The elements of pathological histology with special reference to practical methods / by Anton Weichselbaum ; tr. by W.R. Dawson.

THE ELEMENTS OF PATHOLOGICAL HISTOLOGY.

Fig. 1.

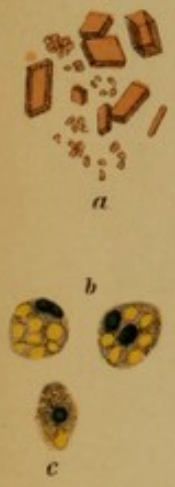


Fig. 3.

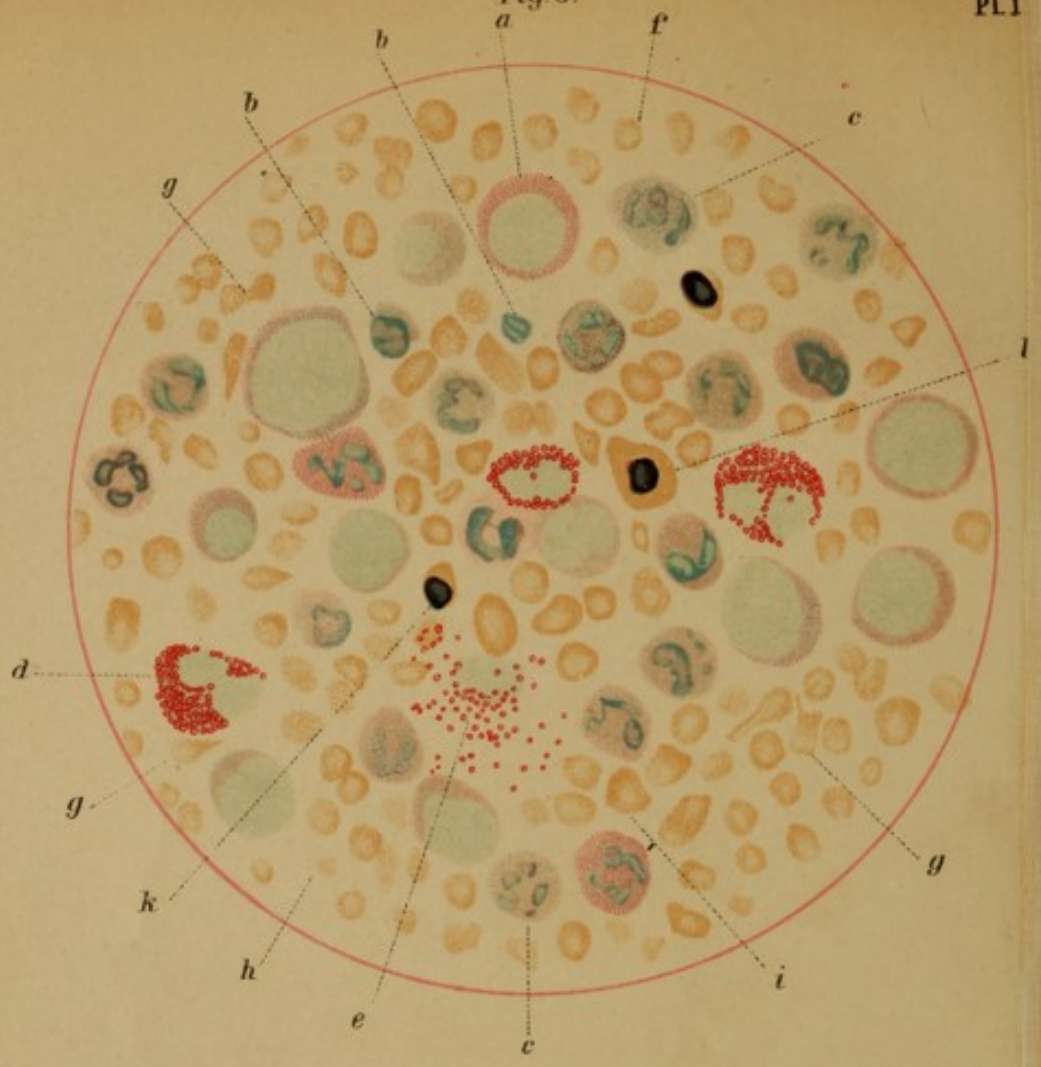


Fig. 2.

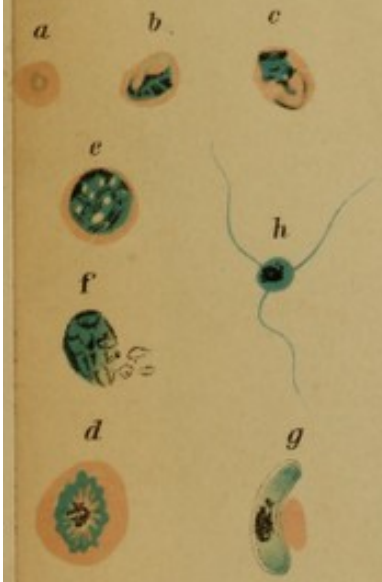
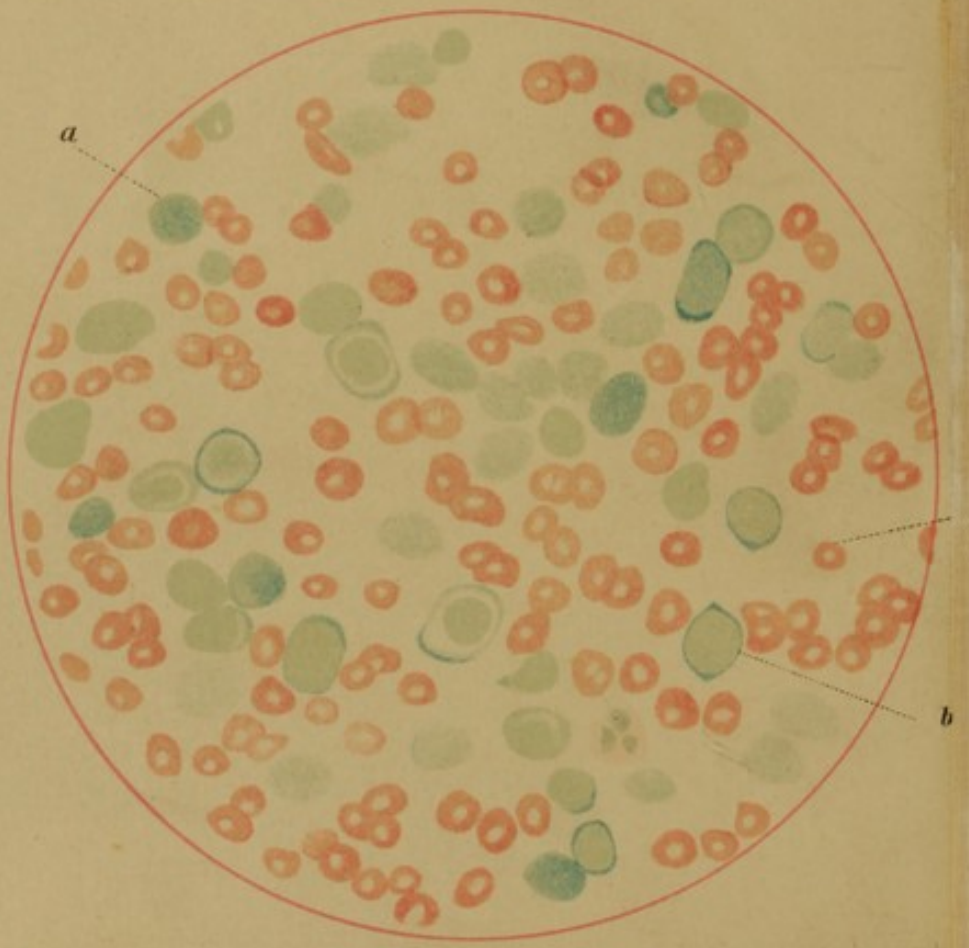


Fig. 4.



Lith. Anst. v. Th. Bannwarth, Wien

THE ELEMENTS

OF

PATHOLOGICAL HISTOLOGY

WITH SPECIAL REFERENCE TO PRACTICAL METHODS

BY

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WITH EIGHT PLATES AND A LARGE NUMBER OF ILLUSTRATIONS IN THE TEXT, SOME OF WHICH ARE COLOURED

LONDON

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AND NEW YORK: 15 EAST 16th STREET

1895

TRANSLATOR'S PREFACE.

APOLOGY or comment seems scarcely necessary in introducing to English readers a work of so well-established a reputation as Professor Weichselbaum's *Grundriss der Pathologischen Histologie.* Neither has it been thought needful or desirable to make many additions, and, consequently, the only ones of any length are the note on the Gum Freezing Method on p. 24 (which the popularity of that method in this country seemed to demand), and the very brief account of Dr. Bevan Lewis's useful process appended to the chapter on the Nervous System (p. 351). Some insertions in the text, chiefly relating to terminology, have been distinguished by square brackets when it seemed worth while, and a few foot-notes similarly and with the letters "—*Tr.*" following. Under the former head may be noted the exact zoological names of the animal parasites, which, when differing from the more popular designations, have been appended to the latter, and for which, as well as for the facts mentioned in the note on p. 180, I am indebted to Professor H. M. Mackintosh, of the University of Dublin, who kindly revised the chapter in question.

Some alterations, however, have been made in the typography and arrangement. Thus the work has been thrown into chapters, English fashion (though these correspond for the most part with the *Abschnitte* in the original), and long sections have in some instances been broken up into two or more. It has also been thought advisable to print the practical portions in a smaller type than the descriptive, which it is hoped will facilitate reference.

It remains for me to express my obligations for much kind assistance in various ways, but especially to Drs. W. F. Robertson

and Wallace Beatty and Mr. Arthur H. Benson, who were good enough to revise the chapters relating to their several specialities, viz., those on the Nervous System, the Skin, and the Eye and Ear respectively; and lastly, my best thanks are due to the Author for the unvarying courtesy and kindness which I have experienced from him.

In translating a work like the present, which deals with a great mass of facts and names, it is scarcely possible, whatever care may be used, to avoid all slips, and I shall feel grateful for having any such pointed out to me.

THE TRANSLATOR.

DUBLIN, *Dec.* 1894.

AUTHOR'S PREFACE.

The chief object which I had in view in preparing the present volume was to provide the tyro in the study of Pathological Histology with a guide for his work in which he might find, given concisely and briefly, not only the doctrines of the science, but also the most useful and practical methods for its investigation.

As I considered it essential to include pathogenesis and etiology in the descriptions, at least so far as their discovery depends on microscopic investigation, it was necessary for me, if the dimensions of the book were not to be unduly large, on the one hand to restrict myself in my choice of material to the relation of the more important facts, leaving unnoticed all points which are of secondary moment or not yet sufficiently well-ascertained, and on the other hand to use the greatest possible brevity of expression. On the same grounds I have also omitted references to the literature and the names of authorities. But whilst on the one hand I have been sparing of letterpress, on the other I have been the more liberal in the insertion of figures, being of opinion that suitably-chosen illustrations produce a clear conception of facts much more quickly and certainly than even the most accurate description. In the execution of the drawings all diagrammatic representation has been carefully avoided, and attention rather paid to reproducing the actual conditions with the greatest possible fidelity.

In consideration of the high importance which methods of investigation possess for the practical study of our science, I have given them a corresponding amount of attention. Thus, the *general* methods have been placed together in a special Part (Part I.), whilst in Parts II. and III. I have appended to the individual chapters and their subdivisions an account of the *special* methods suitable for the study of the subjects therein dealt with. Of course here also, in conformity with the plan of the work, those methods alone have been described which accomplish their purpose with greatest speed and certainty; and only in the case of a few investigations, of

special importance or frequency, have several methods been given together, in order to enable the student to compare them one with another as regards their results.

Since, as already mentioned, I have included etiology in the scope of the present work, it is surely unnecessary to assign any special reasons for describing amongst the methods of investigation those for the examination of bacteria and other micro-organisms, even though it was of course necessary to extend the description so as to include processes of cultivation and experiment on animals in addition to the microscopic methods. Lastly, I have also considered it advisable to have particular regard to the diagnostic value of the methods given, not only for pathological but for clinical purposes.

As a concise description of the pathological histology of the Ear was also desirable for the sake of completeness, this task was undertaken, at my request, by Dr. B. Gomperz, Emeritus-Assistant of Otology in Vienna, who has kept strictly to the plan of the work in carrying it out.

The figures in the text are for the most part wood-cuts, and were almost without exception drawn from original preparations by Mr. W. Schwarz, Candidate of Medicine, who has rendered them with great accuracy. The xylographic establishment of V. Eder in Vienna, where the blocks were engraved, has also made every effort to satisfy my requirements, which were no light ones. A smaller proportion of the illustrations were produced by the zincograph process in the establishment of Angerer & Göschl at Vienna. They are not of course equal in excellence to the wood-cuts. For Figs. 2, 3, and 4 in Plate I. I am indebted to the particular kindness of Dr. A. Klein, who has endeavoured, with success, to represent accurately the shades of staining in the elements of the blood. The photographic multiplication of the micro-photographs in Plates II.-VIII. was carried out at the artistic and photographic establishment of J. Löwy in Vienna.

THE AUTHOR.

VIENNA, *February* 1892.

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PART I.

GENERAL METHODS OF INVESTIGATION.

INTRODUCTION.

The science of Pathological Histology at the present day is not alone concerned with investigation of the minute structure of the tissues, but it has also in many instances to decide particularly as to the presence or absence of bacteria or other micro-organisms in them and their juices, as well as to determine the nature of such micro-organisms should they occur. As, however, widely different species of research are required for these two purposes, the methods of investigation employed in Pathological Histology are naturally divided into **Histological** and **Bacteriological**.

EXPLANATION OF PLATE I.

FIG. 1. *a*, *Hæmatoidin crystals*, partly rhom dal, partly needle-shaped. *b*, Two *corpuscle-holding cells*, one of which shows a flattened nucleus pressed against the cell-wall. *c*, Cell filled with larger and smaller granules of golden-yellow pigment. The preparations were made from a hæmorrhagic focus of tolerably old standing in the brain. × 545.

FIG. 2. *Plasmodium malariæ*. Cover-glass preparations from the blood of a patient suffering from intermittent fever. Stained with methyl blue and eosin. × 925. *a*, Young plasmodium devoid of pigment, shortly after its invasion of a red corpuscle. *b* and *c*, Pigment-bearing plasmodia in the interior of red corpuscles. *d* (partly after Celli and Guarneri), Typical form of segmentation of a plasmodium (daisy-head figure). The hæmoglobin of the red corpuscle is still retained as a feebly stained border. *e*, Atypical form of a commencing segmentation ; and *f* (after Celli and Guarneri), Atypical form of a completed segmentation in which the individual elements are already separating from one another. All from *a* to *f* belong to the form of *Plasmodium malariæ* described as *Hæmamœba ; g*, *Laverania ; h* (after Celli and Guarneri), *Polymitus*.[1]

FIG. 3. *Myelogenic Leucæmia*. Cover-glass preparation of the blood. × 925. Stained with Ehrlich's mixture of orange, acid fuchsin, and methyl green. *a*, Myelocytes. *b*, Lymphocytes. *c*, Polynuclear leucocytes. *d*, Eosinophil cells. *e*, Broken-down eosinophil cell. *f*, Normal red corpuscle. *g*, Poikilocytes. *h*, Microcytes (small red corpuscles). *i*, Macrocytes (large red corpuscles). *k*, Nucleated red corpuscle of normal size (normoblast). *l*, Nucleated red corpuscle of abnormal size (gigantoblast).

FIG. 4. *Lymphatic Leucæmia*. Cover-glass preparation of the blood. × 925. Stained with Ehrlich's mixture of orange, acid fuchsin, and methyl green, in which, however, the acid fuchsin was somewhat in excess, so that the red corpuscles have taken more the colour of the fuchsin than of the orange. *a*, Lymphocytes without visible protoplasm. *b*, Lymphocytes with a narrow rim of protoplasm. *c*, Red corpuscles.

[1] The *Polymitus* in Fig. 2 is represented in colours merely for the sake of uniformity ; in reality this form can only be seen in fresh *unstained* preparations of blood.

EXPLANATION OF PLATE I.

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CHAPTER I.

HISTOLOGICAL METHODS OF INVESTIGATION.

1. The Examination of Fluids.—A medium-sized drop of the fluid to be examined should be placed on a slide by means of a loop of platinum wire or a glass rod. If the fluid is very poor in solid elements, the detection of the latter is facilitated by laying a hair or fine thread in the drop; if, on the other hand, it is very rich in solids, it must be diluted by the addition of an indifferent liquid. A 0·5 to 0·7 per cent. solution of common salt is most frequently used for the latter purpose, but this cannot be kept long in stock, as it readily becomes mouldy. Distilled or tap water may, however, also be used, if not dealing with structures which are very easily damaged.

When the examination is more protracted it is necessary, in order to prevent the object from drying up, from time to time to place at the margin of the cover-glass a drop of the fluid used for diluting, or to smear its edges with vaseline, melted paraffin or wax, glycerin, or the like; or, best of all, to carry out the examination in the *hanging drop* (p. 25). If it is desired to stain any cells which may be present in the fluid, a drop of *picro-carmine*, *alum*, *cochineal*, or of aqueous solutions of the *anilin dyes* (p. 26), can be placed at the margin of the cover-glass, whilst a piece of blotting-paper should be torn off and applied to the opposite margin, so as to increase the speed with which the staining fluid flows in. The superfluous stain can afterwards be removed by irrigation with water or a $\frac{1}{2}$ per cent. solution of acetic acid; and if it is wished to render such a preparation permanent, a 50 per cent. aqueous solution of potassium acetate, or glycerin, may then be similarly applied, and the preparation finally cemented (p. 22). For the mode of applying reagents, see p. 7.

Fluids are also in many cases examined in the dried condition, in what are called *cover-glass preparations* (p. 26).

2. The Examination of Fresh Tissues.—Tissues can be examined either in the *fresh state*, or after preliminary *fixation and hardening*. The former of these methods must not be neglected; indeed, it is absolutely indispensable for the study of certain changes. The procedure consists in scraping the juice from the cut surface of the fresh preparation, or cutting out a very minute particle with a pair of scissors curved on the flat and then tearing it up as finely as possible by means of preparation needles (sewing needles firmly fixed by a clamp in wooden handles) in a drop of an indifferent fluid; or, lastly, by endeavouring to make thin sections, which may be done with a razor or double knife, or, which is far preferable, by means of the freezing microtome (p. 15).

Preparations made in this way are either simply examined in salt solution, or may be treated with stains and reagents, and, if desirable, preserved, in a manner analogous to preparations of fluids. They can also be kept in salt solution for a short period by depositing the slides in a moist chamber, such as is used for culture plates (Fig. 7).

The needling of fresh tissue can be very much facilitated by previous immersion in rather small pieces in *macerating fluids*, for which purpose the following may be used:—*Müller's fluid* (p. 8), or 0·01 to 0·05 per cent. solutions of *chromic acid* (especially for portions of the brain and spinal cord, which are left several days in the fluid); 0·1 per cent. *osmic acid* (particularly for tissue containing fat and for nerves—action twelve to twenty-four hours); 20 per cent. solution of *nitric acid* (isolates smooth muscle fibres in a few days); concentrated *hydrochloric acid* (for the canaliculi of glands—twelve to twenty-four hours' action); *baryta water* and *lime water* (for nerves, muscles, and connective tissue, which remain six hours in the former, several days in the latter); 33 per cent. solution of *caustic potash or soda* (for smooth and striated muscle, the cementing substance of which dissolves even within an hour); and, lastly, 33 per cent. *alcohol* prepared by mixing one volume of 90 per cent. alcohol with two of water (for epithelial structures, which are immersed for one to two days, the fluid being frequently shaken).

Macerated and needled preparations can be examined either in a drop of the macerating fluid itself—which is, indeed, unavoidable when using the 33 per cent. solution of caustic potash or soda—or else in salt solution or water, the latter being indicated after maceration in strong acids. For tearing up objects macerated in osmic acid glass needles must be used, which may easily be obtained by drawing out a glass rod in a gas-flame.

In preparing various objects for microscopic examination, it is advantageous to employ black and white backgrounds for unstained

and stained preparations respectively, for which purpose glass plates painted black and white, or the like, may be used.

3. Reagents.—The ordinary mode of using reagents is either by applying them directly to the uncovered object, or by allowing them to flow in under the cover-glass from the side, a scrap of blotting-paper being laid at the opposite edge in order to secure more rapid penetration. Sections may also be placed for some time in a watch-glass containing the reagent. The following are the most useful reagents:—

(1) *Acetic acid* is usually employed only in very dilute form, as a ½ to 2 per cent. solution, for the purpose of rendering *cell nuclei* and *elastic fibres* more distinctly visible, the albuminoid substances of the body of the cell and the connective-tissue fibres being caused by it to swell and thus become more transparent. *Mucin* is precipitated by acetic acid without re-dissolving in excess of it.

(2) *Hydrochloric acid* is used as a decalcifying reagent in a 3 to 5 per cent. solution. It dissolves calcium carbonate with, calcium phosphate without, liberation of bubbles of gas.

(3) *Sulphuric acid* (in 25 per cent. solution) in like manner dissolves out the calcium salts, with formation of crystals of gypsum—prisms grouped in bunches. It is also used as a reagent for *amyloid substance* and *cholestearin*.

(4) *Osmic acid* in ½ to 1 per cent. solution serves as a test for the recognition of *fat* and *myelin*, which are coloured by it of a tint varying from brown to black. A similar colour is, however, assumed by the granules in the so-called *Mastzellen* and occasionally even by those in cells which have undergone parenchymatous degeneration. The acid must be kept in brown glass bottles, and the vessels and implements used in its application must be made of glass, and be free from organic impurities.

(5) *Caustic potash or soda*, in 1 to 5 per cent. solution, causes all albuminoid bodies, those in cell-nuclei included, as well as gelatinous substances, to swell up and become transparent, so that all the remaining elements come out more distinctly, and thus these reagents can be used for the recognition of *fat, lime, elastic fibres, pigment*, etc.

(6) *Iodine and potassium iodide* are used in *Lugol's solution* (iodine, 1; potassium iodide, 2; distilled water, 300) in testing for *glycogen, amyloid substance*, and *cholestearin*.

(7) *Ether* and *chloroform* for removing fat (p. 53).

4. Fixation and Hardening.—Owing to the incompleteness of the methods for examining fresh tissue, fixation and hardening of the latter must in most cases be carried out, the object being, on the one hand, to ensure the least possible amount of change in the structure

of the tissues, while, on the other, the consistence necessary for the preparation of finer sections is obtained. But since tissue can be *fixed* only while still warm, or immediately after death, it is but seldom that the process can be employed in Pathological Histology, and we must usually be content with merely *hardening* the tissues and organs. For this purpose alcohol and Müller's fluid are most frequently used, and in these also the specimens should be deposited as soon as possible after death or removal from the living organism. In general, pieces are to be chosen which are not more than one or two cubic centimeters in size, or at least pieces into which several deep cuts have been made; and they must, moreover, be placed in wide vessels with a large quantity of fluid, in such a manner that they may lie side by side and not one over the other. The fluid must also be changed repeatedly, *i.e.*, as often as it becomes turbid.

Hardening in Alcohol.—For this purpose absolute, or at least 96 per cent., alcohol is used, in which the specimens should be laid upon a pad of blotting-paper or cotton wool, not directly upon the bottom of the vessel. Hardening in alcohol has the advantage of attaining its object rapidly (even in a few days if the fluid is repeatedly changed); but, on the other hand, it causes great shrinking, especially in specimens which are rich in water, and also dissolves the fat.

Hardening in Müller's Fluid.—This fluid consists of potassium bichromate, 2 parts; sodium sulphate, 1 part; and distilled water, 100 parts; a scrap of camphor or naphthalin being added to prevent the formation of moulds. Müller's solution certainly hardens much more slowly than alcohol, but with less damage to the specimen, and as the red corpuscles and the fat are also retained, *it is in the majority of cases preferable to alcohol*, with the exception of those in which lime salts are to be preserved in the tissues, as these salts would dissolve in the fluid; while for hardening the brain and spinal cord it is used almost exclusively. If the fluid is kept at a temperature of from 30° to 40° C. the result will be more rapidly attained. When hardening is complete, the specimens having been washed in running water so long as the latter shows any colour, are afterwards kept (if it is not a point of importance to retain the fat) in 96 per cent. alcohol, which can be changed once or oftener if necessary. If they have not been thoroughly washed out, precipitates subsequently form in the alcohol, but this may be prevented by keeping in the dark.

In certain cases the *boiling method* can also be used for hardening, namely, when it is intended to preserve albuminous fluids in the tissues, as in pulmonary œdema, nephritis, cysts, and the like. Cubes about 1 c.cm. in size are immersed in boiling water for some seconds

to a few minutes, after which hardening is completed in alcohol or Müller's fluid.

5. Decalcification.—This process must be carried out when dealing with tissues from which, in consequence of their calcareous constituents, no fine sections can be prepared; and the more slowly it proceeds, that is to say, the less concentrated the acids used, the better is the result.

For very small pieces, or when there is but little calcareous matter present, the mere keeping in Müller's fluid may suffice; otherwise the pieces, which should not be too large, are laid—always, however, after previous hardening in alcohol or Müller's fluid—in a solution of hydrochloric or nitric acid of not more than 3 per cent. strength, or, in order to avoid swelling of the interstitial substance, in *Ebner's fluid*, which consists of nitric acid, 5 parts; alcohol, 1000 parts; distilled water, 200; and common salt, 5. The decalcifying fluid given by Gradenigo may also be recommended; it consists of nitric acid, 70 parts; common salt, 15; and distilled water, 2000.

The decalcifying fluid must be frequently changed, and the specimens when decalcified be subjected to a very prolonged washing in running water, that is, until the acid is completely removed; and finally, they must be hardened once more in alcohol.

When it is desired to decalcify very rapidly, phloroglucin may be combined with nitric acid in the following manner:—A gramme of phloroglucin is dissolved in 10 grammes of pure non-fuming nitric acid by slow and *cautious* warming over a flame, and the solution is then diluted before it becomes cool with 50 c.cm. of distilled water. In this fluid the hardened (or fixed) preparations, after having been first carefully washed in water, are deposited until decalcification is complete, which results in as short a time as a half to one hour with the smaller specimens, in several hours with the larger. They are then washed in running water for at least twenty-four hours, and hardening is completed in the ordinary manner.

6. Methods of Injection.—*Artificial injection* of the blood-vessels and lymphatics is but seldom required in Pathological Histology, for the reason that it is the *natural* contents of the vessels which are of paramount interest, and these are retained, so far as the blood-vessels are concerned, when the specimens are examined while fresh in salt solution, and when Müller's fluid is used for hardening.

The masses used for artificial injection may be blue or red, liquid while cold, or requiring to be melted by heat. They may also be purchased of good quality.[1] The actual injection, which should be carried out under a pressure not too high and as constant as possible,

[1] Of Dr. G. Grübler, 12 Bayer'sche Strasse, Leipzig.

may be effected by means of an ordinary syringe or of Hering's apparatus, or, when water is laid on, with an arrangement which can be constructed out of two wash-bottles in the following way:—The two flasks are closed in an air-tight manner with india-rubber corks, each perforated twice and fitted with two glass tubes, one of which is shorter than the other and ends just below the cork, whilst the second and longer extends to the bottom of the flask. Flask A is filled with the injecting-fluid, and the long glass tube is connected with the injection cannula by an india-rubber pipe, while the shorter tube is connected with flask B, the longer glass tube of which again communicates by another rubber pipe with the tap of the water-supply. If, now, water is allowed to flow into flask B the air therein is compressed, and in this way pressure is exerted on the injecting-fluid in flask A. If no supply-pipe is available, water or mercury may be allowed to flow into flask B from a third flask placed at a suitable height.

Before commencing the injection, the cannula tied into the vessel (in the case of organs which have been cut open an elastic catheter may be introduced into the vessel instead of the cannula) is filled with the injecting mass, and is then brought into connection with the injecting apparatus or syringe, avoiding the entrance of air-bubbles; indeed, when the latter instrument is employed a guard apparatus should be arranged between the nozzle of the syringe and the cannula, to ensure that no air-bubbles gain admission in detaching and reconnecting the syringe. The veins should be left open at first, in order that the blood may be able to flow out through them, but they are ligatured before injection is completed. If during the process the injecting mass flows from wounded vessels, the latter must be closed by clip-forceps or other clamping arrangement. In working with a mass which has to be liquefied by heat, it, as well as the organ to be injected, must be placed in water at from 40° to 50° C. When the process is complete the injected organ is immersed in cold water and then in alcohol, but if cold masses are used, directly in alcohol, in which, after some hours, it is cut in pieces.

Lymphatic vessels can also be injected by means of the *puncture method*, that is, by thrusting a fine cannula, resembling the needle of a hypodermic syringe, obliquely into the tissue or through the wall of a vessel into the surrounding structures, and injecting slowly.

7. Methods of Embedding.—In section-cutting, if the sections need not be particularly delicate, and it is wished to arrive rapidly at the results, the preparations may be wedged into a piece of well-hardened amyloid liver; but otherwise they are embedded in celloidin or photoxylin, or in paraffin.

(*a*) *Embedding in Celloidin or Photoxylin.*—The specimens, which should not be more than 1 c.cm. in size, having been dehydrated in absolute (or 96 per cent.) alcohol, are immersed first in a mixture of equal parts of ether and absolute alcohol, next in a thin and then in a thick solution (the latter about the consistence of thick syrup) of finely-cut celloidin in the ether and alcohol mixture just mentioned. In these solutions, which must be kept in well-closed vessels, the specimens remain for a length of time which varies, according to their size and other characteristics, from hours to days and even weeks—*i.e.*, until complete saturation has been attained. They are then attached to blocks of cork or wood, the surface of which must previously be coated with a thin layer of dried celloidin, and they may then be further covered with thick celloidin solution; or, what is often more advantageous, a piece of stiff paper, which must be somewhat higher than the object, is fastened with needles round the edge of the block of cork or wood, and the space between specimen and paper ring is then filled with celloidin solution. When the latter has dried somewhat in the air—in many cases it is better to allow the drying to take place under a bell-glass, as slowly as possible, during from one to three days—the specimen is lastly immersed in 50 to 80 per cent. alcohol, by weighting the wooden block with pieces of lead, etc., and left until it attains the consistence requisite for cutting.

In making sections the block of celloidin is cut to a cube, and the object is freed from the medium covering it, leaving a layer only one or two millimeters thick; the knife is moistened with 50 to 80 per cent. alcohol, which also serves for the reception of the sections. For dehydrating, 96 per cent. alcohol or absolute alcohol (the latter only for a few seconds) is employed, and for clearing (p. 21) not oil of cloves, but oil of bergamot, origanum, or cedar, or xylol, in which, however, the sections must not lie too long, as otherwise they shrivel, this being especially the case with xylol.

Should it be wished to free the sections from celloidin, this is done by immersing them for ten or fifteen minutes in the mixture of ether and alcohol mentioned above, but they should be kept in absolute alcohol for about five minutes before and after this immersion.

Embedding in *photoxylin* is carried out in a similar manner to that in celloidin. The former is more transparent but not so hard.

(*b*) *Embedding in Paraffin.*—In this process we may content ourselves with merely enveloping the object in paraffin, or else it may be completely saturated.

In the former case paraffin is melted over a flame in a vessel of moderate depth, and as soon as it begins to solidify one or more well surface-

dried specimens are pushed into it, any air bubbles which may form being removed. Before the paraffin becomes quite hard the embedded objects, together with the mantle of paraffin covering them, are cut out in the form of prismatic blocks, which are next placed for a short time in alcohol and then cut into sections, being kept wet with alcohol during the process. This method has the advantage of speed, but it is merely a somewhat superior substitute for clamping in amyloid liver.

For the second mode of paraffin embedding, *i.e.*, saturation with paraffin, a special kind, or a mixture, is used which melts at about 51° or 52° C. A harder paraffin should be used for small objects and during the heat of summer; a softer for larger objects and a winter temperature. A mixture of 30 grm. of a paraffin which melts at 45° C. with 25 grm. of one melting at 50° C. is commonly sufficient for a room temperature of 20° C. After dehydration in absolute alcohol, the specimen is first placed in a solvent for paraffin, *i.e.*, chloroform, xylol, or anilin oil,[1] and left there for twelve to twenty-four hours, or until it sinks, when it is transferred to a concentrated solution of paraffin in chloroform (5 grm. paraffin in 25 c.cm. chloroform), xylol, or anilin oil, as the case may be, for two to eight hours or until it sinks, and lastly to melted paraffin in a thermostat[2] set at 51° or 52° C., where it is left in a suitable vessel for from half-an-hour to twenty-four hours, according to its size. The object having been placed in proper position, the paraffin must then be made to solidify *rapidly* by plunging the vessel into cold water.

The specimen embedded in paraffin is next pressed, the paraffin being warmed, upon a block of wood the surface of which has been previously covered with a layer of the same substance. The mass of paraffin is then further trimmed so as to form a rectangular prism, the object only remaining covered by a layer of about 1 mm. thickness.

With regard to the preparation of sections with the microtome (p. 14), in the case of larger specimens the cutting is done slowly, and with the knife fixed obliquely, but with the knife set at right angles and rapidly drawn when the objects are smaller, and in order to obtain ribbon sections—in either case without wetting. The longer sides of the paraffin block must stand parallel with the edge of the knife. Should the sections roll up they are spread out by means of a special section-spreader, or with a soft hair pencil. They are next placed in xylol for the purpose of dissolving the

[1] When anilin oil is used, 96 per cent. alcohol suffices for the preliminary dehydration. If chloroform is employed, the specimen can be transferred from alcohol first to a mixture of equal parts alcohol and chloroform, and thence to pure chloroform.

[2] The thermostats employed in Bacteriology can be used for this purpose.

paraffin, then for five to ten minutes in chloroform, and from that, in case the pieces have already been previously stained *en masse*—though this is but seldom possible in Pathological Histology—are transferred to absolute (or 96 per cent.) alcohol, ethereal oil, and balsam (pp. 21-22); otherwise, however, they are removed from the chloroform into 80 per cent. alcohol, then into water, and finally into aqueous staining solutions.

When the sections are very fragile, or would fall to pieces on dissolving out the paraffin, they (and especially ribbon sections) must, before undergoing further treatment, be fixed upon well-cleaned microscopic slides,[1] either by smearing the latter with a thin layer of a medium consisting of 1 vol. collodion and 2 vols. oil of cloves, and laying and arranging the sections upon this, after which the slides are further placed for ten to thirty minutes in a thermostat at 52° C.; or more simply, by spreading out the sections upon the slide in alcohol, pressing them with Swedish filter paper several times folded, and then transferring the slides for several hours to a thermostat at 35° C. When cool, the slides are treated by the method already given for sections, in order to dissolve the paraffin, for which purpose vessels of such a shape (Fig. 1) as to admit of

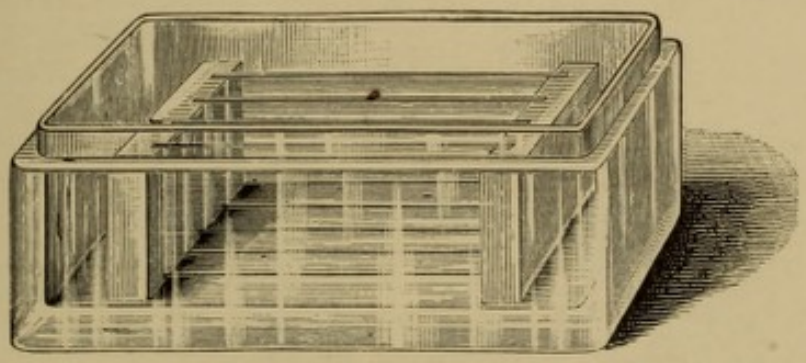

Fig. 1.—Glass Vessel with Slides.

[1] Microscopic slides are cleansed first in absolute alcohol, and then in distilled water; or with still greater certainty by depositing them in concentrated nitric acid, which is then washed away with distilled water, this being further followed by cleansing with absolute alcohol and distilled water, and finally drying with a clean cloth. A very excellent mode of cleaning and disinfecting slides which have already been in use consists in boiling them for a quarter- to half-an-hour, with repeated stirring, in a 5 to 10 per cent. solution of lysol (in which they may also be kept for a longer time), and immediately afterwards, that is, before they have begun to cool, washing them in a strong jet of water until it flows away pure, and finally wiping them in a cloth free from grease. Cover-glasses which have been used can also be cleaned in like manner, but these are first removed from the slides by warming the latter over a flame, and are then boiled separately, in order, as far as possible, to avoid breaking them.

several slides at once being arranged in them in rows may be used with advantage.

The kind of paraffin embedding just described, *i.e.*, saturation, allows of the preparation of very thin sections, and is especially suitable for obtaining *serial sections;* but it has, on the other hand, the disadvantage that, owing to the temperature required to melt the paraffin, shrinkages take place in the tissues, or during the subsequent solution of the medium small particles may drop out of sections if their elements are very loosely connected.

8. The Preparation of Sections. Microtomes.—For rough examination it may be sufficient to make sections by hand only, with a razor ground hollow on both sides or at least on the upper, a smooth cut surface being first secured, and the razor made to work more by

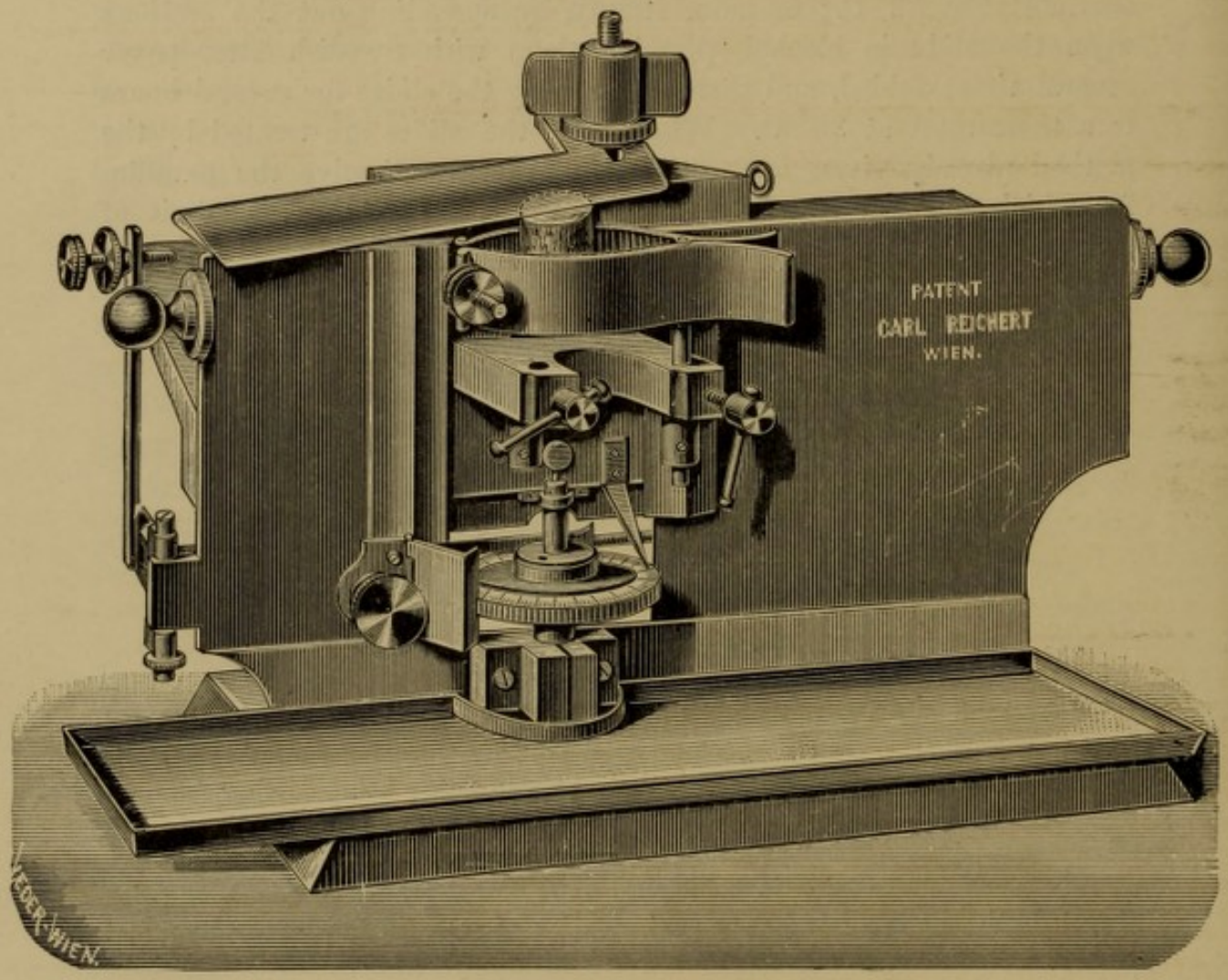

Fig. 2.—Reichert's Sliding Microtome.

drawing than by pressure. The latter must also be kept constantly moistened, in cutting fresh specimens, with a fluid consisting of 2

parts of alcohol and 1 part of glycerin diluted with water to half its strength; in cutting hardened preparations alcohol alone is used.

Nowadays, however, special *microtomes*, of which there are several types, are far more frequently used—that is, when fine and even sections are desired. Those made by Jung of Heidelberg, Reichert (Fig. 2) and Fromme of Vienna, Katsch of Munich, and Schanze of Leipzig, can be recommended: their modes of action may be seen from the catalogues of the respective makers. The objects to be cut are fixed in a suitable clamp, for which purpose preparations which are not embedded must be wedged into amyloid liver, or attached to blocks of cork or wood with glycerin jelly. This is prepared as follows:—Fine gelatin is cut up and allowed to swell for some hours in water; the water is then poured off, and the swollen gelatin boiled up with an equal volume of glycerin to which a little camphor or a trace of corrosive sublimate is added to guard against the growth of mould, filtered through linen, and then allowed to set. In use a small piece is liquefied over a flame and placed on the roughened surface of a cork or wooden block; the preparation, which must not be more than $\frac{1}{2}$ cm. in height, is pressed upon it, and the whole is deposited in strong alcohol to set.

In *cutting*, the knife of the microtome is, as a rule, fixed at the most acute possible angle with the preparation,—indeed, in such a way that the whole of the edge can act; but occasionally a different position is more advantageous. The knife, as well as the preparation, must be kept continually moistened with a hair pencil dipped in alcohol, and the sections are removed by the same means. Only preparations embedded in paraffin are best cut dry (p. 12).

To avoid tearing very large sections, particularly of the brain, it is advisable to carry out the cutting altogether under fluid, and for this purpose the instruments known as *immersion microtomes* are adapted.

Another special variety is the *freezing microtome* (Fig. 3), in which the preparation is laid on a metal plate and frozen by causing an ether spray to act on the lower surface of the latter. The method is applicable to both fresh and hardened objects; in the former, however, the freezing causes certain alterations of structure, and is therefore only to be recommended in cases where it is wished to obtain tolerably fine sections quickly.

In order that the preparations may freeze well, they must be *thoroughly* saturated with water; so that objects hardened in alcohol are to be completely freed from the latter by protracted soaking in water, say for twelve to twenty-four hours. Preparations preserved in Müller's fluid, however, may be used at once, or after lying in water for a short time.

If the red corpuscles are to be retained in *fresh* objects which it is intended to cut with the freezing microtome, the specimens are previously immersed for some hours in Müller's fluid, a proceeding which is, indeed, to be recommended in other cases also.

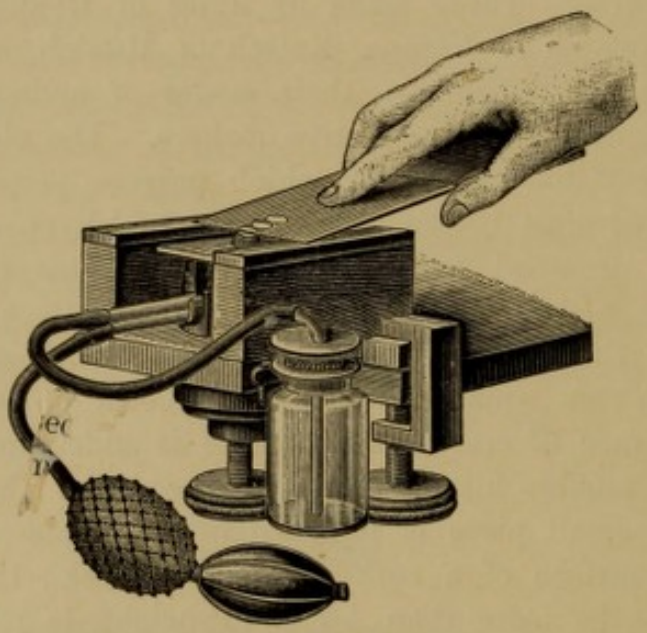

Fig. 3.—Freezing Microtome [known in this country as "Cathcart's Microtome"].

The pieces destined for freezing ought not to be more than about ½ cm. in height, and, while the ether spray is acting, are lightly pressed down upon the plate until they become frozen to it. If there is difficulty in getting this to succeed, the under surface of the preparation may be smeared with liquid glue. The piece, although completely frozen, should not be too hard. Cutting is usually done dry, and the sections transferred to salt solution, or to Müller's fluid diluted with water. The sections are either examined unstained in one of the fluids already mentioned, or are carefully transferred to alcohol (first to weaker, then to stronger), and then stained and treated like sections of hardened objects.

Lastly, preparations which have already been embedded in celloidin may also be cut with the freezing microtome, but they must previously be soaked in water for at least twelve hours.

9. Preparation of Serial Sections.—(*a*) *Of Celloidin Preparations.*—Narrow strips, about twice the width of the sections, are cut from tough paper, such as sanitary paper, and with these the sections are removed from the knife of the microtome by bringing one of the strips, lightly strained, down upon the section as it lies floating in a moderate quantity of alcohol close to the edge of the knife, and then drawing it away to the left in the plane of the surface of the blade. In this way rows of sections are obtained upon the paper strip, in which each

section must always come to the right of the preceding one. The paper strips must, until their transference to the slides, be kept moist with alcohol by spreading them with the sections uppermost upon several layers of blotting paper lying in a flat dish and well saturated with alcohol. As soon as the cutting is finished, the strips are placed, stretched tight and with the sections downwards, upon well-cleaned slides, over which some time previously a thin layer of collodion has been poured. They are then quickly covered with a few layers of filter-paper, pressed with the latter against the slide, and lastly drawn away, when the sections remain adherent to the glass and should still be somewhat moist. The slides are now placed with the sections uppermost in a wide but low cylindrical specimen glass, upon a table-shaped plate made of sheet metal perforated like a sieve; ether is poured on the bottom of the glass, which is cl[illegible]d thus the sections are exposed for any desired length of t[illegible]e to the ether vapour. In this manner the sections become fixed to the slide, and may then be stained and subjected to further treatment.

(*b*) *Of Paraffin Preparations.*—If preparations of not too large dimensions are saturated with a paraffin suitable for room temperature (p. 12), and the paraffin block cut to shape so that two of its sides are parallel with the edge of the knife fixed transversely, the margins of the successive sections adhere, one below the other, when the knife is rapidly worked, and thus *ribbons* of sections are formed, which can be fixed and further treated by the methods given on page 13.

10. Treatment of Sections by Pencilling or Shaking.—This is done, for the purpose of demonstrating the stroma, either by treating the section with perpendicular dabs from a pencil of badger's hair, while it is held fast on a slide by means of a needle and covered with plenty of fluid (water or glycerin), which must be repeatedly changed; or by shaking it up vigorously with water in a test tube.

11. Staining.—The object of staining processes is to cause certain constituents of the tissue or of the cells to stand out with special distinctness; but since such processes invariably bring about alterations in the tissues, preparations should always, at least for more thorough study, be examined in the unstained condition also, which, when they are made from hardened tissues, is done in glycerin, either plain or diluted to half strength with water. In the case of unstained sections the reagents detailed on page 7 can be employed, with the exception of caustic potash and soda, which can act only on fresh tissue.

In all staining processes, the following *general rules* must be observed:—

(1) The staining solutions should be filtered before use.

(2) The sections, on removal from the alcohol in which they are

usually kept, must always be first placed in water[1] before being immersed in the stain selected, and in the latter they must lie side by side, not one over the other. When transferred from alcohol to water the sections usually spread out well.

(3) After staining, the sections must be washed in plenty of water until the latter no longer becomes coloured.

Stains may be divided into *nuclear* and *diffuse*, according as they colour only the nuclei, or the bodies of cells and other protoplasmic substances also.

A. *Nuclear Stains.*—The following can be recommended as being the most useful stains:—

1. *Alum Cochineal* (Czokor).[2]—A gramme of cochineal is well rubbed up with one of powdered alum, and then boiled for half-an-hour or so with 100 grm. of distilled water, until the liquid is evaporated to half its bulk. The mixture is filtered when cold, and protected against mould by the addition of a few drops of concentrated carbolic acid.

Sections of preparations hardened in alcohol remain only ten to twenty minutes at most in the solution, but of those which have been hardened in Müller's fluid somewhat longer, and sections of brain and spinal cord even up to twenty-four hours. Over-staining does not occur. The nuclei of lymphoid and young cells stain most intensely; those of connective-tissue and epithelial cells not so much so.

2. *Alum Carmine* (Grenacher).—A gramme of carmine is boiled for 20 minutes with 100 grm. of a 5 per cent. aqueous solution of alum, and the liquid filtered when cold. Staining and action as with No. 1.

3. *Lithium Carmine* (Orth).—$2\frac{1}{2}$ grm. carmine are dissolved in 100 grm. of a saturated aqueous solution of lithium carbonate.

Staining lasts for two to ten minutes, and is followed by decolorisation in *hydrochloric acid alcohol* (1 grm. of concentrated hydrochloric acid to 100 grm. of 70 per cent. alcohol) for half to one minute, and, lastly, by thorough washing in abundance of water, until the acid is completely removed. Rapidly stains even objects which are in general hard to colour.

4. *Ammonium Carminate* (*Ammonia Carmine*).—1 grm. of finely-powdered carmine[3] and 1 grm. of ammonia are shaken up with 50 to 100 grm. distilled water, allowed to stand uncovered for twenty-

[1] By this is always meant distilled or pure spring water.

[2] As the preparation of staining solutions is sometimes rather complicated and easily liable to fail in unpracticed hands, it is advisable for such to purchase them ready prepared. They can be procured of reliable quality of Dr. G. Grübler, 12 Bayer'sche Strasse, Leipzig.

[3] The kinds of carmine now in the market no longer, in many cases, yield very efficient staining fluids.

four hours, in order that the greater part of the ammonia may evaporate, and then filtered.

The solution stains best when so far diluted with water that a white surface is just visible through it. The sections remain in this for twelve to twenty-four hours (the undiluted solution stains in as short a time as twenty to thirty minutes), and are then, after very careful washing in water, deposited for some minutes in 1 per cent. acetic acid, and, finally, well rinsed again in water.

The solution stains the protoplasm and nuclei of almost all cells, muscular fibres, the interstitial substance of connective tissue, of osteoid tissue, and of decalcified bone, the axis-cylinders of nerves, fibrin, etc.; hence it may be included in both groups of stains, A. and B.

5. *Alum Hæmatoxylin* (Delafield).—To 400 grm. of a saturated solution of ammonia alum are to be added 4 grm. of crystallised hæmatoxylin dissolved in 25 c.cm. of alcohol; the fluid is exposed for three or four days to air and light in an open flask, is then filtered, and a further addition of 100 c.cm. of glycerin and a similar quantity of methyl alcohol is made. The fluid is now allowed to stand until it has become dark, when it is filtered and kept in well-stoppered bottles. It should not be used for two months.

In staining, the solution should be diluted with an equal volume of water, and the sections left in it for one to three minutes,[1] and then rinsed in plenty of water, in which they should afterwards bo allowed to lie as long as possible (up to twenty-four hours). A still better method is to dilute the solution with water to a pale violet colour and leave the sections in it for one or two days. In case of over-staining, the sections can be brought for from one to several hours into a 1 per cent. solution of alum, or for some minutes into hydrochloric acid alcohol (p. 18), after which they are very thoroughly washed. Stains the nuclei of all cells and the ground substance of hyaline cartilage.

6. *Acid Hæmatoxylin* (Ehrlich).—10 grm. hæmatoxylin are dissolved in 100 grm. absolute alcohol, and to this are added 100 grm. saturated solution of alum in distilled water, the same quantity of glycerin, and 10 grm. glacial acetic acid. This mixture also must stand for a considerable time (two or three weeks) in the light, until it assumes an intense red colour. It is then filtered and kept well stoppered. It is used like No. 5.

7. The *basic anilin colours, methyl blue, fuchsin, gentian violet,* and *Bismarck brown,* may also be used in aqueous solution (p. 26)

[1] Preparations hardened in alcohol stain quicker than those which have been lying in Müller's fluid.

as nuclear stains. The sections are immersed in the solution for from five to ten minutes, but must then be decolorised in alcohol or ½ per cent. acetic acid until only the nuclei appear stained.

B. *Diffuse Stains.*—Of these *picric acid* and *eosin* are most frequently used, commonly in association with the nuclear dyes as what are called *contrast stains*, of which that with *carmine and picric acid*, and that with *hæmatoxylin and eosin*, are the most useful. The first-mentioned of these methods can be carried out as follows:—

1. (*a*) *Picro-carmine* (Weigert).—A gramme of carmine is mixed with 5 grm. of ammonia and 50 grm. of distilled water, and when solution is complete, 50 grm. saturated aqueous solution of picric acid are added; the fluid is allowed to stand in a wide open vessel until the ammonia has evaporated, and is then filtered.

The sections remain half an hour to an hour in the solution and are then washed in water or, still better, first for half to three-quarters of an hour in a mixture of 1 part concentrated hydrochloric acid and 100 parts glycerin, and afterwards in water. It is also advantageous to colour the acid glycerin and washing water, as well as the alcohol used for dehydrating, of a light yellow by the addition of picric acid.

The cell-nuclei are stained brownish-red; the bodies of the cells, the interstitial substance of connective tissue, the muscles, keratin, hyaline and colloid substances, and fibrin, yellow.

(*b*) *Picro-lithium-carmine* (Orth).—This is obtained by adding to lithium carmine from twice to three times its bulk of a saturated aqueous solution of picric acid.

The sections are treated as with lithium carmine or picro-carmine.

The double-staining may also be done *separately*, by first staining with any of the above-mentioned carmine solutions, washing in water, then counter-staining for some minutes in a 1 or 2 per cent. aqueous or alcoholic solution of picric acid, and finally washing in water or alcohol respectively; or by dehydrating the sections, stained in carmine in alcohol to which picric acid has been added.

2. *Double-staining with hæmatoxylin and eosin* is best done separately by transferring the sections, after the staining with hæmatoxylin and washing well in water, to a very dilute (about $\frac{1}{10}$ per cent.) aqueous or alcoholic solution of eosin, and then rinsing in water or alcohol respectively; or by using alcohol to which a little eosin has been added for dehydrating the sections stained in hæmatoxylin. *Gentian violet* may also be used instead of the latter. The double-staining can be done with a single solution by adding 0·5 per cent. of eosin to acid hæmatoxylin.

Eosin stains the same substances as picric acid, the red blood corpuscles above all, but gives them a red colour.

The modes of double-staining just described succeed best with preparations hardened in Müller's fluid.

3. In certain cases double-staining with *ammonium carminate and hæmatoxylin* also gives good results, especially for osseous tissue. The sections are first stained in hæmatoxylin, washed for a long time (twelve to twenty-four hours) in water, then left up to twelve hours in extremely dilute carmine (p. 18), and finally once more well washed.

Addendum. On Staining en masse.—This is a process but seldom used in Pathological Histology. Only small pieces are selected for the purpose, and these are most conveniently stained by placing them, after they have been hardened in alcohol, in a $\frac{1}{3}$ per cent. aqueous solution of hæmatoxylin for twelve to twenty-four hours, and after that for the same length of time in a $\frac{1}{2}$ per cent. solution of potassium chromate (p. 12). They are then dehydrated in alcohol, and finally embedded in paraffin and cut into sections.

The methods of staining suitable for *special cases* are not treated of until later, when they will be dealt with in their respective places.

12. Mounting and Preservation of Microscopic Preparations.—Sections of hardened specimens are examined and preserved in special *mounting fluids.*

For *unstained* preparations, a 50 per cent. aqueous solution of potassium acetate is used, or a mixture of water and glycerin in equal parts, glycerin jelly (see p. 15), [Farrant's solution, p. 24], or, lastly, glycerin alone; in the latter, however, the preparations often become too transparent. The sections are first of all transferred from the alcohol in which they are kept to water, where they usually spread out well, and thence to the slide by means of a needle, or if they are very delicate, or have a tendency to fold, of a section-lifter (of thin platinum by preference) along with some water, which is then carefully removed with filter-paper and replaced by a drop of one of the fluids just mentioned.

For *stained* preparations the same mountants may be used, more particularly when, for the purpose of studying certain details of structure, it is thought desirable to avoid too great transparency—in which connection it must be noted that preparations stained with hæmatoxylin or the anilin dyes (except Bismarck brown) in time decolorise in glycerin, and that osmic acid preparations turn brown—or the sections, after being *dehydrated* and *cleared*, are put up in dammar varnish or Canada balsam. In the latter case the sections are transferred by means of needles or section-lifters from the water in which they have been washed (the adherent water being carefully removed with blotting paper) for some seconds or minutes to 96 per cent., and from that to absolute, alcohol, or the former only may be used; then for the purpose of clearing, to oil of bergamot, cloves,

origanum, or cedar, or to turpentine or xylol,[1] for the same length of time; and are conveyed from the latter to the slide, upon which, after removal of the clearing agent with blotting-paper,[2] they are covered with a drop of dammar varnish or Canada balsam, and the cover-glass is applied.

In choosing the clearing agent it must be borne in mind that oil of cloves dissolves the anilin dyes and celloidin; that turpentine clears the more slowly the thinner it is; and that the sections, especially those embedded in celloidin, shrivel up readily in xylol. Moreover, in using the last-named, the sections must be *absolutely* free from water. If *thick* cedar oil be used for clearing, balsam can be dispensed with in mounting.

With regard to the latter process, gum dammar varnish renders the preparations less transparent than Canada balsam, and hence is better adapted for the recognition of details of structure; it is thinned with xylol or turpentine. Canada balsam is also diluted in the same way, or with chloroform; but in the latter case preparations stained with the anilin dyes are in danger of losing their colouring matter.

Preparations not put up in balsam may be further *cemented* to increase their permanence. This may be done *provisionally* by smearing the edges of the cover-glass with melted paraffin or wax (by means of the wick of a wax-light which has just been extinguished), but any vestiges of the mounting fluid which exude from beneath the cover-glass must previously be wiped away with care by means of a rag moistened with absolute alcohol. If it is desired to retain these preparations *permanently*, the rim of paraffin or wax should be covered with asphalt varnish or gold size, which must extend on to the cover-glass as well as the slide; or the varnish may be applied at once.

13. The Microscope.—On the use of the microscope but few remarks need be made. The rule, of course, holds good in Pathological Histology as elsewhere, that the preparations should be examined first with a low and then with a stronger power, which is greatly facilitated by the use of the so-called nose-piece or objective-changer. With low powers either the plane or the concave mirror may be employed, with higher powers only the concave; and in the former case the wider apertures of the diaphragm are to be used, in the latter the narrower.[3]

[1] If the sections, after clearing, show grey or white spots when placed upon a black surface, it is a sign that they are not properly dehydrated, and must consequently be transferred back to alcohol.

[2] For this purpose the blotting-paper, if fine and smooth enough, may be pressed directly upon the section in several layers, but not when xylol is used.

[3] The contrivance known as the "iris diaphragm" is strongly to be recommended, admitting as it does of a rapid narrowing or widening of the aperture to any desired extent.

For purely histological investigations, homogeneous immersion [oil-immersion] systems of lenses are not indispensable, although absolutely so for examining bacteriological preparations. If the latter are stained, Abbé's illuminating apparatus must also be employed, which indeed may render very good service with stained histological preparations also.[1]

The most recently introduced systems of lenses, the so-called *apochromatic objectives*, considerably surpass those hitherto employed in excellence; but they do so in price also, and can, moreover, be perfectly well dispensed with in purely histological research. It is only in bacteriological investigation, and in micro-photography, that their peculiar value comes to the front; and the same also applies to the compensation and projection eye-pieces used in connection with them.

A microscope should be obtained only from a well-known firm, such as, foremost of all, that of Zeiss in Jena, and then, in alphabetical order, those of Hartnack in Potsdam, Leitz in Wetzlar, Reichert in Vienna, and Seibert in Wetzlar. [In England the firms of R. & J. Beck and of J. Swift & Son may be mentioned as making excellent instruments. The lenses of Powell & Lealand also have an unsurpassed reputation, but their prices are extremely high.]

The following combination from Reichert's establishment can be recommended for ordinary histological investigation :—Stand No. III. (with nose-piece for two objectives), dry objectives Nos. 3 and 7*a*, and eye-pieces III. and IV., magnifying from 80 to 440 times; price, £7 11s. For bacteriological research the Abbé's apparatus and the homogeneous immersion lens 18*b* (magnifying 950 times) must further be added, which would raise the total price to £14 1s. If a larger stage[2] be wished for, which can be made to revolve, stand No. II. *b* should be chosen, and the homogeneous immersion 19*b* or 18*a* is also preferable to that before mentioned. If, further, an iris diaphragm is desired, and three dry objectives instead of two—say, Nos. 3, 6, and 8*a*, with nose-piece—and a micrometer eye-piece in addition to the other two,[3] the total price rises to £24 16s. or £26 6s. respectively.

[1] All requisite information regarding the use of immersion systems and of the illuminating apparatus will be found given in the catalogues of the different firms of opticians. Cedar oil is removed from cover-glasses with benzol or xylol, but it is not advisable to do this until the balsam used in mounting has become hard.

[2] Desirable for examining culture plates.

[3] The *approximate* value of the graduated intervals in the micrometer eye-piece can be made out from the table usually given with the microscope; the *exact* value of the intervals for the combinations of objectives and eye-pieces used could only be ascertained by means of a *stage micrometer*, the latter being used as an object.

Of Zeiss microscopes, the following combination would suffice for the same purpose :—Stand No. IV. (with nose-piece), objectives A and D, eye-pieces 3 and 4, magnifying 90-420 times; price, £12 10s. For bacteriological research, Abbé's apparatus and the homogeneous immersion $\frac{1}{12}$ (aperture, 1·20; magnification, 925) would have to be added, which raises the total price to £21 5s.

Generally speaking, microscopic examination should only be carried on by daylight. Should it be necessary, however, to resort to artificial illumination, the yellow light of the flame should be corrected by means of a disc of blue glass laid on the eye-piece or mirror, or of an engraver's globe filled with ammonio-cupric sulphate (some drops of ammonia added to a solution of copper sulphate until it acquires a fine blue colour) and placed between lamp and microscope.

[ADDITIONAL NOTE.

The Gum Freezing Method.—The difficulty of freezing pieces of tissue so that the sections shall not be spoiled by spicules of ice is very great. This may, however, be avoided by freezing in gum instead of water, and indeed for general use the latter method yields results little if at all inferior to those obtained by embedding in celloidin, whilst having the advantage of greater rapidity. When the tissue is hardened, the pieces, which should be thin, are freed from spirit by lying for twenty-four hours in water, and are then immersed in thick gum until thoroughly saturated, which requires from a few hours to some days, according to the density of the tissue, but the more protracted the soaking the better will be the results. It is then laid on the plate of the microtome, frozen, and cut into sections with a dry knife. It should not be frozen too hard, or the sections will be ridged, to obviate which syrup is sometimes added to the gum, as in the following mixture :—Syrup (28·5 grm. sugar to 30 c.cm. water), 4 parts ; mucilage (45·6 grm. gum acacia to 2400 c.cm water), 5 parts ; water, 9 parts. For delicate specimens a further addition of 1 part syrup to 2 of the mixture may be made. Fresh or imperfectly hardened tissues may also be cut by this method.

The sections are transferred to tepid water in order to free them from gum, and may then be stained, etc., as usual, or kept in dilute spirit. For mounting, any of the media mentioned on p. 21 may be used, but *Farrant's solution* is one of the best. It consists of a saturated solution of gum in equal parts glycerin and saturated arsenious acid solution. Preparations mounted in this must be subsequently cemented.

Besides the much-used Cathcart microtome figured in the text, the freezing microtomes of Williams, Rutherford, or Bevan Lewis may be used in making the sections. Freezing attachments can also be obtained for microtomes of the sliding type, such as Reichert's.]—*Tr.*

CHAPTER II.

BACTERIOLOGICAL METHODS OF INVESTIGATION.

1. Introduction.—When in the course of morbid processes we find bacteria in the tissues, the fluids of the body, or the products of disease, the question will arise whether they stand in a *causal* relation to the disease or not. Since, however, we are only justified in assuming such a relation when a specific kind of bacterium is found constantly in the disease, and when this has furthermore been successfully grown pure outside the human organism, and has caused the same affection in animals inoculated with it, bacteriological investigation consequently falls into three sections:—

1st, The recognition of the bacteria in the diseased organism by *microscopic examination;*

2nd, The artificial *cultivation* of the previously-discovered species of bacteria; and

3rd, The *transmission* of pure cultures to animals.

I. THE MICROSCOPIC EXAMINATION OF BACTERIA.

2. Examination of Fluids for Bacteria. The Hanging Drop. Cover-glass Preparations.—The microscopic examination of fluids for bacteria is done either in the *hanging drop* on hollow slides, or in stained cover-glass (*dried* or *smear*) preparations.

The method of *examination in the hanging drop* is less suitable for bacteria occurring in the fluids of the body, as in the unstained condition these would be hard to distinguish from any other very minute bodies which might also be present; hence it is commonly adopted only with bacteria grown artificially on culture media. In

FIG. 4.—HOLLOW SLIDE WITH HANGING DROP, SEEN IN SECTION.

this method of examination, vaselin is first smeared round the edge of the hollow in the slide (Fig. 4), and a drop, which should not

be too large, of the fluid to be examined (in the case of cultures of bacteria on solid media, a very small particle is mixed with a drop of distilled water for this purpose) is then deposited on a well-cleaned [1] cover-glass by means of a loop of platinum wire which has been heated white hot and allowed to cool again,[2] and finally the cover-glass is inverted and laid upon the slide so that the drop hangs over the centre of the cavity in the latter, being protected against evaporation by the rim of vaselin. Powerful dry objectives or oil-immersion systems are used in examining, with diaphragms, and occasion is taken to look also for a possible automatic motion in the bacteria, for which the marginal portions of the drop are best adapted, these being first focussed with a dry objective before they are examined with the oil-immersion lens.

In the second mode of examination (*cover-glass* or *smear* preparations), which may be used for fluids of every sort, the liquid to be examined, with or without dilution with sterilised water, is smeared over a cover-glass in a very thin layer; or, if the fluid is very viscid, it is squeezed between two cover-glasses, which are then slid apart horizontally—a proceeding, indeed, which may be adopted in other cases also, to ensure an even distribution of the fluid.

After the fluid has been dried in the air or over a flame (though at a proper distance from it), the cover-glass is drawn three times, prepared side uppermost, with moderate rapidity through a flame which causes no deposit of soot—too strong heating would impair the staining capability of the bacteria—in order to fix and render homogeneous any albuminoid bodies contained in the fluid. It is then stained.

Smear preparations can also be prepared from substances of pultaceous consistency in like manner as from fluids, by rubbing out a small quantity to a thin layer on a cover-glass with a drop of water.

3. Staining of Bacteria in Cover-glass Preparations.—For staining bacteria the *basic anilin colours* are taken advantage of, of which those most frequently used are *methyl blue, fuchsin, gentian violet* (or *crystal violet*), *Bismarck brown,* and *vesuvin.* It is advisable to have at hand saturated alcoholic solutions of the colours named, these being the only solutions which can be kept for any considerable time. They are prepared by pouring absolute or 96 per cent. alcohol over

[1] The cleaning is done either in the same manner as with slides (see p. 13, note), or by heating the cover-glasses in sulphuric acid, washing in water, and then placing in a liquid composed of equal parts alcohol and ammonia, finally wiping with a cloth free from grease.

[2] It should never be forgotten to raise to a white heat or otherwise disinfect all instruments and utensils which have come in contact with living bacteria.

such a quantity of the dye in a bottle, that after standing for several days and being repeatedly shaken, some pigment still remains undissolved on the bottom. In the case of Bismarck brown only a concentrated *aqueous* solution must be prepared.

For actual staining, however, dilute aqueous solutions alone are used as a rule, these being prepared on each occasion as wanted by dropping some of the concentrated *filtered* alcoholic solutions into a watch-glass of distilled water,[1] until the mixture just begins to turn opaque.

When it is desired to avoid over-staining in dealing with bacteria which take the dye very easily, methyl blue is used, but otherwise fuchsin or gentian violet. The latter stains the most intensely. Vesuvin is but seldom employed.

With bacteria which are very difficult to stain (especially in sections), staining solutions are employed to which substances known as *mordants* or others of similar action have been added, those most frequently so added being alkalies, anilin, or carbolic acid. The following staining compounds are the result :—

(1) *Methyl blue with caustic potash, the Alkaline Methyl Blue of Löffler.*—100 c.cm. of a 0·01 per cent. caustic potash solution (1 part potassium hydrate to 10,000 of distilled water) are added to 30 c.cm. of concentrated alcoholic solution of methyl blue.

(2) *Methyl blue with carbolic acid, Kühne's Carbolic Methyl Blue.*—10 grm. absolute alcohol are poured over 1·5 grm. methyl blue in a mortar, and rubbed up until dissolved, avoiding too strong pressure, with 100 c.cm. of a 5 per cent. aqueous solution of carbolic acid, which is added gradually.

Both the foregoing methyl blue solutions are distinguished above the following stains by their capability of being kept for an indefinite period.

(3) *Fuchsin or gentian violet with anilin, Anilin Fuchsin and Anilin Gentian Violet.*—To 5 c.cm. anilin are added 100 c.cm. distilled water, the whole is very thoroughly shaken and filtered through a moistened filter. Into the filtrate, the so-called *anilin water*, which must be a perfectly clear fluid, a quantity of concentrated alcoholic solution of fuchsin or gentian violet is dropped, each time as required, until the fluid is just beginning to become opaque. The anilin water does not keep, and consequently must be prepared freshly each time.

(4) *Fuchsin with carbolic acid, Ziehl's Carbolic Fuchsin.*—This is prepared by rubbing up 1 grm. fuchsin with 100 c.cm. of a 5 per cent. aqueous solution of carbolic acid, gradually adding 10 c.cm. of alcohol. The solution can be kept. The same result can be

[1] It need hardly be said that this water, as well as in general all fluids used in staining processes, must be free from bacteria.

obtained by adding alcoholic solution of fuchsin to 5 per cent. carbolic acid in water until saturated.

(5) The staining power possessed by Löffler's *Alkaline Anilin Fuchsin, Gentian Violet,* and *Methyl Blue,* is especially strong. They are prepared as follows:—1 c.cm. of a 1 per cent. solution of sodium hydrate is added to 100 c.cm. of saturated anilin water, and in this is dissolved with repeated agitation 4 or 5 grm. of dry fuchsin, gentian violet, or methyl blue, as the case may be. From this concentrated staining fluid, which keeps good for weeks, the required quantity is filtered off on each occasion as used. The fuchsin, gentian violet, or methyl blue may also be first dissolved in anilin water, and only each time when required for use 0·1 per cent. sodium hydrate solution added until the stain, originally clear, begins to turn opaque.

One of the above-mentioned stains having been selected, the cover-glass is allowed to float upon it (in a watch-glass or similar vessel) for not more than five minutes; or the solution is dropped upon the cover-glass held in a suitable forceps, and the glass moved to and fro for a few minutes. In the case of bacteria which are difficult to stain, the penetration of the pigment can be assisted by *slowly* warming the fluid until vapour or even a few bubbles rise. When no over-staining is suspected, the cover-glass is next rinsed in plenty of water, and is examined, when the surface is dry, in a drop of water. If, however, it is desired to preserve the preparations, the cover-glass is first of all thoroughly dried (in the air, over a flame, or between folds of blotting-paper), and is then mounted in Canada balsam diluted with xylol.

If *over-staining* has taken place, which is usually the case when employing gentian violet and staining solutions prepared with mordants, and which has a particularly prejudicial effect if other elements capable of taking stain are present in the fluid besides the bacteria, the preparation must be so far *decolorised* again that only the bacteria appear intensely coloured, all the other elements not at all or but feebly.

The following are used for *decolorising*:—Alcohol, anilin, ½ to 1 per cent. *acetic acid,* dilute *nitric, hydrochloric,* or *sulphuric acid* (about 1 part acid to 6 parts water), acid anilin colours (*tropæolin, fluorescein*), and certain salts (*potassium iodide, potassium permanganate,* and *ferric chloride*), etc. The preparations remain only a short time in the decolorising fluid (in most cases but a few seconds, especially with the mineral acids), after which they are very thoroughly washed in abundance of water, so as to remove every trace of the decolorising fluid, and are then examined.

