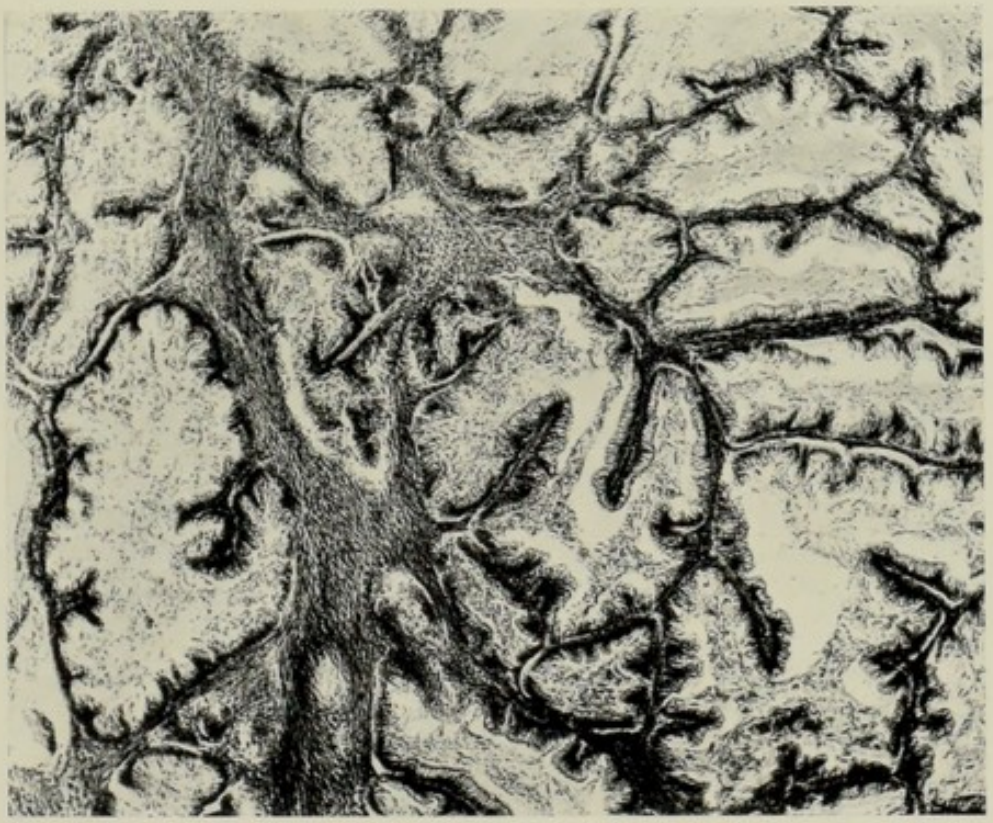

FIG. 93.—Compound Cystic Ovarian Adenoma. Cystic spaces lined by a single layer of columnar epithelium, showing numerous papillomatous ingrowths. Fibrous tissue stroma. ×50.

products—colloid, mucoid, fatty material, etc.; and in some cases it may become calcified.

Supporting Structures.—The stroma of adenomata varies very greatly in character. In some tumours, *e.g.* in the fibro-adenomata, it may be very firm and fibrous; whilst in others it may be soft and cellular, perhaps myxomatous, in character. There is usually, but not invariably, a basement membrane in simple adenomas; and these tumours generally possess a fibrous tissue capsule around them, developed by a condensation of the connective tissue of the organ in which they are growing. The

blood-vessels of the stroma are, as a general rule, well formed and well supported.

PAPILLOMA.—Instead of being arranged in tubules as in adenomas, or forming closed spaces as in cysts, these tumours are outgrowths or projections, consisting of a central core of connective tissue containing blood-vessels, lymphatics, etc., and are covered by epithelial or some other form of "lepidic" cells. In some cases, there may be merely a single polypoid

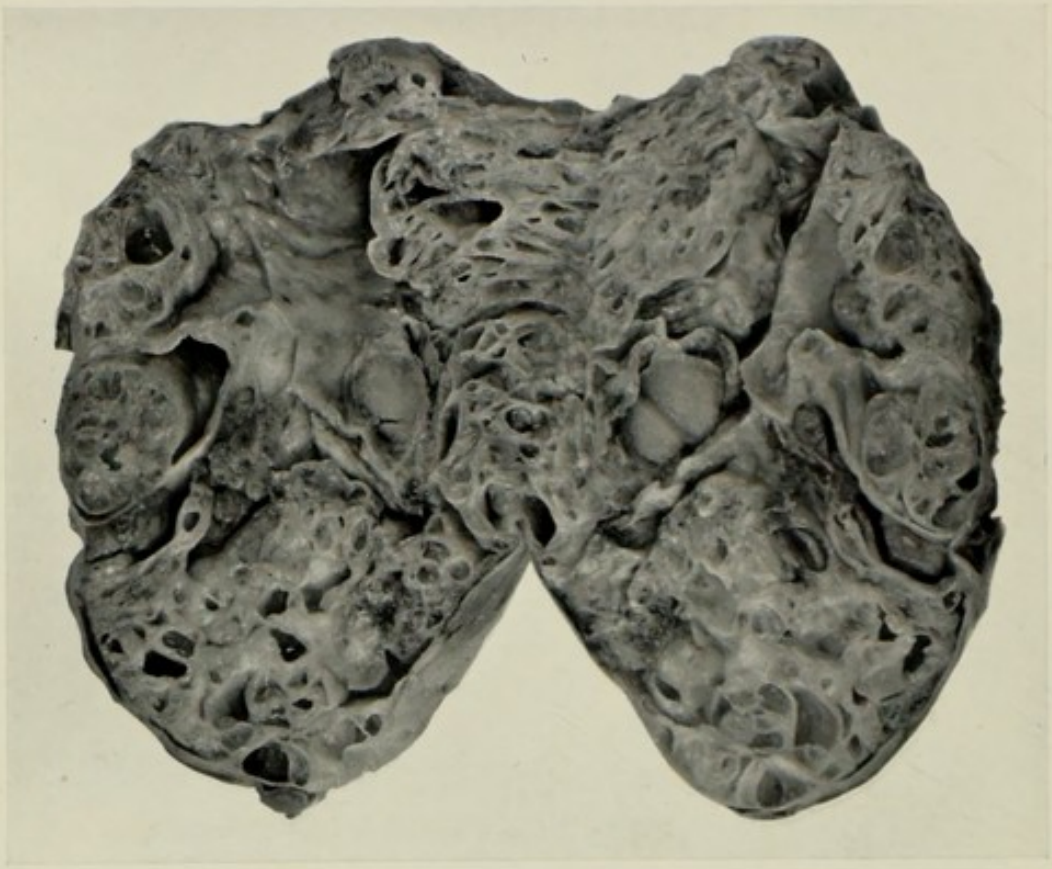

FIG. 94.—Compound Cystic Ovarian Adenoma. Large tumour containing numerous cystic spaces of various sizes.

outgrowth; in others, such an outgrowth may show branching; or, again, as in multiple or "cauliflower" papillomata, there may be innumerable finger-like processes closely massed together. As in the case of some members of the preceding group, it is sometimes difficult to determine which of these elements—connective tissue or lepidic cells—is the essential part of the neoplasm; but probably, in the majority of instances at all events, it is the latter that is to be regarded as such.

Varieties and Sites :—

i. **Squamous Papilloma**, growing from the surface of the skin, mouth, larynx, pharynx, œsophagus, or vagina, *i.e.* the parts of the body covered by squamous epithelium. The normal relationship with regard to the relative position of epithelium to connective tissue core, and of the various layers of the epithelium to one another, is maintained. The epithelial layers covering a squamous papilloma are frequently much

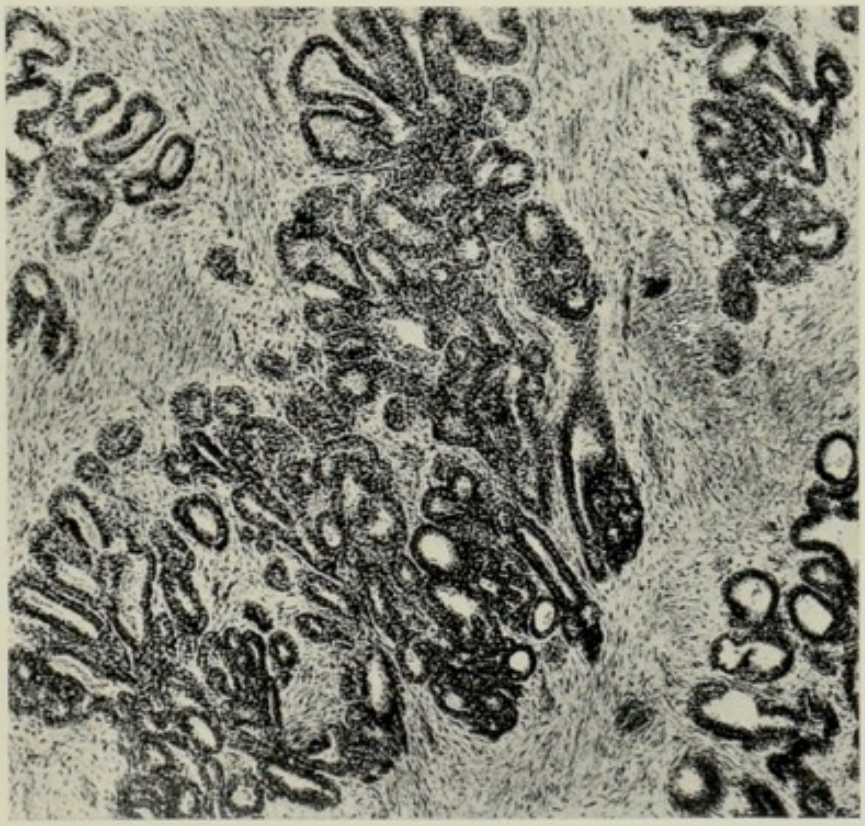

FIG. 95.—Simple Adenoma of Breast. There is considerable proliferation of connective tissue between the groups of acini. The tumour might therefore be classified as a fibro-adenoma. × 50.

thickened, especially in the harder varieties of this tumour, but otherwise, there may be only slight divergence in the appearance of the cells (*e.g.* prickle-cells, etc.) from those of the normal cuticle. The connective tissue core varies considerably in different examples. It may be cellular—perhaps myxomatous—in some cases, more fibrous in others; and it is usually highly vascular, the blood-vessels being frequently thin-walled and somewhat dilated. Secondary inflammatory changes, *e.g.* leucocyte infiltration, are common. In certain

specimens, the connective tissue may very closely resemble sarcomatous tissue.

Some skin papillomata are congenital, whilst others may result from chronic irritation, *e.g.* in petroleum workers. The condylomata and the cauliflower papillomata sometimes developed about the genital organs in syphilis and gonorrhœa

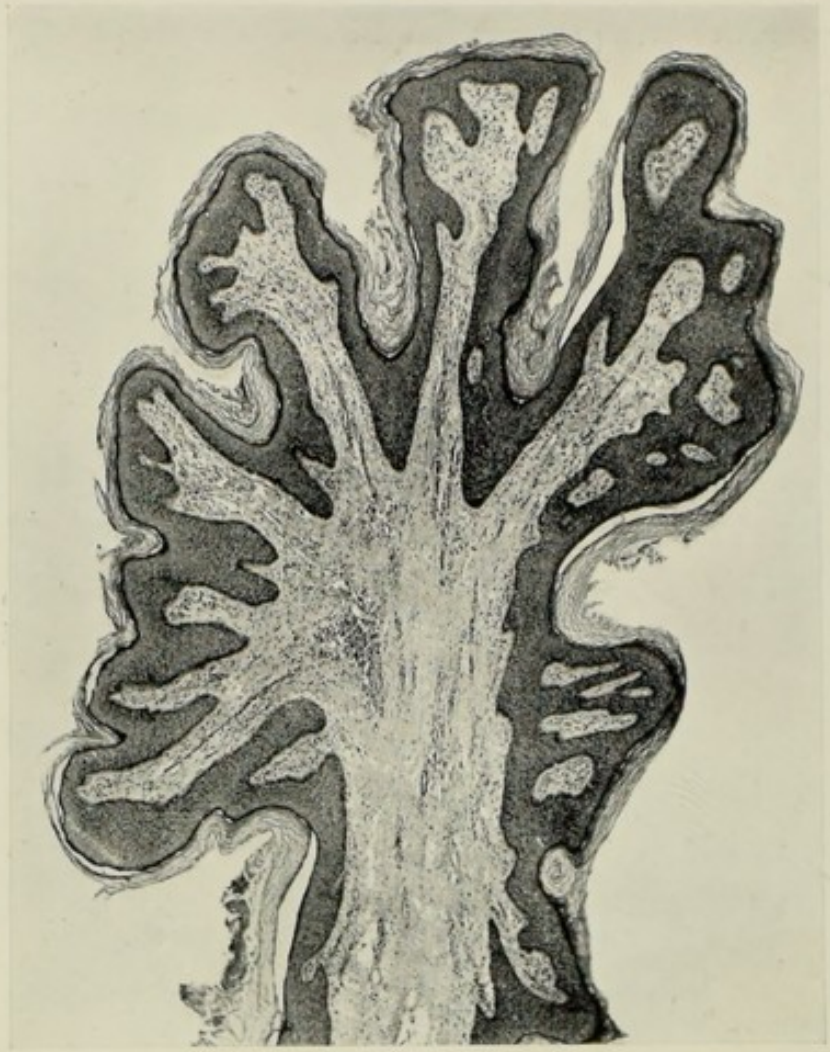

FIG. 96.—Squamous Papilloma, showing thickened skin epithelium, covering a branching vascular connective tissue core. ×38.

appear to be of the nature of squamous papillomata, from which, at all events, they cannot be distinguished histologically. They may result from the irritation caused by the discharges, or may be definitely infective in nature. Similarly, the common cutaneous wart, though structurally identical with a papilloma, is, in some cases, probably due to an infective agent.

ii. **Mucous Papillomata.**—These may grow from any mucous

membrane, but are specially common in the larynx and trachea, alimentary canal, bladder, pelvis of the kidney, uterus, and in various glandular ducts. Polypoidal growths occurring in the nose and naso-pharynx are also common, but these in the majority of instances are now regarded by most authorities as

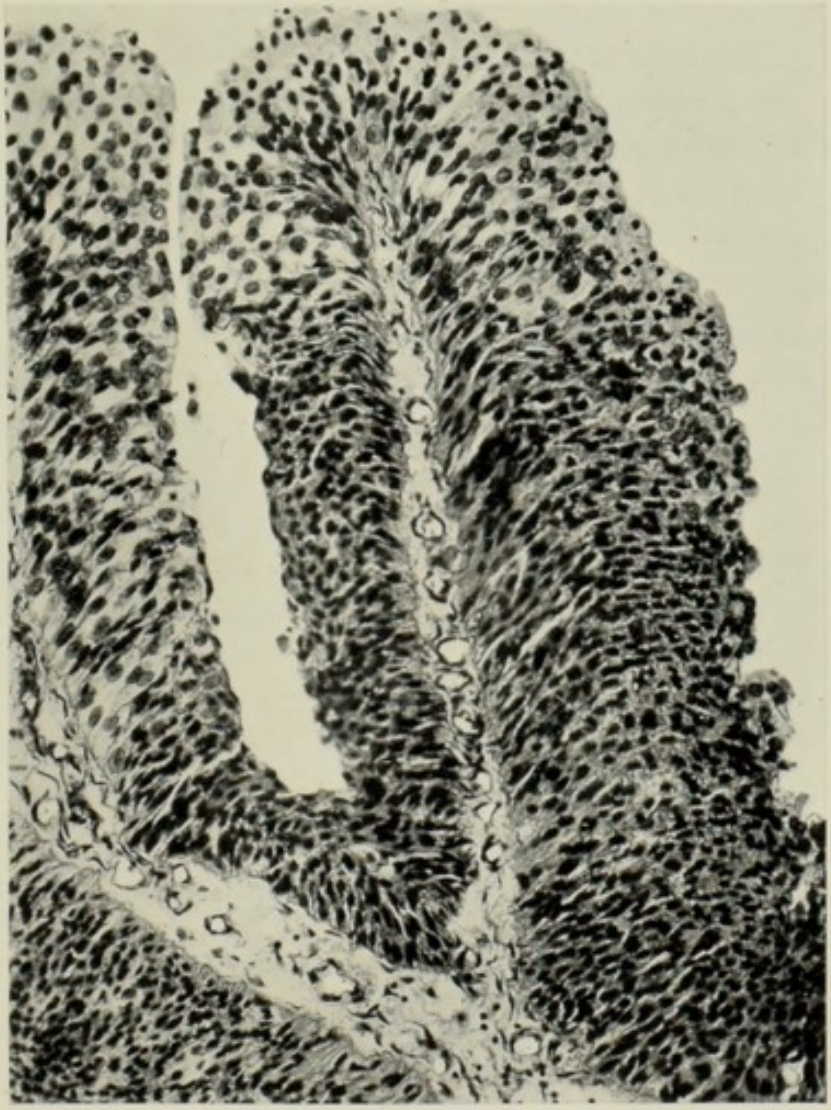

Fig. 97.—Mucous Papilloma of Bladder, composed of long slender branching processes with delicate vascular core covered by proliferated transitional epithelium—the so-called Villous Papilloma. ×200.

chronic inflammatory overgrowths, which become polypoidal owing to the traction of the air passing backwards and forwards over their surface. Similarly, the polypoidal growths which are very common in the large intestine, especially above a stricture, may be due to irritation and to the traction of the intestinal contents. In the case of the bladder, papillomatous

tumours may be composed of long, delicate, branching, finger-like processes, parts of which may break off readily and be passed in the urine, giving rise to intermittent hæmaturia. These tumours are extremely apt to be malignant in character.

iii. **Papillomatous ingrowths from the walls of cystic tumours.**—These have been mentioned when dealing with cysts (p. 307).

iv. **Papillomatous growths may occur from serous membranes,** *e.g.* from the peritoneum, especially in cases of chronic ascites; or from synovial membranes, from which they may become detached to form the so-called "loose bodies" sometimes found in joints. Many of these cases, however, are probably infective in nature, *e.g.* the finger-like processes arising from the synovial membranes in rheumatoid arthritis.

As in adenomas, the cells of papillomata may show considerable variations and aberrations. They may undergo alterations in type and in arrangement, etc.

MALIGNANT OR ATYPICAL LEPIDOMATA, INCLUDING CANCERS OR CARCINOMATA.—The malignant or "atypical" analogues of the preceding group are usually somewhat unscientifically classified into—

i. **Epitheliomas,** when derived from skin and similar epithelial coverings.

ii. **Malignant Adenomas,** when derived from glandular structures.

The essential element of such tumours appears to be the proliferating epithelial or other varieties of lepidic cells, which "invade" or "infiltrate" the subjacent or surrounding tissues. The stroma or supporting connective tissue framework and vessels of the tumour are either those of the part invaded, or are formed by proliferation of these. The epithelium may show some, and frequently very marked, deviation from the original type in character or in arrangement. Thus, in scirrhus cancers the original glandular arrangement is largely lost, and the cells form solid groups or masses lying in spaces surrounded by dense proliferated connective tissue. Further, aberrations in the size as well as in the type of the cells are common, as are also various degenerative changes of a colloid, mucoid, or fatty nature. Myxomatous degeneration may occur in the stroma. On the other hand, the proliferated epithelial cells

may frequently retain—though often very imperfectly—certain of their original characteristics; for example, the arrangement in acini in the case of malignant adenomata, the presence of "prickle cells" in squamous epitheliomata, and so on.

Method of Growth.—As in the case of the preceding group, cancers may form excrescences and papillomatous outgrowths on a surface, or rounded or irregular nodules in the substance of the tissues. These points have been sufficiently dealt with in the chapter upon the general characteristics of tumours; and it need only be added that cancers may spread **locally**, mainly by infiltrating lymphatics; or may form **metastases** in distant parts, this spread occurring chiefly by way of the lymphatics, but also in some cases by the blood-stream.

VARIETIES OF CANCER

A. **SQUAMOUS EPITHELIOMA** (or **PAVEMENT-CELLED CARCINOMA**):—

These grow from the following situations:

i. **From the skin surface**, especially about the lips, anus, scrotum, penis, sites of old scars, etc.

FIG. 98.—Squamous Epithelioma of Lip, showing ulceration of the irregular warty-looking tumour, with raised indurated edges. (Edinburgh University Anatomical Museum. Catalogue No. T. C. a. 6.)

ii. **From mucous membranes** covered by stratified squamous epithelium, *e.g.* mouth, pharynx, larynx, œsophagus, vagina.

iii. **From the remains of the obliterated thyroglossal duct,** in some primary epitheliomata of the thyroid.

The proliferating squamous cells of the skin epithelium seem capable of growing wherever they can get nutriment, *e.g.* in lymphatics, and there may be very little connective tissue formation. As the cells grow, they tend to form layers corresponding more or less with those of skin epithelium. Towards the central parts of the cellular masses they may become compressed and flattened, and undergo horny degeneration or cornification, giving rise to the so-called "**cell-nest**" appearance,

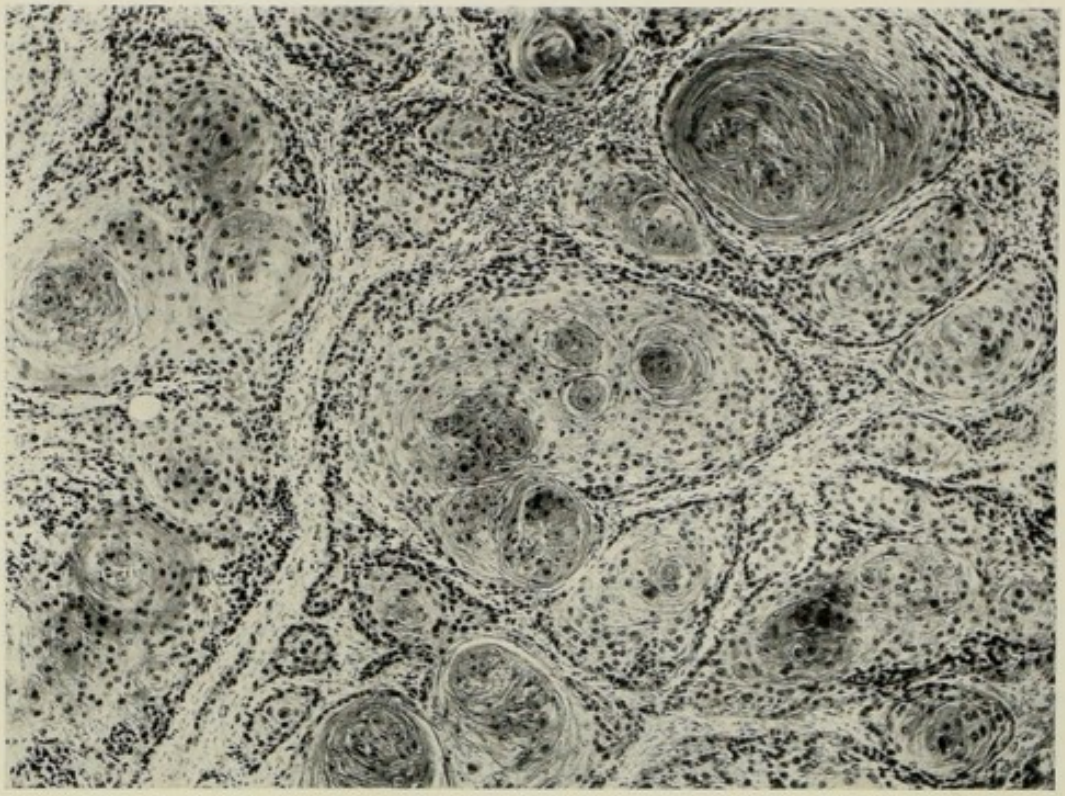

FIG. 99.—Squamous Epithelioma of Penis, showing infiltration of the deeper tissues with squamous epithelium, which at parts shows the characteristic "cell-nest" arrangement. ×50.

the peripheral cells corresponding to the deeper, more actively proliferating, formative layer of epithelium, and the central cells corresponding to the ordinary superficial layer — the stratum corneum. Sometimes, however, cornification does not occur to any great extent. As the masses grow, they infiltrate and compress the other tissues, they themselves also undergoing degeneration very readily. The connective tissue between the masses may be fibro-cellular, and may show leucocyte infiltration, and often a considerable degree of vascularity.

In the process of infiltration by such a tumour, the normal

relationship of the different layers is thus reversed, the condition being an invasion of the deeper by the more superficial elements—in contradistinction to what occurs in the outgrowth of a simple squamous papilloma, in which surface structures remain upon the surface, the normal relationship being preserved.

RODENT ULCER.—This epithelial tumour, which is most commonly situated about the upper part of the face, has a striking resemblance in its histological structure to the epitheliomata. Irregular papilla-like masses of epithelial cells

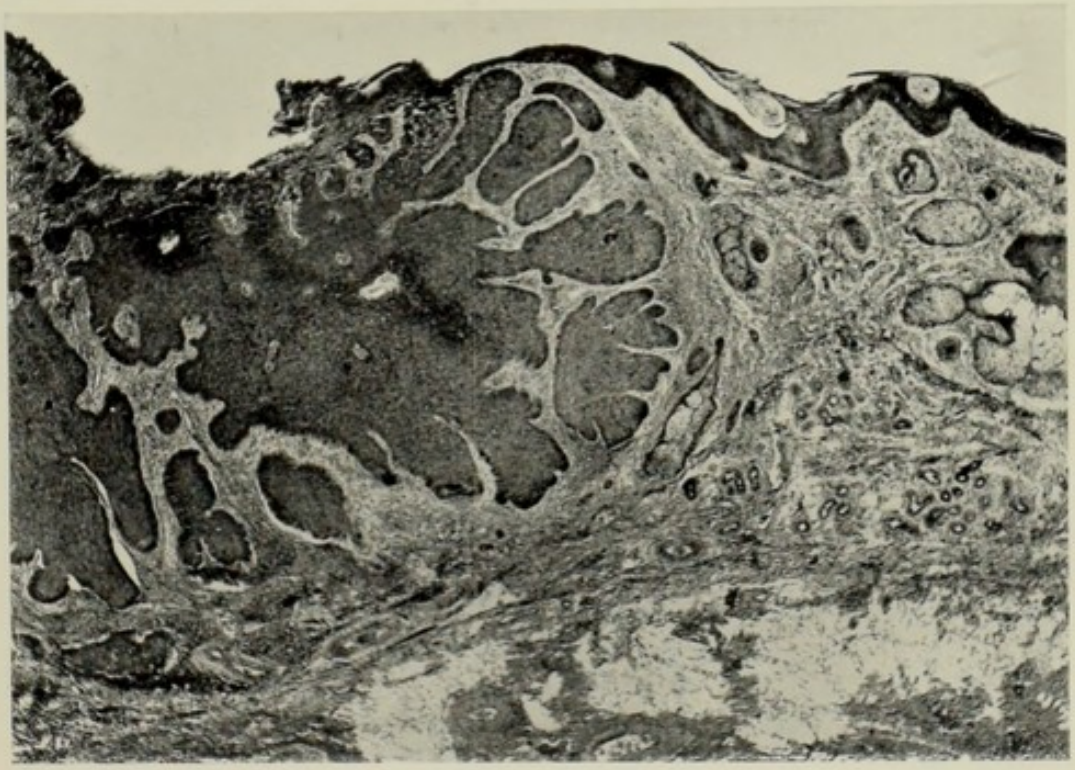

FIG. 100.—Rodent Ulcer of Eyelid, showing papilliform down-growths of epithelium infiltrating the deeper tissues. (Towards the right are seen several normal sebaceous glands.) ×25.

are seen passing downwards in various directions through the cutis and subcutaneous tissues. The cells are cylindrical in type, and usually stain deeply. They are generally smaller than those of epitheliomata, and are not so clearly separated into distinct layers. There is no tendency to cornification or to the formation of cell-nests, and there is no sufficient evidence as to the epithelium from which they originate,—some authorities, however, holding that they arise from that of the sebaceous glands. They always occur near the surface, and ulceration is usual. There is no tendency to metastases.

B. **GLANDULAR CANCERS**, or **MALIGNANT ADENOMAS**:—

These may retain some of the general glandular arrangement, *e.g.*, in acinar or duct-like spaces, as in malignant adenoma;

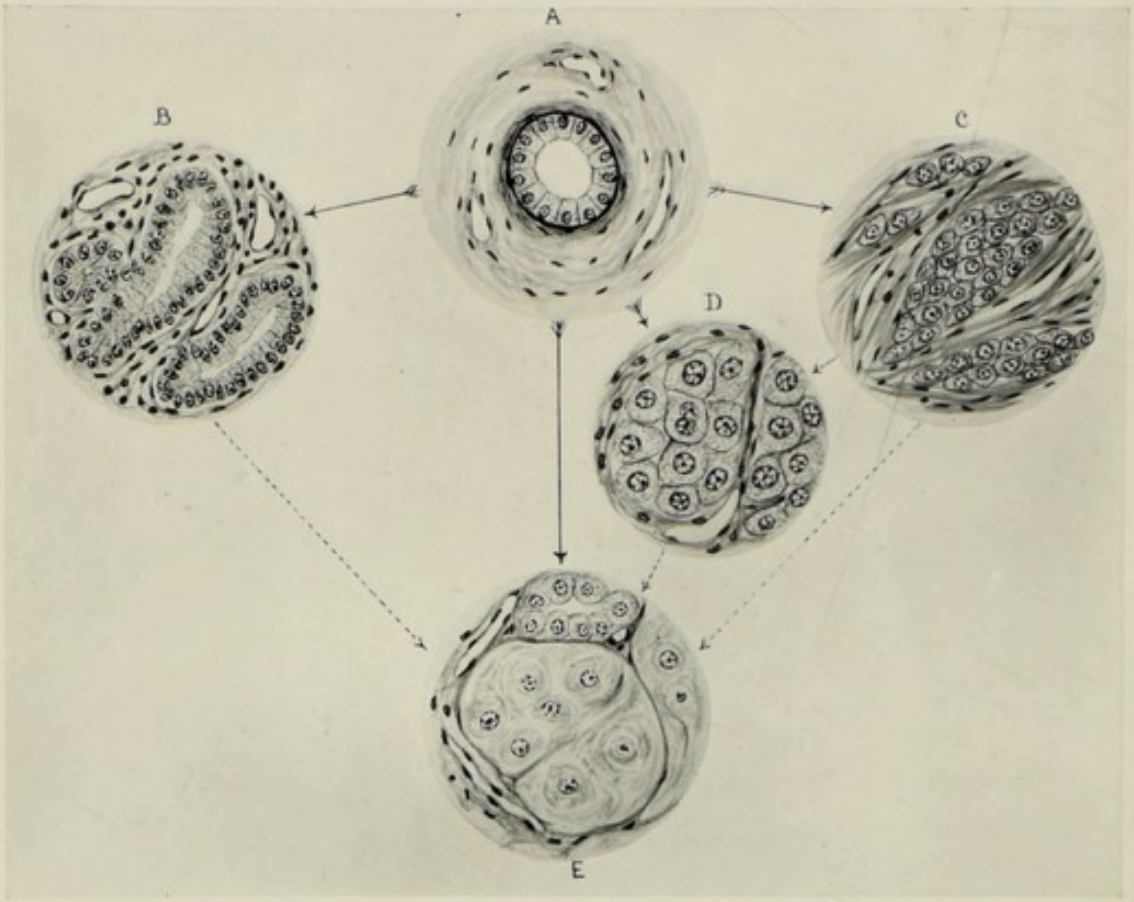

FIG. 101.—Schematic representation of the *varieties of cancer which may arise from glandular epithelium.*

A. Transverse section of *Normal Gland Acinus* consisting of regular epithelium upon a basement membrane, surrounded by a connective tissue stroma containing nutrient vessels. This may give rise to any of the following types of new growth.

B. *Malignant Adenoma*, with irregularity in shape of acini, the lumen of which persists. Absence of basement membrane. Irritation giving rise to proliferative overgrowth, etc., of stroma.

C. *Scirrhus* or *Hard Cancer*, in which solid clumps of cells are formed, and give rise to dense fibrous tissue overgrowth.

D. *Encephaloid* or *Soft Cancer*, which may arise directly, or may supervene upon the harder variety, the two resembling one another in being composed of solid clumps of cells.

E. *Colloid Cancer*, which may arise directly from the normal gland type, or may supervene upon any of the other forms.

or the cells may form solid masses among the fibrous tissue, without definite arrangement, as in the scirrhus and encephaloid varieties; or they may show abnormalities in size, structure,

etc., as in encephaloid cancer, or degenerative changes as in colloid cancer.

VARIETIES OF GLANDULAR CANCER:—

1. **MALIGNANT ADENOMA**, or **ADENO-CARCINOMA** (also called *Adenoid Cancer*, *Duct Cancer*, *Columnar-celled Epithelioma* or *Carcinoma*), where the general glandular arrangement of the epithelium in acinar spaces, etc., is preserved. In the case of

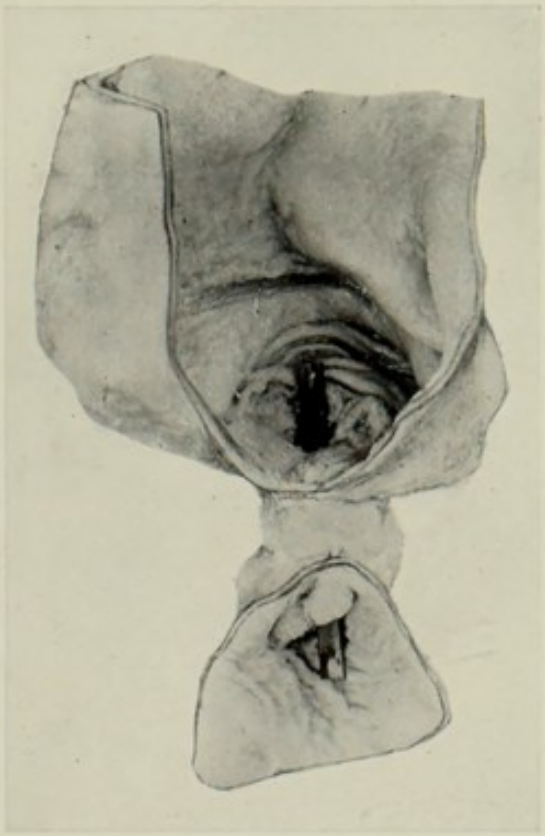

FIG. 102.—*Malignant Adenoma* of the large intestine producing great narrowing —the so-called *Malignant Stricture*. Note dilatation, hypertrophy and ulceration above, and atrophy below the seat of stricture. (Edinburgh University Anatomical Museum. Catalogue No. Al. E. l. 13.)

malignant adenomata arising from glandular organs which do not possess a tubular structure (*e.g.* the liver), the arrangement of epithelium characteristic of the gland may be reproduced, usually in a more or less aberrant fashion. This is well illustrated in the case of primary malignant adenomata of the liver or "liver-celled cancers," in which the epithelial cells are arranged in irregular columns, though an anaplastic tendency to the development of an acinar structure may occur in some cases.

Sites.—Intestine, and, more rarely, the stomach; the ducts

of acinar glands, such as the breast, salivary glands, pancreas, bile ducts, etc. etc.

Microscopical Structure.—The cells are arranged in alveoli or tubes, often very irregular in shape and size, lined by columnar, or in some cases cubical, epithelium — usually

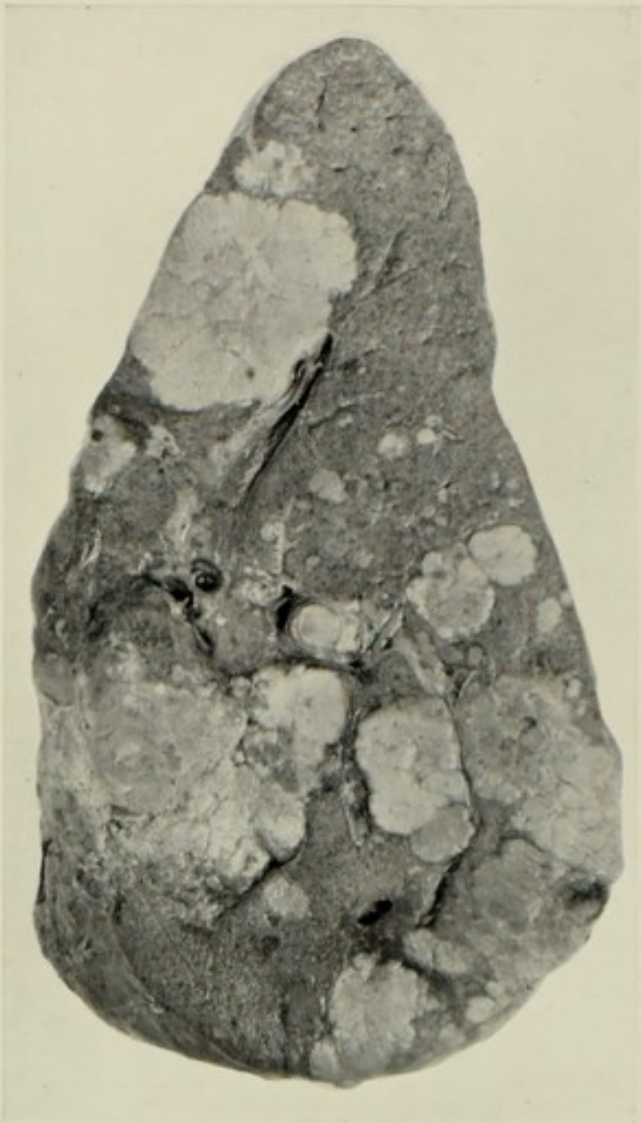

FIG. 103.—*Primary Malignant Adenoma of Liver* or *Liver-celled Cancer* (in which the epithelial cells are arranged in irregular columns resembling those of the liver).

arranged in a single layer. The stroma generally consists of delicate connective tissue, which is often very cellular, and may exhibit the variations and degenerative changes common to all cancers.

The histological distinctions between malignant and simple

adenomata are often difficult and only relative. In malignant cases, there is usually (i) infiltration at the margins, and absence of a definite capsule ; (ii) absence of any basement membrane ; and (iii) evidence of increased activity in cell-division, and greater aberrations in the size and shape of the cells and cell-

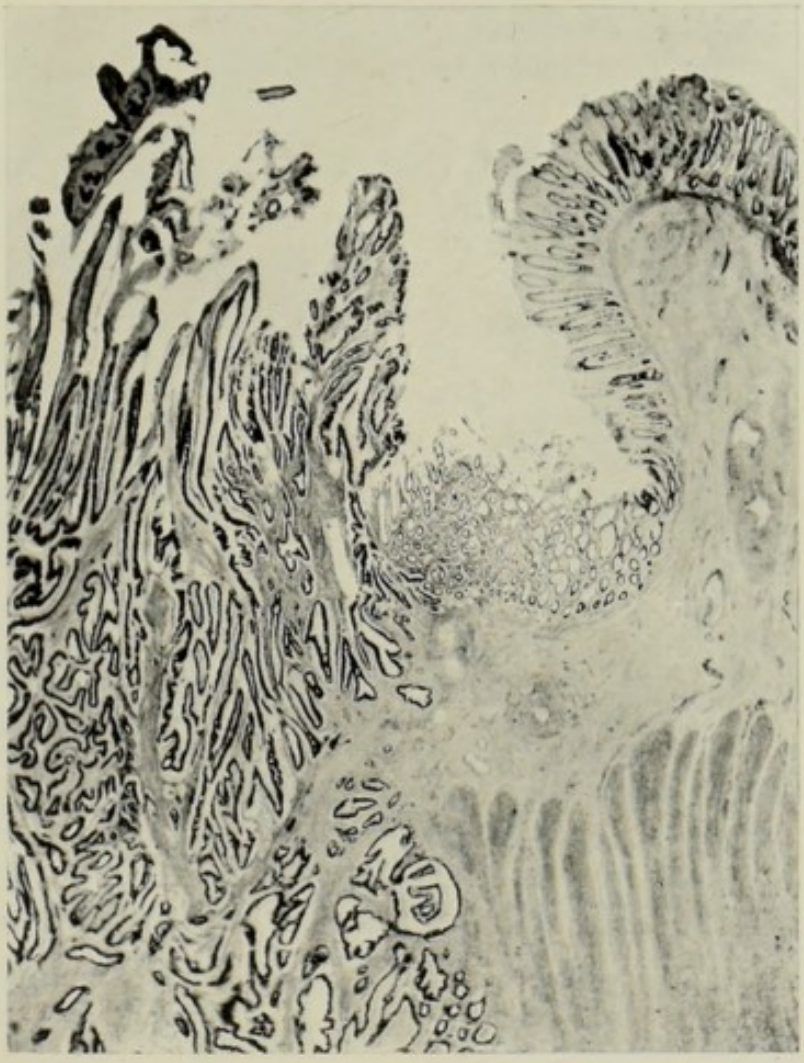

FIG. 104.—Malignant Adenoma. Primary growth in large intestine. Towards the right are seen the normal mucous, submucous, and muscular coats of the bowel. Towards the left are the large, irregular tube-like acini of the new growth, lined by large dark-staining columnar epithelium. Infiltration of the normal structures at the spreading margin is seen. × 10.

groups. The latter are often larger than they are in simple adenomata, and tend to be elongated and distorted, boring their way, as it were, along the lymphatic spaces and between the other tissue elements.

2. **SCIRRHUS** or **HARD CANCER** (*Spheroidal-celled Cancer*).—The density of these tumours is due to the slowness of their

growth, and to the great irritation produced by the cells boring their way into the tissues, and the consequent production of a dense fibrous stroma (figs. 106–8).

Sites.—These tumours are specially common in the mammary gland, and may also be found in the stomach, intestine, ovary, testicle, prostate, kidneys, salivary glands, etc.

Microscopical Structure.—The cells lose their glandular arrangement, and are found in solid masses or clumps, varying

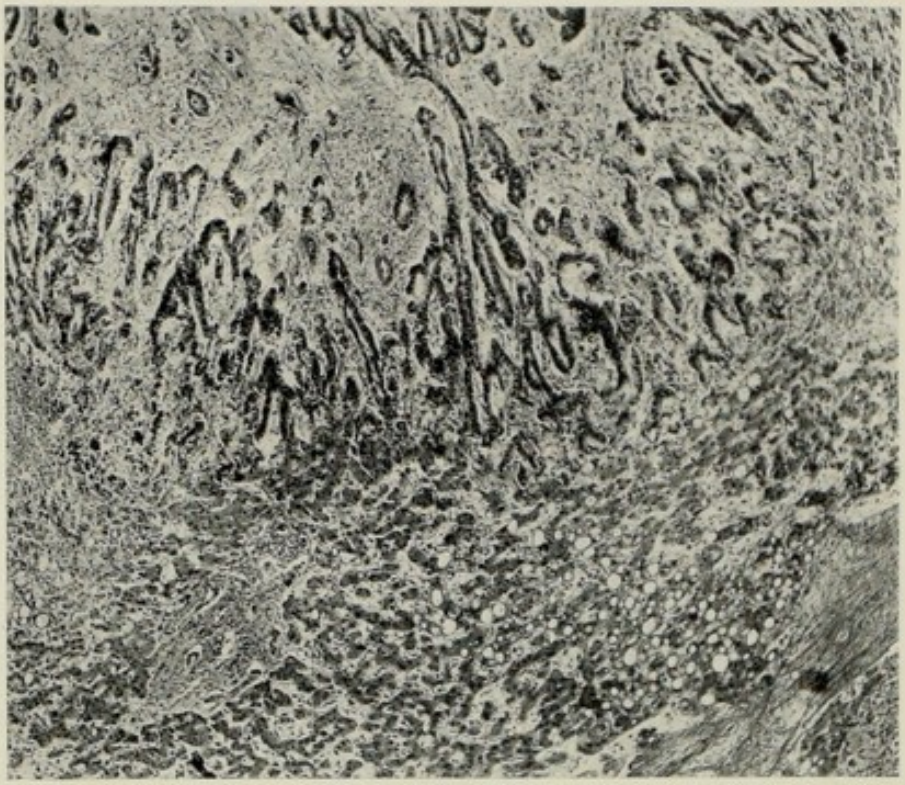

FIG. 105.—Malignant Adenoma. Secondary nodule in liver (Primary growth was in large intestine). Shows infiltration of normal tissues at margin and absence of capsulation. The liver tissue (in the lower part of the section) shows some fatty infiltration. ×50.

greatly in size and shape, and surrounded by a dense fibrous tissue stroma, which may resemble that of cicatricial tissue, with perhaps here and there somewhat more cellular areas, and areas showing "small-celled infiltration" with lymphocyte-like cells. Occasionally there may be an abortive attempt at the formation of a lumen in some of the cell masses.

3. **ENCEPHALOID** or **SOFT CANCER.**—In this variety of tumour, growth is more rapid.

Sites.—These tumours are found specially at the cardiac end

of the stomach, and in other parts of the digestive tract, in the breast, pancreas, liver, and other glandular organs.

Microscopical Structure.—In general structure these tumours resemble scirrhus cancers, but the spaces tend to be considerably larger, and the cells usually show great variety in shape and size, being often large, and exhibiting a marked tendency to degeneration. Cell-proliferation in these neoplasms is usually extremely rapid, and numerous mitotic figures are very frequently to be observed, especially at the spreading edges. These mitotic figures are sometimes abnormal in character, and may show, for example, multipolar division, inequality in the number of chromosomes in the daughter nuclei, etc. (see p. 19). The tumour cells are often very actively phagocytic, and may englobe leucocytes, red blood corpuscles, and other cells, in great numbers (fig. 110).

4. **COLLOID CANCER.**—So named from the tendency of the cells to undergo rapid colloid degeneration.