Where decolorisation has been pushed so far that only the bacteria

remain stained—a proceeding termed *isolated staining* of bacteria—the other elements, the nuclei of cells for example, can be rendered visible by further after-staining with a contrast colour (vesuvin for blue and violet, methyl blue for red).

A method of isolated bacterial staining which is often employed is that of Gram. The cover-glasses are placed in anilin gentian violet, which is slowly warmed until single bubbles rise; then immersed for about half a minute in iodine and potassium iodide (iodine 1, potassium iodide 2, distilled water 300), and then in absolute alcohol as long as they continue to give up colour. Lastly, they can be further double- or counter-stained, using an aqueous solution of vesuvin, saffranin, or eosin. Preliminary staining in picro-carmine (see p. 33) also gives good results.

4. Staining of Spores.—As staining fluids find a difficulty in penetrating the membrane of spores, the latter must be stained in a manner analogous to that adopted with those bacteria which are hard to colour. The cover-glass preparations are placed for an hour in hot, or still better in boiling, carbolic fuchsin, the solution in the latter case being made up from time to time as it evaporates away. They are afterwards decolorised in absolute or hydrochloric acid alcohol (p. 18), or in dilute mineral acids, and counter-stained in aqueous methyl blue solution. In this process the spores remain red, while the remainder of the bacterial protoplasm takes up the blue pigment.

5. Staining of Flagella.—The following mordant is first prepared:—To 10 c.cm. of a solution of tannin (20 parts of tannin in 80 of distilled water) are added 5 c.cm. of a cold saturated solution of ferrous sulphate in water, and 1 c.cm. of aqueous or alcoholic solution of fuchsin. To this mixture are further added certain quantities, varying with the species of bacterium, of 1 per cent. sodium hydrate solution, or of sulphuric acid diluted until it will exactly neutralise an equal quantity of the latter. Thus, for the flagella of cholera bacteria ½ to 1 drop of sulphuric acid is added, and for those of typhoid bacilli, 1 c.cm. of sodium hydrate. The remainder of the process is carried out as follows:—A minute quantity of the pure culture is first suspended in a small drop of water, and from this a number of other drops on cover-glasses (perfectly clean[1] and free from grease) are inoculated, in order to secure dilution of the culture. These drops are spread out and dried in the air, and the cover-glasses are passed through the flame, using the thumb and forefinger in order to guard against heating too strongly. The mordant given above is next placed on the cover-glass in such a way that it completely covers the latter in the form of a convex drop, and it is then warmed over a flame

[1] See page 26, note.

until steam is given off, at which stage the warmed staining fluid is allowed to act for a half to one minute, being kept moving to and fro. The cover-glasses are now rinsed, first in water and then in alcohol, until they appear quite clear, and are next covered with carbolic or alkaline anilin fuchsin in the same manner as with the mordant, warmed again for a minute until steam forms, and finally washed in water. The flagella will come out most distinctly in those preparations in which the culture was most diluted.

6. Examination of Tissues for Bacteria.—Bacteria in tissues can only be recognised with certainty by staining. For this purpose either sections are made at once from the fresh tissue by means of the freezing microtome, and are placed first in a 0·75 per cent. solution of common salt, then carefully immersed in alcohol until any air bubbles that may arise have disappeared, and finally in staining solution: or the specimens are hardened first and then cut into fine sections.

Hardening is done, as a rule, in absolute or 96 per cent. alcohol, although the use of Müller's fluid followed by alcohol is not absolutely precluded. The pieces must be very small, and be introduced while as fresh as possible into the hardening fluid, in which they are laid on pads of blotting-paper or cotton wool.

For *staining* the sections, which are prepared after the methods described on pp. 10-16, either simple aqueous solutions of fuchsin or gentian violet are used, or anilin colours to which mordants have been added, as described above.

Sections are always immersed in water before being transferred to the stain used, in which they must not lie one over the other. The length of time during which the sections are to remain in the staining solution varies from a few minutes to forty-eight hours, but the process is hastened by warming the fluid to incubation temperature. As this method of treatment invariably causes over-staining of the sections, it must always be followed by a corresponding decolorisation by means of the agents detailed on pp. 28-29, in which connection it is to be noted that the decolorising fluid must afterwards be removed, by washing in water, even more carefully than with cover-glass preparations.

A section treated in this way may be examined first of all in water, in order to be able to judge of the degree of staining or decolorisation; otherwise the examination is always made after mounting in balsam. As the agents used to dehydrate the sections, viz., alcohol and anilin, have likewise a decolorising action, it is often advisable to add to them some of the pigment used and to transfer the sections first of all to this mixture, and after that for

a few seconds to the plain alcohol or anilin respectively. For clearing, it is usual not to employ oil of cloves, since it likewise dissolves anilin dyes, but *oil of bergamot*, origanum, or cedar, turpentine, or *xylol;* and for mounting, xylol Canada balsam.

(1) *Staining with Löffler's Alkaline Methyl Blue.*—The sections remain in the staining solution for some minutes, or even longer, and are then transferred for a few seconds to ½ per cent. acetic acid, plain, or else to 1 per cent. acetic acid to which watery solution of tropæolin 00 has been added until it is of a wine-yellow colour; or a mixture of 10 c.cm. distilled water, 2 drops sulphurous acid, and 1 drop 5 per cent. oxalic acid. They are next well washed in plenty of water, or first of all in water rendered feebly alkaline by the addition of a few drops of saturated aqueous solution of lithium carbonate and then in ordinary water, dehydrated in absolute alcohol, cleared, and mounted. (To prevent the alcohol from decolorising too strongly, a few drops of alkaline methyl blue solution may be added to it until it assumes a pale blue colour, and the sections, after being dehydrated in this, may be afterwards dipped for an instant into plain alcohol, from which they are transferred to oil of turpentine, then to xylol, and finally to balsam.)

All the bacteria at present known can be stained by this method. Staining with Löffler's *Alkaline Anilin Methyl Blue* is done in an analogous manner.

(2) *Staining with Kühne's Carbolic Methyl Blue.*—The sections remain in the solution from half an hour to two hours, are well rinsed in water, decolorised in acidulated water (10 drops hydrochloric acid to 500 of water) to a pale blue colour, dipped for a short time into lithium water (6 to 8 drops of a concentrated aqueous solution of lithium carbonate to 10 c.cm. water), and then immersed for some minutes in ordinary water. After they have next been washed for a very short time in absolute alcohol, they are placed for five minutes in anilin methyl blue (prepared by rubbing up as much methyl blue as will lie on the point of a knife with 10 grm. anilin oil, the mixture being poured into a bottle without filtration, and when the oil has cleared by sedimentation after a time, enough of it added to plain anilin oil to produce the desired shade of colour). They are then transferred to pure alcohol for two minutes, from that into oil of turpentine, then to two watch-glasses in succession filled with xylol, and are mounted in balsam. This method is also applicable to all bacteria.

(3) *Staining by Gram's method.*—The sections are placed for half an hour in anilin gentian violet (or crystal violet), then for two or three minutes in iodine and potassium iodide, and then in

alcohol, which is changed as often as it becomes coloured.[1] Finally they are cleared and mounted.

(4) *Weigert's modification of Gram's method.*—The sections are immersed for a few minutes to an hour in anilin gentian (or crystal) violet, washed in solution of common salt, and brought, well spread out, upon a slide. Here they are dried with blotting paper, and then decolorised, first with iodine and potassium iodide for one or two minutes, and subsequently, after drying once more, with anilin oil (or a mixture of 2 parts anilin and 1 part xylol) several times renewed. This must in turn be removed with xylol, after which follows mounting in balsam.

Gram's method and its modification by Weigert give an isolated staining of the bacteria. A number of bacteria are, however, decolorised by the process—such as, amongst the pathogenic bacteria, the gonococci, typhoid and glanders bacilli, Friedländer's pneumobacilli, the bacilli of malignant œdema, *Bacterium coli commune*, cholera bacteria, and the spirilla of relapsing fever. It may further be noted that Weigert's modification has in other respects a much more sparing action during decolorisation than Gram's method itself, and hence is in many cases preferable to the latter.

(5) *Staining with Carbolic Fuchsin, Anilin Fuchsin, or Alkaline Anilin Fuchsin.*—As this mode of staining is, as a rule, only employed for tubercle and lepra bacilli, it will not be dealt with until describing these (p. 132 *et seq.*).

It is also intended to mention which of the methods already described should be used in the case of each of the pathogenic bacteria individually. When dealing, however, with unknown bacteria, it is advisable to stain with Löffler's or Kühne's methyl blue, but in other instances also it is to be recommended in each case first of all to make a trial staining of a section, and thus to ascertain from the result the nature and duration of the staining and decolorising processes required for the other sections.

As the cells[2] and the interstitial substance of the tissues lose their

[1] In order to avoid the precipitates which often occur in Gram's method and give rise to mistakes, the sections may be immersed, as recommended by Günther, for half a minute only in alcohol after removal from the iodine and potassium iodide, then in hydrochloric acid alcohol (3 parts acid to 100 alcohol) for ten seconds, and lastly again in pure alcohol until fully decolorised.

[2] Beginners should beware of mistaking for cocci the *chromatin granules* in the nuclei of cells, which still remain stained when decolorisation has not been thorough ; the former, however, never lie in the interior of nuclei, and are usually upon the whole equal in size. The granules in the so-called *Mastzellen*, which retain the pigment under the decolorising processes, must also not be confounded

colour, either wholly or partially, when the sections are decolorised, it is frequently desirable to subject them to a special staining, particularly in those cases where information is also wished for regarding the finer changes in the tissue. This may be done either before or after the bacteria are stained: for *preliminary* staining use is made, when the bacteria are to be coloured blue or violet, of the simple carmine solutions (pp. 18-19), or of picro-carmine, and with red bacteria, of hæmatoxylin; for *after-staining*, on the other hand, vesuvin, saffranin, or eosin, is used when the bacteria are blue or violet, and methyl blue when their colour is red.

The *preliminary staining* is most frequently chosen when using Gram's method, and is best done with picro-carmine, in which the sections are immersed for twenty or thirty minutes, and then rinsed in water (or hydrochloric acid glycerin, see p. 20), after which they are subjected to Gram's process or Weigert's modification of the same.[1]

In *after-staining*, the decolorised sections, having been washed in water, are immersed for some minutes in an aqueous solution of vesuvin, saffranin (or eosin), or methyl blue, as the case may be; but they must not remain too long in the second anilin dye if it is basic, as otherwise the bacteria also would take up this colour.

For the purpose of after-staining sections treated with Kühne's methyl blue, they are transferred from xylol for five or ten minutes to saffranin oil (prepared in the same manner as the methyl blue anilin oil described on page 31), and then to turpentine, xylol, and Canada balsam.

When there exists a danger that in spite of the use of the lifter or other precautions the sections will fold or shrivel during the different manipulations, it is well to carry out the staining and subsequent operations upon the slide. This holds good especially for Weigert's modification of Gram's method, but the stain must then be left but a short time in contact with the sections. Furthermore, as preparations embedded in celloidin shrivel readily in staining with anilin gentian violet, carbolic fuchsin, and carbolic methyl blue, especially if left in the staining solution for any considerable length of time, it is advisable in such cases first to free the sections from celloidin (p. 11).

II. THE CULTIVATION OF BACTERIA.

7. Sterilisation.—The first condition requisite for the pure cultivation of a species of bacterium is that all objects coming into contact

with cocci; they may, however, be recognised by their inequality in size, and their accumulation round the very feebly stained nucleus.

[1] With Weigert's method a preliminary staining for one or two minutes with a 5 per cent. aqueous solution of saffranin is also very serviceable.

with it shall previously have been rendered entirely free from germs, that is, *sterilised*. It need hardly be said that this can only be done by such means as are capable of killing even the most resistant spores; such are heating to redness, a dry heat of at least 150° C., moving steam at 100° C., and a 0·1 per cent. aqueous solution of corrosive sublimate, the means to be chosen depending on the nature of the object.

Instruments (knives, scissors, forceps, platinum wire) are generally sterilised at a red heat. In doing this, however, it is not necessary, except in the case of platinum wire, to bring the instruments really to a red heat; it is enough to pass them several times slowly to and fro in a flame (Bunsen burner).

Other *articles of metal or glass* (syringes, glass plates, test-tubes, pipettes, and the like), after ordinary cleaning, are exposed for half an hour or an hour to a temperature of 150° to 160° C. in the *hot-air steriliser*, test-tubes being previously closed with plugs of cotton wool. The dry chamber or hot-air sterilising apparatus (Fig. 5) is a double-

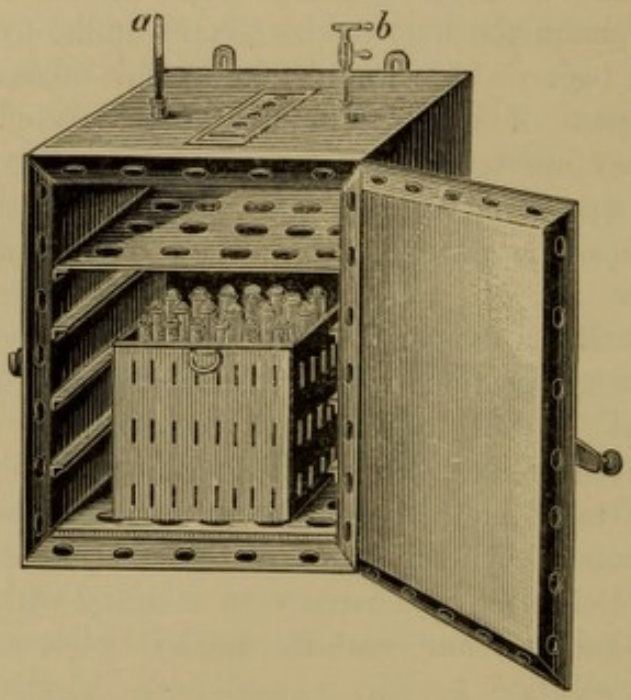

Fig. 5.—Hot-air Sterilising Apparatus. *a*, Thermometer; *b*, Thermoregulator.

walled chest of sheet-iron having a copper bottom, and furnished with a thermometer (*a*), and, in some cases, also with a thermoregulator (*b*).

Nutrient materials, except the serum of blood, are sterilised for half an hour to an hour in *Koch's steam apparatus* (Fig. 6). This consists of a cylindrical vessel of tin (*a*), with a cover which does not close air-tight (*b*), and which has an opening for a thermometer. The cylinder is divided by a grating (*c*), fixed in its lower third, into an under part which is two-thirds filled with water, and an upper part which serves

for the reception of the articles to be sterilised, and is clothed outside, as is also the cover, with felt.

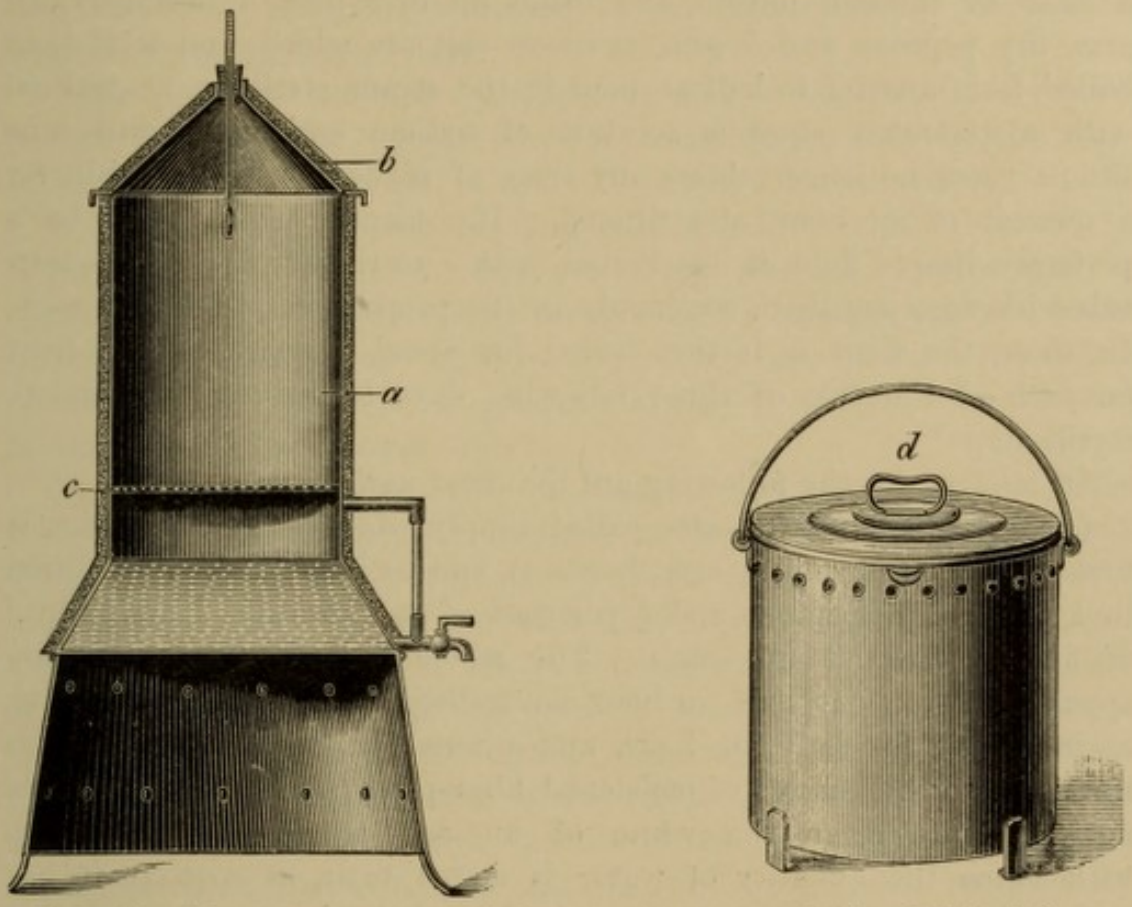

FIG. 6.—KOCH'S STEAM APPARATUS. *a*, Cylindrical vessel; *b*, Cover; *c*, Grating; *d*, Potato-holder.

The *skin*, whether of the operator's own hands, or of patients, dead bodies, or animals used for experiment, is first (or at least after shaving off the hairs) scrubbed with warm water and soap, well washed with alcohol and then with a 0·1 per cent. aqueous solution of corrosive sublimate, after which it is either dried with a clean cloth, or (when taking material for culture from that particular spot, or from internal organs) the sublimate is rinsed away with alcohol, and this with ether. In opening the bodies of animals the cutaneous disinfection, which is difficult of accomplishment, can be dispensed with by stripping off the hide.

8. Preparation of Nutrient Materials.—The nutrient substances used in the cultivation of bacteria are partly fluid and partly solid.

Of the former *meat bouillon* is that most frequently employed, and is prepared as follows:—500 grm. of meat[1] (beef, or other kinds of flesh meat), freed from fat and finely minced, are soaked for twelve

[1] Meat extract can also be used instead of meat, in the proportion of 5 grm. to a litre of water; but 30 grm. peptone must be added, and the whole very carefully sterilised.

to twenty-four hours in a litre of distilled water standing in a cool place. The fluid, called " meat infusion," having been strained through a cloth, or through muslin, and made up to a litre if necessary, 10 grm. dry peptone and 5 grm. common salt are added, and it is then boiled for a quarter to half an hour in the steam steriliser, neutralised with a saturated aqueous solution of sodium carbonate until blue litmus paper no longer shows any trace of reddening, boiled again for a quarter of an hour, and filtered. The filtrate, which must be a perfectly limpid fluid, is distributed with a sterilised pipette into test-tubes likewise sterilised, commonly in the proportion of 10 c.cm. each. In these the fluid is further boiled for about a quarter of an hour on each of the two or three following days to ensure its complete sterilisation.[1]

Of *solid media* the following are the most useful :—

(*a*) *Peptone bouillon gelatin*, called simply *gelatin*. Meat infusion is first prepared (see under *meat bouillon*), and to it is added, in addition to 1 per cent. of peptone and ½ per cent. of common salt, 10 per cent.[2] of fine gelatin cut up small. The whole is boiled in the steam apparatus for about half an hour, neutralised with sodium carbonate, again boiled for half an hour, and filtered *in the steam apparatus* through two thicknesses of moistened filter-paper. Should the filtrate not be quite clear the white of an egg previously shaken up with twice the quantity of water is added to it, as soon as it has cooled down to about 50° C., and the whole having been boiled once more for half an hour is again filtered. The filtrate is then distributed into test-tubes,[3] in the proportion of 10 c.cm. or less in each, and boiled for from fifteen to twenty-five minutes on the three following days. (Too prolonged boiling would impair the solidifying power of the gelatin.)

As gelatin softens at 25° C., for cultivation at *incubation temperature* (between 30° and 40° C.) we use—

(*b*) *Peptone bouillon agar*, spoken of simply as *agar*. To filtered meat bouillon is added 1½ to 2 per cent, of agar-agar (a vegetable gelatin obtained from sea-weed in the Indian Ocean, and appearing commercially in strips or as a powder), which is allowed to swell up in it for some hours, the mixture being then boiled for six to twelve hours in the steam apparatus, neutralised, boiled once more for an hour (with the addition of the white of an egg, if necessary),

[1] Preliminary sterilisation of the test-tubes is not, moreover, absolutely necessary, either here or in the case of the other nutrient substances.

[2] More gelatin must be added when the weather is warm.

[3] New test-tubes must previously be rinsed out with acidulated water, as owing to their alkaline reaction they render the gelatin cloudy when heated.

and filtered in the steam apparatus through a filter made of two thicknesses of moistened paper. The filtrate, after being distributed into test-tubes, is further sterilised in the steam current for half an hour on three successive days.

Agar squeezes out water in setting, and is somewhat less transparent than gelatin. Both may be made to solidify in the test-tubes in a slanting position, in order to obtain a larger surface.

If in preparing peptone bouillon gelatin a further addition of 6 to 8 per cent. of glycerin be made, a nutrient medium, *glycerin agar*, is obtained, which is particularly favourable for the growth of certain bacteria. To prevent too rapid setting of the agar medium in making plates (p. 42) 2 per cent. of gelatin and only 1 of agar may be used in its preparation (*gelatin agar*).

(*c*) *Blood serum.*—In order to obtain this, the blood, usually that of the larger animals slaughtered for food, is caught in tall cylindrical glass vessels (previously filled with corrosive sublimate solution and then rinsed out with alcohol after pouring the former away), care being taken at the same time either to cleanse the neck of the animal, or at least to prevent hairs, particles of dirt and the like from falling in, and not to catch the blood that first flows out. The blood when collected is allowed to stand undisturbed in the ice-tank for one or two days, and the serum which during this time has gathered on the surface of the clot, and which must be perfectly clear, is then distributed into test-tubes with sterilised pipettes, and subjected to the process of *discontinuous sterilisation*, that is, is warmed to 56° or 58° C. in a thermostat during four or five hours daily for a week. If all possible care has been taken to avoid contamination in obtaining the blood, sterilisation may be dispensed with altogether, and the serum at once made to coagulate at a temperature of 65° to 68° C., in a thermostat in which the test-tubes are laid in a slanting position, with a thermometer amongst them. The time which elapses before the serum is fully solidified varies with the species of animal. The fluid expressed during the process is termed *water of condensation*. Good serum has the consistency of the white of a hen's egg boiled hard, and is extremely transparent. In order to test its sterility, the tubes of serum are kept for several days at incubation temperature, and those are removed in which bacteria or moulds have developed during that time.

Instead of the serum of animals, that obtained from the blood of the human placenta, or serous fluid from the cavities of the human body, may be used.

(*d*) *Potatoes.*—Potatoes of a moist kind are chosen, freed from adherent clay by brushing with water, and left for half an hour in

0·1 per cent. corrosive sublimate solution. They are then cooked in the steam apparatus, in a special holder (Fig. 6, *d*), for about three quarters of an hour, held fast with the thumb and one or two fingers of the left hand (dipped in sublimate solution) and cut in halves with broad-bladed knives sterilised by heat, and the halves are then kept in moist chambers. The latter are prepared by covering the bottom of a glass dish with moist blotting-paper, and inverting a bell-glass over it (Fig. 7).

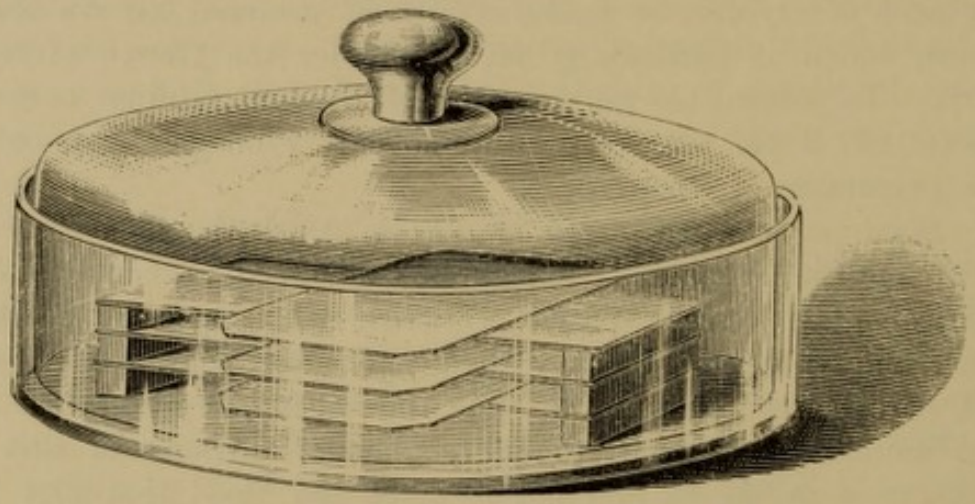

Fig. 7.—Moist Chamber, with glass benches and culture plates.

Another mode of preparing potatoes consists in peeling them while raw, and then either cutting them into round slices or splitting them obliquely into two halves. The former are placed in glass boxes of suitable size, the latter in test-tubes, and then sterilised in the steam apparatus.

Potatoes usually have a slightly acid reaction, and when it is wished for a special purpose to render them a feebly alkaline, the pieces, cut up raw, are deposited for five to ten minutes in a 5 or 10 per cent. solution of soda, after which they are sterilised as usual by steam.

(*e*) *Bread pap.*—Bread dried by a moderate heat is rubbed to a fine powder, and 20 grm. of this having been introduced into an Erlenmeyer's flask, enough water is added to convert it into a soft pap, which is sterilised for an hour in the steam apparatus on three consecutive days. On account of its slightly acid reaction, it is used almost exclusively for the cultivation of moulds.

9. Preparation of Pure Cultures.—When it is desired to obtain pure cultures from material containing bacteria, it is above all essential that the sample be taken from the organism in an *aseptic* manner, that is to say, avoiding so far as possible contamination with foreign microbes. Suppose, for example, that it

is required to cultivate the bacteria from a closed abscess in a patient; the skin must be disinfected after the method given on page 35, the abscess opened with sterilised instruments (as instruments which have been heated to redness cut badly, the scalpels must in this instance be sterilised in the steam apparatus or in boiling water), and a sample of the pus taken with a platinum loop sterilised at a red heat. If pure cultures are to be prepared from an internal organ in a dead body—the spleen, for example—the abdominal cavity should be opened with red-hot instruments as soon as possible after death, the skin having been previously disinfected. The surface of the spleen itself, where there is any possible reason to suppose that contamination with foreign bacteria has already taken place, should be disinfected in a manner analogous to the skin, or seared by means of a broad-bladed knife heated red-hot. A vertical incision is then made with another red-hot knife, and a second at right angles from this with a knife which has been heated to redness but allowed to cool, the material for the cultures being finally taken from this latter incision by means of forceps or platinum loop. A portion of the same material is now first of all examined microscopically in cover-glass preparations, in order to ascertain the form and numbers of the bacteria present, and the other portion is then always treated by Koch's *plate culture process*, since this gives relatively the best results of the methods yet devised.

This process consists in first of all liquefying the nutrient gelatin in a test-tube by heat, and transferring to it a small quantity of the substance containing bacteria, by means of a platinum wire, straight or bent into a loop, which has been heated to redness and cooled again. The substance is now mixed very intimately and evenly with the gelatin by shaking, etc., in order to separate any agglomerations of bacteria, and the edge of the test-tube having been sterilised by passing several times through the flame, and cooled again, the gelatin is poured out on sterilised glass plates, and spread out evenly thereon by means of the sterilised edge of the test-tube, in such a manner, however, that the marginal portions of the plates remain free for a breadth of about 2 cm.

In order that the gelatin may not flow off in one direction, it is merely necessary that the plate should lie perfectly horizontal, which is managed by the use of what is known as the *plate-pouring apparatus.* This (Fig. 8) consists of a wooden triangle resting on levelling-screws, and having laid upon it a larger plate of glass, which can be rendered perfectly horizontal by means of the screws controlled by a level. Upon this large plate the sterilised culture-plates (usually 12 cm. long and 6 cm. wide) are first deposited, being again covered with

a bell-glass. Furthermore, the gelatin when poured out must not be too fluid, and, lastly, its solidification can be accelerated to the greatest possible extent by filling the wooden triangle with ice or cold water.

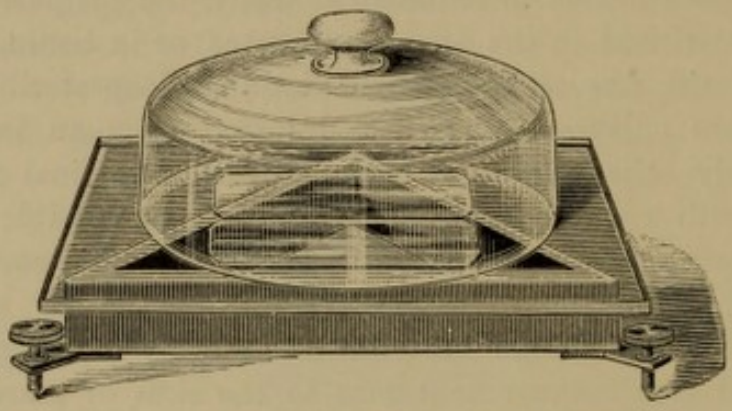

FIG. 8.—APPARATUS FOR MAKING PLATE CULTIVATIONS.

As soon as the gelatin has fully solidified, the plates are stored at room temperature, that is, about 20° C., in a moist chamber, in which indeed several can be placed one above the other upon glass benches (Fig. 7).

In pouring out the gelatin on plates the germs of bacteria contained in the former are widely separated from one another, a condition which, in consequence of being fixed by the solidifying gelatin, they also retain during their development into colonies. Consequently, after several days, as many *isolated* colonies are, as a rule, found upon the plates as there were germs originally present; and, inasmuch as each of these colonies consists of individuals of but one species, a *pure culture* of the original germ is obtained.

If there was only a *single* species of bacterium in the original material, but one kind of colony will occur on the plates; but if several, then the same number of kinds of colony will be found. To settle the question we must examine the colony which has developed, first with the naked eye, and then under the microscope, using weak objectives (those having great focal length), and powerful eye-pieces, along with a narrow aperture of the diaphragm, and noting any differences which may exist in respect of size, shape, gloss, colour, and so forth. With regard to this, however, it is to be observed that colonies occurring in the substance of the gelatin are cramped in their growth, and hence are much smaller and less characteristic, so that the superficial growths are, as a rule, the only ones to be regarded in differentiating the colonies.

Should the mode of examination just sketched not be sufficient to determine their nature, cover-glass preparations can further be made from them by rubbing the whole or portions of them on cover-glasses,

with or without water, and staining. In the case of superficial colonies, an alternative method is simply to press a cover-glass down upon them; an impression of the colonies thus remains upon the glass, which is then dried and stained (*impression preparation*).

If in this manner one or several kinds of colonies, and consequently of bacteria, have been detected, it still remains to test the behaviour of the latter in the different *nutrient substances*. For this purpose the respective colonies are focussed under a low power of the microscope, ascertained to lie completely isolated, and transferred wholly or in part, under control of the microscope, by means of a straight platinum wire or one bent to a hook, to test-tubes containing gelatin, one or more thrusts being made into the latter. The *thrust cultures* thus obtained may, in order to render their purity absolutely certain, be once more poured out on plates, when only one kind of colonies ought to develop from each individual culture.

If the thrust culture in the gelatin tube has proved to be pure, further transmissions are made from it by means of the platinum wire to other nutrient substances, in order to study its growth in them also, which is done either by making a thrust into the nutrient substance in question, or by smearing its surface. In the latter case we have *streak cultures*, but these are usually made only on obliquely solidified media and on potatoes, on the latter of which only the central parts should be smeared. During these transmissions (*inoculations*), as well as in every similar operation, the test-tubes while unplugged must be held as nearly horizontal as possible, or with the mouth completely inverted, in order to prevent the falling in of germs from the air; and, moreover, any stirring up of dust in the laboratory is to be avoided during this procedure, as well as while examining plate cultures and making inoculations from them.

Even when the smallest possible quantity of the substance containing bacteria is taken for the preparation of plate cultures, there are often so many microbes still present in the latter that their colonies would coalesce upon the plates, or at least would lie very closely packed together, and thus differentiation of, or reliable inoculation from, them would not then be possible. For this reason, the customary mode of procedure is to distribute the liquefied gelatine—usually 10 c.cm.—into four test-tubes. Into the first the substance containing bacteria is then introduced, and very thoroughly mixed with the gelatin.[1] From this three loopsful (more or less, according to circumstances) are transferred to the second test-tube and again evenly

[1] To render the separation of the bacteria as certain as possible, the substance containing them may first be well rubbed or broken up in a little sterilised water, and then a fixed quantity of this conveyed into the first test-tube.

mixed with the gelatin, then from the latter again three loopsful to the third test-tube, and finally from the third in a similar manner to the fourth; after which the contents of the test-tubes are poured out upon four plates, in the order in which they were inoculated. The first plate is commonly useless, but the second, and still more the third or fourth plates, show the colonies so far separated from one another that differentiation of them is readily feasible.

Should germs from the air fall upon the plates during the process of pouring, the colonies which develop from them can be distinguished without difficulty from the others by their small number, their superficial position, or other characteristics. They are frequently moulds.

The plate method, therefore, not only yields cultures which may be relied on as being pure, but also in most cases places us in a position to *isolate* the individual species from a mixed mass of bacteria.

In those cases in which it may be expected that the bacteria to be cultivated will grow only at incubation temperature—and this is actually very often the case with the pathogenic bacteria—agar instead of gelatin must be chosen for making plate cultures. The mode of procedure in this case is similar, except that the test-tubes containing the liquefied agar must during the whole operation be kept in a water-bath at about 40 to 43° C., the plate apparatus must be filled with water at approximately the same temperature, and the manipulation must be rapidly conducted in order that the agar may not set prematurely. After the agar poured out upon the plates has become firm, the latter are removed to bell-glasses (moist chambers), and placed along with the latter in a *thermostat*, set at a temperature of 37° C., for one or more days, that is, until the colonies are fully matured.

Such *thermostats* (Fig. 9) have double walls, best made of sheet copper, between which there is water. The temperature is kept at a constant height by means of a *thermoregulator*. When heated by gas, a gas-pressure regulator is also necessary.

Owing to the fact that agar forces out water in solidifying, not only may the colonies float off, but even a slipping away of the entire layer of agar may be caused. To avoid this as far as possible, the blotting-paper covering the bottom of the bell-glass should be but slightly moist, and over the uppermost culture-plate another empty plate should be adjusted, upon which the evaporating water can then condense. An alternative method is to use what are known as *Petri's capsules* (Fig. 10) for pouring into, instead of plates.

The colonies on agar plates are far less distinctive than those on gelatin plates, and the same is true also of test-tube cultures on agar, and of cultures in bouillon, whereas the potato cultures, again, often show exceedingly important characteristics.

As culture plates prepared by the method just described are liable to be contaminated by aërial germs during examination, modes of

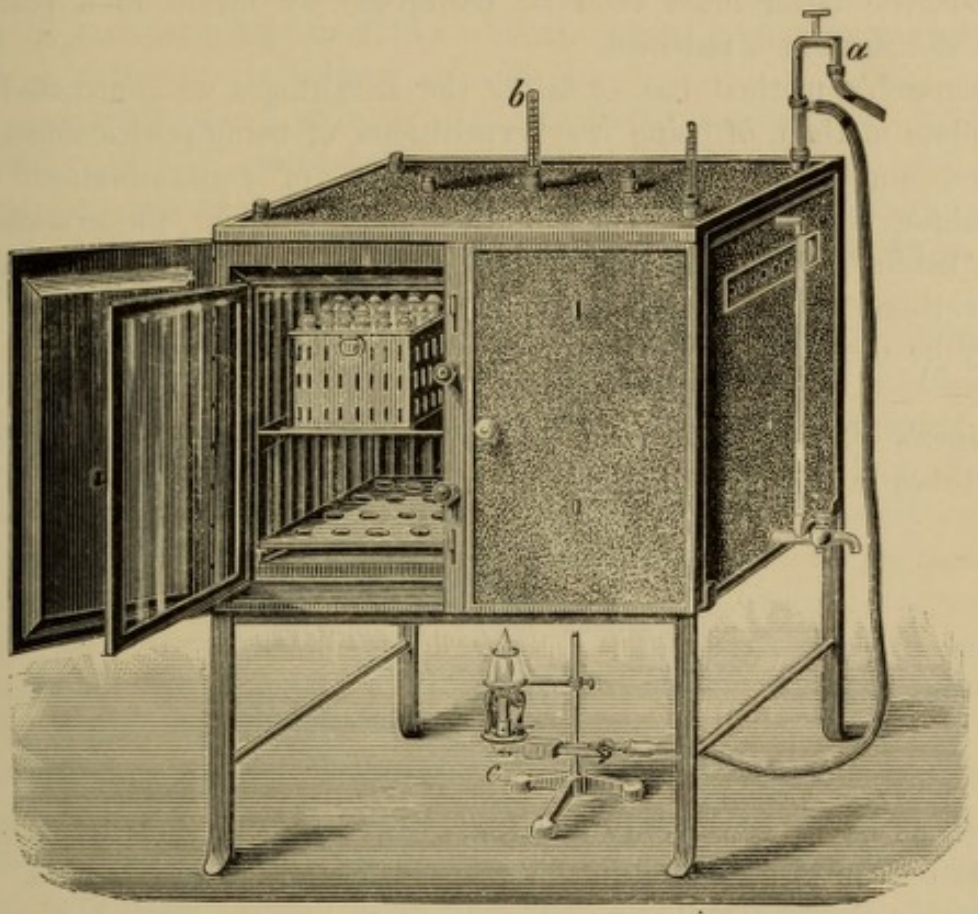

Fig. 9.—Thermostat. *a*, Thermoregulator; *b*, Thermometer; *c*, Koch's burner.

meeting this difficulty have been sought for. Such are the *roll-tube* of Esmarch, and the *culture-flask* of Lipez.

Fig. 10.—Petri's Capsule.

According to *Esmarch's method*, the liquefied gelatin is first of all inoculated in different degrees of dilution, as in the plate method. It is not, however, then poured out, but is diffused over the inner wall of the test-tubes and made to set, by continually turning—*rolling*—the tubes, which are provided with india-rubber caps, in a horizontal position in a vessel of iced water or under the stream from a tap, while the other hand steadies the tube.[1] When the latter is very wide no gelatin will penetrate into the plug in rolling, although

[1] There is also a special apparatus for "rolling" several tubes at the same time by means of a revolving mechanism.

a partial moistening of the latter would do no harm; though if the whole lower surface of the cotton wool should become coated with gelatin, the latter must then be perforated by means of a platinum wire sterilised at a red heat.

Esmarch's method has certainly the advantages, as contrasted with the plate method, of being very expeditious, of being practicable everywhere, and of freedom from any danger of contamination while examining the colonies. On the other hand, however, the examination and "fishing" out of the latter is less convenient, and when amongst them there are some which liquefy gelatin, the entire culture may easily be destroyed. Furthermore, this method cannot be used with agar.

Lipez's *culture-flasks* (Fig. 11) are filled and inoculated like the test-tubes in the plate method, and then simply placed to solidify after

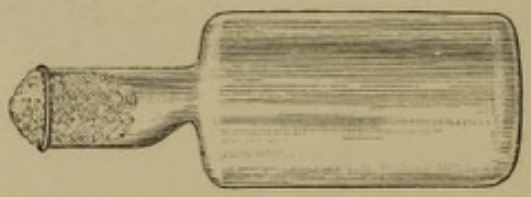

Fig. 11.—Lipez's Culture-Flask.

the germs have been evenly distributed by tilting the gelatin or agar—the latter can also be used in this case—backwards and forwards. This method is therefore still simpler and easier than the foregoing, without having the disadvantage of danger to the cultures from liquefying colonies; but all the colonies cannot be examined so thoroughly and conveniently under the microscope as is the case with the plate method.

When *anaerobic* bacteria are to be cultivated, it is advisable, in the first place, to add some reducing substance (1 or 2 per cent. of grape sugar, or 0·5 per cent. of sodium formate) to the nutrient medium. In preparing plate cultures, the film of gelatin or agar is covered before it sets with small sterilised plates of mica, the edges of which are then coated with melted paraffin; but complete exclusion of air is not attained by this means. The so-called *high-level* media in test-tubes can also be used. For this purpose well-boiled liquid gelatin or agar is filled into test-tubes to a height of 15 or 20 cm., cooled to 40° C., inoculated with the usual dilutions, and lastly made to solidify rapidly in iced water. The *obligate anaerobes* then grow in the deepest layers of the medium, the strict aerobes in the uppermost layers, and all other bacteria develop with a more even distribution. In order, however, to obtain samples from individual colonies, the test-tubes must as a rule be broken.

The other methods commonly employed consist in withdrawal of

oxygen or air, or in replacement of them with hydrogen, and hence require somewhat more complicated apparatus.

For *thrust cultures* of anaerobes the above-mentioned high-level media in test-tubes are used, the colonies being pushed into them as deeply as possible with a long platinum wire.

In preparing *streak cultures* the inoculated test-tube is inverted after any water of condensation present has been poured out, and hydrogen having been passed in by means of a glass tube for some minutes, it is tightly closed from below with a rubber cork, which can be further covered with paraffin.

10. Preservation of Cultures.—Pure cultures are commonly stored in a living condition in the thrust or streak form on a solid medium in test-tubes, as the cotton-wool plugging of the latter prevents the admission of the germs of bacteria, and a solid culture medium always allows any impurities which may enter to be more readily recognised and removed than a liquid. If it is desired, however, to prevent the entrance of moulds also, since these have the power of growing through the cotton-wool plug, the surface of the latter must be singed or moistened with corrosive sublimate solution, and then covered with an india-rubber cap disinfected also in the latter.

Bacteria only retain their vitality in cultures for a certain time, so that they must be transmitted to (re-inoculated on) fresh nutrient material before this time has elapsed. Its length, however, varies greatly with the species. The following table is intended to show the period of time after which re-inoculation is advisable in the case of the bacteria pathogenic for human beings:—

Diplococcus pneumoniæ,	A few days.
Gonococcus,	do.
Streptococcus pyogenes,	Three to four weeks.
Streptococcus erysipelatis,	do.
Bacillus mallei,	do.
Bacillus pneumoniæ,	One to two months.
Bacillus diphtheriæ,	do.
Bacillus pyocyaneus,	do.
Spirillum choleræ Asiaticæ,	do.
Staphylococcus pyogenes aureus,	Several months.
Staphylococcus pyogenes albus,	do.
Micrococcus tetragenus,	do.
Bacillus anthracis,	do.
Bacillus typhi abdominalis,	do.
Bacillus Emmerich,	do.
Bacillus tuberculosis,	do.
Bacterium coli commune,	do.
Bacterium lactis aerogenes,	do.
Spirillum Finkler-Prior,	do.

Re-inoculation is carried out with the same precautions as the transmission of plate-colonies to test-tubes. If the test-tube cultures were not protected against dust by india-rubber caps it is advisable, when re-inoculating, before removing the cotton-wool plug, to burn away the projecting part of it, and to pass the edge of the test-tube through a flame. The prominent part of the plug may be rendered fire-proof by moistening it with water-glass.

If the object in view is to preserve test-tube cultures without regard to their vitality, but retaining their other special characteristics, and for a long time, the cotton-wool plug is pushed some distance into the neck of the tube, singed superficially or moistened with sublimate solution, and then covered with a sufficiently deep layer of melted paraffin.

III. THE TRANSMISSION OF PURE CULTURES TO ANIMALS.

11. The object of **experiments on animals** is, generally speaking, to find whether a species of bacterium is pathogenic for animals or not. Should it prove pathogenic it must be further made out whether its action is *infective* or merely *toxic*, and in the former case, again, whether it is capable of originating a disease the same as that in which it had been found. For the latter purpose the conditions under which *natural* infection takes place should generally be imitated as far as possible in transmission.

In order to establish *infective* action only *very small quantities* of a pure culture must be introduced, and, as a rule, cultures are used for this purpose which while well-grown are as fresh as possible, and which are derived from generations neither too early nor too late.

For testing *toxic* action on the contrary, older cultures are taken in larger quantities, or in a sterile condition, or still better after filtering; and if the toxic substance can be obtained pure from the cultures the experiments should of course be made with it.

The actual cultures may be used for transmission to animals either in the solid state or suspended in fluids, in the latter of which cases either cultures grown in bouillon are used, or cultures grown on solid media are diffused as evenly as possible in sterilised water or in a 0·5 per cent. solution of common salt.

The animals commonly used for experiment are mice, guinea-pigs, and rabbits, and less frequently pigeons, poultry, dogs, or other animals. The following are the modes of transmission most generally adopted:—

(1) *Cutaneous inoculation.*—Perfectly superficial scarifications are

made (usually on the ear) as bloodlessly as possible, as in vaccinating against smallpox, and into these the culture is rubbed.

(2) *Subcutaneous inoculation.*—An incision is made extending as deep as the subcutaneous areolar tissue (in mice above the root of the tail or on the back, in guinea-pigs and rabbits on the abdomen), a pocket is formed by undermining the skin, and into this the culture is introduced; or an injection is made directly into the subcutaneous areolar tissue by means of a small syringe, which must be so constructed as to admit of thorough sterilisation.[1]

(3) *Injection into the thoracic or abdominal cavities.*—This should as a rule only be practised with the larger animals.

(4) *Injection into the circulation,* using the exposed jugular or femoral vein, or (in rabbits) one of the larger veins of the ear.

(5) *Introduction into the anterior chamber of the eye.*—The anterior chamber is opened as in iridectomy, and solid culture material introduced with an iris-forceps. Fluids are introduced simply by injection.

(6) *Transmission by feeding.*—The culture is either mixed with the food or introduced into the stomach by means of an œsophageal tube. In order to eliminate the action of the gastric juice, either sodium carbonate is previously introduced into the stomach, or the culture is injected into the duodenum. Occasionally intestinal peristalsis must also be reduced by injection of tincture of opium.

(7) *Transmission by inhalation.*—This is done by reducing the cultures (suspended in distilled water) to spray by means of a so-called steam atomiser, hand-spray, or other suitable contrivance.

In all the modes of transmission enumerated the cultures must be introduced with the most careful avoidance of all contamination; hence the same precautionary measures are to be adopted as were used in taking from the body matter containing bacteria, for the purpose of preparing pure cultures (p. 38).

As a morbid process occurring after a transmission experiment can only be looked upon as the infective action of the species of bacterium introduced when the latter has multiplied to an extraordinary extent in the body of the animal, the final step is the further recognition of the micro-organism in corresponding numbers in the diseased organs and morbid products by means of the microscope, and by cultivation according to the methods with which the reader is already acquainted.

[1] At present the syringes of Koch and Strohschein are those most to be recommended.

PART II.

GENERAL PATHOLOGICAL HISTOLOGY.

CHAPTER I.

RETROGRADE CHANGES IN TISSUE.

1. Cloudy Swelling, Fatty Infiltration, and Fatty Degeneration.—*Cloudy swelling* (*parenchymatous or granular degeneration*) is a change often taking place in the liver, kidneys, and myocardium in morbid intoxications and infective diseases, in which the cells swell up and become cloudy owing to a deposit of small dark albuminous granules (Fig. 12, *d*). Cloudy swelling may be distinguished from fatty de-

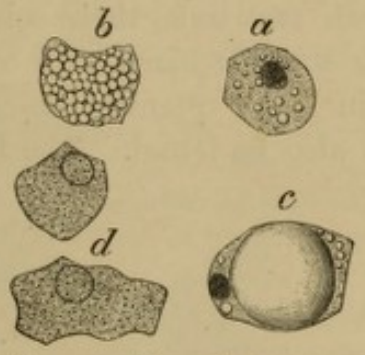

FIG. 12.—CLOUDY SWELLING, FATTY DEGENERATION, AND FATTY INFILTRATION. Fresh needled preparation, magnified 545 diams. *a* and *b*, Fatty degeneration; *a*, Liver cell with several small fat-drops of variable size; *b*, Liver cell completely filled with fat-drops, the nucleus being no longer visible (granule corpuscle); *c*, Fatty infiltration; *d*, Cloudy swelling.

generation (into which, however, it often passes) by the fact that these granules dissolve in dilute acetic acid and caustic potash, but are insoluble in ether.

Fatty infiltration is a pathological condition only when present in unusual degree, or when involving cells in which no fat is normally found. In this condition the fat appears in drops which have a tendency to run together into larger and larger globules, until finally a single large drop fills up the whole of the cell (Fig. 12, *c*), the function of which, although impaired thereby, is not abolished. Fatty infiltration affects especially the cells of connective tissue and of the liver.

In *fatty degeneration* (Fig. 12, *a* and *b*), there first appear in the

cell, near the nucleus, small shining granules with dark outlines, which usually do not coalesce into larger drops. As they increase in number the cell becomes continually larger and more rounded, until finally the nucleus disappears and a so-called *granule cell* or *granule corpuscle* is formed (*b*). In this case the fat is not introduced from without, as in fatty infiltration, but is derived from the albuminoid substances of the cell itself, and the latter may finally break down altogether into a fatty detritus.

This form of degeneration may affect any cells except the red corpuscles of the blood, and takes place either in conditions associated with local or general anæmia, or in morbid intoxications and infective diseases. It can be distinguished from fatty infiltration by the fact that in it the small droplets of fat do not usually run together into very large drops; though in fatty degeneration of the liver and kidneys drops of considerable size may occur in the epithelial cells in addition to the small ones.

Fat drops are distinguishable from other granules, such as albumin, pigment, etc., not only by their optical characters (brightness and colourlessness) but by their insolubility in acetic acid and dilute solutions of caustic potash and soda, their solubility in alcohol, ether, and chloroform, and their staining black with osmic acid.

Where fat is formed in larger quantity, so-called *margaric acid* and *cholestearin* crystals may also be found. The former (Fig. 13) appear

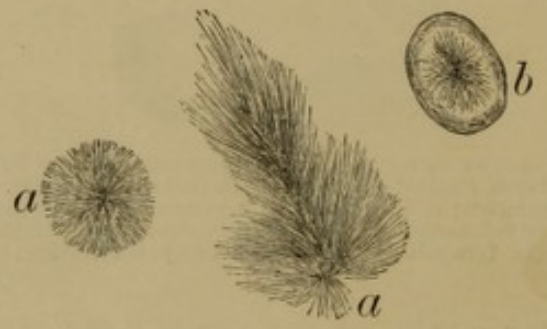

FIG. 13.—MARGARIN CRYSTALS (from Funke's Atlas). *a*, Rosettes and sheaves lying free; *b*, Crystals in the interior of a fat cell.

as exceedingly fine needles, which crystallise out in rosettes and sheaves, partly free (*a*), partly in the interior of cells (*b*); while the latter (Fig. 45, *a*) form thin rhombic tablets, the angles of which are often broken away. When cholestearin is present in considerable quantity it betrays itself even to the naked eye by its glitter.

Methods of Examination.—*Cloudy swelling* is examined in *fresh preparations* made by needling or by scraping off the juice of the parenchyma. The albuminous granules disappear from the cells on addition of 1 per cent. acetic acid.

Fresh preparations are also very well adapted for the study of *fatty degeneration* and *fatty infiltration*, the fat being recognisable in them from its optical peculiarities without reagents, or by the application of dilute acetic acid. The reactions given on page 7 may also be tried on fresh preparations.

When it is desired to use *osmic acid* the fresh preparations are macerated and torn up in the reagent (page 6), or sections cut by means of the freezing microtome, from specimens fresh or immersed for a *short time only* in Müller's fluid, are placed in ½ to 1 per cent. osmic acid, after which they must be *very thoroughly* washed in several changes of distilled water. They may also be counter-stained in carmine and mounted in glycerin (which however becomes brown at first), in potassium acetate, or even in Canada balsam after dehydration and clearing, and in accordance with the directions given below.

For *hardening*, alcohol must never be used with fatty degeneration and infiltration, but either Müller's fluid, osmic acid, or Flemming's solution (p. 69) may be employed. In the latter the specimens (very small pieces, ½ c.cm. in size at most) remain for about four days, and are then *very thoroughly* washed in running water and after-hardened in alcohol of increasing concentration, so that they can be cut with the freezing microtome or after embedding in celloidin. The sections may be mounted, uncoloured or after previous staining with saffranin (p. 69), in glycerin, potassium acetate, or Canada balsam ; but in the latter case a hard balsam requiring to be liquefied by heating over a flame must be selected, and the oil used for clearing carefully removed by pressure with blotting-paper.

Preparations hardened in Müller's fluid[1] are likewise cut with the freezing microtome, and, if they have not been left too long in the solution, may then be further treated with osmic acid.[2]

In hardening with osmic acid (½ to 1 per cent.) pieces not more than 2 or 3 mm. thick are to be immersed for a short time (a day or less) in the fluid, and then very thoroughly washed in running water, after which hardening can be completed by a still longer immersion in Müller's fluid, as the sections then admit of being more readily stained with the nuclear dyes.

If it is wished to test the *solubility of the droplets of fat* in ether and chloroform, with a view to distinguishing them from calcareous granules, the mode of procedure is to first of all dehydrate in absolute alcohol (sections for five or ten minutes, pieces of tissue for one or two days), and then to transfer for the same length of time to ether or chloroform, then back again into absolute alcohol, and finally to examine in water to which a few drops of glacial acetic acid have been added.

Tests may also be applied to *cholestearin* crystals under the microscope, though indeed these are easily recognisable at once from their characteristic shape. Thus if concentrated sulphuric acid is allowed to flow in slowly to the preparation under the cover-glass, the crystals melt from the edge inwards, and gradually change into brownish-red drops ; if, however, Lugol's solution has previously been applied, the crystals, at first brown, become bluish-red, bluish-green, and finally pure blue.

2. Mucous, Colloid, and Hyaline Degenerations.—(1) *Mucous degeneration* occurs normally in the epithelium of the mucous membranes and

[1] If the preparations are to be kept for years in Müller's fluid, it is well to dilute the latter to one half with water.

[2] It is possible to use this even with sections of preparations hardened in alcohol, provided the fat is not entirely dissolved.

mucous glands, as well as in the intervertebral cartilages, and under pathological conditions it also affects either the epithelial cells or connective tissue. In epithelial elements (whether of mucous membranes, cysts, or carcinomata) it manifests itself by the presence of transparent drops in the body of the cell (Fig. 14, *c*), or by metamorphosis of the

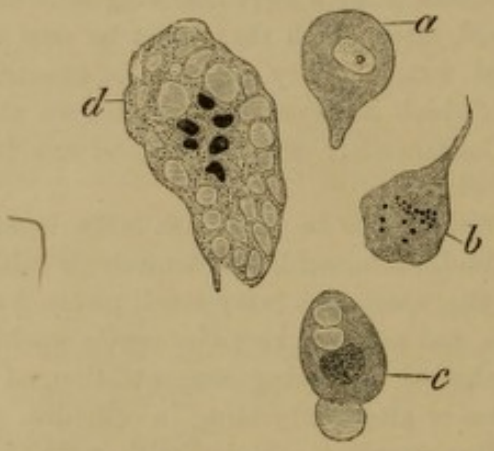

FIG. 14.—MUCOUS DEGENERATION OF THE CILIATED EPITHELIAL CELLS OF A CYSTOMA PAPILLIFERUM OF THE OVARY. × 545. *a*, *b*, *c*, Goblet cells. Torn-up preparation from the fresh tumour. In *a* the protoplasm is evenly homogeneous, in *b* there are in addition fat drops in the vicinity of the nucleus, and in *c* two smaller fat drops are seen in the cell and a larger one passing out of it. *d*, Section through the epithelium of the tumour, after hardening in Müller's fluid and alcohol. The nuclei of the epithelium can be seen in the centre, the parts which have undergone mucous degeneration at the periphery.

latter into a mass of glass-like clearness, dotted with a scanty number of granules (Fig. 14, *a* and *b*). The cells of cylinder epithelium may take the form of goblet-cells in this process (Fig. 14, *a* and *b*).

In the connective tissues (connective tissue proper, cartilage, adipose tissue, bone-marrow, and sarcomatous tissue) the interstitial substance becomes homogeneous and structureless owing to deposit of mucin. The cells themselves may either remain unaffected or may degenerate.

Mucin swells up greatly in water; in acetic acid it coagulates, without dissolving in excess of acid. When present in more considerable quantity, a white clouding becomes visible, even to the naked eye, on addition of acetic acid, whilst under the microscope the coagulated mucin appears in the form of dotted stripes. It is also precipitated by alcohol.

Colloid and *hyaline* degenerations are much less distinctly defined than the other forms of retrograde change, and are not even sharply differentiated from one another.

(2) *Colloid degeneration*, which is normally present in the thyroid gland in elderly people, takes place only in the interior of cells, by the formation of transparent homogeneous drops which either speedily make their way out, or enlarge more and more within the cell until at last scarcely anything of the latter is left. The drops of colloid

substance which become free run together to form homogeneous masses of considerable size (Fig. 112, *a* and *b*).

The colloid substance is distinguished from mucin by the fact that no precipitation, but merely swelling, is caused by acetic acid and alcohol. In addition to the thyroid gland, it occurs also in the pituitary body, in the urinary tubules of diseased kidneys, and in the prostates of old people.

(3) The limits of *Hyaline degeneration* are variously defined. Some make them very wide, including colloid degeneration and certain final products of coagulation necrosis also under this head. According to them, the hyaline material is distinguished by the facts that it does not alter under the action of sulphuric or acetic acids, and is stained an intense red by eosin and acid fuchsin, and yellow by iodine. Others understand under this name a retrograde change in connective tissue which perhaps approximates closely to amyloid degeneration, but does not give the amyloid reaction (Fig. 112, *d*).

It occurs with especial frequency in small blood-vessels, the loops of the renal glomeruli for example, and in later life in other vessels also, as well as the valves of the heart. The connective tissue, or the wall of the vessel as the case may be, becomes perfectly homogeneous and swells up, for the most part irregularly, so that the lumen of the vessel becomes gradually narrowed and finally altogether obliterated. During this process the cells perish.

It can also be observed in the blood-vessels of sarcomata (Fig. 38); and fibrin, blood plates, and colourless blood cells may perhaps also be capable of forming the hyaline substance.

Methods.—*Mucous degeneration* is most conveniently studied in *fresh preparations*, to which the tests for mucin given above (p. 54) can also be applied. Since the mucin coagulates in alcohol, causing great shrinkage of the preparations, it is better to use only Müller's fluid for hardening, and to mount the sections in glycerin containing some water.

With the *colloid* and *hyaline* degenerations, on the other hand, hardening can be done in alcohol as well as in Müller's fluid. For colouring the former the methods of double staining are to be recommended, (p. 20); for the latter eosin or acid fuchsin, but also the double stains.

3. Amyloid Degeneration and Corpora Amylacea; Glycogen Degeneration.—(1) *Amyloid degeneration* attacks by preference the blood-vessels (small arteries, transitional vessels, and capillaries) and the connective tissue system (interstitial substance, membrana propria of glands, sarcolemma), and consists in the deposition of a peculiar albuminoid material, which causes the affected parts to swell up and assume a glassy, homogeneous, and in parts lumpy appearance (Fig. 15, *c*). As a general

rule, the blood-vessels first become diseased (Fig. 146, *b*, *c* and *d*), the change beginning in the middle coat of the small arteries, the lumen of which is thereby gradually narrowed, and finally obliterated. From

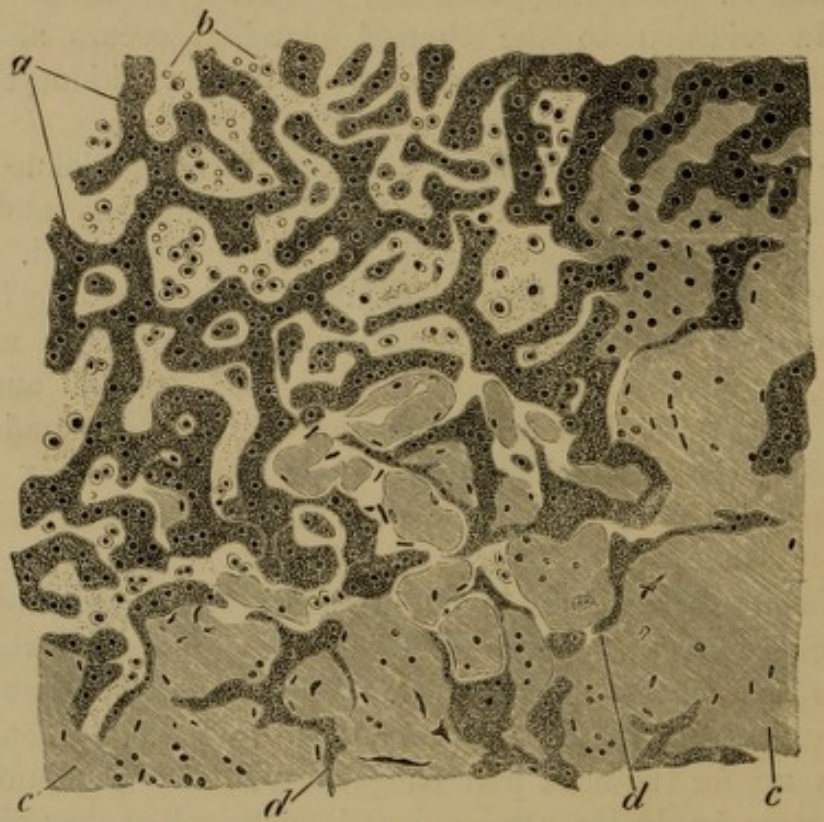

FIG. 15.—AMYLOID DEGENERATION OF THE LIVER. × 285. (Hæmatoxylin and eosin.) *a*, Bands of normal liver cells; *b*, Capillaries dilated in places, but not degenerated, with white and red corpuscles; *c*, Parts which have undergone amyloid degeneration; *d*, Bands of atrophied liver cells.

the vessels the morbid process extends to the adjacent connective tissue, whilst the specific cells of the organ usually remain unaffected by it, merely undergoing fatty degeneration or atrophy (Fig. 15, *d*).

We find this form of degeneration most frequently in the course of suppurative processes involving bone, of syphilis, and of tuberculosis, in which conditions it occurs by preference in the liver, spleen, kidneys, lymphatic glands, and intestinal canal; it may, however, occur independently of any general disease, as in the cartilages of old people, and in tumours.

The *amyloid substance* is characterised by peculiar micro-chemical reactions, being stained reddish-brown by iodine (whereas normal tissue becomes yellow); red, violet, blue or green by iodine and sulphuric acid; and rose-red or ruby by gentian [or methyl] violet, which stains the normal tissue blue or bluish-violet.

The so-called *Corpora Amylacea* are rounded homogeneous bodies, simple or showing stratification, which so far react like the amyloid substance, that they stain dark blue with iodine and sulphuric acid. They

are often met with in the central nervous system in elderly persons, occurring in the ependyma of the cerebral ventricles and in the superficial parts of the spinal cord and cerebrum, as well as in individual cranial nerves, and in the prostate, lungs, etc.

The *corpora amylacea of the nervous system*, however (Fig. 160, *d*), differ from those of other organs in that they remain of a much smaller size, are never concentrically laminated, and do not show the special amyloid reaction when treated with gentian violet, although they are more or less deeply tinged by the nuclear dyes. Whether their occurrence is favoured by certain pathological processes, especially such as involve the destruction of nerve-tissue, is not fully ascertained.

The *corpora amylacea of the prostate* (Fig. 154, *d*), although also occurring by preference in elderly persons, may be much larger than those of the central nervous system, often show a distinct concentric lamination, and some of them at least assume the characteristic coloration of amyloid matter when treated with iodine and sulphuric acid (sometimes even with iodine alone), or with gentian violet. Later they may also *calcify*.

(2) *Glycogen degeneration.*—Glycogen is found normally in many localities, such as the liver, cartilage, muscle, etc. It is, however, considerably increased in diabetes, when the cells of the liver and those of the epithelium of the urinary tubules, especially of the ascending limb of Henle's loops, are almost completely filled with masses of it. Pus corpuscles commonly contain this substance, and it may also occur in tumours—enchondroma, osteo-sarcoma, or carcinoma.

Methods.—The tests distinctive of *amyloid matter and corpora amylacea* may be applied to sections made from tissue either in the fresh state or hardened in alcohol or in Müller's fluid and alcohol as the case may be.

1. *The iodine reaction.*—The sections are first immersed in water (for five or ten minutes in the case of hardened tissues), and then for a few minutes in Lugol's solution (p. 7), after which they are very thoroughly washed in water and examined either in water or glycerin. They may also be preserved for some time in the latter, but greater permanence is secured by mounting in thick gum mucilage to which some glycerin has been added [or in a mixture of Liquor Iodi, B.P., 3½; glycerin and water, of each 6; to which are added about 6 parts of gum arabic].

2. *The sulphuric acid and iodine reaction.*—The sections having been stained with iodine and well washed in water are immersed for several minutes in a 1 or 2 per cent. solution of sulphuric acid, then washed in water and examined as above. An alternative method is to lay a cover-glass on the section and allow a drop of concentrated sulphuric acid to flow in slowly from the side.

3. *The gentian violet reaction*—The sections are transferred from water to 1 per cent. aqueous solution of gentian [or methyl] violet, in which they remain for some minutes, and are then immersed in ½ to 1 per cent. acetic acid until the colours become differentiated, whereupon they are very thoroughly washed in water and examined in water or in glycerin. If it is wished, however, to preserve them they

should be mounted in potassium acetate, or they are transferred to the slides in water, the latter is completely absorbed away with blotting paper, and a drop of levulose or simple syrup is deposited on the section.

The staining in gentian violet may also be preceded by preliminary staining for five minutes in a 2 per cent. alcoholic solution of Bismarck brown, followed by rinsing in absolute alcohol and in water—in the latter for about ten minutes.

The degenerated parts also assume a different tone of colour from the normal parts when stained with alum cochineal (alum carmine) or hæmatoxylin and eosin.

For the demonstration of *glycogen* the tissues must be hardened in absolute alcohol, and the sections, dispensing with water altogether, examined either in iodine glycerin—Lugol's solution diluted to half strength with glycerin—or in iodine gum, made by adding to Lugol's solution enough gum arabic to give the fluid the consistency of syrup; they may also be mounted permanently in the latter. The glycogen is stained brown or brownish-red with iodine, but in contrast to amyloid matter does not change its colour on addition of sulphuric acid, and a further point of distinction is that it dissolves in water.

4. Pigmentation.—Abnormal pigmentation may be caused by pigment either originating in the body itself or derived from without, whilst in the former class again we have to distinguish between the colouring matters manufactured from the blood or bile, and those the origin of which is still unknown.

(1) The *pigment formed within the body* is frequently seen in the interior of cells or replacing them, less often in the interstitial substance. In the cells it always leaves the nucleus free, and appears in the form of minute yellow, brown, or black granules (Plate I., Fig. 1, *c*), which may, however, coalesce to form larger globular or irregular masses. The cell when completely packed with pigment may also break down.

The pigment met with in the rete Malpighii, whether in normal or abnormal pigmentations, probably does not originate in the cells of the rete, but is brought to them by wandering cells or by processes of the connective-tissue cells of the cutis, which extend between and into the cells of the epidermis.

Abnormal pigmentation is in many cases merely an increase of that normally present, as in pregnancy, Addison's disease, and atrophy of the myocardium and of ganglion cells; but in others the pigment is altogether newly formed.

The pigments derived from the colouring matter of the blood are developed whenever red blood corpuscles are destroyed, whether in or out of the circulation. In the latter case, *i.e.*, in extravasations, the order of events is as follows:—A portion of the red blood corpuscles is taken up by the wandering or fixed cells, which thus become what are called *corpuscle-holding cells* (Plate I., Fig. 1, *b*), and changes in their interior into granular yellow, brown, or black

pigment, which may subsequently, however, again become free. Another portion of the red corpuscles, however, is transformed into granular pigment outside of the cells, and directly; or the hæmoglobin diffuses out of them into the surrounding tissue, especially into its cells, where it then again separates out in the form of granules or crystals.

Pigments derived from hæmoglobin either may or may not contain iron. To the latter category belongs *hæmatoidin* (Plate I., Fig. 1, *a*), which occurs partly in the form of orange-yellow or ruby-red granules, partly as rhomboidal, or more rarely needle-shaped, crystals (mostly in the interior of the larger-sized extravasations or in closed cavities) of similar colour; whilst the masses of ferruginous pigment, varying from yellow to brownish-black, are grouped together under the designation of *hæmosiderins*. The latter are found commonly in small extravasations or in the vicinity of larger ones, and yield, though certainly not invariably, the iron reactions, *i.e.*, a blue coloration with hydrochloric acid and potassium ferrocyanide, and a black with ammonium sulphide.

When many red corpuscles are destroyed in the circulation and dissolved, as, for example, after transfusion of blood and in poisoning with potassium chlorate, etc., a *hæmoglobinæmia* follows, accompanied in its higher degrees by an excretion of hæmoglobin through the kidneys, in which process drops of hæmoglobin form in the urinary tubules, and the urine shows a brownish-red colour (*hæmoglobinuria*). Should the pigment, however, be formed from the broken down red corpuscles without solution of the latter—as, for example, in intermittent fever—it is first taken up by white corpuscles, and then accumulates principally in the spleen, liver, and marrow of bones, conditions which are known respectively as *melanæmia* and *melanosis*. In the spleen this pigment (which gives no iron reaction) is found mostly in the cells of the pulp, especially in the vicinity of the follicles. In the liver it appears in the small branches of the portal vein and the capillaries of the acini, partly in the interior of leucocytes, partly free (Fig. 124); but later it also makes its way outwards into the parts surrounding the vessels, where it may be taken up by the cells of the connective tissue.

The blackish-green pigmentation seen in dead bodies undergoing putrefaction (*pseudo-melanosis*) is due to the action of sulphuretted hydrogen upon hæmosiderins, which causes the formation of black granules lying, as a rule, in the interior of cells.

In *icterus* the tissues are usually saturated with bile pigment *in solution*, and only rarely does there occur a separation out of

yellowish-brown granules (most frequently in the liver cells), or of ruby-red rhomboidal crystals of bilirubin strongly resembling those of hæmatoidin, which takes place especially in icterus neonatorum.

(2) Respecting the *pigmentation due to matter derived from external sources*, that of the lungs by the dust of coal, iron, and clay must first be mentioned [see Part III., Chapter VI.]. Carbon pigment, which occurs in the form of angular black granules of unequal size, insoluble in sulphuric acid, is found not only in the tissue of the lungs—in the alveolar epithelium, in the connective-tissue and wandering cells or external to them—but also in the bronchial glands, from which, owing to the softening of adhesions formed between them and the pulmonary veins, it may make its way into the circulation and be disseminated in other organs. Iron filings and stone-dust are distinguished from carbon pigment by differences in colour (red or grey respectively), and by their chemical reaction.

In *argyria*, a condition due to the too-long-continued exhibition of silver preparations by the stomach, very fine black granules are found in the interstitial substance, never in the cells, and most frequently in the walls of the smaller blood-vessels and in their vicinity (Fig. 16, *b*).

Methods.—The appearances can sometimes be examined in *fresh* preparations (after teasing), if the iron reactions hereafter mentioned are not to be tried ; and even in this way very small and slightly tinged granules of pigment can be distinguished from fat-drops by their solubility in concentrated sulphuric acid.

Hæmatoidin may be recognised at once by its colour ; and if concentrated sulphuric or nitric acid be allowed to flow in very slowly beneath the cover-glass from one side, a change of tint to blue, green, and red takes place.

The *hardening* of tissue which contains pigment is carried out in alcohol, or in Müller's fluid and alcohol. For nuclear *staining* alum carmine or alum cochineal is selected.

With the *hæmosiderins* the iron reactions may be tested for in the following ways :—

1. The sections are immersed for some minutes in a 2 per cent. solution of potassium ferrocyanide, and then in glycerin containing a ½ per cent. of acetic acid, when pigment containing iron becomes blue. If nuclear staining is also desired, the sections, after washing in water, are further treated with alum cochineal ; or an alternative method is to immerse them at the commencement in a solution of lithium carmine to which some drops of the potassium ferrocyanide solution have been added, whence they are transferred to hydrochloric acid glycerin (p. 20), or washed in hydrochloric acid alcohol (p. 18).

2. The sections are left in freshly-prepared ammonium sulphide until they have turned blackish-green, which requires from five to twenty minutes ; they are then washed in water and mounted, either in glycerin containing some ammonium sulphide, or in Canada balsam. The pigment assumes a blackish-green or black colour.

It need hardly be said that in carrying out the test-staining for iron all contamination with that substance, such as might come from preparation needles

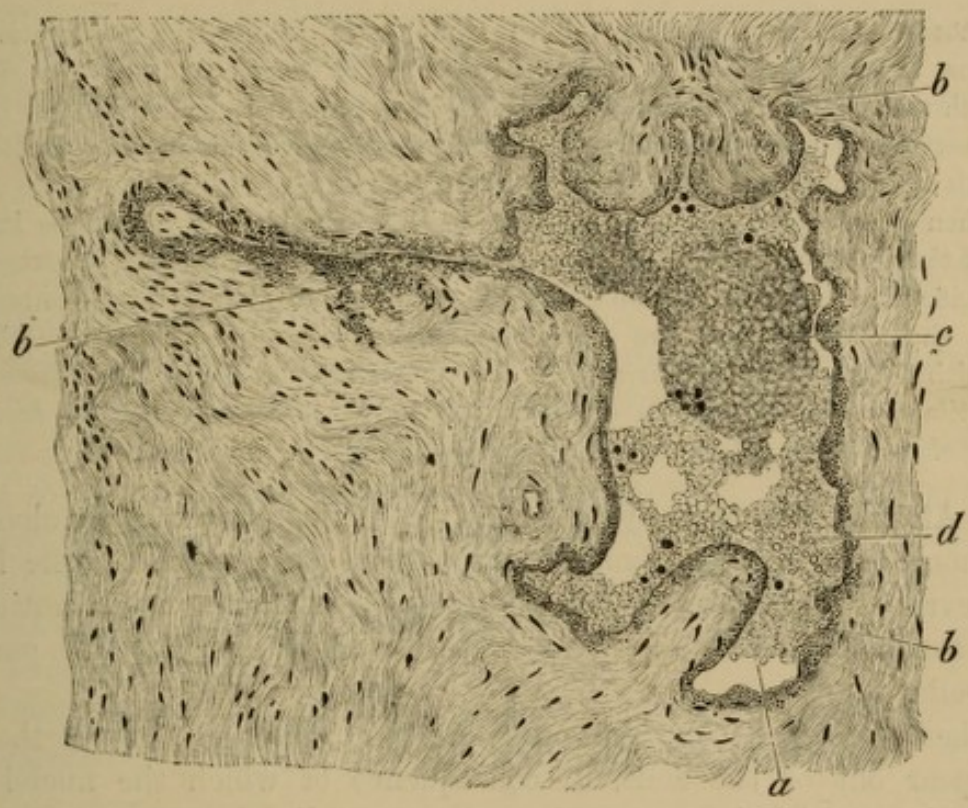

FIG. 16.—ARGYRIA. SUB-PAPILLARY STRATUM OF THE MUCOUS MEMBRANE OF THE TONGUE. × 285. (Stained in alum cochineal.) *a*, Vein; *b*, Granules of silver in the wall of the vein and its immediate neighbourhood; *c*, Fibrinous coagulum; *d*, Red corpuscles.

or from the knife used for cutting, must be avoided; and it should be further borne in mind that ammonium sulphide blackens other metals also, such as lead, mercury, and silver.

5. Calcification.—This as a rule takes place only in necrosed masses, or in tissues which are at least in a lowered state of nutrition, but it also occurs in unaltered tissues in cases of extensive absorption of bone (*metastatic calcification*). It affects the cells as well as the interstitial substance. The lime deposited—chiefly calcium phosphate and carbonate—usually appears at first in the form of minute granules, black by transmitted (Fig. 26, *d*), but shining white by reflected light, which may coalesce later to form more or less homogeneous brightly-shining nodulated or granular masses. Sometimes also laminated concretions are formed, resembling brain-sand (Fig. 37, *b*).

On adding hydrochloric acid the lime dissolves, with development of bubbles of gas if existing in the form of a carbonate; whilst addition of sulphuric acid results in the formation of crystals of gypsum in the shape of prisms grouped in tufts. The lime is insoluble

in ether and chloroform, as well as in solutions of caustic potash and soda.

Methods.—To effect solution of the lime salts in needled preparations or sections, the hydrochloric or sulphuric acid (p. 7) is usually allowed to flow in beneath the cover-glass from one side, a mode of procedure which renders it easy to observe under the microscope any generation of gas-bubbles or formation of crystals of gypsum that may take place.

When it is desired also to obtain hardened preparations of calcareous infiltration of tissues, alcohol only must be used for hardening. To render the recognition of calcification easier in sections, staining with hæmatoxylin is of advantage, by which the calcified parts are coloured reddish-brown; or with alum cochineal, by which they are stained dark red. When hæmatoxylin is employed those parts in cartilage which have been calcified, but have lost their lime salts from the action of an acid, assume an intense blue colour.

6. Atrophy.—In atrophy of tissues and organs the specific elements are much more affected than the supporting tissue; indeed, the latter may even be augmented. Atrophy generally involves a diminution in size, sometimes also an increase in transparency, on the part of the cells.

When *adipose tissue* becomes atrophic, not only does the fat disappear out of the cells, in consequence of which the nuclei and fibrous interstitial tissue come into stronger relief, but an actual multiplication of the nuclei may take place (*atrophic proliferation*); or there is an extravasation of serum, giving the adipose tissue a gelatinous consistence (*serous atrophy*), or pigment is deposited in the form of yellow or brown granules (*pigmentary atrophy*). The latter may also occur in atrophy of other tissues, as around the muscle corpuscles of the myocardium, in ganglionic cells, liver cells, etc.

Methods.—Examination may be made either with needled preparations, especially after adding some ½ per cent. acetic acid; or after hardening in alcohol, or in Müller's fluid and alcohol, and staining the sections with a solution of carmine.

7. Necrosis.—Necrosis, which may be produced by interruption of the blood supply or by injuries, whether mechanical or due to chemical agencies or to heat, is not at first recognisable under the microscope, as the moribund tissues retain their normal structure for a certain length of time; and it is not until *secondary* changes have occurred, which happens sooner or later, that attention is called to the necrosis. Of these changes the most distinct are those taking place in the nucleus, which first of all loses its sharp outlines, then its power of taking up pigment (Fig. 111, *e*), and finally completely disappears (Fig. 121, *a*). (The same effects, however, are produced by post-mortem decomposition.) At other times it breaks down into smaller and smaller fragments and granules, which still stain very intensely

at first, but finally also disappear altogether (Fig. 65, *C*). The protoplasm of the cells becomes cloudy owing to a fine granulation, or changes into a rigid, shining, hyaline mass. If the tissue-components were saturated with lymph at the moment of death a process of coagulation follows, the lymph, which contains fibrinogenic matter, making its way into the dead cells, and forming with the fibrinoplastin of the latter granular, fibrous, or hyaline masses, so that the site of the cells is not seldom occupied by a shining reticulated structure which usually stains deeply (Fig. 133, *b*, and Fig. 151, A). This form is known as *coagulation necrosis.*

A special variety of the last-named is *caseation*, which is prone to occur in very many tissues. It differs from ordinary coagulation necrosis in the greater slowness of its course, and in being associated with a shrinkage of the tissue due to loss of water. The caseous mass is either altogether devoid of nuclei (Fig. 143, *B*), or still contains a few shrunken remains of such (Fig. 172, *a*, *b*, and *d*); otherwise it appears homogeneous or finely granular, and at times also reticulated (Fig. 144, A).

Further changes taking place in necrotic tissue are *colliquefaction*, and *desiccation* owing to evaporation of water (*mummification*). If the

Fig. 17.—Tyrosin Crystals (from Funke's Atlas).

Fig. 18.—Leucin Crystals (from Funke's Atlas).

so-called *putrefactive bacteria*, by which are meant different varieties of micro-organisms not yet very fully worked out, gain access to a piece of dead tissue containing much fluid, a putrid decomposition or *gangrene* is set up, which results in the reduction of the tissue, not uncommonly with development of gases, to a pulpy or fluid discoloured fœtid mass, in which may be found fatty crystals (the so-called *margarin crystals*, Fig. 13), and crystals of tyrosin (Fig. 17), leucin (Fig. 18), and of ammonio-magnesian phosphate, together with hæmatoidin and pigment granules.

Methods.—Examination can be carried out even with *fresh preparations*, the necrotic portions being torn up with the addition of water or salt solution, or some of the juice scraped away.

To demonstrate any *bacteria* which may be present, cover-glass preparations are made and treated with any basic anilin colour desired, or, when the object is the recognition of *particular* bacteria, with the stains given for such (in Chapter V.).

For *hardening*, Müller's fluid and alcohol, or alcohol alone, is employed, and for *staining* sections, one of the carmine solutions given on pp. 18 and 19, or a double stain, pp. 20 and 21.

The nuclei of the necrotic cells no longer, as a rule, stain with the nuclear dyes; but, on the other hand, the necrotic mass takes up the diffuse stains, and is sometimes also stained in a diffuse manner by the nuclear dyes.

The examination of hardened tissues for bacteria is carried out according to the directions given on p. 30 *et seq.*, and in Part II., Chap. V.

CHAPTER II.

PROGRESSIVE TISSUE-CHANGES—INFLAMMATION—INFECTIVE GRANULATION-TISSUE TUMOURS.

I. PROGRESSIVE TISSUE-CHANGES.

1. Hypertrophy, Hyperplasia, and Regeneration.—By the name *hypertrophy* we understand an enlargement, and by that of *hyperplasia* a multiplication, of the constituents, especially the cellular constituents, of a tissue; whilst by *regeneration* is meant the restoration of tissues which have been destroyed.

To determine *with certainty* the existence of a *hypertrophy*, measurement of the parts (*i.e.*, of the cells) is absolutely necessary; but when normal cells are still present in the vicinity of the enlarged ones, a diagnosis will in many cases be possible even without measurement. The more minute changes which take place in hypertrophy are still unknown to us.

The primary change in *hyperplasia* as well as in *regeneration* consists in a new-formation of cells, which starts from the tissue-cells already existing, and takes place, as in physiological tissue-formation, by division of the nucleus and body of the cell. The nuclear division is as a rule *indirect*, that is, it consists in that change in the arrangement of the nuclear network or chromatin, which is known under the name of *karyokinesis* or *karyomitosis*. The alterations in form undergone by the nucleus during this process are the same as in karyokinesis taking place under physiological conditions. Thus after a preliminary increase in the chromatin (Fig. 19, *b*) there forms in the first place a skein of filaments, the *spirem* (Fig. 19, *c*, *d*, and *e*), the nucleus itself remaining sharply demarcated from the body of the cell not only in this but also in the later phases. The loops of filaments, with their convexity inwards, next proceed to group themselves at the equator of the nucleus into a stellate figure, the *aster* (Fig. 19, *e* and *f*), whereupon each loop splits lengthwise into two halves,

which withdraw to opposite poles of the nucleus, and there arrange themselves with the apices of the loops directed outwards in the form of a double star, or *diaster* (Fig. 19, *g* and *h*), around the *nuclear spindle* which has meanwhile developed from the achromatin (Fig. 19, *n*). The daughter nuclei are eventually formed from the diaster, the loops becoming changed back first into skeins (*dispirem*, Fig. 19, *i* and *k*), and then into the intranuclear network of the resting nucleus (Fig. 19, *l*).

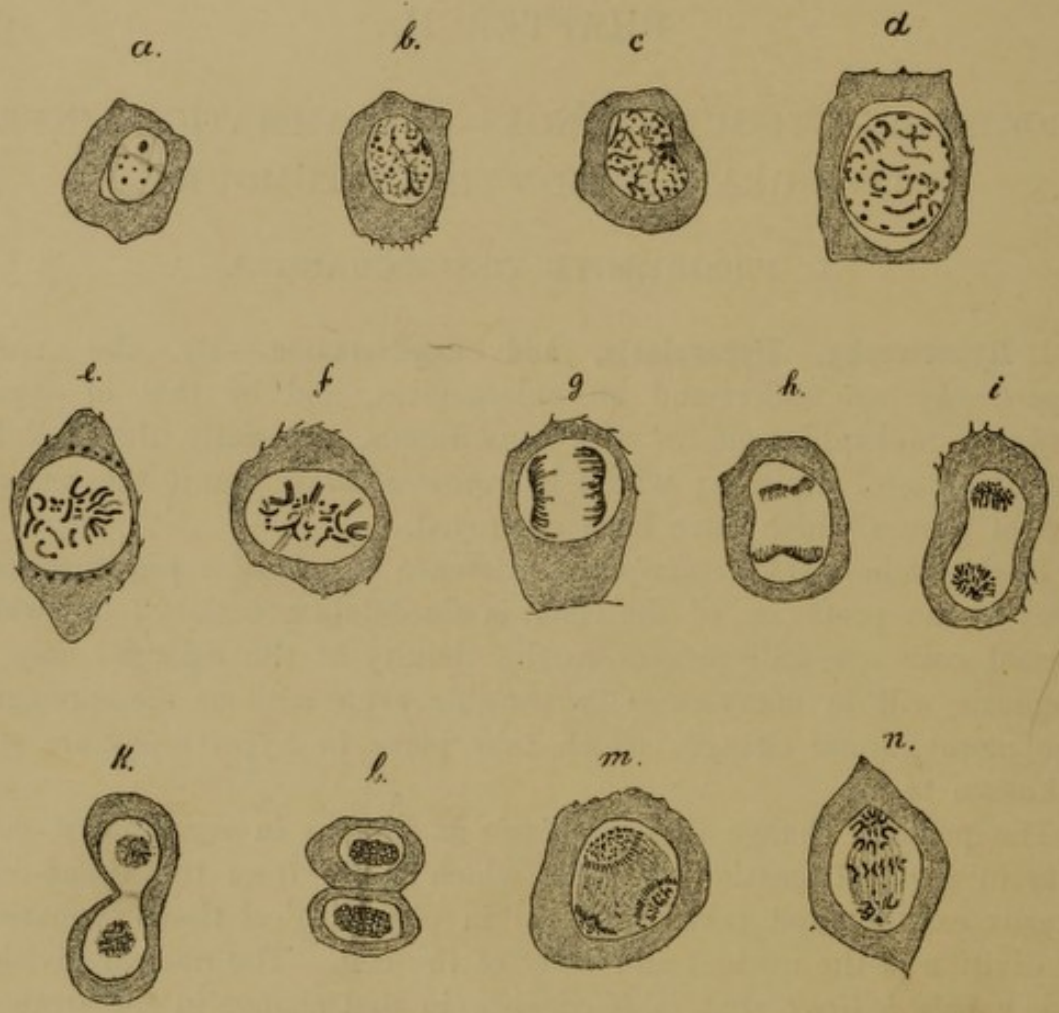

FIG. 19.—KARYOKINETIC FIGURES.

a-l (inclusive), Normal karyokinesis, from the normal epithelium of the prepuce; *m* and *n*, Pathological karyokinetic figures from an epithelioma. × 1100. (Stained principally with saffranin.)

a, Resting nucleus; *b*, Preliminary stage of karyokinesis—enlargement of nucleus, and increase in the chromatin; *c*, Commencement of the skein formation; *d*, Skein (spirem) with the loops ranged at the circumference; *e*, Spirem—central position of loops, with commencing radial arrangement; *f*, Aster, semi-polar view, loops in the equatorial plane, with radiate arrangement and longitudinal division; *g*, Diaster, lateral view; *h*, Diaster; commencing asymmetrical constriction of nucleus; *i*, Diaster in process of change to the dispirem; constriction more advanced; *k*, Dispirem; asymmetrical division of the body of the cell; *l*, Completion of division of nucleus and cell—daughter asters passing into resting state; transformation of the skein into nuclear network; *m*, Multipolar nuclear division; *n*, Aberration of the loops.

There may also occur, however, certain divergences from the typical course of events as just given, divergences which it has hitherto been possible to find with especial frequency in *carcinomata*. These include an increase or diminution in the number of loops, shorten-

ing or aberration of the loops (Fig. 19, *n.*), and also pluripolar mitoses (Fig. 19, *m*), etc.

Division (by constriction) of the cellular protoplasm commonly follows the division of the nucleus (Fig. 19, *k* and *l*); should this, however, fail to occur, binuclear or polynuclear cells are formed, *giant cells*, which may have a round, elongated, or quite irregular shape, and in which the nuclei lie either in the centre or round the margin (Fig. 34, *d*, and Fig. 173, *b*).

Another special mode of cell proliferation is that by *budding* or *sprouting*, which will be described further on in treating of the new-formation of vessels.

The tissue which is formed from the newly-developed cells is always exactly like the old, or at least closely akin to it. Thus, only epithelial tissue can be formed again from epithelial tissue, connective tissue from connective tissue, and so on.

2. The minute **changes which take place in the individual tissues** in hyperplasia and regeneration are briefly as follows:—

In the new formation of *epithelium* the principal part is played by karyomitosis, but budding (*gemmation*) also takes place at times. The new epithelium also preserves the specific peculiarities of the old; that is to say, only pavement epithelium is, as a rule, formed again from pavement epithelium, ciliated from ciliated, and so forth. Only under special conditions, as for example in chronic inflammations of mucous membranes, does a transformation of cylindrical into flat-celled epithelium take place. The superficial epithelium is very readily restored, as is also the epithelium of the gland ducts, but the specialised epithelium of glands themselves only to a certain extent.

In tissues of the *connective-tissue* series both hyperplastic and regenerative processes occur; cartilage, however, has less power of regeneration, and bone none at all, directly. The new cells, which probably develop exclusively by indirect nuclear division of the fixed cells, are in their youngest stage small round elements which, if they lie very close together, and if newly-developed blood-vessels are present amongst them, form a tissue to which the name of *embryonic* or *granulation tissue* is given. This may also, however, contain giant cells in addition to the small round ones.

From this embryonic tissue the different kinds of connective tissue may then be formed according to the particular mode of development of the cells, and the nature of the interstitial substance formed from them. If ordinary *connective tissue* is developed, the embryonic cells become elongated and spindle-shaped (*fibroblasts*, Fig. 21, *e*), and the intercellular substance formed from them acquires a fibrillated structure; if *hyaline cartilage* a hyaline intercellular substance is formed

between the cells (*chondroblasts*), round which latter it is condensed into a capsule ; whilst in the development of *osseous tissue*, the ground substance becomes homogeneous or fibrous, and is impregnated with lime salts, and the cells (*osteoblasts*, Fig. 179, *c*) take indented forms, and come to lie in lacunæ with processes (*bone-corpuscles*). The whole of the embryonic tissue does not, as a rule, change into bone, but merely forms bony trabeculæ, while the remainder becomes medullary tissue.

When *adenoid tissue* forms, a portion of the embryonic cells is changed into a delicate reticulum, in the meshes of which the other cells come to lie.

In the formation of *mucous tissue* the interstitial substance lying between the cells of the embryonic tissue becomes mucinous and homogeneous, while the cells themselves become connected with each other by processes.

Adipose tissue develops simply by the taking of fat into the cells of embryonic or mucous tissue, or of ordinary connective tissue, the nuclei being thereby gradually compressed against the periphery of the cells.

New-formation of *blood-vessels* takes place by the outgrowth from the wall of an already existing vessel—that is to say, from the protoplasm of one of its cells—of an arch which is at first solid and granular, and which runs out into a fine fibre and either turns back again to the same vessel or grows to meet a similar arch proceeding from another vessel. Later the nuclei formed by karyokinesis wander into these processes, the arch itself next becomes hollow, and finally comes into communication with the old vessels.

Hyperplasia and regeneration of *muscle-fibres*, both smooth and striated, of course starts from the muscles already existing, taking place by karyokinesis of their nuclei ; only in the case of striated fibres does a *direct* division of the muscle nuclei take place. The new elements change at a later date into spindle cells, which in the case of striated fibres become very long and gradually, with repeated nuclear division, acquire a transverse striation. (Others, however, hold that the regeneration of striped muscle fibres takes place partly by longitudinal splitting and segmentation in the old and new fibres.)

Regeneration of *nervous tissue* appears only to take place in the peripheral nerves, which it does by the formation of new axis-cylinders by splitting of the axis-cylinders in the old nerves, the new axes then becoming surrounded with white substance and with sheaths of Schwann.

Methods.—To see the *karyokinetic figures*, very small pieces of the tissue, not more than half a centimetre in thickness, must be immersed in a *fixing fluid* while still warm with life, or at latest half an hour after removal from the

living organism. Of human tissues, those best adapted for this purpose are tumours, such as sarcomata or carcinomata, or inflammatory growths, etc., which have been removed by operation.

The best *fixing fluid* is that introduced by Flemming. It consists of 4 vols. of a 2 per cent. aqueous solution of osmic acid, 15 vols. of 1 per cent. chromic acid solution, and 1 vol. of glacial acetic acid. The pieces remain in this fluid during from one to three days, and are then washed very thoroughly (for several hours) in running water, after which hardening is completed in alcohol (of gradually increasing concentration) and the remaining operations carried out as soon as possible.

The sections are *stained* by immersing for half-an-hour to twenty-four hours in 1 per cent. aqueous solution of saffranin or gentian violet (or else concentrated alcoholic solution of the dye selected may be dropped into a watch-glass of water until the mixture begins to lose its transparency), and are then decolorised in hydrochloric acid alcohol (p. 18) as long as colour can be extracted from them. To increase the rapidity of staining, anilin saffranin (made by mixing 2 parts anilin oil with 100 parts water, then adding saffranin powder in excess, warming to 60° C., and filtering) or anilin gentian violet may be used.

The karyokinetic figures are stained very intensely by this method, the resting nuclei but feebly, so that the former catch the eye even with a low magnifying power. Examination with an oil-immersion lens is, however, necessary for more accurate study.

Instead of Flemming's solution *absolute alcohol* may also be used for fixation. Staining is then done by Gram's method or Weigert's modification (pp. 31 and 32).

When it is wished to stain *tubercle bacilli* also, in addition to the karyokinetic figures, the objects should be hardened for several weeks in a dilute aqueous solution of chromic acid, and the sections first stained for twenty-four hours in anilin gentian violet, next decolorised in dilute nitric acid (p. 132), and then brought first into a concentrated alcoholic solution of fuchsin for five to ten minutes, with subsequent rinsing in alcohol, and lastly immersed for five to ten minutes in aqueous methyl blue. After this treatment the tubercle bacilli appear violet, the nuclei and nuclear figures an intense red, and the interstitial substance blue.

II. INFLAMMATION.

3. The Inflammatory Process.—In every inflammation we have to distinguish changes in the vascular apparatus and changes in the tissue cells. The former, which are especially prominent in acute inflammations and in the earlier stages, can be best studied by the repetition of Cohnheim's experiment on the mesentery of the living frog. If a coil of intestine with its mesentery be drawn from the abdominal cavity of this animal and examined in a suitable manner under the microscope, the first effect of the inflammation excited by the pulling and the action of the air is seen to be an increase in the calibre of the blood-vessels and an acceleration of the circulation. Later, however, there follows a slowing of the current [which may increase until there is merely a to-and-fro vibration or complete stasis], so that the corpuscles can be clearly distinguished. Next, the white corpuscles

in the veins gather on the walls (*pavementing*), through which they soon push processes, and then, passing through them bodily, collect outside the vessels. Red corpuscles also pass out from the capillaries, and at the same time an exudation of a highly albuminous fluid, which readily coagulates, takes place from the interior of the vessels.

The order of events is similar in acute inflammations of other tissues and in other animals; probably in consequence of injury to the wall of the vessel by the exciting cause of the inflammation, there always occurs an emigration of blood corpuscles and an extravasation of albuminous fluid, which together are named the *exudation*.

The emigrated white blood corpuscles are partly *mononuclear* and partly *polynuclear* forms (Fig. 21, *a* and *c* respectively), the latter having from two to four nuclei arranged in a crescentic or trefoil figure, of a peculiar shining appearance, and destitute of nucleoli, whereas the former possess a comparatively large nucleus *with* nucleoli. The polynuclear leucocytes occur chiefly at the commencement of inflammations, but retain their preponderance later also when the inflammation is of a suppurative type, whence they are also called *pus corpuscles;* whilst the mononuclear forms are principally met with in inflammations of less intensity or of longer duration.

The exudation will naturally accumulate at the point where it meets with least resistance, and hence will sometimes be found more superficially, at other times in the substance of the tissue. The following *varieties* are distinguished:—

(1) *The serous exudation.*—This is usually found only at the commencement of inflammation or where the process is but slight, and consists of a fluid which contains a somewhat larger proportion of leucocytes and albumen than the transudation fluid of passive congestion, and hence also coagulates more readily than the latter. In hardened preparations, especially when the boiling method has been employed, the serous exudation appears as an extremely finely granular mass, which stains slightly or not at all with the nuclear dyes, and which encloses a limited number of leucocytes (Figs. 139, *c*, and 140, *b*). It shows stages of transition to the second variety, especially under the microscope.

(2) *The fibrinous or croupous exudation.*—In this form, owing to the large amount of fibrinogen and fibrinoplastin present (derived, the former from the fluid, the latter from the dissolved leucocytes and blood-plates), there occurs a copious formation of fibrin. Microscopically, the exudation appears as a felt or network of pale fibres and trabeculæ, or as a finely granular mass with leucocytes embedded in it. (Figs. 101, *a;* 138, *c*, and 171, *b*). When the exudation persists

long the fibrin not uncommonly assumes the form of shining homogeneous bands and masses which stain intensely. It is further characterised by its ready solubility in dilute acetic acid, and by the intense violet colour which it assumes when Weigert's modification of Gram's method is employed.

(3) and (4) *The cellular and purulent exudations.*—The former consists principally of leucocytes, but if associated with a liquefaction of the tissue it becomes the *purulent* exudation, which differs from the preceding varieties in the absence of coagulation. It consists of a fluid, the *liquor puris,* containing leucocytes, amongst which, however, by far the greater number are polynuclear (Figs. 165, *a*, and 166, *a*).

The cells of pus, particularly those of fresh pus, very often contain glycogen. Later they frequently undergo fatty degeneration, showing in their bodies small highly-refractive granules (fat drops) which continuously increase in number until the nucleus disappears and the cell forms a large coarsely granular sphere (granule corpuscle) which finally breaks down into detritus. Besides the pus corpuscles various other formed elements may also be present in pus, such as red blood corpuscles, crystals of hæmatoidin, fat, and triple phosphate, as well as elements from the organs from which the pus is derived (epithelial cells, elastic fibres, etc.), and, lastly, animal and vegetable organisms (hooks of echinococcus, bacteria, actinomyces).

When the purulent exudation also contains flakes of fibrin it is said to be *fibrino-purulent,* and if it contains much serum, *sero-purulent. Mucin* may also be present in pus, in which it is detected by the formation of stripes or granular pieces of coagulum on adding acetic acid, and by their insolubility in excess of acid [*muco-purulent* exudation].

(5) *Catarrhal, hæmorrhagic, diphtheritic,* and *putrid exudations* are also spoken of. In the first-named kind desquamated epithelial cells, and in the second (Fig. 169, *b*) many red blood corpuscles, are mixed with the exudation, whilst in the case of the diphtheritic exudation (Fig. 151, *A*) we find, in addition to the exudation, a coagulation necrosis, and in the putrid exudation a putrid decomposition in consequence of the action of putrefactive bacteria (see pp. 63 and 64).

With reference to the *second* leading change which takes place in inflammation, that, namely, in the *fixed* cells of the tissue, the alteration in the acute forms of inflammation is often at first only of a passive and degenerative kind; indeed, any of the above-described (Chapter I., p. 51 *et seq.*) forms of degeneration may occur, and solution of the cells and interstitial substance, or coagulation necrosis, very often takes place.

4. The Process of Repair.—Sooner or later, however, *active* changes commence in the endothelial cells of the vessels and the fixed cells of the inflamed tissue, changes consisting in swelling of the cells and production by karyokinesis of new elements, which at first strongly resemble mononuclear leucocytes, and may also wander like them. In certain forms of chronic inflammation, which are also called *productive*, the processes of growth described as taking place in the tissue cells are present from the very first or may even be the only ones which occur.

The descendants of the fixed cells of the tissue form, alone or in conjunction with the emigrated leucocytes, a complex mass of cells, which, when it is penetrated by newly-developed vessels, is commonly known as *granulation tissue*, and which in a general way possesses also the significance of *embryonic* tissue. From it *cicatricial tissue* is most frequently developed, but the *specialised* tissues (epithelial, glandular, and osseous) may also form in cases where specific tissue cells have, by proliferating, borne a part in the construction of the granulation tissue.

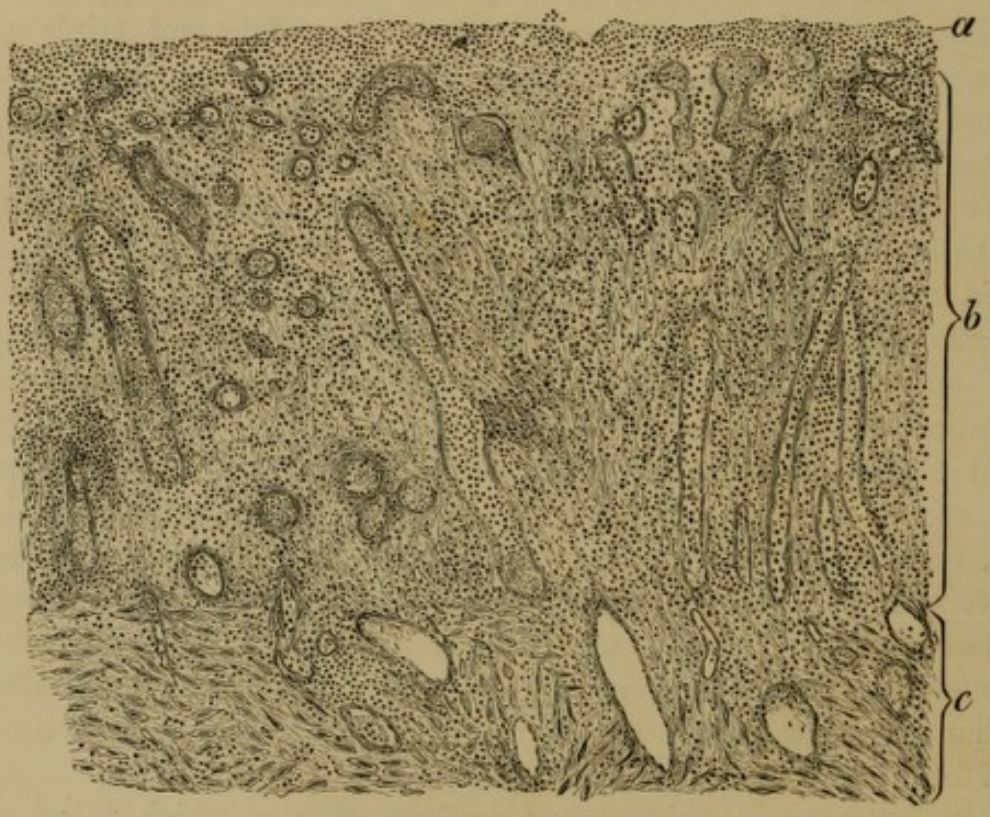

FIG. 20.—GRANULATING CHRONIC ULCER OF THE LEG (GRANULATION TISSUE). × 77. (Hæmatoxylin and eosin). *a*, Layer of pus on surface of granulation tissue; *b*, Youngest part of granulation tissue, consisting of round cells and numerous blood-vessels, the latter for the most part cut obliquely at the bend; *c*, Older part of granulation tissue, consisting principally of spindle cells.

A very suitable object for the study of granulation tissue is formed by the granulations of wounds. The granulations are covered with a layer of pus in wounds healing by second intention (Fig. 20, *a*),

and consist of small round cells lying close together, a very scanty amount of mucous interstitial tissue, and numerous wide capillaries which run parallel with one another and at right angles to the surface, where they bend round so as to form loops (Fig. 20, *b*).

The actual cells are of two kinds: those of one set are polynuclear, looking like pus corpuscles, and consist, like them, of emigrated white blood cells (Fig. 21, *c*); the others are mononuclear, and are either

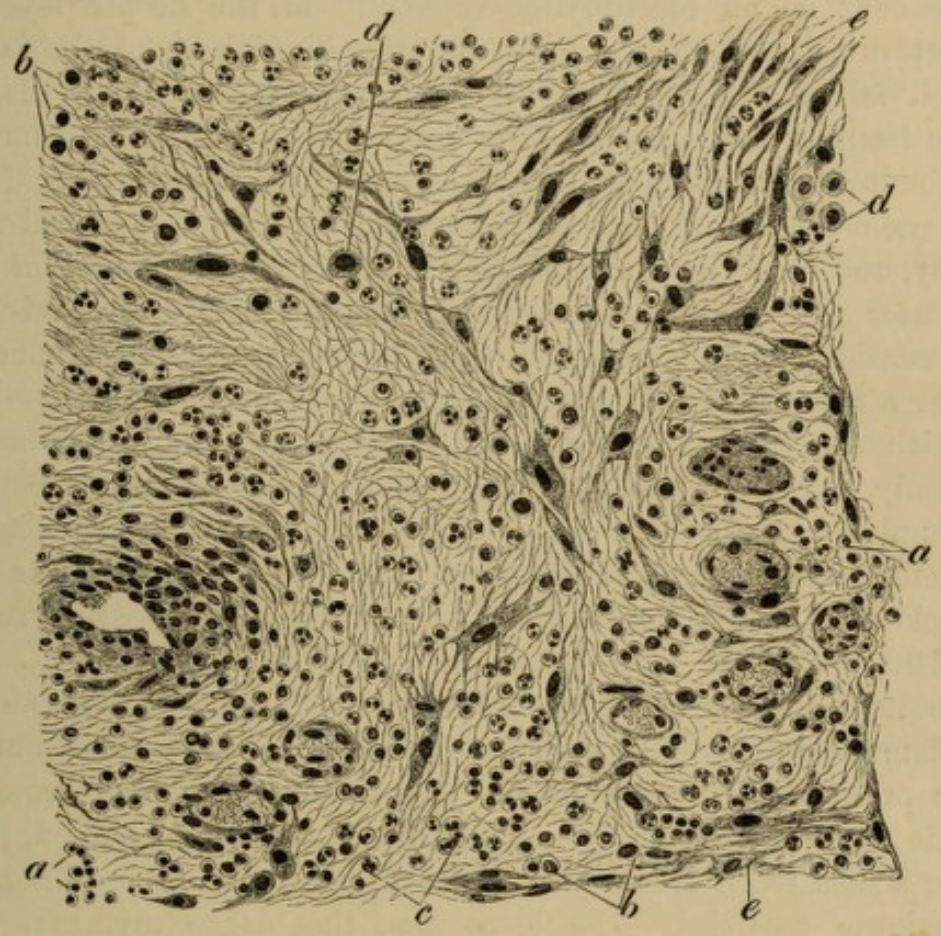

FIG. 21.—GRANULATION TISSUE OF A CHRONIC ULCER OF THE LEG. × 285. (Hæmatoxylin and eosin.) *a*, Small mononuclear round cells; *b*, Larger round mononuclear cells; *c*, Round polynuclear cells; *d*, Rounded fibroblasts; *e*, Fibroblasts with processes.

likewise emigrated leucocytes, or else derivatives of the fixed tissue cells which have partly been formed on the spot and partly wandered thither from the neighbouring regions (Fig. 21, *a* and *b*). The polynuclear cells are incapable of further development, and are taken up and destroyed by the growing tissue cells, for the nourishment of which their substance may perhaps serve. The mononuclear leucocytes probably become transformed, at least in part, into polynuclear forms, which are then in like manner absorbed by the proliferating cells of the tissue. Those mononuclear cells, however, which are derived from the fixed cells of the tissue, and which it is usually possible to distinguish from the mononuclear leucocytes by the larger

size of the cell-body (Fig. 21, *b* and *d*), are used for the formation of connective tissue, and are hence also named *fibroblasts*. During this process they gradually become elongated (Fig. 21, *e*), and take a club, spindle, or stellate shape—in sections they commonly appear spindle-shaped—whilst their nuclei likewise enlarge and become vesicular, thus recalling the appearance of the nuclei of epithelial cells (*epithelioid cells*).

The cells go on multiplying, especially in the deeper layers, by indirect division of their nuclei; and should division of the body of the cell fail to follow, *giant cells* may also be formed, but these are rare in healthy granulations. The interstitial substance then increases in amount and becomes fibrillated (Fig. 21), the cells separate further from each other and become narrower, some of the blood-vessels atrophy, and thus the granulation tissue changes into *cicatricial tissue*. The latter may remain comparatively rich in cells and blood-vessels for a considerable time; but as these become continually reduced in number a condensation of the cicatricial tissue eventually takes place, in which the interstitial substance also becomes firmer and not uncommonly assumes a glassy translucent character (*sclerosis*).

Granulation tissue may also be formed in *serous membranes* in more protracted inflammations of the latter (Fig. 101, *B*), and results either in thickening of the serosa or in the adhesion of opposing surfaces (Fig. 102).

The leucocytes which wander out from the blood-vessels during an inflammation not only seem to be made use of for the nutrition of the proliferating fixed cells, but they also serve for the removal of necrotic tissue elements, of broken-down masses of exudation, and of foreign bodies when either permeable, of small size, or breaking down into minute particles. The leucocytes, that is to say, take these masses of detritus into their substance, becoming thereby transformed into *granule cells* (Fig. 161, *d*), which ultimately pass into the lymphatics and blood-vessels, or make their way along the lymph-paths as far as the nearest lymphatic glands, where they gradually again lose their contents.

When the necrotic masses or foreign bodies are hard, giant cells are frequently found in the granulation tissue enclosing them, these being due to the circumstance that the progressive division of the nuclei in the tissue is not always followed by a corresponding division of the body of the cell. The giant cells range themselves on the surface of the foreign body, and may bring about a gradual *solution* of the latter; when, however, this does not take place, the body becomes *encapsuled* by the granulation tissue, which ultimately changes into cicatricial tissue.

Various deleterious agencies, mechanical, chemical, thermal, etc., may act as the *cause* of inflammation. Acute inflammations are very often due to the action of *bacteria*; in particular, suppurative processes in human beings are invariably originated solely by these microbes, most frequently by the so-called *pyococci* (p. 120).

5. Infective Granulation-tissue Tumours or Granulomata.—*Tuberculosis, leprosy, syphilis, rhinoscleroma, actinomycosis,* and *glanders,* are often grouped under this designation, because they give rise to formations resembling tumours composed of granulation tissue, or at least of a tissue of closely allied form, and are of infective origin. They have in common with the inflammatory new-formation, not only the fact that they consist of emigrated white corpuscles and of derivatives of the fixed cells, and may be partially vascularised, but also that in most of the above-named processes part of the newly-formed tissue may attain a higher degree of development and become transformed into connective or cicatricial tissue. On the other hand, however, retrograde changes may occur, a portion of the cells undergoing caseation, as in tuberculosis and syphilis; or hyaline degeneration, as in leprosy and rhinoscleroma; or suppuration and ulceration being set up in the tissue.

As the causes of the processes excited lie in specific micro-organisms —it is only in the case of syphilis that we are unable as yet to assign it with certainty—it will occasion no surprise that they not only spread locally, but may also lead to disease in more remote organs.

For the respective micro-organisms and other histological peculiarities of these conditions, see Part II., Chapter V.

Methods.—To render it possible to observe the *emigration* of white blood corpuscles in inflammation of living tissue, the following procedure must be adopted (*Cohnheim's experiment*):—

One or two drops of a 1 per cent. solution of curara are injected beneath the dorsal skin of a large male frog, which, as soon as it has become motionless, is laid on its back upon a glass plate. The abdominal cavity is opened at the left side and a coil of intestine drawn out, stretched, together with its mesentery, over a ring of cork attached to the glass plate by means of sealing-wax or Canada balsam, and fastened there with needles. The mesentery may be protected with a cover-glass or left free. The remaining parts of the frog must be protected from drying by covering with compresses of wet blotting-paper.

The following applies to the examination of the different kinds of *exudation*:—

The mode of examining *serous* exudation in the fresh state requires no further explanation. In hardening, recourse may be had with advantage to the boiling method (p. 8), or else alcohol may be used. Cells lying in the exudation are stained with nuclear dyes.

Fibrinous or *croupous exudation* is torn up fine in the fresh condition, and acetic acid may afterwards be added to it. For tissues which have been hardened in alcohol, Weigert's modification of Gram's method, with or without preliminary

staining (pp. 31-33), should be used as a test-stain for fibrin, that substance and its (hyaline) derivatives being stained by this means an intense bluish violet.

In examining *pus* histologically it must be diluted with salt solution, as it contains too many cells. The nuclei of the pus corpuscles are brought out distinctly if water or acetic acid be added, whilst addition of Lugol's solution stains the corpuscles mahogany brown owing to the glycogen contained in them. Any coarser foreign particles that may chance to be mingled with the pus become readily visible if the fluid is spread out over a glass plate laid on a black surface.

The *bacteriological* examination of exudations is done according to the rules laid down for fluids on p. 26 *et seq.* Smear preparations may also be made of flakes of fibrin, if an attempt is made to rub them on cover-glasses by means of forceps.

Alcohol alone, or Müller's fluid and alcohol, may be used for the *hardening* of inflamed tissue, and the nuclear or double stains for colouring sections. The leucocytes stain much more intensely than the other cells.

The methods given on pp. 68 and 69 are resorted to for the recognition of karyokinesis.

CHAPTER III.

TUMOURS OR NEW-FORMATIONS.

1. General Considerations.—Tumours proper do not admit of being sharply marked off from the hyperplastic and inflammatory new-growths, though differing from the latter in a general way in that the tissue of which they are composed deviates to a greater or less extent from that in which they are growing, and finds no *typical* termination to its development.

The *development* of tumours takes place by proliferation of the cells of normal tissue by karyokinesis, and new-formation of blood-vessels by gemmation.

The *ætiology* of tumours is quite obscure. Probably congenital predisposition, hereditary tendency, traumatic influences, or irritative conditions play an important part, as also the age of the individual.

As is well known, a distinction is made between *benign* and *malignant* tumours. The former in growing remain comparatively well separated from the neighbouring parts, whereas the malignant tumours grow without restriction into the surrounding tissues, not only forcing the elements of the latter asunder, but directly replacing them, and also often lead to the formation of *metastases*. The latter may occur by way of the blood-vessels or of the lymphatics, into either of which the tumour cells penetrate, to be carried along them to more distant parts; the daughter tumours are therefore always developed exclusively from the cells conveyed from the original tumour in this way. The more vascular and juicy the tumour is, and the richer it is in mobile cells, the earlier will it form metastatic growths.

Tumours may be divided into *connective-tissue* and *epithelial*, the former of which develop from the tissues of the mesoblast (connective tissues), the latter from derivatives of the epiblast and hypoblast (true epithelia).

Connective-tissue tumours are again subdivided into those in which the tissue becomes more highly organised, and those in which

it continues to stand on a lower level of development; the former, that is to say, consist of the various *mature* forms belonging to the connective-tissue group, the latter of undeveloped *immature* forms in the same group.

I. CONNECTIVE TISSUE TUMOURS.

A. TUMOURS COMPOSED OF MATURE TISSUE.

2. (i.) **Fibroma.**—This is a tumour consisting of fibrous and vascular connective tissue, according to the density or looseness of which hard and soft varieties are distinguished, the latter being also richer in cells, and approximating in this particular to the fibro-sarcomata (Fig. 22).

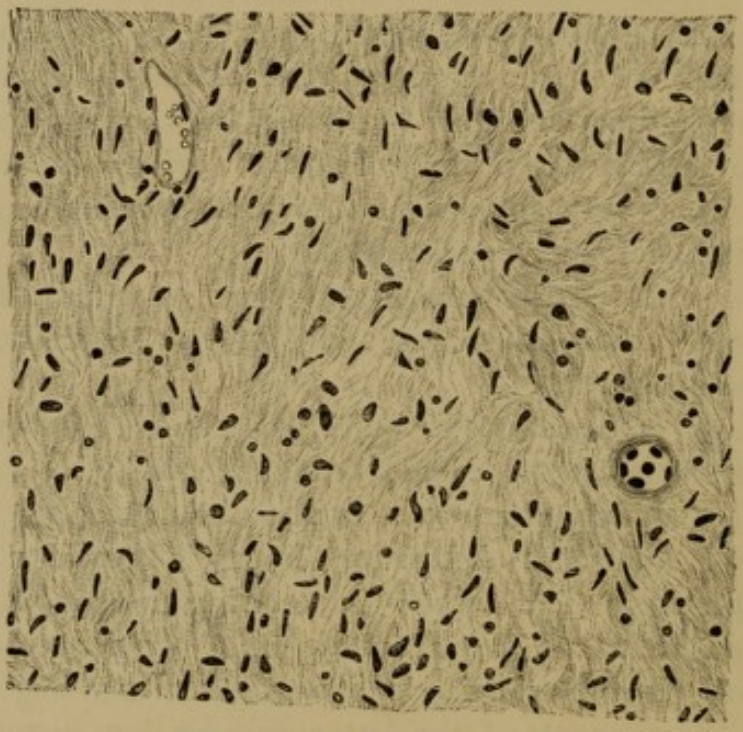

FIG. 22.—SOFT FIBROMA OF THE SKIN. × 285. (Stained with hæmatoxylin and eosin.)

The cells in these tumours may be unevenly distributed, so that more and less cellular portions alternate. They are usually elongated or spindle-shaped, but round cells also occur, not uncommonly in little clusters, which then constitute the youngest spots or *formative tissue* of the tumour.

Œdematous fibromata are those in which venous congestion has resulted in extravasation of serum, and consequent softening and separation or even liquefaction of the fibrils (Fig. 23, A), as well as swelling of the cells. If during this process the latter assume a stellate form (Fig. 23, *a*), a certain resemblance to myxomata results. Of *retrograde* changes, *calcification* is frequently observed.

The fibroma never gives rise to metastatic growths, but it may

originally occur in *multiple* form, as for example in the skin. It has been shown with regard to the multiple fibroma of the skin (also called

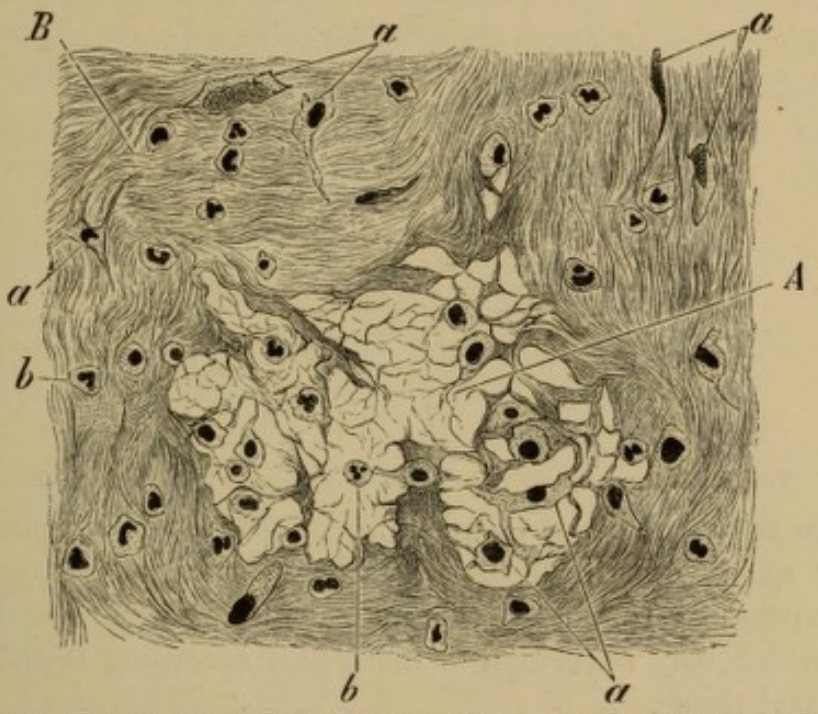

FIG. 23.—FIBROMA OF THE LABIA MAJORA with œdema and commencing inflammation after twisting of the pedicle. × 545. (Stained with alum cochineal.) *A*, Œdematous part, the connective-tissue fibrils pushed asunder by serum, or liquefied; *B*, The non-œdematous part; *a*, Stellate and spindle-shaped connective-tissue cells; *b*, Polynuclear leucocytes which have emigrated in consequence of the inflammation.

fibroma molluscum), that the tumours originate in the fibrous sheaths of the cutaneous nerves, and perhaps also of the vessels and the ducts of the glands. (See Neuroma, p. 82.)

3. (ii.) **Lipoma.**—This consists of adipose tissue, which differs from normal adipose tissue only in the larger size of its cells and lobules.

When the connective tissue framework comes into greater prominence at the expense of the adipose tissue, we speak of a *fibro-lipoma*, or *lipo-fibroma (steatoma)*, and when mucous tissue is present in addition to adipose, of a *myxo-lipoma* or *lipo-myxoma*. Cysts filled with liquid fat (oil cysts) occasionally occur in lipomata. Like the fibroma, the lipoma may occur in multiple form.

4. (iii.) **Myxoma.**—By the name *myxomata* are understood tumours composed of *mucous tissue*, that is, of a homogeneous, or sometimes also striated or delicately fibrous, interstitial substance containing mucin, and in which are embedded stellate cells with anastomosing processes, together with spindle-shaped and round cells (Fig. 24). The tumours have a mucoid aspect even to the naked eye, and shrink very greatly in alcohol. Their structure is distinctly alveolar.

As mucous tissue is an embryonic form of connective tissue, many authorities class the myxoma with the sarcomata (as *myxo-sarcoma*), whilst others again allege that myxomata are developed from lipomata

(by disappearance of fat from the cells), or from fibromata (by œdematous swelling of the connective tisssue).

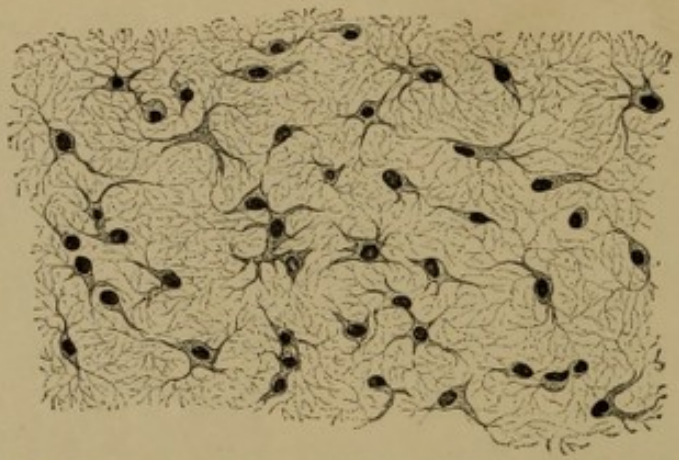

Fig. 24.—Myxoma of the Labia. × 285. (Stained with alum cochineal.)

Mucous tissue is often coupled in tumours with tissues of other kinds, for example with fibrous or adipose tissue, cartilage, bone, or tissue composed of round or spindle cells, thus forming various mixed tumours which may be benign or malignant according to the character of the second tissue.

5. (iv.) **Chondroma.**—This consists of cartilaginous tissue, of which all three varieties may be present, hyaline cartilage being, however, the most frequent. Chondromata always have an envelope of connective tissue in which the vessels run, and which also sends processes into their interior, thus causing a lobulation of the structure.

The cells of the chondroma show the same multiplicity of variations in number, size, and arrangement as those of normal cartilage. Some-

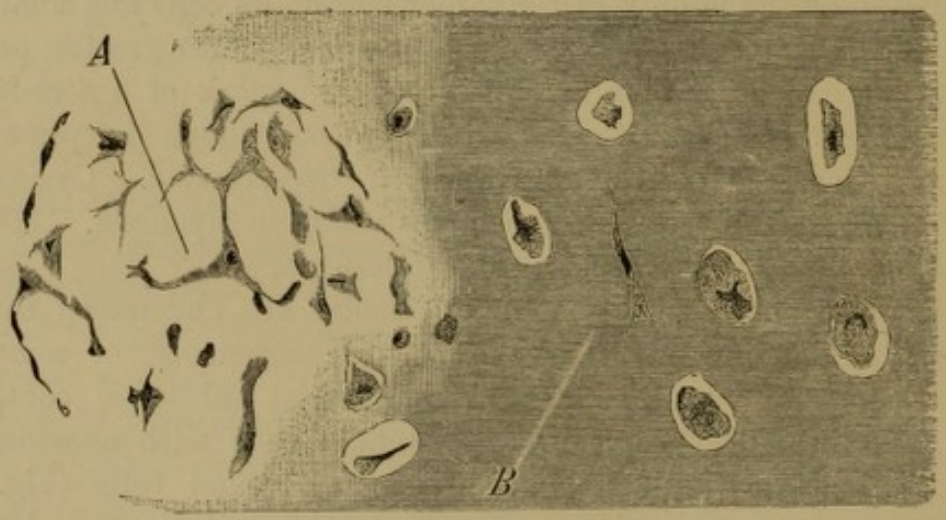

Fig. 25.—Myxochondroma of the Parotid. × 285. (Stained with hæmatoxylin and eosin.) *A*, Mucous tissue; *B*, Hyaline cartilage.

times *transformation into mucous tissue* takes place, the cells losing their capsules and acquiring processes, and the interstitial substance becoming mucinous (*myxo-chondroma* or *chondro-myxoma*) (Fig. 25).

Calcification (Fig. 26) is very frequent, and affects either the interstitial substance, or the capsules and cells. Furthermore, a development of *osseous tissue* may take place in chondromata, the bone either proceeding directly from calcified portions of cartilage, or being formed by the connective tissue of the chondroma assuming in places the function of medullary tissue, and its cells then developing into osteoblasts (Fig. 26, *b*) and bone corpuscles (*osteo-chondroma*).

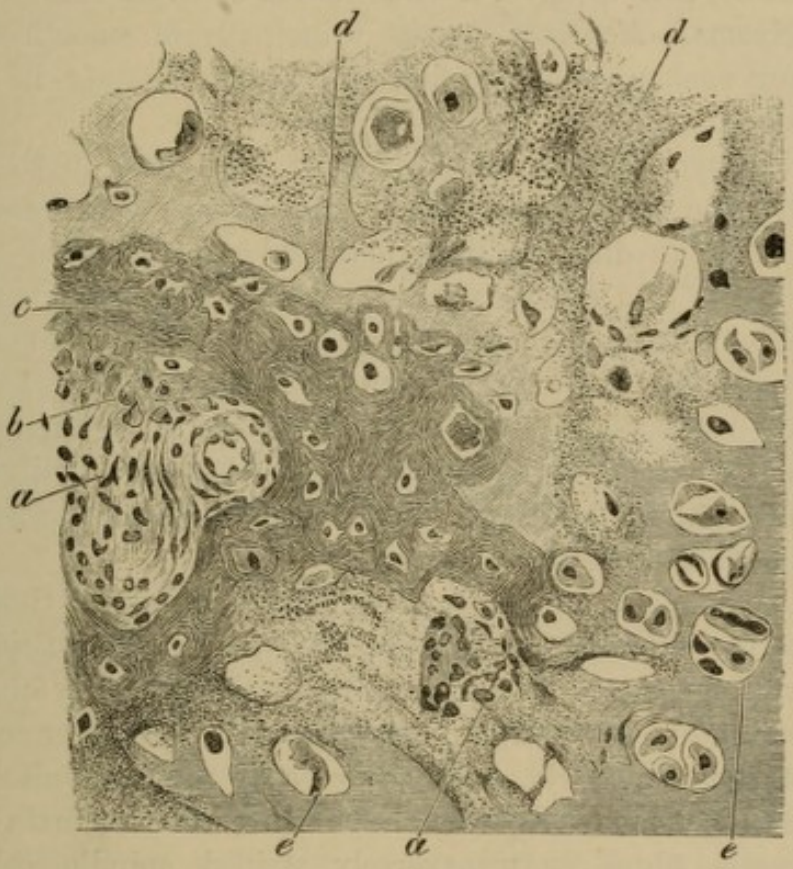

FIG. 26.—OSTEO-CHONDROMA OF A DIGITAL PHALANX. × 240. (Stained with hæmatoxylin and eosin.) *a*, Connective tissue resembling bone-marrow; *b*, Osteoblasts; *c*, Bone, with young bone-corpuscles; *d*, Cartilage which had become calcified, but was partially deprived of its lime salts by treatment with acid; *e*, Uncalcified hyaline cartilage.

Mucous degeneration is also sometimes observed in chondromata, in which case the interstitial substance is liquefied into a mucinous fluid, with destruction of the cells, and cysts due to softening are formed.

Although the chondroma is a benign tumour it may not only occur in multiple form, but may also lead at times to the formation of metastases.

6. (v.) **Osteoma. Odontoma.**—Although a partial new-formation of bone may take place in various tumours, those only are entitled *osteomata* which consist entirely of osseous tissue. Osteomata are divided into *compact* and *spongy* according as they correspond in structure to compact or spongy bone. The bony tissue is either developed from

osteoblasts or formed by metaplasia from an already existing tissue of the connective group.

Osteomata are benign tumours, but may be multiple.

Those tumours on the teeth which consist of odontoid tissue, and develop from the pulp during the period when the teeth are forming, are named *odontomata*, but if they occur at a later period, *odontinoid* tumours. In the latter case they may be composed of enamel, dentine, cement, or of a combination of these substances.

7. (vi.) **Myoma.**—*Myomata* consist principally of smooth or striated muscle, being spoken of in the first case as *leiomyomata*, in the second as *rhabdomyomata*.

In the leiomyomata, which occur most frequently in the uterus or the intestine, the smooth muscular fibres always form bundles which cross each other in different directions and are separated by thinner or thicker layers of a fibrillary connective tissue in which the vessels run; so that in sections the muscular bundles will be found cut not only lengthwise, but also obliquely and transversely (Fig. 157).

Muscular fibres differ from connective tissue in their regularity and compact grouping into bundles—which hence will always be richer in nuclei than bundles of connective tissue of the same thickness—and in their long rod-like nuclei.

Those leiomyomata which are rich in connective tissue, as for example uterine myomata, are entitled *fibro-myomata*. *Calcification* and *softening* are the forms of metamorphosis most frequently observed.

Rhabdomyomata are very uncommon. They either consist exclusively of striped muscle, as in the case of the congenital myomata of the heart, or are really of the nature of sarcomata in which striated muscle fibres or transversely striped spindle cells (young muscle fibres) are present, as in certain tumours of the kidneys and testicles.

8. (vii.) **Glioma.**—Under the name *glioma* are comprised those tumours of the brain, spinal cord, and retina which consist of a tissue similar to neuroglia; that is, of cells in greater or smaller numbers embedded in an interstitial substance of extremely fine fibres, the former appearing in sections of hardened objects almost like naked nuclei, whereas in fresh preparations, especially when made by maceration and needling, they are seen to be cells with numerous fine processes. Sometimes, in addition to neuroglia, nerve fibres (Fig. 174, *c*) and ganglion cells are also found, and we may then speak of a *ganglionic neuroglioma*. Many authorities class the glioma amongst the sarcomata under the title of *glio-sarcoma* or *round-celled sarcoma*.

9. (viii.) **Neuroma.**—True *neuromata* are tumours consisting of nervous tissue (nerve fibres and ganglion cells). If the nerve fibres are medullated

we speak of a *myelinic* neuroma; if not, of an *amyelinic* neuroma; and if ganglion cells as well as nerve fibres are present, of a *ganglionic* neuroma (Fig. 27).

FIG. 27.—GANGLIONIC NEUROMA OF THE SUPRARENAL CAPSULE. × 110. (Stained with alum cochineal.) *a*, Medullary substance of the suprarenal capsule; *b*, Non-medullated nerve fibres of the neuroma; *c*, Accumulation of round cells; *d*, Polynuclear ganglion cell.

With the neuromata are, however, often included also such tumours occurring on the nerves as have been formed by growth of the connective tissue of the latter (*neuro-fibroma*), and contain either no nerve fibres at all or no newly-developed ones, for which reason they are also called *false* neuromata. In their histological nature they are most frequently fibromata, less often myxomata, sarcomata, or lipomata.

The tissue of the fibromata either surrounds the affected nerves and nerve-bundles evenly on all sides, or pushes the latter apart; and the nerve fibres may thereby be gradually destroyed, or else may themselves take part to a certain extent in the growth.

Neuro-fibromata often occur as *multiple* tumours, either on the larger nerve-trunks or on quite fine branches, especially fine cutaneous nerves, in this case forming numerous tumours in the skin (*multiple fibroma of the skin, fibroma molluscum*), which show a tissue fairly rich in cells (Fig. 28). Some neuro-fibromata consist of cords with nodular thickenings and twined in a tendril-like manner, and these are called *plexiform* neuromata.

With regard to the so-called *amputation neuroma*, a tumour which sometimes forms in amputation stumps, it may be counted amongst

the true neuromata, inasmuch as it is composed of newly-formed nerve fibres, which are developed from the old axis-cylinders by a process of division, and grow into the cicatricial tissue on the surface left by the amputation.

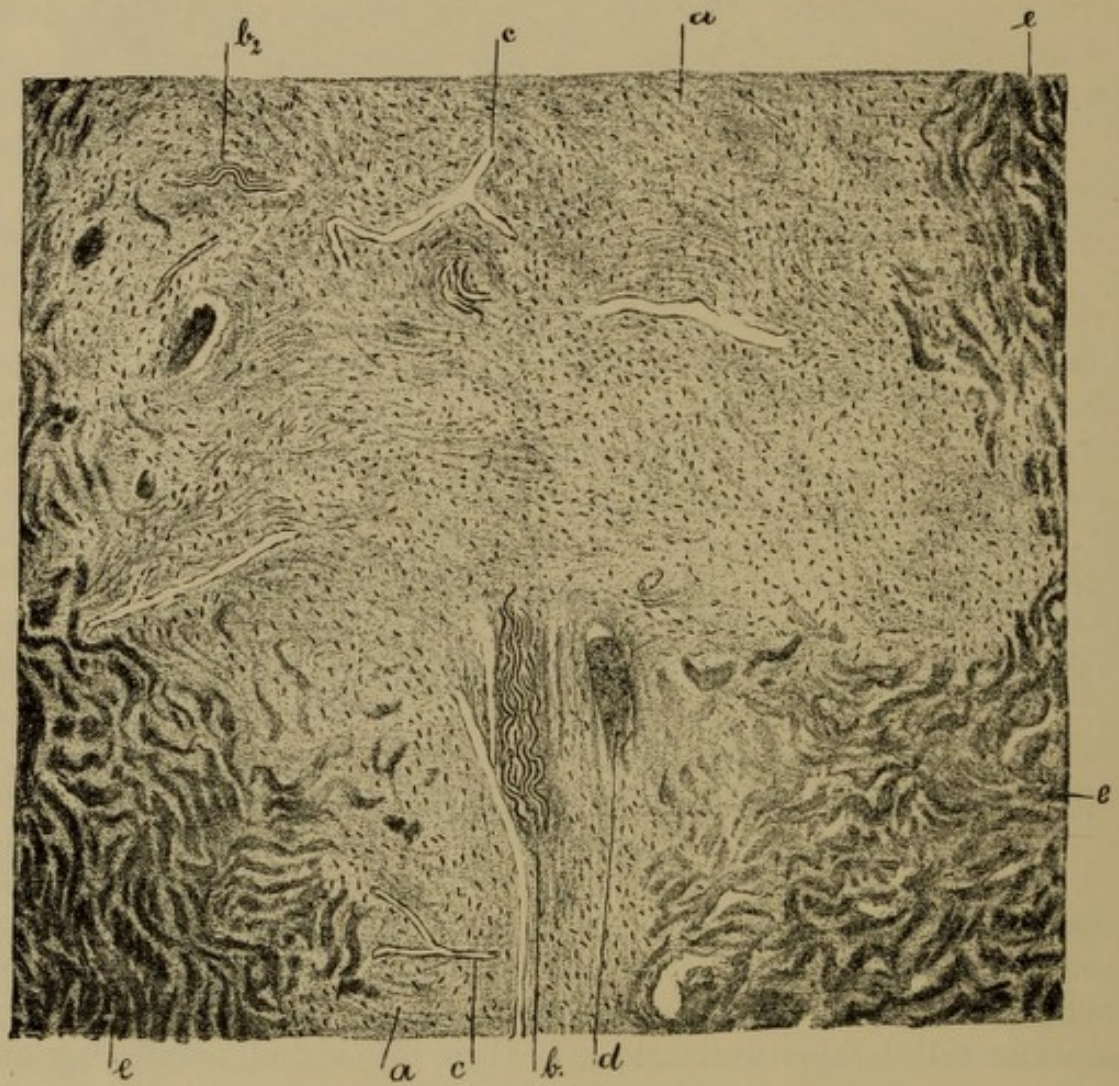

FIG. 28.—SMALL NEURO-FIBROMA OF THE SKIN. × 77. (Stained with Weigert's hæmatoxylin.) *a*, The tissue of the neuro-fibroma, containing spindle cells; b_1, Bundle of nerve-fibres in the pedicle of the neuro-fibroma; b_2, Atrophic bundle of nerve-fibres in the centre of the neuro-fibroma; *c*, Blood-vessels; *d*, Duct of a sweat gland; *e*, Connective-tissue bundles of the cutis.

10. (ix.) **Angioma.**—This form of tumour consists in great part of vessels or of a kind of tissue (cavernous tissue) nearly related thereto. According as the vessels and vascular cavities contain blood or lymph, we speak of a *hæmatangioma* or a *lymphangioma*.

A further distinction is made between *simple* and *cavernous* angiomata. The simple hæmatangioma or *teleangiectasis* is composed of very numerous capillaries and veins, which may present multiple circumscribed dilatations of globular, spindle, or cylindrical form, or may have a greatly thickened wall. The conditions present in *lymphangioma simplex* are similar.

The *cavernous angioma* is analogous in its structure to cavernous tissue, that of the corpus cavernosum urethræ for example, and consequently consists of numerous more or less closely-placed cavities, which are lined with endothelium, and separated from one another by connective tissue containing a larger or smaller number of cells (Figs. 29 and 30). The contents are blood (*hæmatangioma*) or lymph

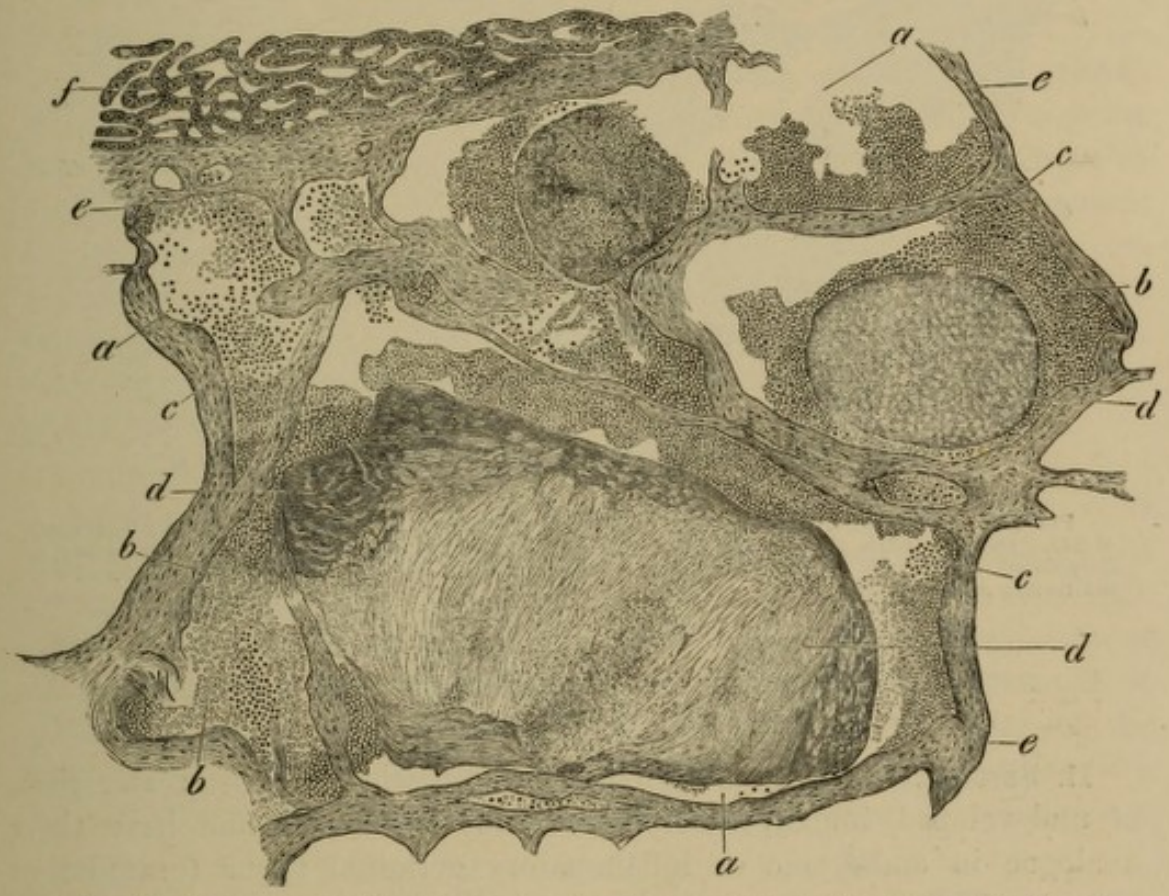

FIG. 29.—HÆMATANGIOMA CAVERNOSUM OF THE LIVER. × 77. (Stained with hæmatoxylin and eosin.) *a*, Cavernous spaces; *b*, Red corpuscles; *c*, White corpuscles; *d*, Fibrin; *e*, Fibrous septa; *f*, Liver tissue.

(*lymphangioma*), the latter of which appears in hardened preparations as a finely-granular mass containing a very scanty number of leucocytes (Fig. 30, *c*). If the contents consist of chyle, as for example in the angiomata which sometimes occur in the mesentery, we may speak of a *cavernous chylangioma*.

The common situation for angiomata is the skin or subcutaneous connective tissue, and they are very often congenital. Congenital teleangiectasis of the skin is also called *nævus vasculosus*.

A cavernous lymphangioma (exceptionally also hæmatangioma) of the tongue or lips respectively may be the cause of the congenital conditions known as *macroglossia* and *macrocheilia*.

Cavernous angiomata are also observed in the internal organs; indeed they are tolerably frequent in the liver in old persons.

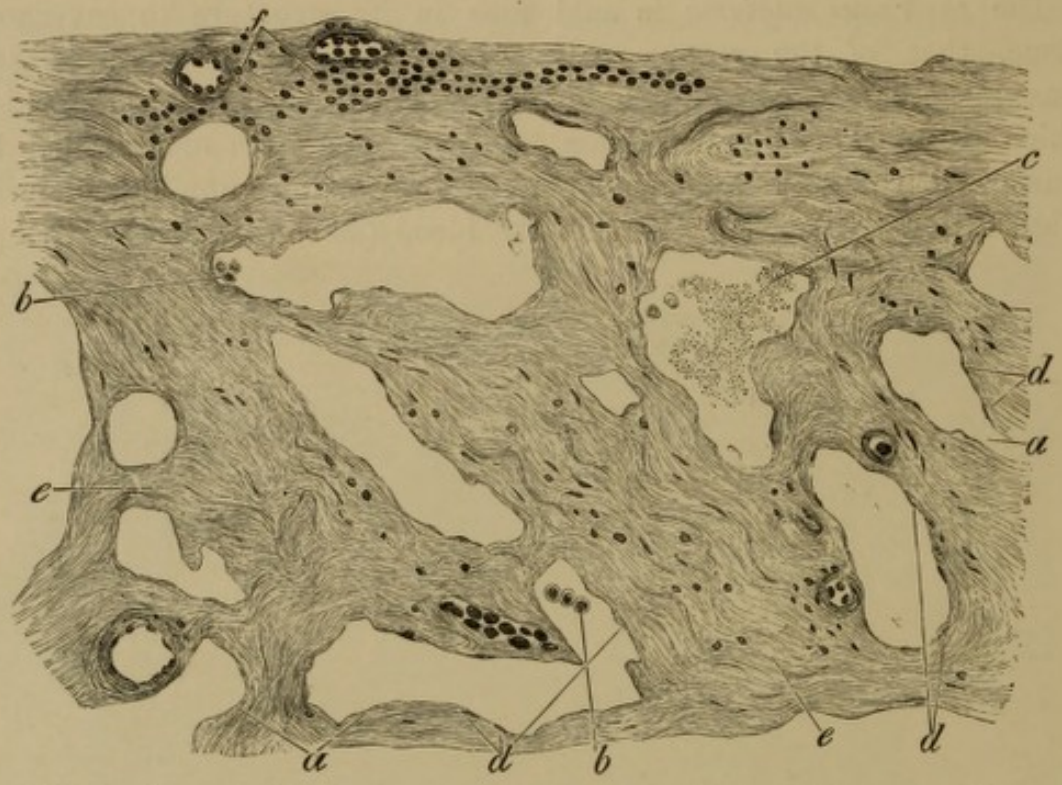

FIG. 30.—CAVERNOUS LYMPHANGIOMA IN THE SUBCUTANEOUS CONNECTIVE TISSUE OF THE FOREARM. × 240. (Stained with alum cochineal.) *a*, Cavernous lymph-spaces; *b*, Lymph corpuscles; *c*, Coagulated lymph; *d*, Endothelial cells; *e*, Stroma with round and spindle cells; *f*, Small-cell infiltration round the vessels.