Sites.—Stomach, intestines, mammary gland, and other situations in which encephaloid cancers and malignant adenomata are found. Wide-spread secondary involvement of the peritoneum or pleura may occur in such cases.

FIG. 106.—*Scirrhus Tumour of Breast*, showing dense bands of tumour growth radiating from the nipple, which is retracted. The specimen has been treated with nitric acid (Stiles' method), the tumour being stained dark, whilst the normal fat remains pale in colour. (Edin. Univ. Anat. Mus., Catalogue No. Gen.-U. R. f. iv. 10.)

Microscopical Structure.—Colloid degeneration may supervene on any of the other types of cancer, especially the encephaloid and some of the malignant adenomatous varieties. The structure, therefore, largely depends upon the nature of the original tumour in which the change has occurred,

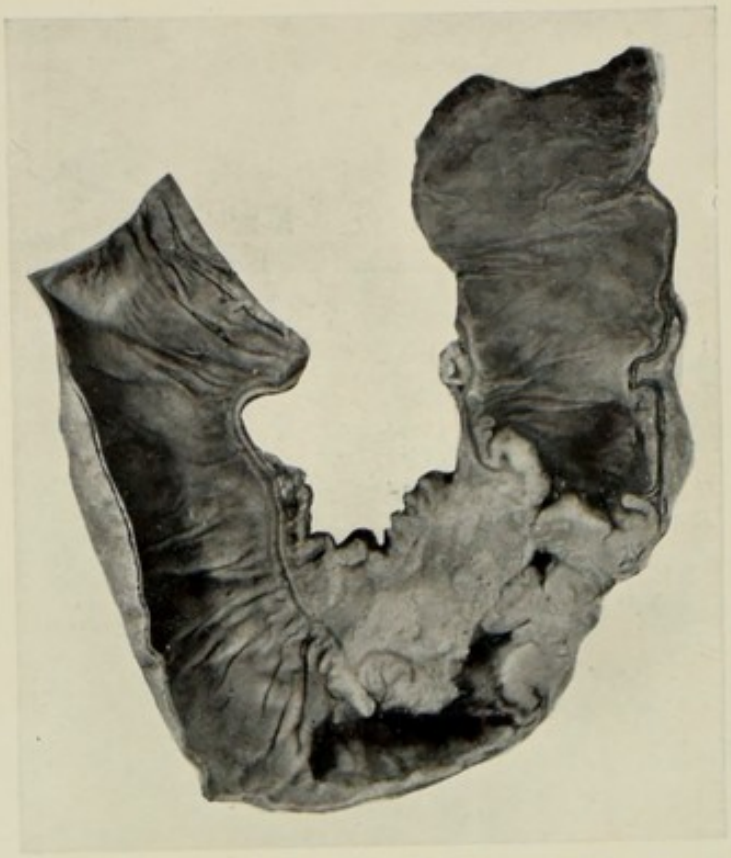

FIG. 107.—*Scirrhus* or *Hard Cancer of Intestine*, producing obstruction of lumen. (Royal College of Surgeons Museum, Edin.)

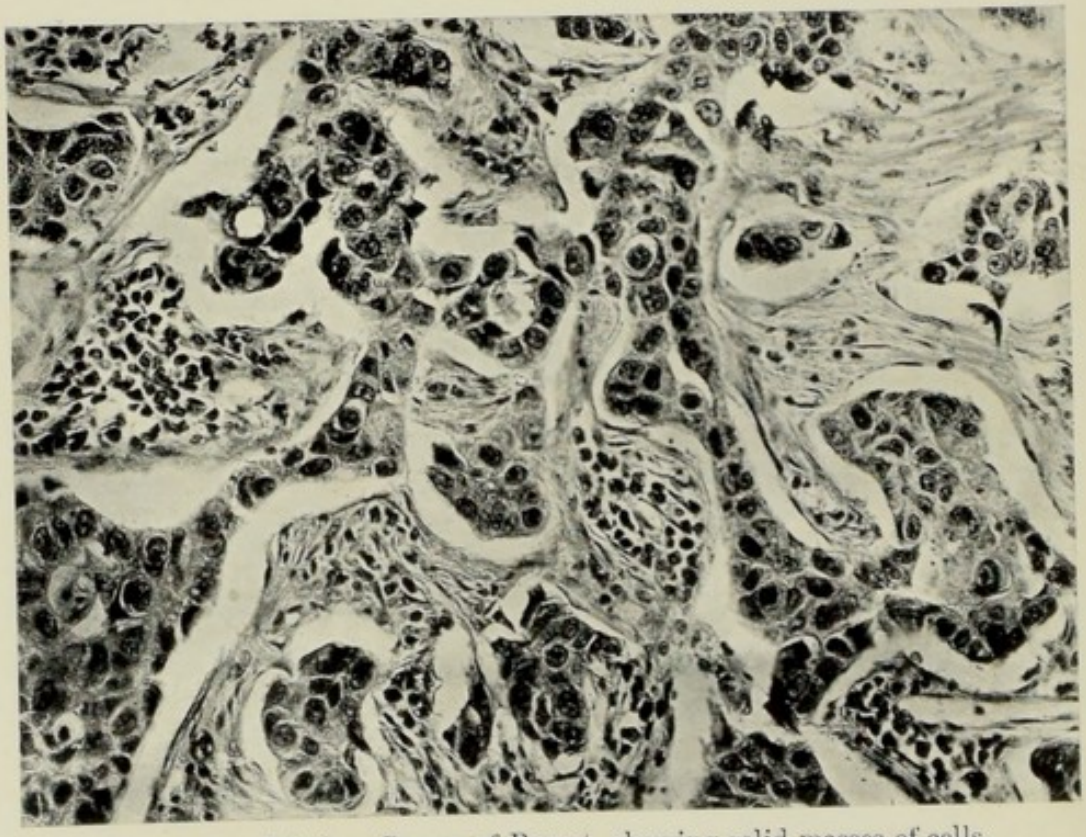

FIG. 108.—Scirrhus Cancer of Breast, showing solid masses of cells among dense fibrous tissue. ×200.

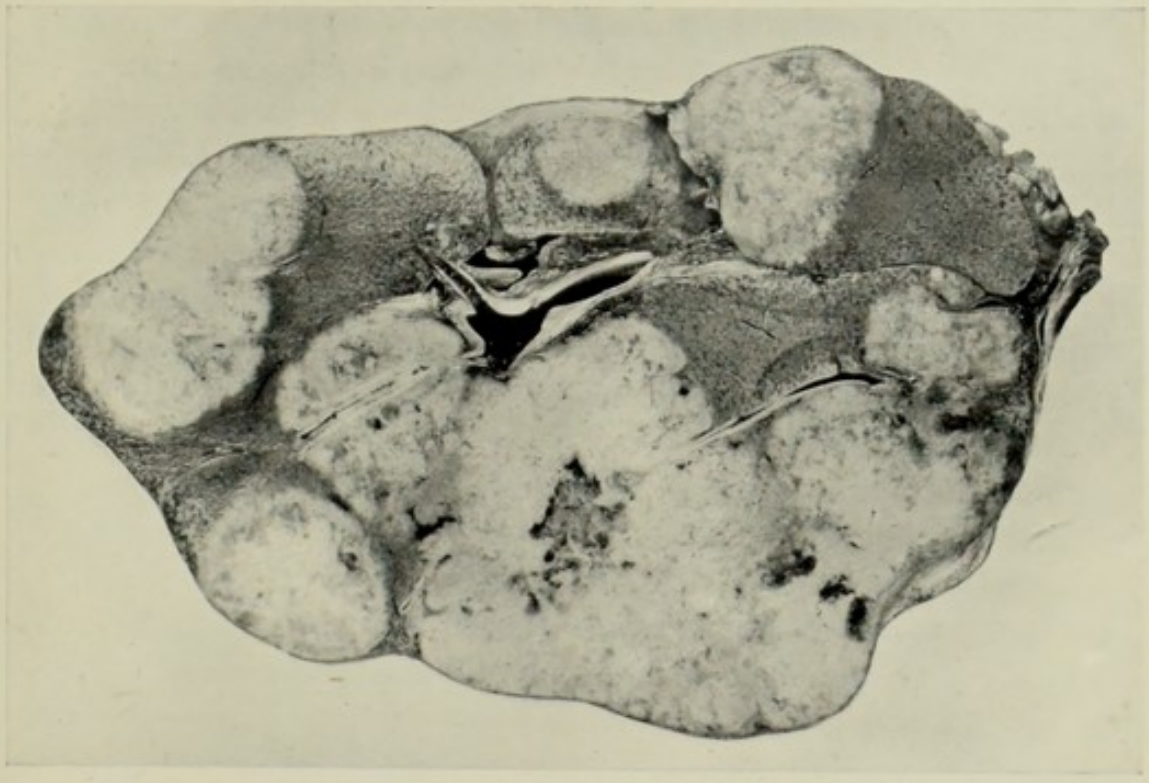

FIG. 109.—*Encephaloid Cancer.* Secondary nodules in liver. The large nodule shows central necrosis.

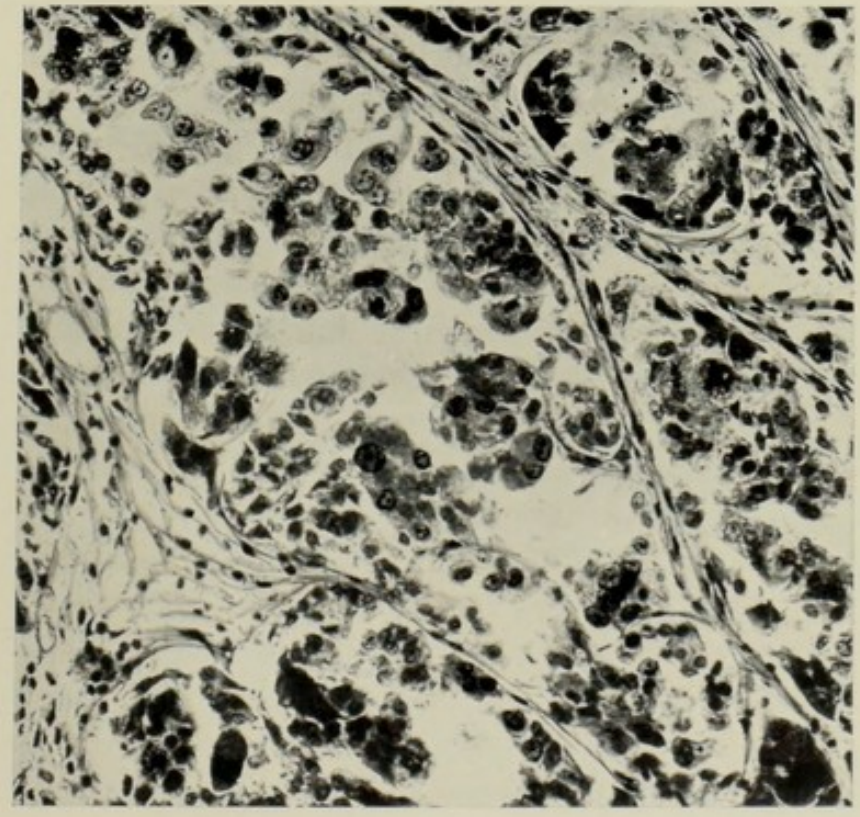

FIG. 110.—Encephaloid or Soft Cancer, showing larger spaces and looser arrangement than in scirrhus.

though in some cases the process of colloid transformation may be present from the first, or at all events may supervene extremely early. Colloid cancers usually present large spaces which may be lined by a layer of cells undergoing the colloid change; or the degenerating cells may be scattered irregularly throughout the colloid material filling the spaces. These spaces are formed in the loose, often œdematous, fibrous tissue, and contain the colloid material formed by the breaking down of the epithelial cells, the degenerating remains of which may usually be seen scattered among it.

5. Certain rare forms of carcinoma, such as **Melanotic Cancer** (*e.g.* growing from skin, the pigment being generally situated in the stroma), "**Telangiectatic**" or "**Vessel-dilatation**" **Cancers**, may perhaps be more accurately included among the Secondary Lepidomata, to which allusion has been made on pp. 273 and 276.

MALIGNANT ENDOTHELIOMA (see p. 302).

TERATOMATA

(including **Placentoma**)

The **Teratomata** have been defined above as tumours which arise from the inclusion of one individual, or the germ-cell or the products of the germ-cell from which that individual would in ordinary circumstances have been developed, within the tissues of another individual of the same species. They may vary from the teratomatous "dermoid cyst," composed of little but ectodermic structures, *e.g.* skin epithelium, sebaceous and sweat glands, hair, teeth, etc.—or, in other cases, in addition to these structures, bones, cartilage, muscle, and even rudimentary viscera, etc.—up to the *fœtus in fœtu* of Meckel. The nature of these has already been discussed on p. 261.

PLACENTOMA, CHORIONEPITHELIOMA, DECIDUOMA, or **SYNCYTIOMA MALIGNUM**, is a form of tumour which stands alone, in that, according to the most recent researches, it is derived from the fœtal syncytial layer of the placenta which proliferates and invades the tissues of the mother. There is also proliferation of the smaller cells from the epithelial covering of the chorionic villi (Langhans' cells). Deciduoma Malignum may supervene at the placental site either after a full-time

pregnancy or an abortion, or in many cases after the expulsion of a "hydatidiform mole." It forms rapidly growing, irregular, soft, spongy, highly vascular masses, which readily break down and give rise to hæmorrhages. It is extremely malignant, and not only invades the walls of the uterus and Fallopian tubes locally, but gives rise to numerous metastases in distant parts, *e.g.* in the lungs, liver, kidney, etc., the spread being usually embolic, and due to the invasion of the uterine veins. A few cases have been described in which no primary growth could be found in the uterus or tubes, the secondary growths arising in these cases apparently from single or small groups of syncytial cells which have become broken off and disseminated by blood-vessels or by lymphatics. Microscopically, two classes of cells are seen irregularly intermingled with one another in varying proportions in different cases, and invading the tissues of the organ in which the tumour is growing. These are—

(1) Large, irregular, plasmodial masses derived from the syncytium, sometimes multinucleated, at other times with a definite cell-outline and a single nucleus; and—

(2) Groups of small polyhedral cells, with very definite cell-outline and a simple nucleus. These are derived from Langhans' layer; and, although they are probably not the essential tumour cells, they always show proliferation.

A very important feature of such cases of chorionepitheliomata lies in the fact that, although they resemble a very highly malignant type of neoplasm, yet, in certain cases, a process of natural healing or spontaneous cure may occur in the secondary tumours after the removal of the primary seat of the disease.[1]

[1] Teacher, "On the Development and Natural Healing of Secondary Tumours of Chorionepithelioma," *Journal of Pathology and Bacteriology*, Cambridge, 1907, vol. xii. p. 131.

APPENDIX TO SECTION ON TUMOURS

(see footnote, page 308)

SYNOPSIS OF VARIETIES OF CYSTS :—

1. **TRUE CYSTIC TUMOURS** or **CYSTOMAS**, arising from the proliferation of glands, mucous membranes, etc., *e.g.* cystic tumours of the thyroid, pituitary, ovary, kidney, etc.
2. **CYSTS ARISING FROM DEVELOPMENTAL ERRORS:**
   (*a*) **From embryonic intermingling**, *e.g.* sebaceous and other cysts, hygromas, etc., arising at the lines of closure of embryonic clefts, or in the middle line (spina bifida, meningoceles, encephaloceles, etc.); and the results of other accidental intermingling or inclusions.
   (*b*) **Congenital Cysts**, due to the persistence and distension of fœtal structures which should normally become obliterated, *e.g.* :
      i. **Urachus.**
      ii. **Remains of Wolffian Duct** (this in the **male** develops into the canal of the epididymis, vas deferens, vesicula seminalis, and common ejaculatory duct; in the **female**, into the longitudinal duct of the parovarium and the hydatids of Morgagni. In **both sexes** it also gives rise to the ureter, pelvis, and tubules of the kidney).
      iii. **Remains of Müllerian Ducts** (from which are normally developed the Fallopian tubes, uterus, and vagina in the **female**; and the hydatids of the epididymis and the utriculus masculinus in the **male**).
      iv. **Remains of the Mesonephros** — part of the primitive excretory organ—from which are developed the vasa efferentia, ductuli aberrantes, and the tubules of the paradidymis (organ of Giraldés) in the **male**; and the rudimentary tubules of the parovarium (epoöphoron) and of the paroöphoron in the **female**.
      v. **Thyroglossal Duct**, etc.
   (*c*) **Teratomas**, *e.g.* "dermoid cysts" due to the inclusion of a so-called "blighted ovum," or possibly of a germ cell.
3. **CYSTS ARISING FROM SEROUS CAVITIES**, *e.g.* from bursæ and tendon-sheaths. Pouch-like dilatations of the latter ("ganglion") may result from injury or may be proliferative. The so-called "loose bodies" in bursæ and joints usually arise from the separation of papilliform ingrowths, which may in some cases undergo degeneration and become calcified. Some cysts may also arise as diverticula from

serous membranes, *e.g.* from the pericardium, pleura, or from the lining of the cerebral ventricles.

(The "common bunion" is a false bursa with thickened connective tissue walls, which arises opposite the first metatarso-phalangeal joint as the result of pressure.)

4. **RETENTION CYSTS** due to the blocking of glandular ducts or tubules by inspissated and retained secretion, calculi, etc.; for example, pancreatic cysts brought about by obstruction of the pancreatic duct or of one of its branches by calculi due to calcified mucus; "ranula," or a cystic dilatation due to the blocking of the duct of a salivary gland; cysts in the kidney due to the blocking of tubules at some part of their course by the contraction of fibrous tissue around them, or to the presence of colloid casts, etc. in their lumen.
5. **DISTENTION CYSTS**, *e.g.* arising from the distention of bursæ, or of the normal cystic spaces of the thyroid or pituitary gland, etc.
6. **SPURIOUS CYSTS** or **PSEUDOCYSTS**; for example, those due to mucoid degeneration, or hæmorrhages which may then become encapsulated. These are common in tumours, *e.g.* in gliomas and in sarcomas, but may also follow hæmorrhage elsewhere — hæmatomas or blood-cysts, such as are sometimes found between the dura mater and the skull, in the brain, etc. All hæmatomas are not necessarily spurious cysts; for example, in the case where hæmorrhage occurs *into* a true cyst. Pseudocysts are also of common occurrence in chondromas.
7. **PARASITIC CYSTS**; for example, hydatid cysts in the liver due to the cystic stage of the *Tænia echinococcus*; coccidial cysts, common in the rabbit's liver, due to the *Coccidium oviforme*.

GRANULOMATA

These are a group of pathological conditions in which the lesions are the result of subacute or chronic inflammatory changes, associated with various protective and reparative processes. They may produce considerable masses which in many respects resemble tumours. All of these lesions, however, are **infective** in nature, and the specific virus has in the majority of them been determined. Further, they are almost always accompanied by various toxic conditions, *e.g.* fever, wasting, amyloid and fatty degenerations, etc. These so-called **granulomata** or **granulation tissue "tumours"** are seen especially in cases of **Tuberculosis, Leprosy, Syphilis, Glanders,** and **infections with various forms of Streptothriceæ.** An allied condition, in which an infective virus has not yet been discovered, is seen in **Lymphadenoma** or **Hodgkin's disease.** As we propose dealing only with the pathological aspect of these diseases, we must, for full descriptions of the morphology, cultural and staining characteristics, etc., of the organisms concerned, refer our readers to text-books on Bacteriology.

I. **TUBERCULOSIS.**—The causal agent of this condition is the *B. tuberculosis*, discovered by Koch. This organism can generally be demonstrated in the various foci of the disease, and, at one time or other, in the development of the lesion, it is present in an active condition. The number of organisms in any given infected area varies considerably; and in some of the very chronic lesions, the organism, although probably in many cases still present, may not be demonstrable. According to the most recent observations, it is clear that tuberculosis in the human subject may be caused either by the bacillus most commonly found in the pulmonary forms of the disease in man—the **human** bacillus; or by the organism found in the disease in cattle—the **bovine** bacillus. Experimental evidence also shows conclusively that many of the lower animals can be infected by means of either form of the bacillus. The organism gains an entrance into the body by various means. Probably one of the commonest is by **inhalation** of dried bacilli, derived from any source, *e.g.* from the dried-up sputum of tuberculous

patients. These bacilli may pass directly to the trachea, larger bronchi, or lungs, or they may be arrested by the moist surfaces of the tonsils or other adenoid tissue of the naso-pharynx, and may then infect neighbouring glands. The bacilli can frequently be demonstrated in the **tonsils**, especially in cases where the cervical glands are involved. The affection of the **lymphatic glands** is, at any rate in children, commoner than that of the lungs. **Ingestion of** tuberculous material is also a fruitful

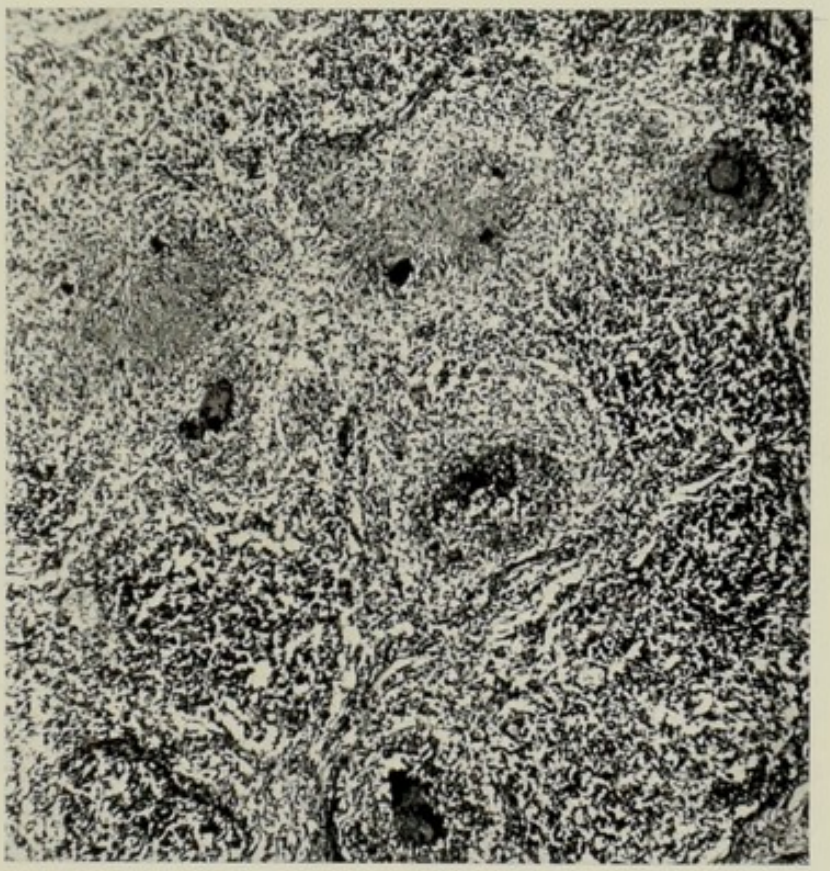

FIG. 111.—Lymphatic Gland, showing tubercle follicles with caseation and giant-cells. × 50.

source of infection. In some cases the tonsils and the pharynx may be affected, but the commoner sites are the intestines and the mesenteric glands. The stomach is rarely involved, though the gastric juice does not kill the organism. The bacilli may pass directly through the wall of the small or large intestine; and the mesenteric glands may become tuberculous without the coats of the intestine being affected. In this way, many of those cases of **tabes mesenterica** in children, in which there is no ulceration of the intestine, are to be explained, as are also some

of those cases, in young adults, where the primary site of infection is apparently the glands in the neighbourhood of the cæcum—the bacilli in these cases passing directly through the wall of the cæcum. In other cases, the walls of the intestine show ulceration in a more or less marked degree. The infection of the intestine and mesenteric glands is common in young children, and especially in those who have been fed largely on cows' milk, and in these cases it is very commonly the bovine bacillus that is present. Intestinal tuberculosis may also occur as the result of the swallowing of sputum by patients suffering from the pulmonary form of the disease.

Infection by means of **abrasions or wounds of the skin** is not common, though *post-mortem* warts, and perhaps also lupus, arise in this way.

There are many cases of the disease, especially in bone or in the brain, where the mode of infection is not at all clear. In some of these, there is probably a spread from the lymph glands by means of lymphatics ; but in other cases, the blood must be regarded as the vehicle by which the bacilli are carried to various parts. This is especially the case in some affections of bones and joints, and in tuberculosis of the testicle ; and in these cases, there is very commonly some local cause determining the site of attack, *e.g.* previous injury or weakness. Where infection is transmitted from mother to child, it has been common to regard the condition as **hereditary** ; but we cannot, with all the evidence before us, consider heredity as anything more than an inherited **predisposition**. The bacillus gets access to the child either by one or other of the methods already described, by the mother's milk, or by direct transmission through the placenta.

Extension of local tuberculosis in the body.—A focus of tuberculosis, once established, has a tendency to spread indefinitely. This spread may be by a direct infiltration of the surrounding tissues, as seen in lupus, or by passage to various parts along the lymphatics, even in a direction opposite to that of the lymph flow. In cases of pulmonary tuberculosis, tubercles may be found in the lymphatic vessels in the lung, as well as in the bronchial glands. Tuberculosis may also be spread along air or other natural passages, along surfaces, and by way of the walls of the blood-vessels or of the blood-stream.

Thus, tuberculous disease of the lung is frequently associated with tuberculosis of the bronchi, trachea, or larynx, or tuberculosis of the intestine; and these lesions are due to the infected material lying constantly in contact with the mucous membranes of these passages. This spread along natural passages is specially well illustrated in cases of genito-urinary tuberculosis, where the disease, starting in the testicle, may extend the whole length of the vas deferens to the vesiculæ seminales and the urinary bladder, and sometimes up the ureter to the kidney.

Again, tuberculosis in the pleural, pericardial, or peritoneal cavities may involve the whole of their serous membranes merely by the bacilli coming in direct contact with these; or the neighbouring glands may become involved by the passage of the bacilli along the lymphatic channels.

Spread by the blood-stream is not so common, but may occur where tuberculous foci ulcerate and open into arteries or veins. Portions of the infective material may become detached and be carried to various organs or tissues, or the spread may take place along the walls of the vessels, or, more especially, along the perivascular lymphatics.

The effect produced by the introduction of the *Bacillus tuberculosis*, or of tissues containing it, into susceptible animals. —These can be well studied by injecting the bacilli into the peritoneal cavity, into the anterior chamber of the eye, or into the liver through a mesenteric vein, as was done by Miller.[1] As the changes are practically identical in whatever focus the bacilli become lodged, it will be sufficient to study them in one situation—the peritoneum.

A preliminary polymorphonuclear leucocytosis, lasting about two days, takes place; and though bacilli may be found englobed by these cells, the most actively phagocytic cells do not appear till a later period. These are mononucleated cells, which are found free in the peritoneal fluid in considerable numbers from the third day onwards, and persist till the death of the animal. They may contain large numbers of ingested bacilli. If the omentum be examined, the bacilli are found lodged in separate foci, and at these points, even in twenty-four hours, mitosis and proliferation of the fixed cells are seen. This proliferation

[1] Miller, James, *Jour. Path. and Bact.*, Nov. 1904, p. 1 *et seq.*

increases, and in from three to five days there is a distinct cellular zone surrounding the bacilli. These cells are rounded or oval, with a vesicular nucleus and with abundant cytoplasm. In some of their characteristics they resemble epithelial or endothelial cells, and have therefore been called the **epithelioid** cells. They are almost certainly derived by a local proliferation from endothelial cells, and possibly from fixed connective tissue corpuscles; though some observers maintain that they are

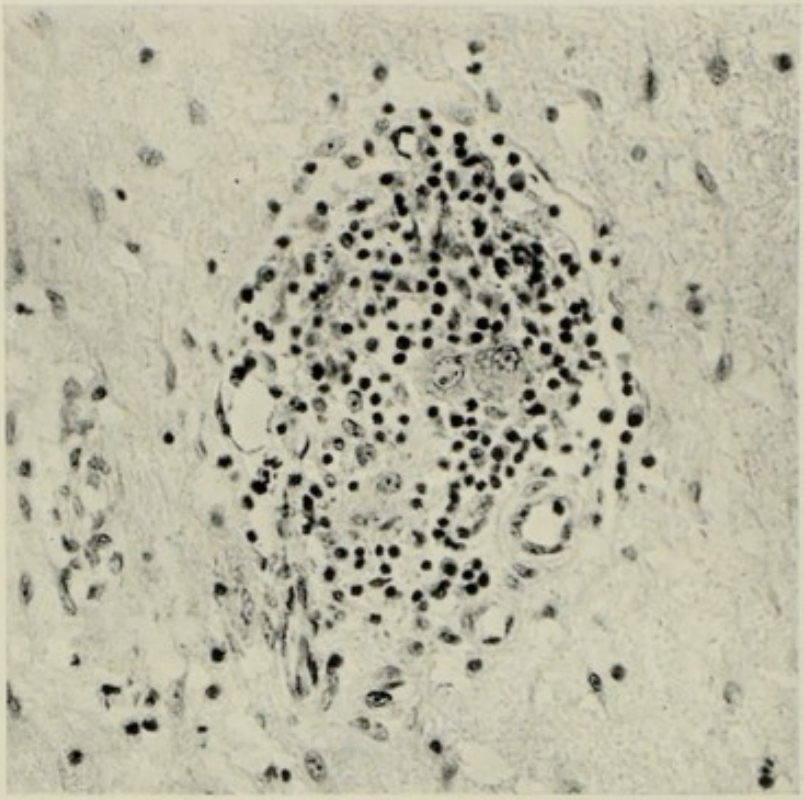

Fig. 112.—Early tubercle nodule from Knee-joint, showing epithelioid cells and lymphocytes. × 300.

derived from the mononuclear cells of the blood. In these cells the bacilli may be found, and are often so numerous as to suggest a local multiplication within the cell-protoplasm.

In from six to ten days these **tubercle follicles** become surrounded by a zone of small round cells, each with a darkly staining nucleus which almost completely fills the cell. These **lymphoid cells** are derived partly by proliferation of local fixed cells, but great numbers of them migrate to the focus from the lymphatic and the blood-vessels. At this stage, the blood shows a distinct increase in lymphocytes. Whether these lymphoid

cells can become epithelioid cells is a matter of doubt. With Miller,[1] we agree that transitions between the two kinds can be seen; but, as has been stated, the lymphoid cells are in part derived from fixed cells of the infected area, and it is possible that these, and these alone, become converted into epithelioid cells. The relative numbers of epithelioid and lymphoid cells vary con-

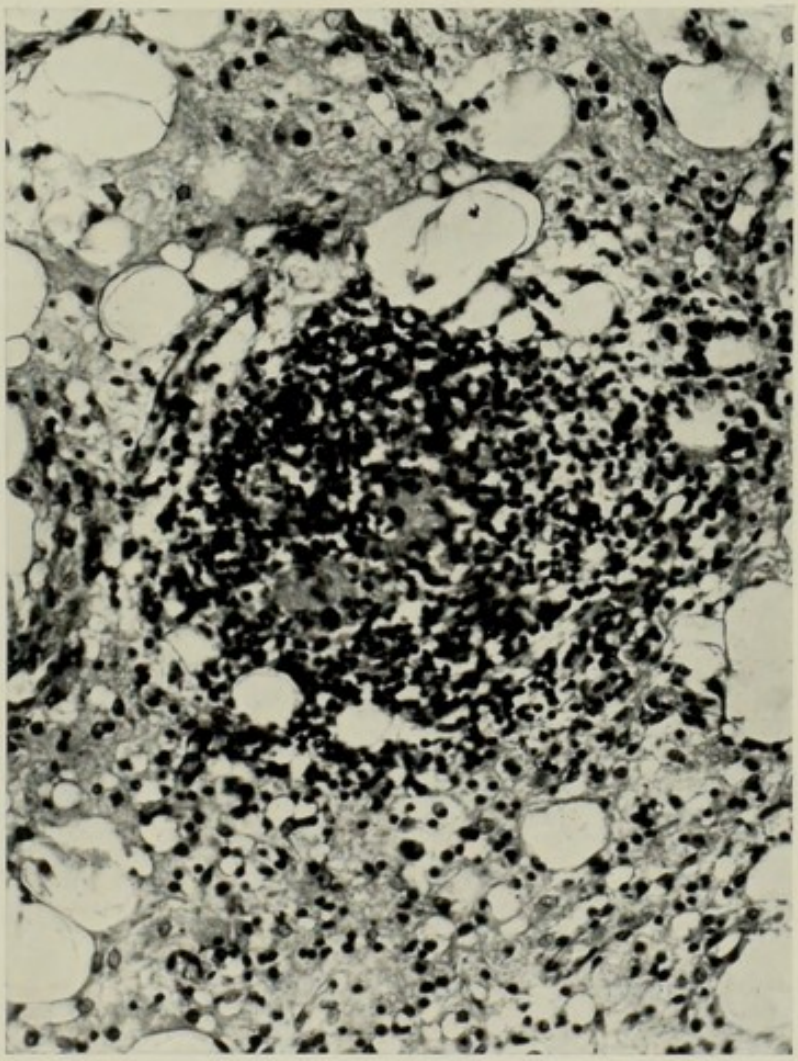

FIG. 113.—Early tubercle nodule from the Omentum, showing loss of outline of central epithelioid cells (caseation). ×200.

siderably in different cases and in different foci of the same case. In some, the epithelioid cells may be very scanty, whilst in others, the lymphoid zone may be scarcely marked. At this period, or usually somewhat later, *e.g.* in from eleven to fifteen days, certain more or less important, though not diagnostic, changes are seen in the follicles. The outlines of

[1] *Loc. cit.*

the epithelioid cells towards the centre of the follicle become indistinct, the protoplasm assumes a granular or "ground-glass" appearance, and the nuclei break up or become obscured. This process of **caseation** extends from the centre to the periphery, and in a short time there is produced a somewhat granular focus, in which cell-outlines and nuclear staining are completely lost, and which is surrounded by a zone of lymphoid or pro-

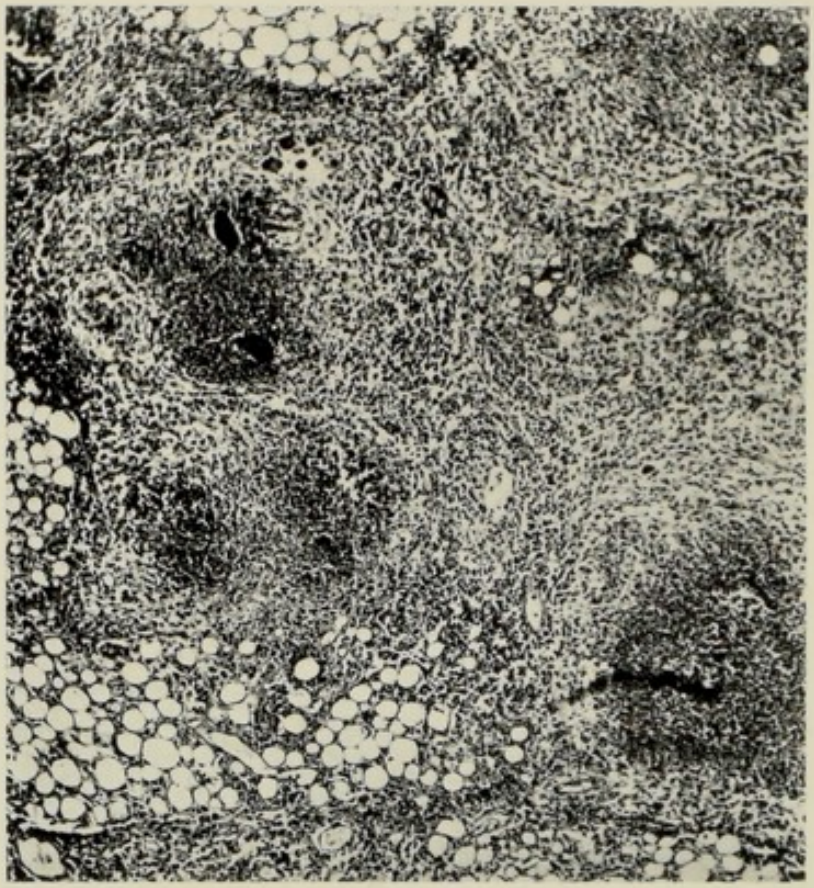

FIG. 114.—Tubercle nodules in the omentum, showing caseation. Giant-cells are seen, as dark oval bodies, in some of the nodules. ×100.

liferated connective tissue cells. In this caseous centre, bacilli may generally be demonstrated. In certain foci, and especially in those more slowly produced, large cells of irregular outline and having numerous nuclei, either scattered throughout the cell or arranged around the periphery, are seen. These are the **giant-cells**, and their protoplasm presents the same granular or ground-glass appearance as is seen in the central caseous mass. Bacilli may be found in these cells also. Various views as to their mode of formation have at different times been pro-

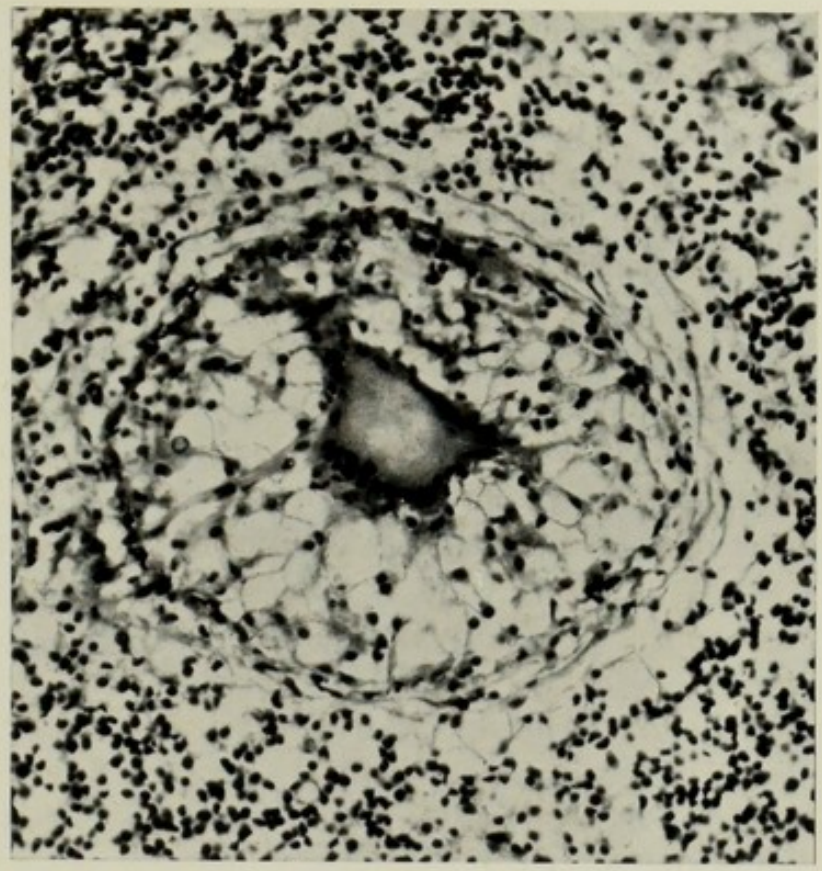

FIG. 115.—A "giant-celled system," showing giant-cell with central caseation, fibrous trabeculæ, and zone of lymphoid cells. ×200.

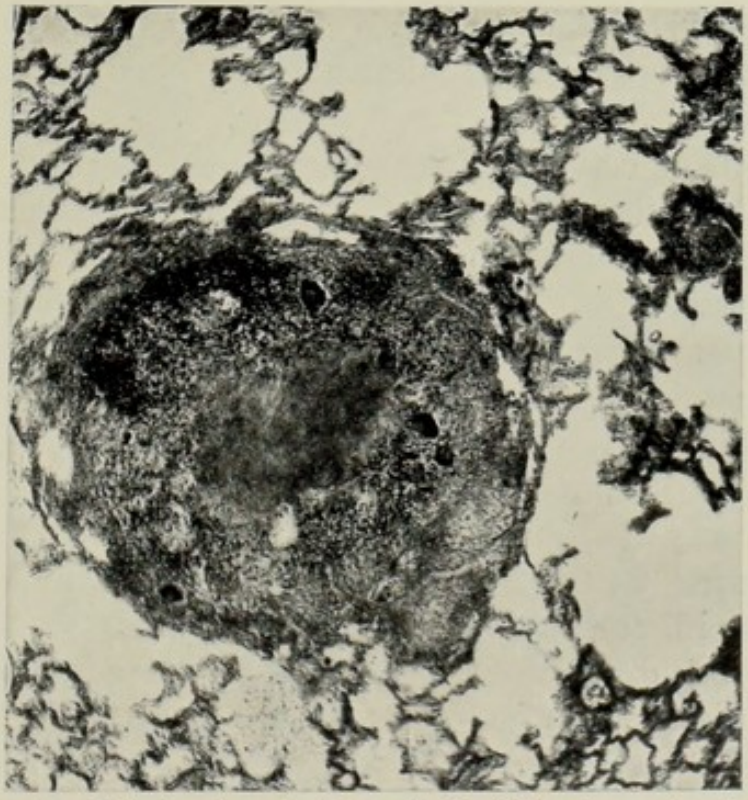

FIG. 116.—A nodule in chronic tuberculosis of the lung, showing central caseation, giant-cell formation, and peripheral fibrous tissue overgrowth.

pounded; but all recent work on the subject seems to indicate that they are formed either by a fusion of the epithelioid cells, or by a multiplication of the nuclei of these cells without corresponding division of their cytoplasm.

The degenerative change or caseation in the nodules is due largely to the action of the tubercle bacilli and their products; though, no doubt, the absence of vessels which have become obliterated during the process, probably by the swelling and degenerative changes in their endothelial lining, plays an important part. Larger areas are formed by fusion of these smaller ones, the central part often breaks down and liquefies, and becomes discharged, irregular cavities or ulcers being thus formed.

Very commonly, especially in the more chronic cases, proliferative changes of the nature of fibrous overgrowth take place in the neighbourhood of the nodules. In this way may be produced wide-spread interstitial changes, the focus of tuberculosis may be surrounded and completely shut in by dense fibrous tissue, and may become invaded by the newly formed tissue, a nodule of fibrous tissue eventually being the sole representative of the original tuberculous focus. Very often, however, caseous or calcareous material may be found in this fibrous nodule; and, microscopically, giant-cells may be seen.

These effects may be briefly summarised thus:—

1. Local proliferative changes at the site of lodgment of the bacilli, emigration of leucocytes from the neighbouring vessels, formation of giant-cells, etc., giving rise to a mass of new tissue—the tubercle follicles or granulomatous masses. These changes are caused by something in the bodies of the bacilli, and may be produced by injecting dead organisms.
2. Degenerative and necrotic changes in these masses—**caseation** due in part to the local action of the living bacilli and their products.
3. General diffusion of the toxins, producing fever and wasting, and also fatty and waxy degenerations, etc.
4. Proliferative changes in the neighbourhood of, and extending from, the local area of tuberculosis. These are

simply an extension of the earlier proliferative changes; and the ratio between these and the destructive changes is an index of the activity of the bacilli, or of the vitality and power of resistance of the tissues. Thus, if the tissues are able to resist the action of the bacillus, either in virtue of their own vitality or through the feebleness of the bacillus, the proliferative changes will be in excess of the destructive ones; whereas, if the bacillus is virulent or the tissues feeble, the destructive changes will predominate.

Macroscopical appearances.—The tubercle nodules are at first very small, rounded or irregular, opaque greyish-white areas, which may be localised or widely diffused, as in the condition of **acute miliary tuberculosis.** These areas may, by individual growth or by coalescence, increase considerably in size and form large tumour-like masses, as is sometimes seen in the brain. These larger areas have very often a yellowish or greenish-yellow appearance, and may show softening or irregular cavities. Some of the more chronic nodules are pearly-white in appearance and very firm, owing to interstitial fibrous overgrowth. Others may show a deposit of lime salts.

TUBERCULOSIS IN THE LOWER ANIMALS. — Tuberculosis is common in cattle, but may also affect, though to a less extent, horses and pigs; in fact, almost all the warm-blooded animals are susceptible to the disease, and it is specially common in domesticated animals. The bacillus of human tuberculosis can infect most of these animals; and, what is of special importance, the organism of bovine tuberculosis, which has been regarded as a different species, can and often does give rise to tuberculosis in the human subject. In cattle, the structures most frequently affected are the serous membranes—the pleura and peritoneum especially. In these positions, large bean-shaped or potato-like nodules are seen attached to the surface, or supported by membranous villous-like projections. They may form very large masses, and are usually white, firm, and frequently calcareous. On account of their size and their pearl-like appearance, the name "perlsucht" has been applied to them in Germany.

II. **LEPROSY.**—A bacillus closely resembling in its morphological characters the *Bacillus tuberculosis* is found constantly, and generally in enormous numbers, in the lesions of leprosy. This *B. lepræ* is regarded as specific, though absolute proof has not yet been established. The disease is localised to certain

districts, and is prevalent in Norway, India, China, Mexico, certain parts of South America, the Sandwich Islands, Egypt, and Abyssinia. It presents itself in two forms—the **tubercular** and the **anæsthetic**.

Lepra tuberculosa.—In this variety, nodular elevations are formed in the skin, especially of the face and hands, and in the mucous membranes of the mouth and larynx. These, at first reddish or bluish in colour, grow very slowly into pale, firm nodules of varying size, which may extend so as to involve mucous surfaces. They are composed of granulation tissue, *i.e.* of proliferated connective tissue cells and leucocytes. New blood-vessels are present in more or less abundance. Many of the cells contain the bacilli, and these apparently multiply in the cytoplasm. The nodules may break down, giving rise to irregular ulcers; and in the neighbourhood of these, extensive fibrous cicatrisation may occur. This formation of fibrous tissue may take place without ulceration. By the formation of the nodules, and by their ulceration and cicatrisation, unsightly deformities may be produced.

Lepra anæsthetica.—In this form, the principal lesion is in the peripheral nerves, on which are seen spindle-shaped swellings. These are really nodular granulation tissue thickenings of the perineurium, which cause inflammatory and degenerative changes in the nerves themselves. Rarely, the new formations are seen in the brain or spinal cord.

These nerve affections give rise to neuralgias, and also to trophic disturbances, leading to atrophy in the skin, the bones, and other tissues.

In the skin, localised patches of anæsthesia occur; and in these there may be a diminution or an increase of pigment, leading to the production of whitish or brownish areas, which are liable to ulcerative or other necrotic changes. The destructive effects, aided no doubt by the results of infection with pyogenetic organisms, may be extremely marked, leading not uncommonly to separation of the fingers or the toes. The nose, the hands, the feet, and even larger parts of limbs may become separated as a result of these necrotic processes. Very commonly the two forms of leprosy are co-existent. Nodular masses of leprous tissue may occur in the lymphatic glands, liver, spleen, testes, lungs, kidneys, etc., but they are not

common, though the bacilli can be easily demonstrated in the internal organs, and microscopic lesions are not infrequent.

III. **SYPHILIS.**—This disease occurs in the human subject. Almost all of the lower animals are immune, but it can be experimentally transmitted to the anthropoid apes and some of the lower monkeys. In 1905, Schaudinn described in syphilitic lesions an organism which he regarded as causal,

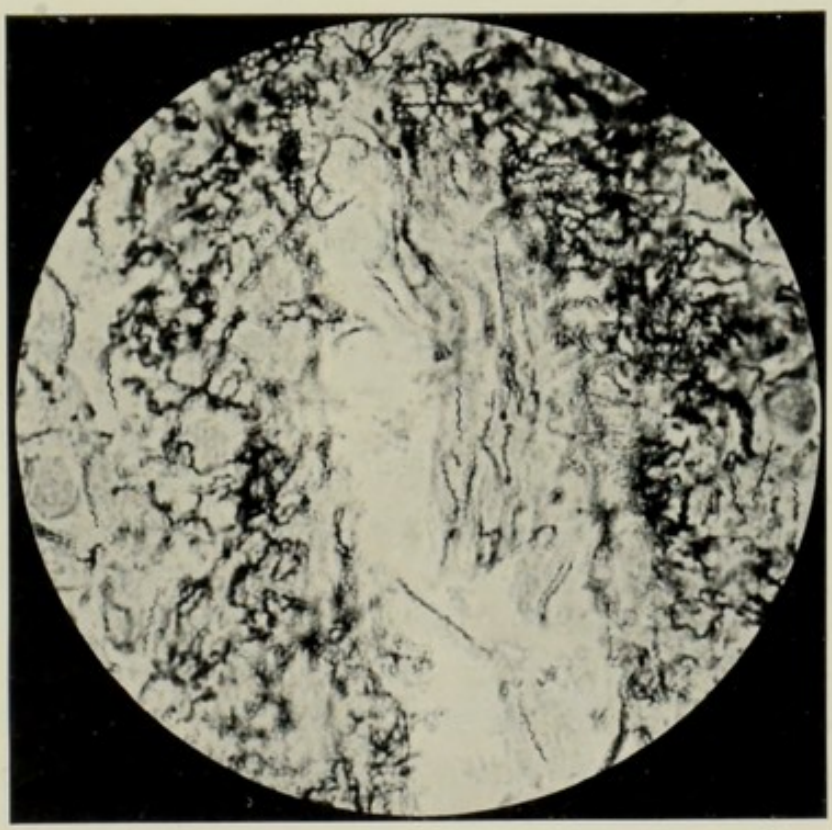

FIG. 117.—Spleen from a case of congenital syphilis, showing numerous spirochætæ pallidæ. ×1000.

and which he at first named *Spirochæta pallida*, and afterwards *Spironema* or *Treponema pallidum*. This is an extremely delicate, actively motile, long, spiral, thread-like organism, the spirals being regular, narrow, and deep. It tapers at the ends to a sharp point. It varies in length from 4 to 20 μ, and the spirals average 8 to 10 in number, though there may be as many as 24 or 26. Terminal flagella have been described. During the "resting state," undulating movements may be observed passing along the length of the organism, and these have suggested the presence of an un-

dulating membrane. Most observers, however, agree that this is not present, or at any rate that its presence has not yet been satisfactorily demonstrated. In certain specimens two flagella at one end have been described, and this appearance has been interpreted by some observers as suggesting an attempt at longitudinal division. There is not sufficient evidence on this point to justify any such conclusion. The organism has been found in the initial lesions in a very considerable proportion of the cases examined, *e.g.* Schaudinn and Hoffmann [1] found it in seven successive cases of uncomplicated syphilitic disease examined by them, though other workers have not been so uniformly successful. It has also been demonstrated in the mucous patches and condylomata, in the secondary papules, in the enlarged lymphatic glands, and, though in a much smaller proportion of cases, in the blood from the roseolar rash and in the circulating blood. It occurs very constantly in the blood and in the organs and tissues of infants suffering from congenital syphilis, but it has not been shown to be present in any of the tertiary lesions of the disease.

Anthropoid apes have been inoculated with discharges containing the organisms and have developed typical syphilitic lesions, in which the spirochætæ have been again found. The organisms, however, have not yet been grown in pure culture outside the body. Thus, though absolute proof of the causal relationship of the organism to the disease has not been definitely established, yet most authorities and practically all investigators of the subject have accepted it as the probable cause of syphilis.

Method of Infection and Spread.—The disease is definitely infective, and in almost all cases it is transmitted from one individual to another by contact. There may be direct passage of the virus through the placenta from the mother to the fœtus. The spread is mainly by the lymphatics, and the glands in the neighbourhood of the primary lesion soon become involved. The presence of the organism in the circulating blood shows that it must be spread by this means also.

Morbid Anatomy and Histology.—The course of the disease may be divided into three stages:—

(*a*) **Primary lesion or chancre.**—This most commonly occurs

[1] Schaudinn and Hoffmann, *Arbeiten aus dem Kaiserlich. Gesund.*, Bd. xxii., Heft 2, Apr. 10, 1905.

about the external generative organs, but may be found on other parts of the body which have been in contact with the syphilitic virus. After a period of incubation of about three weeks or more, a papule or a vesicle makes its appearance. This is usually red and inflamed, the base very soon becomes hard or indurated, and is distinctly "cartilaginous" to the touch. This **hard** or **indurated** or **Hunterian chancre** becomes eroded, and superficial ulceration occurs. Microscopically, this nodule is inflammatory in nature, and is composed at first of rounded lymphoid cells, which very soon become mingled with proliferated connective tissue cells—rounded and spindle-shaped. Giant-cells are rarely present. The blood-vessels show thickening, especially of their inner coat. The newly formed tissue tends to remain undeveloped—*i.e.* the cells do not go on to the formation of fibrous tissue—and cicatrisation is therefore not a usual sequel. When healing takes place, the nodule disappears and leaves very little evidence of its previous presence.

The virus is carried by the lymphatics to the neighbouring glands, which become enlarged and hard, and which, on microscopical examination, show masses of irregularly formed granulation tissue, similar to that seen in the chancre. The *Spirochæta pallida* can generally be demonstrated in the deeper parts of the chancre and in the lymphatic glands.

(*b*) **Secondary lesions.** — These are usually symmetrically arranged, and seem to indicate a distribution of the virus by means of the blood. They are accompanied by fever and constitutional symptoms, and present analogies to similar phenomena in the specific infective fevers. They occur at a varying time after the primary infection—from three or four weeks up to several months. They are most frequent in the skin, where they may show as a roseolar rash, or as papular, macular or scaly eruptions, which usually cause little irritation. Periostitis or pharyngitis may also occur; and slightly raised nodules showing superficial erosion or ulceration—the **mucous patches** and **condylomata**—are seen on mucous membranes and the neighbouring skin, *e.g.* of the mouth, the pharynx, the vulva, or the anus. The microscopical appearances of the mucous patches and condylomata are very similar to those of the primary chancre.

(*c*) **Tertiary lesions.**—These are specially characterised by the presence of local tumour-like formations or **gummata**; but

there are always associated, more or less diffuse, syphilitic changes in the arteries, and in various internal organs, liver, lung, etc. The gummata are whitish or greyish in appearance, commonly with a yellow caseous centre. They vary considerably in size, from microscopic nodules to those the size of a large orange. They are not definitely encapsuled; but

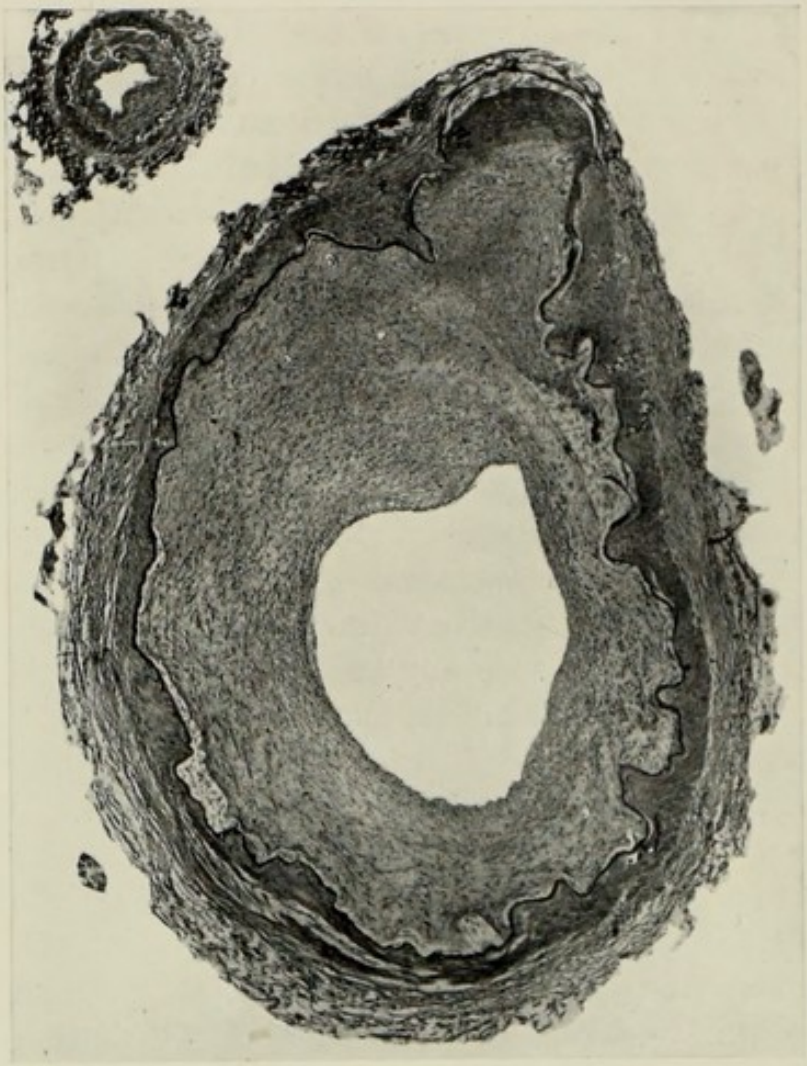

FIG. 118.—Syphilitic artery, showing proliferative changes in the inner coat (endarteritis obliterans), and also a periarteritis. × 30.

the periphery generally merges into a firm connective tissue, which extends somewhat into the surrounding structures, and is a new formation.

Microscopically, a gumma is composed of masses of rounded lymphoid cells and proliferated connective tissue corpuscles, which may be rounded, irregular, or spindle-shaped in outline. Giant-cells and epithelioid cells may also be present. The

giant-cells resemble those seen in tuberculosis, but usually they are somewhat smaller and more irregular, and show less definite caseation in their centres. The blood-vessels nearly always show thickening of their intima, and periarteritis is also a common feature. Secondary changes, giving rise to caseation and fatty degeneration, almost always occur. The gummata may be found in practically any of the tissues or

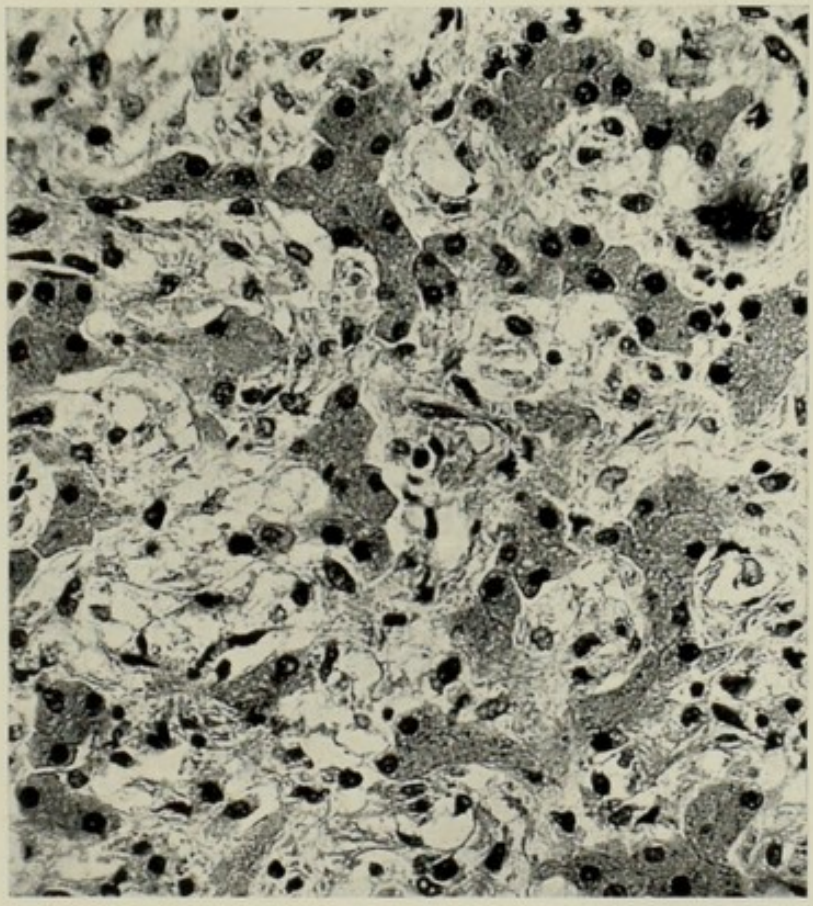

FIG. 119.—Liver from a case of congenital syphilis, showing diffuse overgrowth of connective tissue (intercellular cirrhosis). ×300.

organs of the body, but their most frequent sites are the periosteum and bone, though they are also common in the liver and the brain. If the gummata are situated in mucous membranes or in tissues close to a skin surface, the necrotic changes may lead to ulceration and great destructive changes, or they may erode cartilage or bone and bring about considerable deformity. Concerning the diffuse infiltrations caused by syphilis, little need be said here. They are mainly of the nature of fibrous overgrowths, at first composed of cellular and

vascular granulation tissue, and later becoming developed into well-formed fibrous tissue. These infiltrations are seen in the liver and in the lungs, and in both the inner coat and adventitia of the arteries. Waxy or amyloid degeneration is a frequent result of syphilis in its later stages.

Congenital Syphilis.—Syphilis in young children may either be developed *in utero*, and the child may die in the uterine cavity or be born with syphilitic lesions ; or, on the other hand, it may be acquired during birth by contact with the syphilitic lesions in the passages of the mother. The former alone is in the strict sense congenital syphilis. In the latter form, the changes are practically the same as those of acquired syphilis, but modified by the fact that they are produced in young, growing tissues. Thus, affections of the skin, in the form of roseolar and papular eruptions, fissures and maculæ, inflammations of the cornea and sclerotic, inflammation of the mucous membranes, etc., may occur. In addition, the wedge-shaped or peg-like teeth and the notching of the upper central incisors (Hutchinson's teeth) are commonly seen. In true congenital syphilis, the inflammatory changes may also be present, but the more characteristic lesions are of a chronic nature. They are seen in the liver, lung, periosteum, dura and pia mater, in the bones, and in the arteries ; and are mainly of the nature of a diffuse overgrowth of fibrous tissue, which interferes with the normal cell arrangement or distribution, and often leads to atrophy and absorption of functioning structures. The newly-formed connective tissue itself undergoes contraction, and leads to irregular scars and fissures. Gummata are sometimes present, and are commonly yellowish-white and gelatinous in appearance.

IV. **GLANDERS.**—This is a disease specially attacking the horse and the ass, but it can be communicated to man. The causal organism is *B. mallei*. The disease occurs either in an acute or in a chronic form. In the horse, the acute form manifests itself by the formation of granulation tissue swellings of the mucous membrane or skin. The disease commences in the mucous membrane of the nose, and spreads to the adjacent lymphatic glands, and along the mucous membrane of the bronchi and intestinal tract. The skin may also be attacked. In man,

the disease is usually very acute and rapidly fatal. Nodules and ulcers may appear in the mucous membranes or in the skin; and diffuse spreading inflammation, with purulent infiltration between the muscles, may be seen. Abscesses in the internal organs may follow, death supervening in these cases from pyæmia.

The nodules in glanders are largely inflammatory in nature, and often show necrosis or caseation in their central parts. If near the surface, they may ulcerate. In the more chronic

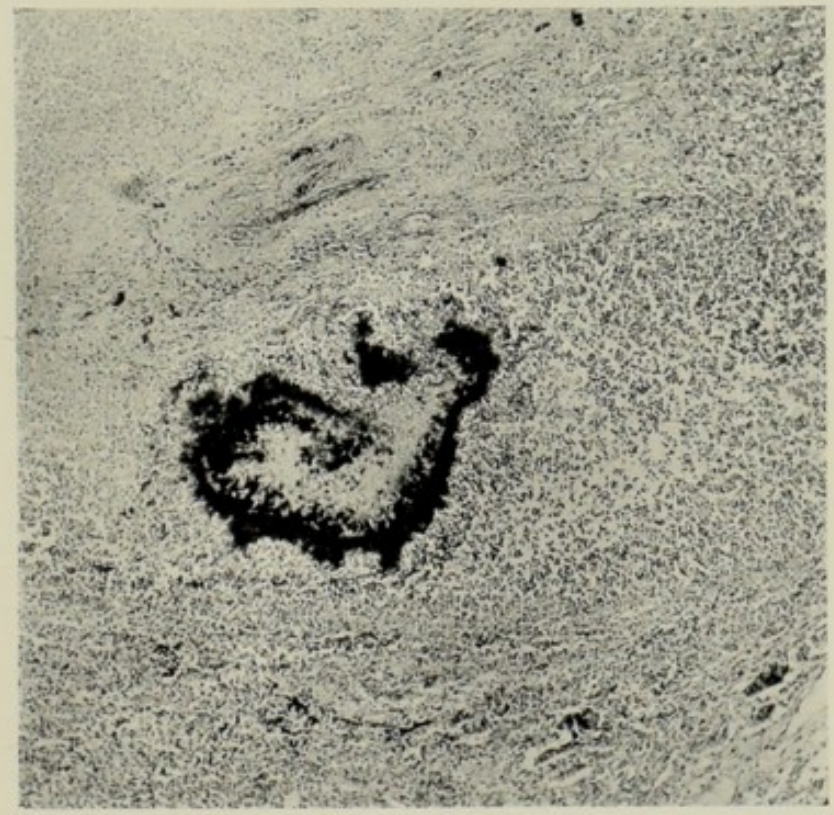

FIG. 120.—Actinomycotic abscess in the lung of a man æt. about 40 years, showing a mass (black) of *Streptothrix actinomyces*. × 60.

forms, there is a spreading inflammatory reaction along the lymphatics, with enlargement of the lymphatic glands, giving rise to irregular "cords" and "knots." To this condition the name **Farcy** has been applied, and the swellings are spoken of as "Farcy buds." In these there is an overgrowth of connective tissue; and necrotic changes and ulceration are liable to occur.

V. **ACTINOMYCOSIS.**—This disease is very common in oxen, the so-called "woody tongue" being its principal manifestation. It occurs with comparative frequency also in man. The causal

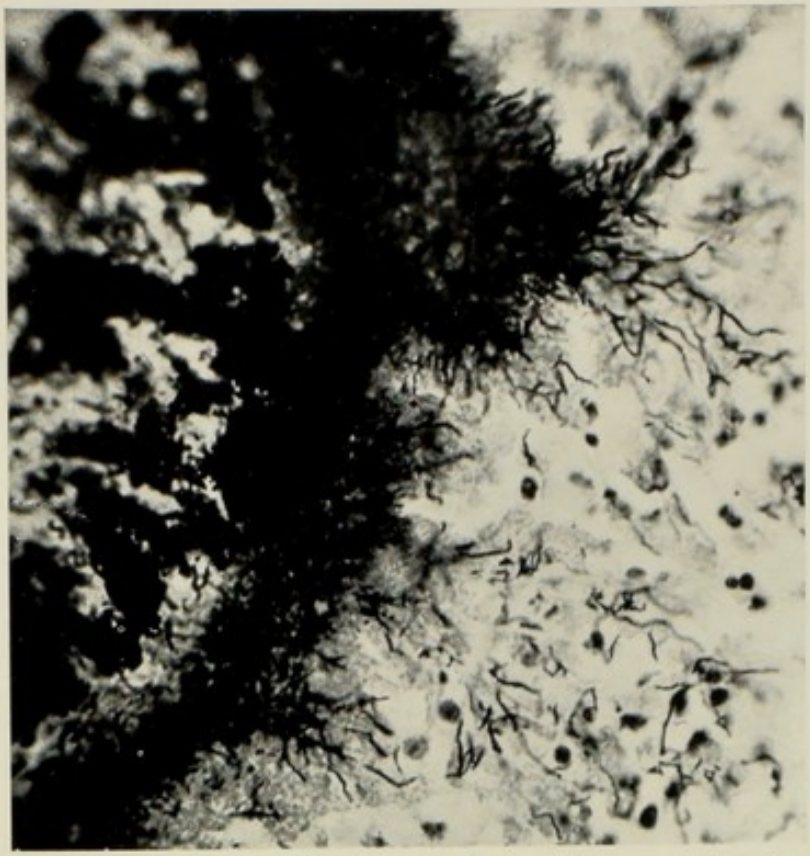

FIG. 121.—Margin of mass of *Streptothrix actinomyces*, showing filamentous structure. × 500.

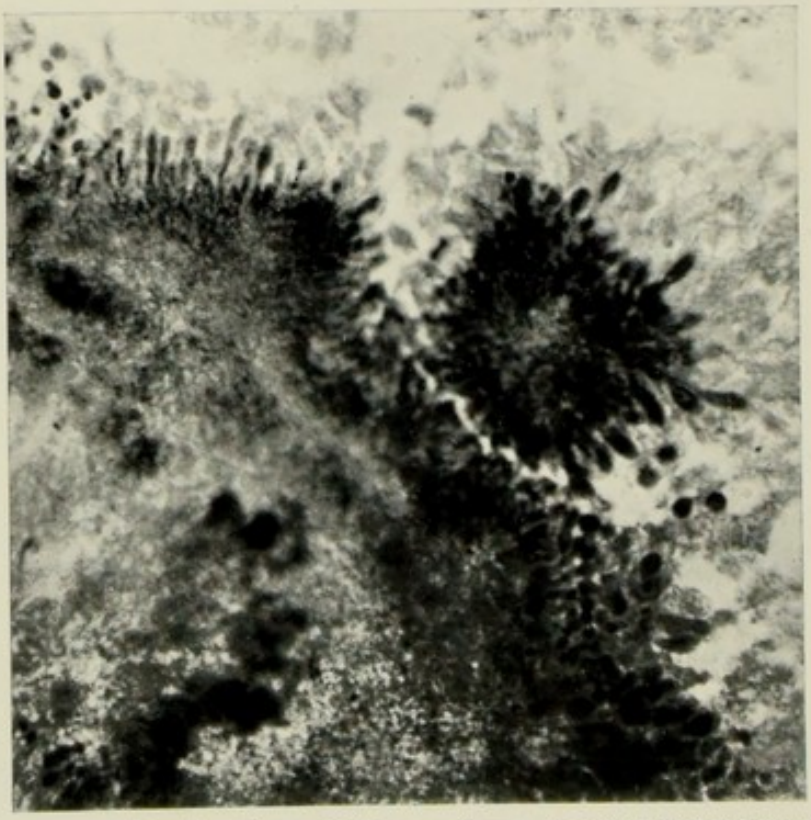

FIG. 122.—Margin of mass in human lung, showing "clubbing" of extremities of the filaments of *Streptothrix actinomyces*. × 500.

organism is the *Streptothrix actinomyces*, or ray fungus, which gains entrance to the body by way of the alimentary canal—very commonly by a breach of continuity in the mucous membrane of the mouth—or by the respiratory passages. It spreads usually by direct continuity, but may be carried to distant parts by the lymphatics or by the blood-vessels, and thus may give rise to multiple foci in widely separated areas.

Characters of the lesions.—In **cattle**, tumour-like nodules may be seen on various serous surfaces, or large masses may occur in the neighbourhood of the jaws and on the tongue—the last being the commonest site of the disease. These masses are composed of granulation tissue infiltrated with the fungus. The nodules tend to become fibrous or calcified, though extensive suppuration may occur in some of them.

In **man**, there is usually suppuration, with necrotic changes. Abscesses may form in any part of the body, and the surrounding tissues may undergo extensive necrosis. The pus is unusually thick, yellowish or greenish in colour, and contains minute yellowish-grey or black masses, which are soft, and which, on microscopical examination, are seen to be masses of the fungus.

Other forms of Streptothrix infection.—Allied to Actinomycosis, and producing in man similar suppurative lesions, with necrosis and sometimes pyæmia, several conditions have been described in which the causal organism resembles in many respects the *Streptothrix actinomyces*. Of these the most important are **Mycetoma**, or **Madura foot**, due to the *S. maduræ*; and the pyæmic conditions produced by the *S. eppinger*, etc.

Hodgkin's disease.—This need only be mentioned here. By some observers it is regarded as a manifestation of tuberculosis; but we agree with those who hold that it is a distinct disease, which, however, has some resemblances to the infective granulomata in its method of spread and development. The cause or causes which produce it are as yet quite unknown.

CHAPTER VI

ANIMAL PARASITES

PARASITES may be defined as organisms which live either temporarily or permanently in the tissues or organs, or upon the surface of other organisms, from which they derive, partially or entirely, their nutriment. Such parasites may belong to the vegetable kingdom, *e.g.* bacteria and moulds; or to the animal kingdom; and it is to the latter—the zooparasites—that reference will be made in this chapter. The most important "permanent" animal parasites which infest man belong either to the **Protozoa** or to the **Helminthes, Vermes** or **Worms**, a somewhat heterogeneous group of the **Invertebrate Metazoa**. Less important *as parasites*, and for the most part temporary or incidental, but sometimes of great importance *as carriers of disease*, are certain members of the **Insecta** and **Arachnida** (*spiders, mites, ticks*, etc.) groups of the **Arthropoda.**

All degrees of parasitism are found, the **permanent** parasites being mainly **entozoa** or **endoparasites** (*i.e.* living **within** the body of their "host," as the animal which harbours the parasites is called); the **occasional** parasites being for the most part—though not invariably—**epizoa** or **ectoparasites**, *i.e.* surface parasites, such as fleas, bugs, ticks, etc.

For the completion of their life-cycle, the great majority of animal parasites—both proto- and meta-zoon—require to pass their mature and their immature stages in different hosts often widely separated in the zoological scale; the **final** or **definitive host** harbouring the mature, and the **intermediate** or **temporary** host harbouring the immature forms of the parasite. In many cases, a **specific** variety of host is required before the development of the parasite can occur. The special site in the body of the host occupied by the parasite is known as the **habitat.**

SECTION I

PROTOZOA

These are organisms, each formed of an undivided mass of protoplasm, with one or more nuclei, and capable of an independent existence. Very commonly, the protoplasm is differentiated into a clear, dense, outer layer, the **ectoplasm**, and a granular and more fluid inner portion, the **endoplasm**. The protoplasmic mass may be naked, or there may be a distinct envelope. A **principal nucleus** composed of chromatin and achromatic substance is always present, but in addition there may be other nuclei, and also fine granules of chromatin scattered in the cytoplasm. These granules are termed **chromidia**, and, though they may occur constantly in a given species, they are more generally formed from the principal nucleus during a special phase of the life cycle. In some forms, there appears in the protoplasm at some part a clear drop of fluid, which gradually enlarges and then empties itself to the exterior by a rapid contraction. This **contractile vacuole** serves as an excretory and respiratory organ. Non-contractile food-vacuoles may be seen at various parts of the endoplasm. Many Protozoa are able to protect themselves against unfavourable conditions by the formation of an envelope or cyst-wall round the body (encystment).

Reproduction takes place usually **by fission**. This may be **simple**, the nucleus dividing into two parts, and later, the protoplasm also dividing so as to form two new individuals; or it may be **multiple**, the nucleus dividing into a number of parts, each of which becomes surrounded by a mass of protoplasm. This is the method of division by **schizogony**, and each of the new individuals is termed a **merozoite**. Only part of the cytoplasm may be used up in this process, whilst the remainder or "residual protoplasm" degenerates or forms a network, in the spaces of which the merozoites lie. The merozoites or, as they are often somewhat inaccurately called, "spores" may be very numerous and actively motile, and are

then known as **swarm-spores.** These may be amœboid (*amœbulæ*), or they may be provided with one or more flagella (*flagellulæ*).

Though reproduction by fission may go on through many generations for an indefinite period, yet it seems necessary that conjugation of sexually mature individuals should take place if the life of the species is to be maintained; and it has been definitely proved that conjugation takes place in many Protozoa at some period of the life-cycle. It may be impossible to distinguish the two conjugating individuals, the **gametes**, from one another; or, on the other hand, they may show certain recognisable and distinct morphological differences. The male element, the **microgamete**, may be smaller, more actively motile, with proportionately larger nucleus, and less laden with reserve food material; while the female or **macrogamete** is often well supplied with such reserve food material, and may be very sluggish or even non-motile. Before conjugation, certain alterations take place in the nuclei of the gametes, a portion of the chromatin being either absorbed in the protoplasm or cast off as **polar bodies.** Probably the rejected chromatin is **vegetative** in character, *i.e.* is concerned with the regulation of the processes of nutrition, cell-growth, etc., whilst that which is retained is largely **generative.** When this process of **maturation**, as it is termed, is complete, the altered nuclei, or, as they are now called, the **pronuclei**, fuse with one another and form a new nucleus or **synkaryon.** If the bodies of the two individual gametes also fuse, the resulting cell-unit is known as a **zygote.** In some cases, the male and female gametes not only differ from one another in appearance, but differ from the ordinary individuals of the species. The mother-cells of these gametes are known as **gametocytes,** and are generally of two kinds, the micro- and the macro-gametocytes, corresponding with the micro- and macro-gametes to which they respectively give rise. **Parthenogenesis**—in which sexually differentiated individuals, without going through the process of conjugation, proceed to reproduction of the ordinary type—and other forms of reproduction, occur in the Protozoa; but as the individual members of the group in which these take place at present appear to be of comparatively small importance from the point of view of human pathology, it is not necessary to give any description of these processes here.

CLASSIFICATION OF THE PROTOZOA

CLASS 1.—SARCODINA (RHIZOPODA)

These are protozoa in which, in the adult, locomotion and capture of food are brought about by means of temporary protoplasmic processes, **pseudopodia**, which can be projected and retracted. From the standpoint of human pathology, the only important members of this class are those belonging to the genus *Amœba* (*Entamœba*).

CLASS 2.—MASTIGOPHORA (FLAGELLATA)

These are protozoa in which, in the adult, there are one or more structures in the form of flagella for locomotion or for the capture of food. The body protoplasm may be naked and amœboid, but in the great majority of cases there is a cuticle or **periplast**, and amœboid movement does not occur. To this group belong the *Trypanosomata*, the *Leishman-Donovan bodies*, some forms of *Spirochætæ*, and the less important *Trichomonas*.

CLASS 3.—SPOROZOA

These are protozoa which are endoparasitic, and which in their adult form do not possess organs for locomotion or for the capture of food. The members of this class multiply by some method of sporulation. The body may be naked, or limited by a distinct cuticle. Amœboid forms are met with, but, according to Minchin,[1] "the amœboid habit of the body is not connected with locomotion, but, if it has any physiological significance, perhaps favours absorption of nutriment at the body surface, or may in other cases serve for temporary attachment of the parasite to internal surfaces of the host."

For descriptive purposes, it is convenient to divide the life cycle of the sporozoa into two stages, the **trophic**, during which the parasite, at this stage called the **trophozoite**, is absorbing nutriment from and growing at the expense of the host; and

[1] Minchin, "Protozoa," *System of Medicine*, Allbutt and Rolleston, 1907, vol. ii., part ii., p. 58.

the **reproductive**, during which new individuals are being produced. These trophic and reproductive phases may be entirely distinct, and the parasite may first grow to its full size before reproductive activity begins; or the reproductive activity may commence very early, and growth and reproduction go on simultaneously. In the former (*e.g.* the *Telosporidia*), the adult trophozoite is uninucleated; and in the latter (*e.g.* the *Neosporidia*), it is multinucleated. These two sub-classes also show differences in the manner in which they undergo the process of sporulation.

In the *Telosporidia* there is a multiple division of the nucleus, the parts of which pass to the periphery of the cell-body, where each becomes surrounded by a zone of protoplasm constricted off from the surface of the body, the whole being termed a **spore-mother cell.** The central portion of the cell-body is left as **"residual protoplasm"** and disintegrates. In the *Neosporidia*, as we have stated, the division of the nucleus commences early, and round each of its subdivisions the protoplasm becomes concentrated, so that a **central** mass of **spore-mother cells,** enveloped in a peripheral layer of growing protoplasm, is produced. From the spore-mother cells arise the spores. In the *Telosporidia*, according to Minchin, one spore arises from each spore-mother cell, which may therefore be termed a **sporoblast**; whilst in the *Neosporidia* each spore-mother cell may give rise to two or more spores, and is known as a **pansporoblast.** The spores may now be set free in the form of **amœbulæ**, as in the *Neosporidia*; or further differentiation may take place, and each spore become divided into the sickle- or rod-shaped **sporozoites,** which are very minute, actively motile bodies.

The *Telosporidia* include, among other species, the *Coccidia* and the *Hæmosporidia* (*Plasmodium malariæ*, etc.); whilst in the *Neosporidia* are placed the *Sarcocystis tenella* and the recently described *Rhinosporidium kinealyi.*

CLASS 4.—CILIATA (INFUSORIA)

Protozoa in which the organs of locomotion consist of cilia. Of this class *Balantidium coli* and *minutum* and *Nyctotherus* have been stated to occur in man, and have been described as giving rise to diarrhœa, but their causal relationship is doubtful.

CLASS 1.—SARCODINA

The only members of this group that we shall describe are the three species of Amœbæ, which are internal parasites of the human body, and to which the generic name *Entamœbæ* has been given.

1. **AMŒBA or ENTAMŒBA COLI.**—This parasite occurs chiefly in the upper part of the large intestine, and appears to be perfectly harmless to its host. It consists of an irregular mass of protoplasm with a large nucleus which is rich in chromatin. No definite distinction can be made between ectoplasm and endoplasm except during the formation of pseudopodia, when the ectoplasm appears as a clear homogeneous substance into which granules from the endoplasm flow. This parasite feeds on bacteria and various substances contained in the intestine, and does not penetrate the mucous membrane.

In the intestine, and especially in soft fæces, multiplication takes place either by simple binary fission or by rapid multiple fission, in which eight small amœbæ are formed, each having the general characters of the parent cell. According to Schaudinn,[1] the organism, under unfavourable conditions, becomes encysted and passes out of the gut in the fæces. In this encysted cell the nucleus divides into two. The daughter nuclei pass to opposite poles of the cell, and the protoplasm partially divides into two segments. Each daughter nucleus becomes resolved into **chromidia**. Some of these chromidia are absorbed by the cell-protoplasm, some are excreted, whilst those remaining unite and form two new nuclei, one in each mass of the partially segmented protoplasm. These new nuclei divide, and one-half of each is absorbed or cast off as a **reduction body**. The retained halves again divide, and again one-half of each is rejected. After this process of reduction, the remaining halves constitute the **generative** nuclei. At this stage the cyst-wall becomes thicker, the protoplasm shrinks, and its partially divided portions fuse into a single mass, which now contains two generative nuclei. Each generative nucleus divides into two parts or **pronuclei**—one being passive

[1] Schaudinn, "Untersuchungen über die Fortpflanzung einiger Rhizopoden," *Arbeit aus dem Kaiserlichen Gesundheitsamte*, Berlin, xix. pp. 547–576.

and one active. The active pronucleus of each pair moves across the protoplasm and fuses with the opposite passive pronucleus, and thus two **synkarya** are formed. Each synkaryon divides into four, and thus each cell contains at this period eight nuclei which form the nuclei of eight spores, protected within the thick cyst-wall. Before further development can take place, the encysted cell requires to be taken into the intestine of a new host, the cyst wall ruptures, and eight small amœbæ are set free.

2. **AMŒBA or ENTAMŒBA HISTOLYTICA.** — This parasite, which is regarded as the cause of amœbic dysentery, is found abundantly in the stools, and also in the submucous tissue of the walls of the intestine in the parts adjacent to the dysenteric ulcers. It is also found in the liver abscesses secondary to dysentery, more especially in their walls, and in the vessels of the liver at considerable distances from the abscess. It has also been described as occurring in the stomach, and as giving rise to abscesses in the kidneys and other organs. In its amœboid condition it consists of an irregular mass of protoplasm, 25 to 30 μ in diameter, which is definitely divided into a clear, hyaline ectoplasm and a granular endoplasm. The pseudopodia are more rigid and tougher than those of *Entamœba coli*, and are formed wholly from the ectoplasm. The nucleus is small, and often placed at one side of the body. It is poor in chromatin, and hence very difficult to stain well. In unfavourable surroundings, and even whilst still present in the stools and in the abscesses, the organism becomes spherical in shape and develops a definite wall. The protoplasm then becomes granular, the distinction between ecto- and endo-plasm being lost. It also shows numerous vacuoles and various inclusions such as bacteria, pigment particles, portions of red blood corpuscles, etc. In its active condition the parasite multiplies by either binary fission or by a process of multiple fission, in which the new individuals are constricted off in the form of buds from the parent cell. The number of these new individuals is indefinite. When the conditions are unfavourable for vegetative activity, for example during the process of healing of the dysenteric ulcers or abscesses, rounded forms with a definite wall are formed. Schaudinn says these are not encysted forms, but true **spores**. In their formation the nucleus first gives off chromidia into the

protoplasm and then disappears. The chromidia collect at the periphery of the cell, and little buds of ectoplasm, each containing numerous chromidia, form. These buds become separated from the parent cell and constitute the spores. The remainder of the original cell degenerates, whilst the spores become surrounded by a definite, tough, resistant membrane. The further details of the development of the spores have not been completely worked out; but Schaudinn, by feeding cats with the dried fæces containing them, succeeded in producing dysentery in these animals, great numbers of amœbæ being afterwards found in their intestines. This experimental observation gives support to the view that *Entamœba histolytica* is the cause of one of the forms of dysentery; but even stronger evidence is to be found in the regularity of the occurrence of the organism in certain forms of the disease, and the constancy of its relationship to the primary and secondary lesions. Definite proof cannot be hoped for until the organism has been isolated and grown in pure culture. Though Musgrove and Clegg and others claim to have grown it in cultures of bacteria, a pure growth of it has not yet been obtained.

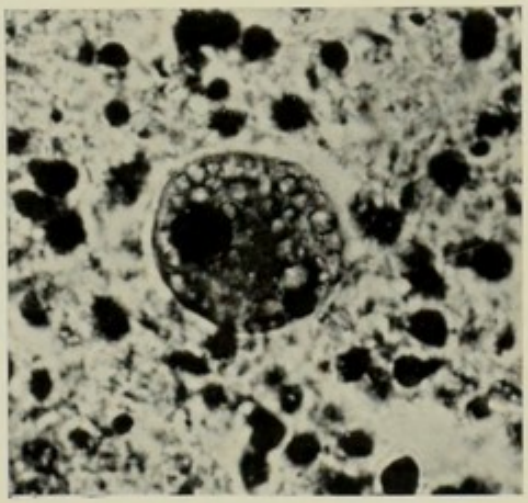

FIG. 123.—*Entamœba histolytica* in an abscess of the liver. ×1000.

3. **ENTAMŒBA BUCCALIS.**—This parasite has been described as occurring in the mouths of persons suffering from dental caries, and in its general morphological characters it resembles *Entamœba histolytica* rather than *Entamœba coli.* Its reproductive cycle has not been fully worked out, but there is some evidence that in this also it resembles the former species.

CLASS 2.—MASTIGOPHORA (FLAGELLATA)

1. **TRYPANOSOMA.**—Some of the **trypanosomes** parasitic in mammals are of special importance, because of their pathological effects. Among these are *T. brucei* of **Nagana**, a disease of

horses and cattle in certain parts of Africa; *T. evansi* of **Surra**, occurring in horses and cattle in India and elsewhere; *T. equinum* of **Mal de caderas** in horses in South America; *T. equiperdum* of **Dourine** in horses in Algeria and other countries; and the especially important *T. gambiense*, the organism of **sleeping sickness** and **Gambia fever** in the human subject. All these species present morphological features which are practically identical, and which render distinctions on morphological grounds alone almost impossible. They all possess a more or less spindle-shaped or eel-like body, along one side of which runs a fin-like protoplasmic structure, **the undulating membrane.** The nucleus is well marked and is usually placed near the centre of the body. At or near one extremity of the body is a granule of chromatin, the **blepharoplast** (micronucleus or centrosome). The **flagellum** takes origin at or near this blepharoplast, and passes along the free edge of the above-mentioned **undulating membrane**, following all its sinuosities, and reaching to the opposite extremity of the body, where it may terminate. More commonly it is prolonged for a variable distance as a free flagellum. The parasite is actively motile. Multiplication takes place by binary fission, and almost always longitudinally to the principal axis of the body. The blepharoplast and the nucleus divide first, and this is followed by the division of the flagellum and the body of the organism.

Conjugation between male and female elements takes place, but the details of sexual development are not yet completely known. For full development, a second invertebrate host is probably necessary. A possible exception to this general rule is the case of *T. equiperdum* of **Dourine**, where transmission is said to take place by coitus. For the other species mentioned, a dipterous insect seems to be the second host required, *T. gambiense* being transmitted by *Glossina palpalis*, and *T. brucei* by a tsetse fly, *Glossina morsitans*. In the blood of the infected mammals, male and female forms of the parasite can be distinguished; but full sexual differentiation occurs only in the invertebrate host. The males show a much more slender body and greater length of flagellum than the females, and are much more active. Their cytoplasm is clear and free from coarse granulations, whilst the nucleus is more or less rod-shaped. The cytoplasm of the females contains numerous

coarse granules (probably reserve food material), and the nucleus is more or less rounded in outline. Before conjugation, in the species whose life-history has been described, the sexual forms undergo a process of **maturation,** during which part of the nucleus is cast off. Then fusion takes place between the male and female, their blepharoplasts, nuclei, and cell-protoplasm becoming amalgamated. The flagellum and undulating membrane disappear. It is said that the new

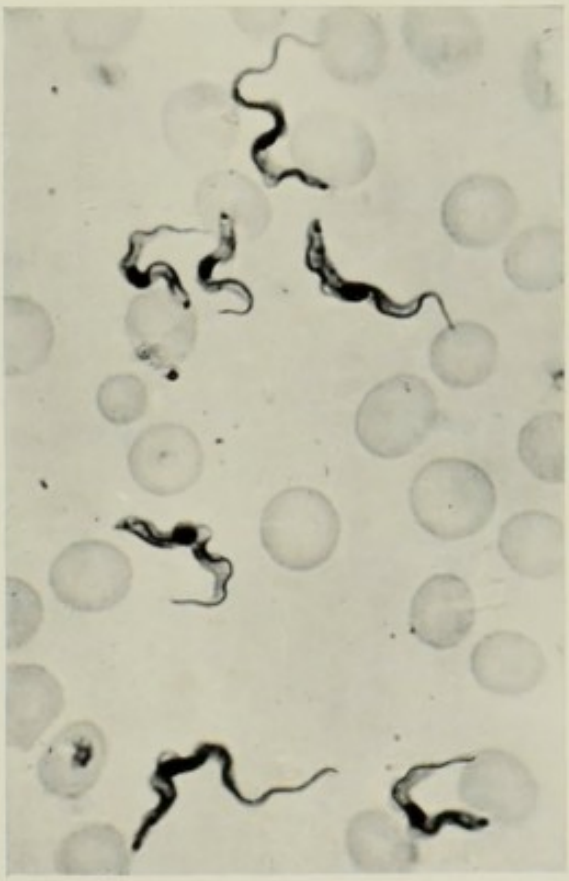

FIG. 124.—*T. gambiense* from the blood of a case of sleeping sickness. × 1000.

blepharoplast formed by fusion passes into the new nucleus, and thus a **synkaryon** is produced. The resulting zygote is a worm-like body—the **vermicule.** In this, division of the nucleus takes place, a new blepharoplast is formed, flagellum and undulating membrane reappear, and thus is produced a new adult trypanosome. Trypanosomes have been cultivated in artificial media by Novy and McNeal, Smedley, and others.