B. TUMOURS COMPOSED OF IMMATURE CONNECTIVE TISSUE—SARCOMATA.

11. Sarcomata are tumours which consist, wholly or in greater part, of undeveloped, immature forms of connective tissue, and have their analogue in embryonic or inflammatory germinal tissue (granulation tissue). They never occur except in a tissue of the connective group, and they form by proliferation of its fixed cells. Although, speaking generally, they are always highly cellular tumours, still the number of the cells may vary as well as their form and size, and so, moreover, may the quantity and nature of the intercellular substance also; and we consequently distinguish species of sarcomata corresponding to these variations.

If the intercellular substance is very sparsely developed it is of a soft or fluid consistence, and appears formless or at most finely reticulated; but when it is present in larger quantity, it approximates in appearance to mature connective tissue, and may, when still more strongly developed, even become more or less distinctly fibrillated.

In some sarcomata a portion of the tissue may develop from its immature state into a fully formed tissue of the connective group, cartilage or bone, for example, in which case we speak of a *chondro-sarcoma* or an *osteo-sarcoma* respectively.

The proportion of blood-vessels in the tumours is variable, some sarcomata, however, being distinguished by a particular abundance of vessels, which are occasionally of very large diameter (*angio-sarcoma*). The walls of the vessels are usually of great delicacy, being sometimes so thin that they can scarcely be distinguished from the surrounding masses of cells.

Retrograde transformations, such as fatty degeneration, caseation, liquefaction, and ulceration, very often take place in sarcomata.

The smaller and more numerous the cells, the quicker is the growth of sarcomata, and the greater their malignancy, and in such tumours many karyokinetic figures are also found. Sarcomata never behave in an indifferent manner to their surroundings, as do the benign tumours; the adjoining connective tissue is always in a state of cellular infiltration, so that no sharp line of demarcation can be drawn microscopically, even when such appears to the naked eye to exist. The *metastatic* dissemination of sarcomata usually takes place by way of the blood-vessels.

The following *varieties* of sarcoma may be distinguished:—

12. (i.) **The Round-Celled Sarcoma.**—This consists of round cells with very little interstitial substance, and has its representative in the youngest stage of granulation tissue. The cells are commonly small, about the size of leucocytes (Fig. 39, *a*), have a very scanty amount of protoplasm and a relatively large round or oval vesicular nucleus. (Owing to the slight development and fragility of the body of the cell, often nothing is seen but naked nuclei when fresh pieces of a tumour of this kind are torn up.) The intercellular substance is so

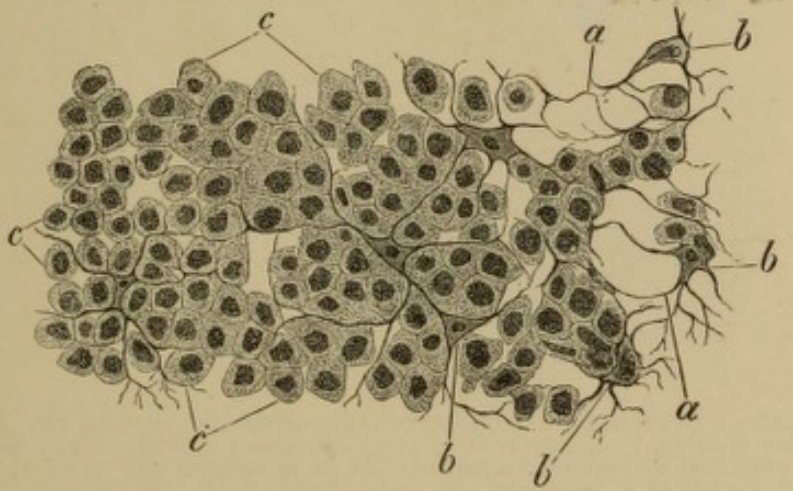

FIG. 31.—METASTATIC LARGE ROUND-CELLED SARCOMA OF THE RIBS. × 545. (Stained with alum cochineal.) *a*, Reticulum; *b*, Stellate cells of reticulum; *c*, Sarcoma cells, round, or flattened where they come in contact.

scanty that pencilling or shaking is often necessary before it becomes visible, and it is formless, finely fibrous, or reticulated (Fig. 31, *a*).

When the reticulum resembles the supporting substance of lymphatic glands, which often happens in round-celled sarcomata of such glands and of the adenoid tissue of mucous membranes, we may also speak of a *lympho-sarcoma.*

In some round-celled sarcomata the cells are perceptibly larger than leucocytes, and their nuclei strikingly large and vesicular. In such a case the sarcoma may be described as a *large round-celled sarcoma* (Fig. 31). The round-celled sarcomata are very soft and juicy owing to their richness in cells, and are likewise very malignant.

13. (ii.) **The Spindle-Celled Sarcoma.**—To this species belong those sarcomata which consist of cells of elongated form, and have their representative in the second stage of granulation tissue. The cells are either purely spindle-shaped, or broader and irregular, or provided with several processes which give them a club-shaped, pyramidal, or stellate form. Here, again, small-celled and large-celled forms are distinguished.

When the cells are purely spindle-shaped they form, in a manner analogous to the smooth muscle-fibres of the myomata and fibro-myomata, bundles of fibres which interlace in all possible directions,

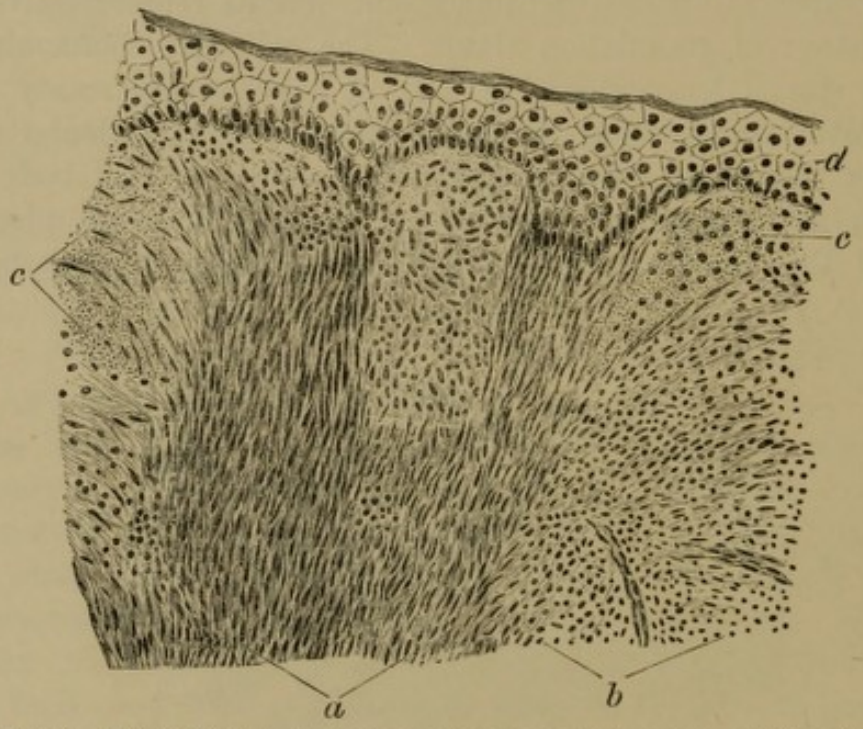

FIG. 32.—SPINDLE-CELLED SARCOMA OF THE SKIN OF THE ABDOMEN. × 240. (Stained with alum cochineal.) *a*, Bundle of spindle cells, seen longitudinally; *b*, Bundle of spindle cells, seen transversely; *c*, Sarcomatous tissue merging into the cutis; cellular growth in the latter; *d*, Epidermis.

but inside of which the cells themselves run parallel to one another (Fig. 32, *a* and *b*). The interstitial substance in spindle-celled sarcomata is extremely scanty and structureless, and in sections often cannot be seen at all. When, however, it is more strongly developed

and fibrillated the tumour is named a *fibro-sarcoma*, which forms the transition stage to fibroma, and recalls the appearance of young

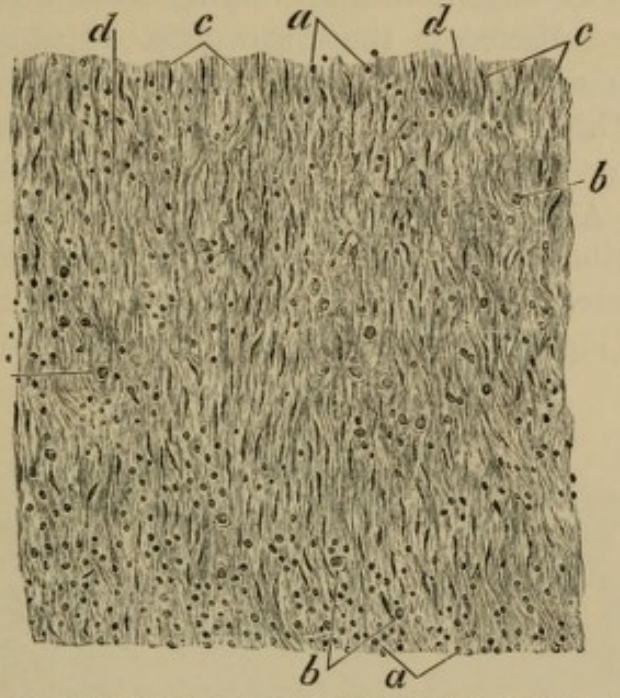

FIG. 33.—FIBRO-SARCOMA OF THE GUM (EPULIS). × 285. (Stained with alum cochineal.) *a*, Small round cells; *b*, Larger round cells; *c*, Spindle cells; *d*, Fibrillated ground substance.

cicatricial tissue. Fibro-sarcomata may also contain round as well as spindle cells (Fig. 33).

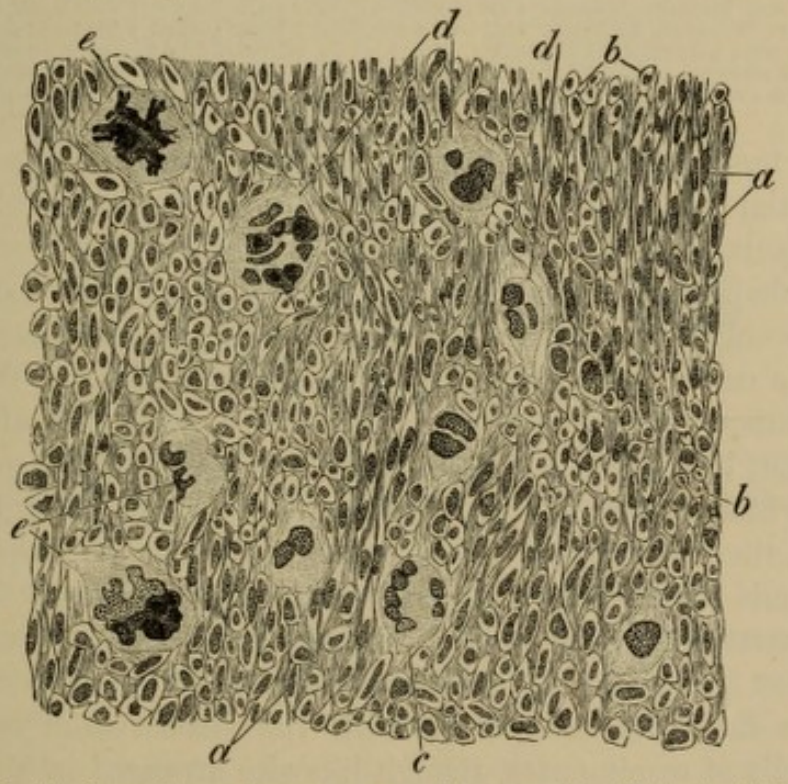

FIG. 34.—GIANT-CELLED SARCOMA OF THE TIBIA. × 285. (Stained with hæmatoxylin and eosin.) *a*, Large spindle cells, seen longitudinally; *b*, Large spindle cells, seen transversely; *c*, Giant cell with nuclei placed at the margin; *d*, Giant cell with centrally arranged nuclei; *e*, Giant cells with branched or lobulated nuclei.

In some spindle-celled sarcomata, especially those which start from the periosteum or medulla of bones, there are found *giant cells*, that is, cells of remarkably large size and varying form which have several nuclei, generally collected in the centre (Fig. 34, *d*, and Fig. 133, *b*). These cells have sometimes peculiarly lobulated or fragmented nuclei (Fig. 34, *e*). This variety of sarcoma is known as the *giant-celled sarcoma*.

14. (iii.) **The Alveolar Sarcoma.**—In this variety the cells are not evenly distributed, but are arranged in groups of different sizes, separated from each other by narrow or broad fibrous septa, in which the vessels run (Fig. 35, *A*). The cells themselves (*a*) are fairly large,

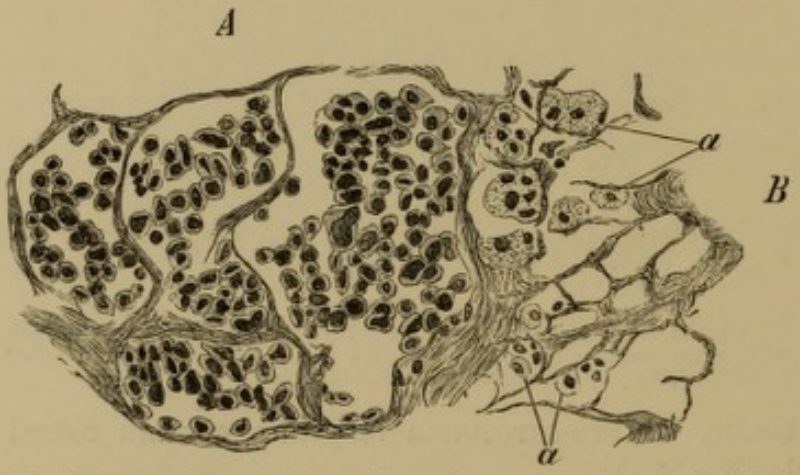

FIG. 35.—ALVEOLAR SARCOMA OF THE FASCIA ILIACA. × 285. (Stained with hæmatoxylin and eosin.) *A*, Large alveoli with sarcoma cells, between which the stroma-fibres are, however, no longer visible, as they have been removed by the pencilling, together with a portion of the cells; *B*, Alveoli in which the processes of stroma still remained after pencilling, so that the large spaces are divided up into many small compartments; *a*, Single sarcoma cells which have remained in position after the pencilling.

round, or more irregular, flat or polygonal, and have a relatively large vesicular nucleus. They thus recall the appearance of epithelial or cancer cells, and as their arrangement is alveolar, and small round or spindle-shaped cells may lie in the stroma, there often exists a very strong resemblance to cancer—indeed, some authorities consider this form to be a carcinoma, or name it *connective-tissue cancer*. When, however, the tumour is more thoroughly examined, especially after careful pencilling out of the sections, it is observed that in the alveoli between the cells, which previously appeared to lie in immediate contact with each other, there commonly stretch also delicate fibrous septa, so that the large and apparently simple alveoli are broken up into many small compartments, each of which affords room but for one or two cells at most (Fig. 35, *B*); and the cells in general are seen to be much more intimately connected with the stroma than is the case with the cells of carcinomata, though likewise arranged in alveoli.

15. (iv.) **The Endothelial Sarcoma or Endothelioma.**—Even in spindle-celled and alveolar sarcomata there are many cells which, by their

flattened shape, recall those of endothelium; and some authors have regarded the spindle cells as endothelial cells lying on their edges, and hence have described the spindle-celled variety as *endothelial sarcoma*. Disregarding these, however, there are still sarcomata in which the cells not only have a form which strongly reminds one of endothelial cells, but have also been developed by proliferation of the latter, especially those of the endothelium of lymphatics. In the latter case they form cylindrical anastomosing columns of cells embedded in connective tissue, which show their origin from lymphatic vessels not only by their configuration but frequently also by the presence of a lumen in the centre of the column (Fig. 36). When, however,

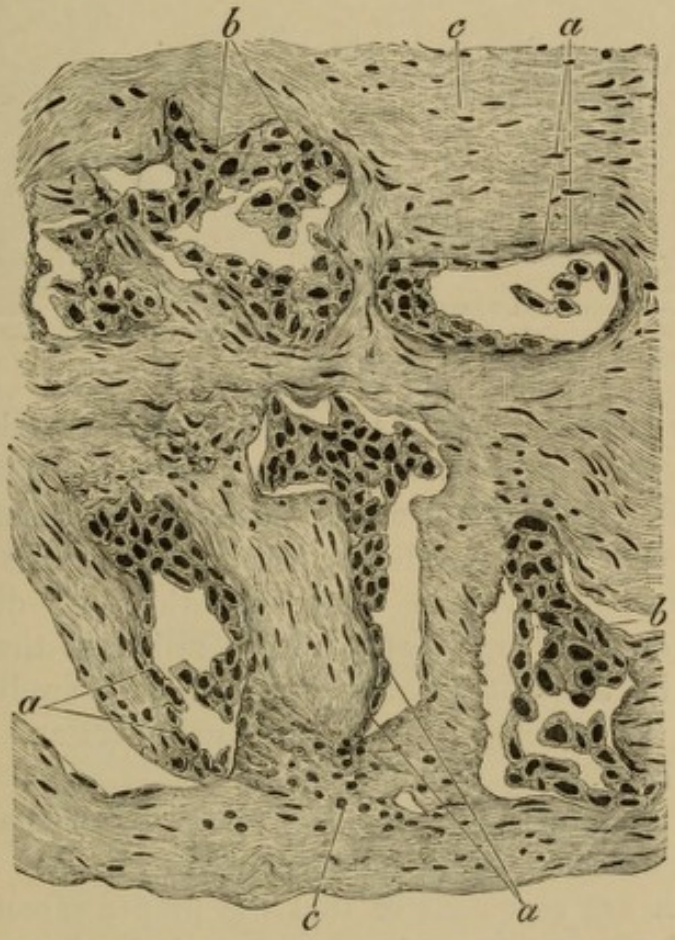

FIG. 36.—ALVEOLAR ENDOTHELIAL SARCOMA OF THE PLEURA, STARTING FROM THE ENDOTHELIUM OF THE LYMPHATICS. × 285. (Stained with alum cochineal.) *a*, Endothelioid sarcoma cells, seen laterally; *b*, Sarcoma cells, seen on the flat; *c*, Connective-tissue stroma.

the lumen is absent, and when the columns of cells appear in the sections cut for the most part transversely and consequently rounded, a great resemblance to carcinoma may arise.

In many sarcomata of the meninges and brain the endothelioid cells combine to form globular concentrically-laminated structures (Fig. 37, *a*). Should a deposition of lime salts then take place in these, so that concretions resembling brain sand

(*b*) are formed, they are spoken of as *psammomata* or *psammo-sarcomata.*

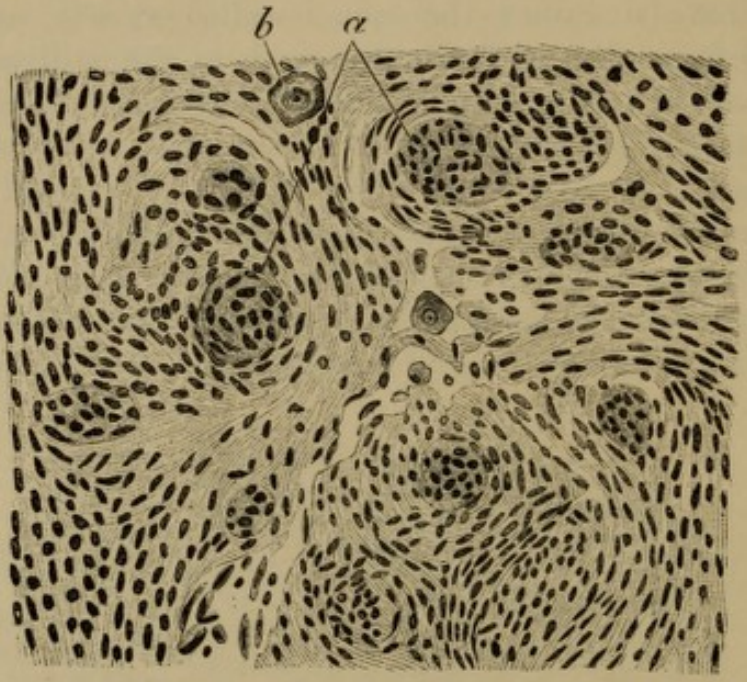

FIG. 37.—ENDOTHELIAL SARCOMA OF THE DURA MATER. × 240. (Stained with hæmatoxylin and eosin.) *a*, Concentrically stratified endothelial cells; *b*, Concentrically stratified concretions.

16. (v.) **The Angio-sarcoma.**—All those sarcomata which are very rich in blood-vessels may be described as *angio-sarcomata.* In them the sarcomatous tissue often comes into more intimate connection with the blood-vessels, enveloping their lumen like a coat. In other cases the blood-vessels show dilatations of different forms (*teleangiectatic sarcoma*) or a *hyaline* degeneration of their walls (Fig. 38, *b*); and in the latter the vessel-wall may swell to the total obliteration of the lumen, so that hyaline cylinders and bulbs are left (*cylindroma*,[1] Fig. 38, *c*).

When, as is often apt to be the case, the walls of the blood-vessels are very delicate, hæmorrhages may readily occur (Fig. 39, *c*), and in many sarcomata are so extensive that the proper sarcomatous tissue, especially in larger tumours, is almost entirely destroyed by them (*fungus hæmatodes*).

17. (vi.) **The Melanotic Sarcoma and the Chloroma.**—The former is a sarcoma in which a portion of the cells, *i.e.*, always the older and larger ones, contains brown or black pigment (Fig. 40); but as regards the *form* of the cells, the tumour may be a round-celled, a spindle-celled, or an alveolar sarcoma. These tumours always take origin from pigmented tissues (skin, choroid, pia mater), and are very malignant.

[1] It is doubtful, however, whether the species of tumour which has been and is understood under this designation is in all cases one and the same.

The name *chloroma* is given to green-coloured tumours having the structure of the round-celled sarcoma. The colour is due to small granules lying in the cells, which give the reaction of fat.

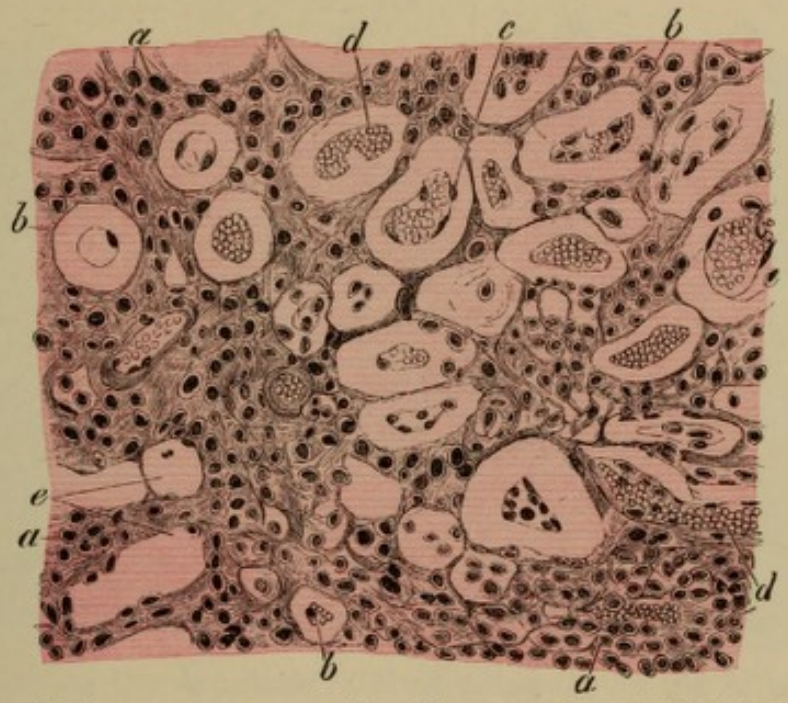

FIG. 38.—ANGIO-SARCOMA OF THE DURA MATER WITH HYALINE DEGENERATION OF THE VESSELS. × 240. (Stained with hæmatoxylin and eosin.) *a*, Sarcoma cells; *b*, Blood-vessels with hyaline-degenerated walls, cut transversely; *c*, Endothelium of intima; *d*, Red corpuscles; *e*, Hyaline-degenerated and obliterated blood-vessels, cut longitudinally and transversely.

18. (vii.) **The Mixed Sarcoma.**—By this designation is meant not so much combinations between the varieties of sarcoma already dealt

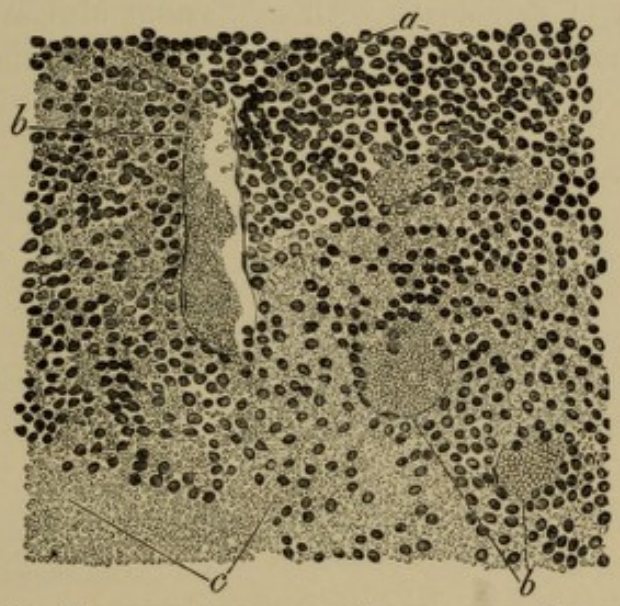

FIG. 39.—METASTATIC HÆMORRHAGIC ANGIO-SARCOMA (FUNGUS HÆMATODES) OF THE LUNG. × 240. (Stained with hæmatoxylin and eosin.) *a*, Round cells; *b*, Blood-vessels; *c*, Extravasated blood.

with, as the association of pure sarcomatous tissue with a mature tissue of the connective group, of which the combinations with cartilage

and with bone (*chondro-sarcoma* and *osteo-sarcoma*) are the most frequent. This mixture may be explained either on the assumption that a portion of the tissue in an already existing sarcoma has not remained

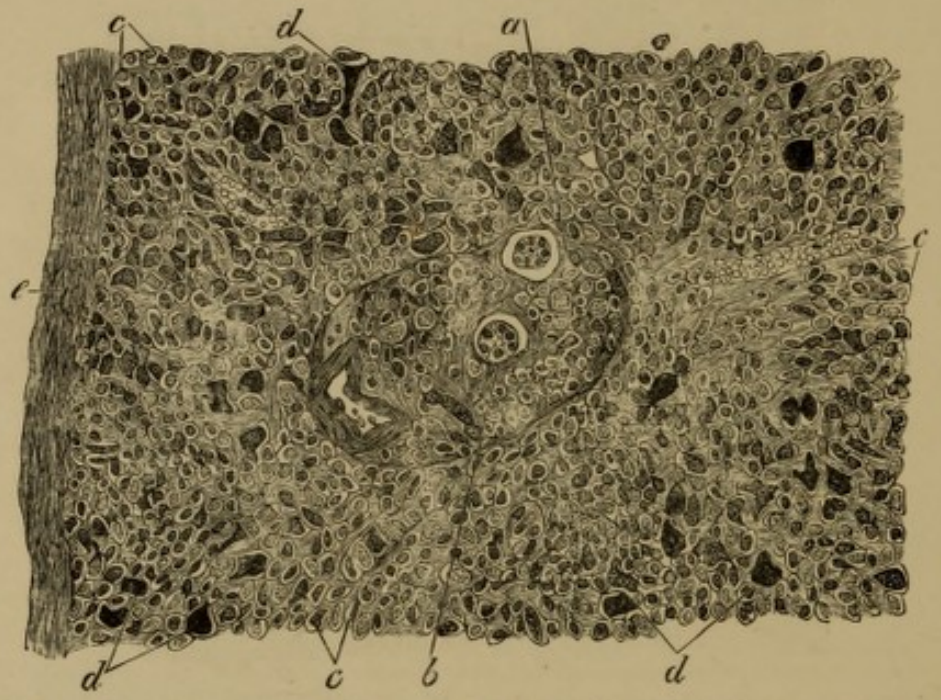

FIG. 40.—DIFFUSE METASTATIC LARGE-CELLED PIGMENTARY SARCOMA OF THE LIVER. × 240. (Stained with alum cochineal.) *a*, Capsule of Glisson, with sarcoma cells mostly free from pigment; *b*, Bile duct; *c*, Non-pigmented sarcoma cells; *d*, Pigmented sarcoma cells; *e*, Capsule of liver.

in its lower stage but has undergone further development, or that a tumour composed of a mature tissue has become sarcomatous.

Combinations of sarcomata with *adenomata* also are met with, but since in them the adenomatous tissue always retains the preponderance, it is intended to postpone mention of them until describing the adenomata.

CHAPTER IV.

TUMOURS OR NEW-FORMATIONS—(CONTINUED.)

II. EPITHELIAL TUMOURS.

1. In **Epithelial Tumours** the principal constituent is formed by the epithelial elements, but they also contain connective tissue with blood-vessels in addition. According as the epithelial elements show a *typical* or *atypical* arrangement we distinguish respectively *adenomata* and *cystomata* on the one hand, and *carcinomata* on the other.

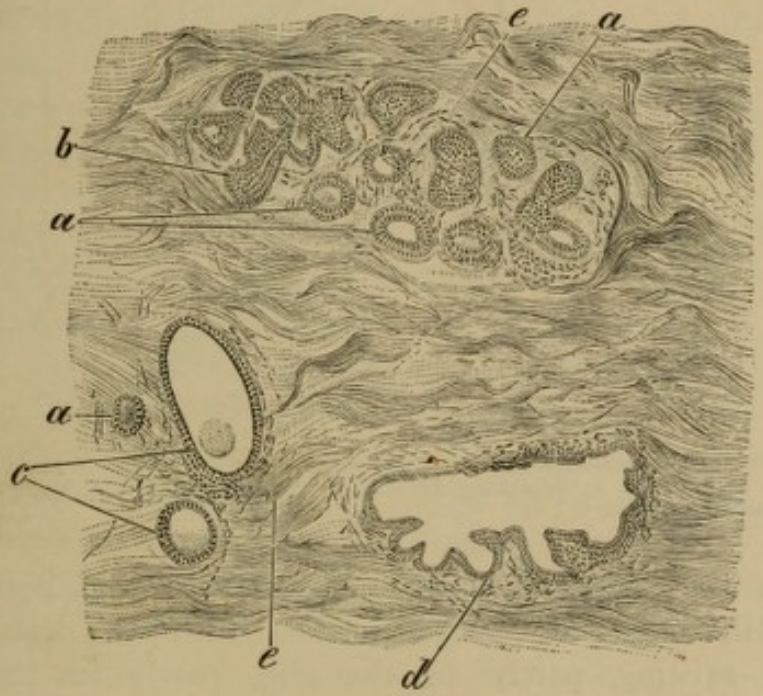

FIG. 41.—CYSTO-ADENO-FIBROMA OF THE MAMMA (ACINOUS FORM). × 77. (Stained with alum cochineal.) *a*, Acini, partly empty; *b*, Branched tubule; *c*, Smaller and larger cysts; *d*, Cysts with papillary elevations of the walls; *e*, Connective tissue.

In addition to these it is also intended to treat *papillomata* and *polypi* amongst the epithelial tumours, as although they approximate to the hyperplastic growths, they still in outward form present more the appearance of tumours.

2. (i.) **Adenoma.**—By this name are understood tumours which copy the type of physiological glandular tissue with a certain degree of exactitude, but without assuming its functions. Two groups may be distinguished amongst them, corresponding to the two principal forms of normal glandular tissue, viz., that of *acinous* and that of *tubular* adenomata.

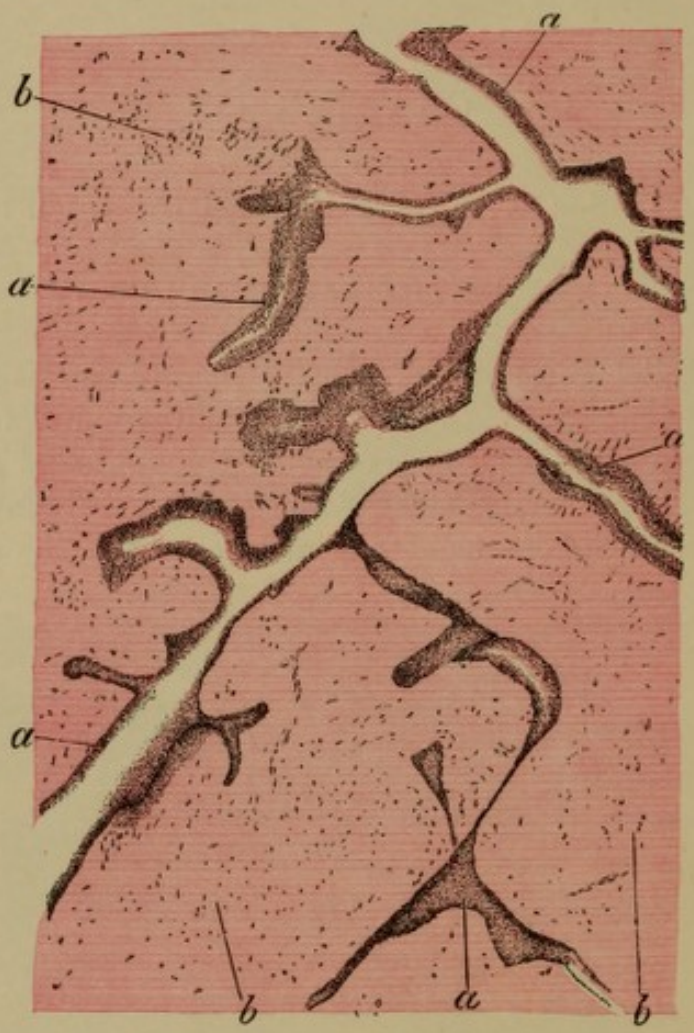

FIG. 42.—ADENO-MYXO-FIBRO-SARCOMA OF THE MAMMA. × 65. (Stained with alum cochineal.) *a*, Branching fissure-like glandular cavity; *b*, Myxo-fibro-sarcomatous tissue.

Although the adenoma imitates the structure of normal glands, there is still no exact correspondence with the latter, certain divergences existing, partly in the size, partly in the form or arrangement, of the epithelial cells. Adenomata occur not only in glandular organs, but on mucous membranes.

Their line of division from the simple glandular hyperplasiæ is not a sharp one, whilst on the other hand again they may be confounded with certain carcinomata, the so-called *glandular carcinomata.* As regards the latter, however, the regular arrangement of the epithelial cells, and the sharp delimitation of the adenoma from the tissue in

its neighbourhood, form important marks of distinction from carcinoma.

The adenomata are frequently *compound tumours* (Fig. 41); that is to say, the accumulation of secretion in them leads to dilatation of one or more glandular cavities, the result being the formation of *cysts* (*c*)—*cysto-adenoma*. Papillary outgrowths (*d*) may further take place from the walls of these cysts, and may even end by filling the entire cavity (*papilliferous* or *proliferous cysto-adenoma*). Moreover, the connective tissue lying between the lobules of gland in the adenoma may become very prominent, and may be either poor (*e*) or rich in cells (*fibro-adenoma, adeno-fibroma*, or *adeno-fibro-sarcoma*, as the case may be). When this is the case the acini of the adenoma may be compressed by the growing interstitial tissue, and dragged apart with the formation of clefts (Fig. 42, *a*): or the interstitial tissue pushes into the glandular cavities in the form of papillary outgrowths (*intracanalicular adeno-fibroma*).

Lastly, with tumours of this kind, which occur most frequently in the mamma, a doubt may arise as to whether the case is really one of adenoma, or whether the tumours are not merely fibromata or fibro-sarcomata, as the case may be, which have developed in a gland, and hence included some of the components of the latter in their substance.

The adenoma is a benign tumour, which does not, as a rule, give rise to metastases, those sometimes observed appearing for the most part to have started from adeno-carcinomata.

3. (ii.) **Cystic Tumours.**—Although strictly speaking only the *cystomata*, that is to say, those cystic tumours which depend on a new formation of tissue, should be treated of in this place, still it will be advantageous also to consider those which are formed by accumulation of secretion in the follicles and ducts of glands—the so-called *retention cysts*—inasmuch as the two kinds do not in all cases admit of being sharply separated from one another. It is also intended to deal here with the *dermoid cysts* and with *cholesteatoma*.

(*a*) **Retention Cysts.**—These may be subdivided into *follicular cysts*, *mucous cysts*, and *cysts of the larger canals*.

To the *follicular cysts* belong *milium* and *atheroma* [or wen], the former of which is developed by accumulation of the secretion in the sebaceous glands themselves, the latter either by accumulation of sebum in the ducts of the sebaceous glands or the part of the hair-follicle corresponding to the opening of the duct (*superficial atheroma*), or else from persisting remains of the branchial clefts, and other epithelial structures occurring abnormally in the subcutaneous tissue (*subcutaneous atheroma*).

The contents of atheromatous cysts consist of desquamated epidermic scales, drops of fat, and cholestearin crystals; whilst in the wall (Fig. 43) there may be distinguished outside of all a thin fibrous layer

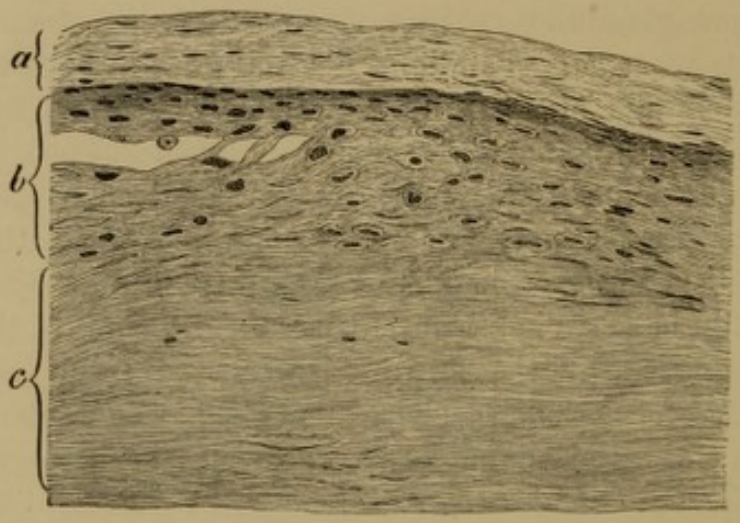

Fig. 43.—Vertical Section through the Wall of an Atheroma. × 285. (Stained with alum cochineal.) *a*, Fibrous portion of the wall; *b*, Flattened nucleated epithelial cells, seen partly in profile, partly on the flat; *c*, Flattened horny epithelial cells, devoid of nuclei.

(*a*), which is succeeded as we pass inwards by a thick stratum of greatly-flattened epithelial cells, only the outer layers of which still retain their nuclei. In the walls of subcutaneous atheromata hairs may also occur, and, on the other hand, papillary outgrowths (similar to those in papilliferous cystoma, p. 100) sometimes develop from their inner surface, and may even fill up the entire cavity.

In *mucous cysts* (Fig. 156, *a*), which are formed by retention of secretion in the glands of mucous membranes, the wall is very delicate, and bears an epithelium corresponding to the locality, but which subsequently becomes more and more flattened. The same is true also of those cysts which develop from the ducts of glands, and from embryonic canals which normally do not persist.

(*b*) **Dermoid Cysts.**—These are very closely related, so far as their origin is concerned, to the subcutaneous atheromata, differing from them only in that they depend on the nipping off during embryonic life of portions of the *entire* rudimentary skin. Their wall consequently shows a dermoid structure, being composed, that is, of epidermis and papillæ, and it sometimes also encloses hairs, sebaceous and sweat glands (Fig. 44), whilst even teeth set in a cartilaginous or bony basis may be met with. Should other tissues also be present, such as perhaps portions of skeleton or intestine and the like, we have an instance of *rudimentary double monstrosity (fœtus in fœtu)*. The pultaceous contents of dermoid cysts consist microscopically of

epithelial cells—fatty-degenerated for the most part—and crystals of fat and cholestearin.

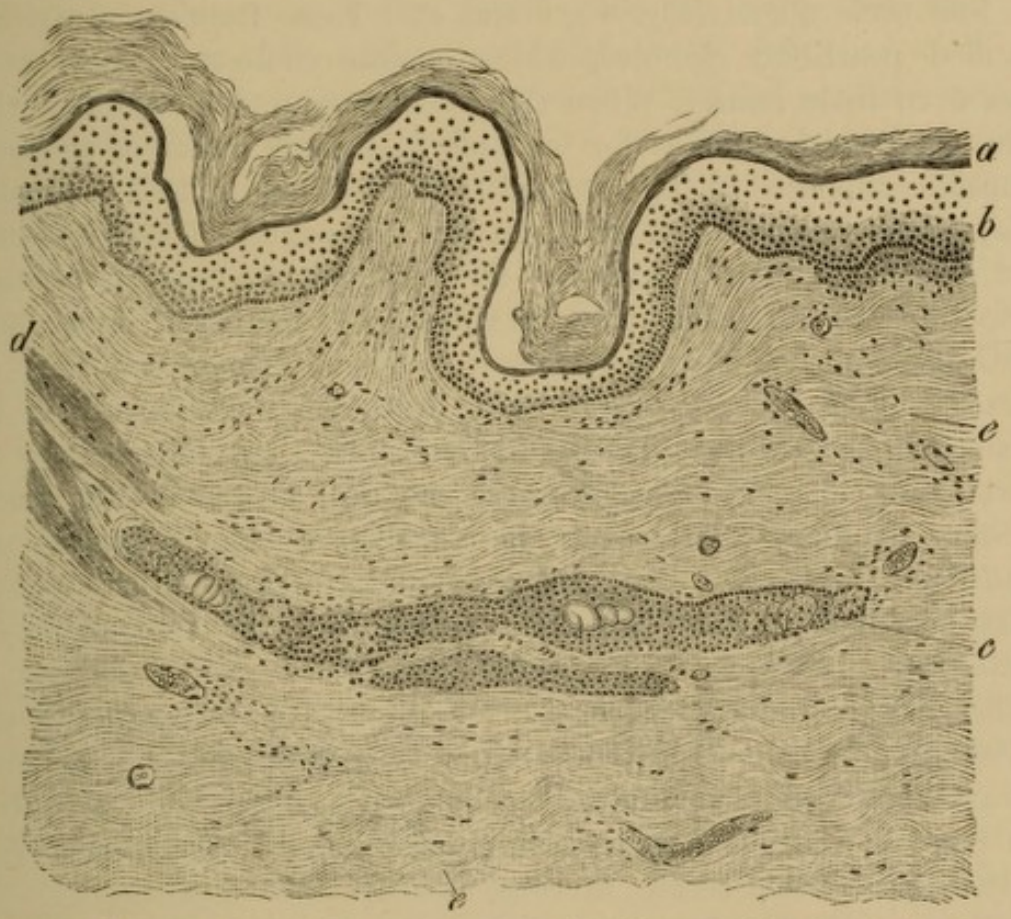

FIG. 44.—WALL OF A DERMOID CYST. × 95. (Stained with hæmatoxylin and eosin.) *a*, Stratum corneum: *b*, Rete Malpighii; *c*, Rudimentary sebaceous gland (?); *d*, Smooth muscular fibres (arrector pili?); *e*, Tissue like that of the cutis.

(*c*) **Cholesteatoma or Pearl Tumour.**—This resembles the atheromata in so far as it has a similar structure and frequently also a similar

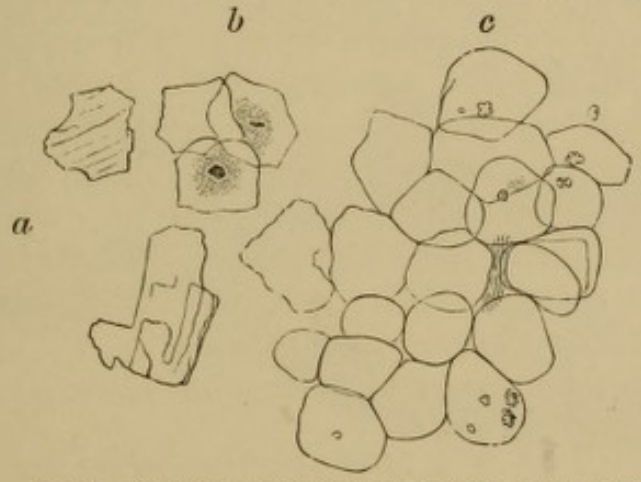

FIG. 45.—CHOLESTEARIN CRYSTALS AND CELLS FROM A CHOLESTEATOMA OF THE TYMPANIC CAVITY. × 240. (Fresh torn-up preparation.) *a*, Crystals; *b*, Nucleated cells; *c*, Non-nucleated cells.

mode of origin. It, too, consists of a delicate fibrous membrane, upon which first there rests frequently a layer of short cylindrical cells, but

this is succeeded by flat structures resembling horny epidermic cells, which at first are thick and nucleated, but later always become thinner and lose their nuclei (Fig. 45, *b* and *c*). These form concentrically-stratified pearl-like globules, which enclose cholestearin and sometimes even little hairs. When the tumour occurs in localities where there is no epithelium, as for example in the pia mater or the brain, it must be supposed to have started from misplaced epithelial germs.

(*d*) **Cystic Tumours of New Formation, Cystomata.**—These invariably start from glandular tissue, by the development first of a tissue resembling that of adenomata, in which a formation of cysts afterwards takes place—in which case the term *adeno-cystoma* may also be used,—or the process begins with cystic degeneration of the pre-existing cavities of the gland, which is only then followed by the growth of the tissue. According as the wall of the cyst is smooth or bears papillary excrescences it is called a *simple cystoma* or a *papilliferous* or *proliferous cystoma;* and further, either a *single* cavity may be present (*unilocular tumour*), or the tumour may be *multilocular*.

The wall of the cavity consists of fibrous connective tissue more or less rich in cells (Fig. 46, *a*), and is coated with a simple epithelium composed of cylindrical cells of varying height, frequently in a state of mucous degeneration (Fig. 46, *c*). The contents of the cavity may be either serous, mucous, or flocculent.

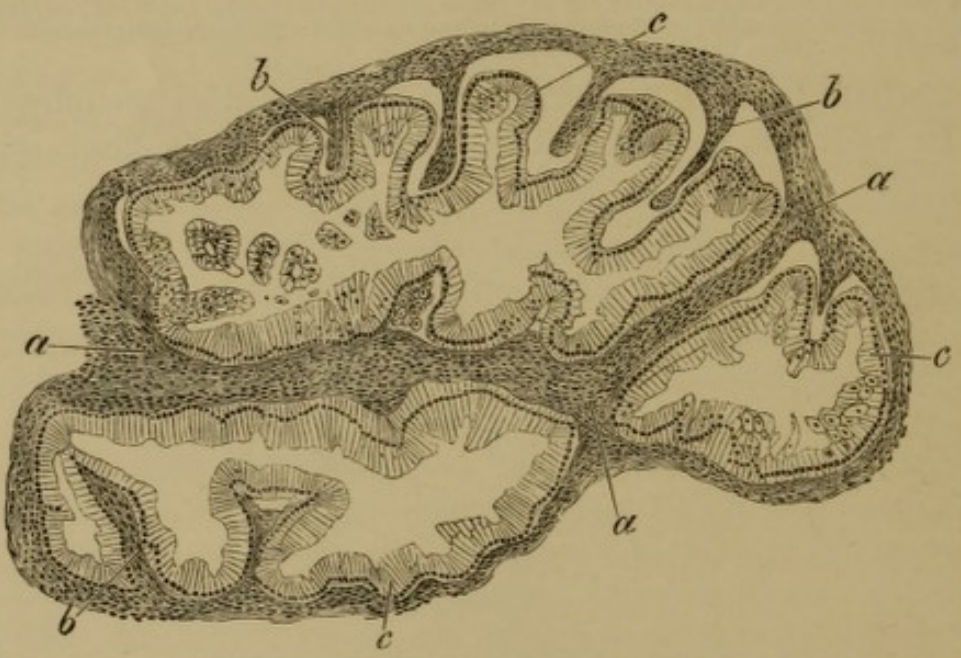

Fig. 46.—Cystoma Papilliferum Ovarii. × 77. (Stained with hæmatoxylin and eosin.) *a*, Connective-tissue wall of cysts; *b*, Papillary excrescences of the wall; *c*, Cylindrical epithelium with mucous degeneration.

In the *papilliferous cystoma* papillary outgrowths of varying length are found on the walls of some or all of the loculi (Fig. 46, *b*). They

consist merely of simple or branched invaginations of the wall, and sometimes fill up the entire cavity.

If the development of the papillæ becomes very luxuriant, and the latter are covered with several layers of epithelial cells, the tumour approximates to the adeno-carcinoma, and the papillary growths may then break through the wall of the cyst, the surface of the organ, or the investing membrane, and even lead to the formation of metastatic growths.

4. (iii.) **Carcinoma.**—*Carcinomata* constitute tumours in which the epithelial elements whereof they are chiefly composed deviate more or less in their arrangement from the type of normal epithelial tissue, that, namely, of superficial epithelium and of glands, and at the same time have a tendency to increase indefinitely. Carcinomata are formed by the proliferation of surface or glandular epithelium, and the infiltration thereby of the surrounding connective tissue, which then likewise begins to proliferate, so that a mutual interpenetration takes place.[1]

Thus every carcinoma has two constituents: the *cancer cells*, which are the proliferated epithelial cells, and the *stroma*, which contains the blood-vessels. The latter, as follows from the mutual interpenetration of epithelial cells and connective tissue, must show an alveolar arrangement (Fig. 50, *d*, and Fig. 51, *b*). In the alveoli the cancer cells, which again may be of different sizes, lie in immediate juxtaposition with one another—so close that even the boundaries of the cells may disappear—and without coming into any very intimate connection with the stroma (Figs. 50 and 51). This constitutes the difference between carcinoma and alveolar sarcoma (see page 90).

Even morphologically the cancer cells betray their origin as derivatives of epithelial elements, consisting as they do of large cells which always possess one or more large round or oval vesicular nuclei with large shining nucleoli. They may also, however, retain to a certain extent the form, arrangement, and other peculiarities of the cells from which they took their origin, so that, for example, when derived from cylinder epithelium they may retain the cylindrical form (Fig. 50, *b* and *c*, and Fig. 130, *h*), or when from cells of the epidermis, may preserve the spines or the tendency to cornification of the latter (Fig. 48), and so on. Usually this is not the case with all cancer cells, and since, in consequence of the rapidity of their growth, they mutually im-

[1] Every epithelial growth, however, which is atypical and penetrates deeply, (as may for example occur in the vicinity of ulcers or in chronic interstitial inflammations of glandular organs, owing to simultaneous proliferation of epithelial cells and glandular tissue), is not to be set down as a carcinoma. Such growths as the above always show a circumscribed increase, while carcinoma, on the contrary, does not.

pede and flatten each other, all possible forms may arise (Fig. 49, *b*), so that *polymorphism* is also a distinguishing characteristic of cancer cells.

The stroma may be of various degrees of development, and affects the consistence of the carcinoma accordingly, producing respectively *soft* [*encephaloid* or *medullary*] and *hard* [or *scirrhous*] cancers. From the cut surface of the *soft* carcinomata when fresh a milky fluid, the *cancer juice*, may be scraped, which contains cancer cells squeezed out of the alveoli. In the stroma itself there are more or less numerous cells, which are at once distinguished from the cancer cells by the smallness of their size, but apart from this may be round or elongated (Fig. 50, *d*, and Fig. 130, *i*), and are partly derivatives of the fixed cells and partly migrated leucocytes. The proportion of blood-vessels which the tumours contain is also variable.

Carcinomata can only develop *primarily* in localities where true epithelium is present. *Metastatic* growths form most frequently in the course of the lymph paths, less frequently in that of the blood-vessels, cancer cells which have pushed into the lumen of the vessel being swept away, until they are caught in narrower tracts of the latter or in the lymph sinuses of lymphatic glands, where they begin to grow. As therefore secondary carcinomata invariably develop only from cells detached from primary carcinomata, they will also show the structural peculiarities of the latter.

The carcinomata are never sharply demarcated off from their surroundings, and the connective tissue of the latter is, as in the case of sarcoma, always in a state of small-celled infiltration (Fig. 130, *a* and *d*).

Retrograde metamorphoses frequently occur, especially fatty degeneration, caseation, and mucous degeneration. If a carcinoma reaches the surface of the skin or mucous membrane in its growth, ulceration almost always takes place, the normal epithelium being displaced by the cancer cells, while the latter readily break down under the action of mechanical or chemical irritants. On the floor of such cancerous ulcers are found partly necrotic cancer tissue, partly pus corpuscles, the latter of which then make their way also into the alveoli of the cancer. The following *varieties* of carcinoma may be distinguished :—

(*a*) **The Flat-celled Epithelial Carcinoma, or Epithelioma.**—This occurs in the skin and in mucous membranes covered with compound squamous epithelium, and is formed by the broadening and elongation of the epithelial depressions of the skin or mucous membrane, in consequence of proliferation of their cells, these depressions penetrating more and more into the deeper parts and pushing out off-shoots which are then nipped off, and come to lie, separated from the parent structure, in the midst of the connective tissue of the cutis or mucous membrane (Fig. 47).

The epithelioma, therefore, consists of conical processes of cancer cells, variable in length and breadth, simple or ramified, and

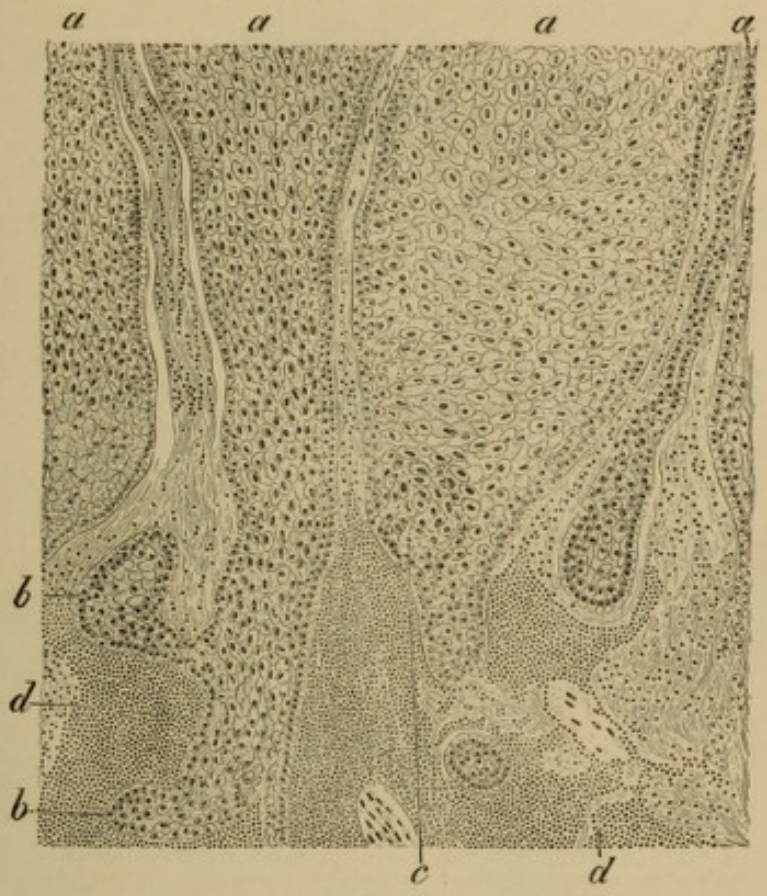

FIG. 47.—COMMENCING DEVELOPMENT OF AN EPITHELIAL CARCINOMA OF THE SKIN. × 70. (Hæmatoxylin and eosin.) *a*, Cone-like processes of the rete Malpighii, much elongated and partly widened also; *b*, Lateral shoots from a cone of epidermis; *c*, Epidermic globule; *d*, Cutis infiltrated with small cells (cancer stroma).

separated one from the other by a more or less cellular stroma in which the vessels run.

The cells composing these cones have retained to a greater or less extent the peculiarities of the epidermic cells, or of the epithelium covering the mucous membrane, as the case may be, and the outermost layer of the cones very often consists of cylindrical cells (Fig. 48, *a*), similar to those in the lowest stratum of the original epithelium. When the cones grow rapidly in width, the cells lying in the centre are compelled from want of space to take up a position on their edges, and then, ranging themselves concentrically about a few cells which have retained their rounded form, they become flattened, and finally cornify. In this manner are formed the so-called *pearls* (*epidermic or cancroid globules*), which even under a low power are differentiated from the surrounding parts by their yellowish colour (Fig. 48, *c*).

If lateral pressure be made upon the cut surface of a fresh epithelioma, white plugs resembling comedones are forced out, which consist of

the cancer-cell cones squeezed out from their places, and which appear drier the larger the number of cancer cells which have become horny.

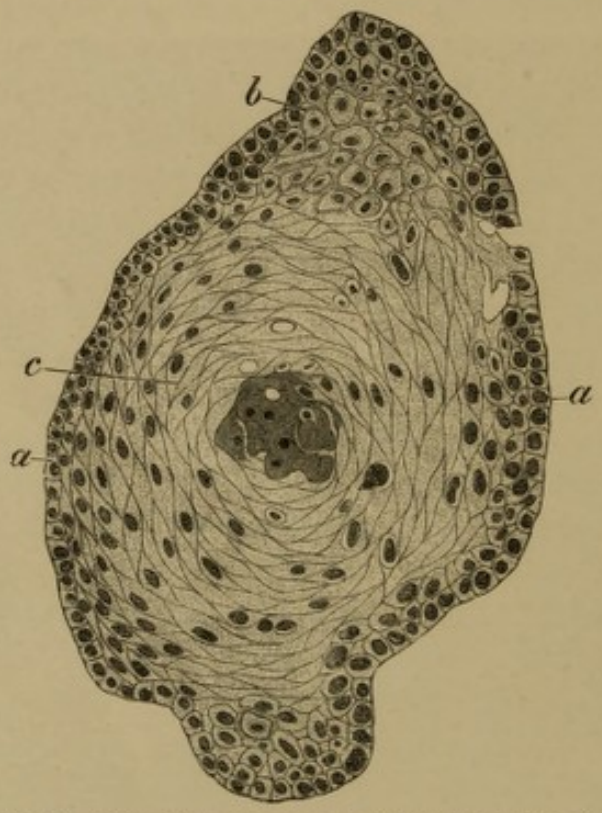

FIG. 48.—CONE OF CANCER-CELLS IN AN EPITHELIAL CARCINOMA. × 200. (Hæmatoxylin and eosin.) *a*, Short cylindrical cancer cells at the circumference of the cone; *b*, Spiny cells; *c*, Concentrically stratified epidermic globule.

In some epitheliomata (those occurring on the vaginal portion of the uterus and in the urinary bladder) the stroma grows out into vascular papillary structures, giving rise to the *villous or papillary carcinoma* (Fig. 49).

(*b*) **The Glandular Carcinoma or Adeno-Carcinoma.**—This occurs in mucous membranes covered with cylinder-celled epithelium and in true glands, and always begins as a growth of the glandular epithelium—in mucous membranes perhaps also of the surface epithelium—(Fig. 50, *a*), thus forming structures which at the beginning retain a certain resemblance to the glands from which they started, recalling the appearance of acini and tubules (Fig. 50, *b*; Fig. 130, *h*; and Fig. 159, *a*), but subsequently deviate more or less from their type, and which at the same time push unrestricted into the deeper parts. The cells in glandular cancer may also preserve to a certain degree the form of the parent-cells, and hence, for example, may be cylindrical in carcinomata of mucous membranes covered with cylindrical epithelium (Fig. 50), a form of carcinoma which is also entitled *cylinder-celled epithelioma.*

The resemblance between the groups of cancer cells and the acini

or tubules of glands is sometimes very great, especially in the younger portions of the tumour, so that the tumour may be taken for an

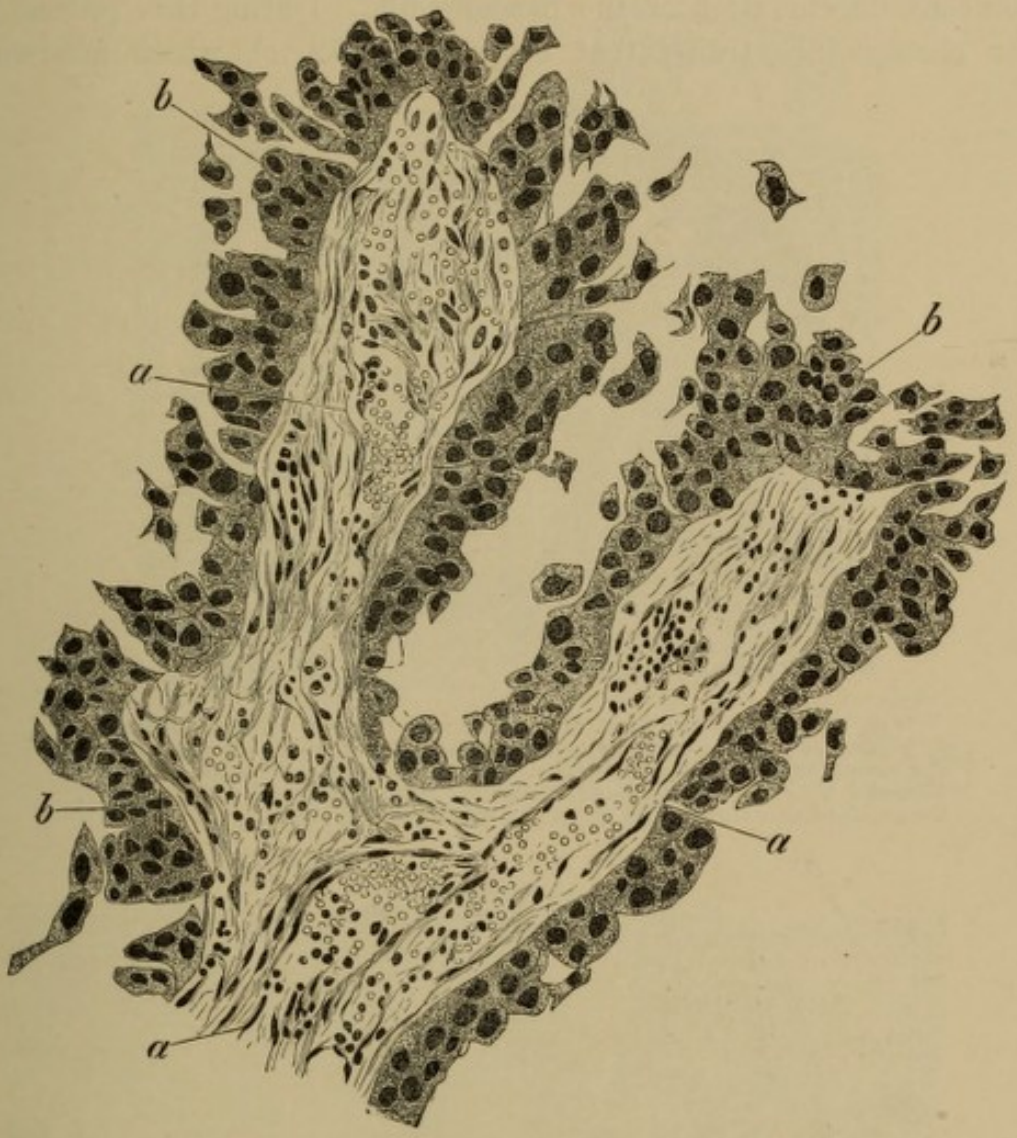

FIG. 49.—BRANCHING VILLUS-LIKE STRUCTURE FROM A VILLOUS CANCER OF THE BLADDER. × 545. (Hæmatoxylin and eosin.) *a*, Connective-tissue stroma of the villus, rich in vessels and cells; *b*, Polymorphous cancer cells, enveloping the villi in the form of a stratified epithelium.

adenoma; but mistake is guarded against by the circumstance that in addition to such groups of cells quite atypical groups may often be found—for example, alveoli which are quite full of cancer cells (Fig. 130, *g*)—or that these cells are growing into the neighbouring tissues, whereas the adenoma always remains sharply marked off from its surroundings, and may even be enveloped in a connective-tissue capsule.

A special variety of glandular carcinoma is the *scirrhus* (Fig. 51). We understand by this name a carcinoma in which the stroma is abundant, the alveoli narrow, and the cancer cells also frequently small. There commonly takes place in the centre of the tumour a fatty degeneration and absorption of the cancer cells, so that only the contracting stroma remains behind.

A further variety is the *gelatinous* or *colloid carcinoma*, which is observed most frequently in the stomach and intestine, and is formed by mucous degeneration of the cancer cells. During this process the latter change into transparent drops (Fig. 52, *c*), which afterwards

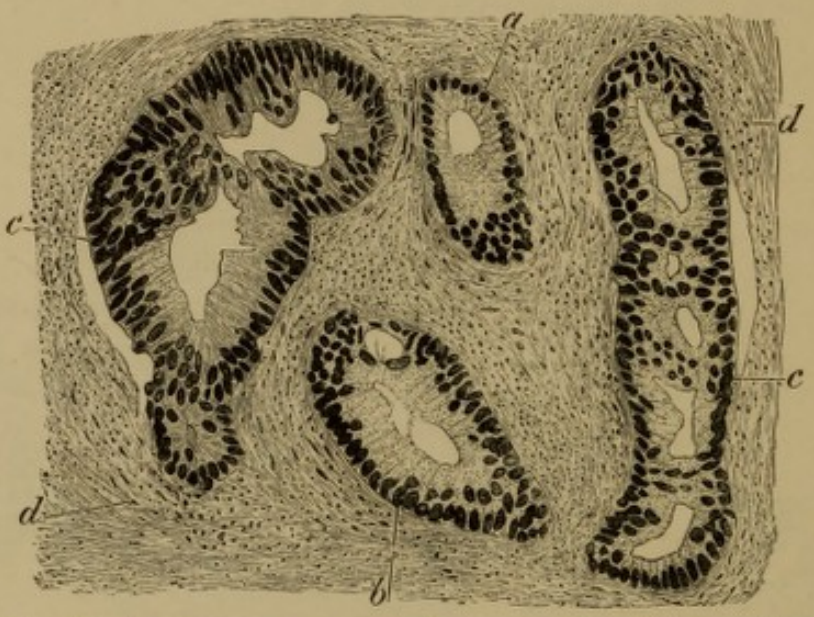

FIG. 50.—ADENO-CARCINOMA OF THE RECTUM. × 240. (Alum cochineal.) *a*, Normal Lieberkühn's glands, the epithelial cells of which are smaller than the cancer cells; *b*, Cancer-cell tube, deviating but little from the type of a Lieberkühn's gland; *c*, Cancer-cell tubes deviating further from this type; *d*, Connective-tissue stroma with round and spindle-shaped cells.

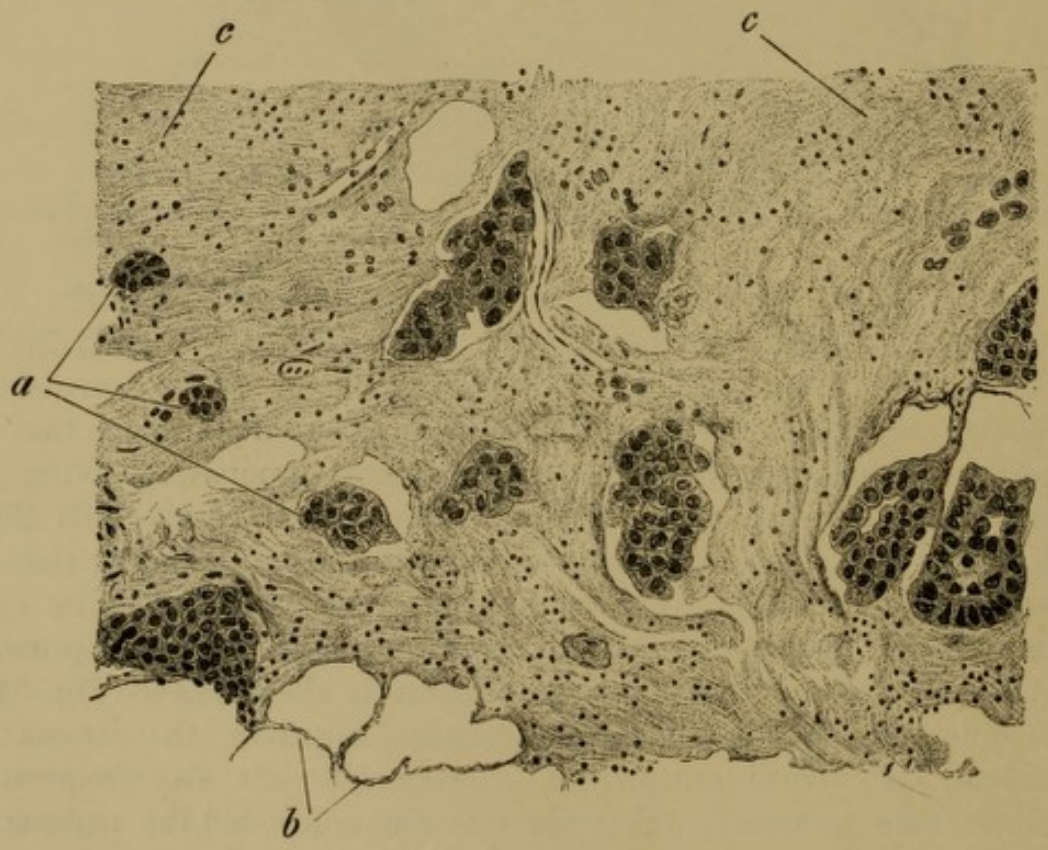

FIG. 51.—SCIRRHUS MAMMÆ. × 240. (Hæmatoxylin and eosin.) *a*, Small cancerous alveoli; *b*, Empty cancerous alveoli; *c*, Greatly developed connective-tissue stroma, partly permeated by round cells.

become confluent, until finally the entire alveolus is filled with a transparent gelatinous substance in which nothing is any longer to be

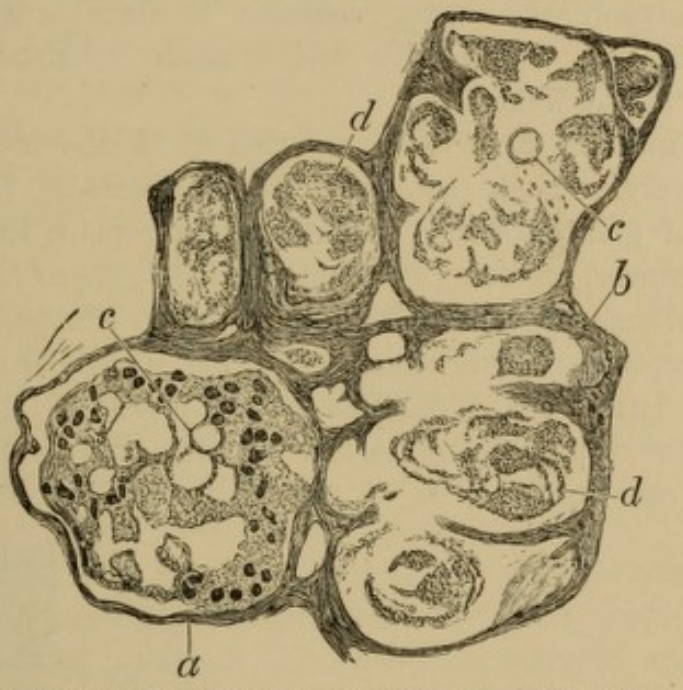

FIG. 52.—COLLOID CANCER OF THE GREAT OMENTUM. × 240. (Alum cochineal.) *a*, Alveoli with cancer cells, some of which are unaltered, others undergoing mucous degeneration; *b*, Groups of alveoli, in which the cancer cells, and partially also the septa, have undergone mucous degeneration; *c*, Cancer cells changed into transparent drops; *d*, Granular remnants of the protoplasm of the degenerated cancer cells.