2. **SPIROCHÆTA.**—Many **spirochætæ** have been confused with bacteria of the genus **Spirillum.** According to Schaudinn, the

former are characterised by the presence of an undulating membrane, and by division taking place in the longitudinal axis. In this group have been classed, by some observers, *Spirillum obermeieri* of relapsing fever; and *Spirochæta pallida*, or *Spironema* or *Treponema pallidum*, recently described as the organism of syphilis. There seems now very little doubt that the organism of relapsing fever must be regarded as a bacterium of the genus **Spirillum**, and not as one of the protozoa. Of the zoological position of *Treponema pallidum* and the allied organism, *Spirochæta pertenuis*, described by Castellani as occurring in Yaws, there is still some uncertainty. According to Minchin,[1] they differ from typical spirochætæ in the following points:—"The body is corkscrew-like, and shows numerous sharp, fine coils, which vary from ten to twenty-six in number, and are preformed, that is to say, are not the result simply of the animal's wriggling movements; an undulating membrane cannot be made out, but appropriate methods reveal a slender prolongation, interpreted by Schaudinn as a flagellum, at each of the pointed tapering ends of the body." *Treponema pallidum* is very actively motile, and is found deeply situated in the syphilitic lesions. At some point, generally near the centre, the curves of the body disappear; and certain authors regard this as the site of the nucleus. Division is said to take place in the long axis of the body, but transverse division has also been described; and Novy and other workers on the subject still regard the organism as a bacterium of the genus **Spirillum**, and *not* as a **Protozoon**.

3. **LEISHMAN-DONOVAN BODIES.**—These are minute, rounded, ovoid or pear-shaped bodies, measuring 2 to 4 μ by 1·5 to 2 μ, and having a distinct cuticle. The cytoplasm is often vacuolated, and it contains two masses of chromatin—a larger spherical one (the nucleus), placed at one pole of the short axis of the body, and a smaller rod-shaped one (the so-called "micronucleus," centrosome or blepharoplast), placed at the opposite pole. These parasites are mainly **intracellular**, and are found in enormous numbers in the endothelial cells and in the leucocytes in the spleen, liver, and bone-marrow in the disease known as **Kala Azar.** Donovan, Laveran, and Mesnil also

[1] Minchin, "Protozoa," *System of Medicine*, Allbutt and Rolleston, 1907, vol. ii., part ii., p. 46.

describe them as occurring in the red blood corpuscles in the general circulation in this disease. Very similar organisms have been described in **Oriental** or **Delhi sore**, **Aleppo boil**, etc. The development of the parasite is not fully known. Rogers, Leishman, and others have succeeded in developing from these bodies, when grown in citrated blood, certain flagellate organisms, resembling but not identical with trypanosomes. Recent work

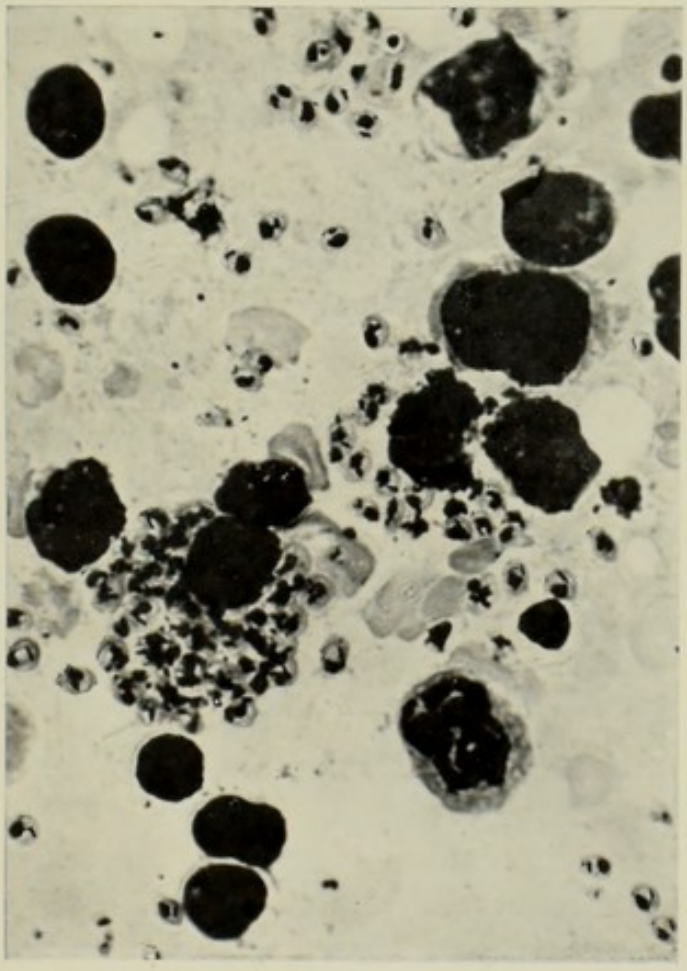

FIG. 125.—Leishman-Donovan bodies from the spleen of a case of Kala Azar. ×1000.

by Patten[1] seems to point to the bed-bug as an agent of infection.

4. **TRICHOMONAS INTESTINALIS** or **HOMINIS**.—This is a pear-shaped organism from 10 to 15 μ in length and about 7 μ in breadth. The anterior end is blunt, and the posterior extremity is prolonged into a sharp, tail-like projection with a definite undulating membrane. At the anterior end there are ten or twelve cilia. This organism is

[1] Patten, *Scientific Memoirs of the Government of India*, 1907, No. 27.

found in the intestine in the human subject, and a similar form has been described in the buccal cavity.

5. **TRICHOMONAS VAGINALIS.**—A similar but smaller organism than the foregoing parasite, possessing three or four cilia at the anterior end, a lateral undulating membrane, and a blunt caudal extremity, has been found in the vagina and also in the male urethra, but its pathological significance is doubtful. Similar organisms have been described in the lung in purulent bronchitis.

6. **LAMBLIA (MEGASTOMA) INTESTINALIS** is a pear-shaped parasite with a flattened body, and inhabits the duodenum and jejunum of man. It adheres to the mucous membrane by a large sucker-like depression on its ventral surface. It has four pairs of flagella. It appears to be perfectly harmless to its host.

CLASS 3.—SPOROZOA.

1. **COCCIDIA.**—These are small, oval bodies from 30 to 40 μ in length and from 15 to 20 μ in width. They are surrounded by a tough capsule, enclosing a mass of granular protoplasm with a definite nucleus—the whole structure somewhat resembling an ovum. They are intracellular, and in the ordinary type found in the liver of the rabbit, the parasites occupy principally the cells lining the biliary passages, though they may also be found in the liver cells and sometimes in cells in the mucous membrane of the intestine. They cause considerable proliferation of the tissues in which they lie; and, in the liver, irregular spaces lined by epithelium and with branching papilliform projections may be found, giving rise to an appearance somewhat resembling an adenomatous cancer. In the cells lining these spaces, and also free in the cavities, numerous coccidia may be seen.

Infection takes place by swallowing spores or sporulating parasites, which are acted upon by the digestive juices, the contained sporozoites being thus liberated. Each sporozoite enters an epithelial cell in the wall of the intestine, and may pass through the wall and migrate to the most suitable habitat—*e.g.* the cells of the biliary passages. There it absorbs nourishment and grows rapidly to the adult form, in which multiplication takes place either by **schizogony** (endogenous "spore" formation), or by **sporogony** (exogenous spore formation). The adult form which multiplies by the former method is called a **schizont**, and that which multiplies by the latter is termed a **sporont**.

In the fully grown schizont the nucleus divides repeatedly into several nuclei, around each of which the protoplasm collects, and thus **merozoites** are formed. These merozoites are now simply enclosed in the remains of the host cell. They then become free, attack fresh cells of the host, and thus give rise to a new generation, which in course of time grows to become either the fully formed schizonts or sporonts. Thus **schizogony** represents the **asexual cycle** in the life-history.

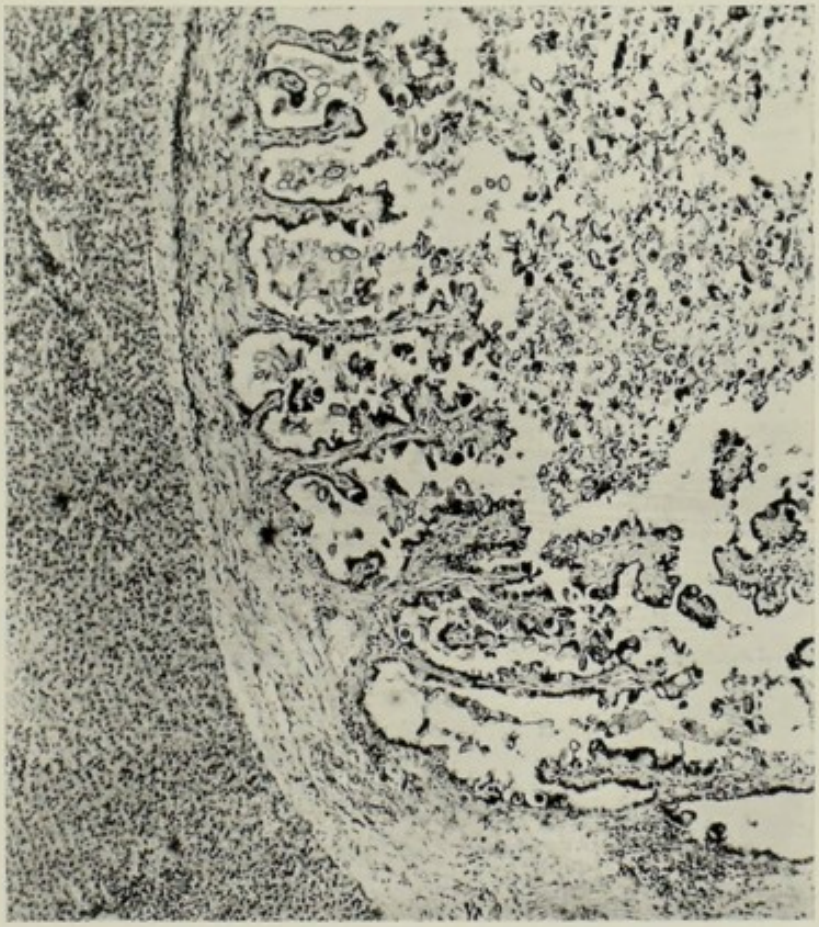

FIG. 126.—Liver from a Rabbit with Coccidiosis, showing adenomatous structure of cyst. × 60.

Under certain conditions **sporogony** or true spore-formation takes place, and this is preceded by conjugation between two individuals—the male and female gametes. The male sporont produces several **microgametes**, and one of these fuses with the female sporont, which, after maturation, becomes the **macrogamete**. This fertilised element becomes encysted to form the **oöcyst**, within which division takes place and four **sporoblasts** are formed, from each of which two sickle-shaped **sporozoites**

arise. The sporozoites still enclosed within the wall of the oöcyst pass into the intestine and escape with the fæces. Only four or five definitely authenticated cases of **coccidiosis** are known to have occurred in the human subject.

2. **HÆMOSPORIDIA**—(Pl. IV.):—

(*a*) **MALARIAL PARASITES.**—There are three species of malarial parasites found in the human subject—*Plasmodium vivax*, the tertian parasite; *P. malariæ*, the quartan parasite; *P. immaculatum*, sometimes but incorrectly called *P. præcox*, or more generally known as *Laverania malariæ*, the parasite of tropical, pernicious or æstivo-autumnal malaria.

These three parasites are distinguished from one another both by their morphological characters and their effects upon the host. Each has an **endogenous** and an **exogenous** life-cycle, the former within the human host, the latter in the body of a mosquito. The **endogenous** cycle (**schizogony**) goes on in the blood or in some of the internal organs of the human subject for an indefinite period, until the asexual reproductive faculty of the parasite is exhausted, or until the parasite itself has been destroyed by spontaneous natural cure or by artificial medicinal interference; whilst, in the mosquito, **sporogony** takes place as a result of conjugation between male and female parasites—this form of propagation being necessary, it is said, for the ultimate continuation of the species.

PLASMODIUM VIVAX—(Pl. IV.).—The sporozoites or true spores derived from the sexual cycle in the mosquito are introduced into the blood of the human host by the bite of the infected insect. After inoculation, certain, as yet imperfectly understood, changes take place in the sporozoites, and the rod-shaped bodies become small amœboid parasites, which are seen free in the blood and lying in close apposition to the envelope of the red blood corpuscles. Small protoplasmic processes from them penetrate the envelope, and are seen projecting into the cytoplasm, and gradually the whole sporozoite enters the red cell, probably in virtue of its amœboid movement. In the red blood corpuscles, it appears as a small, irregularly rounded mass of protoplasm, clear and structureless in appearance, with a chromatin granule (the nucleus), which stains bright red with eosin; and, very commonly, a clear, more or less rounded, unstained area near the centre (the vacuole)—the whole parasite

at this stage having somewhat the appearance of a signet ring. These young **trophozoites**, as they are now called, gradually enlarge, coming to occupy more and more of the interior of the red blood corpuscle. As the parasite increases in size, pigment derived from the hæmoglobin of the blood corpuscle collects in its protoplasm. At a later stage, the vacuole disappears, and the red corpuscle, which has become larger in size and paler in colour, is now seen to be occupied by an irregular, actively amœboid mass of protoplasm possessing a nucleus and containing masses of melanin pigment. Still later, the parasite almost completely fills the corpuscle; the nucleus undergoes division into from **twelve** to **twenty-four parts**, scattered irregularly or sometimes arranged very regularly round the periphery, and the pigment is collected at or near the centre. Before this, however, the amœboid movement has to a very large extent ceased, and the irregular protoplasmic body is then known as the **schizont**. The protoplasm next segments and collects round the parts of the divided nucleus, and thus are formed from **twelve** to **twenty-four merozoites**. These are minute spherical bodies grouped more or less regularly round the residual protoplasm, forming a rosette-like mass. During this process of schizogony, the infected corpuscles gradually disintegrate, and when the process is complete the merozoites are free in the blood-plasma. They wander off, leaving the residual protoplasm, and also the pigment, which is taken up by large mononucleated phagocytic cells, and carried by them to various organs and tissues in which it is deposited. Some of the wandering merozoites are ingested and digested by leucocytes and other phagocytic cells, but some escape this fate, and attack and enter fresh red blood corpuscles, where they become the trophozoites of a second generation. The development and freeing of merozoites in this asexual form of multiplication take place every forty-eight hours, and coincide with the pyrexial attacks, which thus recur every other day. In the great majority of cases, each red corpuscle is invaded by a single parasite, but, in certain instances, two or more merozoites may enter one red cell, and each parasite may undergo the complete process of schizogony. Again, a patient may be bitten by infected mosquitoes on successive days, and thus two sets of parasites, each having a forty-eight hours cycle, may be introduced into his blood. In such a case,

merozoites of each set will develop on alternate days, and the pyrexial attack will in consequence occur daily.

When the parasites are first introduced into the blood, their number is comparatively small, and they therefore produce no appreciable effect on the host. But multiplication by schizogony goes on, and in from six to twelve days — the so-called **incubation period** — the parasites are sufficiently numerous to produce, either by direct action or more probably by some toxic product, the febrile and other symptoms.

According to Schaudinn, the stimulus produced by the presence of the parasite develops in the host a certain amount of resistance against, or even the power of destroying, the parasites during their asexual stage. This reaction determines the production of sexually differentiated individuals or **sporonts**. The same author holds that a merozoite which is destined to develop into a **sporont** does not show the ring-like form in the young trophozoite stage, but otherwise cannot be differentiated from the trophozoite of the schizont.

The sporonts are of two kinds, the **male** and **female gametocytes**. In the **male** the nucleus is larger than in the **female** and the cytoplasm is free from granules of reserve material; whereas in the female it is full of such granules. Sporonts can also be distinguished from schizonts by certain characteristics. The full-grown **schizont** is about 10 μ in diameter, and the nucleus is placed at the periphery of the body. The **female sporont** is 12 to 16 μ in diameter, the nucleus is at the periphery, the cytoplasm stains very deeply, and the grains of melanin pigment are two or three times as large and twice as numerous as those in the schizont. In the **male sporont** the nucleus is large and is placed near the centre of the body, the cytoplasm is feebly granular and stains very faintly, whilst the melanin granules are as well developed as they are in the female. The sporonts are found in the peripheral blood in the later stages, and are taken up from it by the mosquito. The ripe gametocytes (sporonts) are able to resist the digestive juices of the mosquito, and from them, when taken into the stomach of the insect, the formation of **gametes** commences. In the male gametocyte, the nucleus splits up, giving off chromidia, which make their way to the surface of the body of the parasite. With great rapidity, motile threads, four to six in number, are shot out from the

protoplasm and appear at the surface of the body. These are the **microgametes**, and they contain all the peripheral chromidia. They lash about actively, and eventually become free from the microgametocyte. They are slender, flagella-like bodies, sometimes with a thickened extremity or with multiple thickenings in their course, and consist largely of generative chromatin. In the maturation of the female gametocyte, some nuclear substance is eliminated and the cell becomes the **macrogamete**. Each microgamete seeks out and penetrates one of the macrogametes and fuses with its nucleus, and the two elements by their conjugation thus form the **zygote**, which enlarges, becomes elongated in form, and develops into a motile individual termed the **vermicule** or **oökinete**. The vermicule pushes its way through the epithelial lining of the stomach of the mosquito, and comes to rest immediately below its epithelial covering. There it becomes spherical, and grows, coming eventually to bulge towards or into the body cavity of the insect, and forming an encysted body, the **oöcyst.** The nucleus (**synkaryon**) multiplies by division, and the protoplasm collects round the daughter nuclei to form **sporoblasts**, the whole body being now termed the **sporocyst.** In each sporoblast, the nucleus divides into a number of smaller nuclei, which travel to the surface of the sporoblast and grow out each into a bud-like or dagger-like projection of protoplasm to form a **sporozoite.** Thus the cyst becomes crowded with sporozoites, varying in number from hundreds to thousands. The ripe sporocyst now ruptures, the sporozoites are set free into the blood-fluid of the mosquito and pass into various parts, but especially into the salivary gland, in which they accumulate in enormous numbers. When the mosquito again bites its vertebrate host, the sporozoites pass down in the salivary secretion, which is injected through the proboscis, into the blood of that host; in which, after certain changes, they enter the red cells and grow to form schizonts, or later, sporonts. The entire development within the body of the mosquito lasts from ten to twelve days.

PLASMODIUM MALARIÆ—(Pl. IV.)—(**Quartan parasite**).—The parasite of quartan fever is less actively amœboid than that of the tertian form; it is less pigmented; the pigment granules are coarser, and lie towards the periphery. The infected blood corpuscles do not become enlarged, but rather tend to be

smaller than normal, and "are represented by a rim of greenish or brassy-coloured refractive protoplasm" (Thayer[1]). Development takes place, as in the tertian parasite, both by schizogony and by sporogony. In the asexual cycle the merozoites are more regular in distribution than in the tertian parasite, **nine to twelve merozoites** being formed in each schizont, and these are arranged in a definite rosette- or wheel-like form. The merozoite formation takes place every seventy-two hours, and thus the pyrexial attack recurs every three days.

PLASMODIUM IMMACULATUM (the parasite of tropical or pernicious malaria, or æstivo-autumnal fever)—(Pl. IV.).—This organism in its early intracorpuscular stage is also ring-like, but is smaller in size than the parasite of the tertian or quartan type. The most characteristic forms in the peripheral blood in this condition are the crescentic gametocytes or **crescents**, with centrally-placed pigment.

Schizogony takes place at irregular intervals, and occurs mainly in the spleen, the bone-marrow, and the capillaries of the brain. Sporulating forms are very rarely found in the peripheral blood, but are numerous in blood withdrawn by splenic puncture during an attack. In the sporulating forms, the merozoites are from **seven** to **ten** in number. Sporogony takes place and corresponds with what has been described for *Plasmodium vivax*. The male sporont is sausage- or crescent-shaped, with scattered pigment granules; the female is also crescent-shaped, but the pigment granules tend to be more aggregated round the nucleus. When taken into the stomach of the mosquito the crescents first become oval and then round, and correspond with the gametocytes of *Plasmodium vivax*.

MOSQUITOES AND MALARIA.—The developmental cycle of the parasites in the mosquito has already been described, and it may be said generally that this host is necessary to preserve the life of the species. It is true that in certain cases, after long intervals and without reinfection, relapses occur. Schaudinn explains these as the result of multiplication by **parthenogenesis.** The female sporonts, he says, are more resistant than the males; and if the human host is removed

[1] Thayer, *System of Medicine*, Allbutt and Rolleston, 1907, vol. ii., part ii., p. 24, *et seq.*

DESCRIPTION OF PLATE IV

PLATE IV

FIG. 1.—The asexual cycle of the parasite (*Plasmodium vivax*) of simple tertian malaria.

a.—The merozoites freed from the red cell and becoming scattered. Note mass of pigment.

b.c.—The young amœboid parasites (merozoites) entering the red blood corpuscles and becoming trophozoites.

d.—The parasite (trophozoite) in the corpuscle. The nucleus (red) and the unstained central vacuole are shown.

e.f.g.—Stages showing gradual increase in size of the trophozoite, with accumulation of pigment in its protoplasm. The infected red corpuscles are also increased in size.

h.—A further stage, in which the parasite almost fills the red corpuscle. The pigment has accumulated at the centre, and the chromatin granule has become divided into numerous scattered particles.

i.j.k.—Various stages in the segmentation of the parasite (segmenting schizonts) by which the merozoites are formed.

l.—Microgametocyte (male sporont).

m.—Macrogametocyte (female sporont).

n.—Amœboid mononucleated cell which has ingested some of the pigment. × 1000

FIG. 2.—Film of blood from a case of quartan malaria showing various stages in the asexual life-cycle of the parasite (*Plasmodium malariæ*).

a.b.—Young trophozoite in red corpuscle.

c.d.e.f.—More advanced trophozoites.

g.h.—Forms showing segmentation.

i.—Merozoites with central mass of pigment.

k.—Polymorphonuclear leucocyte. × 1000

FIG. 3.—Film of blood from a case of pernicious malaria (*Plasmodium immaculatum*).

a.—Free merozoite.

b.c.—Merozoite entering red corpuscle.

d.—Merozoites (ring form of parasite) in red corpuscles.

d'.—A red corpuscle containing two parasites.

e.e'.—Microgametocyte or male sporont in red corpuscle.

f.—Macrogametocyte or female sporont in red corpuscle.

g.—Mononucleated cell.

h.—Blood-platelets. × 1000

FIG. 4.—*Phagocytosis.*

a.—Polymorphonuclear leucocyte containing several ingested diplococci.

b.—Polymorphonuclear leucocyte which has ingested numerous bacilli.

c.—Polymorphonuclear leucocyte which has ingested a red blood corpuscle.

d.—Mononucleated cell with pseudopodia projected around a polymorphonuclear leucocyte which it is in the act of ingesting.

e.—Mononucleated cell which has ingested a leucocyte and a red corpuscle.

f.—Mononucleated cell which has ingested numerous leucocytes, which are seen in various stages of disintegration (digestion).

g.—Large mononucleated phagocytic cell from the bone-marrow, showing irregular pseudopodia and ingestion of polymorphs.

h.—A large mononucleated cell from the bone-marrow, containing numerous red corpuscles (from a case of pernicious anæmia). × 1000

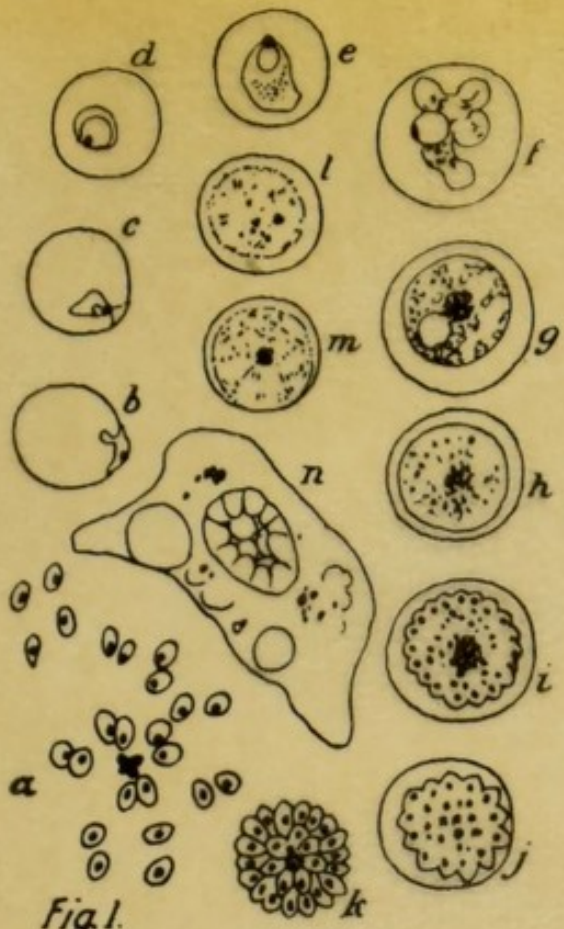

Fig. 1.

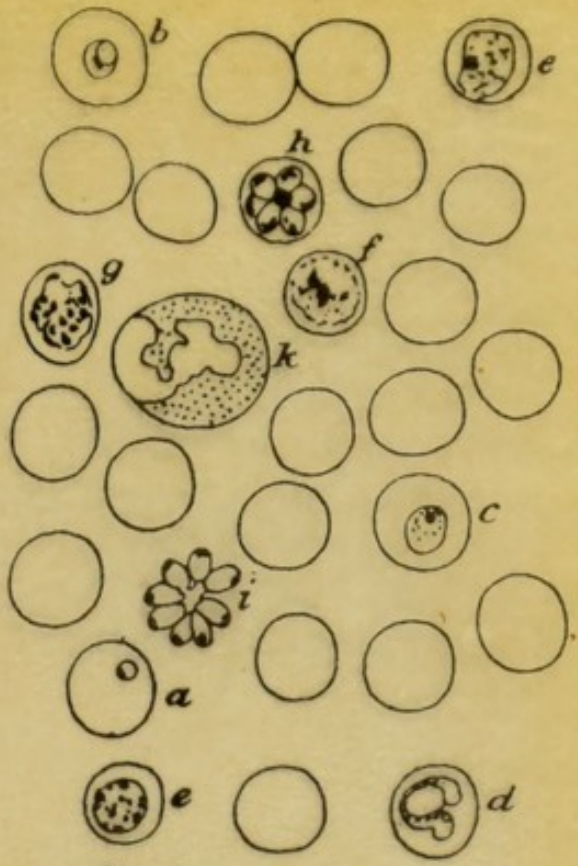

Fig. 2

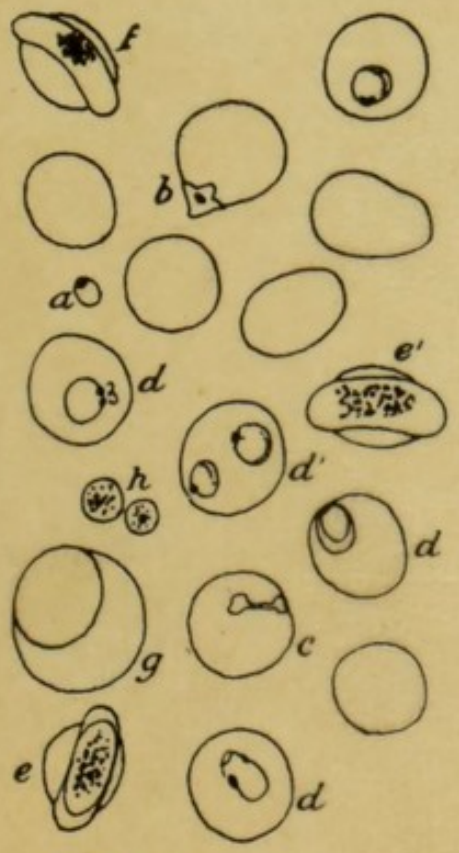

Fig. 3.

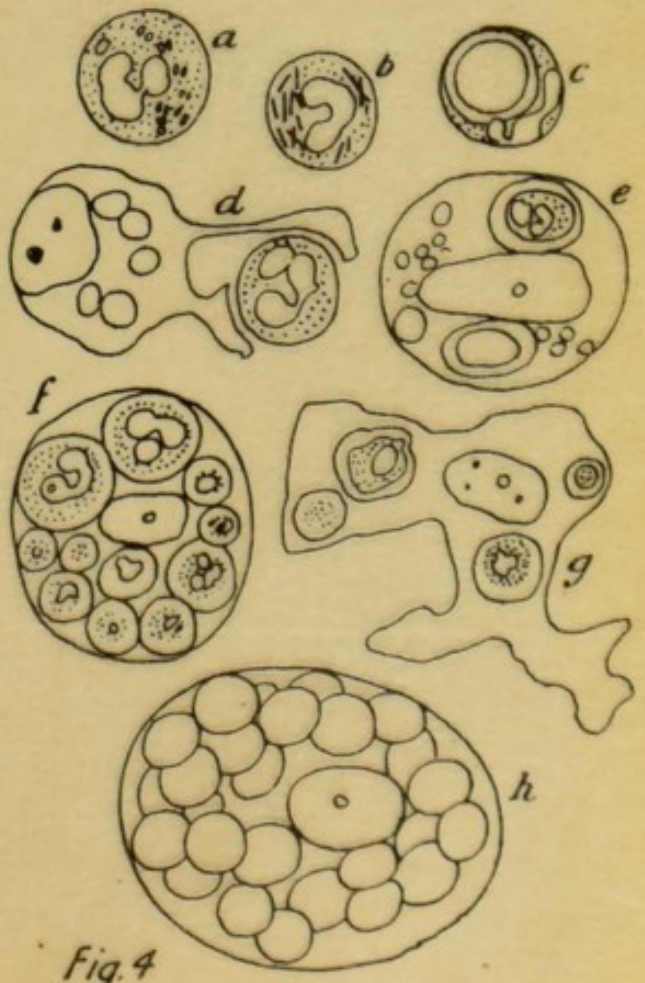

Fig. 4

PLATE IV

FIG. 1.—The asexual cycle of the parasite (*Plasmodium vivax*) of simple tertian malaria.

a.—The merozoites freed from the red cell and becoming scattered. Note mass of pigment.

b.c.—The young amœboid parasites (merozoites) entering the red blood corpuscles and becoming trophozoites.

d.—The parasite (trophozoite) in the corpuscle. The nucleus (red) and the unstained central vacuole are shown.

e.f.g.—Stages showing gradual increase in size of the trophozoite, with accumulation of pigment in its protoplasm. The infected red corpuscles are also increased in size.

h.—A further stage, in which the parasite almost fills the red corpuscle. The pigment has accumulated at the centre, and the chromatin granule has become divided into numerous scattered particles.

i.j.k.—Various stages in the segmentation of the parasite (segmenting schizonts) by which the merozoites are formed.

l.—Microgametocyte (male sporont).

m.—Macrogametocyte (female sporont).

n.—Amœboid mononucleated cell which has ingested some of the pigment. × 1000

FIG. 2.—Film of blood from a case of quartan malaria showing various stages in the asexual life-cycle of the parasite (*Plasmodium malariæ*).

a.b.—Young trophozoite in red corpuscle.

c.d.e.f.—More advanced trophozoites.

g.h.—Forms showing segmentation.

i.—Merozoites with central mass of pigment.

k.—Polymorphonuclear leucocyte. × 1000

FIG. 3.—Film of blood from a case of pernicious malaria (*Plasmodium immaculatum*).

a.—Free merozoite.

b.c.—Merozoite entering red corpuscle.

d.—Merozoites (ring form of parasite) in red corpuscles.

d'.—A red corpuscle containing two parasites.

e.e'.—Microgametocyte or male sporont in red corpuscle.

f.—Macrogametocyte or female sporont in red corpuscle.

g.—Mononucleated cell.

h.—Blood-platelets. × 1000

FIG. 4.—*Phagocytosis.*

a.—Polymorphonuclear leucocyte containing several ingested diplococci.

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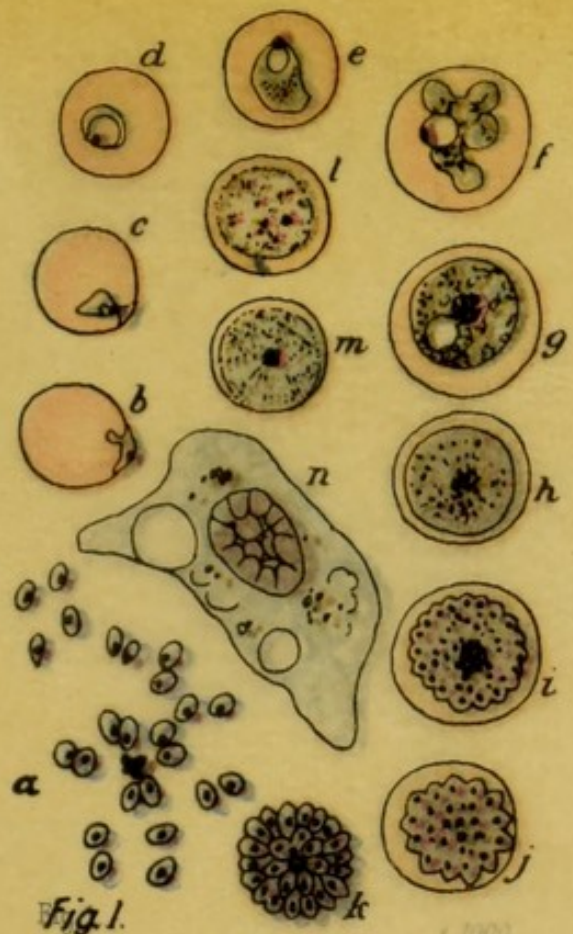


Fig. 1.

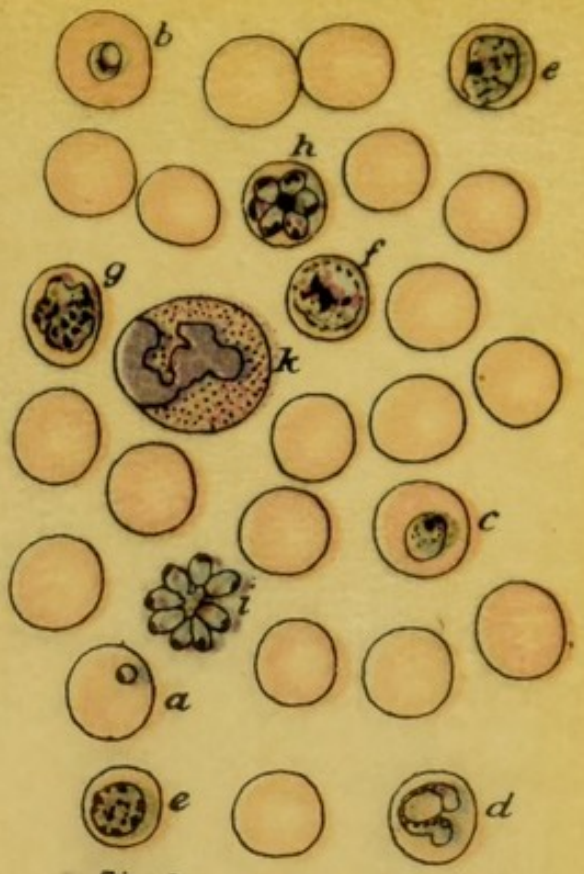


Fig. 2

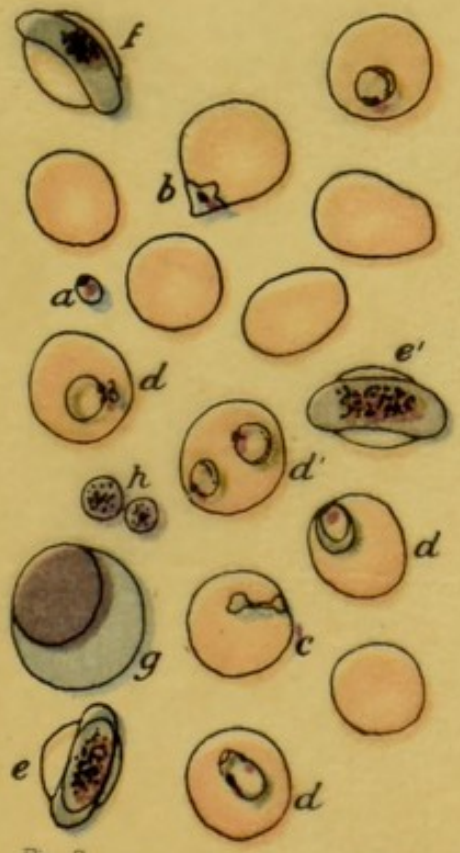


Fig. 3.

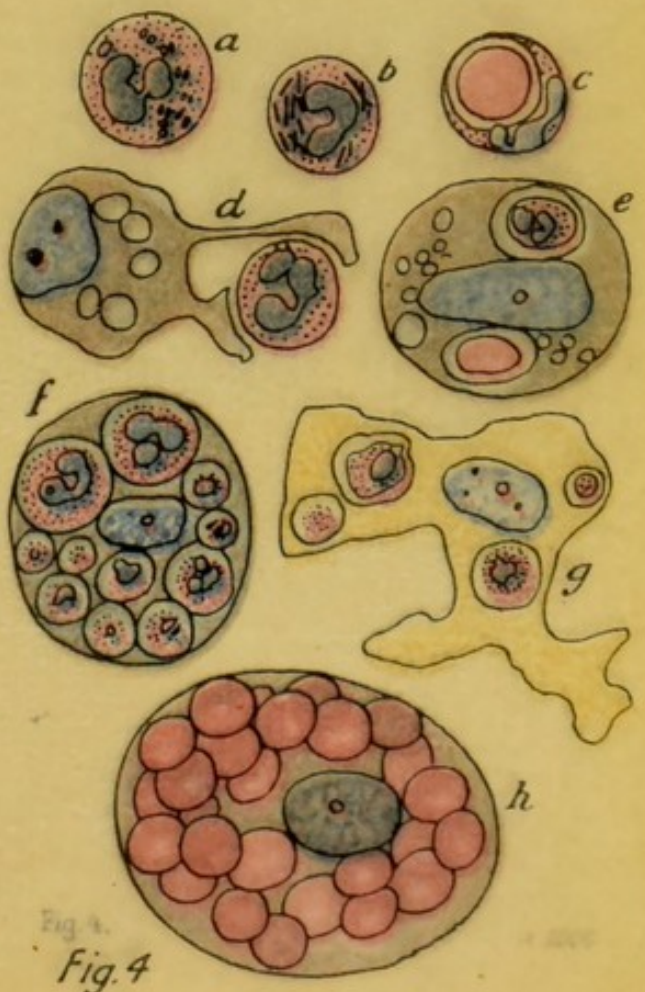


Fig. 4

Plate IV

Fig. 1.

Fig. 2

Fig. 3

Fig. 4

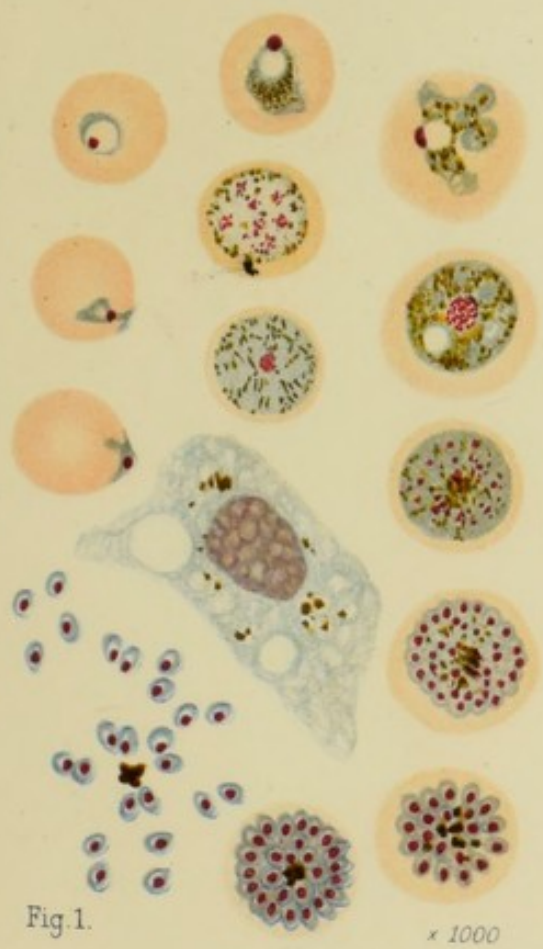


Fig. 1. × 1000

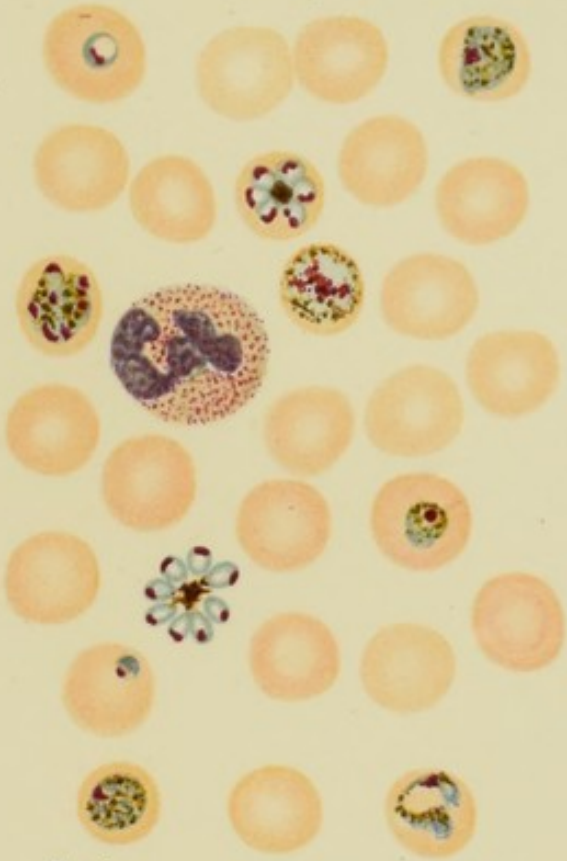


Fig. 2. × 1000

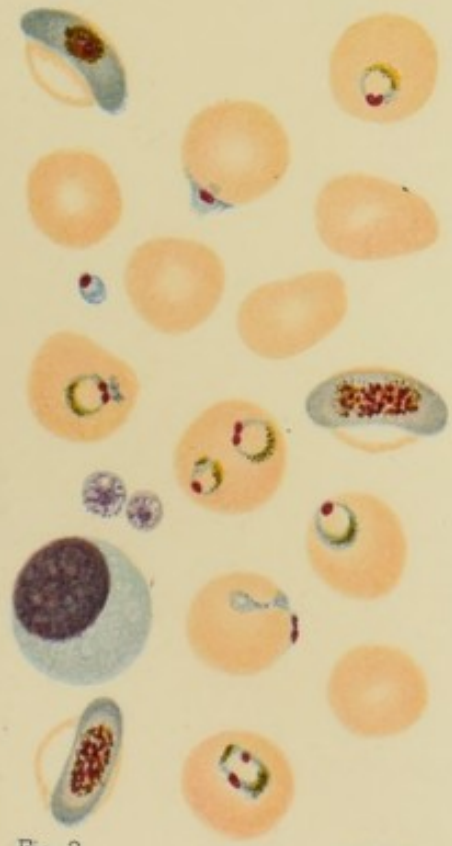


Fig. 3. × 1000

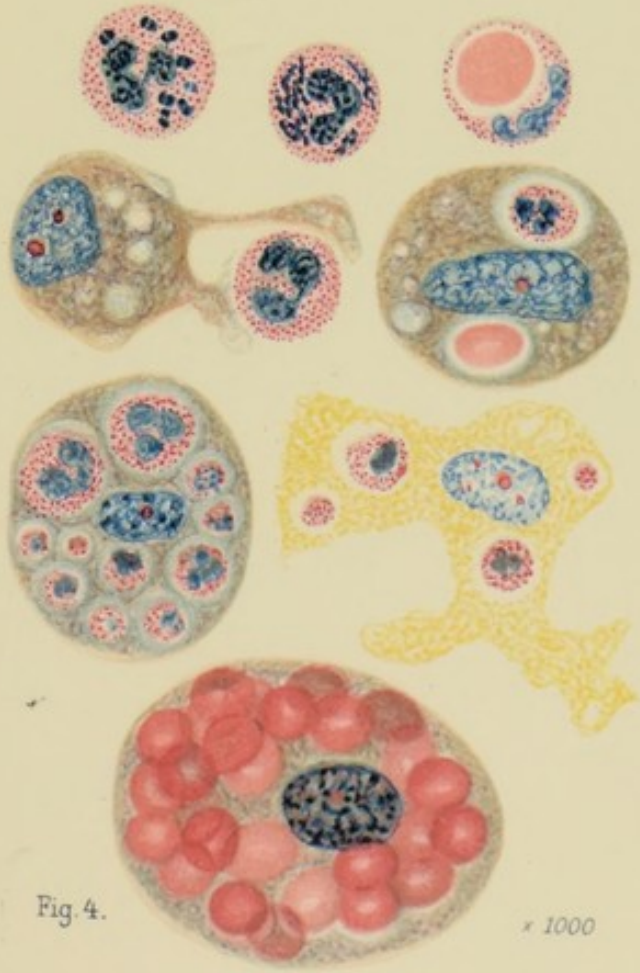


Fig. 4. × 1000

beyond the possibility of reinfection, the individuals of the asexual cycle die out, as also do the male sporonts; but the female sporonts, on account of their abundance of reserve material, may live for a considerable time, and produce without fertilisation a new generation of parasites. It has been shown conclusively by experiment that the development of the parasite takes place in the stomach wall of *Anopheles claviger* and other mosquitoes of this genus, and that healthy men can be inoculated by these infected mosquitoes.

PATHOLOGICAL ANATOMY.—The most important fact is **the destruction of the red blood corpuscles**, with the production of anæmia and the deposit of pigment in the liver, spleen, bone-marrow, brain, etc. (*vide* Chapter on Pigmentation, p. 88). The **spleen** is enlarged, and in acute cases almost diffluent. With frequent attacks it may become very greatly enlarged; and the fibrous trabeculæ, vascular sheaths, etc. may show great thickening. **Waxy** or **amyloid change** has been described as occurring in malaria, but in any given case it is very difficult, and often impossible, to exclude the previous occurrence of syphilis, or some other of the more usual causes of this form of degeneration.

The **liver** is usually enlarged. Parasites may be found in the corpuscles contained in the capillaries, and in the endothelial cells lining them. Focal necrosis may occur, and in long-standing cases definite cirrhosis has been found. The **kidneys** do not usually show any special changes, but both acute and chronic nephritis have been described as a result of malarial infection. Waxy or amyloid change has also been described. The other organs, apart from the deposit of pigment, show no specially characteristic pathological changes.

PROTOZOAL BLOOD PARASITES OF OTHER VERTEBRATES.—Belonging to the hæmosporidia, there are numerous parasites described as occurring in the red blood corpuscles of the lower animals. Some of these, *e.g. Proteosoma* and *Halteridium*, occurring in birds, have been very fully investigated, and the study of them has thrown much light on the problems of the life-history of the malarial parasites; in fact, the work of Ross on *Proteosoma* is the foundation on which the most valuable contributions to malarial parasitology have been built. For further information about these parasites we must refer our readers to the article on Protozoa by Professor Minchin in *A System of Medicine*, Allbutt and Rolleston, 1907, vol. ii., part ii.

THE NEOSPORIDIA.—In this group are included, among others, the human parasites, *Sarcocystis* (Rainey's and Miescher's Tubes), and a sporozoon of the nasal mucous membrane, *Rhinosporidium kinealyi*. These we do not think of sufficient importance to be described here, and must again refer our readers to the article on "Protozoa" in "*A System of Medicine*," by Allbutt and Rolleston, 1907; or to papers by Minchin and Fantham, *Quarterly Journal of Microscopical Science*, 1905, pp. 521–532; and by Beattie, *Journal of Pathology and Bacteriology*, June 1906.

SECTION II

METAZOA. INVERTEBRATA

VERMES, HELMINTHES OR WORMS

PHYLUM I.—PLATYHELMINTHES OR FLAT-WORMS

The **Platyhelminthes** are flattened, bilaterally symmetrical worms, leaf-like (*e.g.* the **Trematoda**) or tape-shaped (*e.g.* the **Cestoda**) in outline. The integument consists of a cuticle with glandular cells, beneath which lies the subcuticular, cellular, or "parenchymatous" layer, in which are embedded the nervous system and the commencement of the excretory water-vascular system. Under these lies the musculo-dermal layer, whilst between this and the alimentary canal is the cellular "mesenchymatous" tissue, containing the sexual glands and other organs if present. The Cestodes or tapeworms do not possess any alimentary canal; whilst in the Trematodes or Flukes this is represented by the mouth, the muscular pharynx, and the mid-gut, which is usually forked. There is no hind-gut or anus.

All the Cestodes and the great majority of the Trematodes are hermaphrodite, the most important exception in the latter group being the diœcious *Schistosomum hæmatobium*.

CLASS 1.—TREMATODA OR FLUKES

These are usually flattened, leaf-shaped, unsegmented worms, the adults being parasitic in vertebrates, and the larval forms being found in some species of mollusc. The adults are mostly hermaphrodite (except *Schistosomum hæmatobium* and a few others), the male and the female organs opening near one another on the ventral surface in the middle line, usually towards the anterior end, either in front of or behind the ventral sucker, the position of the genital pore varying, however, in different species.

LIFE-CYCLE OF THE TREMATODES.—This has been most fully worked out in the case of the Common Liver-fluke (*Fasciola hepatica*) of the sheep, which may be taken as the type. From the ova when mature, if they are deposited in water, a free-

swimming, somewhat elongated, ciliated embryo—the **miracidium**—is liberated. This enters its special intermediate host, a small water snail, usually *Limnæa truncatula*, which is very common in ponds and ditches. In the body of this mollusc it enlarges, becomes hollow, and forms a **sporocyst**, within which are developed either other sporocysts or what are known as **rediæ**—minute, somewhat elongated, cylindrical larval organisms, possessing a sac-like alimentary canal, and a somewhat anteriorly placed "birth pore." The sporocyst then ruptures, and the contained sporocysts or rediæ escape into other parts of the snail. The formation of sporocysts and rediæ may be repeated, but eventually the rediæ proceed to develop within themselves certain actively motile, round bodies—**cercariæ**—which possess a forked gut, two suckers, a tail, and also a special boring spine situated in the oral sucker. These cercariæ make their way out of the body of the snail into water, attach themselves to grass or some aquatic plant, cast off their motile tails and boring apparatus, and become encysted, waiting there until they are taken into the body of their definitive host, probably by the ingestion by the latter of the contaminated vegetable matter or drinking water containing these encysted forms. They then develop into the adult fluke, finding their way from the intestine into the bile-ducts and liver, and occasionally into the portal vein and elsewhere. The life-history of the other fluke-worms is probably very similar, but in many cases has not yet been fully worked out.

Of the numerous families into which the flukes are divided, three only (*Fasciolidæ*, *Schistosomidæ*, and the less important *Paramphistomidæ*) contain members which are parasitic in man.

FAMILY 1.—PARAMPHISTOMIDÆ

These organisms have a slender, tapering, anterior extremity, and a thickened, disc-like, posterior part, the ventral surface of which is concave and possesses a minute sucker at its posterior margin. The only example of any importance belonging to this family is *Gastrodiscus hominis*, which is, however, extremely rare.

FAMILY 2.—FASCIOLIDÆ

The members of this family possess an oral and a ventral sucker (the origin of the misnomer "Distoma"), and a median

ventral genital pore, opening, in *Fasciola hepatica*, between the two suckers. They are hermaphrodite, and the forked intestinal canal generally does not possess secondary diverticula. Their development has already been outlined.

FASCIOLA HEPATICA—(Syn. *Distoma* or *Distomum hepaticum*; *F. humana*, etc.).—The liver-fluke is a common endo-parasite of sheep, deer, cattle, and other herbivorous animals, and is only rarely found in man. It inhabits the bile-ducts, and in the human subject it may occasionally find its way into the portal vein and elsewhere, and has been described as causing abscess-like subcutaneous swellings. In sheep it is the cause of "liver-rot," a very fatal disease—characterised by fever, emaciation, anæmia, ascites, and œdema—which may occur in epidemics in infected districts at certain seasons. In man, if only a few parasites are present, the results may be trifling, but serious abdominal symptoms, such as gastro-intestinal disturbance accompanied by jaundice, and perhaps ascites, may occur. A fatal issue is rare. The condition may be diagnosed by finding the ova on microscopical examination of the fæces, or, less commonly, by the passage of the adult *per anum*.

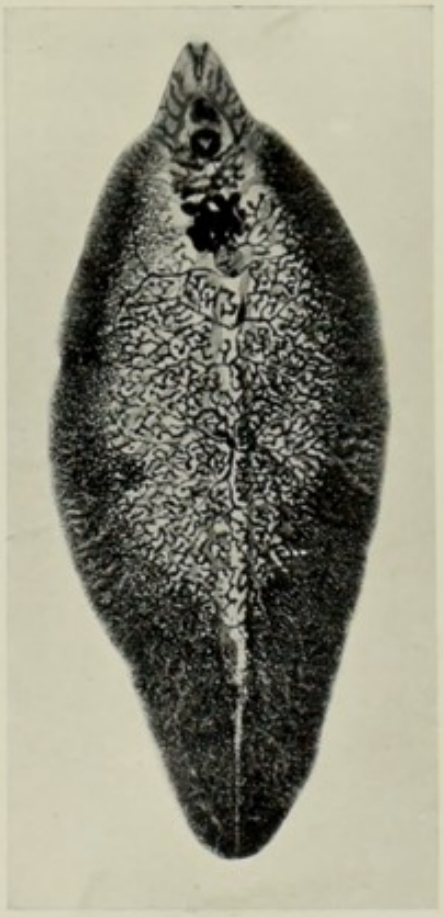


Fig. 127.—*Fasciola hepatica* or Liver Fluke. ×2½.

Morphology.—The adult fluke is leaf- or lancet-shaped, with a somewhat conical anterior extremity, at which is placed the oral sucker. The genital orifice is situated between the two suckers, immediately in front of the ventral non-perforate sucker. The length varies from 20–30 mm., and the breadth from 8–13 mm., the worm being often somewhat curled with the concavity ventrally. The parasite is pale yellowish or slightly brownish-white in colour, with occasionally a delicate pale blue or rose-pink tint.

The **ova** are brown or brownish-yellow in colour, and are oval in shape, with a terminal operculum. They measure about 0·13 by 0·08 mm. in diameter, and may show segmentation. The later development of these has been described on pp. 371–2.

A narrower and more elongated variety of liver-fluke, *F. hepatica*, var. *angusta*, has been described as occurring in Senegal; and another somewhat similar variety, *F. hepatica*, var. *ægyptiaca*, is reported as occurring in Egypt.

FASCIOLOPSIS BUSKI—(Syn. *Distomum buski*; *D. crassum*).—This is the largest fluke-worm found parasitic in man, and measures 24 to 37 or even 70 mm. in length, the breadth varying from 5·5 to 12 or 14 mm. It inhabits the human intestine, and has been found in Eastern and Southern Asia.

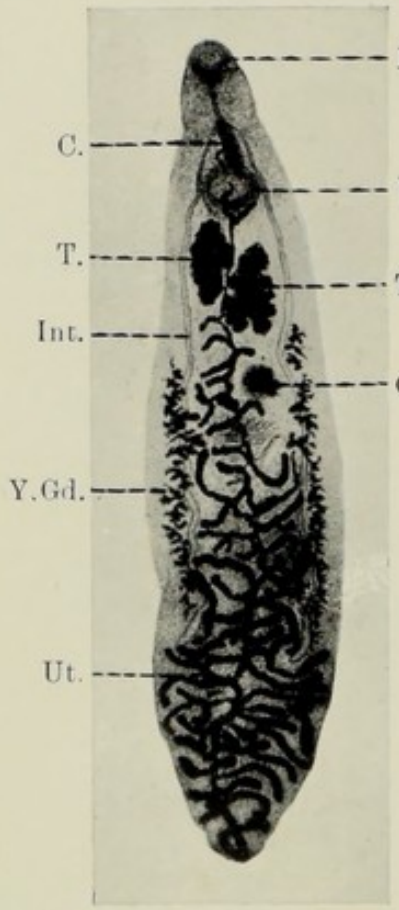


Fig. 128.—*Dicrocœlium lanceatum*. M., mouth surrounded by oral sucker; C., cirrhus recess; V.S., ventral sucker; T.T., testes; Int., forked intestinal canal; Ov., ovarian gland; Y.Gd., yolk-gland; Ut., uterine tubes. ×10

DICROCŒLIUM LANCEATUM—(Syn. *Fasciola lanceolata*; *Distomum lanceolatum*; *Dicrocœlium lanceolatum*).—This is one of the smaller fluke-worms, measuring 8 to 10 mm. in length, and 1·5 to 2·5 mm. in breadth. It occurs in the bile-ducts of sheep, cattle, horses, and other animals, but is rare in man. It has been found in association with *F. hepatica*.

OPISTHORCIS NOVERCA (Syn. *Distoma conjunctum*) and the nearly related **O. SINENSIS** (Syn. *Distoma sinense*) are found in China and Japan, India and elsewhere, their habitat being the bile-ducts of the dog and cat, as well as of man.

PARAGONIMUS WESTERMANI—(Syn. *Distoma westermani*; *D. ringeri*; *D. pulmonale*; *D. pulmonis*; *Mesogonimus westermani*).—This lung-fluke has been found in the human subject in China, Japan, Korea, and neighbouring countries, where it is the cause of **parasitic** or **endemic hæmoptysis**. It has also been found in the lungs of tigers, cats, dogs, and swine. The body of the parasite is somewhat more rounded and less flattened than the

majority of fluke-worms. It is pale reddish-brown in colour, and measures 8 to 10 mm. in length and 4 to 6 mm. in breadth and thickness. The genital orifice is situated near the posterior margin of the ventral sucker, slightly to one side of the middle line. The eggs are oval, brownish-yellow, somewhat thin-shelled and operculated, and their average longitudinal and transverse diameters are 0·09 and 0·06 respectively. In the human subject, these parasites are usually found singly within cyst-like cavities with thick connective tissue walls, associated with the bronchi. The flukes may burrow in the lung substance, especially near the surface under the pleura, and may, by penetrating the walls of the vessels, give rise to hæmoptysis. This parasite may also occur in the brain and other organs. The lung condition may be diagnosed by finding the characteristic ova on microscopical examination of the muco-purulent, rusty or blood-stained sputum. When passed, the yolk usually does not show segmentation; but if incubated in water, a ciliated miracidium may be hatched after an interval of a couple of weeks or more. The method of infection of the lungs has not yet been fully worked out.

COTYLOGONIMUS HETEROPHYES—(Syn. *Distomum*, *Mesogonimus* or *Cœnogonimus heterophyes*).—This is the smallest fluke-worm yet known, measuring about 2 mm. in length by 1 mm. in breadth. It is rare, and has been found in the human subject in Egypt.

FAMILY 3.—SCHISTOSOMIDÆ

These resemble the **Fasciolidæ** in general structure, but are bisexual, not hermaphrodite. The males are usually broader and shorter than the females, and possess thin lateral edges, which curl ventrally to form the so-called gynæcophoric canal which encloses the female. The latter is slender and thread-like, and is considerably longer and usually somewhat darker in colour than the male.

SCHISTOSOMUM HÆMATOBIUM or Blood-fluke—(Syn. *Distoma* or *Distomum hæmatobium*; *Bilharzia hæmatobia*).—This parasite is the cause of **Bilharziasis** or **endemic hæmaturia**, sometimes known as **Egyptian hæmaturia** from the frequency of its occurrence in Egypt, although it is also common in Abyssinia, the Soudan, South Africa, and elsewhere in the African Continent. Cases have also been reported in India and other parts of Asia, and its sporadic occurrence has been described in many other localities.

Morphology.—The **male** usually measures 12 to 14 mm. in length and 0·4 to 0·5 mm. in diameter. It is white in colour.

The oral and ventral suckers are placed close together at the anterior end, the genital aperture being situated in the middle line immediately behind the ventral sucker and at the beginning of the gynæcophoric canal. On account of the curling of the lateral edges of the body, the worm has a cylindrical shape instead of the leaf-like appearance characteristic of the trematodes. The outer or dorsal aspect of the body is covered with innumerable minute spine-like papillæ, which aid in the locomotion of the parasite within the veins. The bifurcation of the intestine occurs immediately in front of the ventral

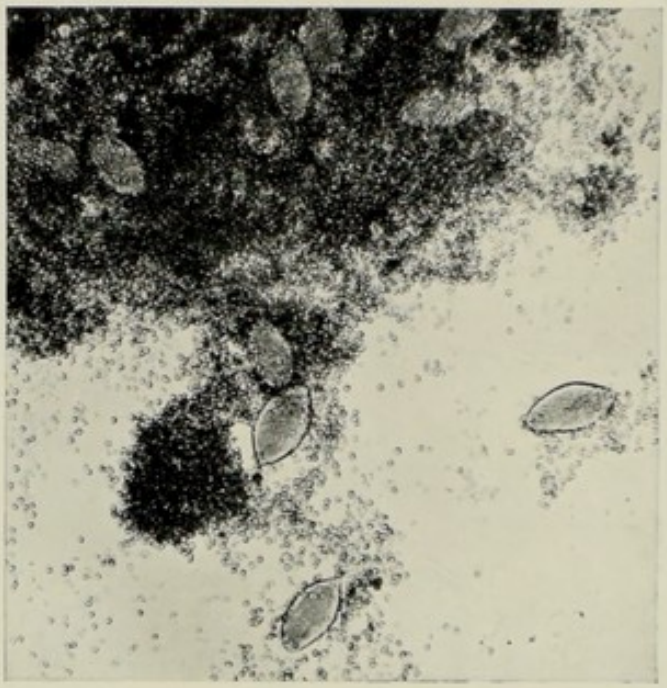


FIG. 129.—Ova of *Schistosomum hæmatobium* and red blood corpuscles in urine. × 60.

sucker, but usually reunion into a single median trunk takes place more posteriorly. The **female** is about twice the length of the male (*i.e.* about 20 mm.), and is more filiform, with tapering extremities, its average diameter being about 0·25 mm. The anterior extremity, with its two suckers, is white in colour; whilst the posterior part is greyish, and contains the reunited intestine, which runs in a zigzag manner to the posterior extremity, and, if filled with ingested blood, shows as a dark reddish or brownish line. The outer surface of the female worm is for the most part smooth, unlike that of the male, upon which it largely depends for migration. The **ova** are

of a very characteristic elliptical or lemon shape. They are non-operculated, pale yellowish in colour, and possess a thin transparent shell, with a minute sharp, thorn-like spine at the posterior extremity. Occasionally, this spine, instead of being terminal, is placed slightly towards the lateral aspect of the extremity of the ovum, a characteristic which is thought by Manson to point to the possibility of there being two different species of the worm. Looss, however, is of opinion that this lateral spine is a malformation brought about mechanically, and is found only in ova produced by **immature** females. In some cases the spine may be entirely absent.

Before these worms reach maturity they live apart in the veins of the liver, but as they become more mature they are found in pairs in the portal vein, from which they migrate—the male carrying the female in the gynæcophoric canal—to the pelvic veins, in which position maturity is attained. The ova are deposited in the small veins of the submucous tissue of the rectum and bladder, and, owing to the alternate contraction and relaxation of these organs, they are gradually moved through the tissues until they reach the interior of the organ, along with the contents of which they are expelled from the body of their host. At this stage the ova may show advanced segmentation, or more usually they contain the fully formed ciliated miracidium; and if placed in water on a microscopical slide and kept suitably warmed, the shell may be seen to split longitudinally, liberating the actively motile, free-swimming miracidium. The intermediate host has not yet been identified; and the further stages of the life-cycle can thus only be conjectured as being probably analogous to that of the liver-fluke detailed above.

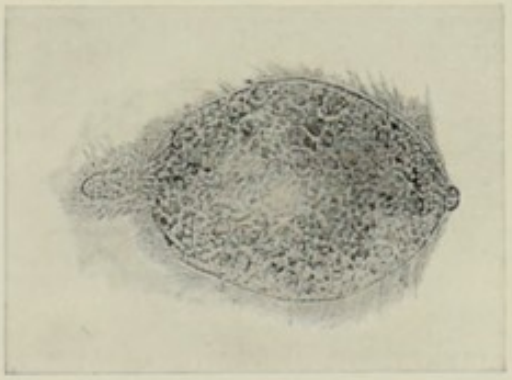


FIG. 130. — Ciliated, free-swimming Miracidium of *Schistosomum hæmatobium* hatched from ovum on warm stage. ×300.

The mode of entry of the parasite into the human body is still unknown. It has usually been supposed that it is ingested along with contaminated drinking water, perhaps in a cercarial or in some encysted form, after passage through an

unknown intermediate host. Looss, however, is of opinion that the miracidium can enter directly through the skin. It would be speedily destroyed, he says, by the hydrochloric acid of the gastric juice, and he suggests that it enters the skin from contaminated water, mud, or moist earth.

Incidence.—In Egypt the disease specially attacks males who work on the flooded land. Females are apparently much less exposed to the infection, but the disease is also found in the case of female children who play in infected water, and adult peasant women who work in the fields under the same conditions as the males. In South Africa it is much commoner in boys than in girls, perhaps because the former contract the disease while bathing in contaminated water. The periodic occurrence of the disease in Lower Egypt shows a distinct relationship to the annual flooding of the Nile. The climate must be sufficiently warm to allow of the growth of the miracidium, which is easily killed by exposure to cold.

Morbid Anatomy.—In cases in which the **urinary bladder** is specially infected, there is catarrh of its mucous membrane, with intermittent hæmaturia, and later, perhaps, pyuria and calculus formation. The ureters, pelvis of the kidney, and the kidney itself may be involved. The bladder-wall may become much thickened and infiltrated by fibrous tissue, suggesting in some cases the fibrosis of slowly developing malignant disease, and there may also be present peculiar wart-like excrescences. In these and in the thickened tissues numerous ova are usually found.

In the **rectum**, analogous changes occur, the production of polypoidal growths being common. The liver usually shows a marked proliferation of the fibrous tissue of the portal tracts, and much of the liver tissue may be replaced by dense nodules of fibrous tissue. In the female, the vagina, and also the vulva and cervix uteri, in addition to the rectum and bladder, are liable to be the seat of inflammation, and later of condyloma-like overgrowths.

By the presence of the ova in the urine and the fæces, diagnosis can be made with certainty.

SCHISTOSOMUM JAPONICUM—(Syn. *S. cattoi*).—This worm, as a parasite in man, was discovered in 1904 by Katsurada, and, later in the same year, was described by Catto. It was

found by the former observer also in dogs and cats in those districts of Japan where an endemic disease characterised by enlargement of the liver and spleen, cachexia, ascites, and diarrhœa, existed. This worm closely resembles *S. hæmatobium*, but is somewhat smaller in size; the body of the male is smooth, not tuberculated; and the ova, which are slightly smaller than those of the foregoing parasite, do not possess spinous processes. The habitat of the adult worm appears to be the smaller mesenteric veins, and perhaps the corresponding arteries. The ovum contains a ciliated miracidium, but nothing is yet known of the life-cycle.

CLASS 2.—CESTODA OR TAPEWORMS

These are endoparasitic, flattened, tape- or ribbon-like worms which do not possess an alimentary canal. The mature stage of the worm is passed in the gastro-intestinal tract—usually of vertebrates—the small intestine being its most frequent habitat. The adult tapeworm consists of a **scolex** or **head**, and a varying number of semi-independent **segments** or **proglottides**, attached to one another and forming the tape- or chain-like body or **strobila**, each segment or **proglottis** possessing when mature a complete set of male and female generative organs.

The **scolex** or "nurse," which produces the chain of proglottides by a process of asexual budding, is very small in size, being usually just visible to the naked eye. It is equipped with four disc- or cup-like, or in some cases either two or four groove-like, **suckers**, or with clinging and boring organs composed of **hooklets**, which vary considerably in number and in arrangement in the different genera. These hooklets are arranged either in a single or in a double circle around the **rostellum** or beak-like anterior extremity of the scolex, in the manner of a rosette or crown. In a few cases this rostellum is rudimentary or absent, its place being taken by a terminal sucker.

The posterior narrow part of the scolex, where it becomes continuous with the strobila, is usually termed the **neck** of the worm. As the strobila is formed by a process of serial budding from the scolex, the most distant proglottides are the largest and most mature, whilst those nearest the scolex are small, and form a slender chain of immature segments. The proglottides vary in different species from a few in number up to several thousands. In practically all the Cestodes the mature segments are **hermaphrodite**, each possessing a complete set of male and female generative organs. The form of the uterus is of importance for purposes of diagnosis, and will be referred to while dealing with the individual worms.

Tapeworms of different species vary enormously in length, *e.g.* from half a millimetre up to as much as nine or ten metres or more.

The surface is covered by a **cuticle**, lying upon the parenchymatous **basal membrane**, beneath which is the **dermo-muscular tube**. The interior of each segment is occupied by parenchyma, in which are embedded the sexual organs, muscular and nerve bundles, etc., together with certain concentrically laminated calcareous bodies. The excretory organs resemble those of the Trematodes.

DEVELOPMENT OF CESTODES. — As the proglottides become mature and the uterus within each becomes distended with **ova**, they break off from the strobila—singly or in small groups—and are passed along with the fæces, or, in some cases, they may actively make their way out of the intestinal canal.

The **ova** are rounded or oval in shape, usually brownish or yellowish in colour, and possess a thin, delicate shell, which, except in the case of Dibothriocephalus, is non-operculated in the more important varieties.

EMBRYONAL DEVELOPMENT.—This usually occurs while the ovum is still within the uterus, but it may take place immediately after its discharge. Segmentation occurs, and **two** envelopes are formed around the embryo. The outer of these, the **investing envelope** or **integument**, usually remains attached to the interior of the delicate shell, and is left behind on hatching. The inner envelope or **embryonal shell** is sometimes, as in the case of the free-swimming embryo of *Dibothriocephalus*, covered with cilia, but is more commonly composed of radially arranged, calcified, rod-like bodies, which produce its characteristic striate appearance. In the interior of this lies the embryo, which has now developed into a rounded or perhaps slightly elongated body, armed with three pairs of hooklets. This **onchosphere**, or **hexacanth**, as the embryo is now called, on leaving the intestine of the definitive host, may be discharged through the "birth-pore" or uterine aperture, or may be freed by the rupture or disintegration of the distended proglottis.

CYSTICERCUS or "**BLADDER-WORM**" **STAGE.**—After ingestion by a suitable intermediate host, the embryonal shell or envelope is dissolved off, and the active, six-hookleted embryo proceeds to bore its way through the intestinal wall. By way of the lymphatics, or more probably by the mesenteric veins, it reaches the liver, which, in the case of *T. echinococcus*, forms the special habitat of the bladder-worm stage. In other instances the embryos travel from the liver—probably by way of the blood-stream—to the muscles or other tissues of the host's body. In whatever situation it is finally lodged, the embryo settles down and becomes passive, loses its hooklets, and undergoes distension with fluid in the case of the tape-worms classified as *Cystici* (e.g. *Tænia solium*, *T. saginata*, and others), thus forming a cyst and entering upon the **bladder-worm** or **cysticercus stage** of its development. In certain tapeworms—the *Cystoidei*—this cystic formation is very slight and rudimentary. In others—the *Echinococci*—the onchosphere becomes enormously distended, and, by proliferation of its cellular internal germinal layer or endocyst, other endogenous secondary or daughter cysts may

be formed, in the interior of which are budded off the "**brood-capsules**," or in some cases a third generation of cysts—"grand-daughter cysts"—may precede the formation of these. In yet a fourth set—the *Plerocerci*—the embryo or onchosphere, in this case termed a "**plerocercoid**," appears to become directly transformed, without cyst formation and metamorphosis, into the scolex of the adult worm, and a certain degree of budding of proglottides may even occur while the parasite is still within the tissues of the intermediate host—sexual maturity, however, not being reached without the usual transference to the intestine of the final host. This form of development occurs in the *Dibothriocephalidæ*, in which the worm may attain a length of 30 mm. in the intermediate host before such transference occurs.

Except in the *Plerocerci*, in which the scolex is, as has just been stated, formed **directly** from the body of the onchosphere without cyst-formation, proliferation of the cells of the cyst-wall occurs at the pole opposite to that at which the six discarded hooklets were situated. The proliferated cells form a hollow bud, usually single, but sometimes, as in the case of *Cœnurus*, multiple, each bud forming a scolex. This bud projects into the cavity of the cyst, and in its interior are developed the suckers, hooklets, rostellum, etc., or other equipment of the adult scolex.

DEVELOPMENT OF THE SCOLEX INTO THE ADULT WORM.—No further development of the **cysticercus** now occurs until the tissues of the intermediate host in which it lies are eaten by the final host, in whose intestinal canal all the parts of the **cysticercus** except the scolex are digested off, the scolex becoming evaginated or turned inside out like the finger of a glove, the suckers being therefore now situated externally as in the adult worm. By means of its suckers and hooklets, if both of these varieties of organ are present, it attaches itself to the intestinal wall of its host, usually in the region of the duodenum or upper part of the jejunum; and it then proceeds to produce the series of proglottides which, together with the scolex, form the adult tapeworm.

Although there are great numbers of tapeworms which are parasitic in the lower animals, only four are of special importance as parasites in man, three of these passing their adult stage, and the fourth—*Tænia echinococcus*—its immature stage in man. The three adult forms are *Tænia solium*, *Tænia saginata*, and *Dibothriocephalus latus*.

FAMILY—TÆNIIDÆ

TÆNIA SOLIUM, the **Armed** or **Pork Tapeworm.**—The average length of this worm is about two to three and a half metres, though it may occasionally be as much as double these dimensions. The **scolex**, which somewhat resembles the head of a small pin in shape, is generally rather less than one

millimetre in diameter, and possesses a retractile terminal **rostellum**, a double crown of **hooklets**, alternately larger and smaller in size, and usually just under thirty in number, and four disc-like **suckers**. The **neck** is somewhat filiform. The **strobila** usually consists of 800 or 900 **proglottides**, which gradually increase in size as they recede from the head. When mature, they are oblong, the longitudinal diameter being considerably greater than the transverse (averaging about 10 × 5 mm., or rather more). The uterus is composed of a median

FIG. 131.—Scolex of *T. solium*, showing hooklets and suckers. × 24.

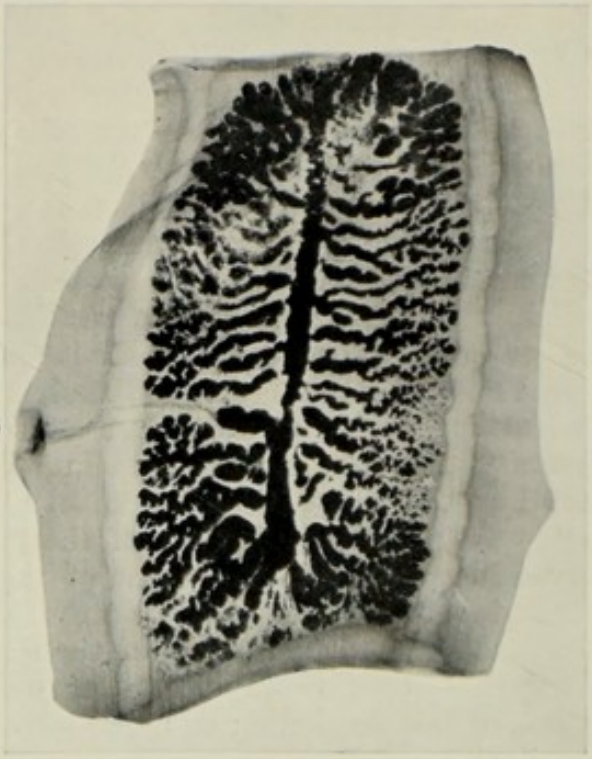


FIG. 132.—Mature Proglottis of *T. solium*, showing uterus, and lateral genital orifice (*a*). × 4.

longitudinal trunk, with about seven to ten transversely placed lateral offshoots, possessing somewhat numerous secondary diverticula. The genital orifices are marginal, usually slightly behind the centre of each segment, and alternate with comparative regularity. The **ova** are thin-shelled, and the **onchospheres** are surrounded by a thick, symmetrically rounded, brownish or brownish-yellow, radially striated embryonal envelope, measuring about 30 to 36 μ in diameter, the globular six-hookleted onchosphere in its interior being about 20 μ in diameter. The segments, which are less actively motile than those of *T. saginata*,

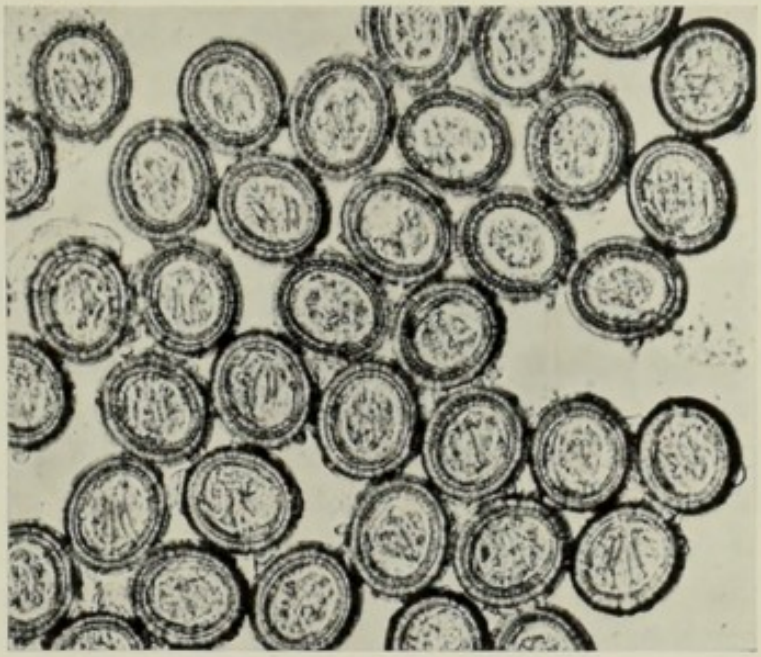


FIG. 133.—Onchospheres of *T. solium*, showing radially striated embryonal envelope, and globular, six-hookleted embryo. ×300.

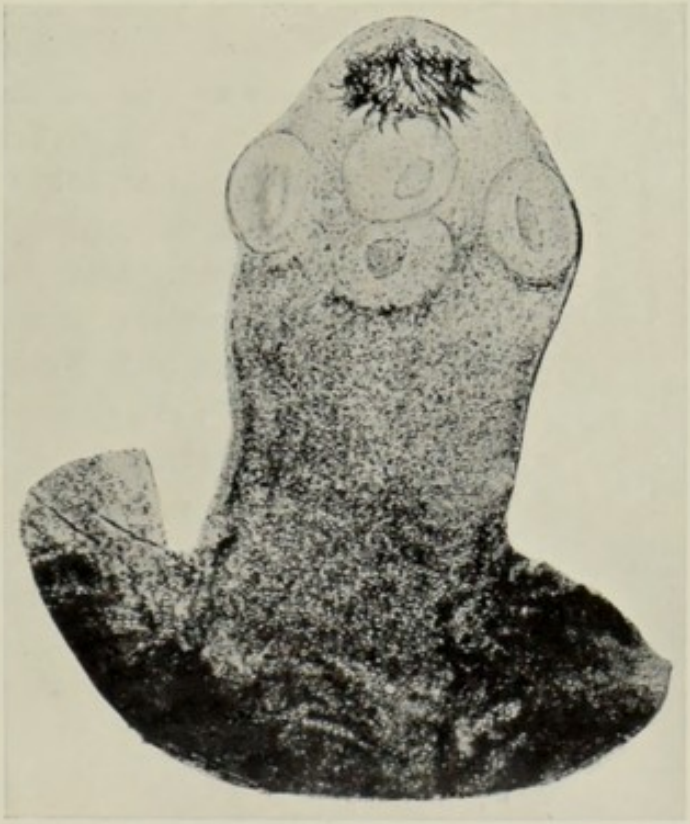


FIG. 134.—Cysticercus cellulosæ or bladder-worm stage of *T. solium*, showing development of scolex armed with hooklets and four suckers ×32.

tend to be voided in short chains from the intestine. In its mature stage, *T. solium* is found only in man; the immature or **cysticercus** stage—the so-called **cysticercus cellulosæ**—occurring especially in the intramuscular connective tissue of the pig, and less commonly in other mammals. It is also by no means infrequent in man, not only in muscle, but in various organs, especially the eye and the brain. In the latter organ the cysts may attain a considerable size, and may develop numerous diverticula, for which reason they have been termed the *Cysticercus* "*racemosus*," "*botryoides*," or "*multilocularis*." In the eye, **cysticerci** have been known to persist for as long as twenty years. In the pig the condition is known as "**measly pork**," the cysticerci forming little, elliptical, bladder-like vesicles, which can easily be seen with the naked eye, their average length being about 8 or 10 mm.

Tænia solium is very common in certain parts of Germany, France, Italy, and Britain, but is naturally rare in Eastern countries where pork is not eaten.

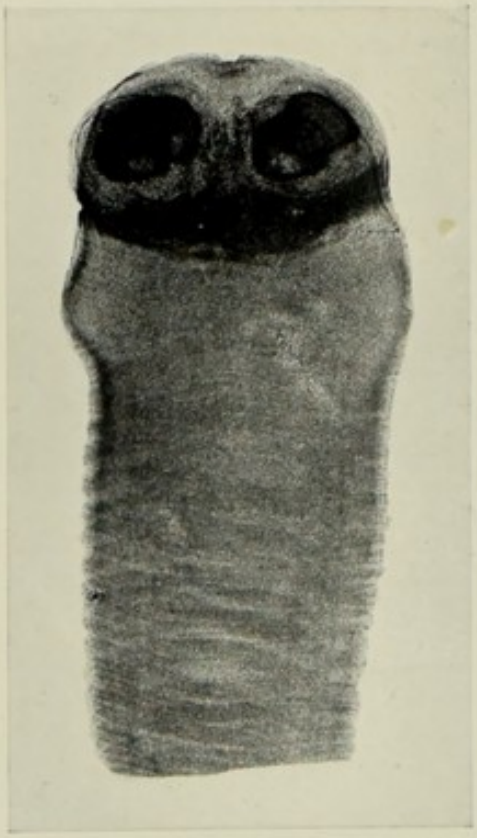


Fig. 135.—Scolex of *T. saginata*, showing suckers and absence of hooklets. ×20.

TÆNIA SAGINATA—(Syn. *T. mediocanellata*, *T. inermis*)—the **unarmed** or **beef tapeworm**—is usually somewhat longer than the pork tapeworm, its average length being from four to eight or ten metres. As a rule, only one parasite is found, whilst in the case of *T. solium* several adult worms may be present at one time in the intestine of the same patient, man being the specific final host of both varieties.

The **scolex** is somewhat cubical in shape, measuring 1·5 to 2 mm. in diameter. It possesses four cup-like suckers, but no rostellum or hooklets. The **proglottides** usually number over a thousand, gradually increasing in size

on passing backwards, and, as they mature, coming to measure 16–20 mm. in length by 4–7 mm. in breadth. The genital pore is marginal, opening slightly behind the centre of each segment, and alternating irregularly. The centrally placed uterine trunk gives off from 20 to 35 transverse lateral branches, which in

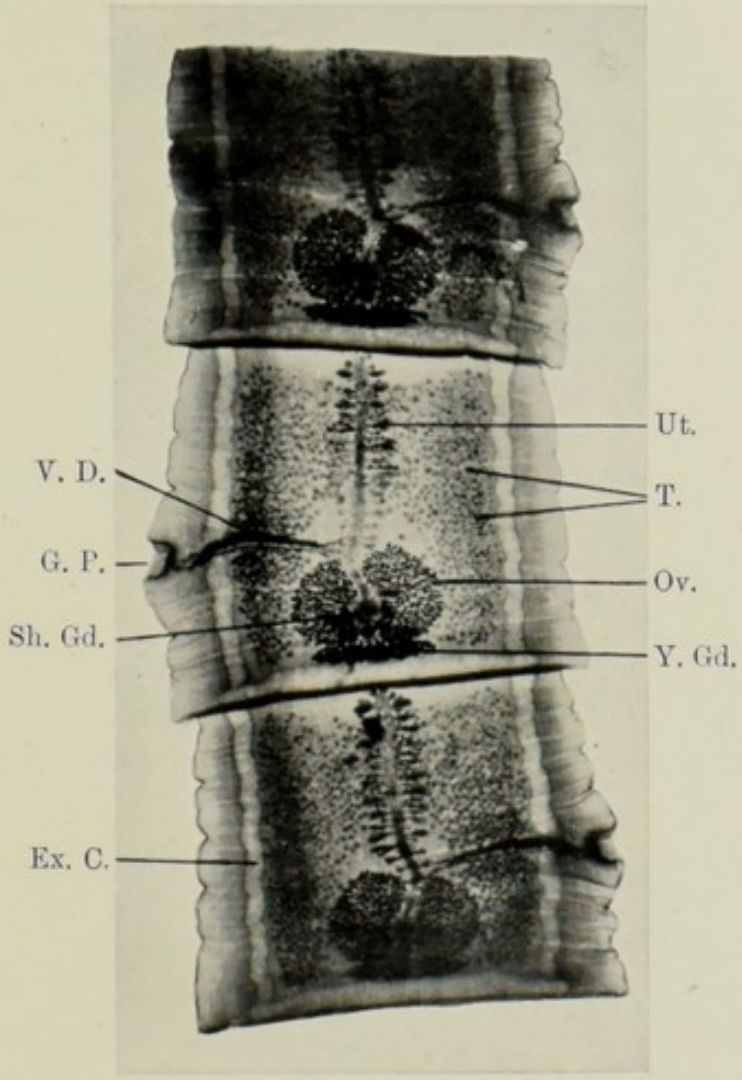


Fig. 136.—Immature Proglottides of *T. saginata*. Ut., uterus; T., testes; Ov., ovaries; Y. Gd., yolk-gland; Sh. Gd., shell-gland; G. P., genital pore; V. D., vas deferens, immediately beneath which lies the oviduct; Ex. C., excretory or water-vascular canal. Transverse canals joining the lateral longitudinal canals at posterior part of each segment. Note alternation of genital pores in successive segments. × 8.

turn may show a few secondary subdivisions. The segments are more muscular and motile than those of *T. solium*. They may leave the intestine singly or in short chains. The **ova** are rounded and thin-shelled, and contain an **onchosphere** with a radially striated embryonal investment closely resembling that

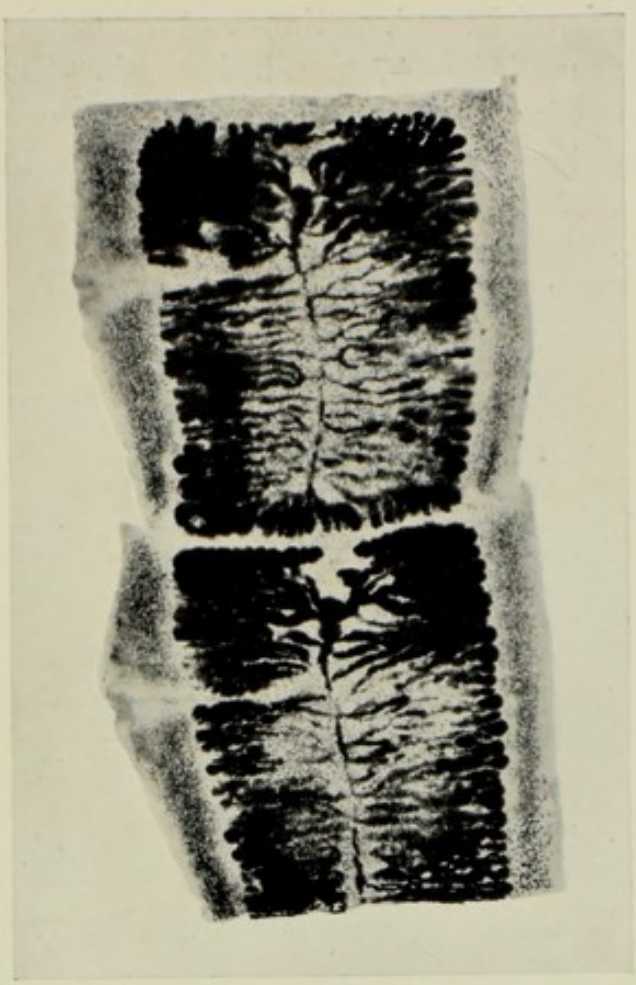


FIG. 137.—Mature Proglottis of *T. saginata*, showing uterus. ×6.

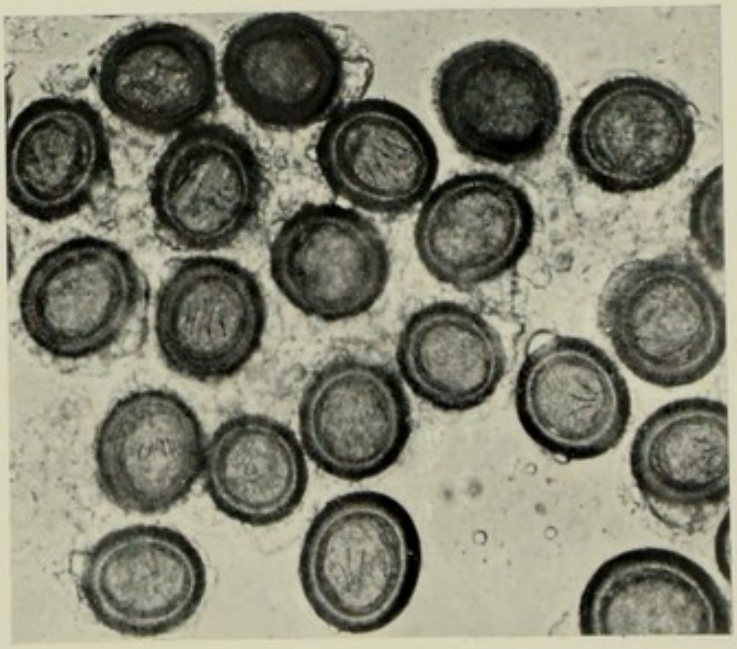


FIG. 138.—Onchospheres of *T. saginata*. ×300.

of *T. solium*, except for the fact that it is usually somewhat oval (30 or 40 by 20 or 30 μ in diameter), whereas the onchosphere of the pork tapeworm is more nearly spherical in outline.

The bladder-worm stage—**cysticercus bovis**—is passed in the ox, the little elliptical cysts measuring from 7·5 to 9 mm. in length by 5·5 mm. in breadth. The cysticerci are usually not numerous, and are specially found in certain of the muscles of mastication. They very rarely occur in man.

The adult worm is specially found in Eastern Europe, and in Asia, Africa, and some parts of South America. It is extremely common in Abyssinia and in certain districts of India. The worm is usually attached high up in the small intestine, burying its head among the villi. It can be detached only with difficulty; and because of this, and on account of its greater muscularity and more active movements, it gives rise to greater irritation than does *T. solium*.

TÆNIA ECHINOCOCCUS—(Syn. *T. nana*; *Echinococcifer echinococcus*). — This parasite is one of great importance, the presence of its immature stage in man constituting the serious disease known as **Hydatids**.

FIG. 139. — *T. echinococcus* (adult). ×15. (After Leuckart.)