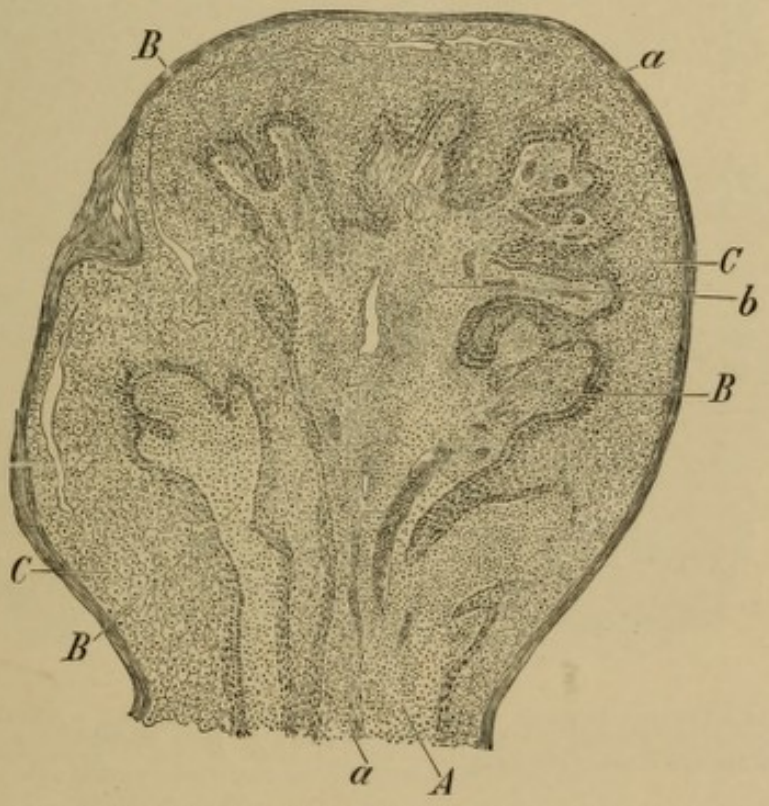

FIG. 53.—EXCRESCENCE OF A PAPILLOMA OF THE LABIA. × 65. (Alum cochineal.) *A*, Trunk of the papilla; *B*, Branches of the papilla; *C*, Stratified pavement epithelium of the papilla; *a*, Blood-vessels; *b*, Round cells in the connective tissue of the papilla.

seen of the cancer cells excepting here and there granular remnants of protoplasm (Fig. 52, *d*). Since a like degeneration affects the septa of the alveoli, the latter coalesce to form larger and larger spaces (Fig. 52, *b*), which give the tumour a distinctly alveolar structure even to the naked eye.

The stroma in many cancers is very rich in blood-vessels, or consists almost exclusively of such (*teleangiectatic carcinoma*). In these cases hæmorrhages of greater or less extent may take place into the parenchyma of the cancer, resulting in pigmentation (*fungus hæmatodes*).

5. (iv.) **Papilloma.**—Even with the naked eye the papilloma can be seen to be composed of excrescences varying in length and thickness. Each of these latter, again, consists of a simple or ramified papilla, formed after the type of the papillæ of the skin or mucous membrane as the case may be, or of the villi, and carrying a covering

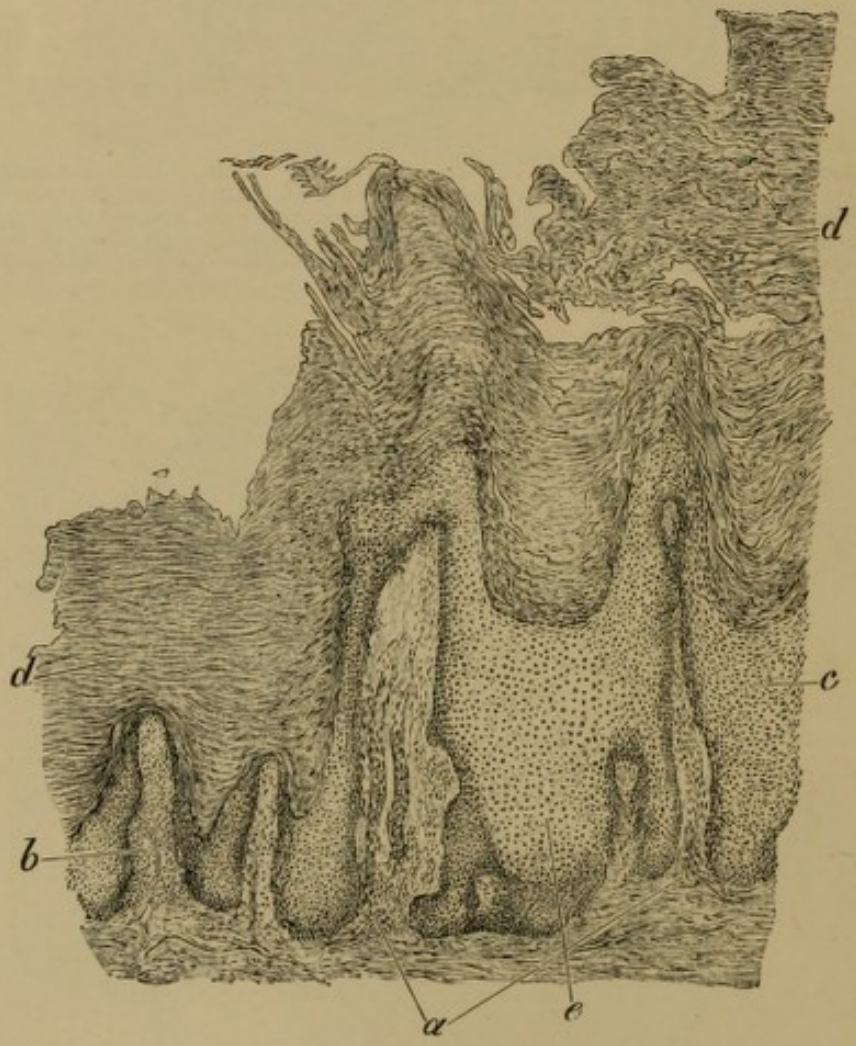

FIG. 54.—VERRUCA DURA OF THE SKIN. × 95. (Alum cochineal.) *a*, Greatly elongated papillæ; *b*, Papillæ not so much elongated; *c*, Rete Malpighii; *d*, Greatly thickened fissured stratum corneum.

of epithelium of variable thickness (Fig. 53 and Fig. 153). The connective tissue in these papillæ and villi is commonly much richer

in cells and blood-vessels than in those of the original tissue, and the layer of epithelium may also be considerably thicker, although in all its other characteristics it usually corresponds with that of the region in which the tumour is situated. Papillomata arise from the normal papillæ of the skin and mucous membranes, and in their formation there occurs not only an enlargement of the latter but also a new formation of papillæ.

Cutaneous warts are papillomata with an abnormal degree of horny transformation of the epidermis, causing the latter to rise in a conical form above the enlarged or newly-developed papillæ (Fig. 54). The *acuminate condyloma* likewise belongs to the papillomata.

Those papillomata of mucous membranes which are constructed more after the type of the intestinal or synovial villi, as for example the papillomata which occur on the mucous membrane of the urinary bladder, are also called *villous tumours* (Fig. 153).

6. (v.) **Polypi.**—These occur only upon mucous membranes, of which they form outgrowths or circumscribed elevations, containing as a rule elements similar to those in the particular mucous membrane itself, and hence always covered with an epithelial coat which usually corresponds to that of the parent tissue (Figs. 55 and 56, *a*).

Fig. 55.—Mucous Polypus of the Nose. × 285. (Hæmatoxylin and eosin.) *a*, Cylindrical epithelium consisting of several layers of cells; *b*, Round cells; *c*, Spindle-shaped cells; *d*, Stellate cells, with and without pigment; *e*, Injected blood-vessels.

The rest of the tissue of polypi shows a somewhat variable composition. It consists either of fibrous connective tissue with but

few cells (*fibrous polypus*), or of an œdematous connective tissue or mucous tissue (*mucous polypus*, Fig, 55), or lastly of a round-celled tissue (*sarcomatous polypus*). In many polypi there also occur more or less abundant glands (Fig. 56, *b*), which correspond in size and general character with those of the particular mucous membrane, but often exhibit cystic dilatations (*cystic polypi*).

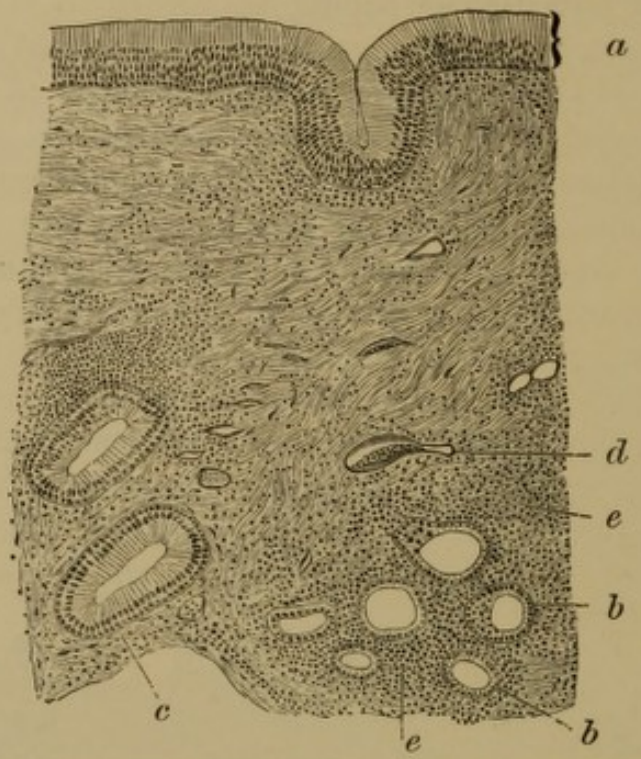

FIG. 56.—GLANDULAR NASAL POLYPUS. × 110. (Alum cochineal.) *a*, Stratified cylindrical epithelium of surface; *b*, Acini, some rather dilated, with cubical epithelium; *c*, Ducts with stratified cylindrical epithelium; *d*, Blood-vessels; *e*, Small-cell infiltration.

The degree of vascularity also varies, some polypi being poorly supplied with vessels, whilst others on the contrary are so vascular that they resemble a cavernous tumour, in which case hæmorrhages and pigmentation readily occur (Fig. 55). The surface of polypi is usually smooth, but occasionally shows shallow (Fig. 56) or deep depressions like those in a papilloma (*papillary polypi*).

Examination of Tumours.—This may be carried out while the tumours are *fresh*, as well as after hardening. In the former case, either the juice of the parenchyma is examined, which can usually be obtained only from the cut surface of the carcinomata and of the highly cellular sarcomata by scraping; or else torn up preparations, or lastly, sections made with the freezing microtome are used.

The *juice of the parenchyma* may be stained *before* transferring it to the slide by agitating it with picro-carmine or alum cochineal in a watchglass, and then after some minutes with a like quantity of glycerin, and taking a drop from this to examine. Needled preparations may be subjected to a similar process.

In order to isolate the *smooth muscular fibres in myomata*, small pieces are laid in a 33 per cent. caustic potash or soda solution, or in 20 per cent. nitric

acid (p. 6); and to isolate the non-medullated *nerve-fibres of neuromata*, in half per cent. acetic acid.

For the specific reactions of *fat*, *mucin*, and deposits of *lime* and *pigment*, the methods given on pp. 53, 55 and 60-62 may be resorted to.

Hardening of tumours is done in alcohol when it is desired to attain that end rapidly or to preserve any calcareous deposits that may be present. If, however, the red blood-corpuscles are to be retained, hardening should be done first in Müller's fluid and then in alcohol, a proceeding which is also to be recommended for very soft or mucinous tumours, and in general in the majority of cases.

For *staining*, carmine solutions and the double stains (pp. 18-21) in general are used, the latter especially with preparations hardened in Müller's fluid. In addition to the above the following should also be noted for *individual* varieties of new-formations :—

In examining and staining *chondromata* and *osteomata*, the methods given in Part III., Chapter X., may be employed.

For staining the *smooth muscle fibres* in myomata, hæmatoxylin and eosin, and picro-carmine or picro-lithium-carmine, are to be recommended.

To stain the *medullated nerve fibres* in neuromata, the methods described in Part III., Chapter IX., are to be referred to.

Hæmatangiomata, after hardening in Müller's fluid, are stained with hæmatoxylin and eosin.

Both single and double stains are suitable for *sarcomata* and *carcinomata*. For the purpose of distinguishing alveolar sarcoma from carcinoma, as well as generally for the demonstration of the stroma, sections are to be carefully brushed with a hair pencil or shaken up in water (p. 17).

The majority of the benign tumours, such as fibroma, lipoma, chondroma, osteoma, and angioma, can commonly be determined even from their macroscopic appearance; but in the case of the other tumours also, an important indication for diagnosis is afforded by certain gross anatomical or clinical characteristics. Thus rapidity of growth, indefiniteness of boundary, great softness, ulceration, and the formation of metastases, point to sarcoma and carcinoma; a milky juice which may be scraped from the cut surface, to carcinoma or highly cellular sarcoma (usually of the round-celled variety); and the appearance of plugs resembling comedones on lateral pressure upon the cut surface, to epithelioma.

When the juice of the tumour is examined microscopically there are found, in case it is derived from a carcinoma, large polymorphic epithelioid cells with large vesicular nuclei and distinct nucleoli, which in part lie singly, in part are tightly rolled up into round or cylindrical groups, with or without pearl globules; but in this case the juice must always be taken from the *interior* of the tumour. If, on the other hand, a sarcoma is being dealt with, the juice, except in the case of large-celled sarcomata, will contain only comparatively small cells, the great majority of which are rounded or spindle-shaped, or it will be rather poor in cells of any kind.

Although a tolerably definite diagnosis may not unfrequently be arrived at even by this method of investigation, still as a rule sections ought also to be examined, especially when the problem is to ascertain whether the tumours present are malignant. Such sections are made from fresh specimens, or from the tumour after hardening, and should always be taken from the youngest portions, as free as possible from retrograde metamorphoses.

CHAPTER V.

THE PARASITES.

I. VEGETABLE PARASITES.

1. Introductory.—By the term *Parasites* are understood those living creatures which vegetate in or upon another living organism, and at its expense. The injury inflicted on the host by the parasites is sometimes very slight, but in other cases considerable local troubles arise, and in others again severe general symptoms may even be caused. The parasites of man are derived partly from the vegetable and partly from the animal kingdom, belonging in the former case to the *Bacteria*, *Yeasts*, and *Moulds*, in the latter to the *Protozoa*, *Vermes*, and *Arthropoda*.

A. BACTERIA [SCHIZOMYCETES].

2. General Bacteriology.—*Bacteria* are excessively minute unicellular organisms, for the most part destitute of chlorophyll, which often unite to form combinations or colonies.

The bacterial cell consists of a [protoplasmic] substance and a surrounding *membrane*, the former of which behaves towards stains as do the cell-nuclei of more highly organised beings; but whether structures resembling nuclei really exist in the contents of the bacterial cell has not as yet been certainly made out.[1] The membrane is properly speaking only the condensed innermost layer of a gelatinous envelope surrounding the cells, which is recognisable in many bacteria both with and without staining, and is then termed a *capsule* (Plate IV., Fig. 1).

Although it is not possible at the present moment to undertake a classification of the bacteria which shall rest upon a natural basis, still there can be no doubt whatever that there are amongst them well-characterised genera and species which do not merge

[1] [Some believe the protoplasmic body to be itself the nucleus].—*Tr.*

one into the other, but admit of being sharply differentiated by unchanging morphological and physiological peculiarities; though it must certainly be observed that the so-called 'constancy' of these peculiarities is not absolute; that is to say, a certain variability is perceptible, dependent on the age of the bacteria, the composition of the culture medium, etc., and manifested both in form (as in the occurrence of involution and degenerative forms, and the like) and also in action (decrease in the virulence of pathogenic bacteria, etc.).

If we consider the vegetative forms of the bacteria, we can distinguish first of all three principal groups, viz., (1) *Micrococci* (Plate II.), which consist of round or oval cells; (2) *Bacilli* (Plates V.-VIII.), which consist of straight or curved rod-shaped cells, and (3) *Spirilla* (Plate IX.), which consist of screw-shaped cells.

All bacteria multiply by progressive *fission*. If after division has taken place the new individuals remain to a certain extent connected with one another, combinations of bacteria result, which again may vary in form. In the case of micrococci, if each pair lie close together, they are spoken of as *diplococci* (Plate IV., Fig. 1); if several lie lengthwise in a row, as *streptococci* (Plate II., Fig. 2); if each four are arranged in one plane, as *tetrads* (Fig. 143 *c*); if each eight are grouped in three directions of space at right angles to each other, so as to form combinations resembling bales of goods, as *sarcinæ;* and lastly, if the cocci form irregular clumps like clusters of grapes, as *staphylococci* (Plate II., Fig. 1). In the case of bacilli, only the arrangement in longitudinal rows has any special designation, such combinations being known as *filaments* (Plate V., Fig. 2), and if the individual cells in them are distinctly visible, as articulated filaments. Spirilla when strung together form shorter or longer *spirals*. Lastly, when bacteria and combinations of them unite to form large and sometimes sharply defined masses, visible even to the naked eye, we speak of *colonies* and of *zooglœa masses*.

Another mode in which bacteria multiply under certain conditions consists in the formation of *spores*, of which *endogenous* and *arthrogenous* varieties are distinguished. The former, to which most study has been given, but which have hitherto been observed only in bacilli and spirilla, develop in the centre (Plate V., Fig. 2) or at one end (Plate VII., Fig. 2) of a rod in the form of an oval, brightly glancing structure, surrounded by a stout envelope, the *spore-membrane*, not more than one spore ever occurring in a cell. This body eventually becomes free, and in this condition, as a *resistant form*, can withstand the most widely different influences (such as drying, cold, heat, and chemical agents),

requiring to be subjected to a dry heat of about 150° C., or moving steam at 100° C., or a 0·1 per cent. aqueous solution of corrosive sublimate, before it is destroyed, though of course the resistance of spores may also undergo certain fluctuations. When the spores meet with a suitable nutrient soil they germinate, and their contents are transformed into new bacterial cells.

Arthrogenous sporulation consists in the change of isolated members of a bacterial combination into resistant forms, which outlive the rest, and are capable of germinating again should opportunity arise. During this process they may also gain in size and refracting power, and acquire a somewhat stronger envelope. Whether, however, the significance of *fructification* is not really to be ascribed to this process has not yet been finally determined.

With few exceptions, micrococci possess no power of automatic, but merely a molecular, movement; whereas, on the other hand, a number of bacilli and spirilla are endowed with motility, and in many of the motile bacteria special motor organs may be recognised by suitable staining, in the form of whiplike filaments which project from one or both ends or from the lateral surface of the cell.

From their physiological peculiarities, bacteria are divided into *saprophytes* and *parasites* according as they vegetate on dead organic matter or on living beings respectively. Many of the bacteria, however, are capable of adopting either mode of life by turns, and these, in order to distinguish them from the rest, the *obligate* parasites and saprophytes, are termed *facultative parasites* when they usually live as saprophytes and are only occasionally parasitic, and *facultative saprophytes* when the reverse is the case.

The bacteria can only procure the carbon necessary for their vital processes from previously-formed organic carbon compounds, whilst they satisfy their need of nitrogen from inorganic as well as organic substances. The nutrient medium must have an alkaline or neutral action.

Certain bacteria can only thrive when the oxygen of the air has free access, others only in its absence, the former being known as *obligate aerobes*, and the latter as *obligate anaerobes*. Between these two extremes there are a number of bacteria which, indeed, can generally vegetate either in the presence or in the absence of atmospheric oxygen, but usually in one case better than in the other; these are called *facultative aerobes* and *facultative anaerobes*.

Bacteria are capable of increase only within certain definite limits of temperature. Under 5° and above 45° C. growth ceases in the case of most of them, and we know that a temperature above 50° or

60° C. actually destroys the vegetative forms of very many, whereas the influence of cold in this respect has not yet been very thoroughly studied. The *optimum* temperature is, however, for the saprophytes one of about 20° C. (" room temperature "), and for parasitic bacteria about 37° C. (" body " or " incubation temperature," " blood heat ").

The *saprophytic* bacteria are either the exciting cause of fermentation or of putrefaction, or bring about those transmutations in the medium which are described as *nitration* or *nitrification;* whilst others again manufacture pigment, phosphorescent bodies, gases, and so forth. Amongst the products of their metabolism there are also some of a very poisonous nature, which are simply named *ptomains* or *toxins.*

With reference to the relationship which bacteria bear to disease, a distinction is made between *pathogenic* and *non-pathogenic* varieties, according as their introduction into the organism does or does not give rise to a morbid condition. In the case of the former, however, it must be further distinguished whether their morbific action is dependent on their multiplication in the organism or merely on the introduction along with them of poisonous products of metabolism already formed outside the body; indeed, saprophytic bacteria may also act pathogenetically in the latter way if taken into the body in sufficient quantity. This is, however, a purely toxic action and must be distinguished from that which is set up solely by the growth of the bacteria in the interior of the living organism and is described as an *infective* action, although in the ultimate analysis the formation of specific poisons is the most important factor in this also.

The bacteria which act *infectively*, which develop their noxious influence when introduced into the organism even in small quantity, constitute the *pathogenic bacteria* in the more restricted sense of the term, and these alone—indeed, only the bacteria which are pathogenic for human beings—will be dealt with in the following sections. In the case of each individual species, the morphological and physiological peculiarities, and amongst the latter, again, its behaviour in artificial cultures and in the organisms of men and animals, will be described in detail.

3. The bacteria which are pathogenic for man belong partly to the parasites, obligate or facultative, partly to the facultative saprophytes, and, as regards their attitude towards atmospheric oxygen, with few exceptions to the facultative aerobes. Their optimum temperature lies at about 37° C.

They may gain entrance into the organism by the digestive or respiratory tracts, or through the outer skin and certain mucous membranes, their entry being materially assisted by the existence of

lesions of these parts. They then spread over the entire organism by the lymphatics and blood-vessels, or remain restricted to certain areas. Their further behaviour, and notably the possibility of their multiplication, is dependent on various factors, especially on the number and virulence of the bacteria which have gained entrance, as well as on the general and local diathesis of the individual attacked, though the more minute conditions upon which this diathesis depends are still unknown to us. Certain pathogenic bacteria appear to perish in the circulating blood, whilst others can even multiply in it.

In the *action* of the pathogenic bacteria upon the tissues, purely *mechanical* processes come but seldom into consideration. On the other hand, the influence which the products of the metabolism of bacteria, products which belong to the alkaloids or toxalbumins, exert upon the tissues is much more important. The changes brought about in this way have in general the character of inflammatory processes running an acute or a chronic course; but these processes may also be preceded or followed by degenerative changes, especially of a necrotic kind.

Not unfrequently the bacteria are taken up by leucocytes, and then either destroyed in their interior (*phagocytism*) or else transported in a living state to other parts. It need hardly be said that bacteria which are dead or in the act of dying may also be taken up by leucocytes.

Bacteria circulating in the blood may be excreted through the kidneys, probably in cases where, owing to some changes in the walls of the vessels and the membrana propria of the urinary tubules, the passage of the bacteria through them is rendered possible or favoured. They may also, under analogous conditions, traverse the membrana propria of the mammary glands and appear in the milk, or during pregnancy may travel through the placenta into the fœtus.

The pathogenic bacteria may be classed in the following three groups, according to their three principal forms.

(*a*) *PATHOGENIC COCCI.*

4. (i.) **Staphylococcus Pyogenes Aureus.**—This appears (Plate II., Fig. 1) in the form of round immotile cells tending to unite in irregular clumps and aggregations, the larger groups of which may sometimes resemble grape clusters. Although up to the present no spores have been observed in it, the micro-organism is distinguished by a certain degree of resistance to drying, heat, and chemical agents. It admits of being readily stained, which can also be done by Gram's method.

In artificial cultures it thrives even at room temperature and upon all our media, its mode of growth on agar and potatoes being the most characteristic.

Upon *gelatin plates* there occur whitish colonies which soon liquefy the gelatin in a circular form, in the centre of which an orange-yellow pigment appears.

On the *agar plate* the deep colonies remain somewhat small, whilst the superficial ones form discs, several millimetres in diameter, which are at first greyish-white, but subsequently turn orange-yellow, especially in the centre. Under a low power of the microscope (by which is always understood an amplification of about 80 diameters), the colonies on gelatin and agar plates appear for the most part round, smooth-edged, finely granular, and of a dark brown colour.

In *gelatin tubes* a total liquefaction of the medium gradually ensues, the latter at the same time becoming cloudy, whilst a yellow sediment makes its appearance at the bottom.

In *agar tubes* the growth is equally good whether along the track of a thrust inoculation or on the surface, but in the latter position the colour of the growth, at first greyish-white, changes to a more or less intense orange-yellow. The pigment develops most distinctly on agar solidified obliquely, and at room temperature. *Meat bouillon* is evenly clouded.

Upon *potatoes* there forms a luxuriant growth in which the orange-yellow coloration becomes particularly deep, and here, as well as on the other media, a somewhat sour smell makes itself perceived.

The *Staphylococcus pyogenes aureus* is found in the most various forms of acute inflammation of the connective-tissue system, particularly in those *which remain circumscribed and rapidly pass into suppuration.* Hence it is present in furuncles, carbuncles, and other circumscribed suppurations of the skin and subcutaneous connective tissue, but also in endocarditis and acute osteomyelitis, in suppurative inflammations in the serous cavities or internal organs, and so forth. Should *pyæmia* intervene in the course of these processes (p. 119), the coccus is met with also in the metastases, and in isolated instances even in the blood.

The diseased conditions just mentioned may also be excited by inoculation of pure cultures into the animals ordinarily used for experiment, if a suitable method be selected; and even in human beings artificial inoculations have been made with successful results. The issue of experiments on animals is of course influenced by the very variable degree of virulence which the staphylococcus may originally possess or may acquire in the course of cultivation,—a peculiarity which it shares with the other pus-cocci and with the *Diplococcus pneumoniæ.* Injection into the circulation produces

relatively the most certain effect, and this method is followed with especial frequency by the formation of small abscesses and infarctions in the kidneys, and sometimes also by suppuration in the joints.

Small wounds of the skin or mucous membranes very often form the gates of entry for the natural infection in the case of human beings, but invasion by the cocci is also possible even when the surface is unbroken. When the multiplication of the cocci in the affected tissues is very rapid, necrosis first ensues (as for example in furuncles, ulcerative endocarditis, pulmonary gangrene, etc.), and suppuration only secondarily, whereas otherwise inflammation and suppuration appear to follow immediately upon their incursion.

5. (ii.) **Staphylococcus Pyogenes Citreus and Albus.**—Both differ from the preceding only in artificial cultures, the one (*citreus*) forming a lemon-yellow, the other (*albus*) a white pigment upon the culture media. They also occur less often than the *Staphylococcus aureus* in the before-mentioned morbid conditions, and the *Staphylococcus pyogenes albus* appears besides to be less virulent than the *Staphylococcus aureus*, and is usually found not alone, but in company with the latter.

6. (iii.) **Streptococcus Pyogenes** (together with the **Micrococcus Tetragenus, Bacillus Pyogenes Fœtidus**, and **Bacillus Pyocyaneus**).—The *Streptococcus pyogenes* (Plate II., Fig. 2) shows small round cocci, which are destitute of motility, and mostly arrange themselves in longer or shorter chains, sometimes with numerous twists. It behaves like the *Staphylococcus pyogenes* as regards its staining capabilities.

Under artificial cultivation it grows even at room temperature, and upon all nutrient substances excepting potatoes. The behaviour of the superficial colonies on agar plates is the most characteristic.

Growth takes place slowly on the *gelatin plate*, and it is not until after three or four days that small white colonies develop, which do not enlarge beyond the size of pin's heads at most. Under a low power they appear as round, smooth-edged granular formations of a yellowish-brown colour.

Colonies appear on *agar plates* as early as the second day, the more deeply situated constituting barely visible greyish-white points, the superficial somewhat larger but very delicate discs, the centre of which is opaque and white, but the periphery grey and transparent. Under the microscope the former are yellowish-brown or brown according to their density, finely granulated, and their edge frequently somewhat ravelled. The central part of the superficial colonies shows a similar constitution, whilst their periphery is frequently resolved into looped or tendril-like chains, which can be recognised with especial distinctness under a power magnifying 200 diameters. The

latter feature is characteristic of the *Streptococcus pyogenes* (and *Streptococcus erysipelatis*), but is not always present.

In *gelatin thrust-cultures* the growth is most vigorous along the needle-track. Small white globules appear which, when the sowing has been more abundant and a platinum loop has been used, coalesce to form a more even band-like stripe, and can only be distinctly recognised at the border of the latter. Superficially a delicate veil-like greyish-white coating forms only in the immediate neighbourhood of the puncture. The growth in *agar tubes* is similar, only still more delicate on the surface.

If *streak cultures* are made on agar or gelatin, there form on the surface of the medium small colonies like dew-drops, which correspond in their appearance with the superficial colonies on agar or gelatin plates.

In *meat bouillon* particularly long chains of cocci develop, which, however, do not render the fluid turbid, but sink to the bottom as flocculent whitish masses. Upon *potatoes* no growth takes place.

The *Streptococcus pyogenes* may be found in the same diseased conditions as the staphylococci previously described, either alone or in company with the latter. The processes set up by the sole action of the *Streptococcus pyogenes*, however, frequently differ from those in which the staphylococci are found, in that the former show a tendency to spread superficially, and that in them the exudation is principally fibrinous, or does not become purulent until comparatively late. Furthermore, the streptococcus makes its way still more easily than does the staphylococcus from the tissues in which it has settled into the lymphatics and blood-vessels, and then leads to a vasculitis or thrombo-vasculitis (p. 203); or in case the vessels are very small, they are completely plugged by the growing cocci (Fig. 185, *d*) and not uncommonly also show varicose dilatations. When small particles break away from the thrombi or masses of cocci they may be caught in the vessels of different organs and tissues, and in this way give rise to the formation of metastatic foci, which will show the characters described on pp. 212 and 213 (*pyæmia*). In these cases the streptococci can be recognised also in the blood, though certainly only in small numbers.

Regarding experiments on animals the same holds good as in the case of *Staphylococcus pyogenes aureus*, except that with the streptococcus subcutaneous injections seem to act more surely, and intravascular injections less so, than with the *Staphylococcus aureus*. The result of the experiment otherwise depends in this case also upon the very variable degree of virulence.

As the *Streptococcus* or *Staphylococcus pyogenes* are found as a rule in

all acute suppurations, and are to be regarded as the specific causes of pus-formation, they are also called simply *pyococci*. They are very widely distributed, and not only occur in the vicinity of human beings, but may also be found, even under normal conditions, in such of their cavities as communicate with the outer world (those of the mouth, nose, and pharynx). Since moreover they possess the property of thriving well upon tissues which have already undergone morbid changes from the action of other infective micro-organisms, it is not to be wondered at that they frequently invade the organism in the course of a variety of diseases of infective origin (the acute exanthemata, influenza, diphtheria, etc.), thus giving rise to complications or so-called *secondary infections*.

In company with the cocci just described there often occur in suppurations still further varieties of bacteria, but it has not been determined in what relation they stand to the suppurative process. To these belong :—

(1.) **Micrococcus Tetragenus** (Fig. 143, *c*), consisting of large round cocci, which, in the organism, are as a rule arranged in tetrads, and surrounded by a very broad capsule. The micro-organism stains readily, and also by Gram's method.

It grows even at room temperature, forming colonies on the *gelatin plate*, which resemble those of the *Bacillus pneumoniæ* (p. 150), in *gelatin tubes* spherical white masses in the needle-track and a shining deposit on the surface, an extensive white vegetation upon *agar* and *serum*, and a luxuriant viscous coat on *potatoes*.

The coccus has hitherto been found in tubercular cavities in the lungs, and in abscesses, but it also occurs in normal saliva. It is pathogenic for white mice and guinea-pigs, in the former of which it appears in considerable quantity in the blood and internal organs after subcutaneous injection, in the latter in the pus of peritonitis following injection into the abdominal cavity.

(2.) **Bacillus Pyogenes Fœtidus** consists of short rods with rounded ends and slight automatic motility. On *gelatin plates* it forms greyish-white colonies, in *gelatin tubes* a delicate, veil-like, greyish-white vegetation which gradually spreads over the entire surface, and small dots in the needle-track, and on *potatoes* a shining yellowish-brown coating. *All colonies exhale a putrid fetor.* It has been only rarely met with up to the present, and almost invariably in company with the *Staphylococcus pyogenes aureus*.

It is pathogenic for mice, guinea-pigs, and rabbits, in the latter of which foul-smelling abscesses may be set up by introduction of cultures, in the former septicæmia.

(3.) **Bacillus Pyocyaneus.**—This appears in the form of small slender highly-motile rodlets with rounded ends, which frequently unite to form short filaments.

It grows at room temperature, and is characterised by the formation of a green fluorescent pigment (*pyocyanin*) in *gelatin*, the latter being at the same time liquefied. Upon *agar* and *potatoes* there forms a yellowish coating, and the neighbouring parts are stained green. A variety of the above is the *Bacillus pyocyaneus* β, which produces a blue pigment. Both occur in pus when the conditions are favourable, commonly together, and they then produce a bluish-green coloration of the fluid.

The *Bacillus pyocyaneus* is pathogenic for guinea-pigs and rabbits, its introduction setting up suppurative processes which may even result in death.

7. (iv.) **Streptococcus Erysipelatis.**—This micro-organism cannot be distinguished either morphologically or by cultivation from the *Streptococcus pyogenes*. In experiments on animals, however, and still more in

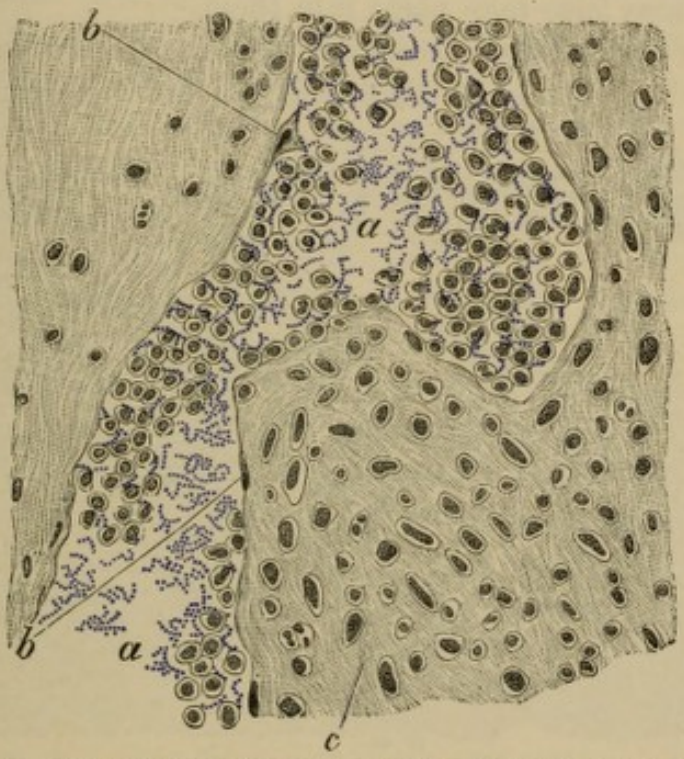

FIG. 57.—ERYSIPELAS OF THE SKIN. × 550. The cocci drawn in under a power magnifying 980 times. (Stained by Weigert's modification of Gram's method.) *a*, Lymphatic vessel partly distended by accumulation of mono- and polynuclear leucocytes, with erysipelas cocci inside and outside the cells; *b*, Endothelial cells of the lymphatic vessel; *c*, Adjoining cutis, permeated by leucocytes and proliferated connective-tissue cells.

its behaviour in the human organism, certain differences do exist, which justify, at least provisionally, a separation of the two; presupposing, of course, that a general distinction is also made between erysipelas and phlegmon. Thus, when a subcutaneous inoculation is

made into a rabbit's ear, there is apt to ensue often merely a superficial inflammation resembling erysipelas in man, whereas a similar introduction of *Streptococcus pyogenes* is followed at times by processes which take a deeper hold, and end in necrosis and suppuration.

Furthermore, in the human erysipelas the *Streptococcus erysipelatis* is found restricted, as a rule, to the lymphatics (Fig. 57, *a*), and the adjacent fissures in the connective tissue of those parts of the skin where the process is still actually advancing; whereas in a phlegmon caused by the *Streptococcus pyogenes* the cocci may be found everywhere in the tissue, as well as in the interior of blood-vessels and in different situations in the inflamed parts.

Lastly, a further difference may be brought out in connection with the pathological anatomy, in the fact that human erysipelas, in contrast to a phlegmon caused by streptococci, runs its course chiefly in the skin and takes but little hold on the deeper parts, and that the exudation is not, as a rule, either fibrinous or purulent. Only in facial erysipelas does the exudation in the loose tissue of the eyelids assume a purulent character, and when an erysipelas extends over joints purulent effusions may also take place into them.

When the epidermis is raised into blebs in the course of erysipelas, cocci are either not found in them at all, or but very sparingly.

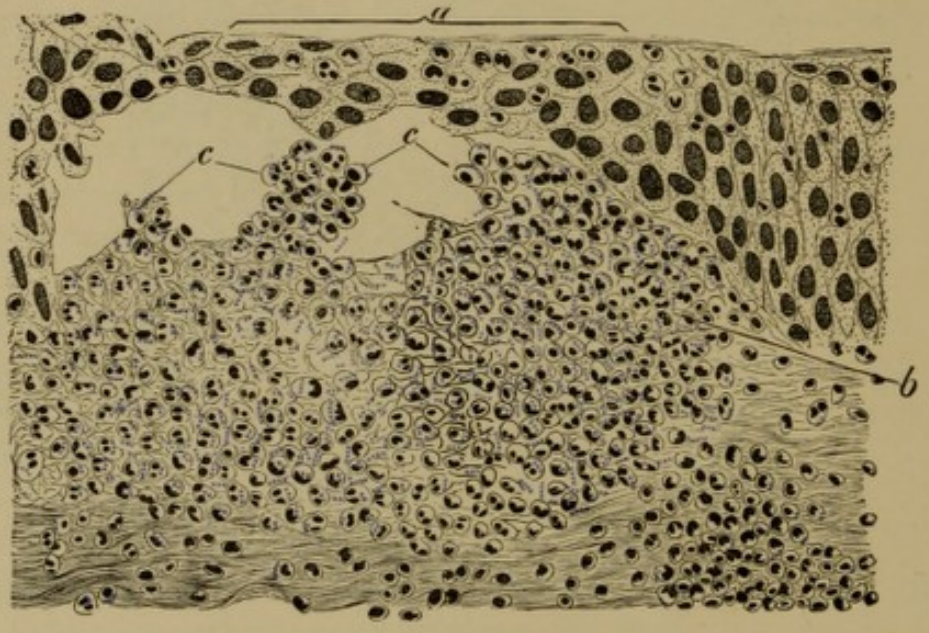

FIG. 58.—ERYSIPELAS OF THE EYELID. × 440. The cocci drawn in under a power magnifying 980 times. (Stained by Weigert's modification of Gram's method.) *a*, Thinned epidermis, permeated by pus corpuscles; *b*, Purulent infiltration of cutis; *c*, Cocci of erysipelas in the pus cells.

Examination of Pus-Cocci and of the Streptococcus Erysipelatis.—*Cover-glass preparations* may be stained with any of the basic anilin colours.

For *sections* Gram's method is suitable, or still better Weigert's modification of it, with preliminary staining. Under these processes, however, the cocci also may be partially or altogether decolorised. This occurs in cases where they were in the

act of dying at the time, and therefore in such cases staining with Löffler's or Kühne's methyl blue should also be tried.

8. (v.) **Gonococcus.**—We have here to do with moderately large cocci (Plate III., Fig. 1), which are frequently grouped in pairs (as diplococci), and may then be somewhat flattened on the surfaces which come in contact. They lie for the most part *in the interior of cells*, not infrequently in such numbers that the body of the cell is packed quite full of them, and only the nuclei remain free. This intracellular lodgment is an important point of distinction between this and other diplococci. The gonococcus can be stained with all basic anilin dyes, but not by Gram's method.

Cultivation succeeds only at incubation temperature, best upon human blood serum, and the cultures look as if composed of minute droplets. Upon the serum of animals and on agar the gonococci grow also, but very sparingly.

A purulent peritonitis can be set up in white mice and guinea-pigs by introducing cultures (together with pieces of the culture medium) into the abdominal cavity.

The gonococci are met with not only in gonorrhœa but also in gonorrhœal blennorrhœa of the conjunctiva. In the former they are found not alone in the secretion of the mucous membranes primarily affected by the disease (the urethra, vagina, or cervix uteri), but also in certain complications of gonorrhœa, as in para- and periurethral abscesses, inflammation of Bartholin's glands, of the Fallopian tubes, the perimetrium and parametrium, and the joints; whilst still further complications may be caused by pyococci.

The cocci are present in the gonorrhœal secretion in greater abundance the more recent the process. In the diseased mucous membrane they lie in the superficial layers, mostly between the cells, into the bodies of which they do not penetrate until after they (the cells) have been shed.

The *causal* connection of gonococci with gonorrhœa has been proved beyond a doubt by successful transmission of pure cultures to the human urethra.

Methods.—*Cover-glass preparations* are treated with aqueous solution of fuchsin or gentian violet when there is no question of differential diagnosis between gonococci and other cocci, the cell-body being only slightly tinged thereby, whilst the nuclei and the cocci stain very intensely. If double staining is desired, the cover-glasses are first laid for some minutes in a warm concentrated alcoholic solution of eosin, and thence transferred, after removal of superfluous eosin with blotting paper, to a concentrated alcoholic solution of methyl blue, in which, however, they only remain a few seconds, being finally rinsed in water. The nuclei and cocci appear blue, the body of the cells red.

It is just as difficult to recognise gonococci in the chronic stage of the gonorrhœal inflammation as it is easy to do so in cases where the process is quite recent, as in the former the specific cocci are present in very small numbers, and may be very hard to distinguish from other cocci perhaps occurring along with them (as, for example, in chronic gonorrhœal inflammations of the female genital tract) if they happen not to lie in the interior of cells. In such cases, when examining the living, artificial intensification of the process by the injection of a weak solution of corrosive sublimate may afford help, this leading to a multiplication of the gonococci, while the other bacteria are destroyed; or for the purpose of distinguishing the gonococci from other cocci, cover-glass preparations are first treated by Gram's method and afterwards stained for five seconds with alkaline methyl blue which has been diluted with four times the quantity of water, by which means the gonococci are stained blue, but the rest of the bacteria blackish. A still more certain method, however, in doubtful cases, is to prepare plate cultures from the secretion, using for this purpose human serum to which an equal quantity of warm agar solution has been added in order to make it solidify.

Sections are stained with carbolic methyl blue, after Kühne's method.

9. (vi.) **Diplococcus Pneumoniæ.**—This micro-organism (Plate IV., Fig. 1) consists of structures which, though round at the beginning of their development, usually become oval or lancet-shaped[1] at a later stage, and are arranged for the most part in pairs or short chains, less frequently in chains of greater length. They are destitute of motility. In the organism they are very often seen, especially during vigorous development and at the beginning of the inflammatory process, to be surrounded by a conspicuously visible mucoid envelope of varying breadth, sharply marked off from its surroundings, and capable of being stained, which is named the *capsule*. This envelope cannot usually be recognised in artificial cultures. While the cocci admit of being easily stained, which can also be done by Gram's method, the capsule only takes the colouring matter with difficulty.

The *Diplococcus pneumoniæ* does not *usually* grow under 24° C., and thrives best at incubation temperature. Its cultures generally bear a resemblance to those of *Streptococcus pyogenes*, except that they appear much more delicate and scanty. On *agar plates* the deeper-lying colonies remain so small as to be scarcely visible to the naked eye. Under the microscope they appear from pale yellow to brown, finely granular, and often somewhat fringed at the edge. The superficial colonies are rather larger, about the size of those of *Streptococcus pyogenes*, but usually still more transparent. Microscopically they show a compact finely-granular centre and a very pale surrounding area in which, under a medium power, short or

[1] Many authorities include the *Diplococcus pneumoniæ* among the bacilli, on account of its elongated shape.

moderately long chains arranged in concentric lines can be recognised towards the periphery, but as a rule no distinct formation of loops and tendrils.

Upon *gelatin plates*, which remain solid if a 15 per cent. gelatin is used and they are kept at a temperature not much above 24° C., the colonies are also very small, and appear under the microscope of a light or dark grey colour, finely granulated or made up of lines (chains) and points.

Thrust-cultures in agar show a similar appearance to those of *Streptococcus pyogenes*, except that the vegetation is less vigorous along the needle-track, and is not at all or but very feebly developed on the surface in the neighbourhood of the puncture. *Thrust-cultures in* 15 *per cent. gelatin* at 24° C. show a similar condition, but when sparsely sown only isolated globules form in the thrust canal. Upon *obliquely-solidified agar and serum* there forms a barely-visible film, consisting of structures resembling drops of dew. A white sediment, often very scanty, forms in *bouillon*, while the fluid appears somewhat turbid.

The cultures of the pneumococcus possess the additional peculiarity that they not only speedily lose their virulence, but also die very early, although deviations from this rule occur.

The *Diplococcus pneumoniæ* is found, in the first place, in croupous or lobar pneumonia, of which it is the most frequent cause; and it likewise forms the causative agent in many cases of acute lobular pneumonia. Furthermore, it is present in those diseases (pleurisy, peritonitis, endo- and pericarditis, otitis, meningitis, etc.) which may occur as complications of pneumonia; and it may also form the cause of the same morbid conditions at times when they occur *independently of the latter*. Hence it follows, that although the inflammations set up by the *Diplococcus pneumoniæ* occur primarily with greatest frequency in the lung, they may, under certain circumstances, occur primarily in other tissues and organs also, all these inflammatory processes having this much in common, that they run a comparatively rapid course, that their exudations are principally of a fibrinous character, and that the *Diplococcus pneumoniæ* may be recognised in them the more abundantly and certainly the more recent the inflammation.

The coccus is also found in the sputum during an attack of pneumonia caused by it, more plentifully as a rule at the beginning of the process than later, but its capsule is for the most part not very well developed.

Finally, it occurs not uncommonly in the buccal and nasal cavities (in the saliva and nasal secretion) of various persons

even when no pneumonia is present, but here it can usually be recognised only by cultivation or experiment on animals. Should certain predisposing influences intervene it may penetrate from the above-named portals of entrance of the respiratory system into the lungs or other organs, and may there develop its pathogenic action.

Of the animals commonly used for experiment, those most sensitive to the *Diplococcus pneumoniæ* are mice and rabbits, which often die of septicæmia in as short a time as one or two days after subcutaneous injection of very virulent cultures, no other anatomical changes developing than a slight serous or fibrinous exudation at the site of injection and swelling of the spleen, although the blood and all the organs show numerous encapsuled cocci. Injection into the thoracic or abdominal cavities is followed by inflammatory processes in those regions, commonly accompanied also in the former case by pneumonic consolidations of the lung. A very distinctly characteristic pneumonia may occur in rabbits after injection into the trachea or subcutaneous introduction of attenuated cultures.

Methods.—In case it is wished to stain the capsule also, cover-glass preparations are first placed in anilin or carbolic fuchsin or anilin gentian violet, which is warmed until bubbles rise, and are then rapidly passed through alcohol several times and rinsed in water. If the staining is successful the cocci appear of an intense red and the capsules only pale red (or violet, as the case may be). When it is a question of diagnosis from the *Bacillus pneumoniæ* (p. 150), staining is done by Gram's method, as the latter is decolorised thereby, whilst the *Diplococcus pneumoniæ* retains the stain.

When examining *pneumonic sputum*, care should be taken to obtain it as free from saliva as possible. If this is done successfully, it is often possible to recognise the pneumococci with certainty, as then scarcely any but cocci of the form and arrangement of *Diplococcus pneumoniæ* are found in the sputum.

For *sections*, Weigert's modification of Gram's method is best suited, with preliminary counter-staining, but it is advisable to leave the sections in the gentian violet for a very long time, as much as an hour. The capsule takes the carmine stain. Besides this, however, staining with alkaline or carbolic methyl blue also renders good service.

(b) PATHOGENIC BACILLI.

10. (i.) **Bacillus Anthracis.**—This bacillus (Plate V., Figs. 1 and 2) attains the greatest longitudinal dimensions of all the pathogenic species, namely from 5 to 10 μ (about the diameter of a human red blood corpuscle); its breadth, however, only amounts to 1 or 1·5 μ. The ends of the bacillus are separated by sharp angles from its sides, and are frequently concave, so that when several bacilli unite to form filaments, oval spaces, which are perfectly characteristic, may appear between the segments (Plate V., Fig. 1). Moreover, in stained pre-

parations from the juices of tissues or from blood, it is not infrequently possible to make out a capsule-like envelope which shows a light violet or rose tint after staining with methyl blue, whereas the protoplasm of the rod itself is of a dark blue colour.

Anthrax bacilli are immotile and have a tendency to develop into filaments, which in cultures are usually very long (Plate V., Fig. 2), but in the organism consist for the most part of only a few segments. Under certain conditions, including above all free access of oxygen and a suitable temperature—one at all events not below 24° C.—a formation of oval spores takes place, of which there is invariably only one in the centre of each rod (Plate V., Fig. 2). The bacilli admit of being easily stained, which can also be done by Gram's method. They grow in artificial cultures at room temperature, and upon all our nutrient media. The appearances presented by plate-cultures and by thrust-cultures in gelatin are the most characteristic.

Upon *gelatin and agar plates* the superficial colonies appear irregular and greyish-white, and under a low power show at the margin a characteristic feltwork of closely-lying fibres which are usually curved in a wavy manner. In *thrust-cultures in gelatin* tubes, short bristle-like processes are usually seen running out in a horizontal direction from the needle-track. The gelatin is meanwhile evenly liquefied from the surface downwards, but remains clear, while the growth gathers at the bottom as a white cloudy mass. On oblique *agar* and on *potatoes* there forms a luxuriant greyish-white tenacious vegetation, which on the latter often assumes a delicate rose tint at the margin. Cultures on *serum* show nothing in particular beyond a liquefaction of the medium.

When anthrax bacilli are grown for some weeks at a temperature between 42° and 43° C. a diminution of their virulence results, and animals which are inoculated with cultures thus attenuated are then *immune* towards virulent anthrax also. Anthrax is set up in human beings either by infection starting from the skin (usually through wounds or the stings of insects), or from the lungs or digestive tract. In the first case there usually develops a pustule, the *malignant pustule*, more rarely an extensive œdema in which the uppermost layers of the corium are found to be permeated with a hæmorrhagic, serous, or sero-fibrinous exudation containing numbers of bacilli, the deeper parts in a state of cellular infiltration.

Infection by the lungs, which is apt to occur most frequently in the sorting of rags or wool, from the entrance of dust containing spores ("rag-picker's" or "wool-sorter's disease"), is followed by œdema of the lungs or pneumonia, serous effusions into the pleural sacs, serous infiltration of the mediastinal connective tissue, swelling of the bronchial glands, frequently also carbuncular foci on the mucous

membrane of the trachea and bronchi, and, lastly, enlargement of the spleen. In this case the bacilli are to be found chiefly in the greatly-distended lymphatic vessels of the pleura and lungs, but also in the serous and fibrinous exudation in the pulmonary alveoli, in the fluid transuded into the pleural cavities, and in the bronchial glands.

When the infection proceeds from the digestive tract, which also can only take place as a rule by means of material containing spores, there form on the mucous membrane of the intestine, especially of the small intestine, hæmorrhagic patches having a greyish-yellow slough in the centre, and the mesenteric glands are usually also swollen and infiltrated with blood.

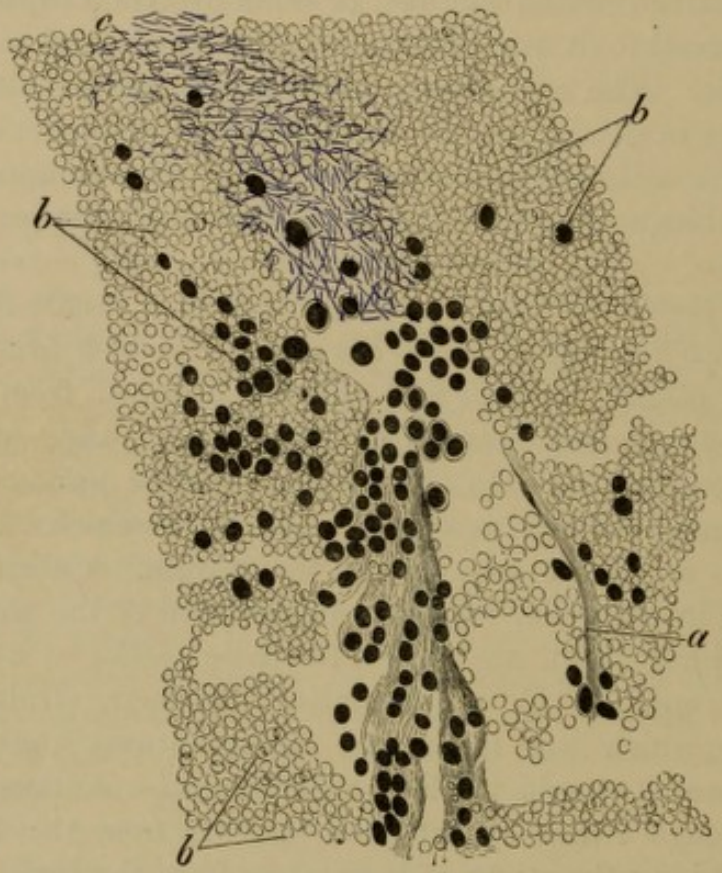

Fig. 59.—Punctiform Hæmorrhage in the Cerebral Cortex in Intestinal Anthrax. × 545. (Stained by Weigert's modification of Gram's method.) *a*, Small vein ruptured; *b*, Extravasation of blood (red and white corpuscles); *c*, Anthrax bacilli.

In all three varieties of anthrax disease, but especially in the last two, a *general infection* may ensue owing to penetration of the bacilli into the circulation, and (besides swelling of the spleen) hæmorrhages into the brain, or serous effusions into the thoracic and abdominal cavities may take place in consequence. The bacilli are then found not only in the transudations and hæmorrhages (Fig. 59) already mentioned, but also in larger numbers in the blood, chiefly in the capillaries, and especially those of the spleen. In the blood they usually form only short filaments of from 2 to 5 segments, and

never spores, though the latter may develop (owing to access of oxygen) after the body has been opened.

Of our experimental animals, mice are the most susceptible to inoculated anthrax, and then guinea-pigs and rabbits. Mice usually die in as short a time as a day or a day and a half. An extensive œdema of the subcutaneous tissue and great swelling of the spleen are found to follow hypodermic injection.

Methods.—Owing to their comparatively large size, anthrax bacilli may be recognised even in *unstained preparations* of blood, as immotile glassy rods; otherwise they are best stained in *cover-glass preparations* with aqueous methyl blue or fuchsin. In dead bodies the juice of the spleen should above all be used for the detection of the bacilli. The spores are stained by the method given on page 29.

Sections may either be stained with aqueous fuchsin or gentian violet, or by Gram's (or Weigert's) method; but in using Gram's method the sections must not be left lying too long in iodine and alcohol, or else the bacilli will also be decolorised.

11. (ii.) **Bacillus Œdematis Maligni.**—This resembles the bacillus of anthrax, but is thinner, and its ends are rounded off or pointed. It furthermore possesses laterally-placed flagella, by means of which it keeps up active movements, and it forms spores which occasionally bulge out the contour of the rod somewhat. It is decolorised by Gram's method. The bacillus grows at room temperature, and belongs to the obligate anaerobes, so that the methods given on p. 44 must be used for its cultivation.

On *gelatin plates*, the colonies when examined under a rather high power show a dense felting together of fibres in the centre, and a radiating arrangement at the margin in consequence of liquefaction of the gelatin; on *agar plates* they show a much-ramified and branching mass. Growth in *test-tube cultures* takes place only in the deeper parts, and is usually associated with the generation of foul-smelling gases. Gelatin is liquefied and rendered turbid.

The so-called *malignant œdema*, with the bacilli peculiar to it, has been several times observed in human beings, when it occurred after compound fractures and other wounds, and also after subcutaneous injections of tincture of musk, being characterised by a gangrenous inflammation attended with development of gas (*progressive gangrenous emphysema*). The bacilli are, however, very widely distributed in external nature, being met with in dust, in garden earth, in dirty water, etc., insomuch that the disease can be easily set up in mice, guinea-pigs, or rabbits by the introduction of one of the above into pockets made beneath the skin; but in this case the bacilli are usually mixed with other anaerobic bacteria.

Inoculation of pure cultures is followed by an infiltration of the subcutaneous connective tissue and superficial muscles with reddish serum, but without great development of gas, and also by a moderate enlargement of the spleen. When the examination is made shortly after death, the bacilli are present only in the œdematous fluid and on the surface of the large organs; subsequently, however, they penetrate into the interior of the latter and into the blood-vessels. Only in mice are they found everywhere from the outset.

Staining is done in a manner analogous to that adopted with anthrax bacilli, except that Gram's method is not admissible.

12. (iii.) **Bacillus Tuberculosis.**—This micro-organism occurs in the form of very fine rods rounded at the ends, which are shorter than the diameter of a red blood corpuscle (about 4 μ in length), and often somewhat curved or broken, occur either singly or in filaments of 2 to 6 segments, and are destitute of motility (Plate VI., Fig. 1, and Fig. 143, *a*). They are amongst the most difficult of bacteria to stain, aqueous solutions of the anilin dyes penetrating them only after prolonged action, and even then not into all the rods; hence they are usually stained with solutions containing *mordants*, which, however, they then retain very thoroughly.

In stained preparations, particularly those made from sputum, spots which remain unstained are often seen at regular intervals in the filaments of bacilli, such filaments then looking as if composed of granules. These are probably merely vacuoles, but at all events cannot be spores.

The tubercle bacilli are counted amongst the obligate parasites, inasmuch as they are incapable of thriving in the outside world, except in artificial cultures. They grow only upon solidified serum, glycerin agar (3 to 5 per cent. of glycerin), and glycerin meat bouillon, and everywhere very slowly. The optimum temperature is about 37° C.

On *serum or glycerin agar* there form, after a lapse of two or three weeks, small dry greyish-white scales or fragments, which in freely-growing cultures coalesce in two or three weeks more into an uneven greyish-white coating. This may even extend as a pellicle over the surface of the water of condensation also, but without rendering it turbid.

In *glycerin bouillon* there form greyish-white scales and fragments, which only at times unite into larger conglomerations.

The tubercle bacilli are the exciting cause of tuberculosis, including under this term, however, the caseating inflammations, scrofula, lupus, and tubercular disease of the serous membranes (*Perlsucht*).

In man, infection takes place most frequently by the inhalation of tubercular sputum which has become dried and reduced to dust; and next by the introduction of tubercle bacilli with the food (oftenest in the unboiled milk of tubercular cows); by penetration of the bacilli into wounds of the skin and mucous membranes; and perhaps also by transmission of tubercle bacilli to the ovum with the semen, or to the fœtus through the placenta.

The entrance of tubercle bacilli into the tissues is followed by a growth of the fixed cells of the latter, from which there are formed cells of larger size and usually containing oval vesicular nuclei which do not stain very deeply, *epithelioid cells* (Fig. 60, *a*).

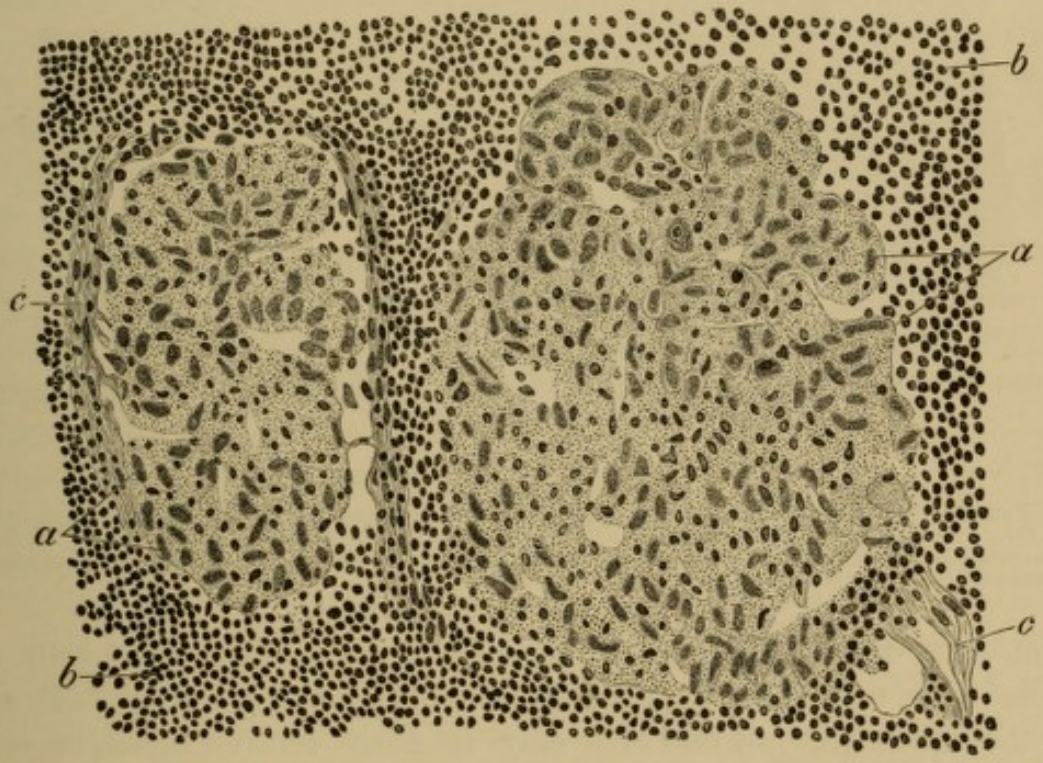

Fig. 60.—Two Epithelioid-celled Tubercles in a Lymphatic Gland. × 240. (Alum cochineal.) *a*, Epithelioid cells; *b*, Round cells of gland; *c*, Reticulum.

These then by their accumulation form rounded tolerably sharply-defined nodules containing no blood-vessels (*epithelioid-celled tubercles*). The stroma of the parent tissue, being forced apart by the epithelioid cells, assumes a more or less distinctly reticular structure as far as the tubercle extends (*reticulated tubercle;* Fig. 61, *d*). A further result is usually the emigration from the neighbouring blood-vessels of leucocytes, mostly of the mononuclear variety, which collect as a rule at the periphery of the nodule (Fig. 61, *a*), but may also penetrate into its interior; and when the emigration takes place very early, or at all events to an excessive degree, nodules occur which are composed exclusively of lymphoid cells (*lymphoid tubercles*). In the centre of tubercles, especially when slow-growing and poor

in bacilli, *giant cells* (Fig. 61, *c*) are tolerably often found; that is, polynuclear cells which are formed by continued proliferation of the nuclei without subsequent division of the cells (*giant-celled tubercles*).

When the tubercle has attained a certain size it caseates from the centre outwards (Fig. 61, *e*), its cells dying and shrivelling up (p. 63), until finally a molecular detritus is left which at first

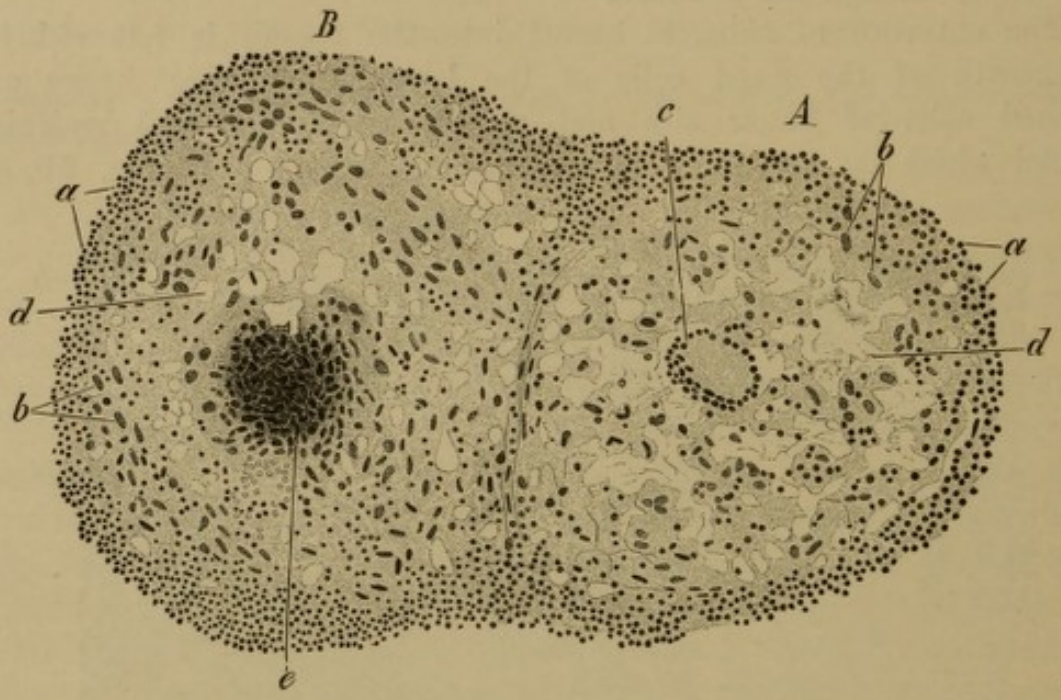

Fig. 61.—Two Young Tubercles of the Spleen in General Acute Miliary Tuberculosis. × 240. (Hæmatoxylin and eosin.) *A*, Giant-celled tubercle; *B*, Tubercle with commencing caseation; *a*, Leucocytes; *b*, Epithelioid cells with elongated nuclei; *c*, Giant cells; *d*, Connective-tissue reticulum; *e*, Caseation.

stains even more deeply than normal, but at a later stage will no longer take up colour at all. As the giant cells are also affected by the caseation, but at first only in their centre, there is very often seen in them a perfectly characteristic marginal arrangement of their nuclei.

New nodules soon develop in the neighbourhood of the first, and unite with one another to form ever-enlarging masses and foci, visible even to the naked eye (*conglomerate tubercles*). When the tubercles lie near a free surface or natural cavity, caseation is, as a rule, eventually succeeded by softening and breaking down, so that *ulcers* or *cavities* are formed. The neighbourhood of the tubercle always shows inflammatory changes, which sometimes become so prominent that it is no longer possible to make out any distinct nodules.

Tuberculosis is at the beginning a *local* process, which does not always, however, develop at the point of entry of the tubercular virus, but often in localities very far removed from it. In favourable cases it also remains local, the accompanying inflammatory growth of the

tissues gradually leading to the formation of cicatricial tissue, by which the tubercular products, together with the bacilli, are to a certain extent encapsuled. Subsequently a deposition of lime-salts or *calcification* takes place, and if the tubercle bacilli also die (which sometimes, however, does not happen until very late), the process heals, leaving a cicatrix. In other cases, however, the tubercle bacilli become further disseminated, causing infection of neighbouring or remote tissues and organs. This dissemination takes place either by the *lymph paths* (the most frequent mode), by *excretions* (*e.g.*, infection of the respiratory passages and digestive tract by the expectoration or swallowing of tubercular sputum, or of the urinary organs by urine containing bacilli, and so on), or by the *blood-vessels*. Should a tubercular nodule, very rich in bacilli, break into the latter or into the thoracic duct, the circulation may be inundated with tubercle bacilli and a *general miliary tuberculosis* be set up as the result.

The tubercle bacilli are present not only in the tubercular tissues but also in the excretions coming from them, *e.g.*, sputum, pus, fæces, and urine, and in general acute miliary tuberculosis in the blood also. They are generally found in greater numbers the more rapid the course run by the process, and *vice versa*. In chronic forms they are sometimes extraordinarily scanty, as, for instance, in tuberculosis of bones and joints, scrofula, and lupus. In the tissues the bacilli lie either free or in the interior of cells; but in the caseous parts they are mostly already dead, which is also the reason why in the giant cells they are usually met with only in the vicinity of the nuclei.

Inoculations of pure cultures or of tuberculous substances into animals (guinea-pigs and rabbits) may be made in different ways; subcutaneously, into the anterior chamber of the eye, into the abdominal cavity, into the circulation, or by feeding or inhalation. The result, except when they are introduced into the circulation, is at first a tubercular process at the site of inoculation, this process then extending with greater or less rapidity.

Methods.—The following is the simplest method of staining *cover-glass preparations:*—The cover-glasses are laid upon the surface of anilin or carbolic fuchsin, which is heated until bubbles rise, after which they are washed in water and immersed in a concentrated alcoholic solution of methyl blue until they appear entirely blue, which usually takes only a few minutes. They are then washed again in water, dried, and examined.

The red of the tubercle bacilli is brought out with peculiar distinctness when the above method is modified according to Czaplewski's process, viz., by immersing the cover-glasses, after staining in fuchsin, first for some seconds in *fluorescein methyl blue*—that is to say, in a saturated solution of methyl blue in concentrated alcoholic fluorescein—and after that for as short a time in the concentrated alcoholic solution of methyl blue.

The *Koch-Ehrlich method* consists in immersing the cover-glasses, after staining in warm anilin fuchsin or anilin gentian violet, for some seconds in dilute nitric acid (1 part of the concentrated acid of the Austrian pharmacopœia[1] to 6 parts water), and then in dilute (70 per cent.) alcohol until they cease to give up colouring matter, after which they are washed in water and counter-stained in aqueous methyl blue or vesuvin respectively.

The *Ziehl-Neelsen method* differs from the foregoing in the use of carbolic fuchsin for staining, and of 5 per cent. sulphuric acid, instead of nitric acid, for decolorising.

By the *Gabbet-Ernst* method, which has been much used of late, the cover-glasses are immersed for two minutes, without warming, in carbolic fuchsin, and, after being washed in water, for one minute in a mixture of 100 parts of 25 per cent. sulphuric acid and 1 or 2 parts methyl blue.

All these methods have the advantage that not only the ground, but also any other bacteria which may occur along with the tubercle bacilli, are coloured by the double staining; but, on the other hand, the staining of the ground has the disadvantage that tubercle bacilli may be concealed by it, especially if it proves very intense. In order to obviate the latter fault the cover-glasses stained with carbolic fuchsin, after being dipped for some seconds in dilute nitric acid[2] and rinsed in water, may (partly following Kühne's method) be brought for one or two minutes into a concentrated alcoholic solution of picric acid, which causes the ground to assume a yellow coloration that does not in any way mask the red tubercle bacilli; but of course in this case the simultaneous staining of other bacteria must be dispensed with.

To examine *sputum* for tubercle bacilli, a small particle, which should in all cases be taken only from the opaque or crumbly parts, is placed upon a cover-glass, a second cover-glass is laid over it, and the tenacious sputum is then distributed in as even a layer as possible by repeated pressure on the glasses, after which the latter are drawn apart slowly and in a horizontal direction. When the sputum is of a very tenacious consistency, some help may also be gained by mixing it with about the same quantity of more or less concentrated solution of borax, and then shaking them up well together or rubbing in a mortar.

As the tubercle bacilli may be very unevenly distributed in the sputum, the method of Biedert is to be recommended in those cases where the actual number of bacilli present is small. In carrying out this method, about a tablespoonful of sputum is agitated with two tablespoonfuls of water and 4 to 8 drops of caustic soda solution, and boiled with gradual addition of 4 to 6 tablespoonfuls of water more until a tolerably fluid mass is formed, which is allowed to settle in a conical glass for a period of one or two days; or sedimentation can be brought about in a few minutes by the use of Stenbeck's centrifugal machine. The sediment is then examined as above. A similar procedure may be followed in examining the fluid of *pleuritic or peritoneal exudations* for tubercle bacilli.

In attempting the demonstration of tubercle bacilli in *urine*—in which they are either very abundant and then frequently arranged in coiled or S-shaped groups, or else are very scanty—three possible cases have to be considered: the

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[1] [The strength of the Austrian concentrated acid is only 48 per cent., whereas that of the B.P. is 70 per cent.]—*Tr.*

[2] In all methods involving the use of a mineral acid the preparations must not remain in the latter until completely decolorised, otherwise the tubercle bacilli may also lose their colouring matter.

urine may be comparatively clear, in which case it is at once sedimentated by means of Stenbeck's apparatus; or it may have an extremely purulent consistency, and is then first treated by Biedert's method before being placed in the centrifugal machine; or, lastly, it may be very rich in urates. In the latter case, according to the process of Sehlen-Wendriner, there is added to the urine, placed to sediment in a pointed glass, about one-fifth to one-third of its bulk of a solution of borax and boric acid prepared in the following manner:—12 per cent. of powdered borax is dissolved in hot distilled water, a like quantity of boric acid is gradually added with shaking, and the solution is filtered while warm; when allowed to stand for a considerable time a crystalline deposit forms in the bottle, but adheres so firmly to the wall that the solution itself remains clear. The uric acid, urates, and earthy phosphates are dissolved by mixture of the urine with this solution, whilst the organised elements remain unchanged. This mixture may then be allowed to stand in a conical glass until sedimentation is complete without having to fear decomposition of the urine, or it may be at once subjected to the process of centrifuging.