The **adult** is a small tapeworm, varying from 2·5 to 5 or 6 mm. in length. It inhabits the intestine of the domestic dog, in which it is extremely common, and often present in large numbers. It is also found in the fox, wolf, and jackal, but has never been found in man. The **scolex**, which is like a miniature of that of *T. solium* in appearance, is usually about a third of a millimetre in breadth, and is armed with four suckers and numerous hooklets, usually thirty or forty in number, arranged in a double circle around the rostellum, those of the inner circle being the larger and measuring 40 to 45 μ in length, whilst those of the outer row are usually between 30 and 40 μ in length. The whole worm consists of the scolex and three, or occasionally only two, segments, the last of which alone is mature, and

may exceed the rest of the worm in size. The uterus consists of a central trunk with lateral protuberances; and the genital aperture is lateral, and situated slightly behind the middle of the segment. The **ovum** is thin-shelled, the enclosed embryonal envelope being also somewhat thin, rounded, and radially striated. It measures 30 to 36 μ in diameter. The **onchospheres** are discharged in or from the terminal segment, and may be ingested by man in contaminated drinking water, in dust, or by using imperfectly cleaned dishes from which dogs have been allowed to feed. The embryonal envelope is dissolved off in the alimentary canal, and the liberated onchosphere or six-hooked embryo then makes its way to the tissues —most commonly the liver, peritoneum, lungs, or pleura—in which it settles down and passes its cystic stage. It may also, however, be found in the spleen, heart and pericardium, brain, spinal cord, kidneys, muscles, subcutaneous tissue, the eye, or elsewhere. In some of these positions, especially in the peritoneum, the cysts may form large masses; and in whatever position they are found, they usually give rise to very serious results.

STRUCTURE AND DEVELOPMENT OF THE HYDATID CYST.—These have already been outlined on page 380, but a somewhat more detailed account of them is needful. The following structures may be distinguished:—

i. **An outer covering of fibrous tissue**, derived from the proliferation of the connective tissue of the organ or other structure in which the parasite is growing. In some situations this "**capsule**" may be slight, or even absent.

ii. **The ectocyst**—the true cyst-wall or **hydatid membrane** —is composed of a stratified elastic cuticle, which in turn encloses within it the more delicate endocyst or germinal layer. The ectocyst is opaque, whitish in colour, somewhat opalescent, and bears some resemblance to boiled white of egg in appearance. It may be stripped off in delicate layers, the laminæ tending to curl inwards.

Microscopically, it shows fine concentric lamination, each lamina exhibiting a delicate cross striation.

Chemically, the material of which it is composed resembles chitin in composition.

iii. **Endocyst.**—This consists of a cellular germinal layer, which

may in turn be differentiated into an **outer layer** of smaller cells, and an **inner layer** of larger, somewhat hexagonal cells. Muscular fibres and calcareous bodies are also described as occurring in the endocyst. From the endocyst are developed bud-like projections or **brood-capsules**, which become hollow, and within each of which a varying number of **scolices** develops. Several "generations" of endogenous cysts may be formed from the germinal layer, the "mother cyst" coming to contain several "daughter cysts," in the interior of which there may develop "granddaughter" and even a further generation of cysts before the development of the **brood-capsules** in their interior.

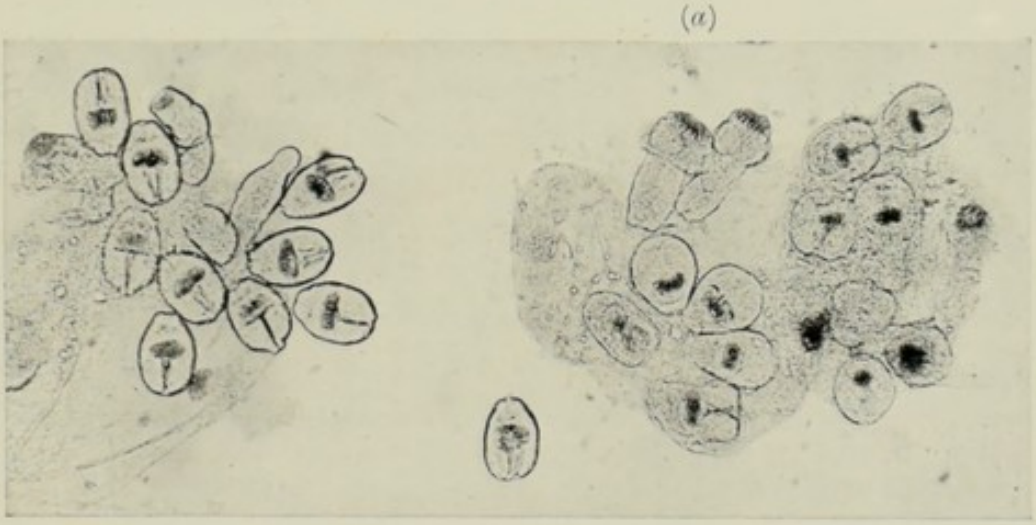


FIG. 140.—Ruptured brood-capsules of *T. echinococcus* with numerous scolices, which are mostly still inverted or invaginated. Two scolices at (*a*) have become everted or evaginated. × 60.

These endogenous cysts and the brood-capsules are filled with and float in a clear, limpid, watery fluid of low specific gravity —usually 1004–6, or a little more. This fluid contains almost no albuminous material (unless inflammation has occurred). About half the total amount of solid constituents consists of sodium chloride; whilst traces of other salts, as well as of dextrose, cholesterin, leucin, tyrosin, succinic acid, and some toxic substance of the nature of a leucomaine are also found. The **brood-capsules** possess a structure somewhat similar to that of the parent cyst, but with the layers reversed, *i.e.* a thin cuticular layer internally, and a cellular layer on their outer surface. Authorities differ as to the exact method of scolex formation, some regarding them as endogenous buds, whilst Leuckart, who

is supported by Stirling and Verco,[1] is of opinion that they are formed as "an externally situated club-shaped process, perforated longitudinally by a canal-like continuation of the interior cavity of the brood-capsule." At the distal end of this protrusion the suckers and hooklets characteristic of the adult scolex are developed. After further development, the head becomes invaginated into the interior of the brood-capsule, just as the finger of a glove might be pushed into the body of the glove and at the same time turned outside in. Ten, fifteen, or twenty scolices may thus be formed within each brood-capsule, of which there may be many thousands present within the larger cysts. The base of the young scolex, by which it is attached to the interior of the brood-capsule, becomes constricted, loses its lumen, and forms a delicate pedicle attaching the scolex, which has now become a somewhat globular or slightly ovoid body, in the interior of which are the hooklets and suckers. In this form it remains until it is ingested by the final host, in whose alimentary canal all parts except the scolex disappear. The scolex itself becomes evaginated, attaches itself to the mucous membrane of the intestine, and develops into the adult worm by the usual process of budding.

FIG. 141. — Hydatid Scolex under slightly higher power to show hooklets. The head is still in the inverted position. Note pedicle at upper part. × 200.

Varieties of Cyst:—

i. In some cases there may be only **a single large cyst**, without daughter cysts, the brood-capsules being situated on its inner surface. This form is said by Braun to occur especially in domesticated animals, though Stirling and Verco state that in their experience in Australia it is not common in the domestic herbivora, while it is frequently found in man.

ii. "**Acephalocysts**" or **sterile cysts** resemble the above, but remain barren, *i.e.* do not develop brood-capsules in their interior. These are specially found in cattle.

iii. **Endogenous Cysts**, *i.e.* "mother-cysts," producing

[1] Stirling and Verco, "Hydatid Disease," Allbutt and Rolleston's *System of Medicine*, 1907, vol. ii., part ii., p. 976.

"daughter-" and "granddaughter-cysts," etc., by a process of endogenous or "cyst-within-cyst" formation. This method of development occurs specially in the case of man, and is rare in cattle.

iv. **Exogenous Cysts** are similar to the foregoing, except for the fact that the daughter-cysts are formed externally to the parent-cyst. All the four above-mentioned varieties are believed to be merely different forms of the **same** parasite, growing, it may be, under different circumstances and in different positions. Thus in man the cysts occurring in the liver commonly multiply endogenously; whilst those in bone are almost always, and those in the brain very frequently, exogenous.

v. **Alveolar Cysts.**—Alveolar Hydatids, or hydatids with an alveolar arrangement of the cysts, are rare in man, and are more usually found in cattle, giving rise to a sponge-like growth, which may in some cases resemble a colloid cancer in its naked-eye appearance.

They are most commonly found in the liver. It is important to note that, though the cyst-wall possesses both chitinous cuticular and cellular parenchymatous elements in its structure, the latter is found not only internal but external to the former, and hence reproduction of scolices occurs outside as well as inside. According to the work of Melnikow-Raswedenkow,[1] not only scolices, but actively amœboid **embryos** are developed, and these lead to extension both locally and at a distance. Further, he maintains that highly virulent toxins are elaborated by the parasite. Most of the cases of alveolar hydatids have occurred in Central and Eastern Europe. None have been reported from Great Britain, or from Australia or Iceland, where the ordinary *T. echinococcus* "*hydatidosus*" is so common; and it would thus seem probable that the parasite of this disease is specifically distinct from the *T. echinococcus*. Its complete life-cycle is still unknown.

Secondary Changes which may occur in hydatid cysts.—Spontaneous cure may in some instances occur. The hydatids may die off and the fluid become gradually absorbed. The cyst may shrink, its contents degenerating, and perhaps undergoing calcification, the hooklets persisting, and remaining recognisable microscopically for a very long period. Such changes may possibly be produced by the entrance of bile, or by injury to the cyst-wall.

Inflammatory changes and the formation of pus, due to the entrance of bacteria—e.g. *B. coli*—may occur, and, as a result,

[1] Melnikow-Raswedenkow, *Studien über den Echinococcus alveolaris sive multilocularis*, 1901.

spontaneous evacuation may take place. If the cyst is in the liver, such evacuation may be through the diaphragm into the pleural cavity or into the lung if there are adhesions present, and the contents, having passed into the bronchi, may be expectorated. On the other hand, the cyst may rupture into the peritoneal cavity, and wide-spread growth of hydatids be thus set up there.

DIPYLIDIUM CANINUM—(Syn. *T. canina*; *T. cucumerina*; *D. cucumerinum*).—This tapeworm is a common intestinal

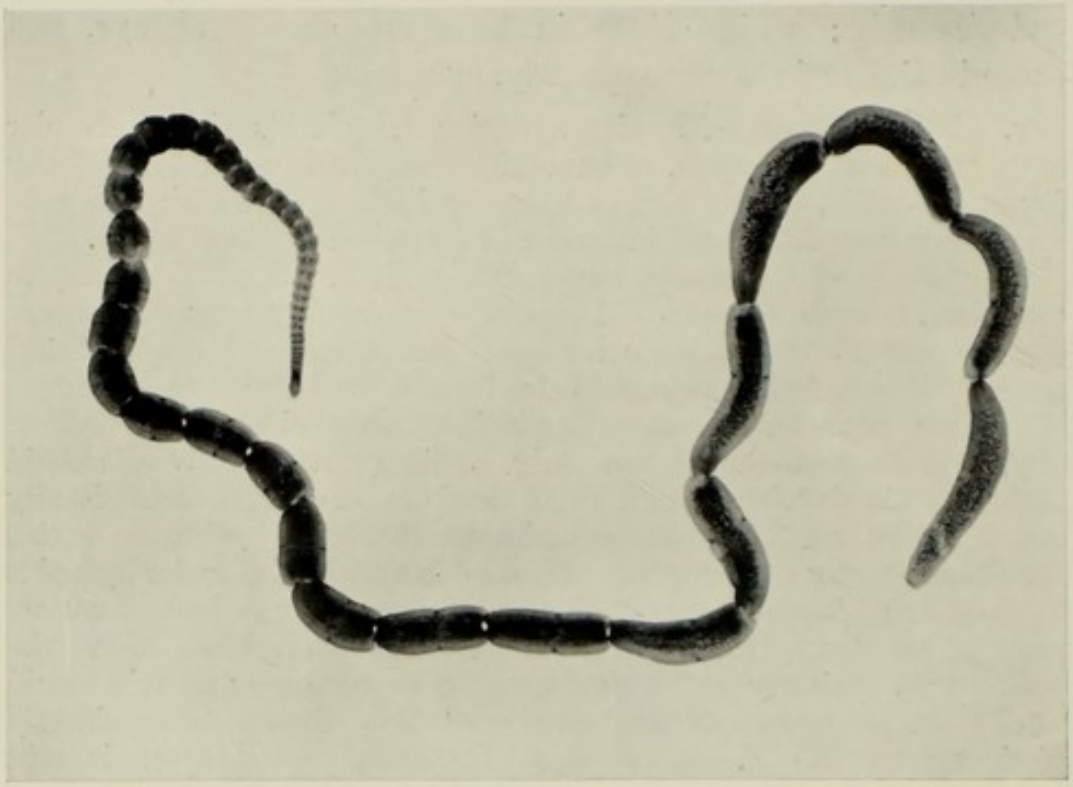


FIG. 142.—*Dipylidium caninum*, showing the general structure of a tapeworm, *i.e.* head or scolex, neck, immature and mature proglottides. ×4.

parasite of dogs and cats, but it is occasionally also found in the human subject, especially in young children who play with these animals. The worm usually measures from 15 to 35 cm. in length and 1·5 to 3 mm. in breadth. The **head** possesses four suckers and a hookleted rostellum; and the mature **segments**, which resemble cucumber or melon seeds in appearance, are 6 or 7 mm. long and 2 or 3 mm. broad, and are usually of a somewhat reddish colour. Each segment contains a single, centrally placed, reticulated uterus, whilst the other sexual organs are arranged in two similar sets, situated one on either side of the

uterus, one genital pore opening symmetrically at each lateral border.

DIBOTHRIOCEPHALUS LATUS—(Syn. *T. lata*; *Bothriocephalus latus*; *Dibothrium latum*).—This is the longest tapeworm found in man, in whom it may attain a length of from 2 to 9 metres or more. It is greyish-yellow in colour. The **head**, which is very minute, is elongated and somewhat flattened at the sides, or almond-shaped, with deep, lateral, longitudinal, suctorial grooves. It possesses no hooklets or rostellum. The **neck** is extremely delicate. The **proglottides** may number 3000 or 4000, or more. Towards the middle of the worm each segment measures about 4 or 5 mm. in longitudinal and 10 to 12 mm. in transverse diameter. Towards the posterior end they become narrower and more elongated, the terminal segments being almost square in outline, and containing little but the dilated uterus, which is centrally placed and consists of numerous transversely directed convolutions which, in the ripe segments, give it the rosette shape so characteristic of this worm (fig. 144). The sexual openings are situated on the flat surface of each segment, somewhat anterior to its centre.

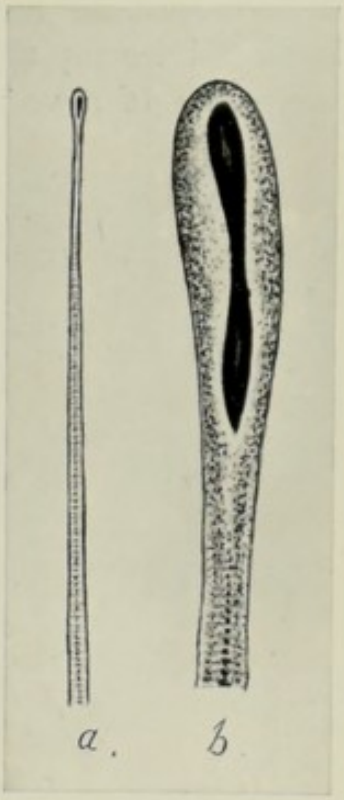


FIG. 143.—*Dibothriocephalus latus.*
a. Scolex, neck and commencement of strobila (natural size).
b. Anterior extremity of the same more highly magnified.

The *ova*, unlike those of *T. solium* and *T. saginata*, do not undergo full embryonic development while still in the uterus. They retain their thin, brownish, operculated shells after they have been discharged and evacuated along with the intestinal contents. If carried to water, a free-swimming onchosphere with a ciliated embryonal envelope is hatched after an interval of several weeks. Its complete life-cycle is at present unknown. The ciliated embryo apparently enters an intermediate host—usually a fresh-water fish, such as the pike, burbot, perch, certain of the salmonidæ, etc.—and it there develops into the scolex of the adult worm. In the flesh of the fish it is trans-

ferred to the alimentary canal of its final host, *e.g.* man, dog, cat, etc.; and if not killed by efficient cooking, it then rapidly develops into the adult worm. It is most commonly found in Central and Eastern Europe and in Asia, especially Turkestan and Japan.

In the majority of cases, the symptoms produced in man are not very serious, but in certain instances, probably owing to the secretion of some toxin or to poisons produced by the death and decomposition of the worm itself, it may lead to the production of a very profound anæmia, resembling pernicious

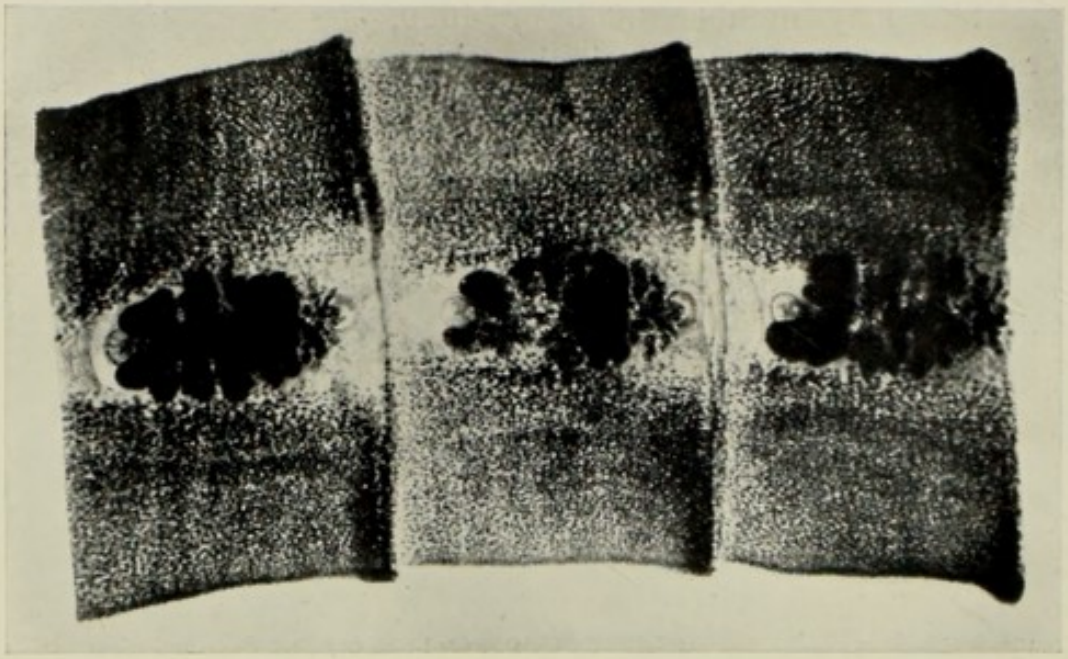


Fig. 144.—Mature Proglottides of *Dibothriocephalus latus*, showing central rosette-shaped uterus. × 8.

anæmia in type. Recovery, however, usually takes place after the expulsion of the worm. The diagnosis can be made by the examination of the fæces for ova and segments.

PHYLUM.—II. NEMATHELMINTHES

CLASS 1.—*NEMATODES, Round-Worms* or *Thread-Worms*

The **Nematodes** are elongated, cylindrical, filiform, or slightly spindle-shaped worms. They are non-segmented, and are covered by a chitinous cuticle, which may show transverse striation. They usually taper towards the head or anterior extremity, where the mouth, which may often show certain characteristic peculiarities in

structure, is situated. The sexes are in nearly all cases separate, the male being generally smaller than—usually about half the length of —the female. The posterior extremity may be tapering or rounded, and is generally straight in the case of the female; whilst in the male it is usually curved, and may show peculiar modifications, such as the development of a bursal or wing-like expansion, or it may be bilobed.

DEVELOPMENT.—Fertilisation of the ova occurs within the uterus. The female is usually oviparous, but is sometimes ovo-viviparous, or in a few cases viviparous. The embryos are minute, filiform, worm-like bodies, which generally lie coiled up within the ova. In some cases these embryos, apart from their smaller size, closely resemble the parent worm. In other instances they at first may possess certain characters which they eventually lose by a process of metamorphosis, and must then be regarded as **larval** forms.

These miniature nematodes may reach the alimentary canal of their next host while still contained within the egg; or they may hatch in the open, and live in mud or water or elsewhere before entering the body of the final host. In other important instances, *e.g.* in the **Filariæ**, the immature forms are present in the blood of the definitive host, and do not undergo further development until they are transferred to the body of an intermediate host—often a blood-sucking insect—*e.g.* a mosquito in the case of *Filaria sanguinis hominis*, in which they then undergo metamorphosis.

In certain exceptional cases, *e.g.* in *Trichinella*, the embryos do not leave the body of the host which harbours the parent worms, but utilise it also as the intermediate host, encysting in the muscles or elsewhere, until they are transferred, along with the tissue in which they are embedded, to the alimentary canal of the second host, which may or may not be of the same species as the first. In their new host they then undergo further development and become mature.

In other nematodes what is known as **Heterogony** occurs, in which there may be alteration of fully developed sexual generations, one generation being perhaps hermaphrodite, and the other dicœcious, as in *Rhabdonema*. The bisexual *rhabditis* forms, as they are termed, are free-living, and are much smaller than the hermaphrodite parasitic form.

Some nematodes are parasitic only during their larval stage, the adult form being free-living in water or in mud.

FAMILY 1.—ASCARIDÆ

In the members of this family, the mouth is provided with three lip-like papillæ, one dorsal and two ventral. The œsophagus possesses a bulb-like expansion. The tail of the male is curved, and the genital aperture is furnished with two spicules and numerous small papillæ. The female genital opening is situated, as a rule, anterior to the middle of the worm, which is oviparous. No intermediate host is required, development being direct.

ASCARIS LUMBRICOIDES or common ROUND-WORM.—This parasite somewhat resembles the common earth-worm in appearance, having a long, cylindrical body, tapering towards both ends. The **female** may measure from 20 to 25 or even as much as 40 cm. in length, and about 5 mm. in diameter; the length of the **male** being from 15 to 17 up to 25 cm., and its breadth about 3 mm. In colour they are reddish or greyish-yellow. In their general characters and structure these worms conform to the family description given above, the tail of the female being straight, and that of the male strongly hooked or curved ventrally.

The **ova** are oval in outline, measuring 50 to 70 μ in length by 40 to 50 μ in breadth. They possess a transparent shell, surrounded externally by a thick albuminous envelope, which has a rough, knobbed, or mammillated appearance externally, and which stains yellowish-brown with the bile of the fæces, in which it may occur in enormous numbers. The ova when passed are usually unsegmented, the embryo taking several weeks to develop. They are very resistant, and may survive desiccation, cold, etc., for a prolonged period. In favourable circumstances they may remain alive for as long as five years or more. Infection appears to be due to the direct ingestion of the ovum with its contained embryo, no intermediate host being necessary.

The parasite occurs especially in the upper and middle parts of the small intestine, but it may occasionally find its way into the stomach. Usually only a few worms are present, *e.g.* two to six, but in exceptional cases enormous numbers may be found. Its geographical distribution is practically universal.

The pathological effects of the presence of the worm in the intestine vary greatly. They may be slight, or in other cases may produce severe nervous symptoms, but whether these are toxic or merely reflex in nature is not known. They may cause obstruction of the common bile-duct or pancreatic duct; and in exceptional cases they may bore through the intestinal wall, and give rise to peritonitis or to localised abscess formation.

Occasionally the worm may migrate up the œsophagus and appear in the mouth or nose. Cases of suffocation due to their impaction in the glottis have been described. In some febrile

and toxic diseases, and also sometimes just before the death of the host, the worms may migrate from the body.

OXYURIS VERMICULARIS—The THREAD-WORM or SEAT-WORM.—These are small, white round-worms, the **female** measuring some 10 mm. in length by about 0·5 mm. in breadth, and the **male** usually 3 to 5 mm. by 0·16 to 0·2 mm. The posterior end of the male is truncated and markedly curved, and is furnished with a single spicule and six anal papillæ, while that of the female is long and tapers to a sharp point.

Female. Male.

FIG. 145.—*Oxyuris vermicularis*, showing relative size of male and female, and characteristic curved tail of the former. ×10.

The **ova** are minute, oval, thin-shelled bodies, measuring about 50 μ in length and 16 to 24 μ in breadth, and are somewhat flattened on one side. They usually contain a small, coiled-up embryo, which is not liberated from the shell until it reaches the human stomach. Direct infection occurs through the mouth, to which the ova may be conveyed by the fingers, *e.g.* infected finger-nails, or by fruit or vegetables, dust, etc. which have been contaminated with the ova. Development is complete in three or four weeks. The ova keep well when dry, but are said to perish after prolonged immersion in water. An intermediate host is not required.

These parasites are common in children. The habitat is the small intestine and cæcum, and perhaps the upper part of the colon. The impregnated females, when mature, descend into the rectum, where they produce their ova, they themselves passing out with the fæces. They may also pass out *per anum*, especially when the patient is warm in bed, and may cause great itching and irritation. They may enter the vulva, vagina, or bladder, giving rise to considerable irritation in these parts. Their presence in the intestine may, in some instances, produce little or no obvious pathological effects, but in other cases, and

especially in weakly children, they may cause serious reflex nervous symptoms, fits, enuresis, etc. Severe eczema may in some cases be produced around the anus.

FAMILY 2.—STRONGYLIDÆ

This is a large and important family, the members of which are characterised by the possession of six oral papillæ, and the mouth may also be armed with chitinous teeth. The posterior extremity of the male is furnished with an umbrella-like copulatory expansion and one or two spicules.

EUSTRONGYLUS GIGAS—(Syn. *Strongylus gigas*).—The giant strongyle is the largest nematode found in man, in whom, however, it is very rare. It is blood-red in colour, the **female** attaining sometimes the length of 100 cm. and a breadth of 12 mm. The length and thickness of the **male** are usually a little less than half those of the female worm. The anterior extremity is tapering, and the posterior extremity of the male is furnished with a collar-like bursal expansion and a single spicule.

The **ova** are oval in shape, and possess a thick, brownish shell, which shows numerous small irregular depressions externally.

The habitat of this worm is the pelvis of the kidney of the seal, otter, dog, horse, and other animals, and only very exceptionally of man, in whom it may be diagnosed by the hæmaturia and the presence of the characteristic ova in the urine.

ANKYLOSTOMA DUODENALE or HOOK-WORM—(Syn. *Dochmius anchylostomum*; *Strongylus duodenalis*; *Dochmius duodenalis*; and, in America, *Uncinaria duodenalis*).

This extremely important parasite is, in its adult form, the cause of **Egyptian chlorosis**, **miners' disease**, **miners' anæmia**, **brickmakers' anæmia**, or **tunnel-disease**; whilst its embryonic form may cause skin eruptions variously known as **ground-itch**, **coolie-itch**, etc. It is widely distributed throughout most tropical and subtropical countries, more especially in Egypt, India and Ceylon, the Far East, Brazil, and many other parts of America, etc. It is also found in Southern Europe, having been first discovered by Dubini in Italy in 1843. It is also endemic in certain parts of Germany, Austro-Hungary, and other parts of Central Europe; and in Cornwall, among the tin-miners, it is by no means uncommon.

The worm is cylindrical in shape, the head being somewhat tapering, and the posterior extremity more truncated. The length of the **female** varies from 12 to 18 mm., and its breadth

is usually about 1 mm. The anus is subterminal, and the posterior extremity is furnished with a small spine. The vulvar orifice is situated ventrally, and is slightly behind the junction of the middle and posterior third of the body. The **male** is usually from 8 to 10 mm. in length, and about 0·4 to 0·5 mm. in diameter; and its posterior extremity is furnished with a characteristic umbrella-like copulatory bursa, supported by eleven chitinous rays or ribs, and possessing three (two large lateral and one smaller dorsal) wing-like processes. The genital orifice, situated in the concavity of the bursa, is equipped with two long, slender spicules.

Fig. 146.—*Ankylostoma duodenale*, showing relative sizes of male and female. Both show the characteristic hooked anterior extremity. The male is smaller than the female, and its posterior extremity shows the umbrella-like copulatory bursal expansion. ×7.

The worm is whitish in colour, or brownish-red if gorged with blood. The head in both sexes is slanting or bent, the mouth being directed dorsally. The oral cavity is armed with four hook-like teeth, situated ventrally (but, because of the direction of the mouth, appearing as if anterior). These are directed backwards, two on each side of the middle line, and in the opposite or dorsal surface of the mouth are two conical teeth pointing forwards. The muscular œsophagus is strongly developed, and by means of this structure the worm draws in the intestinal mucous membrane of its host and fixes it by means of the powerful buccal armature above described. The **ova** are elliptical in shape, measuring 55 to 65 μ in length by 32 to 45 μ in breadth. They possess a thin transparent shell, which does not stain with bile, and through which the segmented embryo may be seen (fig. 147).

The habitat of the worm is especially the upper part of the

jejunum, and to a less degree the duodenum. In exceptional circumstances it may be found in the stomach, or in the ileum or large intestine. The worm attaches itself to the mucous membrane, upon the cells of which it appears to feed, as well as possibly upon the blood which it sucks, though Looss is of opinion that the former and not the latter constitutes its main food.

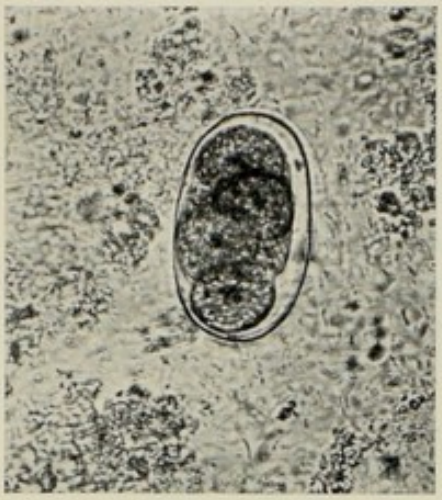


FIG. 147.—Ovum of *Ankylostoma duodenale* in fæces, showing thin transparent shell and segmentation of embryo. ×300.

The profound anæmia to which the presence of the worm gives rise may be due to the injection of some toxic hæmolytic substance, elaborated, perhaps, by the two large head-glands with which the worm is furnished — aided, no doubt, by the withdrawal of blood by the parasite, the hæmorrhage from the wound in the mucous membrane after the worm has changed its position, and the interference with digestion caused by its presence. Examination of the blood shows that the red corpuscles are reduced in number, *e.g.* to a million or less per c.mm. in serious cases; whilst the hæmoglobin is reduced both in percentage amount and in amount per corpuscle, in the latter case the colour-index being frequently reduced to less than a third of the normal. Normoblasts are often present, megaloblasts less commonly, and the red corpuscles usually show considerable poikilocytosis, and sometimes polychromatophilia. In recent infections, the leucocytes are usually increased, *e.g.* up to 56,000 (Boycott and Haldane). The coarsely granular eosinophils are, as in the majority of cases of helminthiasis, specially increased in number, and in this disease usually constitute about 8 per cent. or more of the total leucocytes, the highest percentage of eosinophils, recorded by Boycott and Haldane, being 66 per cent. in two cases of recent infection in which the total leucocyte counts were respectively 56,000 and 44,000 per c.mm. The eosinophilia usually becomes less pronounced as the disease becomes more chronic. In cases which have not progressed too far, rapid recovery may occur after the expulsion of the parasites.

In addition to the changes due to the anæmia—*e.g.* pallor and œdema of the tissues, serous effusions, fatty degeneration of the organs, and perhaps the accumulation of iron pigment in the liver—evidence of the nature of the disease may be seen in the small intestine itself. The worms may be found still adhering to the mucous membrane in considerable numbers; or—and especially if the *post-mortem* is made some time after death—they may have relaxed their hold, and may then be found in the lumen of the bowel.

The positions recently occupied by the worms on the mucous membrane may be seen as numerous little punctiform hæmorrhages, each with a minute wound in its centre, whilst little points of pigmentation mark the older sites. Acute or chronic intestinal catarrh is often present, and locally the affected part may be covered with slightly blood-stained mucus, though marked melæna is uncommon.

Development.—The segmenting ovum, on leaving the body of the definitive host in the fæces, rapidly develops if placed under suitable conditions of moisture and temperature (*e.g.* 20° to 25° C.), development being retarded if too much water is present, and also if there is an insufficient supply of oxygen. In a day or two an actively motile rod-shaped embryo, measuring 0·2 mm. in length and 14 μ in diameter, is hatched out. These grow rapidly in moist earth or mud, moulting their cuticle twice, and attaining a length of about half a millimetre and a diameter of 24 μ. Further growth now ceases, and a more sluggish stage supervenes, during which the embryo may remain alive in water or moist earth for several months. During this period it may be ingested by man, either in contaminated drinking water or in other ways, and so reach the alimentary canal; or it may, as has been demonstrated by Looss, actively make its way through the skin if brought in contact with the latter in water or mud. The larvæ bore their way, sometimes by way of the hair follicles, into the skin and subcutaneous tissue, where they may wander about, causing an eczema-like skin eruption ("ground-itch," "coolie-itch," etc.). The larvæ may then enter the lymphatic channels, and pass by them into the thoracic duct, and thus into the venous circulation; or in other instances they may enter a small subcutaneous vein, and so reach the venous circulation directly. They are then carried through

the right side of the heart to the lungs, in which they burrow into the air-vesicles, and later into the bronchi, where they cast their envelope for the third time. They next make their way up the bronchi and trachea, either in the mucous secretion in the lumen, or along or in the substance of the mucous membrane. On reaching the glottis they are swallowed, or make their way down the œsophagus to the stomach and intestine, where the final moult occurs. The worm having now become sexually mature, and having attained its adult form, attaches itself to the mucous membrane of the intestine.

NECATOR AMERICANUS—(Syn. *Uncinaria americana*).—The American variety of **hook-** or **tunnel-worm** closely resembles *Ankylostoma duodenale* both in general structure and with regard to the symptoms which it produces. It may, however, be distinguished from the latter by its smaller size and the absence of the four ventral hook-like teeth, instead of which it possesses a semi-lunar cutting-plate on each side. The dorsal margin of the mouth is furnished with two slightly developed chitinous plates. The buccal cavity is small, and has, deeply placed within it, two pairs of lancet-like teeth. There are also certain minor differences found in the copulatory bursa of the male; and the ova are somewhat larger than those of *A. duodenale*, measuring 64 to 75 μ in length and 36 to 40 μ in breadth.

This worm has been found only in man. It occurs in North and South America, and has also been described as occurring in India, Assam, and Burma.

FAMILY 3.—TRICHOTRACHELIDÆ

TRICHOCEPHALUS TRICHIURIS — (Syn. *Ascaris trichiura*; *Trichocephalus hominis*; *T. dispar*).— The *T. trichiuris*, or **common whipworm**, is a frequent parasite in man. The thin, thread-like, cephalic extremity, constituting about the anterior three-fifths of its entire length, resembles the lash of a whip, the "handle" being formed by the stouter posterior two-fifths of the worm. The **female** measures 45 to 50 mm. in length, the thick posterior part being straight, whilst in the **male**, which measures 40 to 45 mm. in length, the posterior part is curled up into a spiral. The **eggs** are oval or somewhat

barrel-shaped, with a thick brownish shell, showing at each end a characteristic, clear, knob-like plug resembling a "stopper."

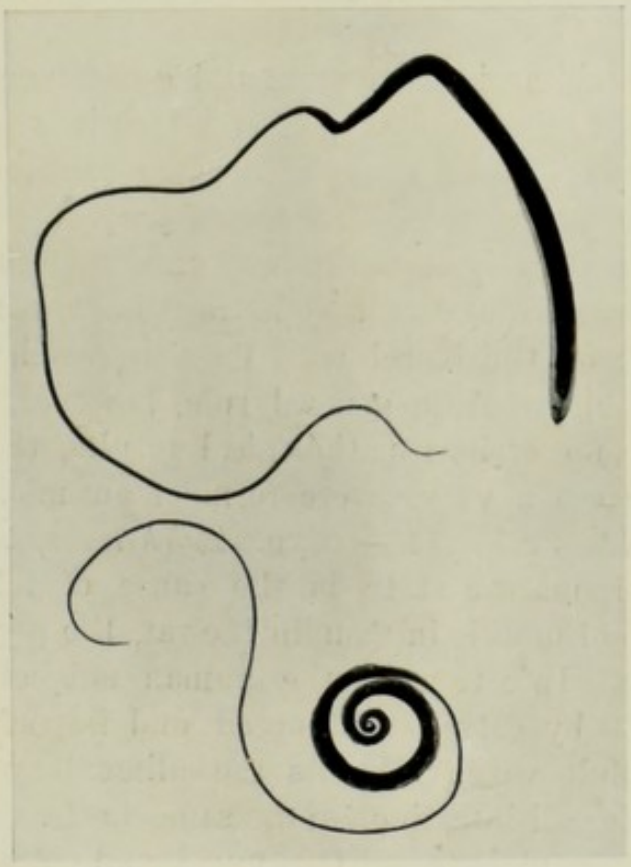


FIG. 148.—*Trichocephalus trichiuris.* F. female. M. Male. ×2½.

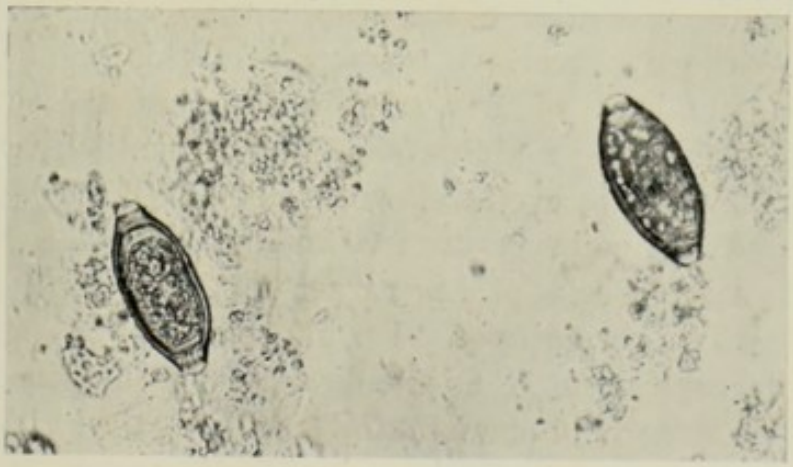


FIG. 149.—Ova of *Trichocephalus trichiuris* in faeces. ×300.

The ova usually measure 50 to 55 μ in length, and about 25 μ in breadth. They are extremely resistant both to cold and drying, and are usually unsegmented when passed, incubation taking

place in water or mud. No intermediate host is necessary. On reaching the human stomach, the shell is digested away, and the embryo, thus liberated, becomes mature in four or five weeks.

Its special habitat is the cæcum and commencement of the large intestine, to the inner surface of which it is said to attach itself by transfixing a fold of the mucous membrane with its thin anterior extremity or by burrowing its pointed head into a gland. It occasionally finds its way into the interior of the vermiform appendix, and it may in rare instances even penetrate the wall of the bowel with its sharp cephalic end and produce peritonitis. As a general rule, however, its presence gives rise to no serious pathological results, though it may occasionally cause a very severe form of anæmia.

TRICHINELLA SPIRALIS. — (Syn. *Trichina spiralis*). — This worm, in its immature state, is the cause of **trichinosis** (or **trichinelliasis**) of muscle in man, in the rat, the pig, and several other animals. Infection of the human subject is usually brought about by eating trichinosed and imperfectly cooked pork. The adult worm inhabits the alimentary canal, more especially the small intestine, of the same hosts. The **male** is about 1·4 to 1·6 mm. long and 0·04 mm. broad. After impregnation, the **female**, which usually measures 3 to 4 mm. in length and 0·06 mm. in diameter, increases considerably in size, chiefly on account of the dilatation of the ovarian tube, which also acts as a uterus. The upper or posterior part of this organ contains enormous numbers of **ova**, and on tracing these forward, segmentation and the rapid development of the little, worm-like embryos may be observed to have occurred. The egg-shell disappears, and the embryos are free within the mother, which in the five to seven weeks of her career may give birth to many thousands of living embryos. During this period she has made her way through the mucous membrane, either by passing down the interior of a gland or more probably by actively boring her way until she comes to lie in a lymphatic space. There she liberates her young into the lymph-stream, by which they then enter the circulation and are carried to all parts of the body, the diameter of the newly-born larva (6 μ) being somewhat less than that of a red blood corpuscle, and its length 90 to 100 μ. The larvæ are motile, but in reaching the striped

muscles, in which they finally aggregate, active migration plays a minor part. In the main they appear to be carried passively by the lymph- and blood-streams. They may be found in all the voluntary muscles, but are specially seen in those of the abdomen and thorax, diaphragm, tongue and pharynx. They are said not to infect the myocardium. In the muscles they are usually aggregated towards the surface and ends, perhaps because of the relatively slighter degree of movement in these parts. Enormous numbers of larvæ thus reach the muscle, each larva entering one of the muscular fibres. These become enlarged and lose their transverse striation, the nuclei at the same time undergoing proliferation. The little worm-like embryos have

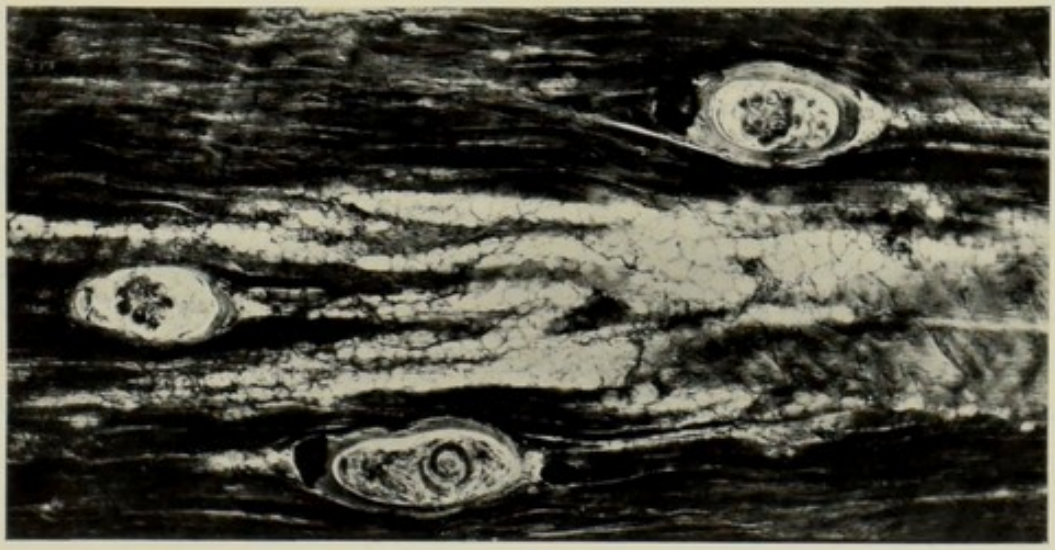


Fig. 150.—*Trichinella* embryos encysted in human muscle. ×40.

by this time enlarged somewhat, and traces of the alimentary canal appear. They now enter upon a quiescent stage and become spirally coiled up within cyst-like capsules formed by the transformation of the damaged muscular fibre and surrounding tissues, possibly aided by the presence of some substance secreted by the larvæ themselves. This process of encystment in the muscles may be completed in about eighteen days after the primary intestinal infection, and the next host is infected by ingesting the flesh of the animal in which they are encysted. The fully formed cyst is typically lemon-shaped, with somewhat pointed ends, its long axis lying in the same direction as that of the muscle-fibres, which are pushed aside to make room for it. The wall is composed of clear, somewhat refractile homo-

geneous-looking material and shows a double contour. Some slight proliferation of connective tissue may occur around the cyst, and a few fat cells usually develop at each pole. After several months, the wall of the cyst begins to undergo calcification, the process generally commencing at the poles and spreading towards the equator of the cyst. The larva, if uncoiled, measures about a millimetre in length, and in its encysted condition may remain alive and capable of further development for many years—over thirty in some cases, it is said, in man. Sometimes, however, the larvæ may die off and become calcified. When the muscle infected with living *Trichinella* larvæ is ingested by the next host, the calcified cyst-wall is dissolved by the gastric juice, and the liberated larva develops in a few days into the adult worm, which then reaches its habitat in the duodenum and the jejunum. Copulation may occur as early as two days after their ingestion. The males then die, and the females enlarge and bore their way into the mucous membrane, as already described.

Pathological Effects in Man.—During the period of invasion of the muscles by the larvæ, there may be severe pain and myositis, the muscles becoming swollen and hard, and later there is usually extensive œdema of the body. Severe cases somewhat resemble and have been mistaken for typhoid fever. Convalescence may supervene about the fifth or sixth week; or death may occur from interference with the action of the respiratory muscles, or from pneumonia or some other secondary complication. There may be a moderate leucocytosis, of which the eosinophils may constitute 30 per cent. or more. The degree of the eosinophilia varies very considerably in different cases, and is generally most marked during the period following the intestinal infection, until encapsulation of the larvæ in the muscle is complete.

The disease usually occurs in epidemics, especially in countries where uncooked or partially cooked pork is eaten in considerable amount.

FAMILY 4.—FILARIDÆ

FILARIA MEDINENSIS—(Syn. *F. dracunculus*; *Dracunculus medinensis*; *Guinea-worm*; *Medina worm*; *Dragonneau*).—This parasite is found in Arabia, Persia, Egypt, Tropical Africa,

especially along the West Coast, India, and in many other localities, and its geographical distribution is said to have some relation to the presence of rivers. It produces subcutaneous swellings, followed in some cases by abscess, especially of the lower limbs.

The **female** is usually 50 to 80 cm. in length, and 0·5 to 1·7 mm. in diameter. Occasionally it may reach a length of as much as a metre and a half, or even more. It is white or yellowish-white in colour, with faint transverse striation, and is uniformly cylindrical, except for a slight degree of tapering towards the cephalic end. The greater part of the body-cavity is occupied by the enormous uterus, which runs almost the entire length of the worm, and is crowded with larvæ, the female being viviparous.

The **male** is very much smaller, and has only recently been discovered. It usually measures 20 to 30 mm. or a little more in length, and has been found attached to the female some 14 mm. from the anterior extremity of the latter. The males probably die off soon after copulation.

The female, when it reaches sexual maturity, gradually works its way through the tissues of the host, generally in a downward direction, till it reaches the surface, usually on the lower limb, in the neighbourhood of the ankle. Its head pierces through the true skin, but not through the cuticle, a minute, clear blister filled with fluid being formed. This then ruptures, a little ulcer being formed, in the centre of which is a small pore or hole through which the female periodically discharges her larvæ in enormous numbers. This process may be artificially stimulated by douching the skin of the part with cold water, this being apparently the natural stimulus required, as the larvæ after their discharge probably pass the next stage of their existence in the body of a minute fresh-water crustacean (copepod) belonging to the genus *Cyclops* (e.g. *C. bicuspidatus*, *C. quadricornis*, *C. strenuus*, *C. viridis*, and perhaps others). The **larvæ** measure about 0·6 mm. in length by 17 or 18 μ in diameter, their anterior three-fifths consisting of a thicker part—the "body"—which is not cylindrical, but distinctly flattened, shows a fine cross striation, and contains a rudimentary alimentary canal; whilst the posterior two-fifths forms a long, slender, finely tapering "tail." While still within the

uterus of the parent worm, the thicker part of the larva is coiled up like a watch-spring, the posterior thin extremity or "tail" being held straight. When passed into water, these little larvæ unroll themselves and become actively motile. They swim about until they gain entrance to the body of the *Cyclops*, either by piercing the cuticle, or possibly in some cases entering by the mouth. In the body-cavity of this little crustacean the larvæ are at first actively motile, but after three weeks or a month they enter upon a quiescent stage, the

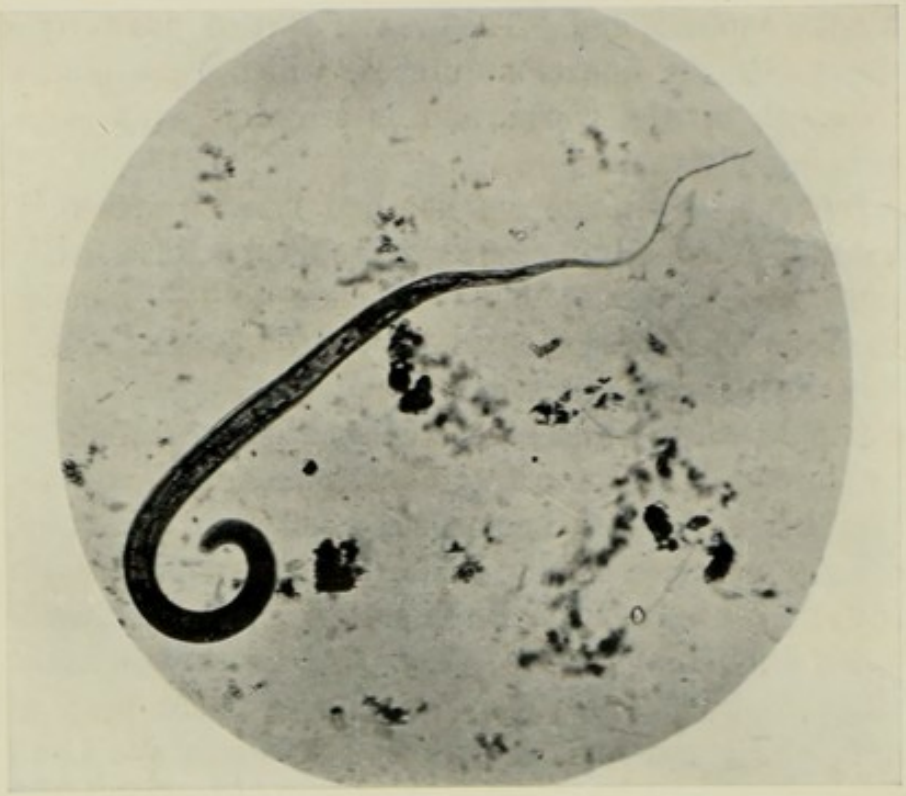


FIG. 151.—*Microfilaria medinensis* or larval form of *Filaria medinensis*, showing coiled up "body" and tapering "tail." × 200.

cuticle and the tail being cast off. While in this condition, and while still within the *Cyclops*, they may be ingested in drinking water by man, or they may possibly escape from the body of the *Cyclops* and gain entrance to the human body by the mouth, or, as has been recently suggested, by directly boring their way through the skin. After feeding monkeys on the infected *Cyclops*, the adult worm may develop in them. The hydrochloric acid of the gastric juice kills the *Cyclops*, the larvæ resume their motility, and it is supposed that they bore their way through the wall of the alimentary canal, and then

slowly migrate through the tissues as they mature, a process which may take a period of from eight or nine up to fifteen months or more.

Pathological Effects.—During the migration of the maturing worm through the tissues, the patient may be quite unaware of its presence. On its appearance at the surface, however, the little blister and ulcer are formed, and may cause great irritation, especially if the parent worm is injured during an injudicious attempt at extraction, or in any other way. Very serious inflammatory changes, abscess formation, etc., may supervene upon the liberation from the injured worm of larvæ into the tissues, and amputation may be rendered necessary. After the female worm has emptied its uterus by the periodic discharge of the larvæ, a proceeding which usually occupies a fortnight or more, it tends to leave the body of its host. In some cases it may succeed in doing so spontaneously, or the process may be aided by gentle traction. If the parasite during its period of migration fails to reach the surface of the body, it may die and undergo complete calcification.

FILARIA SANGUINIS HOMINIS.—Under the term **Filariasis** is included a group of diseases which in man are caused by at least four distinct species belonging to the genus *Filaria*, the larvæ of which are parasitic in the blood, whilst the parent worms inhabit the tissues, blood-vessels, or lymphatics of the same host.

Considerable confusion has arisen in the nomenclature of these parasites, the adult and immature forms of the same parasite in some cases bearing different names. In order to simplify the confusion in some small degree, we propose to follow the example of Manson and Shipley[1] in adopting the suggestion of Le Dantec that the parent worms should be designated *Filariæ* and the larval form *Microfilariæ*, the name of the adult form being, of course, regarded as that of the species.

The following list of the *Filariæ*, and the corresponding hæmatozoon larval *Microfilariæ* known to occur in man, is given by Manson and Shipley.[2]

[1] Manson and Shipley, *Filaria Sanguinis Hominis* in article on "Parasitic Worms," Allbutt and Rolleston's *System of Medicine*, 1907, vol. ii., part ii., p. 927.

[2] Note.—In this list the term "*Microfilaria*" has been substituted for *Filaria* in the case of the larval forms.

Adult Form.	Larval Form.
1. *Filaria bancrofti.*	1. *Microfilaria nocturna.*
2. *Filaria loa.*	2. *Microfilaria diurna.*
3. *Filaria perstans.*	3. *Microfilaria perstans.*
4. *Filaria magalhæsi.*	4. ? ?
5. *Filaria demarquayi.*	5. *Microfilaria demarquayi.*
6. *Filaria volvulus.*	6. ? ?
7. ? ?	7. *Microfilaria powelli.*

As is seen from the above list, the adult form of the *Microfilaria powelli*, and the larval forms of the *F. magalhæsi* and *F. volvulus*, are as yet undiscovered.

The most important of these parasites are the—

FILARIA BANCROFTI, and its larval form **MICROFILARIA NOCTURNA** (*Filaria sanguinis hominis nocturna*).—The adult worm inhabits the lymphatic system, and may be found in lymphatic vessels—especially about the pelvis and groins—in the thoracic duct, or in glandular swellings. The **female** is a thin, filiform worm, whitish or brownish-white in colour, which may measure 76 to 80 mm. or more in length by 0·21 to 0·28 mm. in diameter. It is uniformly cylindrical, with no very distinctive characters. Both extremities are somewhat blunt and rounded, and the tail of the female is curved or hooked, whilst in the **male** it is helical, resembling a corkscrew or the tendril of a vine. The male may be distinguished, even on naked-eye examination, by its spirally twisted tail and its smaller size—about 40 mm in length by 0·1 mm. in diameter.

The male and female are usually found coiled up in a mass together. They are generally few in number, but as many as eighteen have been found in one swelling. The two long uterine tubes of the female are crowded with ova and larvæ in all stages of development. The **ova** containing these coiled-up larvæ measure 50 μ in length and about 34 μ (*i.e.* some four or five times the diameter of a red blood corpuscle) in breadth. In the later stages of development, the larvæ cause the shell or vitelline membrane to elongate so as to form a delicate sheath or investing membrane round them. This they retain after birth. Under exceptional circumstances, the female may give birth to ova instead of elongated larvæ, a point of considerable importance, as the greater breadth of these may cause blocking of the lymphatics; whereas the

larvæ, which are about 0·3 mm. long, possess a breadth of only about 8 μ—*i.e.* are seldom very much broader than the diameter of a red blood corpuscle, and may therefore easily pass through lymphatics and capillaries.

When examined alive in fresh blood, the larva is seen to be a little eel- or snake-like worm, which is transparent and colourless, with a rounded anterior and a finely tapering posterior extremity. It is enclosed within the clear, colourless, transparent sheath, the origin of which has been explained above. This chorional sheath is usually about one-third longer than the larva, which may be seen wriggling actively, and also elongating and retracting itself within it. By these movements it stirs up the corpuscles around it, but it does not appear to travel with any rapidity from one place to another. The larvæ are covered by a musculo-cutaneous layer which shows fine transverse striation. At the thicker anterior end there is a delicate, six-lipped, prepuce-like retractile structure, which may be seen alternately covering and uncovering the head, from which an extremely fine, sharply pointed spine or fang may be observed protruding at intervals. The use of this cephalic boring apparatus, whilst the embryo is present in human blood, is said to be prevented by the presence of the chorional sheath. Slightly behind the anterior end of the larva is situated the so-called V-shaped spot, possibly excretory in its functions. The posterior extremity is finely tapering and sharp.

Fig. 152.—*Microfilaria nocturna* (the larval form of *Filaria bancrofti*) in the blood. The larva is enclosed in the chorional sheath which is seen projecting at the ends of the worm. ×300.

Periodicity and Location of the Larvæ.—From the body of the mother worm the larvæ pass directly into the lymph-stream, and are carried by it into the blood. They are found

in the peripheral circulation only at night, or rather during the hours of sleep, as they may be found during the day if the patient sleeps during that period. In ordinary circumstances, the *microfilariæ* begin to appear in the peripheral blood about five or six in the evening, and increase in numbers until midnight. They then gradually diminish, and by seven or eight in the morning have usually quite disappeared. During the day they appear to lodge in the thoracic viscera, more especially in the lungs and larger blood-vessels. They do not accumulate to any degree in spleen, liver, or kidney.

This periodic process may go on indefinitely in man, sometimes for many years, the *microfilariæ* never becoming mature worms, a process which can only occur on transference to a suitable intermediate host, in this case the *Culex* genus of Mosquito.

Metamorphosis in the Mosquito.—The females of certain genera and species of *Mosquito*,[1] more especially, it is said, those belonging to the genus *Culex*, on biting an infected person while the larvæ are in the peripheral circulation, may ingest some of these along with the blood it draws. In virtue of the viscid character which the blood assumes in the stomach of the mosquito, the sheath is, as it were, held or fixed, and the *microfilaria*, by means of the finely pointed spine at its anterior end, ruptures the sheath and escapes. The free, actively motile larva can now travel from one locality to another. By means of its cephalic boring apparatus—which, because of the presence of the sheath, was prevented from functioning while the parasite was still in the human blood—it penetrates through the stomach-wall and bores its way to and lodges in the large thoracic or wing muscles of the mosquito. In this position, which it reaches within a few hours after ingestion, it becomes quiescent, and undergoes a process of maturation and metamorphosis which occupies from one to three weeks. During this period it becomes shorter and thicker, forming a sort of pupa- or cocoon-like body; and develops a mouth surrounded by four lip-like structures, and also an alimentary canal and a trilobed tail. It increases enormously in size and

[1] Note.—Manson and Shipley say that "*Culex fatigans*, *Anopheles rossi*, *Anopheles costalis*, *Panoplites africanus*, *Stegomyia fasciata*, are all said to be efficient intermediaries," *loc. cit.*, p. 938.

activity, attaining a length of about 1·5 mm. and a breadth of 0·25 mm. It then leaves the thoracic muscles, bores its way forward through the prothorax and neck, passes into the head of the insect, and comes to lie near the base of the proboscis—not in the salivary gland or duct, as in the case of the malaria parasite. Later, it passes into the proboscis, where it lies free among the stilettes, waiting until the mosquito bites a suitable host. The parasites have been observed to pass out in pairs—probably male and female together. Man, the final host, is thus re-inoculated when bitten by an infected mosquito, and the male and female worms pass into the lymphatics, where they become mature, and in turn give rise to further generations of larval embryos.

Pathological Effects of Filarial Infection.—These may be extremely varied, and for a full description of them reference should be made to text-books on Tropical Medicine. They may be epitomised as follows.

Large numbers of persons may be infected by both parent and embryo worms with little or no evident pathological results. If the blood be examined in such cases, there is usually found to be present in it a varying degree of eosinophilia, which may show cyclical variations corresponding to the periodicity of the *microfilariæ* in the peripheral circulation. The healthy, fully formed larva appears to be practically harmless; and in the same way the healthy parent worms may give rise to little trouble. In other cases, however, the parent worms, which lie coiled up in the lymphatic trunks or in the thoracic duct, may cause **mechanical obstruction of these.** They are probably more liable to do so if they themselves are diseased, and they may then produce very serious results. Thus, around the diseased or perhaps dying or dead worms, great inflammatory thickening of the lymphatic trunks in which they lie, and also of the surrounding tissues, may occur. This may bring about narrowing or thrombosis of the lymphatic vessels, leading to **varicosity** of the distal vessels, or to **lymphatic œdema** in the corresponding drainage area, or, it may be, to a combination of both these conditions. Occasionally, **abscess formation** may occur around the diseased or dead worms.

Because of this blockage of the larger lymphatic channels and thoracic duct, the lymph and chyle cannot pass into the

blood by the usual route, and a compensatory collateral circulation is slowly established. A backward flow occurs through the lymphatic vessels of the pelvis, perineum, groins, and external genitals, by which the chyle from the intestines and the lymph from the lower half of the body are passed on through the lymphatics of the anterior abdominal wall and back. It can then be carried by the larger afferent channels which reach the thoracic duct above the level of the obstruction. From the increase of pressure in these various groups of lymphatics, great varicosity may be produced in them. In this way may arise the so-called **elephantoid** conditions, a group of diseases of which the following are the most important:—

i. **Lymphatic varices**, *e.g.* of the thoracic duct, pelvic and other lymphatics. These may also occur in lymphatic glands, which may become much distended with chylous lymph. Clinically, this condition may show as **varicosity of the inguinal glands**, but on *post-mortem* examination these are found to be merely the superficial, and therefore visible, representatives of a much larger series of enlarged glands, those of the pelvis being usually most affected.

ii. **Lymphatic ulcers** are produced by inflammation or injury of superficial lymphatic varices, and may be characterised by extensive lymphorrhœa.

iii. **Lymph Scrotum**, or enlargement of the scrotum from the distension of its lymphatics, is also brought about by the establishment of this collateral anastomosis, and may be accompanied by such complications as **orchitis**, **chylocele**, etc. In the same way the **labia**, etc., may become affected in the female.

iv. By the rupture of some of the distended lymphatic channels, escape of the regurgitating chyle and lymph may occur in different localities:—

Chyluria—from the rupture of renal, vesical, or other lymphatics, allowing escape into the urine.

Chylous Diarrhœa—an analogous condition in the intestine.

Chylocele—the escape of chylous fluid into the cavity of the tunica vaginalis testis.

Chylous Ascites—its escape into the peritoneal cavity.

v. If—as for some unknown reason appears in some instances to be the case—the adult female worm gives rise to **ova** in place of larvæ (*i.e.* if a species of "abortion" takes place), extensive blocking of the smaller lymphatic channels may be produced, as the ova are some four or five times—whilst the breadth of the fully elongated larva is only equal to—the diameter of a red blood corpuscle. The ova, therefore, if thus discharged in great numbers, are of such a size as to readily block the smaller lymphatic channels, and hence may cause a wide-spread lymphatic œdema. Thus we have a probable explanation, **in part** at all events, of the causation of **Elephantiasis Arabum**, a disease in which there is enormous thickening and induration of certain parts of the body; and we also have the explanation of the fact that the elongated or normal hæmatozoon form of the *microfilaria* is often not found in the circulating blood of patients with this disease. The mere passive blocking of lymphatics is, however, not alone sufficient to bring about the condition of elephantiasis. There is always in such cases a history of recurrent attacks of **lymphangitis** in the affected area, irritation and inflammatory changes being also apparently necessary to its causation. Whether these recurrent attacks of lymphangitis are due to special toxic substances secreted by the parasite, or are produced by some secondary infection, *e.g.* with bacteria, has not yet been decided. Whatever be their cause, the products of the inflammatory process cannot, because of the obstruction of lymphatics, be properly absorbed. The inflammation is very liable to recur; and these various processes all tend towards the production of a gradually progressive swelling and induration of the tissues, which in some situations may become enormous in amount. For the production, therefore, of Elephantiasis Arabum there are required:—

1. **The presence of the adult female filaria**, which, from injury or disease, gives rise, not to larvæ, but to—

2. **Ova**, which block the small lymphatics and glands, producing **lymph-stasis**. To this must then be added—

3. **Recurrent attacks of Lymphangitis** in the affected area.

Sites of Elephantiasis.—In some 90 or 95 per cent. of the cases it is the **lower limbs**, either one or both, that are affected. The **scrotum** is also frequently attacked, and may reach enormous dimensions, *e.g.* 10, 20, 40, or 50 pounds, and in some cases very much more. Elephantiasis of the **upper limbs** is comparatively rare, and of the vulva and mammæ is still rarer. Occasionally, limited areas of skin may be involved, *e.g.* of the groin, thigh, neck, etc.

FILARIA LOA—(Syn. **Adult**—*F. oculi*; *F. subconjunctivalis*; *Dracunculus oculi*; *D. loa*. **Larva—MICROFILARIA DIURNA**; *F. sanguinis hominis*, var. *major*; *F. diurna*).—The male of *F. loa* measures from 25 to 30 mm. in length and 0·3 to 0·35 mm. in diameter. The **female** may be from about 30 to 40 mm. long, and about 0·5 broad. Both sexes are covered with small, irregularly distributed, chitinous protuberances. The cephalic end is blunt, and the tail is tapering, that of the male being incurvated. The **ova**, when the contained larvæ are developed, are about 50 by 25 μ in diameter; whilst the uncoiled larvæ measure about 0·26 or 0·3 mm. in length, and 6 to 8 μ in diameter. The habitat is usually the connective tissue of the conjunctiva and other parts of the orbit and elsewhere, the infection being frequently multiple.

MICROFILARIA DIURNA is believed by Manson to be the larval form of *F. loa*. As its name implies, it is found in the peripheral circulation during the day. It possesses a sheath, and in general characters closely resembles *Microfilaria nocturna*. This parasite is found on the West Coast of Africa, and its life-history has not yet been fully worked out.

FILARIA PERSTANS—(Syn. for **larva**—*F. sanguinis hominis*, var. *minor*; *F. ozzardi*, truncated variety).—The **female** measures 70 or 80 mm. in length, and about 0·12 mm. in breadth, these measurements being about twice those of the **male**. The **larva** does not possess a sheath, and its posterior extremity is blunt, not tapering as in *Microfilaria nocturna* and *diurna*. It is freely motile, and there appears to be no regular periodicity in its movements.

This parasite is found in Central and other parts of Africa,

South America, and elsewhere. Its complete life-cycle is not yet known.

FILARIA MAGALHÆSI is an extremely rare member of this family, the sole recorded case having occurred in Rio de Janeiro. The larval form is unknown.

FILARIA DEMARQUAYI is also rather uncommon. The **female** has been found in the connective tissue of the mesentery. The **male** has not yet been discovered. The **larva** is actively motile, does not possess a sheath, is sharp-tailed, and measures 0·2 mm. in length by 5 μ in breadth. It has been found in the West Indies and elsewhere.

ARTHROPODA

A. **ARACHNIDA.**—Of the numerous orders belonging to this class, only two require mention here, viz. the **Acari** (Ticks and Mites) and the **Linguatulidæ**. Certain members of the former are of importance, not only as parasites, but as carriers of disease.

MITES

LEPTUS AUTUMNALIS.—This name is applied to the larvæ of several species of mites which are specially plentiful in the late summer and autumn, and are variously known as "harvest-," "autumn-," or "grass-mites," "gooseberry-bugs," etc. These larvæ are minute reddish bodies about 0·23 mm. in length. They possess a long hypopharynx—the so-called "suctorial proboscis"—which they insert into the skin in order to suck the blood of their host. They give rise to great irritation, and are parasitic, not only on man, but on many other mammals.

SARCOPTES SCABIEI—(Syn. *Acarus scabiei*)—or Itch-mite.—The **male** measures 0·2 to 0·3 mm. and the **female** 0·33 to 0·45 mm. in length. They are more or less spheroidal in shape and pale in colour, the back and legs being covered with chitinous bristles. The **larvæ** possess only three pairs of legs, but in the next stage of development—the nymph—another pair appears. These then develop into the adult sexual forms. The male lives upon the surface of the skin, but the impregnated female, after casting her cuticle, undergoes certain

modifications in structure, and then proceeds to burrow in the epidermis, laying her eggs, usually about the rate of two per day, until some fifty ova in all are deposited at intervals in the tunnel. The ova hatch in a few days, giving rise to the six-legged larvæ. Maturity is reached in about a fortnight. The females are found at one end of the burrows, which are usually from a few millimetres to about one centimetre in length, and may be seen as minute curved or wavy dark lines in the skin,

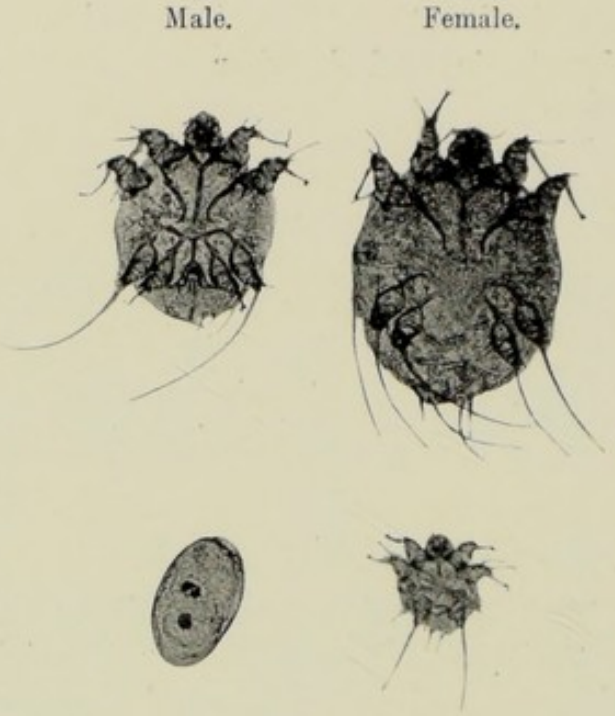


FIG. 153.—*Sarcoptes scabiei* or Itch-mite. ×80.

most commonly between the fingers, and over the wrists, elbows, and knees, axillæ, breasts, etc. Minute vesicles usually form at the points of entrance, and sometimes also at the positions occupied by the females. Suppuration may occur in these vesicles, the surrounding skin becoming red and inflamed. Crusts may also be formed over the affected part.

Numerous forms of itch-mite are found in other mammals besides man.

DEMODEX FOLLICULORUM.—This is a small, degenerate form of mite, several varieties of which are parasitic in man in the hair-follicles, and in the Meibomian and sebaceous glands. It is of comparatively little pathological importance.

LINGUATULA RHINARIA — (Syn. *L. tænioides*; *Pentastoma tænioides*).—The **adult** lives in the nose and accessory sinuses of some mammals. It is rare in man. The **ova** pass out with the nasal secretion, and are swallowed by their intermediate host, usually one of the herbivora. The **larvæ**, which hatch out in the stomach, bore their way to the liver, where they encyst, and, after various transformations, become more mature. They then migrate, probably passing to their final habitat by way of the lungs, bronchi, trachea, etc., though it is possible that they may gain access to the nasal cavity, etc., by other routes. They then moult and develop into the adult form.

TICKS

These are of importance from the fact that, in addition to being found as epiparasites upon man and many of the lower animals, especially on birds, they may act as carriers of protozoal and bacterial diseases.

Ticks are divided into two families, *Argasidæ* and *Ixodidæ*, to the former of which belong practically all the members of this group which have been as yet found to be pathogenetic in man.

ORNITHODOROS MOUBATA.—This tick is widely distributed in Africa, and is the carrier of the *Spirochæta* of **Tick Fever.** This species of tick is also a possible intermediate host of *Filaria perstans.*[1]

DERMACENTOR RETICULATUS is found in Europe, Asia, and America. It is the carrier of *Piroplasma canis*, and is said by Wilson and Chowning[2] also to convey a protozoon which they call "*Pyroplasma hominis*" (*Piroplasma hominis*), and which they believe to be the cause of the "Spotted Fever of the Rocky Mountains," which disease they therefore term "**Pyroplasmosis hominis**" (Piroplasmosis hominis).

MARGAROPUS ANNULATUS.—The adult of this species is epiparasitic, especially on cattle. It is the carrier of *Piroplasma bigeminum*, the cause of **Texas** or **red-water fever** in cattle.

Some species of ticks have been described as being the carriers of various diseases caused by other protozoa, and form an

[1] Wellman, "Preliminary Note on some bodies found in Ticks—*Ornithodoros moubata* (Murray)—fed on Blood containing Embryos of *Filaria perstans* (Manson)," *Brit. Med. Jour.*, July 20, 1907, p. 142.

[2] Wilson and Chowning, "Studies in *Pyroplasmosis hominis* ('Spotted Fever' or 'Tick Fever' of the Rocky Mountains)," *Journal of Infectious Diseases*, 1904, i. pp. 31–57.

important field for further study and research. During the life-history of the majority of ticks three hosts are necessary, one being required for each of the three developmental stages, larval, nymphal, and adult, although in some instances two or even all three of these stages may be completed upon the same host; and in *Ornithodoros moubata* the transformation from larva to nymph occurs within the egg-shell.

In some, though not in all cases, pathogenetic protozoa are transmitted from the adult female tick to the ova, and thus to the resulting larvæ, which may then carry the disease to the host which they attack. In other instances, the protozoa remain quiescent until the infected larvæ attain maturity, the disease being then transmitted by the adult tick.

B. **INSECTA.**—Many insects are casual or occasional epiparasites upon man. Some produce severe irritation by injecting a salivary secretion when they bite. Others may convey pathogenetic bacteria or protozoa, and may thus produce serious results. Reference has already been made to the part played by the mosquito in the propagation of malaria and filariasis.

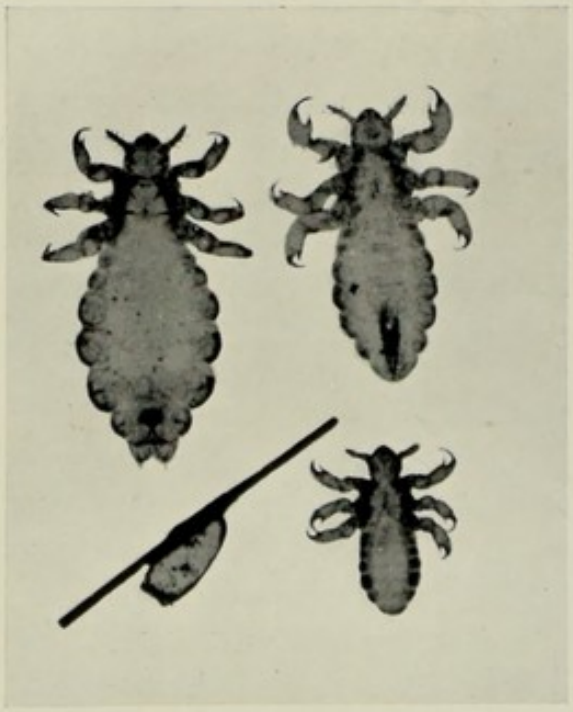


FIG. 154.—*Pediculus capitis* or Head-louse. ×10.

Some of the parasitic **Hemipteria**, *e.g.* the **Pediculi** or **Lice**, and certain of the **Bugs**, have become much degraded in consequence of their parasitic habits, the wings characteristic of other non-parasitic hemipterous insects having disappeared. We omit a detailed account of these parasites, and refer our readers to the illustrations.

PEDICULUS CAPITIS or **HEAD-LOUSE.**—The **male** measures from 1 to 1·5 mm. and the **female** from 1·8 to 2 mm. in length, the colour varying from light grey to dark brownish-

black. The operculated **ova** or "nits" are minute, white, oval, or pear-shaped bodies, visible to the naked eye. They are attached to the hairs and hatch in about a week, and the young insects mature in from three weeks to a month, the adult being somewhat oblong in shape.

PEDICULUS VESTIMENTI — (Syn. *P. vestmentorum*). — The clothes- or body-louse lives upon the surface of the body, and

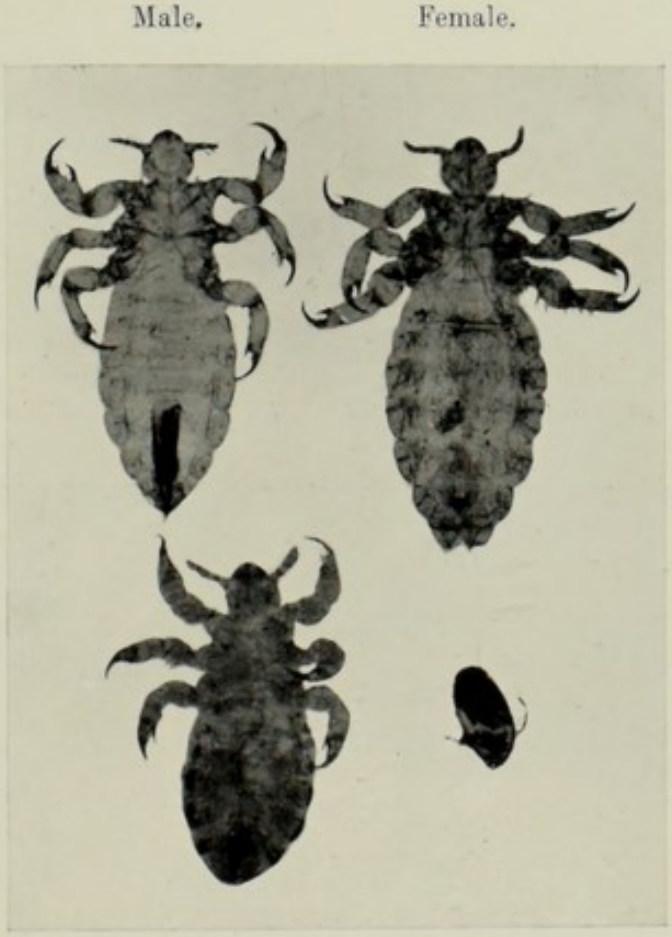
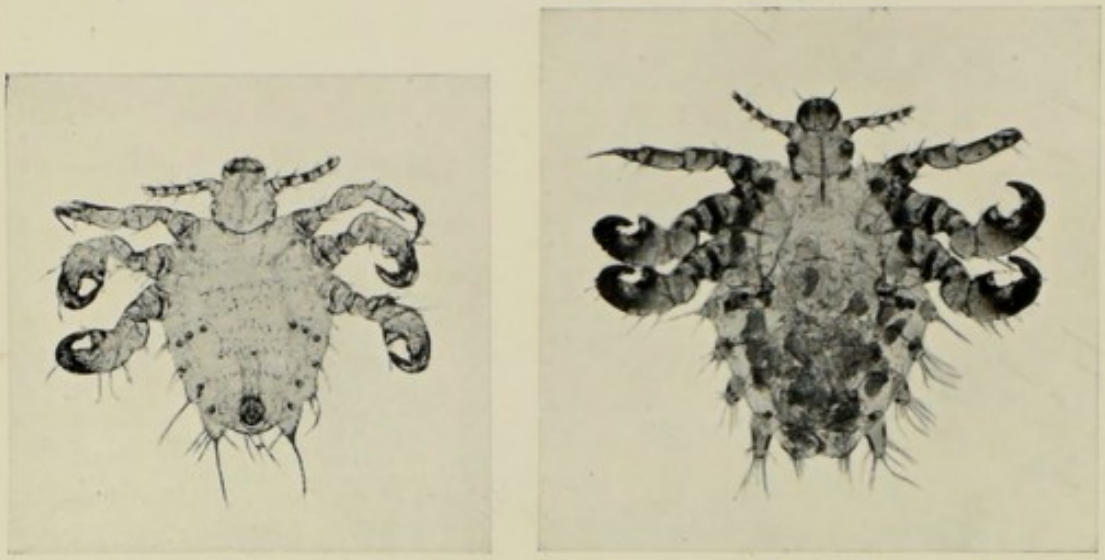


Fig. 155.—*Pediculus vestimenti*, Clothes- or Body-louse. ×10.

breeds in the clothing next the skin, as well as on the skin itself. It lives by sucking blood, and may cause very severe eczema, due to the irritation of some toxic substance which it injects when it bites, the scratching induced by the itching, and secondary bacterial infection. It may produce serious anæmia in weakly children.

PEDICULUS PUBIS—(Syn. *Phthirius inguinalis*).—This variety, known as the crab-louse, lives on the hairy parts of the body (with the exception of the head), and is specially found in the

pubic region. The **male** measures 0·8 to 1 mm. and the **female** about 1·1 to 1·2 mm. in length.



Male. Female.

FIG. 156.—*Pediculus pubis, Phthirius inguinalis* or Crab-louse. ×17.

FIG. 157.—*Cimex lectularius* or Common Bed-bug (male). ×10.

CIMEX LECTULARIUS or common bed-bug is reddish-brown in colour, and measures 4 to 5 mm. in length and about 3 mm.

in breadth. It lives in bedding, furniture, etc., and usually attacks man during the night. Numerous varieties of bed-bug and other closely allied species of bugs are described.

DIPTERA.—Fleas are wingless members of this group of insects.

PULEX IRRITANS or common flea.—The **male** is from 2 to 2·5 mm. and the **female** about 4 mm. in length. They are reddish-brown in colour, and the flattened body and legs are covered

FIG. 158.—*Pulex irritans* (male). ×22.

with fine hair-like bristles. The **ova** are barrel-shaped. The larva is an elongated, segmented body without legs.

DERMATOPHILUS PENETRANS—(Syn. *Sarcopsylla* or *Pulex penetrans*, or "Jigger," "Chigger," or "Chigoe")—is an important parasite in some parts of Africa, the West Indies, India, and elsewhere. The **male** is about 1 mm. in length, and rarely attacks man. The **unimpregnated female** is about the same size as the male; but when **impregnated**, the abdomen becomes enormously distended with ova. After impregnation, the female burrows beneath the skin, especially on the soles of the feet and between the toes, laying her eggs and causing inflam-

mation and ulceration. Abscesses may form, and serious secondary infections such as tetanus may supervene.

Fig. 159.—*Pulex irritans* (female). ×22.

PULEX CHEOPIS—the common rat-flea of India, Australia, and Manila—is of importance in connection with the spread of plague, and may convey *B. pestis*, not only from animal to animal, but in all probability from infected rats to man, as this species of flea will also attack the human subject.

CHAPTER VII

IMMUNITY

THE very marked differences in susceptibility to disease in different species of animals, in different races, and in different individuals of the same species or race, need no emphasis. They are recognised by everyone; but the explanation of these differences has lead to a multiplicity of theories. The subject of **Immunity**, however, is of such importance that we feel we must devote more space to it than would at first seem justified in a text-book primarily intended for students of medicine. It is convenient to deal first with the subject under two headings—**Natural Immunity** and **Acquired Immunity.**

NATURAL IMMUNITY.—As has been already stated, there are undoubtedly very marked differences in susceptibility to disease exhibited by different animals and different races; but it is doubtful if, in the strictest sense, a **natural** immunity exists. It is generally held that the lower animals are not susceptible to cholera, scarlet fever, leprosy, etc., and that the human species is unaffected by some of the bacteria which cause disease among the lower animals; but when the evidence is examined more closely, and especially by experimental methods, it is found that there is a **relative** rather than an **absolute** insusceptibility. Cholera may be produced in the guinea-pig and in the rabbit if certain special methods of experimentation be employed; and, again, very large doses of a bacterium may produce disease in an animal in which moderate doses would have no effect; or ordinary doses may produce disease in an animal whose vitality has been much lowered. In the light of these facts, **natural** immunity may be defined as **the inherited resisting power to bacterial or toxic invasion and damage, exhibited by man and certain of the lower animals in their natural conditions and surroundings.**

ACQUIRED IMMUNITY.—It is a well-known fact that tolerance to certain foods and drugs may be acquired by using them over prolonged periods. De Quincey's *Opium Eater* might be a text-book on acquired immunity.

In the sphere of infectious diseases there are innumerable examples. Children are specially susceptible to measles, scarlet fever, etc. They usually become infected in early life, and a second attack is not common. They have acquired a protection, probably by substances which have been introduced into, or, rather, developed in the system during an attack; or it may be, as some observers maintain, by what might be called an *education* of the cell, so that it is able in future to deal satisfactorily with the bacteria when they enter. These observed facts were utilised by Jenner in his great discovery of vaccination against smallpox; but to Pasteur and his co-workers must be given the credit of laying the foundation on which the whole superstructure of protective inoculation has been built.

By introducing bacteria or their products into the system, under conditions to be described later, immunity against these bacteria or these bacterial products can be produced. This immunity is what is termed **Experimental Acquired Immunity**, or **Artificial Immunity**; and it is due to the production of substances, the so-called **Antibodies**, or bodies antagonistic to the bacteria themselves or to their products, the toxins.

This artificial immunity may be produced in either of two ways:—

1. By an injection or by repeated injections, in graduated non-fatal doses, of an organism or of its toxin. Immunity thus produced is **active** or **direct**, the antibodies being elaborated by the animal itself.
2. By the injection of the serum of another animal highly immunised by method 1. This is **passive** or **indirect** immunity, and the antibodies are supplied by the first animal.

ACTIVE or DIRECT IMMUNITY.—It is quite obvious that this method can, in general, only be used as a preventive measure. In an acute infective disease where the bacteria are multiplying rapidly or where bacterial products are causing an acute toxæmia, it would be folly to introduce more of the poison in the hope of arresting the progress of the infection. In such cases, the

defensive power of the leucocytes is insufficient to arrest the progress of the disease. This means either that the leucocytes do not respond to the toxic stimulus, or that they have responded to their utmost. In either case, it would appear that the injection of more toxin could only have an injurious result. In more chronic disease, where the bacteria are localised, and their products either feebly toxic or endotoxic, *i.e.* only set free by destruction of the bacteria, it may be justifiable to inject very small doses of the products or of the dead bodies of the causal bacteria, on the grounds that these bacteria or bacterial products act in some way on the cells, stimulating them to greater phagocytic action, or causing them to produce some substance injurious to the life of the bacteria. On this ground the **opsonic** treatment (*vide* p. 450) may be justified, but it is a treatment which must be used with very great care, and only in selected cases and, according to Wright, after careful estimation of the opsonic index.

For the production of active or direct immunity, inoculation may be carried out with **cultures of the organisms which have been subjected to conditions which kill the bacteria**; or with **living cultures, the virulence of which has been modified in some way.**

The starting-point of this work was Jenner's discovery that man could be protected against smallpox if he were subjected to a mild non-infectious attack of vaccinia or cow-pox. This **vaccination** probably depends on the attenuation of the unknown variola germ or some allied species in its passage through the cow. Pasteur reopened the question nearly eighty years later by producing an immunity against fowl-cholera by means of the injection of attenuated cultures of the causal organism; and by his immunisation experiments against anthrax, produced by the injection of cultures which he had rendered asporogenous by growing them at a temperature of 42° C. On the same lines were the observations of Greenfield, that cattle were immune against anthrax if the injected bacilli were first passed through the guinea-pig, and thus had their virulence diminished. Other observers have shown that the *Bacillus of Quarter Evil* (*Symptomatic Anthrax*), when dried and exposed to a temperature of 85° C. for some hours, is no longer pathogenic for cattle, but, when inoculated into them, produces an

immunity against living cultures of the bacterium. In some cases, it is apparently the intracellular substances in the bodies of the bacteria which are the important immunity-producing agents; in other cases these intracellular substances are combined with extracellular products found in the fluids in which the bacteria grow.

The injections may be of (1) **cultures which have been exposed to heat sufficient to kill the bacteria**; or of **bacteria which have triturated in various ways and washed** so that they are freed from their toxic products; or, again, of **cultures whose virulence has been lessened** in some way; followed by inoculation with more virulent cultures. These injection preparations, however produced, are known as **vaccines**, and have been used by Haffkine in immunisation against cholera and plague; and by Wright in immunisation against typhoid fever; and also by Wright and others in the treatment of infections produced by various bacteria, *e.g. B. tuberculosis*, *B. coli*, *Staphylococci*, etc.

(2) **Living virulent cultures in non-lethal doses.**—This method has a very limited application, and can hardly be regarded as a therapeutic agent. The virulence of the organism with which we are dealing may be estimated, and thus its doses regulated; but it is not possible to estimate the power of resistance of the individual animal, for the difference in susceptibility, even of animals of the same species, is so great, that what may be a non-lethal dose for one may be a fatal dose for another.

(3) **The separated products or toxins.**—These toxins are injected in graduated doses, until eventually a very large quantity can be borne; and in the animals so inoculated there are developed bodies which specially antagonise the toxin. These are the **antitoxins**. Behring and Roux, in their great discovery of diphtheria antitoxin and tetanus antitoxin, carried out this line of research. Calmette, Fraser, Ehrlich, Morgenroth, and many others have shown that immunity can be produced against snake-venoms; vegetable poisons, *e.g.* ricin and abrin; ferments, *e.g.* rennin, etc.—by repeated injections of these bodies in small and gradually increasing doses; and they have further shown that this immunity is due to the presence in the serum of the inoculated animals of a substance or substances which neutralise the toxins which were injected.

PASSIVE OR INDIRECT IMMUNITY. — In producing passive

immunity, the serum of an animal which has been immunised by the direct method is used as the injection medium. This serum, as has been stated above, contains (*a*) substances antagonistic to bacteria (**antibacterial bodies**), or (*b*) substances antagonistic to toxins (**antitoxic bodies**); or a mixture of both of these. The difference between antibacterial and antitoxic bodies must be clearly understood. The antibacterial bodies are produced as a result of the injection of the bacteria themselves, and they act as bacteriolytic but not as antitoxic substances. The antitoxins, on the other hand, are produced as the result of the injection of the toxins; and their main function is to antagonise toxins. From this, it is evident that the production of passive immunity may be used, not only as a preventive, but also as a curative agent. An antitoxin or an antibacterial body may be produced in a healthy animal, and that animal will then be enabled to resist an injection of either the corresponding toxin or bacterium. Further, if the animal is already infected with a toxin or with bacteria, the corresponding antagonistic body can be injected, and it will neutralise the toxin already present, or weaken, and it may be destroy, the bacteria which are causing the disease. Experimentally, in the lower animals, this law of the neutralisation of toxin by antitoxin, and the destruction of bacteria by antibacterial substances, can be definitely established; but in disease in man, the law is not nearly so definite in its application. To this subject, however, reference will be made later.

ANTITOXIN OR ANTITOXIC SERUM:—

(1) **Preparation of Toxin.**—The essential point is that the bacteria are grown in the most suitable medium, and under the most favourable conditions of temperature, etc. These are determined by experiment, and vary with different organisms. When the maximum toxicity is reached—again determined by experiment—the culture fluid is filtered through a porcelain filter, and the filtrate, which is now free from bacteria, contains—and is commonly known as—the **toxin**. Some authors regard these toxins as of the nature of albumoses. They are dialysable, and can be precipitated from solutions by alcohol and by ammonium sulphate. The toxic property is modified by acids and alkalies, and is also largely destroyed by heating to 80° C. for one hour.

(2) **Estimation of Toxicity.**—A series of healthy guinea-pigs (*a* to *x*) of given weight—generally about 250 grammes—is selected, and into each of these is injected a dose of toxin. These doses are definitely graduated so that the animal at the *a* end of the series receives a very small dose, while that at the *x* end receives a comparatively large dose. Some of the intermediate animals of the series die on the fourth or fifth day, and the doses given to these are noted. Another similar series of experiments is carried out, using doses which are between the lowest and the highest fatal doses of the former series. Gradually in this way, the smallest quantity which will with certainty kill a guinea-pig of 250 grammes weight on the fourth or fifth day is determined. This amount of toxin has been arbitrarily denominated the minimum lethal dose (M.L.D.).