When examining the *intestinal contents* for tubercle bacilli, the flakes composed of pus cells are sought out. If tubercle bacilli are found, however, they may also be derived from swallowed sputum. It need scarcely be said that they must not be confounded with the spores of a species of bacterium often met with in the intestine, which retain the first stain just as do the tubercle bacilli, but are oval and much thicker than the latter.

While it is possible to draw a certain deduction as to the existence of tubercular disease from the presence of but one single tubercle bacillus in the excretions, one must be very cautious in coming to conclusions when examination gives negative results, as in many chronic forms of tuberculosis the actual bacilli may be very few in number, and on the other hand need not necessarily be always present in the excretions.

The examination of *sections* for tubercle bacilli is done in the following manner:—The sections are left for twelve to twenty-four hours in anilin fuchsin or anilin gentian violet, or for one hour in carbolic fuchsin, are then dipped for some seconds into dilute nitric acid, decolorised in alcohol as long as any stain comes away, and finally counter-stained for some minutes in aqueous methyl blue or vesuvin, as the case may be.

The Gabbet-Ernst method (see above) is also suitable for sections, and lastly, the tubercle bacilli in sections may also be stained by Gram's method [in which case the sections should be left in the violet stain for 24 hours], or with Löffler's or Kühne's methyl blue.

With regard to the cultivation of tubercle bacilli in the pure state, which is rather difficult, the best method is to crush the tuberculous substance between two sterilised knives or microscopic slides, and then to rub[1] it upon the moderately firm surface of serum[2] or glycerin agar by means of a platinum wire shaped

[1] The seed material must also be firmly rubbed into the nutrient medium when making further inoculations from cultures; and if it is desired to obtain very luxuriant growths, the water of condensation should from time to time be made to flow over the inoculated surface of the agar.

[2] Serum may also be sterilised by allowing excess of chloroform (which is soluble in serum to about 0·4 per cent.) to act on it for some weeks or months in sterile vessels, which must be well closed with paraffined plugs of india-rubber.

like a spatula, but without breaking the surface. The outer surface of the cotton-wool plugs having been singed and moistened with corrosive sublimate, the test-tubes are covered with india-rubber caps[1] likewise disinfected in sublimate, and are kept at incubation temperature for four or five weeks, or even longer.

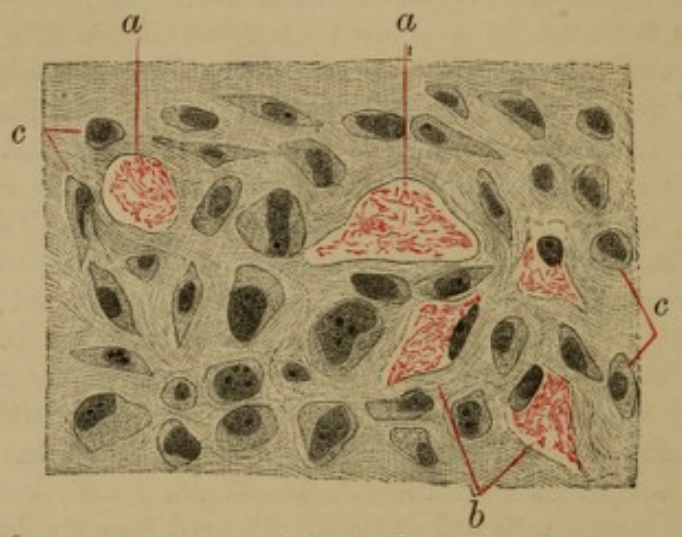

FIG. 62.—A PORTION OF A LEPROUS NODULE IN THE SKIN. × 925. (Stained by the Koch-Ehrlich method.) *a*, Large hyaline cells devoid of nuclei (*lepra cells*), packed with bacilli; *b*, Lepra cells containing bacilli, but still retaining nuclei; *c*, Round and elongated cells without bacilli.

13. (iv.) **Bacillus Lepræ.**—The bacilli of leprosy strongly resemble those of tuberculosis, differing from them at most in being somewhat shorter and having pointed ends (Fig. 62). In their behaviour towards anilin colours, also, there exists only a difference in degree, as they generally stain more readily and quickly than the tubercle bacilli, so that they can be well dyed *even with simple aqueous solutions;* but if they are treated with solutions containing mordants they retain the colouring matter just as firmly as do the tubercle bacilli. The spots in the bacilli which remain unstained have the same significance as those in the tubercle bacilli.

The cultivation of lepra bacilli in a manner admitting of no doubt has hitherto been as unsuccessful as has inoculation of animals with the products of leprous disease. Nevertheless, there is scarcely any doubt that the bacilli described are the cause of leprosy, inasmuch as they are only found in that disease, and are present in very large numbers.

Leprosy affects chiefly the *skin and peripheral nerves*, but also extends to the neighbouring lymphatic glands and mucous membranes, rarely to other organs. It is characterised histologically by the occurrence of nodular and cord-like infiltrations (Fig. 63, *c*) composed of a vascularised granulation tissue, in which, however, not only small round cells (leucocytes) are found, but also larger

[1] In general the india-rubber caps must always be made use of where it is desired to prevent drying up of the medium in cultures which have to be kept in the thermostat for any length of time.

(epithelioid) cells of a round, spindle, or club shape, and sometimes even giant cells. A more or less abundant fibrillated interstitial substance lies between the cells.

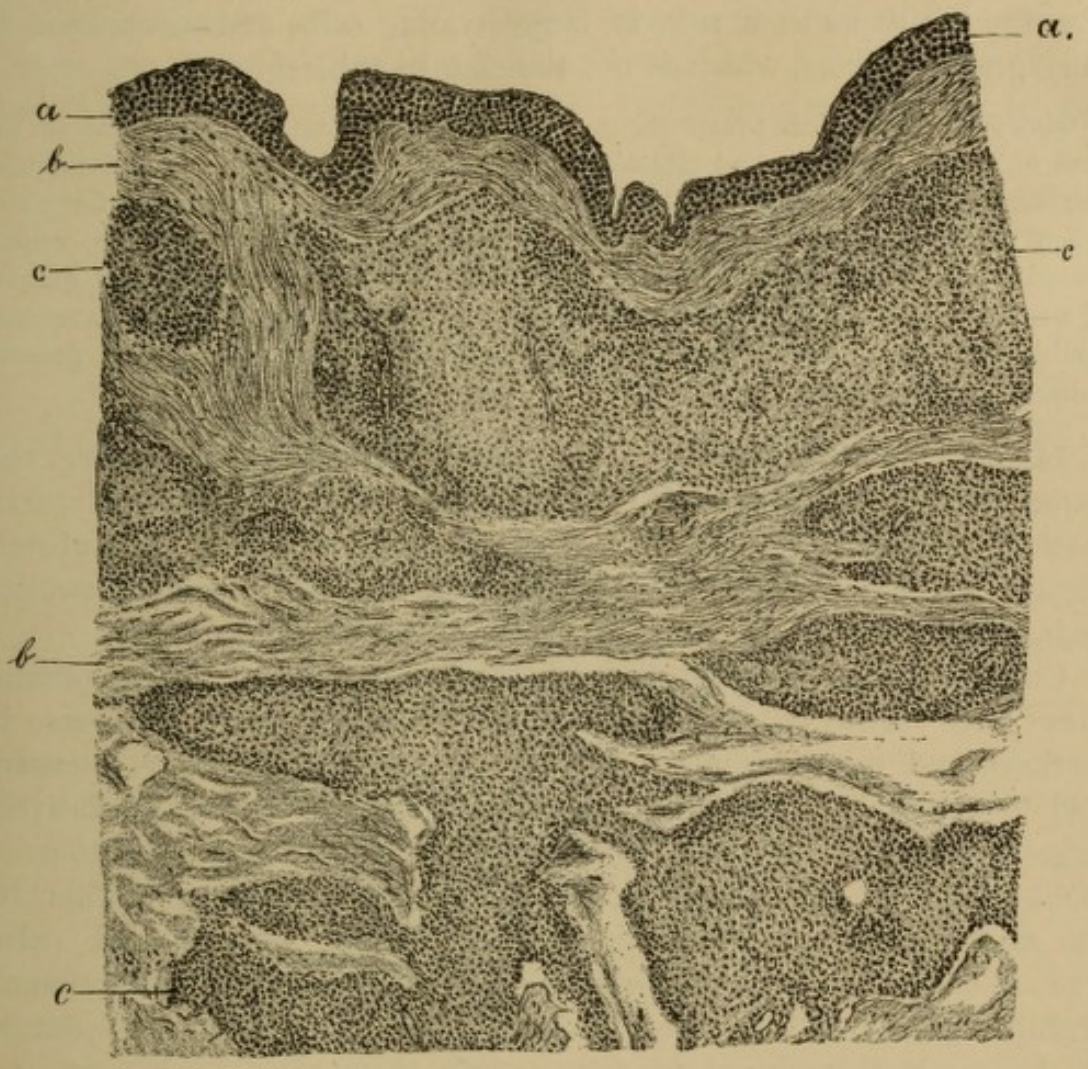

Fig. 63.—Lepra Nodosa of the Skin. × 65. (Alum cochineal.) *a*, Epidermis; *b*, Cutis; *c*, Infiltration of cells in the form of nodules and bands.

In the skin the chief seats of infiltration are the cutis (excepting the uppermost stratum) and subcutaneous tissue, especially in the vicinity of the sweat-glands and hair-follicles; in the nerves, the interstitial connective tissue. Caseation never occurs, and ulceration only from external causes. In the *macular* form of leprosy, subsidence of the hyperæmia is followed by a formation of pigment.

The lepra bacilli are usually present in great numbers, and lie for the most part in large round or oval hyaline cells, often devoid of nuclei (Fig. 62, *a*), which are almost completely packed with them (*lepra cells*); but in the diseased nerves they are chiefly found in the ganglion cells, which then degenerate. Whether leprosy is transmitted by contagion or inheritance, or in both ways, is a question on which opinion is still divided.

Leprosy may be distinguished from tuberculosis by the absence of the typical epithelioid and giant-celled tubercles met with in the latter, and above all by the non-occurrence of caseation. In leprosy also the bacilli lie as a rule in large hyaline cells, and are present in very great numbers, which is not the case in tuberculosis.

Methods.—*Cover-glass preparations* and *sections* are stained exactly as in the case of tubercle bacilli, and Gram's method may also be used. To distinguish the bacilli from those of tubercle it is recommended to leave the sections for six or seven minutes in a diluted alcoholic solution of fuchsin (5 drops of the concentrated alcoholic solution to a watch-glass of water), then to decolorise for a quarter of a minute in acid alcohol (1 of nitric acid to 10 of alcohol), wash in water, and double stain in methyl blue. Whilst lepra bacilli stain red by this process, tubercle bacilli remain uncoloured.

14. (v.) Bacillus Syphilis.—The bacilli here described under this name are those discovered by Lustgarten, by means of a special method of staining. They likewise strongly resemble the tubercle bacilli, but are still oftener curved, have slightly knobbed swollen ends, and in the tissue always lie in the interior of large cells.

Cultivation has not yet been successful, and as up to the present they have always been found only in very small numbers in sections, and moreover not in all syphilitic products, their causative rôle in syphilis is still very doubtful. They are found in relatively largest numbers and with greatest certainty in the secretion of moist papules; but since bacilli which are similar and stain by the same method occur in the smegma of the prepuce and vulva (the so-called *smegma bacilli*), the *diagnostic* value of Lustgarten's syphilis bacilli is also small, apart from the complicated nature of the methods required to demonstrate them.

The syphilitic virus exists exclusively within the human organism, and can only be transmitted directly from one individual to another. In this case it usually penetrates into the organism through the skin or mucous membranes, but it may also be conveyed to the ovum in coitus, or to the fœtus through the medium of the placenta during pregnancy. On entering the skin or mucous membrane, the poison first sets up a *local* affection [*primary syphilis*] in the form of the so-called *initial sclerosis* [hard or Hunterian chancre]; but later it makes its way into the circulation, whereupon *general symptoms* ensue in the form of affections of the lymphatic glands, skin, and mucous membranes (*secondary syphilis*), and still later diseased conditions of the internal organs, bones, and blood-vessels (*tertiary syphilis*).

All these affections have the character of inflammations, mostly circumscribed, resulting in the majority of cases in the formation

of a round-celled tissue, which subsequently either atrophies again or else breaks down. The atrophy and breaking down always begin in the centre of the nodule of new tissue and progress towards the circumference. In the former the round-celled tissue may change first into a cicatricial tissue, whereas the breaking down takes the form either of caseation or of suppuration and ulceration.

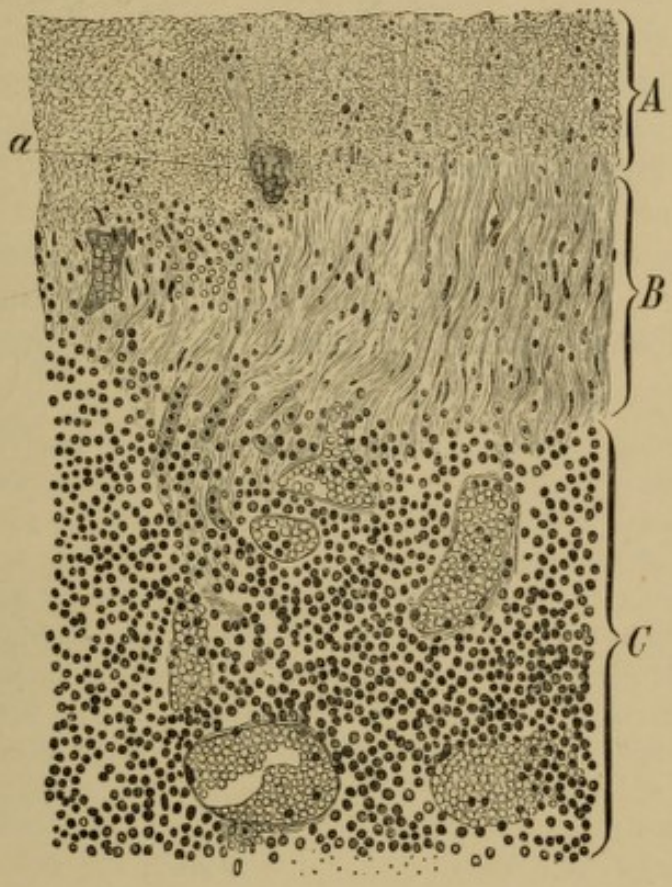

FIG. 64.—GUMMA IN THE PERIOSTEUM OF THE CLAVICLE. × 240. (Hæmatoxylin and eosin.) *A*, Caseous portion; *B*, Connective tissue; *C*, Vascular granulation tissue; *a*, Caseated blood-vessel.

The most significant form of syphilitic affection, from a histological point of view, is the *syphilitic gumma or syphiloma* which belongs to the tertiary period. So long as it is small and young, indeed, this also consists merely of a granulation tissue; but if, as it becomes larger, caseation occur in the central parts so that one or more caseous foci are thus formed (Fig. 173, *c*), the syphilitic granulation tissue immediately surrounding the latter changes into spindle-celled and cicatricial tissue. Hence *three distinct zones* can usually be made out in such preparations (Fig. 64): a caseous centre (*A*), immediately outside this a zone of spindle-celled or connective tissue (*B*), and still further out the granulation tissue (*C*), in which isolated giant cells sometimes occur (Fig. 173, *b*). The neighbouring blood-vessels also frequently show those changes

which are described as *syphilitic vasculitis* (p 206). Gummata may also suppurate or ulcerate.

Syphilis is not always easy to distinguish histologically from tuberculosis; not only is a round-celled tissue present in both cases, but nodular foci may also form in syphilis, the tissue of which possesses much similarity to that of a tubercle. Thus a young syphiloma may be confounded with a lymphoid tubercle, and a large syphiloma with a caseating tubercle, although the latter is composed at its circumference of epithelioid and round cells, and not of connective tissue unless it is actually in process of healing. The most important point of difference, however, consists in the fact that in tuberculosis, as a rule, nodules in *different stages of development* are likely to be present, for example, epithelioid- and giant-celled tubercles, as well as lymphoid; and finally, the presence of tubercle bacilli will decide with absolute certainty for tuberculosis.

Methods.—*Sections* are left in anilin gentian violet for twelve to twenty-four hours at room temperature, or for two hours at 40° C., are then washed in absolute alcohol, thence transferred, for the purpose of decolorising, to a 1·5 per cent. aqueous solution of potassium permanganate for ten seconds, and from that for one or two seconds to an aqueous solution of sulphurous acid, after which they are well washed in water. The process of decolorising in potassium permanganate and sulphurous acid, together with washing in water, is repeated until the sections have become quite colourless. *Cover-glasses* are treated in like manner, except that after staining in gentian violet they are washed in distilled water instead of alcohol.

Another method consists in staining cover-glasses for five minutes in hot, and sections for twenty-four hours in cold, anilin fuchsin, and then decolorising by immersion first in greatly diluted, and then in concentrated, solution of ferrous chloride, and finally washing, cover-glasses in water, sections in alcohol.

15. (vi.) **Bacillus Mallei.**—The bacilli of glanders (Plate VII., Fig. 1) have approximately the form and dimensions of tubercle bacilli, but are usually somewhat thicker. They lie for the most part singly or in pairs, sometimes also forming longer filaments in older cultures, and show no power of automatic movement, although a very lively molecular motion is visible. In the centre of the rodlets in stained preparations rounded structures are often seen which remain colourless but admit of being stained after the manner of spores, and hence, perhaps, possess the significance of such. Glanders bacilli stain only slightly in methyl blue, but better in fuchsin and gentian violet, as well as in Löffler's and Kühne's methyl blue, and are decolorised by Gram's method. They grow upon all our media, but only at a temperature above 25° C., best at incubation heat.

The cultures in general are distinguished by their viscosity,

but those on *potatoes* are the most characteristic, as a copious honey-yellow vegetation forms thereon, which gradually turns dark brown. Rounded colonies, which appear finely granulated under a low power and have almost smooth margins, grow upon *agar plates*. Upon *oblique agar and serum*, when the inoculation is sparing,

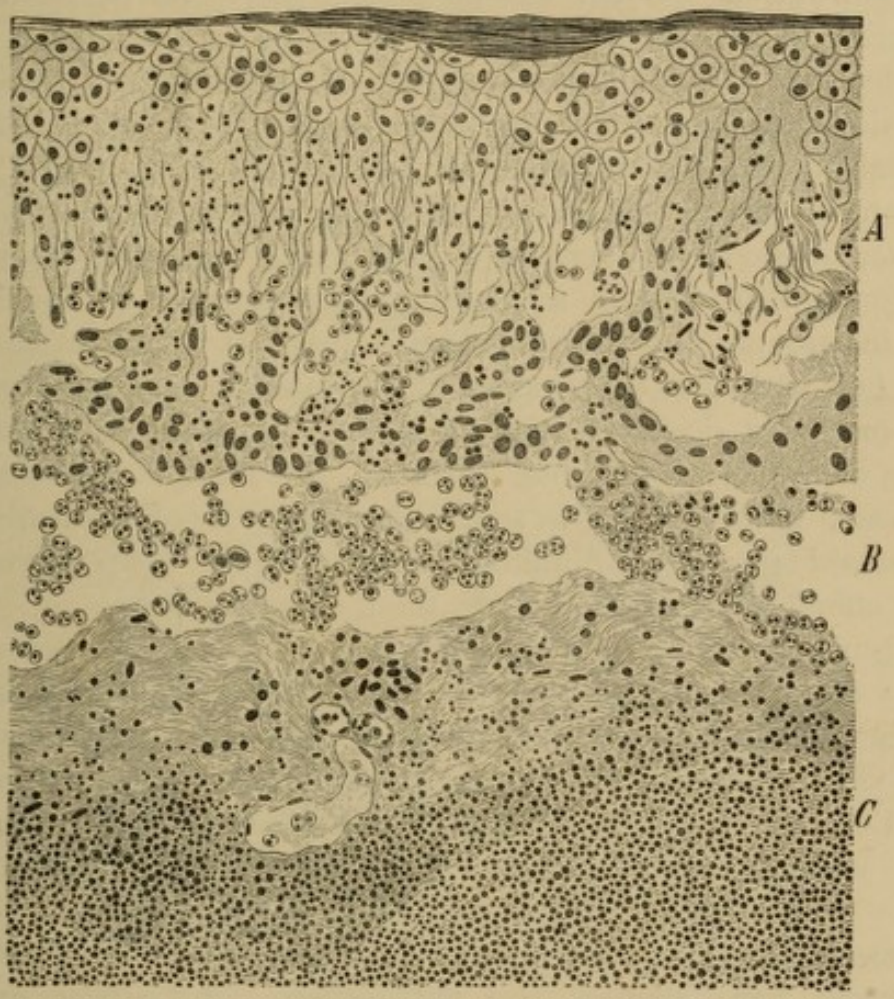

FIG. 65.—GLANDERS NODULE IN THE SKIN OF THE FOREHEAD. × 285. (Alum cochineal.) *A*, Epidermis, with commencing purulent infiltration; *B*, Collection of pus between epidermis and cutis; *C*, The uppermost portions of a glanders nodule, consisting of pus corpuscles which have partly broken down into granular debris.

single small droplets form, which are almost as clear as water, but later become whitish; when the inoculation is more plentiful, however, there develops, especially upon *glycerin agar*, an even greyish-white coating with a moist gloss. A whitish sediment, viscid like mucus, is found in *meat bouillon*.

Glanders bacilli have been demonstrated with absolute certainty to be the cause of acute and chronic glanders in animals (horses and asses) and in men. In the latter they may effect an entrance by wounds in the skin or mucous membranes, or perhaps also by the lungs.

The diseased products occur in the form of larger and smaller

nodules, less often as diffuse infiltrations, and are composed of densely-packed round cells (without giant cells), which indeed, as the nodules suppurate very rapidly, are mostly polynuclear leucocytes, whose nuclei soon break down into small, intensely-staining granules (Fig. 65, *C*). The tissue in the neighbourhood of the nodules often shows hæmorrhagic infiltration. When the glanders nodules lie in proximity to the surface of the skin or mucous membranes, a migration of pus corpuscles into the epidermis (Fig. 65, *A*), or epithelium respectively, soon follows, leading to the formation in it of little suppurative foci, or to raising of the epidermis *in toto* by pus (Fig. 65, *B*). The collections of pus next coalesce and burst, and thus give rise to the formation of *glanders ulcers*. So long as the glanders nodules are quite young they contain a tolerably large number of bacilli, lying partly in groups, and isolated bacilli may be found even in the blood; but with the suppuration of the nodules the number of the bacilli markedly decreases, and in chronic glanders it is no longer possible, as a rule, to recognise them at all with the microscope. In such cases, however, the test of cultivation, or of transmission of the diseased products to animals, may still give a positive result, and so afford information of weight for diagnosis.

Field-mice are the most susceptible of our experimental animals, as they die of general glanders even in a few days. Guinea-pigs are somewhat less sensitive, and rabbits less still, whilst house-mice are altogether refractory. In guinea-pigs and rabbits subcutaneous inoculation first sets up a local morbid process; that is to say, a nodule, which suppurates and breaks, appears after some days on the site of inoculation. The neighbouring glands then swell, and lastly metastases are found in the internal organs, though often not until weeks have elapsed. Of the organs, the testicles are often affected in guinea-pigs, and many submiliary nodules are likewise found in the spleen; in field-mice the liver shows numerous barely-visible nodules, and the spleen somewhat larger ones.

Methods.—*Cover-glass preparations* are best stained with aqueous gentian violet, or with Löffler's or Kühne's methyl blue, and then merely rinsed in water, and the latter methods are also those best adapted for *sections*.

If examination of the tissue elements be dispensed with, the sections having been stained according to Kühne's method for *several hours* in carbolic methyl blue and then subjected to the treatment with hydrochloric acid water, lithium water, and ordinary water, may be dried upon the slide by means of ball-bellows, cleared with xylol, and put up in balsam.

When it is required to establish the diagnosis in doubtful cases, especially during life, pus from unopened pustules, or from nodules which have not ulcerated, is first examined in stained cover-glass preparations. If the case is one of acute glanders, bacilli will be found (though certainly only in small numbers,

as a rule), which there is generally no difficulty in distinguishing from other pathogenic species. Should no bacilli be found, or should their nature be doubtful, cultures must be made from the pus, or it must be inoculated into susceptible animals. The mode of procedure is similar when chronic glanders is suspected.

16. (vii.) **Bacillus Typhosus.**—The bacilli of typhoid fever (Plate III., Fig. 2) are short rods about half as long as the diameter of a red corpuscle, and rounded at the ends. Their length is often scarcely three times their breadth, but in cultures they may also grow out into long filaments. They are marked, especially the filaments, by active, snake-like movements, which are set up by flagella placed along their sides. In many rods, especially when grown on potatoes at incubation temperature, round or oval shining bodies are seen at one end, which stain quickly and intensely. Besides these, spots which remain colourless (Fig. 66, *d*) are not uncommonly observed in stained bacilli at the centre or more towards the end; but

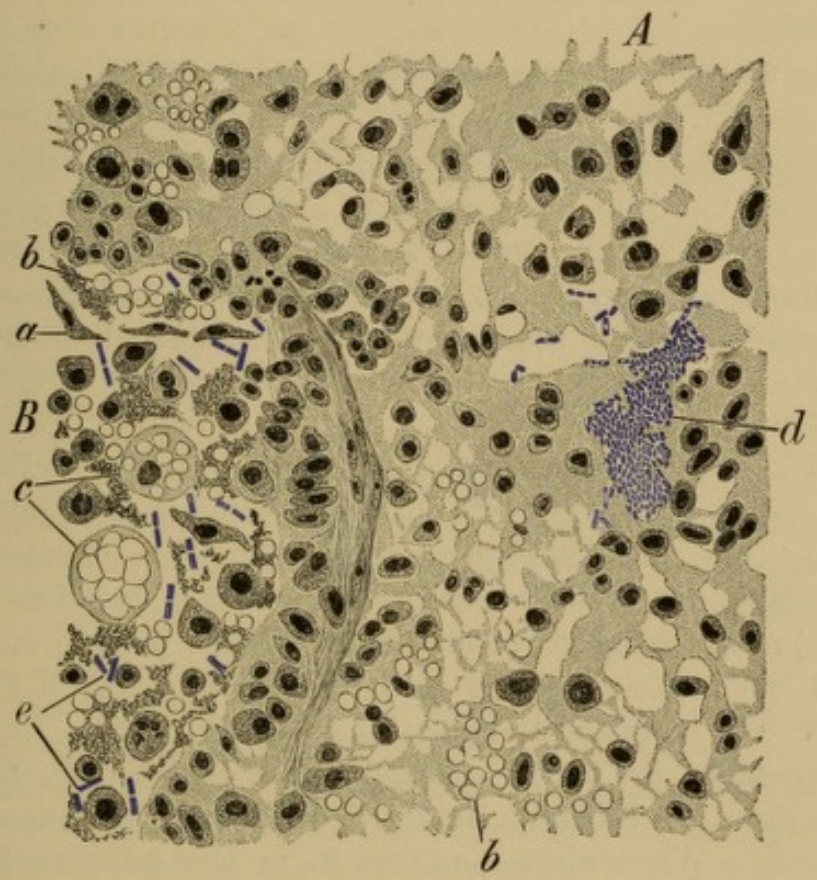

FIG. 66.—SPLEEN IN TYPHOID FEVER. × 730. (Alkaline methyl blue.) *A*, Pulp; *B*, Part of a splenic vein seen in transverse section; *a*, Separated cells from the endothelium of the vein; *b*, Red blood corpuscles; *c*, Cells containing blood corpuscles; *d*, A collection of typhoid bacilli in the pulp; *e*, Foreign bacilli in the vein, which probably had settled secondarily in the intestinal ulcers and thence made their way into the circulation.

neither these nor the bodies first mentioned have the significance of spores. Typhoid bacilli behave towards the anilin dyes as do the bacilli of glanders. They grow at room temperature and upon all media,

most characteristically on *potatoes* and *gelatin plates*. The superficial colonies on the latter constitute very thin discs, bluish-white and iridescent, but somewhat thicker and more opaque in the centre, and having indented margin. These show under a low power, in addition to the more or less indented edges and a round, yellowish, often excentrically placed nucleus, a characteristic system of numerous anastomosing lines or furrows recalling the appearance of the veins of leaves. Whilst the colonies at first appear almost evenly white under the microscope, a yellow coloration sets in later, and gradually extends from the centre outwards. The deeper colonies on the *gelatin plates*, as well as those on *agar plates*, are not characteristic.

In *gelatin tubes* the growth on the surface is somewhat better than that in the deeper part, a thin whitish vegetation with a gloss like mother-of-pearl and indented edges developing on the former, and gradually extending out to the sides. At a later period a milky turbidity, due to formation of acid, occurs in the superficial layers of the gelatin.

Upon *agar and serum* there develops a moist whitish coating, but on *potatoes* a growth forms which, though luxuriant, is generally invisible, the surface of the potato merely appearing somewhat moister; if, however, the platinum loop be passed over it, large numbers of bacilli are obtained. This *invisible* growth is extremely characteristic. Upon many potatoes, however, that is, when they chance to have an alkaline reaction, and also upon potatoes artificially rendered alkaline, there occurs a *visible* yellowish vegetation. A strong and even turbidity occurs in *bouillon*.

Typhoid bacilli furthermore grow very well in milk, and in sterilised water they can not only maintain their vitality for a considerable time, but actually multiply. They are found constantly and exclusively in typhoid fever, and in larger numbers the more recent the process, lying above all in the Peyer's patches and solitary follicles of the intestine, in the mesenteric glands, and in the spleen. In both of the last-named organs they usually occur in the form of small irregular very densely packed groups (Fig. 66, *d*), in which it is often impossible to distinguish the individual bacilli except at the circumference. When ulceration sets in in the intestine the bacilli make their way into its lumen, and may from that time on appear in the fæces also. They are less constantly met with in other organs, such as the liver and kidneys, in which they likewise occur only in groups; and they have also been found several times in the rose-spots. On the other hand, they often appear in the urine in no inconsiderable numbers, and during a rather long time. Infection with typhoid bacilli takes place through the digestive tract by the food, especially

drinking-water, in which, indeed, it is said, typhoid bacilli could be detected in several instances.[1]

The *complications* which occur in the course of typhoid fever (parotitis, laryngeal ulcers, lobular and lobar pneumonia, pleurisy, suppurative interstitial nephritis, periostitis, osteitis and arthritis, phlegmons, furuncles, and so forth) are usually the consequences of secondary infection, for the most part with pyococci, which make their way into the organs and tissues from the intestinal ulcers or the cavity of the mouth or pharynx. Still, it has been possible to find typhoid bacilli, either alone or with pyococci, in many of these complications also, especially in periostitis.

Typhoid fever cannot be set up in animals by inoculation with typhoid bacilli. Injection of cultures into the blood or digestive tract may indeed kill rabbits, but this takes place, as it appears, not by infection, but merely by intoxication.

Methods.—Typhoid bacilli can be stained in *cover-glass preparations* in the same manner as glanders bacilli, or with aqueous or carbolic fuchsin, the preparations merely requiring to be washed with water afterwards.

A similar process to that adopted with glanders bacilli is also useful for *sections*, or they may be left lying for twenty-four hours in Löffler's or Kühne's methyl blue or in carbolic fuchsin, and then merely washed in water.

Since, as remarked above, the bacilli in the spleen and mesenteric glands usually lie in groups, it is advisable first to look for the latter in sections with a low power, under which they may be recognised by their deep colour and irregular shape.

It must be borne in mind when examining urine for typhoid bacilli that the quantity of the latter present is rather variable. Sometimes, however, they are so numerous that the urine is distinctly clouded by them, remaining turbid even after filtration. In such a case a drop examined on a hollow slide without staining shows motile rods and filaments, which, if contaminations can be excluded, may be determined even by this kind of examination to be with great probability typhoid bacilli, though cultivation is necessary in addition in order to arrive at complete certainty.[2] As typhoid bacilli may occur in the urine even from the third day of the disease, the bacteriological examination of the latter has a diagnostic value which is not unimportant, and is at all events to be preferred to an examination of the stools, as the typhoid bacilli cannot appear in the latter earlier than the ninth day, and moreover do not admit of being distinguished at all microscopically, and only with considerable difficulty by cultivation, from certain fæcal bacteria.

[1] Besides this there are in water several species of bacteria which morphologically as well as in cultivations bear a greater or less resemblance to typhoid bacilli, but which still can be most certainly distinguished from the latter by the differences which they show when grown on potatoes.

[2] Other pathogenic bacteria, especially pyococci, may be found in the urine in *complications* of typhoid fever.

17. (viii.) **Bacterium Coli Commune** (including the **Bacterium Lactis Aerogenes** and **Bacillus Emmerich**).—The *Bacterium coli commune* shows a very close general resemblance to the bacillus of typhoid fever. It has approximately the same shape and size as the latter, except that the youngest individuals are often even shorter, and hence are frequently scarcely distinguishable from cocci, and it also possesses only a sluggish motility. It is decolorised by Gram's method. In artificial cultures growth takes place at room temperature.

Upon *gelatin plates* the deep-lying colonies remain small and occasionally allow a dark irregular core and a lighter circumference to be made out under the microscope. The superficial colonies, however, extend widely over the surface, have frequently a jagged or indented edge, and decrease gradually in thickness from the centre towards the circumference. Under a low power they likewise show a peculiar system of lines and furrows, but the latter are not so deep nor so sharply marked as in the case of the typhoid bacilli, and also disappear much more quickly.

On *agar plates* also the superficial colonies are much larger than the deep-lying ones, are tolerably flat, greyish-white, and show a moist gloss. Microscopically the deep colonies appear yellowish or yellow-brown, and composed of fragments of different sizes. A similar appearance is presented by the centre of the superficial colonies, whilst their peripheral part gradually grows more transparent on passing outwards, and only when a very narrow aperture of the diaphragm is used allows a fine granulation to be seen, with a concentric striation and shallow indentations at the margin.

The growth in *gelatin* and *agar tubes* as well as in *bouillon* also recalls that of typhoid cultures, but on *potatoes*, in contrast to the typhoid bacilli, a distinctly-visible vegetation of a dirty yellowish colour always forms.

The *Bacterium coli* occurs regularly in the intestinal canal, especially its lower part, in healthy as well as in diseased persons. It seems, however, to multiply very abundantly in conditions of constipation; and in slowing or complete arrest of the circulation in the intestinal wall (as for example in strangulation or extreme distension of the gut) it is likewise enabled to penetrate into the intestinal membranes and finally into the abdominal cavity itself, and then to set up a peritonitis, usually with scanty exudation. For this reason it commonly occurs also in the fluid exudation of incarcerated hernias. It likewise makes its way into the peritoneal cavity in wounds and perforations of the intestine, and the so-called *perforation peritonitis* is due altogether or in greatest part to its action. Injection of cultures of the bacterium into the peritoneal cavity of rabbits and dogs

is capable of setting up peritonitis, whilst after introduction into the blood the animals quickly perish, and usually show inflammatory appearances in the intestinal canal.

Besides the *Bacterium coli*, the **Bacterium Lactis Aerogenes** is also constantly found in the intestine when a milk diet is used. It is very similar to the former, being only distinguished from it by the fact that the colonies on *gelatin plates* are not flat but convex, that cultures in *gelatin tubes* also grow more superficially and may even take a nail form, and that gas-bubbles appear in cultivations upon *potatoes*. The species of bacterium mentioned may also be found along with the *Bacterium coli* in the exudation of the abdominal cavity in perforation peritonitis.

The **Bacillus Emmerich**, which may in like manner be present in the healthy and the diseased intestine, is also very like the *Bacterium coli*, perhaps even identical with it.

Methods.—The examination is conducted in the same manner as that of the typhoid bacillus.

18. (ix.) **Bacillus Diphtheriæ** (including the **Pseudo-Diphtheritic Bacillus**).—The bacilli of diphtheria (Plate VII., Fig. 2) are of about the same length as tubercle bacilli, but twice their thickness, are usually a little curved, have rounded ends, and are destitute of motility. As they become older not only does their length increase, but they frequently also, especially in cultures, show involution and degenerative forms, the rods swelling into bulbs at one or both ends, and usually appearing segmented; and there further occur at the poles or elsewhere, as in the typhoid bacilli, shining globules which stain much more rapidly and intensely than the remainder of the rod, but which have not the significance of spores.[1] The bacilli grow only slowly at room temperature, but rapidly, on the other hand, at that of the incubator.

On *gelatin plates* small whitish colonies form which appear yellowish-brown and coarsely granular under the microscope. The colonies on *agar plates* also are only the size of millet-seed, and microscopically show a coarsely granular texture. The growth is pretty nearly alike in *gelatin and agar tubes*, that is, principally along the thrust and only sparingly on the surface, at least in the earliest generations; but when the later generations have been reached the surface growth also becomes more vigorous.

A thick whitish coating forms on coagulated *serum* with every 3 parts of which have been mixed 1 part of bouillon, 1 per cent. of

[1] Nevertheless diphtheria bacilli can retain their vitality for a certain time even in the dried condition.

peptone, 1 per cent. of dextrin, and ½ per cent. of common salt. Small lumps form in *bouillon*, which adhere to the sides of the vessel or quickly sink to the bottom, the bouillon itself remaining clear. Diphtheria bacilli also grow perfectly well in sterilised *milk*.

The bacilli are found constantly present in diphtheria, alike whether the latter gives rise to a catarrhal, croupous, or diphtheritic exudation, whether it affects the pharynx and larynx, or the nasal cavity and the conjunctiva, and whether it occurs primarily or secondarily (in scarlatina, measles, etc.). They only occur in the *local* products of the disease, but not in the blood or internal organs; hence we must assume that the *general* phenomena in diphtheria are partly dependent on the absorption of a poison, probably a toxalbumin, produced by the bacilli, partly to be ascribed to a *secondary* infection with the *Streptococcus* or *Staphylococcus pyogenes*. The cocci mentioned, and particularly the *Streptococcus pyogenes* (Fig. 67, *c*) are certainly found with extraordinary frequency not only in

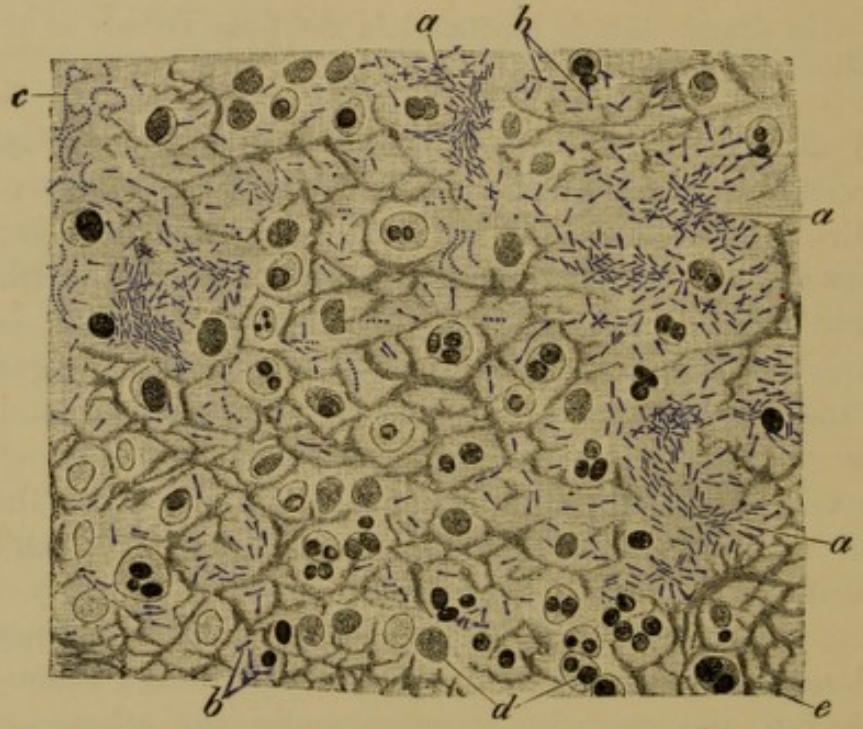

Fig. 67.—False Membrane on the Uvula in Diphtheria, with Diphtheria Bacilli and Streptococcus Pyogenes. × 925. (Alkaline methyl blue.) *a*, Groups of diphtheria bacilli; *b*, Diphtheria bacilli lying singly, some with swollen ends; *c*, *Streptococcus pyogenes*; *d*, Living and necrotic leucocytes; *e*. Reticular arrangement of trabeculæ.

the false membrane and the tissue under it, but also in the lobular pneumonia or the nephritis which often complicates diphtheria, as well as in the spleen. Thus the changes induced by the diphtheria bacillus appear to favour in an extraordinary degree the entrance of the pyococci.

The diphtheria bacillus is pathogenic for pigeons, poultry, cats, rabbits, and especially for guinea-pigs. Subcutaneous introduction

is followed in the latter by the formation of false membranes on the site of inoculation, an extensive hæmorrhagic œdema in the surrounding tissue, and not infrequently pleurisy and lobular pneumonia. Here also, however, the bacilli are present only in the false membrane.

Transmission to a *wounded* mucous membrane gives rise to a process accompanied by the formation of false membranes and resembling human diphtheria, and even paralytic conditions may follow the introduction of cultures, or of the products of cultures freed from bacteria by filtration. Consequently there can be scarcely a doubt any longer that the diphtheria bacillus is the cause of the disease. It seems, however, to be present in the pharynx even under normal circumstances, but it is not yet ascertained whether this is frequently or only exceptionally the case. Under certain conditions it is capable of penetrating even into an intact mucous membrane, but still lesions of the latter have the power to greatly facilitate the invasion.

Sometimes in addition to the true diphtheria bacillus there is found in the false diphtheritic membranes another very like it, the **pseudo-diphtheritic bacillus**. It differs from the former, however, in showing a vigorous surface growth in gelatin and agar tubes, and in causing a higher degree of turbidity in bouillon; and moreover it is not pathogenic for animals.

Methods.—*Cover-glass preparations* may be stained with aqueous fuchsin or alkaline methyl blue, and *sections* after the manner of typhoid or glanders bacilli, or else by Weigert's modification of Gram's method, with or without previous counter-staining.

19. (x.) **Bacillus Tetani.**—In this instance (Plate VI., Fig. 2) we have to deal with tolerably long motile rods, which frequently grow out into threads, and form terminal spores in the organism as well as in cultures, the end in question becoming swollen, whilst the other may be attenuated, so that a form resembling that of a pin is the result. The bacilli stain easily, and Gram's method may be employed. Tetanus bacilli grow at room temperature, and still better at that of the incubator, but only when atmospheric oxygen is absolutely excluded—that is to say, they belong to the obligate anaerobes.

On *gelatin plates* radiating colonies form which liquefy the medium, and whose border shows very numerous fine processes under the microscope. A *thrust culture* made in a tube filled high with grape-sugar gelatin remains sterile in the upper part of the needle-track, while numerous pointed processes radiate out from the lower parts, and liquefaction of the gelatin sets in at the same time. In *agar tubes*

the growth in the needle-tract extends somewhat higher up; and numerous bubbles of gas, having a peculiarly unpleasant smell, are also liberated. The generation of gas is particularly abundant in *bouillon* containing grape-sugar.

The bacilli are present in the tetanus of adults as well as of new-born infants, and in that of animals (horses and asses), occurring as a rule only in the secretion of wounds. Other bacteria are usually present in addition, mostly pus cocci, but also anaerobic species. Outside the organism they have been found up to the present in garden earth, old rubbish of walls, sweepings, manure, etc., so that their entrance into the organism probably occurs as a consequence of the contamination of wounds or other injuries with the substances just mentioned.

The most susceptible of our experimental animals to inoculation with tetanus cultures are mice, and in somewhat less degree guinea-pigs and rabbits. The tonic spasms set in first in the groups of muscles lying nearest to the seat of infection, but they then extend over the entire body. The anatomical changes found also in experiments upon animals are extremely slight, consisting at most merely in a somewhat infiltrated appearance of the site of inoculation. Even the bacilli may be wanting there, or may be present in very small quantity. It must hence be assumed that the bacilli produce a very strong poison (probably a toxalbumin) which still continues to act after their death.

Methods.—*Staining* may be done with any basic anilin colour desired, as well as by Gram's method.

Cultivation is carried out according to the methods given on p. 44 for strict anaerobes. As in the human organism the tetanus bacilli are usually mixed with other bacteria, isolation is attained by first transferring the wound-secretion containing the bacilli to oblique agar, and keeping it for some days at incubation temperature. The mixed culture which develops in this way is then heated to 80° C. for about an hour in a water-bath, after which only the spores of the tetanus bacilli remain alive. Finally, a platinum loopful is either conveyed from this culture, observing the directions given on p. 44 for the cultivation of anaerobes, into test-tubes filled high with melted gelatin (or agar), or is mixed with melted gelatin and poured out into flat culture flasks like those of Lipez, through which hydrogen is then passed.

20. (xi.) **Bacillus Pneumoniæ.**—This bacillus (Plate IV., Fig. 2) is sometimes so short as to resemble a coccus, but frequently attains the length of typhoid bacilli, and, like them, has rounded ends. It is, however, perceptibly thicker, and is devoid of motility. The rodlets often lie in rows of from two to four, and in cultures, as well as occasionally in tissue, form even longer filaments. A characteristic feature is that

in the organism as well as in cultures it very often shows a broad gelatinous envelope or *capsule*, visible with or without staining, which may even enclose several rods at once, and exactly corresponds to the capsule of the *Diplococcus pneumoniæ*. The bacillus readily takes the anilin dyes, but is decolorised when treated by Gram's method. Growth progresses even at room temperature, and upon all our media, the cultures being of a viscid consistency like those of glanders bacilli, and often showing a generation of gas.

The superficial colonies on *gelatin plates* grow very vigorously in the vertical direction, and are white, with a gloss like porcelain. Under the microscope they appear globular and smooth-edged, streaked with light or dark grey, or of uneven grain. On *agar plates* there form flat greyish-white colonies of a jelly-like appearance, which show under the microscope a structure similar to those on gelatin plates.

The most characteristic growth is that in *gelatin tubes*. In these, namely, the so-called *nail-culture* forms, where, in addition to the growth along the needle-track, there develops on the surface of the gelatin, provided it is firm enough, a more or less raised white top, with a porcelain-like gloss, and resembling the head of a nail. In older cultures the superficial layers of the gelatin assume a light-brownish tint. On *agar* and *serum* a greyish-white opalescent coating forms, on *potatoes* a thick cream-coloured fur, and in *bouillon* an even turbidity.

The *Bacillus pneumoniæ* has been found in lobular and lobar pneumonia, alone or in association with the *Diplococcus pneumoniæ* or the pyococci; also in pleurisy, endocarditis, otitis, and meningitis, though as yet in but few cases. Nevertheless there seems to exist no doubt that it gave rise to the disease which was present in the cases alluded to. In those instances in which it forms the cause of a lobar pneumonia it is usually present in perfectly enormous numbers, and most plentifully in situations where the process is still quite recent. There also it generally shows a well-developed and easily-stained capsule, whereas in parts where the process is older, not only does it no longer possess a capsule but it has actually become narrower, stains worse or shows spots which remain unstained, and, in short, is in the act of dying. In pneumonia it may also be present in the sputum, and even in the blood, spleen, and kidneys; and if pleurisy exists simultaneously, of course also in the pleuritic exudation, its presence in quantity imparting a viscid consistency to exudations, particularly that of pneumonia. It must also be remarked that it can sometimes be detected even in healthy people in the normal or inflamed nasal cavity, as well as in the saliva; but cultivation is the only mode of doing this

with certainty. Its entry into the lungs or other organs would be favoured by the same predisposing influences as that of *Diplococcus pneumoniæ*.

Of the animals commonly used in experiment, mice (and, in a less degree, guinea-pigs and dogs) are susceptible to the *Bacillus pneumoniæ*, whereas rabbits generally prove refractory. Inhalation of cultures or injection into the thoracic cavity is followed by pneumonia and pleurisy, together with swelling of the spleen, and in this case the exudations, spleen, and blood contain the bacillus in very copious quantity, and usually with a well-developed capsule.

Methods.—*Cover-glass preparations* are stained as in the case of the *Diplococcus pneumoniæ*, especially when the capsule is to be demonstrated at the same time; but in preparations made from cultures the capsule is sometimes successfully stained also by treatment with simple aqueous fuchsin and subsequent washing in water. The decolorisation of the bacillus under Gram's process forms a means of distinguishing it from the *Diplococcus*.

Sections are immersed, in order to stain the capsule, in a mixture of 50 grm. concentrated alcoholic gentian violet, 100 grm. distilled water, and 10 grm. glacial acetic acid, during twenty-four hours, and are then decolorised in dilute acetic acid. Otherwise they can be treated with Löffler's or Kühne's methyl blue, with which also a feeble staining of the capsule may sometimes be obtained.

21. (xii.) **Bacillus Rhinoscleromatis.**—This shows a great similarity to the *Bacillus pneumoniæ* in its morphological character and behaviour in cultivation, the difference between them consisting merely in the facts that the bacillus of rhinoscleroma does not decolorise by Gram's method, or at least not so easily; that it furthermore forms a transparent, greyish-white, and less prominent head, whereas in the case of *Bacillus pneumoniæ* the head looks perfectly white and opaque; and that the rhinoscleroma bacillus shows little or no virulence for our experimental animals.

It has been found constantly up to the present in a particular form of chronic inflammation of the naso-pharyngeal or laryngo-tracheal mucous membrane named rhinoscleroma, which causes the formation of a granulation tissue passing in places into cicatricial tissue (Fig. 68). In this, however, in addition to the densely packed small round cells, there are found in varying numbers peculiar homogeneous cells of larger size and usually devoid of nuclei, which are most probably derived from the former by hyaline degeneration and are the special seat of the bacilli, though the latter may also be present in the dilated lymph-spaces, or in or between the small round cells.

Introduction of cultures into animals has hitherto failed to set up a process like rhinoscleroma; nevertheless the bacilli described,

which ought not to be identified with the *Bacillus pneumoniæ*, are most probably the cause of the process in question.

Method.—Examination may be carried out as with the *Bacillus pneumoniæ*, and Gram's method, as well as Weigert's modification, is also admissible.

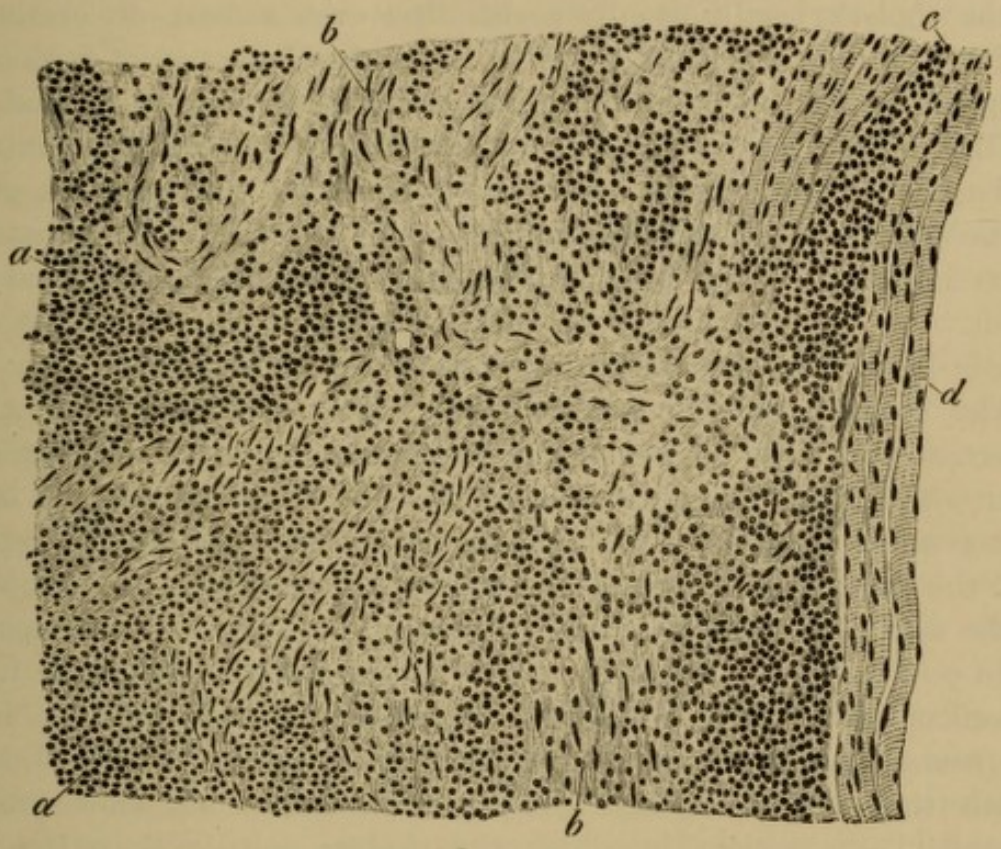

Fig. 68.—Rhinoscleroma of the Nose. × 285. (Alum cochineal.) *a*, Tissue of round cells; *b*, Connective tissue rich in spindle cells; *c*, A process composed of round cells pushing in between the transversely striated muscle fibres, *d*.

(*c*) *PATHOGENIC SPIRILLA.*

22. (i.) **Spirillum (Vibrio) Choleræ Asiaticæ** (including the **Spirillum Finkler-Prior**).—This micro-organism appears in the form (Plate VIII., Fig. 1) of more or less curved rods which, since the two ends do not lie in the same plane, are to be regarded as segments of a screw, and thus as screw-bacteria or spirilla. The degree of curvature varies from that of a comma (hence also the designation of *comma bacillus*) to a semicircular form, whilst on the other hand the youngest and shortest individuals are nearly straight. As regards their other characteristics, the cholera bacteria are shorter than tubercle bacilli, but much thicker, have blunt ends, and show a very lively motility, due to a flagellum curved in a slightly wavy manner and usually situated only at one end of the rod. The bacteria lie singly for the most part, or two unite so as to form the figure of an **S** lying on its side; but sometimes also more extensive

combinations occur in the form of long spirals, generally when the conditions of growth are unfavourable.

While on one hand any kind of spore-formation is denied, others state that they have observed the existence of arthrospores; but at all events the latter must possess little power of resistance, as the cholera bacilli usually perish after even a short desiccation, as well as at a temperature above 50° C., or under the action of weak acids. They can be stained by all dyes, but decolorise by Gram's method.

They grow even at room temperature, and upon all our nutrient media, liquefying gelatin and serum; and they may also be grown anaerobically, under which condition they produce toxic substances much more rapidly and energetically, but at the same time become very sensitive to external influences. The growths of cholera spirilla upon gelatin plates and in gelatin tubes are the most characteristic.

The colonies on the *gelatin plates*, when examined with a low power, at first show an indented contour and uneven surface, are of a clear white colour and glassy sheen. Liquefaction of the gelatin begins on the second or third day, and sinks downwards in a funnel shape, so that the culture plate looks as if dotted with holes or air-bubbles, whilst at the same time the colonies progressively acquire a rosy shimmer.

In *gelatin tubes* liquefaction also takes place in a funnel form in the superficial part of the needle track, and as evaporation of the liquid progresses simultaneously a cavity like an air-bubble is formed, below which the culture collects. Liquefaction makes but slow progress downwards, a pellicle, in which the cholera spirilla show the most diverse involution, forms, not uncommonly developing on the surface at a later period.

A whitish culture forms upon *agar*, which is not characteristic, but in which the bacteria will retain their vitality for nearly three-fourths of a year, whereas they die much more rapidly in gelatin. The growth upon *serum* is also not characteristic.

In *bouillon*, which, especially in a very dilute state, constitutes an exceedingly good nutrient medium for cholera bacteria, a wrinkled membrane forms upon the surface, particularly at incubation temperature, whilst the liquid itself is little clouded. If dilute sulphuric acid be added to such a culture, a characteristic purple-red or reddish-violet reaction is produced (*indol reaction*). Upon *potatoes* the cholera bacilli grow only at incubation temperature, if at all, and then form a deposit like a culture of glanders bacillus, but often somewhat less deeply coloured. Furthermore, they grow in sterilised milk, without producing any noticeable change in the latter; and also upon moist linen or moist earth. In sterilised water, too, they can multiply, whereas in ordinary water they succumb more or less speedily in the struggle with the

other bacteria—at least, in experiments; but under natural conditions, on the other hand, multiplication of cholera bacteria in impure water has also been observed.

The bacteria are present exclusively and constantly in Asiatic cholera, but only in the intestine, especially the lower portion of the ileum, and the evacuations therefrom, whilst they are usually wanting in vomited matters. They occur in larger numbers the more recent and intense the process, and may even be present as practically pure cultures in the intestinal contents; whilst, when the process has gone on longer, they gradually decrease in numbers, and in the end disappear altogether. Outside the organism also the cholera spirilla in the stools usually perish fairly quickly, but cases have been observed in which they behaved in the opposite manner.

Cholera is a disease which is endemic in India, and can only exist with us through being imported. Infection always takes place by way of the digestive tract, along with the food, especially with drinking water when cholera bacteria are present in it and are not killed by the gastric juice. As during the course of the disease they can only vegetate in the intestinal canal, we must suppose that the general symptoms peculiar to cholera are due to absorption of a poison produced by the cholera bacteria.

Guinea-pigs are the most suitable animals for artificial infection, but about 5 c.cm. of a 5 per cent. solution of sodium carbonate must first be introduced by means of an œsophageal tube, in order to neutralise the gastric juice, the intestinal peristalsis must be diminished by injection of tincture of opium (1 grm. to every 200 grm. of the animal's body-weight) into the abdominal cavity, and only after this the culture (about 10 c.cm. of a bouillon cultivation) poured in through the œsophageal tube.

The appearances presented by the intestine are similar to those seen in human cholera, the small intestine being reddened and filled with a watery fluid in which the cholera bacteria are present in extraordinary numbers and as a pure culture. Inasmuch as there is on record, besides this, an unintentional but successful experiment on a human being, the proof that these bacteria are the cause of cholera must be regarded as complete.

There exist several species of bacteria which resemble the cholera spirilla in form, though differing from them entirely in other particulars. Of these, only the **Finkler-Prior Spirillum** deserves a brief mention here, since it was at one time regarded by its discoverers as identical with the spirillum of cholera. It differs from the latter, however, even microscopically, being somewhat larger and thicker; but in addition to this,

its growth is considerably more rapid, its colonies on *gelatin plates* usually show *smooth* contours before liquefaction sets in, whilst in *gelatin tubes* the latter begins much earlier and takes a cylindrical ("stocking") form, and a greyish-yellow slimy vegetation develops on *potato* even at room temperature.

It has been found in the intestine several times up to the present, in healthy and diseased individuals, and has no infective action. If cultures of it are introduced into guinea-pigs in a similar manner to cholera bacteria the animals are certainly also destroyed, but less often, and with other anatomical appearances than are found after infection with cholera spirilla.

Methods.—*Cover-glass preparations* are best stained with aqueous fuchsin, but the staining should continue for at least ten minutes, or the solution be warmed, the preparations being then washed in water.

In examining the *intestinal contents or evacuations*, any flakes which may be present should above all be picked out and cover-glass preparations first made from them. In recent and very intense cases of cholera, in which cholera bacteria *alone* are present, a diagnosis may be made with great probability even from the examination of cover-glass preparations, but the additional test by cultivation is always necessary for complete certainty.

If the specimen examined contains other bacteria in addition to the cholera spirilla it is advisable, besides preparing the ordinary gelatin plate cultures, also to make sowings in several test-tubes containing bouillon greatly diluted (with 6 to 10 parts water), and to keep the latter at incubation temperature. Should a pellicle show itself in one or other of the test-tubes within twenty-four hours, and be found when examined under the microscope to contain suspicious bacteria, pure cultures should, on the one hand, be made from it by the plate process, as well as a fresh sowing in dilute bouillon, while, on the other, the above-mentioned indol reaction may be tried. *Sections* are stained in aqueous fuchsin for twenty-four hours, or in Löffler's or Kühne's methyl blue. The staining of the Finkler-Prior spirillum is done in a similar manner to that of the cholera bacteria.

23. (ii.) Spirillum Febris Recurrentis.—The spirillum of relapsing fever (Plate VIII., Fig. 2) occurs in the form of very actively moving wavy filaments, 16 to 40 μ in length, which are very like the spiral threads of the cholera bacteria, and can be readily stained with the basic anilin colours. They are found only in relapsing fever, and during the attack exclusively in the blood, lying singly or in groups, whilst between the attacks they accumulate in the spleen. Transmission of blood containing the spirilla has been successful in setting up relapsing fever in men and apes.

Methods.—The blood is examined either in the *hanging drop*, or in *dried preparations* stained with aqueous fuchsin or alkaline methyl blue. In the former the spirillum betrays its presence even under a low power by the currents which it sets up in the fluid. To avoid overlooking the spirilla when

present in very scanty amount, some grammes of blood should be drawn with a cupping-glass and allowed to coagulate, when the spirilla often accumulate in groups of considerable size at the periphery of the clot.

Sections are stained with Löffler's or Kühne's methyl blue.

(*d*) *ADDENDUM TO THE BACTERIA.*

24. Actinomyces.—The *actinomyces* or *ray-fungus* (Fig. 69) is at the present day rather generally counted amongst the *Cladotricheæ*, which again may either be ranked with the bacteria, or else constituted as a separate class in themselves. It usually appears in the

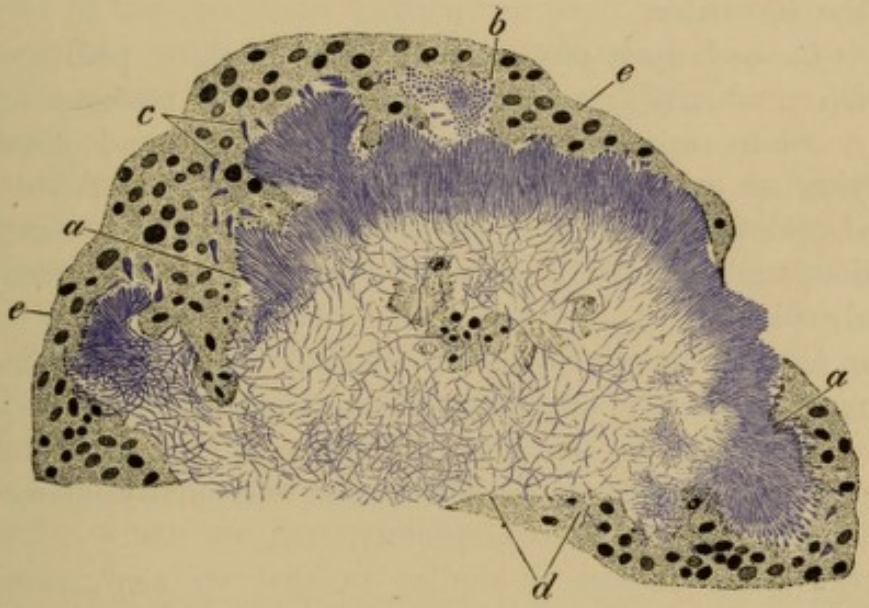

FIG. 69.—ACTINOMYCES NODULE, WITH GRANULATION TISSUE. Section, × 530. (Stained by Weigert's modification of Gram's method.) *a*, Fan-shaped bundle of "rays" with club-like swelling of the ends; *b*, Bundle of "rays" cut transversely; *c*, Clubs lying singly; *d*, Network composed of branching and partly granular fibres; *e*, Granulation tissue.

form of groups of considerable size, which can be recognised even with the naked eye as grey, whitish, or yellowish granules about the size of a pin's head or even smaller. When these are examined in cover-glass preparations (by pressing or rubbing them), in addition to numerous filaments, there are found also structures resembling rodlets and cocci. The filaments always appear more or less undulating, sometimes even spirally curved, single or branched, frequently with club-shaped swellings at their free ends, and more or less distinctly segmented. As the segments are of different lengths they resemble longer or shorter rodlets, and even coccus-like figures; and besides these, small roundish granules also occur both in the interior of the segments and free. On account of this multiplicity of forms it is customary to include the actinomyces also amongst the "*pleomorphic*" bacteria.

Sections teach us that the actinomyces form closed groups (agglomerations), in the shape of hollow globules, the spherical covering of which consists of radially arranged and very closely packed filaments branching freely and having their free ends swollen into clubs (Fig. 69, *a*), together with coccus-like figures, whilst in the interior of the sphere the threads are less branched and more regularly arranged. The older the actinomyces, the more numerous do the bulbous enlargements of the filaments become (being probably degenerative forms), and with the death of the fungus even calcification of the nodule may occur. The actinomyces may be stained by Gram's method. It grows at room temperature, but best at that of the incubator.

On *gelatin and agar plates* small greyish-white points form at first, which gradually reach the surface of the medium and then assume a white appearance. On *glycerin agar* and *blood serum* closely lying or confluent colonies form, miliary or of the size of hemp-seed, and firmly adherent to the medium. These usually show umbilication, and gradually acquire a yellowish (on serum also a yellow-red) colour.

Gelatin is very slowly liquefied, but remains clear, agglomerations of varying sizes merely appearing at the bottom. Miliary granules also form in *bouillon* on the sides or bottom of the test-tube, subsequently gather together into larger masses, and finally change into a slimy sediment, the fluid remaining clear.

The growth on *potatoes* is similar to that on agar, except that the granules assume a dry appearance and a somewhat paler colour, and pile themselves up one over the other into thick strata. The actinomyces can also grow anaerobically, and its cultures may retain their vitality for a long time even in the dried state. Whilst in young cultures only filaments are found, in older ones, just as in the fungus nodules in the interior of the organism, rod- and coccus-like figures are also met with, as well as club-shaped and globular forms.

The actinomyces is very often present, as it appears, upon certain kinds of corn, especially upon the beards of barley, and certainly in the majority of cases effects its entrance by the medium of the latter into the organism of men and animals. The most usual gate of entry is the digestive tract, in which the fungus either finds a favourable place of development at once in the cavities of the mouth and pharynx and the parts in their vicinity, or its germs pass thence into the bronchi and lungs by aspiration, or into the stomach and intestinal canal by swallowing. In some cases it penetrates into the skin from outside.

At the spot where it develops the fungus causes a formation of granulation tissue (Fig. 69, *e*), which in animals assumes a tumour-like character, but in the human being, owing to disintegration and softening, takes the form of circumscribed or more superficially extending suppurations, the characteristic fungus granules being present in the so-called pus as well as in the granulation tissue.

In *actinomycosis of the lungs* there are usually found nodular broncho-pneumonic foci consisting of granulation tissue, which later become confluent, and by softening and breaking down lead to the formation of cavities. Should the latter break through into branches of the bronchi, actinomyces granules appear in the sputum also. The spread of the process to surrounding parts may lead to formation of circumscribed "suppurations" in the mediastinum, along the ribs or spinal column, and to gravitation abscesses; whilst, on the other hand, metastases may also occur in different organs.

In *intestinal actinomycosis* circumscribed flat or nodular infiltrations appear in the mucous membrane and submucosa of the digestive tract, which break down and ulcerate. The process then extending to the peritoneum or abdominal wall, encapsuled abscesses form, which rupture either into one of the organs in the abdominal cavity, or externally. Metastases may also occur with this form, especially in the liver.

The inoculations performed on animals by different authorities have given results which are partly positive, partly negative.

Methods.—When *excretions* (pus, sputum, fæces) have to be examined, search is made in them first of all for the fungus granules described above, which is facilitated by spreading the excretions out in a flat glass dish upon a black surface. The granules found are then either torn up and examined unstained, or squeezed out upon, or rubbed between, cover-glasses, and stained by Gram's method.

In order, however, to obtain a more thorough insight into the structure of the granules, these, or the masses of pus and granulations containing them, are hardened in alcohol and embedded in celloidin, and the sections, after previous staining with picro-carmine, are treated by Gram's method or Weigert's modification, in doing which it is advisable to leave the sections in the anilin gentian violet for a somewhat longer time than usual, say up to an hour.

In cultivating, it is recommended that the fungus granules should first be well rubbed up in a watch-glass, and that a great number of granules be used, as many of them may be already dead.

B. YEASTS OR BUDDING FUNGI [SACCHAROMYCETES].

25. In **yeasts** the organisation is still very simple, as they consist, like the cocci, of round or oval cells, which are, however, larger in

the present instance (from 2 to 15 μ in diameter) and possess a granular vacuolated protoplasm. They also multiply, not by division but by gemmation, a small bud first forming on the surface of the parent cell, which becomes gradually larger and is finally nipped off. The new individuals either separate one from the other or form chain-like combinations. The yeasts are the cause of certain *fermentative processes*, and only occur in the human organism in localities where fluids containing sugar are present for a considerable time, as, for example, in the stomach (especially in gastric dilatation), or in the urinary bladder in diabetes.

Methods.—They may be stained with all basic anilin dyes, but they can also be recognised even without staining from their high refractiveness.

C. MOULDS OR FILAMENTOUS FUNGI [HYPHOMYCETES].

26. The **moulds** in general show a more complex structure than the vegetable parasites hitherto described, and admit of being separated into two categories, of which one is more highly organised than the other. In the *first* category, viz., the higher order of moulds, two constituent parts may readily be distinguished, viz., *mycelium* and *fruit-bearing organs* (Fig. 70, *a* and *b*), whereas in the *second* category special fruit-bearing organs are still wanting.

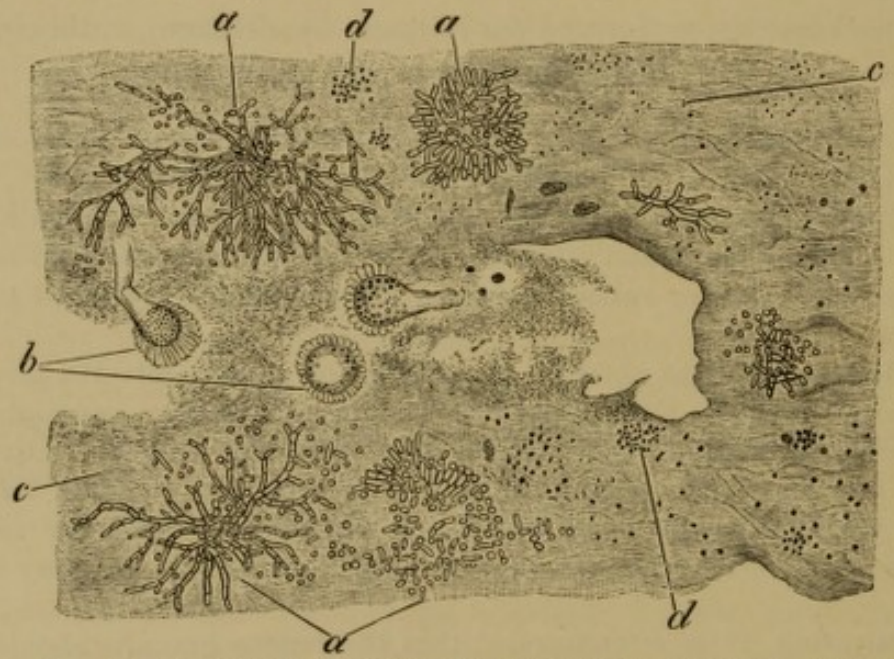

FIG. 70.—PNEUMOMYCOSIS ASPERGILLINA (*Aspergillus fumigatus*). Section, × 285. (Alum cochineal.) *a*, Mycelium of the aspergillus in the form of a rosette-like growth; *b*, Fructification heads; *c*, Necrotic lung tissue; *d*, Carbon pigment.

The *mycelium* (Figs. 70 and 71, *a*) consists of more or less closely interwoven, branched, and usually segmented filaments, which penetrate as roots into the nutrient substratum, whilst the fruit-bearing organs or fruit hyphæ (Fig. 70, *b*) raise themselves vertically from

the mycelium and develop spores at their free extremities, either by constriction off from the terminal cell of the fruit-bearer, or in a special organ of fructification which is termed a *sporangium* or *ascus*. Upon this variation in the mode of forming spores rests the division of the moulds into numerous orders or families.

The majority of moulds form woolly or cloud-like layers, readily recognisable even with the naked eye, of whitish, green, yellow, or black colour, which may be met with upon all possible dead substances, and which grow better upon acid than upon alkaline nutrient media. The moulds which are met with in the human organism belong either to the more highly organised varieties—indeed, to the genera *Aspergillus*, *Eurotium*, and *Mucor*—or to those of lower order (*Oidium*), or they form species intermediate between the moulds and the yeasts.

27. The Representatives of the Higher Order of Moulds but seldom in general play the part of excitants of disease in the human organism, usually living merely as saprophytes in localities which stand in communication with the outer world, such as the respiratory passages, the external auditory meatus, and the like.

(i.) In *Aspergillus* (Fig. 70) the formation of spores takes place in the following way: The extremity of the fruit-bearer swells up into a little head, from the uppermost half of which radially arranged cones, *sterigmata*, sprout out, and from these the spores are then segmented off. The members of this genus most frequently observed in the human organism are the *Aspergillus fumigatus* (having a mycelium which is at first blue-green and later ashen grey, and small fructification heads) and *Aspergillus niger* (with a dark brown mycelium).