(3) **Preparation or Development of Antitoxin.**—The animal (generally a horse) which is to be immunised is very carefully selected. Having determined, as far as possible, that it is in a perfectly healthy condition, excluding especially glanders by the mallein test, a dose of toxin which is known to have little or no effect (about $\frac{1}{100}$ c.c.) is injected subcutaneously. The animal is allowed to recover completely from any ill effects of the injection, and then the dosage is gradually increased, care being taken that the animal is kept in as perfect a condition as possible. The antitoxic power of the animal's serum is tested from time to time against a standard toxin, and, when it is deemed sufficiently high, the animal is bled under strictly aseptic precautions, the serum being then allowed to separate. This serum is what is sold commercially as **antitoxin.**

(4) **The Standardisation of the Antitoxic Serum.**—The antiserum when dried is more stable than the toxin, hence the antitoxin has been made the standard for testing purposes. An arbitrary unit of antitoxin has been fixed by Ehrlich, and is now generally accepted by pathologists. It is that amount of antitoxin which would exactly neutralise two hundred minimal lethal doses of a hypothetical toxin containing toxin only. Having determined the minimal lethal dose of the toxin, varying amounts of this toxin are mixed with one standard unit of antitoxin and injected subcutaneously into guinea-pigs of 250 grammes weight. In this way is determined the maximum amount of toxin which is just neutralised by one unit of

standard antitoxin (L_0. dose); and also the amount of toxin which is unneutralised to the extent that death occurs on the fourth or fifth day (L_4. dose). The L_4. dose having been determined with great accuracy, is employed to standardise the diphtheria antitoxin which has been prepared. In estimating the number of antitoxic units in the serum for the one unit of Ehrlich in the above test, varying quantities (fractions of a cubic centimetre) of the serum to be tested are substituted and injected subcutaneously, along with the L_4. dose, into guinea-pigs of 250 grammes weight. That fraction which delays death till the fourth or fifth day contains one unit of Ehrlich, and from this the strength of the serum can be easily deduced. For example, if $\frac{1}{100}$ c.c. of the serum delays death till the fourth or fifth day, that serum contains exactly 100 units of antitoxin.

The Chemical and Physical Properties of Antitoxins.—The chemical composition of these bodies is as yet very imperfectly understood. Several unsuccessful attempts have been made to obtain protein-free antitoxin, but in serum the antitoxin is invariably united to the globulins. In the horse, at least, it is the **pseudoglobulin** which contains practically all the antitoxin. Antitoxins are precipitated by alcohol and by ammonium sulphate; and are destroyed by boiling for a short time, or by prolonged exposure to a temperature of 60° or 70° C. In their dry condition they can withstand a temperature of 140° C. for fifteen minutes.

NATURE OF THE ANTAGONISM BETWEEN TOXIN AND ANTITOXIN.—There are at least two possible explanations of the fact that the action of a given dose of toxin of known virulence can be neutralised by a given amount of antitoxin. Either the antitoxin may break up or combine with the toxin and thus render it harmless; or, on the other hand, the toxin may act in one way on the tissues and the antitoxin in the opposite way, and thus damage may be prevented. The first or chemical view is the one generally held, though the latter or physiological view has many supporters.

1. **Physiological Antagonism.**—Calmette, working with snake-venom, found that its toxic properties were not destroyed by a temperature which destroyed the neutralising powers of the corresponding antivenin. He then made a neutral mixture

of venin and antivenin, heated this to 68° C. for ten minutes, and found that the mixture was now toxic; or, in other words, that the antivenin or toxin-neutralising substance was destroyed. From this he inferred that no actual combination took place between these two substances, but that they existed side by side, and that the neutralising effect was brought about only within the body of the animal into which they were injected. Martin and Cherry showed, however, that these results were obtained only if the heat was applied very soon after the mixture was made. They found that, if time were allowed for interaction between the venin and antivenin, the toxic properties were not restored by the action of heat.

2. **The Chemical Theory.**—The view was put forward by Ehrlich that the antitoxin is capable of combining in a strictly chemical way with the toxin and neutralising it. That definite combination takes place *in vitro* seems to be beyond dispute. Toxin will pass through a Chamberland filter coated with gelatin, if high pressure is applied; but antitoxin will not, probably on account of the relatively large size of its component molecules. Martin and Cherry made a neutral mixture of diphtheria toxin and antitoxin, and allowed sufficient time for interaction. They then attempted in the same way to filter the mixture under pressure, and found that the filtrate was non-toxic. It follows from this that the toxin must either have been destroyed by or have combined with the antitoxin—otherwise the filtrate would have been toxic. Martin concludes that there was definite combination *in vitro* between the diphtheria toxin and antitoxin; and he draws similar conclusions from the experiments with venin and antivenin referred to above. Numerous other experiments point in the same direction, but perhaps the most conclusive is one by Morgenroth. He injected the ordinary milk-curdling ferment—rennet—into a goat, and found that after a time the goat's serum had the power of preventing the curdling of cow's milk by rennet. Here there is produced a substance definitely antagonistic to rennet, and this must combine with the rennet in order to prevent its action. Physiological action is in this instance out of the question, for we are dealing with the albumins of milk, which must be regarded as inert chemical substances. Further, Ehrlich showed

that if ricin be added to blood, the coagulation of which was prevented by the addition of citrate of sodium, the corpuscles agglutinate in masses and become sedimented. If, however, some antiricin— *i.e.* the serum of an animal immunised against ricin—be previously added to the blood, the agglutination does not take place. This reaction is a definitely quantitative one; and further, the process is hastened by heat, and retarded by cold and by dilution. As has already been indicated, this union between toxin and antitoxin appears to be a chemical one, and follows definite chemical laws. This being the case, it might be anticipated that, if to an exactly neutral mixture of toxin and antitoxin there was added a minimum killing dose of toxin, an injection of this mixture would prove fatal to a guinea-pig of 250 grammes weight within four days. It is found, however, that this is not the case, but that five, ten, or even more minimum lethal doses may require to be added before the mixture becomes toxic. This is explained by the presence in the toxin of **toxoids** or **toxons**. According to Ehrlich, the toxin is made up of at least two molecular groups, a toxophore and a haptophore; and the toxic properties of a toxin can be weakened or destroyed by mere exposure to light, air, or heat. These weakened true toxins are called **toxoids**. The weakening is a gradual process, and affects mainly the toxophore element. The haptophore group may be increased in combining activity (**protoxoid** of Ehrlich); or unchanged (**syntoxoid**); or decreased (**epitoxoid**). It has also been shown that there are poisons whose haptophore as well as whose toxophore activities are weak. These weakened toxins are called **epitoxoids** or **toxons**, and are specially found in young cultures. The **toxons** are probably not degenerated toxins. They are formed in cultures directly during the growth of the bacilli. They may thus be regarded as weak or imperfectly developed toxins, or bodies allied to toxins but with a somewhat different molecular structure, so that they have less poisoning power, and less affinity for antitoxins. On this view, ordinary diphtheria toxin contains more than one toxic substance, *i.e.* (i) **a true toxin**, which causes the acute symptoms; (ii) **a toxon**, which, acting later, may cause the characteristic paralysis; and further, the true toxin in time degenerates into (iii) **a toxoid**, or even into a substance indistinguishable from a toxon.

The above explanation may be graphically represented as follows :—

$$\textbf{Toxin (T)} = \begin{cases} \text{Toxin—a full combining power (Tc.).} \\ \text{Toxon—of diminished combining power (Tw.).} \end{cases}$$

The total amount of T is a fixed quantity, but in it the relative amounts of its two components—Tc. and Tw.—may vary in any given case. Now Tc. has a greater combining affinity for antitoxin (At) than has Tw.

Take ten volumes of toxin, and suppose that in a given instance it is composed of 8 volumes of Tc. and 2 volumes of Tw.; and add to it sufficient (say x) antitoxin to make the mixture "**neutral.**"

Then :—8 Tc. + 2 Tw. + x (At) is "neutral."

To this neutral mixture add a minimum lethal dose of toxin, say 3 T, which on examination is found to contain, say, 2 Tc. + 1 Tw.

The mixture may therefore at this stage be thus represented :—

(8 Tc. + 2 Tw. + x At) + (2 Tc. + 1 Tw.).

But in this mixture 2 Tc. will displace 2 Tw. in virtue of its stronger combining power with At, and the following reaction is obtained :—

(8 Tc. + 2 Tc. + x At) + 2 Tw. + 1 Tw.
= (10 Tc. + x At) + 3 Tw.

Thus, there are uncombined or loosely combined in one mixture —*i.e.* available for action—three volumes of toxon, which is *less* than the minimum lethal dose.

These views of Ehrlich have given rise to much criticism, but we do not think it profitable to discuss them further here, especially as the controversy is still unsettled. It seems undoubted that weakened toxins do exist, and that chemical union between toxin and antitoxin takes place. It may be, as Madsen holds, that the toxin-antitoxin reactions are reversible, and that the toxin can be disassociated from the antitoxin; but the subject is one of too great complexity to enter upon here.

There is abundant evidence that toxin rapidly disappears from the circulating blood, and that it becomes "fixed" to or by the protoplasm of various cells of the body.

The Source of the Antitoxin.—The opposing views that the antitoxin is an enzyme produced in the culture-tube during

the growth of the toxin or, on the other hand, that it is derived from the toxin by the vital activity of the cells of the body, need not be discussed. The amount of antitoxin produced is always so much in excess of the toxin introduced, that it is inconceivable that it could be produced from the toxin by the action of the cells. The toxins may and probably do act in some unknown way on the cells of the body, and it is now generally admitted that the antitoxin is derived from the cells.

In order to explain the production of antitoxin from the cells, Ehrlich propounded his "**side-chain**" **theory**; and whether this view explains all the facts or not, there cannot be the least doubt that the theory has proved of great value to workers in the field of immunity.

Toxin which has been stored deteriorates not only in its toxic power but also in its combining capacity with antitoxin. The toxic power, however, is diminished in a far greater degree than the combining power. On this observation, Ehrlich stated that the toxin possesses at least two molecular groups—a toxic one (the **toxophore**) and a combining one (the **haptophore**). The toxophore group is very unstable, and can be destroyed at a temperature of 55° C.; and its potency is considerably diminished even by exposure to light and to air. The haptophore group is much more stable. Thus toxin may be represented in graphic chemical formula:

T ⟨ (combining arm).
  ⟨ (toxic arm).

Ehrlich further postulates that the protoplasmic molecules of the cells of the body are equipped with certain "side-chains," "arms," or atomic groups, the function of which, under normal circumstances, is to "fix" or chemically combine with certain food-stuffs required by the cell, and so enable them to become available for cell-life. These atomic groups may vary in character and in function, one form being specially fitted for combination with the molecules of one kind of food, another for those of another kind, and so on. The molecule, or, for convenience, the cell itself, may be graphically represented, as is shown in fig. 160.

The toxins and the protein food elements are allied in composition and combining affinities; and therefore it is quite

reasonable to assume that certain of the "side-chains" or "receptors" of the cells have combining affinities suitable for the haptophore group of the toxins. Thus, when toxins are introduced into the body, they, by means of their haptophore group, combine with suitable receptors of the cells; and the toxophore molecule, which is a poison, can then act injuriously on the life of the cell—this toxic agent not being able to act until it becomes anchored to the cell by its "haptophore arm." During disease, an increasing amount of toxin is being poured

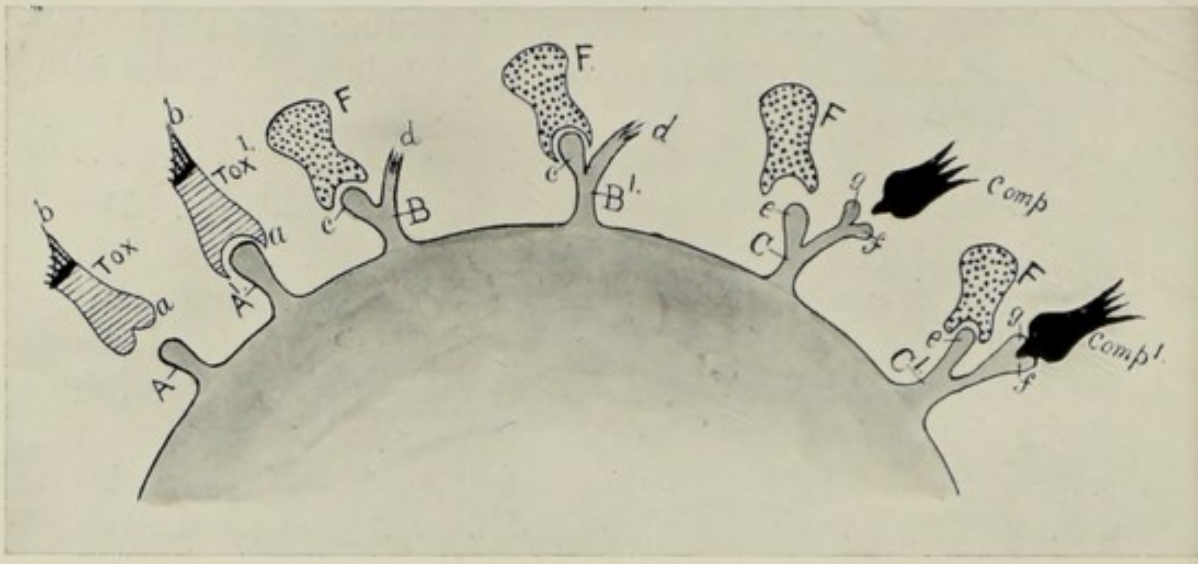


FIG. 160.—Diagram of Receptors (after Ehrlich).

A, A¹. Receptors of the *first* order (uniceptors), with a single haptophore group.

Tox, Tox¹. Toxin molecule, with a haptophore part (*a*) and a toxophore part (*b*). At A¹ the toxin is united to the cell by its haptophore (*a*).

B, B¹. Receptors of the *second* order, with a single haptophore group (*c*) and a group with a ferment capacity (zymophore) (*d*). F = molecules of nutrient material, protein matter, or bacterial bodies.

At B¹, the nutrient material, F, is united to the cell by the haptophore group (*c*), and in this condition the ferment (*d*) can act upon it.

C, C¹. Receptors of the *third* order (amboceptors) with two haptophore groups, one of which combines with F, and the other with the haptophore group of the *complement*. The complement has a haptophore and a zymotoxic group.

into the system, and all the suitable receptors of the cells become used up. The cell is thus not only being poisoned, but it is being deprived of its normal nutriment as well, because its food receptors have become linked to, and are thus used up by, the toxin receptors. Nature, however, attempts to compensate for this; and, according to Weigert's well-established law of regeneration, **new receptors** are developed. These, in turn, become

used up, and further regeneration goes on. This process may continue and the receptors be formed in great excess; until ultimately the cells can no longer contain them, and they are cast off into the blood-serum or lymph in enormous numbers. These cast-off side-chains or receptors form the **antitoxin.** When more toxin is introduced into the system, it meets and combines with the **free antitoxin** present in the body fluids, its toxic effect is neutralised, and the cell escapes damage (fig. 161).

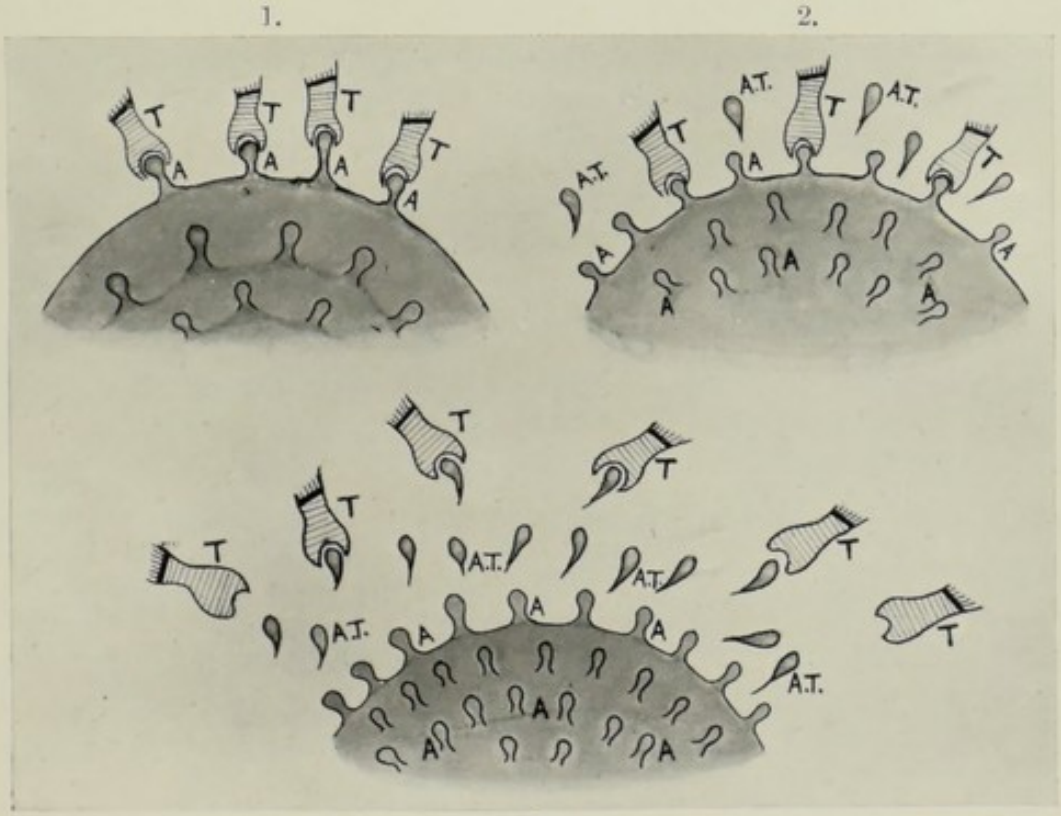


Fig. 161.—Diagram of ormation of antitoxin (after Ehrlich).

1. Uniceptors (A) used up by toxin molecule (T).
2. Cell with increase of uniceptors, some of which are "cast off" as antitoxin (A.T.).
3. Free antitoxin (A.T.), arresting toxin (T), and so preventing its union with and consequent damage to the cell.

If an active tetanus toxin be rubbed up with the brain-tissue of a guinea-pig to form an emulsion, its toxic power is lost; and if the emulsion is now injected into an animal, no tetanic symptoms develop. The most reasonable explanation of this is that a union has taken place between the toxin and the protoplasm of the brain-cells.

The Action and Uses of Antitoxin.—The two most important antitoxins yet known are those produced for the treatment of

diphtheria and **tetanus**. The toxins of these two diseases act probably in much the same way, viz. by becoming linked to the cells. The antitoxin acts by uniting with the **free** toxin; but it can have little or no effect on that which is already chemically "fixed." It follows, that if a fatal dose of toxin has become united to the cells, then no antitoxic treatment can save the life of the patient. Fortunately, the "fixation" of the toxin—at any rate of diphtheria toxin—to the cells is a comparatively slow process. Dönitz showed that **the longer the time elapsing between the injection of toxin and antitoxin, the less the chance of recovery.** He found, for example, that if the **antitoxin** followed the **toxin** within ten minutes, a simple neutralising dose would save life; but, if more than a quarter of an hour had elapsed, a much larger quantity was necessary. Further, he showed that if only slightly more than a minimum lethal dose of toxin were given, large doses of **antitoxin** were successful after six hours, and in one case even after eight hours. But with two and a half times the fatal dose, **antitoxin** was useless after four hours; and with very large doses, no amount of antitoxin would save after about one hour.

From these experiments it follows that large doses of antitoxin should be given; and, what is of far more importance, that **the antitoxin should be given as early as possible**; for it will neutralise the toxin free in the blood, it may destroy toxin which is only feebly combined with cells, and it will render harmless the fresh output of toxin; but it will **not** repair damage already done.

ANTIBACTERIAL SERUM.—As has been previously stated, if an animal be injected with gradually increasing quantities of bacteria, care being taken at first to use doses considerably below the minimum lethal dose, the animal gradually becomes immune, and ultimately large doses of even virulent cultures can be tolerated. The serum of such an animal is highly bactericidal to the special variety of bacteria originally injected, and small doses of this serum will protect other animals—at any rate, animals of the same species—against doses which would be fatal to the unprotected animal. Pfeiffer found that ·002 c.c. of serum from an animal highly immunised against cholera would protect another animal against ten times the minimum lethal dose of a living culture. This method of

protection against disease has been applied in cases of typhoid fever, plague, cholera, etc., and the method has also been used in the treatment of septic infection in the human subject, *e.g.* in puerperal septicæmia, etc.

Preparation of Antibacterial Sera.—As in the preparation of antitoxic sera, a reliable animal is selected. At first, killed cultures are injected subcutaneously, and later, intravenously, and then living cultures intravenously. The serum should be tested from time to time for toxicity and for the presence of living organisms.

Standardisation of Antibacterial Sera.—Determine the minimal lethal dose of the micro-organism by a method similar to that used in the case of toxins. Then inoculate a series of rabbits intravenously with ten minimal lethal doses, and at the same time inoculate them subcutaneously with measured volumes of the serum to be tested. Thus is determined the amount of serum required to preserve the life of the animal, or, in other words, sufficient to neutralise ten minimum lethal doses. It is also customary to inject a series of rabbits after infection to determine the curative action of the serum.

The Method of Action of the Antibacterial Serum.—If the spirilla of cholera be injected into the peritoneal cavity of a guinea-pig which has been highly immunised against these organisms, they rapidly lose their motility, gradually become granular, break up into irregular droplets, and finally undergo solution and disappear entirely from the peritoneal fluid, the animal meanwhile remaining apparently in a perfectly healthy condition. This "**reaction of Pfeiffer**" is the basis on which the theory of the action of antibacterial serum has been built. A similar reaction is found in the case of *B. typhosus* and many other organisms, provided the immunisation is carried out with the organism afterwards injected into the peritoneal cavity. In other words, the reaction is *specific*; *i.e.* the serum of a guinea-pig immunised against *B. typhosus* will, in the peritoneal cavity, cause a bacteriolysis of *B. typhosus*, but will have no action on *S. choleræ*, and *vice versa*. Later investigations by Bordet, Metchnikoff, and others have shown that this bacteriolysis can be produced *in vitro* if the bacteria are mixed with freshly withdrawn peritoneal fluid from the immunised animal, but does not take place in immune serum

which has been kept for some time or which has been heated from 55° to 65° C. Further, they have shown that this **inactivated** immune serum can be **reactivated** by the addition of freshly drawn serum from a normal (*i.e.* non-immunised) animal. From these researches it has been concluded that in order to bring about bacteriolysis in serum, at least **two** substances are necessary. One of these is present in the healthy serum of an uninoculated animal, and is very unstable, being easily destroyed at a temperature of from 55° to 65° C., and also by exposure to light and air; the other substance is stable, is developed during the process of immunisation, is more or less specific in each case, and gives to the **antiserum** its special character. The former of these bodies is the **complement**, or **cytase**, or **alexin**; the latter, the **immune body**, or **fixative**, or **amboceptor.**

TABULATED SUMMARY OF THE ABOVE EXPERIMENTS

Let B. = bacteria: N.S. = serum of a healthy uninoculated animal: I.S. = immune serum.

Note.—It must always be clearly understood that the immune serum of the experiments is produced by injection of the specific bacterium which undergoes bacteriolysis.

Experiment 1.—B. + N.S. (in peritoneal cavity or *in vitro*) = no bacteriolysis.

„ 2.—B. + I.S. (in peritoneal cavity of immunised animal) = bacteriolysis.

Therefore in I.S. there must be one or more bacteriolytic bodies which are not present in N.S., and which must therefore have been developed during the process of immunisation.

Experiment 3.—B. + I.S. freshly withdrawn (*in vitro*) = bacteriolysis.

„ 4.—B. + I.S. (heated or exposed to light, etc., for some time (*in vitro*)) = no bacteriolysis.

Therefore I.S. can be "**inactivated**"; and by this process one or more of the bacteriolytic bodies must be destroyed, weakened, or altered in some way.

Experiment 5.—But B. + I.S. ("inactivated") + N.S. (*in vitro*) = bacteriolysis.

Thus, "**inactivated**" I.S. can be "**reactivated**" by the addition of N.S.; but N.S. of itself cannot produce bacteriolysis. From this it necessarily follows that there must be at least two bodies concerned in this bacteriolytic action: one present in N.S.—the **complement**; and one in I.S.—the **immune body.**

During the process of immunisation the **immune body** is developed and gradually increased in amount and potency: the **complement**, however, is not altered. It is present along with the immune body in active immune serum, simply because it was present in the serum **before** immunisation, and has not been destroyed during the immunising process, *i.e.* it is a normal constituent of the serum in health.

From these experiments this formula is established :—

B. + I.B. (immune body) + C. (complement) = **Lysis.**

It has been shown that this law is not peculiar to bacteria, but applies equally to erythrocytes, leucocytes, and various other cells of the body, though in some cases not with absolute specificity.

The subject has been largely studied in connection with red blood corpuscles, and the **hæmolysins** correspond closely with the **bacteriolysins**, both in their action and in the mechanism of their formation.

HÆMOLYSIS.—The blood-serum of some animals possesses marked powers of dissolving the red blood corpuscles of certain animals of another species, and thus of setting free their contained hæmoglobin. To take a specific example: the serum of a healthy goat, mixed with the erythrocytes of a rabbit or of a guinea-pig, brings about **hæmolysis**. Further, if an animal be injected with the erythrocytes of another species, its blood-serum may gradually acquire the property of dissolving the red blood corpuscles of the animal whose blood was injected. The serum of a normal guinea-pig has no hæmolytic action on the red blood corpuscles of the rabbit; but if the guinea-pig receive a few injections of defibrinated rabbit's blood, its blood-serum rapidly acquires hæmolytic properties and dissolves the red blood corpuscles of the rabbit. If this active hæmolytic serum is heated at 56° C., it loses its hæmolysing power, but it can be reactivated by the addition of fresh serum from an uninoculated animal. Normal serum, however, after its withdrawal, very soon loses its reactivating power.

The parallelism between hæmolysis and bacteriolysis is best shown by a series of experiments analogous to those given on page 440.

In carrying out these experiments, 5 parts of rabbit's blood are mixed with 100 parts of a 0·8 per cent. solution of sodium chloride.

Ten cubic centimetres of this mixture are placed in each of a series of test-tubes, and to these are added small quantities of normal or of immune serum.

Experiment 1.—Erythrocytes (rabbit) + N.S. (guinea-pig) = No hæmolysis.

,, 2.—Erythrocytes (rabbit) + I.S. (guinea-pig immunised with corpuscles of a rabbit) = Hæmolysis.

Therefore in I.S. there must be one or more hæmolytic bodies.

Experiment 3.—Erythrocytes (rabbit) + I.S. (inactivated) = No hæmolysis.

Therefore during inactivation one or more of the hæmolytic bodies must be destroyed.

Experiment 4.—Erythrocytes (rabbit) + I.S. (inactivated) + N.S. (guinea-pig) = hæmolysis.

Thus, again, the inactivated immune hæmolytic serum can be reactivated by the addition of normal guinea-pig serum.

For **hæmolysis**, therefore, we require (i) the immune body present in the immune serum, and (ii) the complement of normal serum.

By the injection of epithelial cells, or other tissue-cells into animals, **epitheliolysins** or other **cytolysins** may be produced, and inoculation with these various lysins or toxins gives rise to another important set of antagonistic bodies—**antilysins**. Work in this field gives hope that, in diseases where lysis of the various cells is the pronounced feature—*e.g.* in pernicious anæmia and paroxysmal hæmoglobinuria—these antilysins may in the future be employed therapeutically. At present, however, their practical application to the treatment of disease in the human subject has been very imperfectly tested.

Therapeutic use of Antibacterial Serum.—The value of antibacterial sera in the treatment of disease is still a much disputed question. Many workers hold that they are of little value. We have emphasised the fact that both complement and immune body are necessary in order that bacteriolysis may take place. During the preparation of a serum, the immune body is increased considerably; but there may be little or perhaps no corresponding increase in the amount of the complement. In the therapeutic application of the serum, therefore, practically immune body alone is injected. The complement of the patient may soon become exhausted, and then, no matter how much serum is injected, it can have no destructive effect upon the bacteria. Further, experiment seems to show that the

complement of one animal may not be complementary to the immune body of an animal of a different species; that the immune body and the complement will act on bacteria only if present in certain proportions; and that, if one or other of these is in great excess, no bactericidal action takes place. The whole subject is one of very great difficulty, and we do not consider that it would be profitable to discuss it more fully here.

THEORIES OF IMMUNITY.—The various theories put forward to explain the phenomena of immunity may be grouped into two classes :—

1. The **Cellular** theory.
2. The **Serum** or **Humoral** theory.

1. **The Cellular theory.**—To the brilliant work of Elias Metchnikoff we owe our knowledge of the important part played by phagocytic cells in the economy of nature. When bacteria are introduced into the body of an animal, whether it be into the blood-stream or into one of the serous cavities, these bacteria are, in a short time, found within the cytoplasm of the leucocytes, especially those of the polymorphonuclear type. According to Metchnikoff and his pupils, the leucocytes are attracted to bacteria (positive chemiotaxis), or repelled by them (negative chemiotaxis). In the majority of cases, **positive** chemiotaxis exists; the leuococytes are drawn towards the bacteria, take them into their cytoplasm, and there digest them by means of an enzyme—the **cytase**. These phagocytic cells produce this cytase, but it is **not excreted** by them. It is retained in the cell-reticulum, and is found free in the serum only where a **phagolysis** or breaking up of these phagocytic cells has taken place. This cytase corresponds with the **complement** of Ehrlich. According to Metchnikoff, two kinds of cytases exist, of which one—the **microcytase**—acts principally on micro-organisms; the other—the **macrocytase**—acts specially on cells and other elements of animal origin. The microcytase is principally, if not wholly, found in the polymorphonuclear leucocytes, and is set free only if there has been a phagolysis. The macrocytase is found in the mononuclear leucocytes, endothelial cells, etc., and is also retained in them. In the serum the **immune body** or **fixative** is free. **Whence, then, does it arise?** 'There exists . . . a constant relation between the degree of phago-

cytosis and the amount of the fixative produced. As this fixative facilitates the access of the cytase to the cells, and as the resorption of these elements takes place specially in the macrophages, we are bound to come to the conclusion that the fixative is a second phagocytic ferment which is produced in abundance during the process of intracellular digestion. Only, instead of remaining in the substance of the phagocytes, this fixative is in part thrown out from the elements. It passes into the plasma of the blood and into the other fluids, and ends by disappearing from the organism, probably being eliminated by the excretory channels."[1]

The production of acquired immunity against bacteria means simply, according to this view, that by repeated injections the phagocytes become much more active. Their positive chemiotaxis is increased, and they acquire the faculty of digesting micro-organisms in a greatly intensified degree. With this increased digestive power there is necessarily associated an over-production and increased excretion of fixative or immune body. Metchnikoff maintains that the fixative or immune body becomes attached to the bacteria, but that these are not in any way injured by it. They are ingested by the phagocytic cells, and digested by the cytase of these. Extra-cellular digestion, if it takes place at all, does so only to a minimum degree. **Natural Immunity** is explained by the fact that the leucocytes of the immune animal are powerfully phagocytic to the invading organism. The immunity against toxins is more difficult to explain on this theory. We must presume that the leucocytes, stimulated in some way by the toxin, are the producers of the **antitoxin**. The **macrophages** appear to be chiefly concerned in this process. It is extremely difficult to demonstrate the correctness of this view, and we must simply state that Metchnikoff puts it forward as a hypothesis or "guiding idea for new researches," and refer our reader to the elaborate experimental work in his most fascinating book.[2]

2. **The Humoral theory**.—Fodor found that the defibrinated blood of the rabbit was capable of destroying, *in vitro*, a great number of anthrax bacilli. From this he concluded that the

[1] *Immunity in Infective Diseases*, by Elie Metchnikoff; English translation by F. G. Binnie; Cambridge University Press, 1905, pp. 103 and 104.
[2] *Loc. cit.*

fluids of the body, by their destructive action upon certain bacteria, were capable of conferring immunity against bacterial disease. Much further work on this line was carried out by Flügge, Nuttall, and von Behring, all of which tended to confirm the work of Fodor; and, as a result, a reaction set in against the phagocytic theory, these and other observers maintaining that immunity did not depend in any way on phagocytosis, but was wholly due to a destructive action on the bacteria by the fluids of the body. In 1887, Emmerich vaccinated rabbits against the bacillus of swine erysipelas, and found in the blood a very powerful antibacterial substance. To this substance, and not to the phagocytes, he attributed the acquired immunity. Then Buchner of Munich confirmed Nuttall's observations, and concluded from a series of experiments that the bactericidal power of the blood depends on the presence of certain albuminoid substances, to which he gave the name **alexins.** He considered that these substances acted upon the bacteria, and that the phagocytes simply carried off their dead bodies, **natural immunity,** according to this observer, being therefore due to the presence of these bactericidal substances in the serum. In a susceptible animal they were absent, or present in very small amount. In **artificial immunity,** these substances are produced during the immunising processes. While Buchner and others admit that the alexin is a leucocyte product, Pfeiffer and his school still maintain that the bactericidal substance, which they do not identify with alexin, is not a product of the leucocytes. It would not be profitable to enter into a full account of the experiments and arguments brought forward by these various workers in support of their special views. It must suffice here to say that the general conclusion is that in the plasma of refractory and immunised animals there are substances which have an injurious action on bacterial products; and that these substances are derived from the leucocytes or from various other cells. The substances correspond with the **alexins** of Buchner, the **bactericidal substance** of Pfeiffer, or the **antitoxin** of other observers. Whether this product is a secretion from the cells, or whether it is a substance which, according to Metchnikoff, is only freed by destruction of the cell (**phagolysis**), for our purpose matters very little. Basing his conclusion on the staining reactions, etc.,

of actively functioning cells in inflammatory exudates, one of the authors[1] has concluded that the mononucleated phagocytes during active life discharge into the serum **a nutritive agent**, or some special ferment, or an **antitoxic body**; and further, that the cells stimulated by the bacteria or by their products become specially active, and secrete a substance which not only digests included bacilli and cells, but produces changes in the blood-serum which render it inimical to the life of bacteria, and possibly also neutralises, by chemical combination or other means, toxic bodies already circulating in the blood or lymph. This is largely in accord with Metchnikoff's view; but we are still of the opinion that the bacteria are in most cases altered in some way before the phagocytes ingest them, though we have not the least doubt that the phagocytes can ingest and digest living bacteria.

The side-chain theory of Ehrlich.—We have already dealt in some detail with Ehrlich's views on the production of antitoxin; but, as his theory of the development of antibacterial bodies is somewhat similar, it will be necessary to refer again to the antitoxin formation, and to deal somewhat more fully with some points.

When toxins are introduced into the system, they are "fixed" by means of their haptophore groups to the "**side-chains**" or "**receptors**" of the protoplasmic molecules of the cell protoplasm. The toxophore group is now able to destroy cell-protoplasm, and the symptoms of toxic poisoning follow; new side-chains are developed in excess, and great numbers are "cast off" and appear in the blood and other fluids of the body as **antitoxin**. A toxin molecule cannot injure a cell unless it becomes attached to it by its haptophore arm, and therefore, in the presence of antitoxin it is harmless, because its haptophore arm becomes linked to the antitoxin which encounters it while both are free in the serum. The toxophore group of the toxin is still intact, but, its haptophore group being already engaged, the toxin cannot become anchored to the cell, and therefore the cell is protected from, or in other words is immune to, its action. A corresponding explanation is given for immunity against bacteria. The molecules of bacterial

[1] Beattie, "The Cells of Inflammatory Exudations," *Journal of Pathology and Bacteriology*, 1902, pp. 168 and 169.

bodies, possessing as they do the same chemical composition as certain food elements necessary to cell-life, *e.g.* the albumins, may come to act as food-stuffs unsuitable to the cells, and may use up the protoplasmic **receptors** which are eligible combining equivalents. These protoplasmic molecules are physically of larger size than the molecules of toxin, and their combining equivalents in the cell are of a different kind. They are the receptors of the third order. These receptors (**amboceptors**) have two combining affinities, one for the bacterial body, the other for a ferment—the **complement**—present in

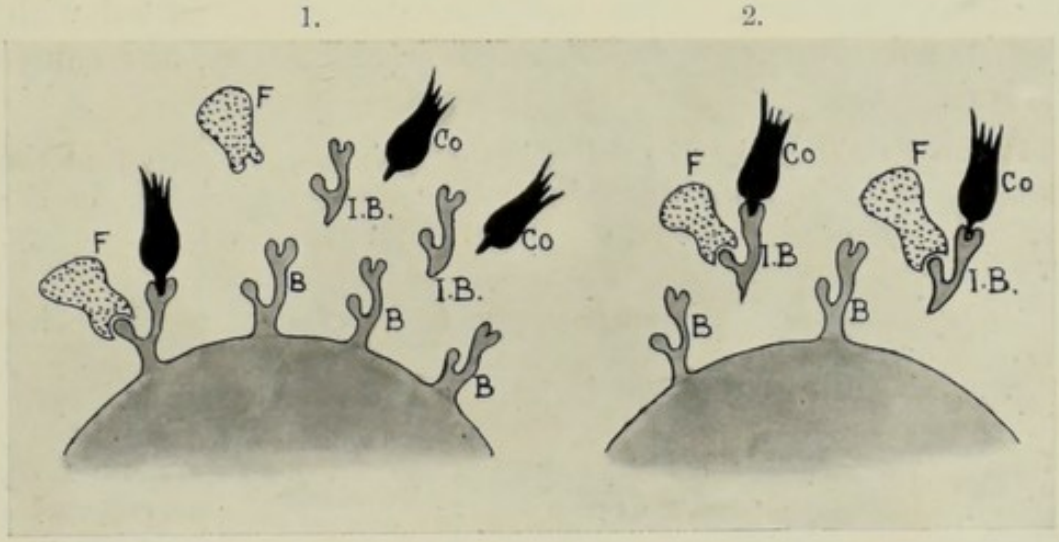


Fig. 162.—Diagram of formation of Immune Body.

1. Cell with increase of amboceptors, some of which are cast off as immune body (amboceptor), I.B.
2. Free immune body (I.B.) arresting nutrient molecule, red blood corpuscle, or bacterial body (F), and combining with complement (Co.). F undergoes lysis and cell remains uninjured.

the blood-serum. One affinity of these receptors becomes linked to the micro-organism, and the other to the complement. Thus the micro-organism is brought in contact with the complement, which is the main factor in causing its destruction. During the process of immunising, these amboceptors, which are normally present, are produced in excess, and numbers of them are cast off into the blood-stream. These correspond with the **immune body**. Without the intervention of this immune body, the combination of the complement with the micro-organism can never take place, because the receptors of the micro-organism are not adapted to the receptors of the complement.

This same theory is equally applicable to the case of hæmolysis and cytolysis in general, the red blood corpuscles or other cells being substituted for the micro-organism. Thus, in immune serum there are present the complement and the immune body, which act in combination with one another, and bring about destruction of the bacteria, the erythrocytes, etc. The theory is diagrammatically represented in fig. 162.

The complement, by means of its haptophore arm, becomes linked to the immune body, which is already attached to the micro-organism, or erythrocyte, or food molecule. In this way the toxophore group of the complement becomes united with, and is enabled to act upon, the micro-organism, etc., and causes its lysis.

It can be shown by the following experiments, *in vitro*, that the immune body becomes "fixed" to the micro-organisms, or to the erythrocytes, or to certain of the normal food molecules (*e.g.* proteins):—

Experiment 1.—The immune serum (*I.S.*) of a goat, which has been immunised by injections of the blood corpuscles of a sheep (*S.r.b.c.*), is heated to 55°–60° C. in order to destroy the complement. This heated immune serum is mixed with the red blood corpuscles of a sheep, and kept at a temperature of 40° C. for fifteen minutes, and then centrifugalised so as to separate the red blood corpuscles (treated *r.b.c.*) from the fluid (*f*). (*f* represents the heated immune serum from which the treated *r.b.c.* have been removed.) Now, *f* + fresh *S.r.b.c.* + complement (normal goat's serum) = no hæmolysis. Therefore the *I.B.* is not present in this mixture.

But "treated" *r.b.c.* + complement (normal goat's serum) = hæmolysis.

Thus the *I.B.* must be present, and must therefore have been attached to the *r.b.c.*, as we have shown that it was not present in the fluid.

Experiment 2.—The immune serum of the goat (*I.S.*) used in the last experiment is again inactivated by heat. The corpuscles of a normal sheep (*S.r.b.c.*) are mixed with the complement of a normal goat and centrifugalised, so that the corpuscles ("treated" *S.r.b.c.*) are again separated from the serum (*f*).

"Treated" *S.r.b.c.* + *I.S.* (inactivated) = no hæmolysis; but *f* + "treated" *S.r.b.c.* + *I.S.* (inactivated) = hæmolysis.

In both, the *I.B.* is present, but the complement only in the latter; and therefore it must be in *f*, and not attached to "treated" *S.r.b.c.*

On the question of the **specific** nature of immune body and complement, and the existence of **complementoids** or weakened complements, we need only say that Ehrlich maintains that

there is a multiplicity of immune bodies, and probably also of complements. Bordet, on the other hand, holds that the complement is single, while, as has been already stated, Metchnikoff is of opinion that there are two complements—the micro- and the macro-cytase. The presence of complementoids or complements with diminished cytotoxic properties seems also to be established, but the subject is one of too great complexity to enter into here.

AGGLUTINATION AND AGGLUTININS.—The serum of a patient suffering from typhoid fever or from Malta fever, after a certain period of the illness has elapsed, has the power of causing the respective organisms of these diseases to aggregate in irregular masses or "clumps" of varying size. Similarly, the serum of animals which have been immunised by repeated injections of *Bacillus typhosus*, *Spirillum choleræ*, or other organisms, has the power of **agglutinating** cultures of the specific organisms with which the immunisation was carried out. The substances in the serum which bring about this reaction are known as **agglutinins**. These agglutinins seem to be present in small amount in normal serum. The **specific** nature of these bodies has been questioned, and the position taken up by Durham is probably most correct, viz. that the antiserum may not only agglutinate the organism with which it has been prepared, but it may also affect allied species, though perhaps not with the same dilution or to the same extent. The value of the agglutination in the diagnosis of typhoid fever, Malta fever, etc., has, we think, been firmly established, and we believe that the inaccurate methods very commonly employed are responsible for much of the doubt which has been cast on the **Widal**, or as it should be termed more correctly, the **Grünbaum-Durham reaction**. A sufficient dilution of the blood before it is brought in contact with the bacteria, and a more careful measurement of such dilutions, are essential to the obtaining of accurate results. The origin of the agglutinins and their relation to immunity, interesting though they are, must be left for special text-books.

PRECIPITINS.—If milk, blood, white of egg, or other rich albumin-containing substances be injected under the skin or into the peritoneal cavity of laboratory animals, bodies are developed in their serum which have the power of producing

a precipitate in these fluids. These bodies are the **precipitins**. Thus, if an animal receives several injections of milk, its serum acquires the power of bringing about the precipitation of casein in that milk; or, if blood is injected, the serum will, if added to the blood of an animal of the same species, bring about the formation of an opalescent ring of precipitate at the junction of the two fluids. The **specific** character of this reaction has not been fully established; and though the test has been employed and has proved of value in medico-legal work, yet it cannot at present be regarded as one on which, in the differentiation of bloods of different species of animals, absolute reliance can be placed.

OPSONINS.—Mainly on account of the work of Wright, the study of the **opsonic** power of the blood has recently occupied a considerable amount of attention. We can deal with it only very shortly, and must leave its practical application in diagnosis and treatment to text-books of Clinical Medicine and Surgery. Wright has shown that normal human serum may have no bacteriolytic effect on certain organisms, *e.g. Staphylococci*, *Bacillus pestis*, and *Micrococcus melitensis*; and yet at the same time that there is a marked phagocytosis of these organisms by the leucocytes. In order to test this fact more fully, he separated the leucocytes from the serum, and washed them thoroughly in 0·85 per cent. saline solution, so that all trace of serum might be washed away. These washed leucocytes, whose phagocytic power is now almost negative, are mixed with the serum of another individual, and the mixture incubated for about fifteen minutes. The leucocytes are now markedly phagocytic. Further, if the serum is heated to 65° C. before it is mixed with the leucocytes, the **phagocytic index** is very low. To obtain this **phagocytic index** two observations are required, *i.e.* (i) the average number of bacteria ingested by a given number—say 30, 50, or 100—normal leucocytes exposed to the action of the serum to be tested; and (ii) the average number of bacteria ingested by a similar number of leucocytes (from the same source), exposed under identical conditions as to time, temperature, etc., to the action of normal or healthy serum. The **ratio** between these average numbers constitutes the so-called **phagocytic** or **opsonic index**, the latter observation being taken as unity. Thus, if in the former observation the average number of bacteria ingested

was found to be eight, and in the latter ten, the index would be $\frac{8}{10}$ of unity, *i.e.* 0·8. If, on the other hand, these numbers had been found to be ten and eight respectively, the index would be $\frac{10}{8}$, *i.e.* 1·25. Such experiments seem to show that to the body fluids an important rôle in the phenomenon of phagocytosis must be ascribed. Many experiments by other workers have now confirmed Wright's observations, and from these it may be concluded that, though the blood-serum may not be bacteriolytic, it must in some way **modify the bacteria**, so as to render them an easier prey to the phagocytes. This phenomenon is spoken of as the **opsonic** effect, and the substances in the serum which bring it about as the **opsonins** (*opsono—I cater for*, or *I prepare victuals for*).

The opsonin of normal serum is to a very considerable degree **thermolabile**, and can usually be almost completely destroyed by heating at 65° C. for half an hour. By injecting animals with cultures in which the bacteria have been killed by heat, or with vaccines prepared in other ways (*e.g.* tuberculin R. in suitable doses), the phagocytic power of the leucocytes to the bacteria with which the vaccine was prepared (in this case *B. tuberculosis*) can be raised, and thus the protective action against bacterial infection greatly increased. Recent experiments by Dean, Robert Muir, and others seem to show that this **immune opsonin** is, unlike the opsonin of normal serum, a **thermostable** body. The relation of this **immune opsonin** to **immune body** or to **complement**, and the **origin of the opsonins**, are not sufficiently established to justify any definite statement being made at present.

AGGRESSINS.—Bail found that, if a mixture of tubercle bacilli with sterilised tuberculous exudate were injected into the peritoneal cavity of healthy animals, sudden death resulted; whereas the injection of each separately had no such effect. He therefore assumed that something in the exudate increases the virulence of the micro-organisms, and to this hypothetical substance he gave the name **aggressin.** The lymphocytic character of tuberculous exudates, Bail suggests, is due to the presence of such aggressins, which inhibit the migration of polymorphonuclear leucocytes, and so act upon them that phagocytosis is prevented.

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