(ii.) *Eurotium* differs from aspergillus but very slightly, *i.e.*, in forming perithecia in the shape of small, easily-crushed yellow bodies.

(iii.) In *Mucor* the formation of spores takes place in the interior of globular vesicles (*sporangia*) situated on the free extremity of the fruit-bearer, and divided up into small compartments by numerous septa.

The species of the genera just enumerated which occur in the human organism are all distinguished by the fact that they thrive only at a rather high temperature (28° to 40° C.).

In the *external auditory meatus* they may settle (in certain diseased conditions) upon and in the neighbourhood of the tympanic membrane, but without penetrating into the depth of the tissues.

In the *lungs* they have been found in hæmorrhagic infarcts and cavities and other centres of disease, and perhaps what occurred in these cases was not always an accidental and secondary immigration

of mould fungi, but an independent mycosis. It has also been possible in several instances to recognise the fungi in the sputum of such patients.

When the spores of the moulds, enumerated above, which grow at the temperature of the body, are injected into the circulation of animals (rabbits), they may germinate in their organs into mycelial filaments, giving rise to the formation of peculiar morbid foci with central necrosis and inflammatory reaction in the surrounding parts; but further multiplication of the fungi by sporulation does not take place.

28. The Moulds of the Lower Order occurring in the human organism are those which give rise to favus (*Achorion Schœnleinii*), to herpes tonsurans (*Trichophyton tonsurans*), and to pityriasis versicolor (*Microsporon furfur*). These consequently do not form fructification heads, but their spores become constricted off in rows from the mycelial threads.

The fungi named differ but little from each other morphologically; generally speaking the mycelial threads (*hyphæ*) are most abundantly developed in *Achorion Schœnleinii* (Fig. 71, *a*), and at the same time

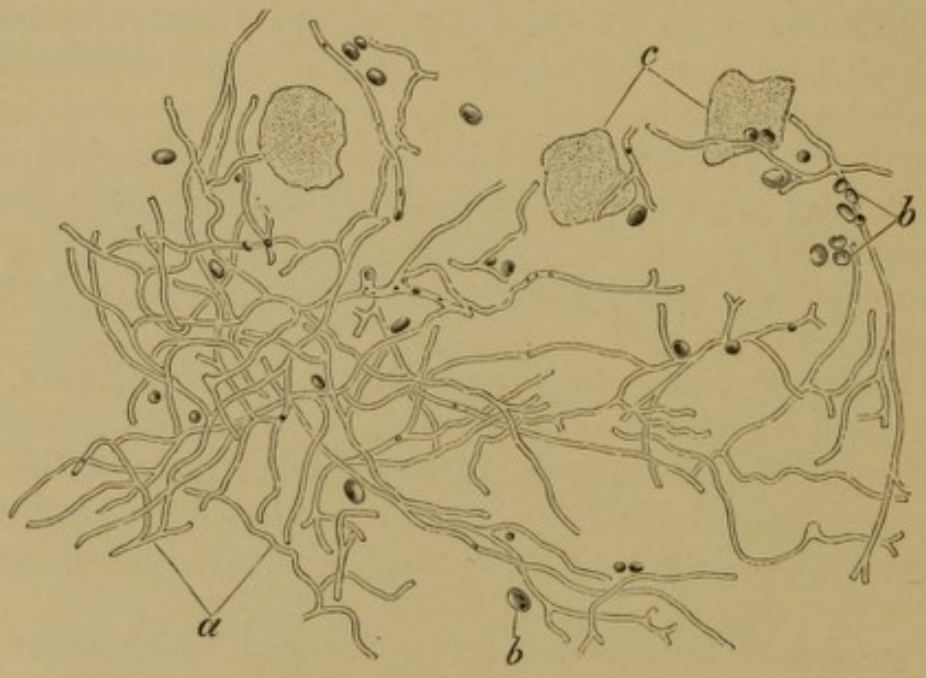

Fig. 71.—Favus Fungus from a Crust, demonstrated by needling after treatment with 5 per cent. caustic potash. × 535. *a*, Branched mycelial threads; *b*, Spores; *c*, Swollen epidermic cells.

thickest and most ramified, whilst *Trichophyton tonsurans* forms hyphæ of moderate thickness and little branched, and *Microsporon furfur* chiefly spores (*conidia*), which are often arranged in clusters. A certain differential diagnosis, however, can only be made by the process of cultivation.

(*a*) *Achorion Schœnleinii* grows best at incubation temperature, and most luxuriantly on agar. On *gelatin plates* it at first shows growth only in the depth of the medium, and it is not until several weeks have elapsed that prominent greyish-yellow deposits form, accompanied by liquefaction and yellow staining of the gelatin. On *agar plates* there speedily develop tolerably large greyish-yellow vegetations, with moss-like outgrowths. In *gelatin tubes* the growth is similar to that on gelatin plates, except that here also short outgrowths radiate from the culture and no liquefaction, but merely a softening, of the gelatin occurs. Upon *oblique agar* and *serum*—more rapidly on the former—there develops a greyish-yellow coating, which has processes extending radially into the substance of the medium in all directions.[1] A flocculent globular mass forms in *bouillon*, and is likewise bounded by fine outgrowths. Lastly, growth on *potatoes* is very slow, and results in the formation of a tolerably elevated greyish-yellow culture.

If the development on oblique agar at incubation temperature be followed with the microscope, there is found, even in two days, a mycelium with filaments many times branched, divided by septa, and having bulbous enlargements at their free extremities. On the fourth day minute yellow bodies occur here and there, especially in the bulbous enlargements, which subsequently burst; and on the fifth day the metamorphosis of the hyphæ into spores (conidia) begins.

The fungus finds a nidus most frequently on the hairy scalp, where it leads to the formation of yellow disc-shaped umbilicated crusts (*scutula*) of the size of lentils. It develops in the root-sheaths of the hairs, and in the rete Malpighii of the epidermis bounding them; but it also permeates the shaft and even the root of the hair, which is then destroyed. The portions of the rete Malpighii lying beneath the scutulum are found depressed, and in the cutis under the rete a small-celled infiltration is visible. The stratum corneum of the epidermis is subsequently shed. Favus occurs more rarely on parts of the body not covered with hair, and it has even been found in one case upon the mucous membrane of the digestive tract.

(*b*) *Trichophyton tonsurans* likewise grows better at incubation than at room temperature. In *bouillon* it forms at first small greyish-white clumps, composed of a fine felt of fibres, which subsequently sink to the bottom, where they may coalesce to form larger agglomerations, the fluid remaining clear. In *gelatin tubes* an extremely finely fibrous mass, recalling the appearance of an anthrax culture, forms in the

[1] The particulars of growth hitherto given hold good only when the sowing is very sparse.

thrust, slowly liquefying the gelatin and becoming covered superficially with a white down. In *agar* the colonies which grow deeply show very finely fibrous, radiating outgrowths at their periphery, whilst the superficial colonies become covered with a loose woolly down. On *potatoes*, lastly, snow-white vegetations form which look like fine wool.

The disease, herpes tonsurans, set up by this fungus, occurs on hairy and non-hairy parts. On the former there develop round nearly hairless spots somewhat reddened at the periphery, and at times also pustules and crusts; on the hairless parts, on the other hand, vesicles are seen arranged in rings, or red scaly patches.

The fungus vegetates principally in the hair, which it infiltrates with its spores from the root to the surface of the skin.

(*c*) *Microsporon furfur* has not yet been cultivated on solid media It causes the appearance on the trunk and upper extremities of light brown patches showing a branny desquamation, within the area of which the epidermis is permeated with short hyphæ, but chiefly with the spores arranged in round groups.

29. The Thrush-Fungus (Oidium Albicans), which occurs especially in the mouth, pharnyx, and œsophagus of children, forms the transition stage from the moulds to the yeasts. It occurs as soft, whitish deposits on the mucous membrane, and consists of ramified, bent, and jointed filaments, together with spores, the latter appearing either on the unattached extremities of the filaments or already free. In addition to the above, cells resembling those of yeast are also seen, these being, however, no extraneous contamination, but belonging to the cycle of development of the fungus itself.

It may be cultivated even at room temperature, forms non-liquefactive snow-white colonies on *gelatin plates*, grows in nail form in *gelatin* and *agar tubes*, with a whitish head and delicate rays running out from the needle-track, and forms granular white colonies on *potatoes*.

In nutrient media containing sugar, and almost invariably also upon *gelatin plates*, it produces yeast-like cells only, whereas in the deep parts of tube cultures it grows out into a mycelium. It is pathogenic for rabbits, which are destroyed by injection of cultures into the circulation, the internal organs being then found to be permeated with the mycelium of the fungus. In the human organism it usually remains restricted in its growth to the epithelium of the mucous membrane, but it may, though rarely, penetrate deeper also, and even into the blood-vessels; whilst in a few cases actual metastases in the internal organs (brain, kidneys) have been observed.

Methods.—The moulds or their constituent parts can be examined without

staining, in water or glycerin, under a medium power of the microscope. In dealing with cultures or larger vegetations of any kind, which are visible to the naked eye, the specimens may be torn up in a mixture of equal parts alcohol and ammonia, and then examined in glycerin. When staining is desired, *cover-glass preparations* should be made and the alkaline methyl blue used.

In order to examine the fungi which are found on the *skin*, the crusts (scutula) or epidermic scales are first allowed to lie for some time in a 5 per cent. solution of caustic potash or soda, and then torn up and examined in the same. If it is wished to preserve the preparations, a drop of glycerin is applied to them after they have been torn up.

In *sections*, the moulds can be stained with alkaline methyl blue, or with carbolic fuchsin, or by Weigert's modification of Gram's method.

The *isolation and pure cultivation* of the moulds is generally carried out after similar methods and with the same nutrient substances as are used for bacteria. Sterilised bread-pap (p. 38) is, however, specially well suited for the cultivation of the higher order of fungi.

To isolate the fungus of favus, a good method is to rub up particles of a scutulum in a porcelain capsule with silicic acid which has been freshly raised to a white heat, to mix one or two loopfuls of this well with agar, and to prepare plates therefrom of various degrees of dilution, afterwards making inoculations, under control of the microscope, from such of the mycelia on the plates as have started from a single germ and lie perfectly isolated.

CHAPTER VI.

THE PARASITES—(CONTINUED.)

II. ANIMAL PARASITES.

A. PROTOZOA.

1. **Protozoa** belong to the lowest animal organisms, which in part consist merely of simple cells, in part of groups of such. Three classes are distinguished, as follows :—

(i.) **Rhizopoda.**—These possess the simplest structure, as they consist merely of nucleated masses of protoplasm which progress by pushing out and drawing in processes. To them belong :—

(*a*) *Amœba coli* (Fig. 72), which has been repeatedly found in

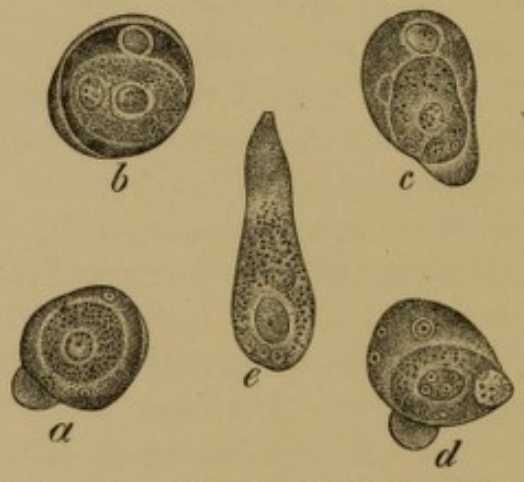

FIG. 72.—AMŒBA COLI (from Kartulis). × 730. *a*, *b*, *c*, and *d*, The same amœba under different changes of form; *e*, An amœba which is pouring the protoplasm of its body into the process.

dysentery (especially in the chronic sporadic form), in the contents of the intestine and on the base of the dysenteric ulcers, as well as in the hepatic abscesses which often accompany tropical dysentery, and is regarded by many as the cause of the disease. It is considerably larger than a red corpuscle, its diameter varying between

0·012 and 0·030 mm., is usually rounded in the resting state, and possesses a plasma granulated in its central layers, several vacuoles, and a tolerably large round nucleus. Plasma and nucleus stain quite alike with the nuclear dyes, whereas the vacuoles remain unstained, and hence come out distinctly in the stained amœbæ.

(*b*) The *Plasmodium malariæ*—regarding which, however, it still remains doubtful whether it is to be included in the present or another class of Protozoa, viz., the *Sporozoa* (p. 168). It is the cause of intermittent fever, in which it occurs in the blood in three forms,[1] though whether these are to be regarded as independent species, or merely as different developmental stages of one and the same, is still undecided.

The first form, which is also named *Hæmamœba* (Plate I., Fig. 2, *a–f*), is found in the blood in the quartan, tertian, and quotidian types of intermittent fever, and there goes through a definite course of development, which probably is always completed between two attacks of fever. This developmental cycle is best studied in the quartan type, and consists in the following:—The *Hæmamœba* forms at the commencement a colourless amœboid structure lying in the interior of a red blood corpuscle; it gradually increases in size, and soon also black pigment granules derived from broken down hæmoglobin may be observed in its body (Plate I., Fig. 2, *b* and *c*). These next gather usually in the centre of the micro-organism (*d*), while at the circumference there occurs a radial cleavage and segmentation (formation of daisy-like figures), and finally a separation of the segments (6 to 12), which are free from pigment, from the pigmented centre. In this way the former become free, and can now as young plasmodia again make their way into red blood corpuscles, thus starting a new attack of fever.

In tertian and quotidian fever the development is accomplished in two days and one day respectively, the plasmodia in them showing much more active movements, and the red corpuscles being more speedily destroyed. The plasmodia are also more delicate, and in dividing break up into more numerous segments.

The *second* form of plasmodium, also named *Laverania*, consists of a minute semilunar or sickle-shaped body, pigmented in the centre (Plate I., Fig. 2, *g*), which also lies at first in the interior of red corpuscles, and is said to multiply likewise by segmentation. It is found in atypical intermittent fever, alone or along with the preceding form.

The *third* form, also known as *Polymitus* (Plate I., Fig. 2, *h*), is found far less often (and only in fresh blood), appearing as a

[1] Quite recently still further forms have been described.

round structure with pigment arranged in a coronoid figure, and with from one to four flagella.

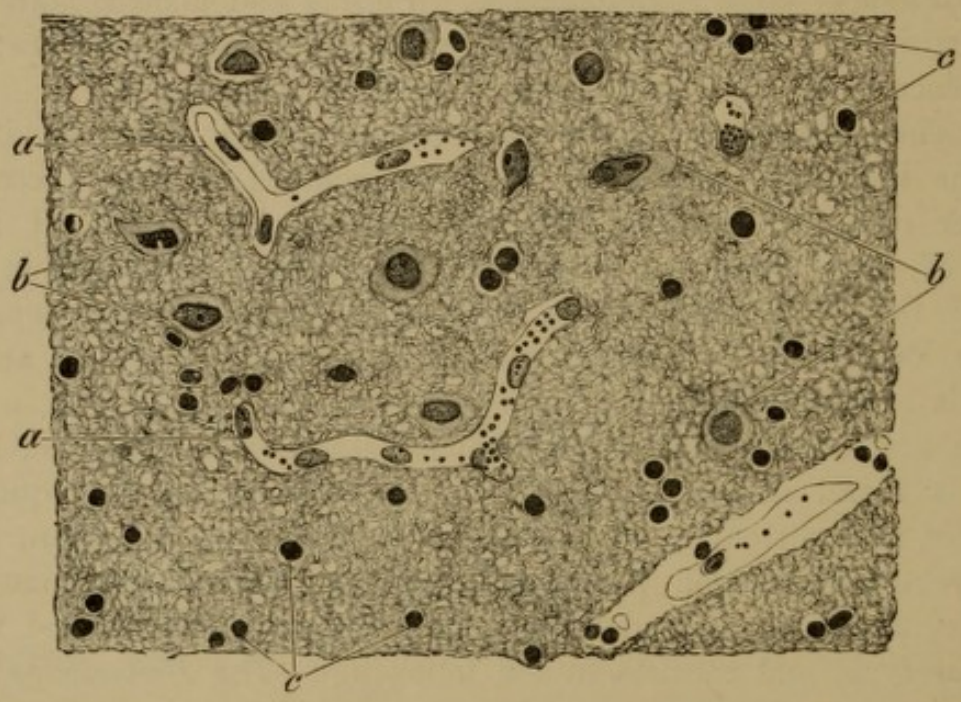

FIG. 73.—MELANOSIS OF THE BRAIN AFTER INTERMITTENT FEVER. × 545. (Alum cochineal.) *a*, Blood capillaries with black pigment granules; *b*, Ganglion cells; *c*, Cells of the neuroglia.

The three forms of the plasmodium described may also be observed in the blood of birds from malarial districts. In what manner they exist outside the organism, and how they effect an entrance into the latter, is still unknown. Owing to the destruction of the red corpuscles by the plasmodia, there is formed from the hæmoglobin a granular black pigment, *melanin*, which at the commencement appears in the substance of the plasmodia, but subsequently is in part taken up by the leucocytes, in part present free in the blood, and which accumulates especially in the spleen and the liver (*melanæmia* and *melanosis*, see p. 59). In severe cases accumulation of pigment (or of blood corpuscles containing plasmodia) may take place even in the capillaries of the brain (Fig. 73), with consequent necrosis of the portions of brain-substance occupying the area supplied by these capillaries.

2. (ii.) **Sporozoa (Gregarinæ).**—These are unicellular structures with a cuticle and nucleus, but without cilia and flagella. As they multiply by spores, which form in the interior of the body of the cell, they stand in close relationship to the lowest *vegetable* organisms. Of these the order *Gregarinidæ*, and in this again the family *Coccidiidæ*, require notice. The latter are of oval or globular shape, and become encysted before sporulation. They may easily be mistaken for lymphoid cells or for the nuclei of epithelial cells, and in their

earliest stages of development for vacuoles; later, the double contour of the membrane and the presence of globular spores in their interior are characteristic.

They occur as parasites chiefly in the epithelial cells of men and animals, and the granular bodies found in the epithelial cells (*molluscum corpuscles*) of molluscum contagiosum probably belong to them.

Coccidia (Fig. 74) have further been observed in the bile-ducts of

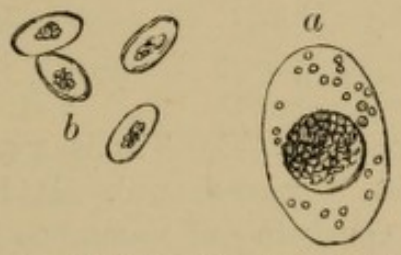

FIG. 74.—COCCIDIA FROM THE HUMAN LIVER, under powers magnifying (*a*) 300, (*b*) 100 diameters (from Leuckart).

the liver and in the nuclei of the hepatic cells, in the latter instance causing pigmentary atrophy of the cells, and even cirrhosis. Figures resembling coccidia have also been repeatedly noticed in the nuclei of cancer cells, and have even been assigned an ætiological relationship to the carcinomata.

3. (iii.) **Infusoria.**—The structure of these is somewhat more complicated, inasmuch as the protoplasm separates into a cortical and a medullary substance, and an oral and anal orifice are in most cases present, as well as special locomotor organs (flagella, cilia, sucking-tubes). The following occur as parasites in the human organism:—

(*a*) *Paramœcium or Balantidium Coli* (Fig. 75).—This infusorium

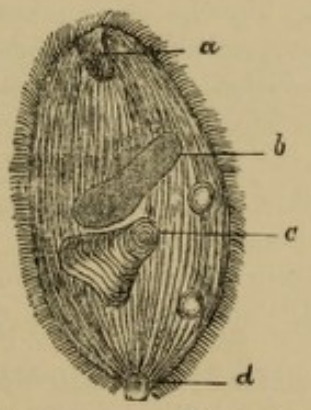

FIG. 75.—PARAMÆCIUM OR BALANTIDIUM COLI (from Claus). Highly magnified. *a*, Mouth; *b*, Nucleus; *c*, Starch granule taken into the interior; *d*, Foreign body in the act of being expelled.

is oval, 0·1 mm. in length, thickly set with hair-like cilia at the periphery, and provided internally with a nucleus and two contractile vesicles. It is occasionally present in the large intestine and stools (in diarrhœic disorders).

(*b*) *Cercomonas intestinalis* (Fig. 76) is a pear-shaped infusorium provided with a distinct nucleus, and having at one end flagella, at the other a spine-like process. It has hitherto been found in the intestine in diseased conditions associated with diarrhœa.

FIG. 76.—CERCOMONAS INTESTINALIS (from Davaine).

FIG. 77.—TRICHOMONAS INTESTINALIS (from Zenker).

(*c*) *Trichomonas intestinalis* (Fig. 77) is somewhat larger than the preceding, and, like it, is pear-shaped. It has, however, a comb-like ciliary apparatus consisting of numerous hairs. It has likewise been found in diarrhœic stools.

Examination of the Protozoa.—The *plasmodia of malaria* are examined in a manner similar in general to that adopted with bacteria. They may be recognised even in the unstained state, if examined in the hanging drop; but it is better to make dried preparations[1] of the blood in the usual way, and to stain them with methyl blue. If a concentrated alcoholic solution of the latter is used for this purpose the staining is effected in a few seconds.

A pretty double staining—plasmodia and nuclei of cells blue, red blood corpuscles and eosinophil granulations red—is obtained by the following method: Half a gramme of eosin is dissolved in 100 grm. of a not quite concentrated aqueous solution of methyl blue, to which some drops of absolute alcohol have also been added. The cover-glass preparations, instead of being passed through the flame, are first of all immersed in a mixture of equal parts ether and alcohol for some forty minutes, and then for at least ten or fifteen minutes in the warmed staining solution, whereupon they are rinsed in water.

The remaining protozoa can likewise be examined unstained as well as stained. In the former case they are submitted to the microscope in the fluid in which they are found, or in salt solution, best on a hollow slide. If it is desired to see the amœbæ in dysenteric stools still in a state of movement, samples of the latter (particles of pus or of blood-stained mucus being most suitable) must be examined as soon as possible, and at body temperature, with a magnification of about 400 diameters. The same processes can be used for staining protozoa that were employed for bacteria; and for staining their flagella and cilia the methods given on p. 29 for the cilia of bacteria can likewise be followed.

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[1] The blood may also be stained while still fluid by adding, by means of a glass rod, to a drop obtained by pricking the skin (of the finger pulp, or lobule of the ear) a drop of solution of methyl blue in ascitic fluid (a certain quantity of methyl blue in powder is added to ascitic fluid received with aseptic precautions into sterilised test-tubes, and the fluid is filtered after solution has taken place). A small quantity of the mixture is placed upon a cover-glass, and the fluid then allowed to spread out between the latter and a slide under gentle pressure. To secure a distinct coloration the preparations should further remain lying for one to three hours in a moist chamber.

B. VERMES.

4. The orders *Cestodes*, *Trematodes*, and *Nematodes* are the only ones of which members occur as parasites in man.

(i.) **Cestodes (Tape-Worms).**—These are destitute of mouth and intestinal canal, and develop from an immature form which remains sexless (*scolex*), by the progressive budding out at its lower end of segments, which range themselves in line, gradually increase in size, and produce the germs of future scolices (ova). The last and largest segments in the series eventually become detached and quit the intestine of their host. They may then, in the course of their developmental cycle, either make their way as such into the stomach of a new host with the food, or else, the body being destroyed by putrefaction, only the ova contained in them are taken into the stomach. Here the embryos are set free, and, either by active migration, or by being carried along the vessels, make their way into various organs, in which they are transformed into cyst-like larvæ (*bladder-worms*, *measles*). Should such cysts (on the walls of which, meanwhile, new scolices have been formed by budding) make their way into the intestine of a second host, a tape-worm develops in the manner described at the beginning. The following are the most important species:—

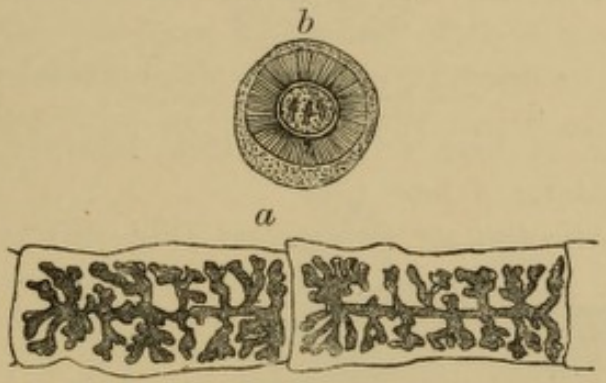

FIG. 78.—TAENIA SOLIUM (from Leuckart). *a*, Two proglottides with uterus, about twice the natural size; *b*, Ovum with primitive vitelline membrane. × 300.

(*a*) *Tænia solium.*—The rounded head (scolex), about the size of a millet seed, possesses four sucking discs, and on the vertex, which is frequently pigmented, a rostellum with about 26 hooks (Fig. 79). Behind the head comes a neck about 2 cm. in length, and after that the series of segments (*proglottides*), of which the first are still very short. Their length, however, gradually increases, until at last it exceeds the breadth (Fig. 78, *a*). The ripe segments are 9 to 10 mm. long and 6 to 7 mm. wide, and have rounded angles; the sexual aperture is at the side behind the central point; the uterus is but little branched. This tape-worm may

reach a length of from 2 to 3 metres, and lives in the human small intestine. The *ova* (fig. 78, *b*) are elliptical, 0·036 mm. long and 0·03 mm. wide, and have a thick radially-striated shell. In their interior the hooks of the embryo can already be recognised in most cases. The corresponding *bladder-worm*, *Cysticercus cellulosæ*, or the true measle, most often occurs in the intermuscular and subcutaneous connective tissue, and in the brain and eye, appearing as a rounded or oval cyst, usually enveloped in a thin capsule of connective tissue, and containing a serous fluid and the head (scolex) of the tape-worm, which is commonly dotted with numerous calcareous bodies (Fig. 79). After the death of the scolex the cyst

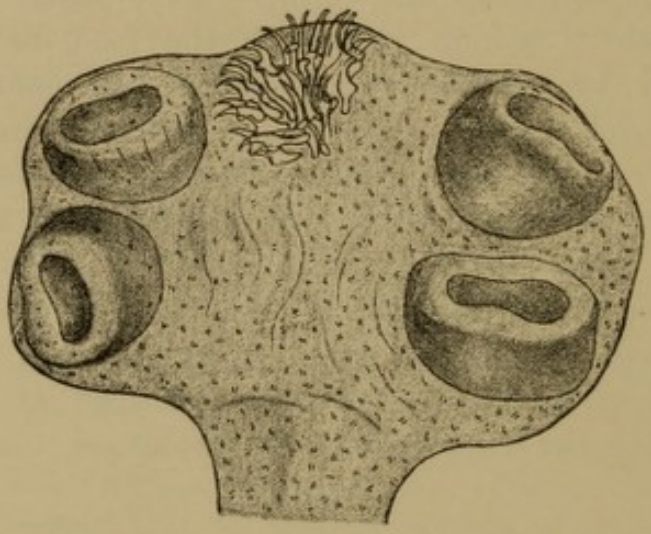

Fig. 79.—Head of a Cysticercus Cellulosæ of the Brain (from Heller). Highly magnified.

fills with masses of lime salts, in which, however, the hooks may still be preserved for a long time.

(*b*) *Tænia mediocanellata or saginata* (Fig, 80) is longer, broader,

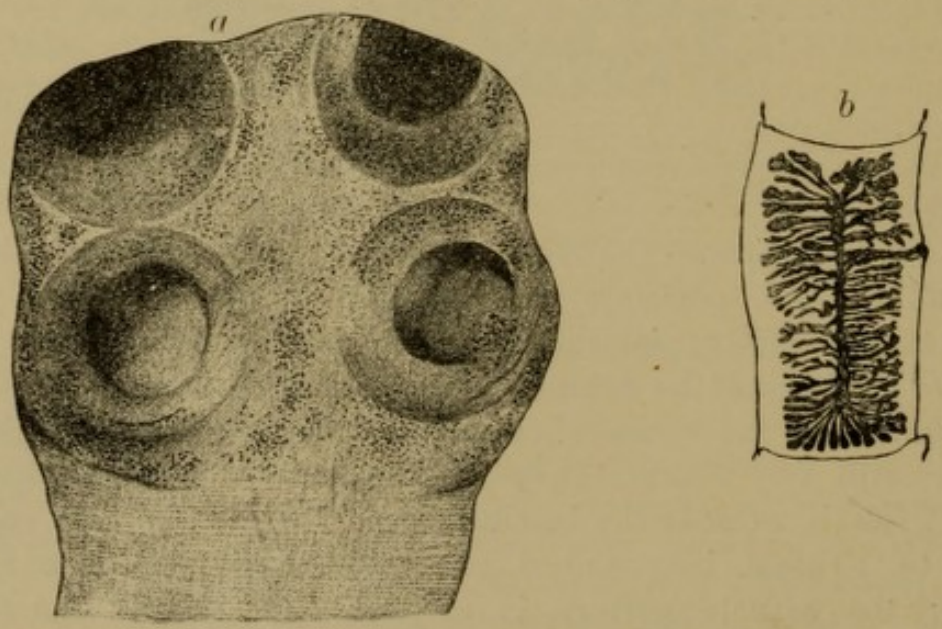

Fig. 80.—Tænia Mediocanellata. *a*, Head, magnified 30 diams.; *b* (from Leuckart), a segment with uterus, magnified about 1½ diams.

and thicker than the preceding, and its segments are also larger. The head (*a*) has neither circlet of hooks nor rostellum, but merely four sucking discs edged round with black pigment. The sexual aperture lies posteriorly to the centre of the lateral margin. The uterus (*b*) is very freely branched. [The total length is about 4 metres.] The *ova* are very like those of the *Tænia solium*, only still more elliptical, and no hooks are visible in them. The corresponding *bladder-worm* is found in oxen, so that human beings may acquire this tape-worm by partaking of uncooked beef.

(*c*) *Tænia nana* is only from 8 to 15 mm. long and 0·5 mm. broad. The head carries four sucking discs, and a deeply retractable rostellum with circlet of hooks. The segments are very short, the length even of the hindmost scarcely amounting to a fourth of its breadth. The *ova*, of 0·03 to 0·04 mm. diameter, show no radial striations in their shell, but in the interior the embryo can be seen provided with five or six hooks. This worm has hitherto been observed only in Egypt and Italy, especially in children, but appears also to occur amongst ourselves.

(*d*) *Tænia cucumerina or elliptica* is 18 to 25 cm. long, and has on its head a rostellum, capable of being protruded, which is surrounded with some sixty irregularly arranged hooks. The ripe segments are reddish, and the hindmost are considerably longer than their breadth. The *ova* have a diameter of 0·05 mm., and show the embryo already provided with hooks. It occurs in man but rarely, mostly in children, who probably acquire it owing to their intercourse with dogs.

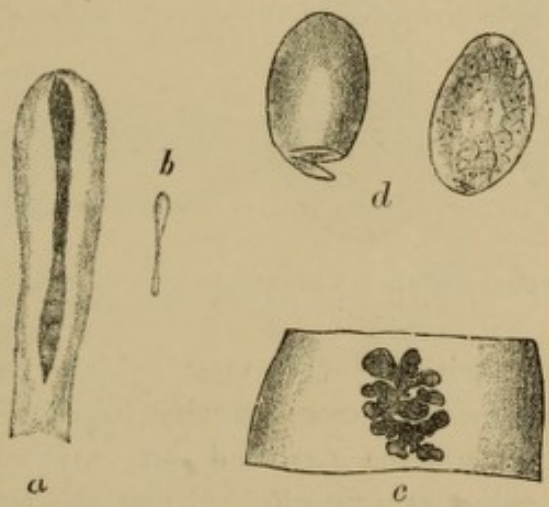

FIG. 81.—BOTHRIOCEPHALUS LATUS (from Leuckart). *a*, Head seen from the side, magnified; *b*, Head seen on the flat, natural size; *c*, Ripe segment with uterus, magnified 6 times; *d*, Ova (one after evacuation of the contained yolk).

(*e*) *Bothriocephalus latus* (Fig. 81) attains a length of 5 to 8 metres. The head (*a* and *b*) is club-shaped, and possesses a slit-like

sucking groove on each lateral margin. The segments are remarkably broad, especially in the central parts of the worm, where their breadth amounts to 10 or 12 mm., their length only to 3·5 mm. The ripe segments (*c*) are further characterised by a rosette-like tracing formed by the uterus filled with ova. The *ova* (*d*) are elliptical, 0·07 mm. long and 0·045 mm. wide, surrounded by a thin brown shell, which possesses a little valvular lid at the end. The tape-worm can be acquired by eating fish, as the measle belonging to it inhabits certain species (pike and others). It is said sometimes to cause the symptoms of pernicious anæmia.

(*f*) *Tænia echinococcus* lives in dogs. Should its eggs make their way into the stomach of a human being, the development of the corresponding measle, the *Echinococcus* (Fig. 82), follows, and the

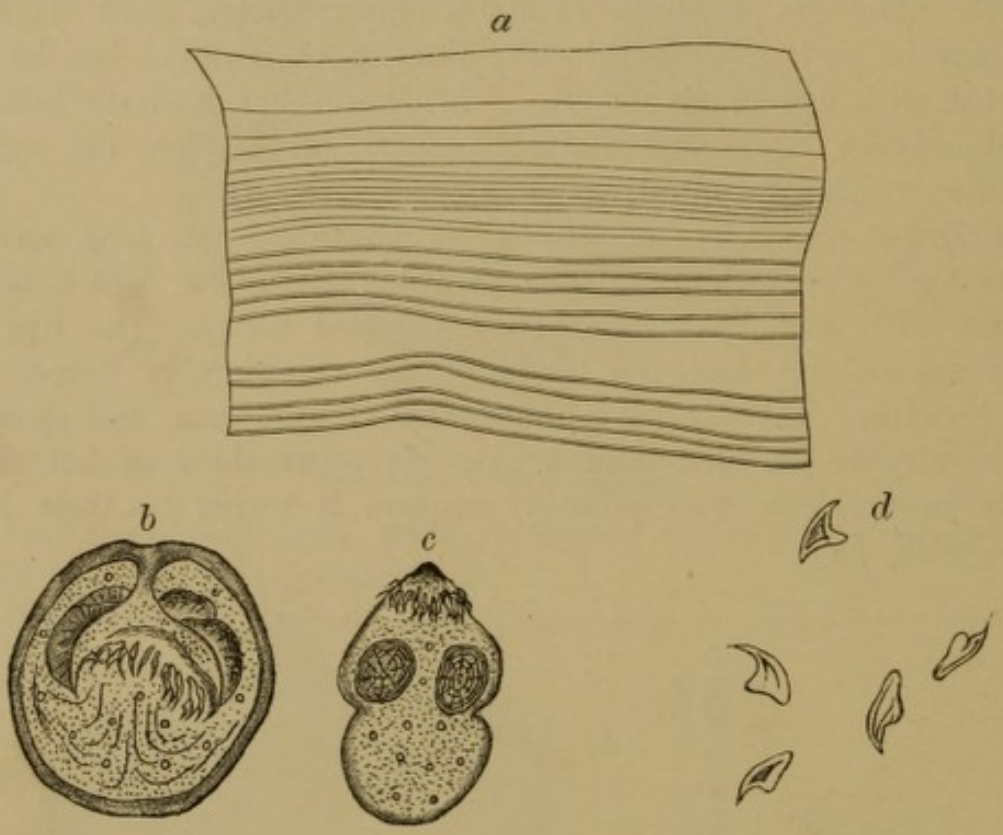

Fig. 82.—Echinococcus (from Heller). *a*, Cuticle; *b*, Scolex with invaginated, and *c*, Scolex with everted rostellum; *d*, Separate hooklets.

latter may be met with in the most widely diverse organs, but oftenest in the liver. The cyst of the measle is composed of a cuticle stratified in lamellæ (*a*) and an internal parenchymatous layer consisting of cells and granules. From the latter brood-capsules develop, and on these again the scolices (*b* and *c*), which are 0·3 mm. long, possess four sucking discs and a frequently invaginated rostellum with small hooks (*d*), and are dotted with little calcareous bodies. The echinococcus cyst either remains simple (in which case, however, new brood-capsules may form on its inner surface, showing

through as white points), or daughter-cysts develop. In both cases the cysts are filled with a clear fluid, and are usually surrounded externally with a capsule of connective tissue. Should the scolices die, a deposit of chalk-like masses takes place in the cysts, in which the hooks may still be preserved for some time.

A special form of the above is the *Echinococcus multilocularis*, which occurs mostly in the liver as a tumour of alveolar structure, consisting of numerous very small and usually sterile cysts embedded in a connective-tissue stroma.

5. (ii.) **Trematodes (Flukes).**—These are of a leaf- or tongue-shaped figure, are usually hermaphrodite, and in addition to an adhesive apparatus (sucking discs), have also an intestinal canal. The following species occur in man :—

(*a*) *Distoma hepaticum* [*Fasciola hepatica*] is a leaf-shaped worm of 28 mm. length and 12 mm. breadth, with two sucking discs, one of which is placed on the head, the other on the ventral surface, the sexual opening lying between the two. The uterus consists of a coiled tube. The *ova* are elliptical, 0·13 mm. long and 0·08 mm. broad, of a brown colour, and provided with a lid at the anterior end. It occurs but seldom in man, when it is found in the bile-ducts, and may then cause obstruction of them with the usual consequences. The same is true also of

(*b*) *Distoma lanceolatum*, which bears a general resemblance to the preceding, but is much smaller (8 to 9 mm. long, and 2 to 2·5 broad), and is lancet-shaped. The *eggs* are 0·04 mm. long and 0·03 broad, and contain the embryo while still in the uterus.

(*c*) *Distoma hæmatobium* [*Bilharzia hæmatobia*] (Fig. 83) has

Fig. 83.—Distoma Hæmatobium (from Leuckart). *a*, Male and female, the latter in the gynæcophoric canal of the former. × 10. *b*, Ovum with terminal spine ; and *c*, Ovum with lateral spine. × 150.

separate sexes, is white, and is provided with an oral and a ventral sucking disc, behind the latter of which lies the sexual opening. The male is 12 to 14 mm. long, and has on its ventral surface a gutter-like canal for the reception of the female, which is somewhat thinner and longer. The *ova* (*b* and *c*) are 0·12 mm. long and 0·04 mm. broad, and carry a spine either at one end or at the side.

The worm occurs in the portal vein and its radicles, as well as in the veins of the large intestine and bladder, and in the kidney, and has hitherto been observed only in Egypt. The eggs deposited in the mucous membrane of the large intestine, urinary bladder, and urethra, give rise to ulcerative inflammations, hæmaturia, and possibly also to the formation of concretions.

6. (iii.) **Nematodes (Round-worms).**—These worms have an elongated cord-like body, with a well-developed digestive apparatus, are of separate sexes, and reproduce partly by ova, partly by embryos. To these belong:—

(*a*) *Ascaris lumbricoides*, the common round-worm. No microscopic examination is necessary for its recognition. It inhabits the small intestine, in most cases without causing any particular troubles, but under certain circumstances it may also make its way into the ductus choledochus, or from the pharynx into the larynx. The *ova* (Fig. 84) are rounded, yellowish-brown, have a diameter of 0·05 to 0·06 mm., and a double shell, which is further surrounded by an uneven albuminous envelope.

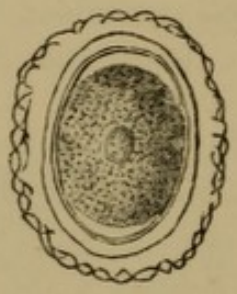

Fig. 84.—Ovum of Ascaris Lumbricoides with Shell and Albuminous Envelope (from Leuckart). × 300.

Fig. 85.—Ova of Oxyuris Vermicularis in different stages of development (from Zenker and Heller). *a*, *b*, and c, Segmentation of the yolk; *d*, Tadpole-shaped embryo. × 500.

(*b*) *Oxyuris vermicularis*, or thread-worm. The male is 4 mm., the female 10 mm. long. The former has a blunt posterior extremity, the latter is thin and pointed in the shape of an awl. They live in the large and in the lower end of the small intestine, and when they wander out of the rectum into the neighbouring parts cause itching. The *ova* (Fig. 85) are 0·05 mm. long and 0·02 to 0·03 mm. broad, have a membrane showing a double or triple contour, and frequently allow the embryo to be seen in the interior.

(*c*) *Anchylostomum duodenale* (*Dochmius or Strongylus duodenalis*).—The body is cylindrical, and the cephalic end (Fig. 86), which is curved backwards, is provided with a distended oral capsule, which

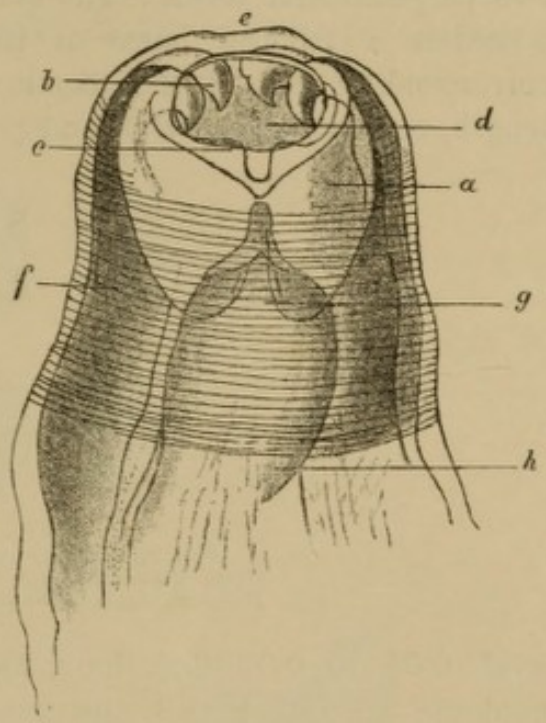

FIG. 86.—HEAD OF ANCHYLOSTOMUM DUODENALE (from Schultheiss). *a*, Oral capsule; *b*, Teeth of the ventral margin; *c*, Teeth of the dorsal margin; *d*, Buccal cavity; *e*, Cutaneous prominence on the ventral aspect of the head; *f*, Muscular layer; *g*, Dorsal fissure; *h*, Œsophagus.

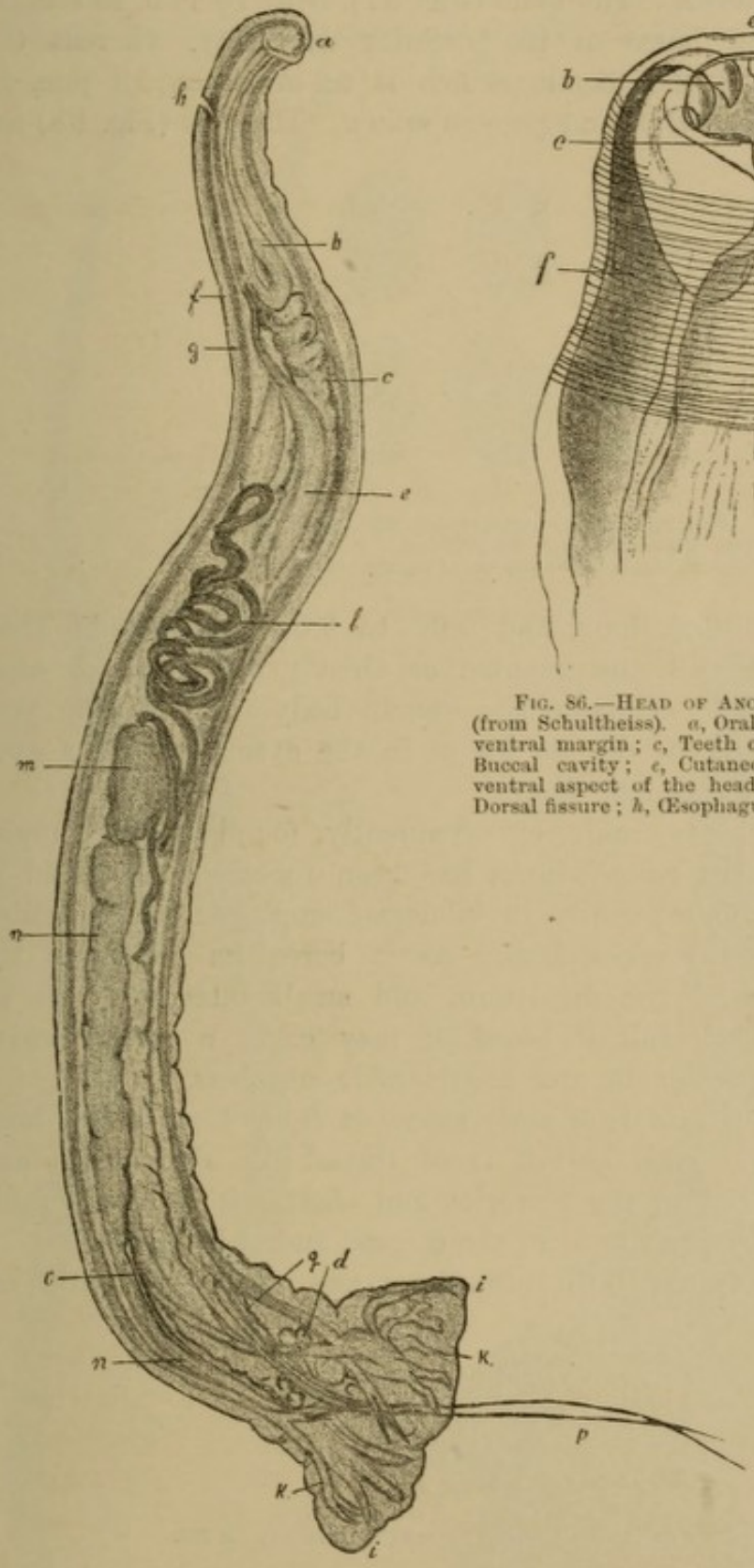

FIG. 87.—MALE OF ANCHYLOSTOMUM DUODENALE (from Schultheiss). × 20. *a*, Head with oral capsule; *b*, Œsophagus; *c*, Intestine; *d*, Anal glands; *e*, Cervical glands; *f*, Skin; *g*, Muscular layer; *h*, Excretory pore; *i*, tri-lobed bursa; *k*, Ribs of the bursa; *l*, Testicular canal; *m*, Vesicula seminalis; *n*, Ejaculatory duct; *o*, Furrow in latter; *p*, Penis; *q*, Sheath of penis.

is almost completely split at the back, and carries four incurved and two perpendicular teeth. The male (Fig. 87), 6 to 10 mm. in length, possesses a trilobed bursa at its posterior extremity, whereas the corresponding end of the female, which is as much as 18 mm. in length, runs out into a thin and pointed spine. The *eggs* (Fig. 88) are

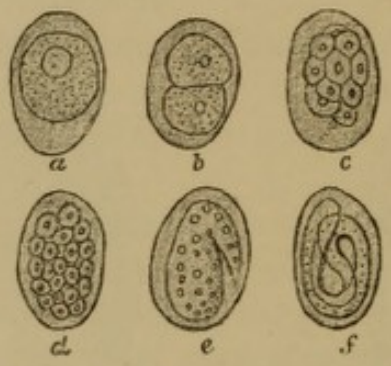

FIG. 88.—OVA OF ANCHYLOSTOMUM DUODENALE (from Perroncito and Schultheiss). × 200. *a-d*, Different stages in the process of segmentation.

oval, 0·05 to 0·06 mm. long, and 0·03 to 0·04 mm. broad. Their contents are either still unsegmented or already show two or more segmentation spheres. Outside the human body they develop very rapidly, so that embryos can be found in the evacuated fæces even in twenty-four to forty-eight hours.

The worm is chiefly, and very frequently, found in the tropics (Egypt), but in more recent times has been repeatedly detected in our own regions also, especially in labourers employed in tunnelling and mining, and in brick-makers. As it bores its way into the mucous membrane of the duodenum and small intestine with its teeth, and sucks itself full of blood, it may cause a severe degree of anæmia when present in any considerable numbers.

(*d*) *Trichocephalus dispar, or whip-worm*, is from 4 to 5 cm. long. In its anterior and longer half it is of thread-like slenderness and is spirally coiled, but in the posterior and shorter it is considerably thicker. It lives by preference in the cæcum, and is harmless.

The *ova* (Fig. 89) are 0·05 mm. long and 0·02 wide, and are

FIG. 89.—OVUM OF TRICHOCEPHALUS DISPAR (from Heller). × 350.

surrounded by a double-contoured shell, which shows a conical protuberance (lid) at each pole.

(*e*) *Trichina spiralis*.—This occurs in man and many mammalian

animals, as *intestinal trichinæ* in the fully developed and sexually mature condition, and as *muscle trichinæ* in the undeveloped state.

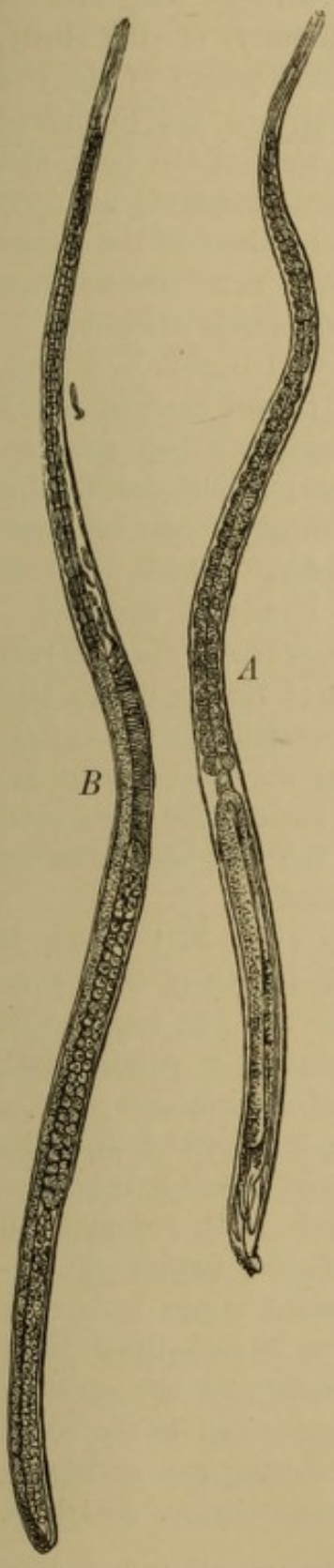

FIG. 90.—SEXUALLY MATURE TRICHINA SPIRALIS (from Leuckart). × 120. *A*, Male; *B*, Female.

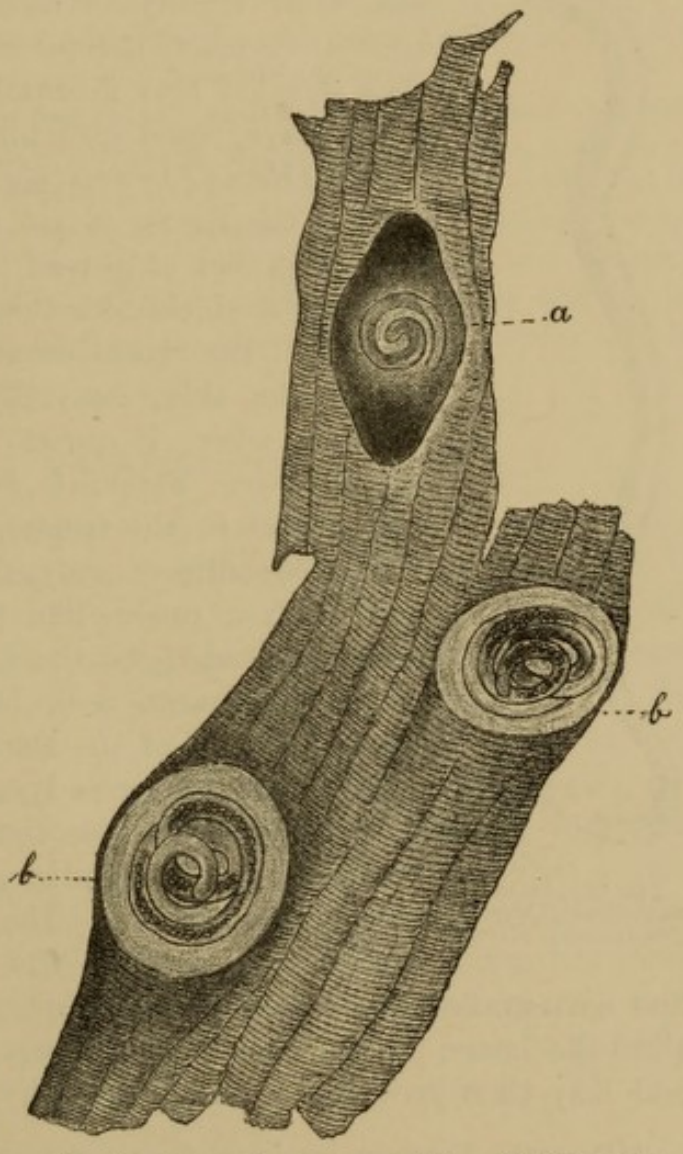

FIG. 91.—MUSCLE TRICHINÆ. × 100. *a*, Partially calcified trichina; *b*, Calcified trichinæ after solution of the lime-salts.

(1) *Intestinal trichinæ* (Fig. 90).—The male (*A*) is 1·5 mm. long and carries four knob-like papillæ between the two conical projections at the end. The female (*B*) is almost twice as long, and its tubular ovary, situated at the posterior extremity of the body, passes forwards into the uterus, in which the development of the ova into embryos takes place. The latter, however, are not evacuated with the fæces, but bore through the intestinal wall of the host, and then migrate into the transversely striated muscles (in largest numbers into the diaphragm, tongue, intercostal muscles, and those of the throat and larynx), in which they accumulate, especially near the tendons, and grow in about a fortnight into fully formed muscle trichinæ.

(2) *Muscle trichinæ* (Fig. 91).—These are 0·7 to 1·0 mm. in length, usually coiled up in a spiral, and enveloped in a fibrous capsule, which eventually calcifies. In this condition they may retain their vitality for many years; and if during this time they reach the intestinal canal of another host, they develop into intestinal trichinæ, which, even in a few days, again give birth to numerous embryos.

Fig. 92.—Filaria Sanguinis Hominis (from Lewis). × 400.

(*f*) *Filaria* [*Dracunculus*] *medinensis* (*Guinea-worm*).—Only the female is yet known;[1] this is 60 to 100 cm. long, thin as thread, and covered with a cuticle showing a shield-like thickening at the cephalic extremity. The worm occurs in Africa and Asia, and infests the skin, especially in the neighbourhood of the foot, where it causes abscesses.

(*g*) *Filaria sanguinis hominis* (Fig. 92), which is only found in the tropics, has a length of 0·34 mm. and a breadth of only 0·0075 mm., a rounded-off head with a tongue-like process, and a pointed tail. It is believed to be the larva of *Filaria Bancrofti*, a thread-like worm, 8 to 10 cm. long, which inhabits the lymphatics of the scrotum and lower extremities, and is said to cause lymph-stasis, with œdema and a thickening of the tissue of the nature of elephantiasis, or lymphatic abscesses, chylous hydrocele, and chylous ascites. The ova or larvæ—the *Filariæ sanguinis*—pass from the lymphatics of the scrotum and extremities to the rest of the lymphatic system and to the blood (into the latter, however, for the most part, only during rest at night), and may then give rise to hæmaturia, chyluria, and chylous diarrhœa.

[1] [Recently, however, male and female worms *in coitu* are said to have been observed in the sub-peritoneal tissue of human subjects, whence it is inferred that they enter by the intestinal canal, and that the male subsequently atrophies].—*Tr.*

Methods.—The parasites visible to the naked eye can be examined in water without further preparation.

The head and segments of *tape-worms* are best examined in glycerin, and may also be compressed between two slides. The scolices of *Cysticercus* and *Echinococcus*, which are obtained free by tearing up the cyst or detaching them from its wall, are treated in a similar manner.

The diagnosis of the last-mentioned parasites is at once rendered certain by the discovery of separate hooks, which may still be found even in calcified cysts. In the case of *Echinococcus* the recognition of the lamellar stratification of the cyst-wall, of which sections are made with razor or scissors and examined in water, is sufficient for the diagnosis. When fluids have to be inspected for indications of the presence of hooks or vestiges of cysts, they should be allowed to settle in a conical glass, and the sediment then examined.[1]

The *ova* can be examined under a medium power in water or glycerin. To demonstrate them in the fæces, water should repeatedly be added to the latter and then allowed to settle,[1] and the deposit examined. If in a case where *Anchylostomum* is suspected neither ova nor parasites are seen at first, the fæces should be allowed to stand for two or three days at 25° to 30° C., during which time the process of segmentation will have become more distinct in any ova that may be present, or the embryos will have already escaped.

Samples of blood to be tried for *Filaria sanguinis* must be taken at night. In searching for *muscle trichinæ*, small pieces should be picked out from those muscles in which trichinæ are usually present in largest numbers, and from as near the tendon as possible (in the living subject the pieces are obtained by means of a fine harpoon trocar), torn up in 1 per cent. acetic acid, and examined under a low power. When the trichinæ are calcified, hydrochloric acid should be applied. Alcohol should be used for *hardening* parasites. *Sections* may be stained with solutions of carmine.

C. ARTHROPODA.

7. Of the **Arthropods** which live parasitically in the human organism, only the following two species come within the scope of microscopic research :—

(*a*) *Acarus* [*Sarcoptes*] *scabiei or Itch-mite* (Fig. 93).—The body, about the size of a pin's head, bears two pairs of feet set with bristles on the anterior, and the same on the posterior, half of the ventral surface, of which the anterior pairs, and in the male the posterior also, end in pedunculated prehensile discs, whilst the rest run out into long bristles. The dorsum bears tooth-shaped processes. The animal excavates tunnels in the epidermis from 1 to 3 cm. long, in which the female lays her eggs. The young mites formed from the latter develop at once into sexually mature animals, penetrating still more into the epidermis. The irritation set up thereby, in conjunction with the scratching, causes an inflammation of the skin.

[1] When more rapid sedimentation is desired, Stenbeck's centrifuge can be used with advantage.

(*b*) *Acarus* [*Demodex*] *folliculorum hominis*, which is often met with in the sebaceous and hair follicles, is about 0·3 mm. long, and has at the cephalic end a proboscis with two antennæ, and on the anterior part of the body four pairs of short thick feet.

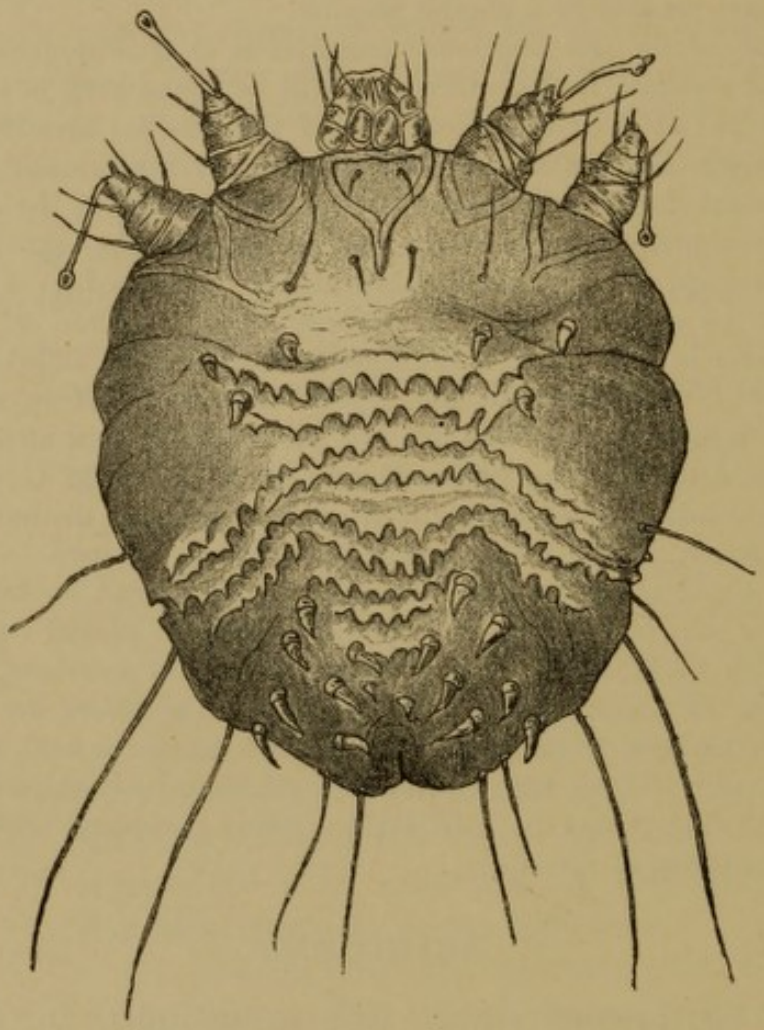

Fig. 93.—Female Itch-mite, seen from the dorsal aspect (from Hebra's *Atlas der Hautkrankheiten*). × 200.

It should further be mentioned here, by way of appendix, that the *larvæ of various species of flies* make their way into the stomach and intestine along with food eaten uncooked, such as meat, cream, or cheese, and may even develop further there, and hence be found also in vomited matters or in the stools.

Methods.—The itch-mite is found if the point of a knife or cataract needle be thrust into the epidermis near the yellowish-white dot at the end of the characteristic burrow, and the contents of the latter brought out. The animal (the female) appears to the naked eye as a minute yellowish-white body, which is quite perceptible, but which can then be further inspected under the microscope, using a low power. If it is desired to examine the actual burrow, it is cut out with scissors and squeezed between two slides. Under a low power the mite will then be observed at the end of the burrow, and in the remaining portion of the latter ova and their capsules will be seen, together with little black bodies (fæces).

PART III.

SPECIAL PATHOLOGICAL HISTOLOGY.

CHAPTER I.

THE BLOOD.

1. Changes in the Red Corpuscles.—These changes affect partly the number and partly the size, shape, or other characters of the red corpuscles.

(i.) *Oligocythæmia rubra*, or decrease in the total quantity of red corpuscles, in which their number may sink from the 4-5,000,000 per cubic millimetre of the healthy adult to 2,000,000, or even to half-a-million and under (as in pernicious anæmia, for example), occurs as a temporary condition after severe hæmorrhages, or permanently in the so-called *hæmic diseases* (leucæmia, chlorosis, and pernicious anæmia), as well as in conditions of inanition, phthisical disease, and certain intoxications and infections. The higher grades can at once be recognised from the pale colour of the blood, and from the strikingly small number of the red corpuscles in microscopic preparations; the slighter grades only by actual counting of the corpuscles.

(ii.) *Macrocythæmia rubra* (Plate I., Fig. 3, *i*), or increase in the diameter of isolated red corpuscles from the normal 7·8 μ to 10 or 15 μ, is not to be confounded with the swelling of the red corpuscles in hydræmic blood. It is observed in all severe anæmias, but especially in pernicious anæmia, and sometimes also in leucæmia and chlorosis.

(iii.) *Microcythæmia rubra* (Plate I., Fig. 3, *h*), the occurrence of globular elements which are smaller and also as a rule of deeper colour than normal red corpuscles, and which perhaps are formed by degeneration of the latter, is present in most anæmias, a few intoxications, and also after burns and hæmorrhages of severer degree.

(iv.) *Poikilocytosis* (Plate I., Fig. 3, *g*) is that condition in which the red corpuscles assume very varied forms (flask-, kidney-, anvil-, or cup-shapes), but the significance of which is still quite obscure. It is present to a moderate extent in almost all severe anæmias,

notably also in leucæmia, but to a conspicuous degree in pernicious anæmia. It must not be confounded with the mulberry and thorn-apple forms of red corpuscle which occur very soon after the blood is drawn off, in consequence of evaporation.

(v.) *Nucleated red corpuscles* (Plate I., Fig. 3, *k* and *l*). These are found in severe anæmias and in myelogenic leucæmia, as well as after extensive hæmorrhages. They are either of normal size (*normoblasts*) or considerably larger (*megaloblasts*), the latter indicating a bad type of disease.

2. Changes in the White Corpuscles.—The most frequent change is an increase in number, occurring either as simple *leucocytosis*, or as *leucæmia*.

In normal blood the following five forms of white corpuscles occur, of which the later in series in each instance always develops from that which precedes:—

(1) *Small lymphocytes* (Plate I., Fig. 4, *a*), about the size of red corpuscles, with a relatively large nucleus which stains intensely.

(2) *Large lymphocytes* (Plate I., Fig. 4, *b*), at least twice the size of the former, having nuclei which are likewise large but often stain less deeply, and a cell-body usually somewhat broader.

(3) *Mononuclear transitional forms*, the nucleus of which is indented in the centre, and whose protoplasm commonly already shows the first traces of the so-called neutrophil granulation.

(4) *Polynuclear leucocytes* (Plate I., Fig. 3, *c*). These are larger than red corpuscles, and usually smaller than the large lymphocytes (No. 2), have several nuclei which take a deep colour, and usually show in their protoplasm numerous granulations which will stain only in *neutral* anilin colours, *i.e.*, *neutrophil granulations*, these being subject to certain fluctuations in size, but still in general finer than those in the following variety of cells.

(5) *Eosinophil leucocytes* (Plate I., Fig. 3, *d*), which usually possess two less strongly-staining nuclei or one indented nucleus, and have in their protoplasm coccus-like granules, which stain readily in *acid* anilin colours, and are, as a rule, coarser than the granules of the preceding variety of leucocytes. The eosinophil cells are often found in a disorganised condition (*e*).

According to countings made with dried preparations of normal blood, the lymphocytes (Nos. 1 and 2) constitute approximately 25 per cent., and the polynuclear leucocytes 60 to 70 per cent. of the total number of white corpuscles, whilst the remainder is made up of transitional forms and eosinophil cells.

(i.) In *leucocytosis*, which is temporarily present during digestion, and also occurs after hæmorrhages and in various infective diseases

and cachexies, as well as very often before the death-agony, and is in general of little significance, there exists merely an increase in the numbers of the polynuclear leucocytes, or at least only of the kinds of white corpuscles normally present in the blood, in which latter case, however, the normal ratio between the percentages of the different kinds of leucocytes remains unaltered.

(ii.) *Leucæmia* is either *myelogenic* (*myelo-splenic*) or *lymphatic*, in either of which forms the number of white corpuscles may so increase as to equal or even exceed that of the red, while the latter are commonly diminished in amount, and show poikilocytosis.

(*a*) The *first form* of leucæmia (Plate I., Fig. 3) is characterised by multiplication of the eosinophil cells (*d* and *e*), and particularly by the presence in very large numbers of round mononuclear leucocytes. These are probably derived from the marrow of bones (*myelocytes*, *a*), and differ from the large lymphocytes of normal blood, with which they might most readily be confounded, in being in general larger, sometimes even considerably so, and in the facts that their remarkably large nuclei stain still more feebly than those of the lymphocytes, and that their protoplasm usually exhibits neutrophil granulations. The constant presence of nucleated red corpuscles of normal (*k*) or excessive (*l*) size is also characteristic of this form of leucæmia.

(*b*) In the *second form* (Plate I., Fig. 4), which is more rarely observed, it is only the mononuclear leucocytes of the blood (*lymphocytes*, *a* and *b*), especially the small forms, which are increased, and these may multiply until they constitute as much as 95 per cent. of all the white corpuscles. On the other hand, none or almost none of the nucleated red corpuscles are present, and but few eosinophil cells. After death in leucæmia the so-called *Charcot's crystals* are met with in the blood as well as in the marrow of bones and in the spleen. These are colourless elongated octohedra, which, as is well known, are constantly present in the semen, and sometimes also in the sputum [*e.g.* in asthma; see p. 289].

The higher degrees of leucæmia can be recognised from characters of the blood which are apparent even to the naked eye (inasmuch as it is thinner, paler, and more turbid than normal, whilst the post-mortem clots are of a reddish-grey or even yellowish-green pus-like colour), as well as in microscopic preparations from the extraordinarily large number of the white corpuscles. A *slight* increase in the numbers of the white corpuscles, however, can only be recognised by counting, it being borne in mind that the normal ratio of the white to the red corpuscles may fluctuate between 1 : 500 and 1 : 1000, and that slight deviations from this ratio should scarcely be regarded as pathological conditions.

3. Melanæmia and Lipæmia.—For *Melanæmia*, see pp. 59 and 168.

Lipæmia occurs physiologically during digestion, and otherwise is present in chronic alcoholism, chronic nephritis, and diabetes, as well as after fractures, where fat enters the blood in consequence of injury to the marrow. Numerous small shining globules, some of them enclosed in white corpuscles, are found under the microscope.

4. Animal and Vegetable Parasites in the Blood.—The only *vegetable parasites* met with are Bacteria, of which the following are found:—

(1) *Anthrax bacilli* in anthrax, when a general infection has taken place (p. 128).

(2) *Spirilla Obermeieri* in relapsing fever (p. 156).

(3) The following also occur inconstantly, and in isolated cases:—*Streptococcus* and *Staphylococcus pyogenes* in pyæmia, and in the cases of ulcerative endocarditis due to these micro-organisms; *tubercle bacilli* in general acute tuberculosis; *glanders bacilli* in acute glanders; and, with still less constancy, *Diplococcus pneumoniæ* in pneumonia and the form of endocarditis produced by this species of bacterium; and lastly, *Streptococcus erysipelatis* in severe cases of erysipelas. In many of these cases, however, even when the attempt to find the respective bacteria with the microscope has failed, it will still be possible to demonstrate their presence by the process of cultivation.

Of the *animal parasites*, the *Plasmodium malariæ* must first be mentioned, then also *Filaria sanguinis hominis* and *Distoma hæmatobium*. The two latter, however, only occur in the tropics.

Examination of the Blood.—A. Histological Examination. 1. *General.*—Blood is obtained from the living by puncturing the skin (previously purified) of the finger-tip or lobule of the ear with a sterilised needle, bringing a cover-glass down upon the blood as it oozes out, and spreading a very small quantity of the latter in a very thin film upon a slide. If it is desired to prevent shrivelling of the red corpuscles, the examination should be carried out in 0·75 per cent. salt solution, a drop of which may be placed upon the skin and the puncture made through it; but otherwise it is better to examine the blood undiluted.

A simple examination of this kind is not usually sufficient, however, for the recognition of the different diseases of the blood, accurate counting, and perhaps also measurement and special staining, of the blood-cells being necessary in addition, as well as a determination of the contained hæmoglobin.

2. *Counting and measurement of the corpuscles.*—For accurate determination of the number of the red and white corpuscles the Thoma-Zeiss apparatus should be used. This consists of a chamber 0·1 mm. in depth, upon the bottom of which are ruled 400 squares, each having a superficial area of $\frac{1}{400}$ of a square millimetre, so that the cubic contents of the column of fluid over each square amount to $\frac{1}{4000}$ of a cubic millimetre. The blood must be previously diluted, which is most simply done by means of the bulbed pipette (*mélangeur*) supplied with the apparatus, using a 3 per cent. solution of common salt coloured with a little methyl or gentian violet (0·1 grm. dye to 150 grm. of the 3 per

cent. salt solution) in order to stain the white corpuscles. The blood obtained by pricking the skin is first sucked up as far as the mark at the commencement of the bulb, and the *filtered* diluting fluid drawn in immediately afterwards until the mixture reaches the mark above the bulb. Since the latter holds one hundred times as much as the portion of pipette below it, a dilution of the blood of one hundred times is thus obtained. An even distribution of the blood-cells having been secured by shaking the fluid so as to mix it, the Thoma-Zeiss apparatus is filled from the pipette, a cover-glass laid over it, and the blood corpuscles then counted under a medium power in as many squares as possible, including not only the corpuscles within the squares but also those on the boundary lines. If now the sum-total thus obtained is multiplied by 4000 (*i.e.*, the cubic contents of the counting chamber), and by the number expressing the degree of dilution (*i.e.*, usually 100), and divided by the number of squares counted, we obtain the total number of corpuscles in a cubic millimetre of undiluted blood.

To *measure the size* of the corpuscles, a cover-glass is slightly warmed and brought over the drop of blood as it oozes out, and the latter is then examined in the dry state, the actual measurement being made by means of an eyepiece micrometer (see p. 23, note).

3. *Staining of the corpuscles.*—For the purpose of staining the different forms of blood-cells (in leucæmia, anæmia, etc.), the methods introduced by Ehrlich are resorted to. The blood is smeared upon cover-glasses, previously well cleaned[1] with alcohol, in a very thin and equal layer, by laying two cover-glasses one upon the other and drawing them quickly and evenly apart. When dry, they are heated for half-an-hour to two hours[2] at 120°-130° C. (in a small dry oven or in the hot-air sterilising apparatus, p. 34) in order to fix the hæmoglobin, and then stained with one of the two following mixtures:—

(1) *Thoroughly saturated* aqueous solutions are first prepared of orange G, acid fuchsin, and methyl green—some undissolved pigment must still remain on the bottom of each bottle after standing for several days in a warm place—50 c.cm. of each solution are then, without shaking the bottles, poured together into a fresh flask, and a further addition of 50 c.cm. absolute alcohol, and 100 c.cm. water, is made to the mixture. The latter must be left standing for several weeks until the precipitate formed has completely subsided to the bottom, and should then be of a rusty-brown colour. The fluid must not be filtered, so that it is always used by conveying to the cover-glass to be stained a few drops taken from the central part by means of a dry pipette or glass rod. By rocking the cover-glass continually to and fro the stain is kept from drying up anywhere for some minutes, after which the glass is rinsed in water and examined in thin Canada balsam. The nuclei of the cells now appear from greenish-blue or light-blue to bluish-violet (Plate I., Fig. 3), the neutrophil granules greyish- to reddish-violet (Plate I., Fig. 3, *c*), the eosinophil granulations yellowish-red to dark-red (Plate I., Fig. 3, *d*), and the hæmoglobin orange-yellow (Plate I., Fig. 3, *f* and *g*).

Unfortunately the mixture just given is not constant in its action, in many

[1] For the mode of cleaning, see also above, p. 26, note.

[2] It is impossible to give the exact time, as the behaviour of the hæmoglobin in this respect is very different in different cases. Instead of heating, the cover-glasses may also be deposited for two hours or longer in a mixture of equal parts alcohol and ether.

cases not staining well until it has become rather old, whilst at other times the reverse is the case. It may also happen that one or other of the pigments in the mixture fails to make itself sufficiently prominent in the staining of preparations, in which case more must be added.

(2) The second staining-fluid is prepared as follows:—10 grm. *crystallised* eosin, 13 to 15 grm. crystallised nigrosin, 8 grm. orange, and 70 to 100 grm. glycerin are well rubbed up together and allowed to stand for some days at 60° C. This mixture also is not filtered. In use, a drop having been placed upon a slide, the cover-glass after being smeared with the blood and heated is laid upon it, and the dye allowed to act for a considerable time, six hours at least. The cover-glass is then lastly rinsed in water and examined in Canada balsam. By this method the nuclei are stained black, the hæmoglobin yellow, and the eosinophil granules red, while the neutrophil granules remain unstained.

Besides these two staining solutions the double staining with methyl blue and eosin mentioned amongst the methods of examining Protozoa (p. 170) may be resorted to with advantage, as the different formed elements of the blood are characteristically stained in this way likewise.

Sections may also be prepared from blood. For this purpose some drops are let fall into a glass of 20 c.cm. capacity containing 5 c.cm. of a 2 per cent. osmic acid solution, the blood is distributed through it by shaking to and fro, and the vessel is then allowed to stand at rest. (As the red corpuscles sink first, then the white corpuscles, and lastly the blood-plates, the elements can also be obtained isolated in this way.) In twenty-four hours the mixture is shaken up afresh, and four or five drops transferred from it by means of a pipette to about 5 c.cm. of agar, kept fluid at a temperature of 37° C. This is poured into a little paper box or a capsule, and is hardened in 83 per cent. alcohol after it has set. It can then be cut into sections.

In case it is desired to stain the blood-cells in such sections, or in sections of hardened tissues and organs, by Ehrlich's method, Heidenhain recommends that thoroughly saturated (but filtered) solutions of orange, acid fuchsin, and methyl green, should also be first prepared, and 100 c.cm. of orange solution then mixed with 20 c.cm. of acid fuchsin, to which 50 c.cm. of methyl green are added with gentle agitation. For actual staining this mixture is diluted with water in the proportion of 1 to 60–100. The fluid when diluted to this extent should become a deeper red on the addition of acetic acid, and should make a spot upon filter-paper which appears bluish-green in the centre and orange towards the margin. Should any one of the colours come out too strongly, or not strongly enough, in this test, the proportions of the mixture must be altered accordingly. The sections remain in the solution from six to twenty-four hours, and are decolorised with alcohol. The karyokinetic figures and the fragmented nuclei of the leucocytes are stained green, the resting nuclei blue, and the red corpuscles red.

4. *Determination of the hæmoglobin.*—This does not, strictly speaking, come within the bounds of Pathological Histology, but as it is indispensable for the differential diagnosis of certain diseases of the blood, it is proposed to describe the process briefly in this place. For this estimation Fleischl's *hæmometer* may be employed with advantage. In this instrument the colour of the blood to be examined, which is dissolved in water, is compared with that of a wedge of red-tinted glass, which is pushed beneath a little table, arranged after the manner of the stage of a microscope, and having a circular aperture in its

centre. Over this aperture fits a short metal tube closed below by a little plate of glass, and divided by a vertical partition into two halves, one of which is adjusted so as to stand above the coloured wedge, the other merely over the empty aperture. Some water is first delivered into both halves, and then the blood, having been collected by means of a capillary tube which is supplied with the apparatus, is transferred to the half which does not lie above the coloured wedge. Both halves are now completely filled with water, and the glass wedge is then pushed along until the fluid in the two appears to be of the same depth of red, when the scale is lastly read off. The apparatus can only be used by artificial light, the illumination coming from a plate of gypsum occupying the position of the mirror in a microscope, and reflecting the light from a lamp or gas-flame.

The number read off on the scale, 70 for instance, signifies that the blood contains 70 per cent. of the normal quantity of haemoglobin ; and if we now compare the contained hæmoglobin thus estimated with the number of the red corpuscles as previously ascertained, we learn whether the amount of hæmoglobin, *i.e.*, the *colour index*, of the individual red corpuscle remains normal or has become larger or smaller than it should be. This determination is of importance from the point of view of diagnosis, inasmuch as in chlorosis the *number* of the red corpuscles is frequently not diminished, although the *colour index* is ; whereas in pernicious anæmia this is reversed, and in other forms of anæmia both numbers may be reduced.

5. *Recognition of blood and fibrin.*—Should proof be needed in the case of dried blood that it really is blood which has to be dealt with, the required evidence may be supplied by the recognition of red corpuscles or the demonstration of hæmin crystals. The former result can be gained by softening in a 0·8 per cent. solution of common salt or a 33 per cent. solution of caustic potash ; but no conclusion must be drawn from the relative sizes of the softened red corpuscles as to the source of the blood, *i.e.*, whether from men or animals.

To show Teichmann's hæmin crystals, some drops of glacial acetic acid and a minute grain of salt are added to small dry particles of the substance under examination which have been placed upon a slide, and the whole is carefully heated until bubbles are given off. The crystals are dark-brown rhombic plates.

For the special staining of fibrin, see p. 75.

B. Bacteriological Examination.—As in the case of other fluids, this is done as a rule by making stained *cover-glass preparations* (p. 26). If it is desired to stain the red corpuscles as well as the bacteria, the preparations after treatment by Gram's[1] method should be transferred to eosin as a counter-stain (p. 29) ; but where simple decolorisation of the red corpuscles is required, the cover-glasses, after being passed through the flame, are first laid for about ten seconds in 1 to 5 per cent. acetic acid (which decolorises the red corpuscles), then thoroughly washed with water and dried, and lastly stained. With regard to the choice of stain and the nature of the process required for each individual bacterium and for the *Plasmodium malariæ*, see Part II., Chapters V. and VI. Should it be desired to make cultivation experiments with the blood of living individuals, the skin must be disinfected in the manner described on p. 35. If this is very carefully done the blood may sometimes be transferred directly to oblique agar or to bouillon,—that is, when but few bacteria are suspected to be present in it.

[1] When the bacteria in question admit of staining by this method.

CHAPTER II.

THE CIRCULATORY APPARATUS.

I. THE HEART AND PERICARDIUM.

1. Atrophy, Degeneration, Softening, and Hypertrophy of the Heart.—*Brown atrophy of the heart.*—In this form of atrophy not only do the muscle-cells appear reduced in size, but the small yellow or brownish pigment granules normally present, especially in elderly individuals, at the poles of the nuclei are seen to be greatly augmented, and the lines of cement between the cell-territories come out more distinctly,[1] while at the same time the sub-pericardial fatty tissue assumes a jelly-like consistence owing to serous atrophy (p. 62). This condition occurs in marastic or cachectic individuals.

Degenerations.—In *cloudy swelling* the muscular fibres look as if covered with dust, owing to being infiltrated with small albuminoid granules, soluble in acetic acid, which may lie so densely as to mask the transverse striation and the nuclei of the muscle-cells. This condition is found notably in acute infective diseases, and is frequently the preliminary stage of

Fatty degeneration (Fig. 94), which, however, apart from diseases due to infection and intoxication, may also be found in valvular insufficiency, narrowing of the coronary arteries, and general anæmia, occurring either diffusely or in a circumscribed form as small yellow spots, especially under the endocardium of the musculi papillares.

[1] A very conspicuous prominence of the cementing substance in the form of broad or swollen-looking stripes may also be frequently observed in cases of sudden death, especially when occurring in consequence of rupture of the heart or sclerosis of the coronary arteries, as well as in certain infective diseases; and this change may even advance to such a degree that gaping fissures appear on the site of the bands of cement. As what takes place here is evidently solution of the connection between the cells of the myocardium, the condition is described as *dissociation* or *fragmentation*. It may probably be, however, that it only takes place in the death-struggle.

In this condition the primitive bundles are found covered or infiltrated with more or less numerous fat-drops arranged at first in

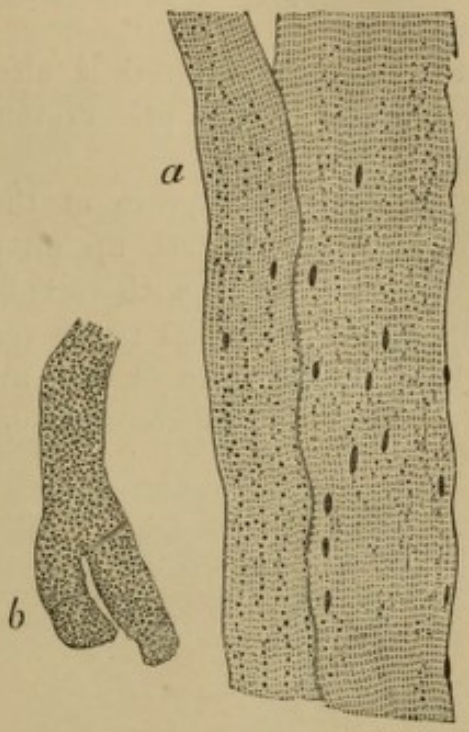

Fig. 94.—Fatty Degeneration of Striped Muscular Fibres. × 285. Preparation made by teasing after action of acetic acid. *a*, Primitive bundles of the Rectus Abdominis muscle; commencing degeneration; *b*, Branched primitive bundle of myocardium; advanced degeneration.

longitudinal rows. All these droplets, or at least the greater number, are very minute, and when present in large quantity no longer allow the nuclei or striation to be distinguished (*b*).

Fatty degeneration must not be confounded with *fatty infiltration* of the heart (*cor adiposum*), which however does not affect the muscular tissue, but merely the subserous and interstitial connective tissue. It consists in a change of the latter into adipose tissue. *Amyloid*, *hyaline*, and *waxy degenerations* also occur in the heart, where they present the same microscopic appearances as elsewhere; and lastly, *fatty* and *mucous degenerations* of the endocardium are also found, especially on the valves, as well as *incrustation* (calcification) of the latter.

Myomalacia (or *infarction*) of the heart is observed most frequently in the anterior wall of the left ventricle near the apex, as a consequence of narrowing or obstruction of that branch of the left coronary artery which runs in the anterior longitudinal sulcus. It may take the form either of an anæmic [white] or of a hæmorrhagic infarction. In the former case the muscular fibres at first show a dense finely-granular clouding, with simultaneous disappearance of the transverse striation, whilst their nuclei, and in part also those

of the interstitial connective tissue, no longer take up stain; or the primitive bundles become homogeneous and fissured as in waxy degeneration (see Part III., Chapter X.). Finally, they break down into a granular detritus.

In the second case, extravasated blood is also seen, the red corpuscles of which at first remain in good preservation, but are eventually transformed into granular pigment.

If death does not result from rupture of the heart or in some other way, reparative processes are set up after absorption of the detritus, the defect becoming filled in with vascular granulation tissue, which gradually changes into cicatricial tissue (cardiac cicatrix). In this there may still be included more or less numerous but usually atrophic muscular fibres, as well as masses of pigment (Fig. 95).

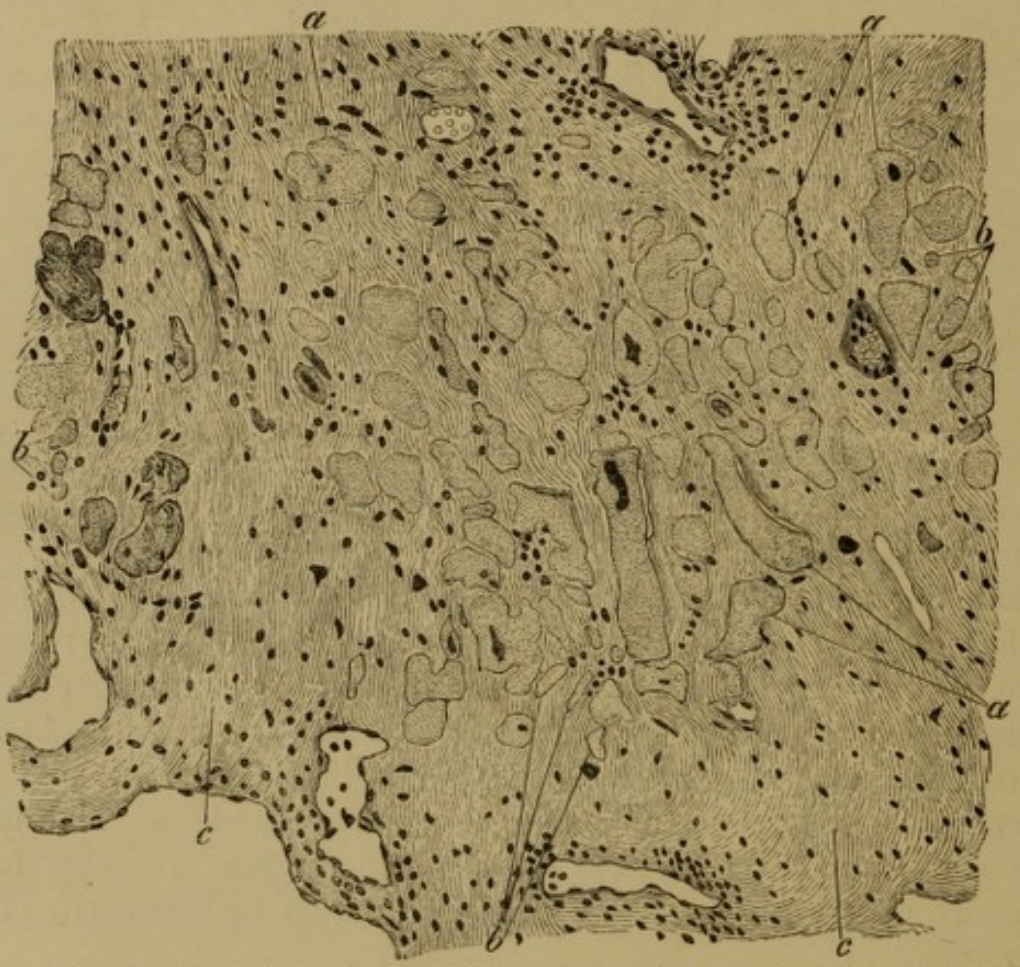

FIG. 95.—CICATRIX IN THE MYOCARDIUM. × 240. (Hæmatoxylin and eosin.) *a*, Primitive muscular bundles, cut transversely and obliquely; *b*, Atrophic muscular bundles; *c*, Newly-formed connective tissue.

Should the softening extend so deeply as to reach the endocardium, this also becomes involved in cicatricial thickening; and a further result may be the formation of a *cardiac aneurysm* and of *thrombi* in its interior (Fig. 108).

Hypertrophy of the heart usually takes place when there is mechanical obstruction to the progress of the blood. It is charac-

terised microscopically not only by thickening of the muscular fibres, but by multiplication of their nuclei.

2. Inflammation.—*Acute endocarditis* (Fig. 96) chiefly affects the

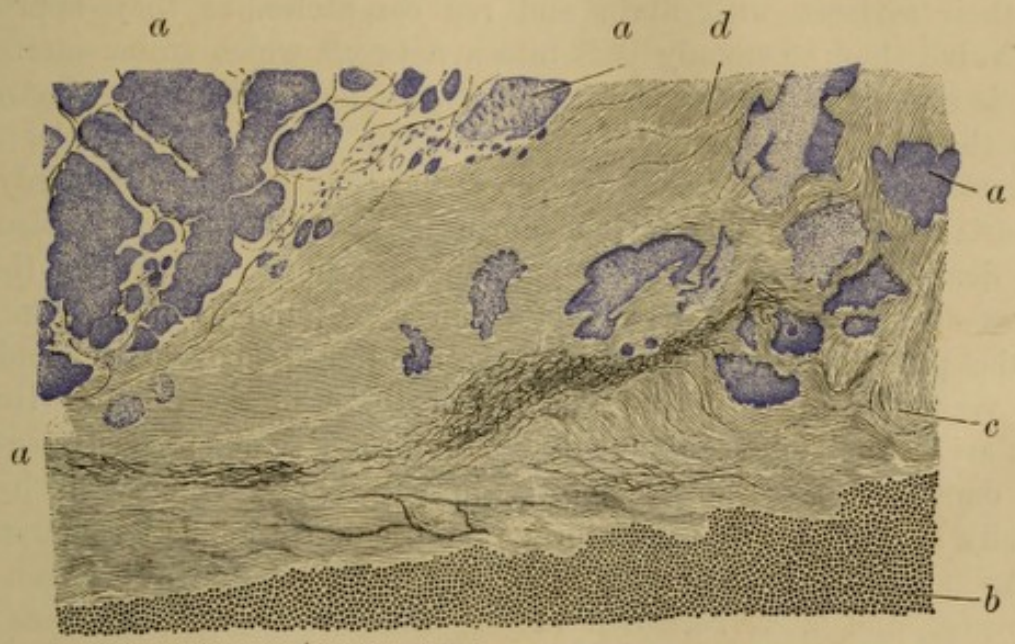

FIG. 96.—ULCERATIVE ENDOCARDITIS OF THE AORTIC VALVES. × 110. (Weigert's modification of Gram's method.) *a*, Accumulations of cocci; *b*, Small-celled infiltration of the valve; *c*, Necrotic valve-tissue; *d*, Thrombus on the valve.

valves, especially those of the left side of the heart—during fœtal life, on the contrary, the right side—and appears to be practically always due to bacteria. Those most frequently present are the *Staphylococcus pyogenes aureus*, *Streptococcus pyogenes*, and *Diplococcus pneumoniæ;* but other kinds have also been observed in isolated cases, and sometimes not alone one but two or three species of bacteria may be found together. The respective micro-organisms, which usually make their way into the valves from the blood-current, especially along the lines where the cusps come in contact (a process which is sometimes favoured by certain changes, such as thickenings and irregularities, etc., in the valves themselves), either affect the endocardium primarily or are derived from other diseased organs. Their first effect on the valves involved is to produce a more or less extensive superficial necrosis (*c*), which can be recognised either by the absence of nuclear staining alone, or under the well-marked form of coagulation necrosis. There then ensue, on the one hand, thrombotic deposits (*d*) upon the altered portions of the valves, and on the other, reactive inflammation (*b*) of the tissue of the valve lying beneath the necrosis.

The *thrombotic deposits* or *vegetations* are of varying size and shape, the smaller being always lobulated or finely warty in appearance, whilst the larger may also take globular or polypoid forms.

Microscopically they show a finely-granular mass consisting of adherent blood-platelets, and frequently full of fissure-like branching spaces in which leucocytes lie. While the vegetations may be covered on their surfaces with fibrin and red corpuscles, as they approach the valve they commonly pass into a network which stains intensely and is sometimes infiltrated with leucocytes, and which also penetrates into the valve-substance. The latter itself is devoid of nuclei (*i.e.*, necrotic) immediately beneath the vegetation, though commonly to a variable extent; but further down it is infiltrated with more or less densely-lying and frequently polynuclear leucocytes, which themselves again may be partly involved in a granular disintegration (*b*). If the process is recent the bacteria mentioned above are found in the vegetations and in the vicinity of the necrotic valvular tissue, and are sometimes so abundant as to form the chief constituent of the deposits (*a*). They lie mostly in masses and groups which are usually round, but sometimes form very peculiarly lobulated figures.

An anatomical distinction has hitherto been drawn between an *ulcerative* and a *verrucose* form of endocarditis, according as its destructive character does or does not come into prominence. Between these two forms, however, there exists only a difference in degree, dependent on the quantity, and perhaps also on the virulence, of the bacteria.

In *ulcerative* endocarditis the necrotic destruction and reactive inflammation of the valves are much more extensive, and hence also more conspicuous to the eye. This process may result in the formation of so-called *valvular aneurysms* (when only a thin lamella of the valve is left and this bulges out under the pressure of the blood), or to perforation of the valvular curtains; and it may also not uncommonly extend to the parts in their vicinity (chordæ tendineæ, sinus of Valsalva, myocardium, etc.).

In the *verrucose* form, however, the necrosis (or other tissue degeneration) caused by the bacteria restricts itself to a much smaller portion of the valve, in most cases to the lines of contact; and hence the thrombotic deposits are not so bulky and the reactive changes in the valve not so considerable. For this reason the issue of this form of the disease is either not fatal at all or only at a late stage, when the bacteria may be already dead.

When minute particles are torn from the thrombotic deposits by the blood-current, they commonly give rise, if caught in terminal arteries, to *infarctions*, which are of the simple hæmorrhagic or anæmic variety only when the particles are free from bacteria, but otherwise (*i.e.*, if the particles torn off contained pyococci) change into abscesses. Sometimes mere collections of bacteria break loose from the deposits

on the valves, or, at all events, particles so minute that they do not stick until they reach the capillaries, in which case quite small and more rounded metastatic foci form as a result. (See also *Thrombosis and Embolism*, p. 208 *et seq.*)

If the endocarditis does not cause death before the height of the process is reached, *regenerative changes* set in (Fig. 97). There are

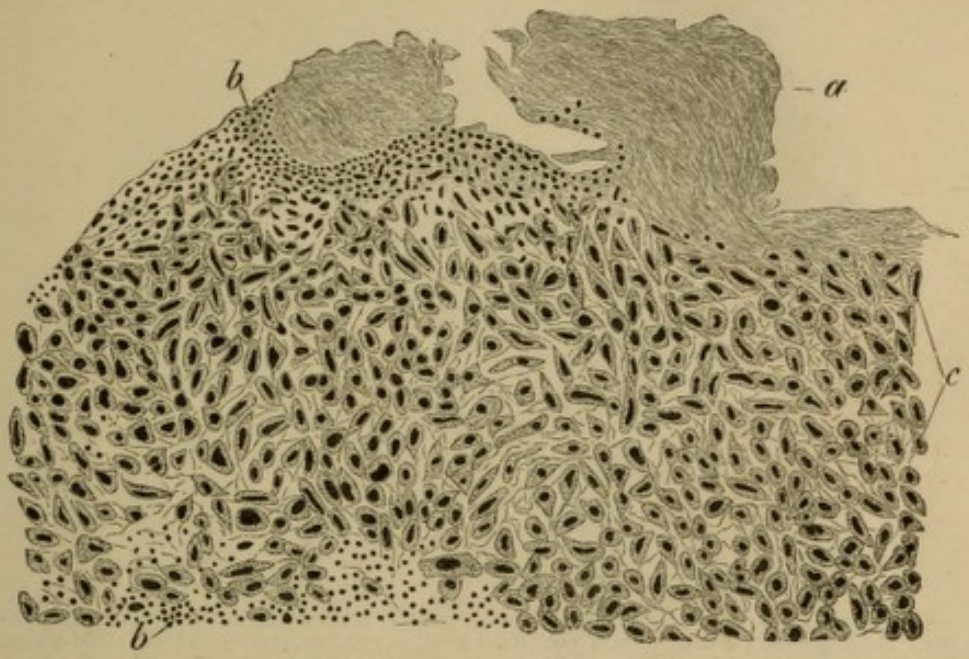

Fig. 97.—Endocarditis Verrucosa in Process of Healing. × 330. (Alum cochineal.)
a, Valve thrombus; *b*, Small round cells; *c*, Larger epithelioid cells (fibroblasts).

then found in the deeper parts of the valve, besides small mononuclear cells, larger epithelioid or spindle-shaped elements, which together with the newly-formed blood-vessels (derived from those already existing in the valves or neighbouring myocardium) form an embryonic tissue which invades the necrotic parts of the valves and the thrombotic deposits, and finally replaces them. As it eventually changes into a connective tissue which becomes progressively poorer in cells and firmer, it produces the well-known thickenings, adhesions and shrinkages of the valve-curtains and chordæ tendineæ, which may lead to insufficiency of the valvular apparatus. The phase of the process last described is termed by many *chronic endocarditis*, under which designation is usually included also the extension of a *chronic endarteritis* (p. 204) to the valves.

We may meet with *thrombotic deposits* upon the valves in other cases also apart from endocarditis, and especially in marastic individuals, and upon parts of the valves which are irregular, thickened, or otherwise altered. These thrombi (Fig. 98), moreover, show a similar structure to those in endocarditis, except that they are invariably free from bacteria, and that consequently the tissue of the valve

under them shows neither necrotic nor inflammatory changes. They may, however, likewise become organised when they have existed for

FIG. 98.—THROMBUS ON AN AORTIC VALVE, DUE TO MARASMUS, in process of organisation. Low power (× 65). (Alum cochineal.) *a*, Thrombus, composed of blood-plates and leucocytes; *b*, Valve-tissue growing into the thrombus.

a considerable time, the valvular tissue growing into (Fig. 99) and gradually replacing them.

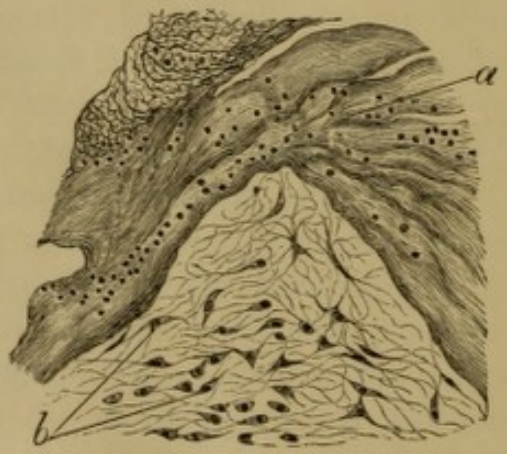

FIG. 99.—THE THROMBUS IN FIG. 97 MORE HIGHLY MAGNIFIED (× 240). *a*, Thrombus, composed of blood-platelets and leucocytes; *b*, Proliferated stellate and spindle-shaped connective-tissue cells of the valve.

Myocarditis is set up either by the extension of an endocarditis to the myocardium, or as a consequence of embolism; that is, when the specific excitants of some mycotic inflammation, existing in another part of the body, succeed in reaching the arteries of the heart. In the latter case foci form which are numerous, though mostly very

minute, whilst in the former the inflammation may also attain a considerable extent. The embolic foci (Fig. 100) consist of bacteria

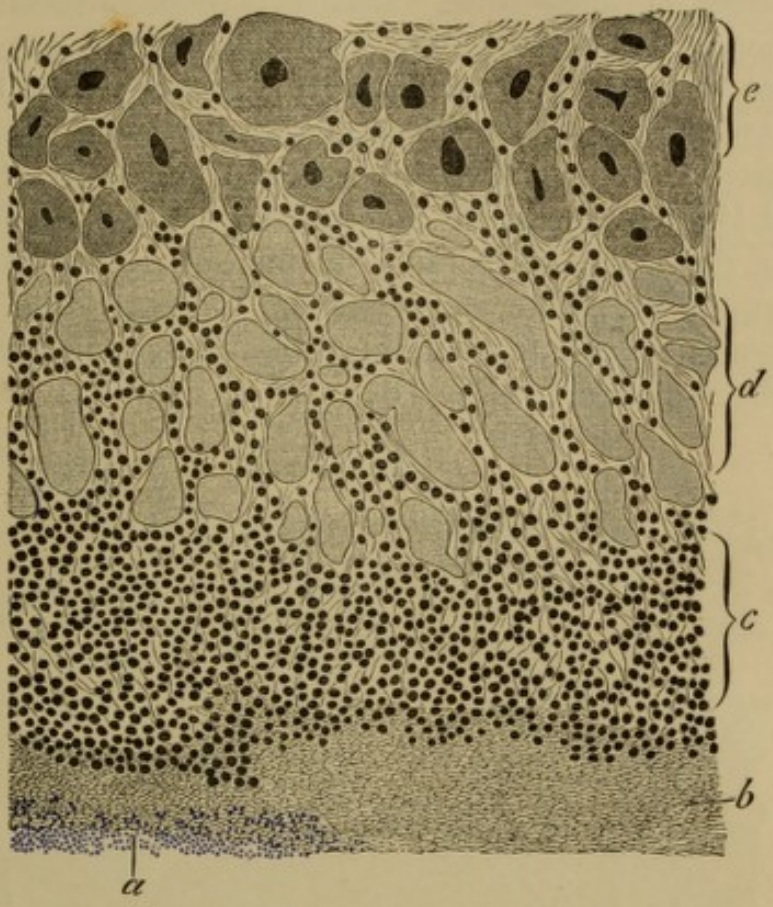

FIG. 100.—METASTATIC MYOCARDITIS IN PYÆMIA. × 545; the cocci drawn in under a power of × 180 times. (Weigert's modification of Gram's method.) *a*, Staphylococci; *b*, Necrotic tissue; *c*, Round cells; *d*, Necrotic primitive muscular bundles, with small-celled infiltration of the interstitial connective tissue; *e*, normal primitive muscular bundles.

(*a*) and necrotic (often waxy-degenerated) muscle fibres (*d*), together with a small-celled infiltration (*c*), which latter, if due to the action of pus bacteria, soon assumes a purulent character, so that the foci grow into abscesses of larger or smaller size. The latter may advance until they lead to rupture of the heart, or else may heal up by cicatrisation, with or without calcification.

Acute pericarditis is in the majority of cases of secondary origin, being due either to the extension of inflammation to the pericardium from a neighbouring part, most frequently the pleura, peritoneum, or heart itself, or to the entrance into the circulation of the specific excitants of an inflammation present in some other region, in which case, of course, not only the specific micro-organisms but also to a certain extent the anatomico-histological characters of the pericarditis will correspond with those of the primary inflammation. Of pathogenic bacteria those which we find most frequently are the *Diplococcus pneumoniæ* and the *Streptococcus and Staphylococcus pyogenes.*

The *exudation* in acute pericarditis, as in inflammations of the serous membranes generally, is either serous, fibrinous, or purulent; or combinations of these three varieties may be present, the character of the exudation depending upon the stage of the process as well as upon the nature of the bacteria. In the serous form which usually occurs at the commencement of the pericarditis the pericardial fluid is increased in quantity, and rendered turbid by the presence of migrated leucocytes, cast-off endothelial cells, and bacteria. Later on, however, there ensues a continually increasing exudation of fibrin, or an emigration of white corpuscles, in consequence of which the exudation becomes either more fibrinous or more purulent respectively.

Under the microscope (Fig. 101) the pericardium is seen even

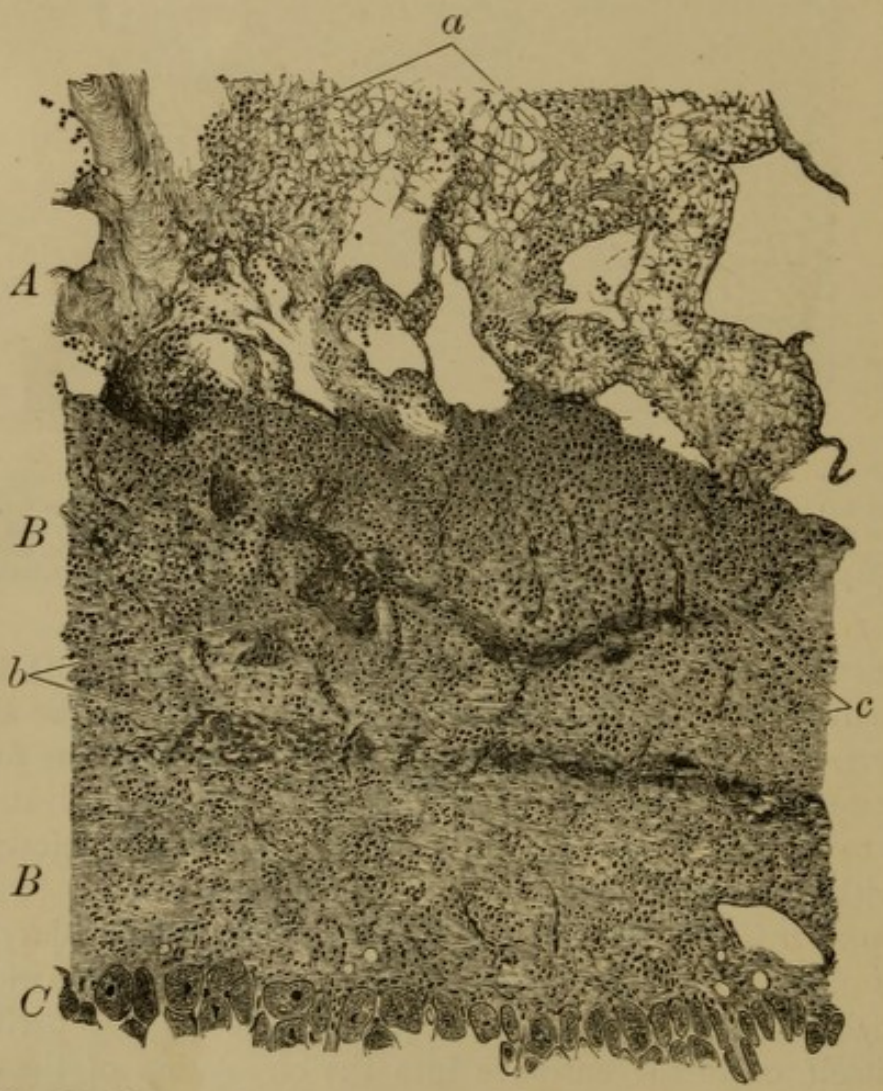

FIG. 101.—FIBRINOUS PERICARDITIS. × 65. (Hæmatoxylin and eosin.) *A*, Fibrinous exudation on the surface of the pericardium; *B*, Pericardium infiltrated with cells (granulation tissue); *C*, Myocardium; *a*, Fibrinous reticulum with leucocytes; *b*, Fibrinous bands in the pericardium; *c*, Newly-formed blood-vessels.

at the commencement of the inflammation to be hyperæmic and infiltrated with leucocytes (*B*). With increase of the latter in the tissue there next ensues also exudation of fibrin and emigration of leuco-

cytes upon the surface of the pericardium (*A*), one or other process predominating according to the character of the inflammation, whilst the exudation may attain different degrees of thickness. When the acme of the process is past, with simultaneous new-formation of blood-vessels (*c*), mononuclear round cells and fibroblasts appear in the pericardium, in the place of the pus corpuscles, and these cells also penetrate into the exudation covering the surface. If the latter is of a fibrinous nature, as is mostly the case, it appears at first as a delicate reticulum (*a*), later in the form of thick and homogeneous bands (*b*), but by degrees becomes permeated and replaced by the advancing embryonic tissue (Fig. 102, *c* and *d*). This again eventually changes

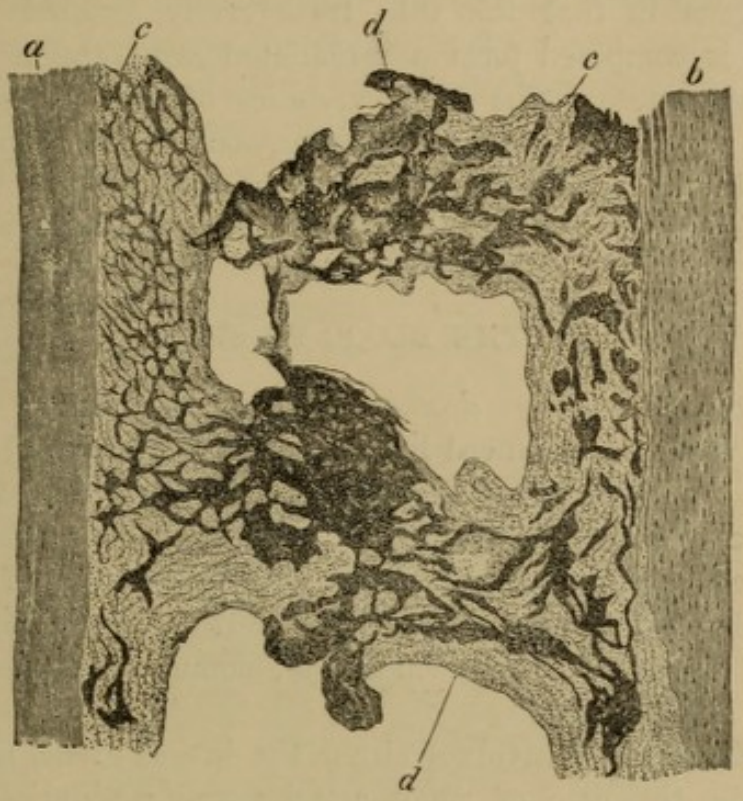

FIG. 102.—COMMENCING ADHESION OF THE TWO LAYERS OF THE PERICARDIUM IN PERICARDITIS. × 30. (Hæmatoxylin and eosin.) *a*, Visceral layer of pericardium; *b*, Parietal layer; *c*, Young connective tissue overlaying both layers and still containing abundant remains of fibrin; *d*, Connecting bridges composed of the same tissue.

into firm connective tissue, which in slight degrees of inflammation occurs in the form of *tendinous spots*, but in higher degrees composes bands or patches of *adhesion* between the two surfaces of the pericardium (Fig. 102), whilst calcareous deposits may also take place in the new connective tissue.

3. Infective Granulomata and New Growths.—The former are as a rule but rarely met with in the heart. *Tubercles* occur either as small miliary nodules (in general acute miliary tuberculosis), most frequently lying under the endocardium of the right conus arteriosus; or as larger caseous nodules, usually in the substance of the wall.

They are more frequent on the pericardium, where they may also take the form either of miliary nodules (in large numbers, however), or of caseous and often disintegrating nodes enclosed in newly-formed vascular connective tissue. At the same time a hæmorrhagic or fibrinous exudation is present, or concretio pericardii already exists.

Syphilomata are always embedded in cicatricial tissue in the wall of the heart, and in all other respects are of similar structure to those in other organs (see p. 139).

Of *tumours proper*, the *rhabdomyoma* should especially be mentioned. It is *congenital*, and differs from tumours of the same name in other organs in that the thin transversely striated muscle-cells of which it is composed form a reticulated structure of bands with numerous interspaces. The other varieties of tumour are somewhat rarely met with. They may, however, occur either primarily or secondarily, in the myocardium or upon the endocardium. Of *animal parasites*, *Echinococcus* and *Cysticercus* have been observed.

II. THE BLOOD-VESSELS.

4. Degenerations.—*Fatty degeneration*, which usually occurs in arteries and veins (in advanced life especially in the aorta) in different diseases due to infection or intoxication, anæmia, etc., but may also involve the capillaries, chiefly affects the cells of the intima and the smooth muscular fibres of the media, the protoplasm of these cells becoming filled with little drops of fat. It frequently terminates in *calcification*. Both conditions, moreover, commonly occur as a part of *atheroma* (see p. 204).

Hyaline degeneration involves either the intima alone, or the media, or else, as in the case of small arteries and capillaries, the entire wall. The membrane may swell up quite irregularly and form nodose protuberances inwards or outwards. *Amyloid degeneration* is very frequent in the blood-vessels, as has already been observed (p. 55), and especially so in the arteries.

5. Inflammation (Vasculitis).—This affects the arteries, veins, or capillaries (*arteritis*, *phlebitis*, and *capillary vasculitis* respectively), and may be acute or chronic.

Acute vasculitis, again, may be either *primary* or *secondary*. In the former case it is caused by the presence of specific bacteria, of certain toxic bodies, or of an infected thrombus, the last mode of origin (*i.e.*, when the thrombus contains specific bacteria, especially pyococci) being that best known. Owing to the presence and multiplication of these micro-organisms the thrombus undergoes a purulent

liquefaction (see p. 208), and as the pus-cocci or other bacteria make their way from thence into the wall of the vessel, the latter is also involved in a suppurative or necrotic inflammation (*purulent thrombo-arteritis* or *thrombo-phlebitis*); that is, we then find the wall, together with the perivascular connective tissue, more or less densely infiltrated with pus cells, or to a variable extent necrotic.

In large vessels such as the aorta an inflammation resembling acute endocarditis may also occur, and from the same causes as the latter.

The vasculitis excited by *toxic bodies* chiefly involves the smaller vessels of the organ (the kidney) through which the elimination of these substances is effected, and appears to manifest itself partly in the form of degenerations (fatty, hyaline, and amyloid), partly in that of cellular infiltration. Its histological peculiarities in other respects have not yet been fully ascertained.

A vasculitis may occur *secondarily* whenever an acute inflammation existing in a tissue or organ spreads to the blood-vessels. This very often happens in those inflammations which are caused by bacteria, owing to the penetration of the latter into the blood-vessels from the tissue, as is the case notably with *Streptococcus pyogenes* (see p. 119).

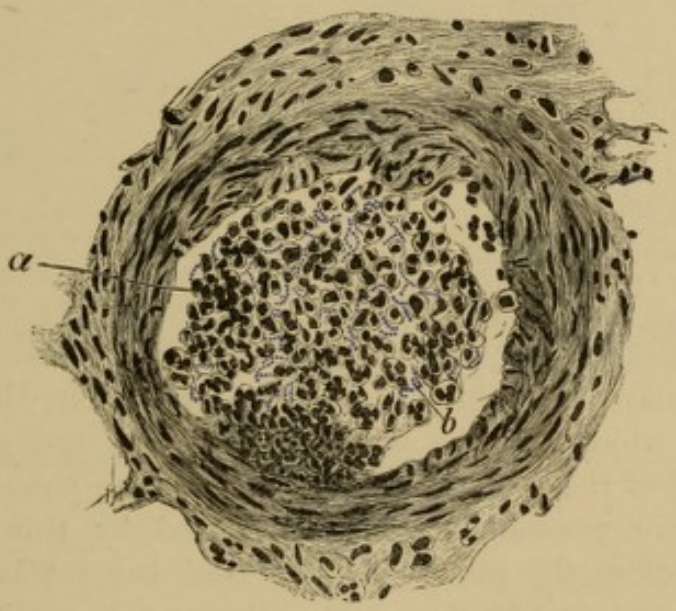

FIG. 103.—SECONDARY VASCULITIS OF A SMALL VEIN OF THE LEG IN PHLEGMON due to *Streptococcus pyogenes*. × 545; the cocci, however, drawn in under an amplification of × 765. (Weigert's modification of Gram's method.) *a*, Accumulation of leucocytes, in part polynuclear, in the lumen of the vein; *b*, Streptococci.

When the smaller blood-vessels (Fig. 103) are involved, there occurs at first an ever-increasing accumulation of leucocytes (*a*) in their lumen, and, should this be further followed by deposition of fibrin, a so-called *white thrombus* is formed (see p. 208), which again,

should pyococci have gained entrance into the vessel, eventually undergoes purulent liquefaction. In addition to this, leucocytes will also emigrate into the wall of the vessel and into the perivascular connective tissue.

Should, however, an inflammation due to pyococci extend to blood-vessels of larger size (Fig. 104), an active growth of the penetrating

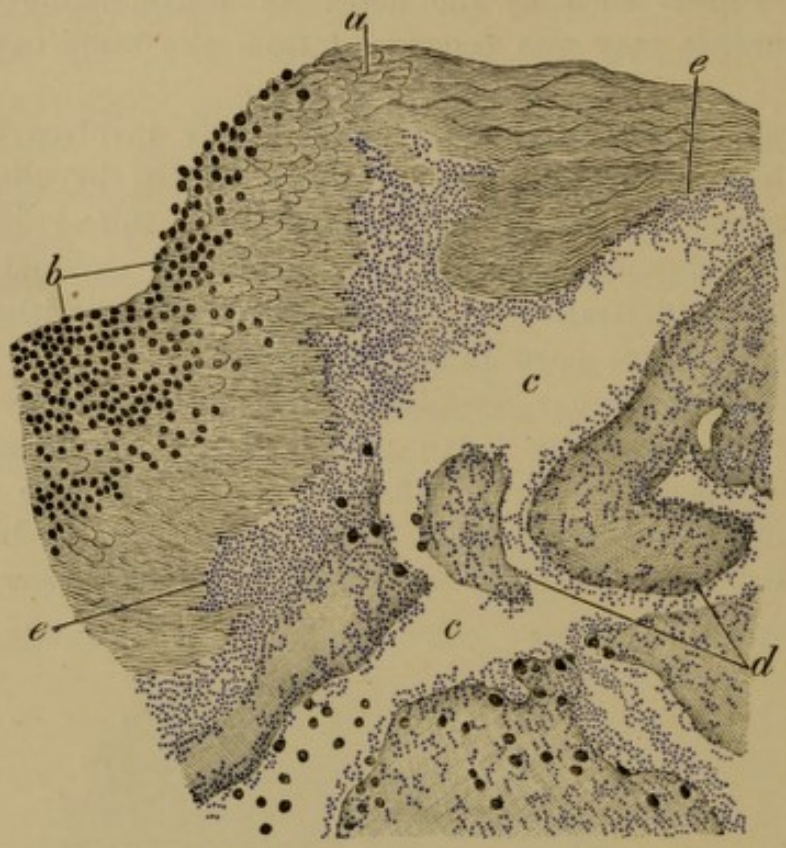

FIG. 104.—SECONDARY VASCULITIS OF THE INNOMINATE ARTERY, with rupture of the vessel, due to *Streptococcus pyogenes*, starting from a tracheotomy wound in a diphtheritic child. × 440; the cocci drawn in under a power of × 980. (Weigert's modification of Gram's method.) *a*, Necrotic and undermined intima; *b*, Small-celled infiltration of intima; *c*, Fissures and cavities between the necrotic portions of the wall of the vessel; *d*, Torn and separated necrotic portions of the wall: *e*, Cocci.

bacteria (*e*) may ensue in the walls of the latter, the further consequences of which may be partly necrosis (*a*) and partly purulent infiltration (*b*) of the coats of the vessel. As the powers of resistance of the wall are presumably greatly reduced by this process, there may occur, before the lumen of the vessel has yet become occluded by thrombus as already described, either an immediate rupture of the vessel, or, the outer coats (*d*) having been destroyed, the inner become protruded under the pressure of the blood, leading in the first instance to the formation of so-called *hernial aneurysms*, though these may likewise eventually burst.

Under the name *chronic vasculitis* we include:—(*a*) *Atheroma or arteriosclerosis* (*chronic endarteritis*).—This process either involves the whole of the arterial system, or is restricted to isolated areas only

(aorta, arteries of brain, kidneys and heart), but in both cases chiefly affects the points where the branches come off. Its cause probably lies in a diminution of the elasticity of the vessel-wall brought about by *general* disturbances of nutrition (advanced age, alcoholism, etc.), which is afterwards followed by increased expansion of the wall by the blood-pressure, leading to widening of the lumen and slowing of the blood-current, and lastly by a new formation of connective tissue in the intima. The latter change, which is preceded also by an increased development of the vasa vasorum, begins microscopically with the appearance in the intima of collections of small cells, which gradually change to connective tissue and lead to thickenings of this coat, usually circumscribed (Fig. 105, *a*). In this way an adaptation of

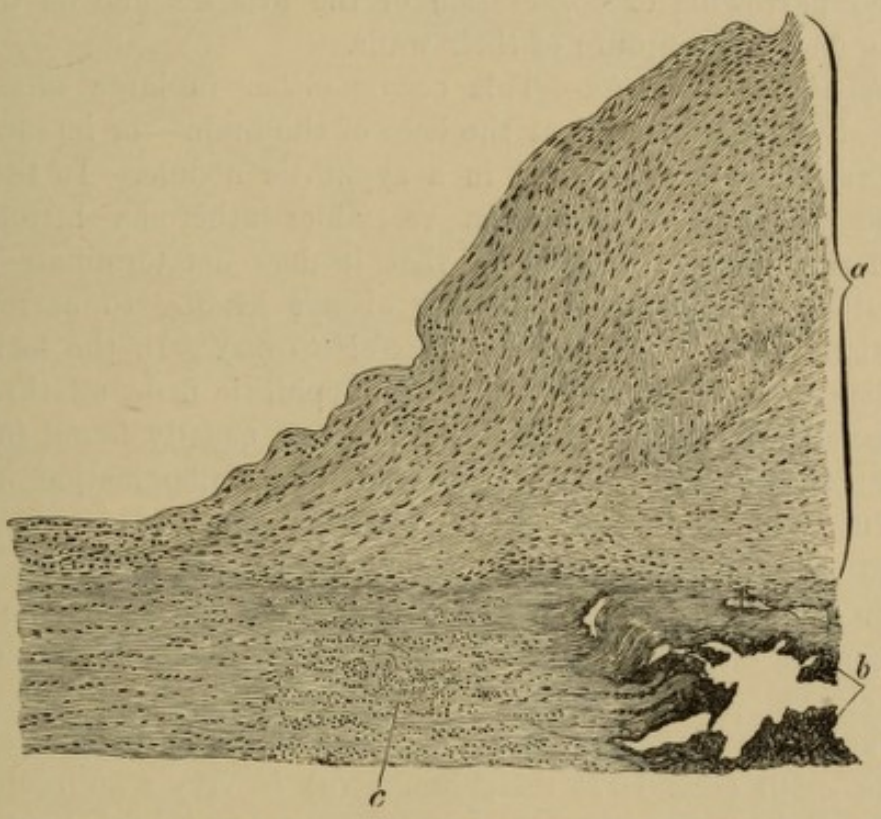

FIG. 105.—ATHEROMA OF AORTA. × 80. (Alum cochineal.) *a*, Thickened intima; *b*, Deposit of lime in middle coat; *c*, Cellular infiltration of middle coat.

the calibre of the arteries to the altered current would again be attained if degeneration, partly hyaline and partly fatty, did not subsequently set in. Owing to the former the connective tissue of the thickened intima becomes homogeneous, losing its striation and its cells, while the latter causes the appearance of minute droplets of fat in the protoplasm of the connective-tissue cells, and also external to them. The thickened intima may also at times assume the character of mucous tissue.

In consequence of insufficient nutrition, the new tissue often breaks down subsequently into a finely-granular detritus mixed with fat-drop-

lets and crystals of cholestearin (atheromatous pulp); and this process, advancing towards the internal surface of the artery, leads finally to rupture of the intima and formation of a so-called *atheromatous ulcer*, upon which thrombi are deposited. At the same time the cellular growth in the vicinity is further increased, owing to the breaking down of the tissues, and may then extend into the media (*c*) and adventitia, which it does by creeping along the vasa vasorum. A not uncommon occurrence also is the deposition of lime as minute granules in the centres of disease in the intima, which may result in the end, however, in the production of quite large calcareous plates; and the calcification may, like the fatty degeneration, also affect the media (*b*). The *consequences* of the atheromatous process are on the one hand narrowing or obliteration of the arteries, and on the other softening and even rupture of their walls.

(*b*) *Syphilitic vasculitis.*—This occurs either in large unsupported arteries—those for example at the base of the brain—or in such of the smaller vessels as are involved in a syphilitic nodule. In the former case the syphilitic inflammation resembles atheroma histologically, only differing from the latter in that it does not terminate in fatty degeneration or calcification, though always leading to narrowing or obliteration of the vessel (*endarteritis obliterans*). In the latter case, *i.e.*, in disease of the vessels lying in a syphilitic node, all three coats, but especially the intima and adventitia, are usually found infiltrated with numerous small round cells when the inflammation is recent (Fig. 202, *d*), and the endothelium is seen to be undergoing proliferation. Subsequently the thickened vessel-wall again becomes poorer in cells, but, owing to the irregular thickening of the intima, the lumen is either eccentrically narrowed (Fig. 106, *a*) or completely closed.

(*c*) *Tubercular vasculitis.*—When the vessels affected by this process are quite small (Fig. 107) their lumen (*a*) is very soon occluded by a mixed cellular mass consisting of leucocytes and epithelioid cells, in which mass the elements composing the wall of the affected vessel also merge, so that on the site of the latter a miliary tubercle (*b*) of more or less typical structure is developed. This, however, still allows the outlines of the vessel to be distinguished (*c*), not only at the beginning of its development, but not uncommonly even at a later period when it is already caseous.

In larger vessels tubercular vasculitis manifests itself either by the formation of isolated tubercles in the wall, or by a more diffuse transformation of the latter into a tissue composed of round and epithelioid cells, and undergoing caseation. Should the process advance as far as the internal coat, either a thrombosis ensues which

may lead to obliteration of the vessel, or, the softened intima having ruptured, the tubercular nodule breaks into the lumen of the vessel,

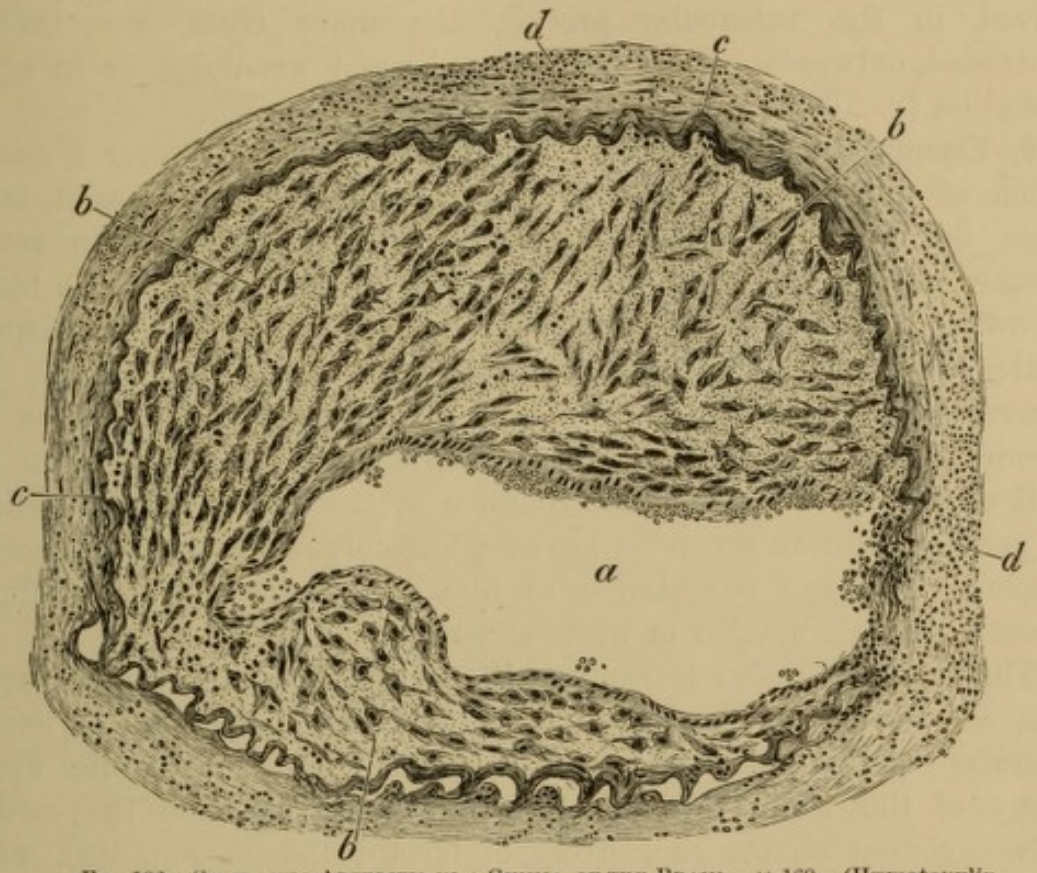

FIG. 106.—SYPHILITIC ARTERITIS IN A GUMMA OF THE BRAIN. × 160. (Hæmatoxylin and eosin.) *a*, Eccentrically narrowed lumen of vessel; *b*, Irregularly thickened intima, consisting of young connective tissue; *c*, Internal elastic lamina; *d*, Middle coat, infiltrated with round cells.

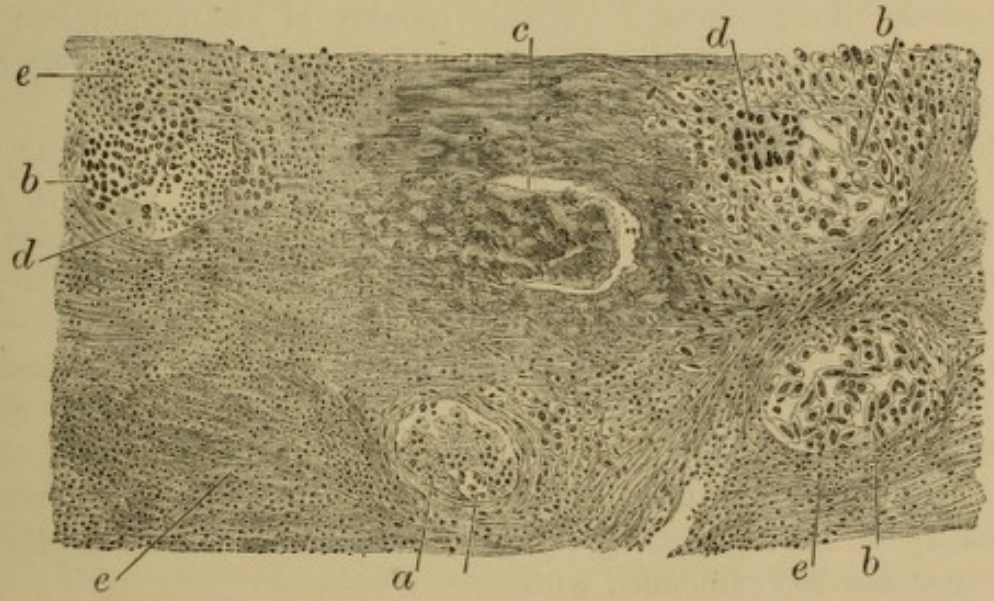

FIG. 107.—TUBERCULAR VASCULITIS IN ACUTE MILIARY TUBERCULOSIS OF THE PIA MATER. × 160. (Alum cochineal.) *a*, Commencing tubercular vasculitis; the vessel wall as yet little altered; *b*, Advanced tubercular vasculitis; site of vessels occupied by miliary tubercles; *c*, Caseous tubercle, which still allows the outlines of the vessel to be recognised; *d*, Giant cells; *e*, Round cells.

in consequence of which tubercle bacilli find their way into the circulation and give rise to the formation of secondary tubercles, or, when

the bacilli enter the blood in very large numbers, to general acute miliary tuberculosis. If the outer coats of the vessel only are involved in the tubercular process, the inner coats may become protruded outwards in the form of a hernial aneurysm as in acute vasculitis (p. 204).

6. Thrombosis and Embolism.—*Thrombosis* occurs whenever a coagulation of the blood, or separation out of a solid mass from it, takes place during life in the blood-vessels or heart, whether in consequence of changes in the intima or in the composition of the blood, or owing to arrest of the flow of the latter. Should this happen while the blood is in motion, *white* or *mixed thrombi* form, but otherwise *red thrombi*. In the former case the development of the thrombus may begin with an accumulation of blood-platelets on the wall of the vessel and mutual cohesion of the former (*conglutination*), or perhaps with an accumulation of white corpuscles. This is usually accompanied by a coagulation of filamentous fibrin which still encloses a variable number of white and red corpuscles.

The *white thrombus* is composed of blood-platelets, white corpuscles, and fibrin, the blood-platelets (Fig. 108), *d* appearing as evenly granular masses, the fibrin in reticula (*a*) or bundles of parallel fibres. Many of the white thrombi, as for instance those on the cardiac valves, consist almost exclusively of blood-platelets (Fig. 98), while in others again the white corpuscles are more prominent.

The *mixed thrombus* (Fig. 108), in addition to the elements just mentioned, also contains a variable number of red corpuscles; and the colourless and red cells may alternate in such regular layers as to cause a *stratification* of the thrombus.

The *red thrombus* has the same composition as a post-mortem clot, and consequently consists chiefly of red corpuscles, together with isolated leucocytes and fibrin coagulated in filaments or granules.

When the thrombus has existed for a greater length of time the following *changes* may take place in it:—

(*a*) *Simple softening*, especially frequent in the large white cardiac thrombi, in which cavities filled with a puriform fluid develop in the interior owing to fatty degeneration or granular disintegration of the white corpuscles, fibrin, and blood-platelets, while the red corpuscles shrivel up, or are replaced by crystalline or granular masses of pigment. This must not be confounded with

(*b*) *Purulent softening*, which is dependent on the action of bacteria (mostly pyococci), and in which large numbers of pus-cells are found, together with finely-granular detritus. This may then occasion a purulent vasculitis, or it may occur as a sequel of such. (See *Purulent thrombo-arteritis* and *thrombo-phlebitis*, p. 203.)

(*c*) *Shrinking and Calcification.*—The thrombus, especially if in a vein, may become continuously drier and firmer, and finally calcify, forming a *phlebolith.*

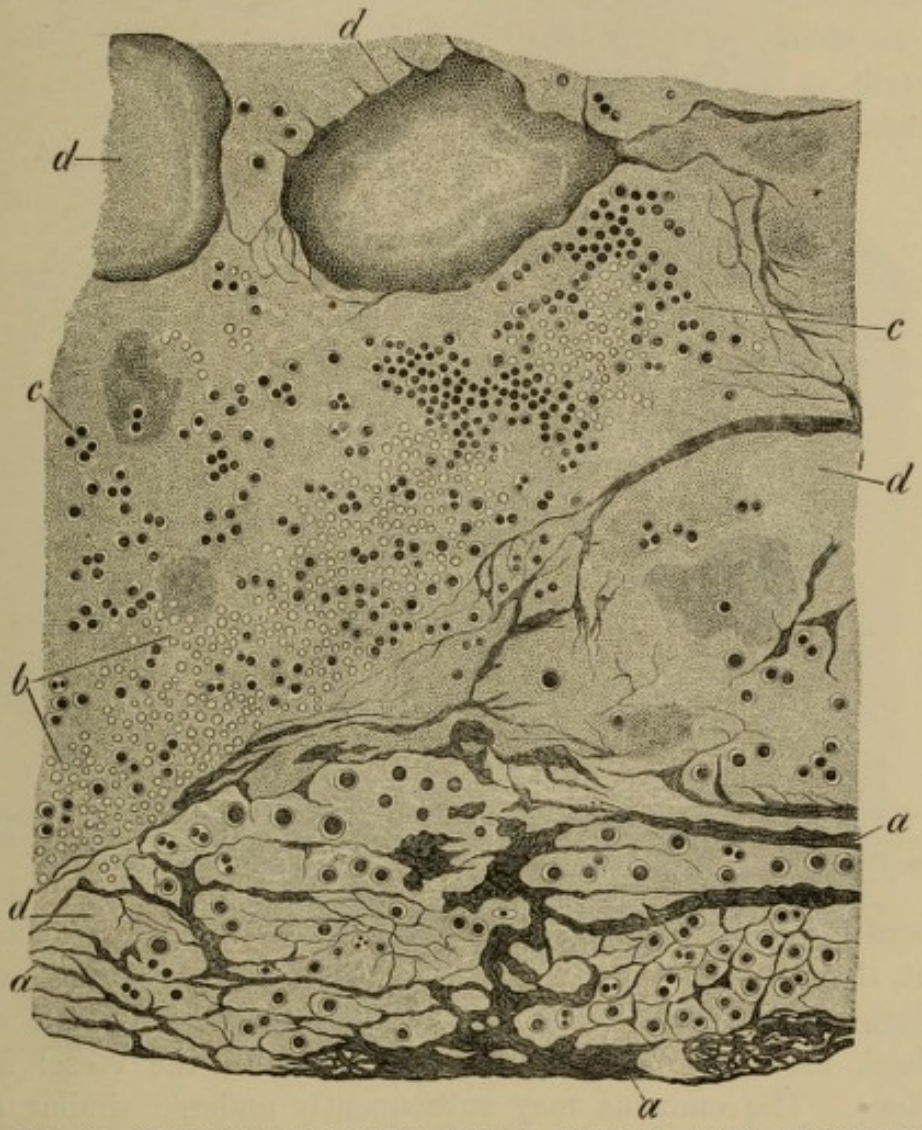

Fig. 108.—Mixed Thrombus from a Cardiac Aneurysm. × 440. (Hæmatoxylin and eosin.) *a*, Fibrinous reticulum; *b*, Red corpuscles; *c*, White corpuscles; *d*, Blood-platelets, collected in clumps in places.

(*d*) *Organisation*, in which the wall of the vessel alone takes an active part. In this process small round cells appear in the latter, which have in part emigrated from the vasa vasorum, in part been formed by proliferation of the fixed cells of the wall; and these subsequently accumulate also between the intima and the thrombus. As the derivatives of the fixed cells change into stellate and spindle-shaped fibroblasts (Fig. 109, *b*)—which, together with the newly-formed vessels (*c*) proceeding from the vasa vasorum, permeate the clot—the thrombus, its cellular elements having been destroyed, is replaced by an embryonic tissue, which at the outset still encloses much pigment, and which gradually changes into firm connective tissue containing few cells or vessels. This then either occasions a permanent

abolition of the lumen of the vessel (*obliteration*), or may eventually again subside, by absorption, to a slight thickening of the intima.

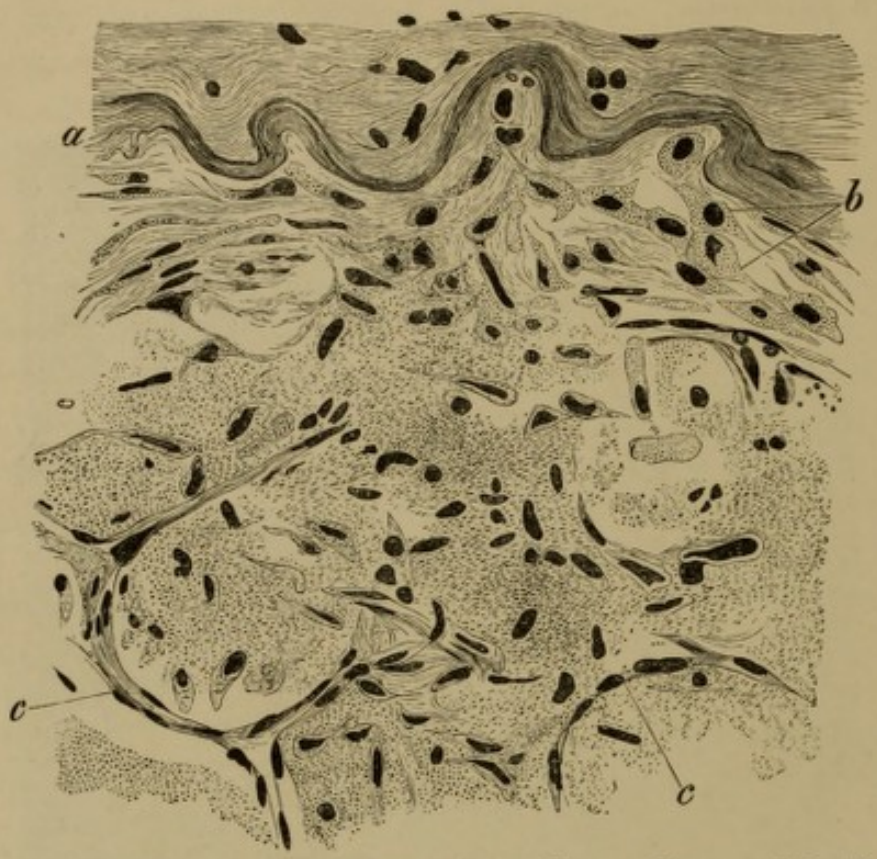

FIG. 109.—ORGANISED THROMBUS OF A SMALL SPLENIC VEIN. × 545. (Hæmatoxylin and eosin.) *a*, Intima; *b*, Elongated and stellate fibroblasts; *c*, Newly-formed capillaries.

When little particles are torn away from thrombi by the blood-current, they may become impacted in the districts where the vessels are narrow, and, fibrin being precipitated upon their surfaces from the blood, may lead to complete obstruction of the vessel involved (*embolism*). The embolus may subsequently undergo similar changes to those seen in a thrombus, especially purulent softening, or organisation.

The *consequences* of thrombosis and embolism depend upon the nature of the thrombus or embolus respectively, and of the area of vessels occluded by them. As regards the latter, if the vessel affected be an *artery*, the circulation behind the obstruction (towards the periphery) ceases immediately on the occurrence of the latter, while in front of the obstruction (centrally) the blood-pressure rises. If now the artery affected still stands in communication by its branches with other arteries behind the occluded spot, it soon obtains enough blood from these, as the anastomosing branches at the same time enlarge, and the circulation is again established. If, however, such an anastomosis does not exist, that is to say, if the occluded vessel is what is known as a *terminal artery*, the district supplied by it either

remains permanently bloodless and dies (*anæmic infarction*), or, owing to a retrogressive flow from the veins or capillaries in the neighbourhood, blood subsequently makes its way again by degrees into the vessels of the anæmic area. This blood, however, stands at a low pressure, and hence does not move rapidly forward, so that stasis and finally hæmorrhages into the tissue (Fig. 110, *a*) take place

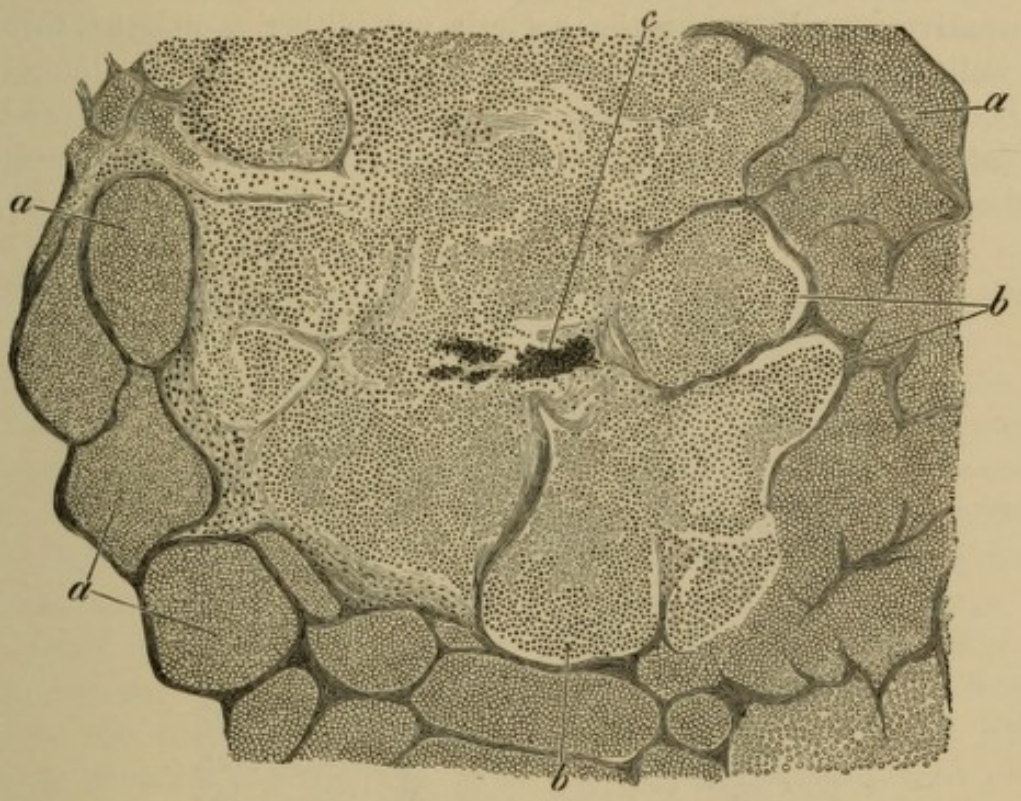

FIG. 110.—SUPPURATING HÆMORRHAGIC INFARCTION OF THE LUNG IN PYAEMIA. × 90. (Alum cochineal.) *a*, Alveoli of lung filled with red corpuscles; *b*, Alveoli with red corpuscles and pus corpuscles; *c*, Clumps of cocci.

(*hæmorrhagic infarction*). Hæmorrhage is further favoured by the degeneration which the vessels have undergone in consequence of being cut off for some time from a supply of blood. Infarctions are also not uncommonly found which are hæmorrhagic only at the circumference, but anæmic in the centre.

Not only the anæmic but the hæmorrhagic parts suffer necrosis (coagulation necrosis), but this need not involve all the tissue elements, as the less sensitive, such, for example, as the cells of the supporting substance, may be preserved. The further changes in those cases in which the thrombus or embolus contains no (pathogenic) bacteria, and is consequently indifferent, consist in the breaking down of the necrotic tissue of the infarct into a finely-granular detritus, while the red corpuscles lose their colour or become partially changed into pigment. This detritus may then be absorbed, whilst at the same time, through growth of the connective tissue in the vicinity,

or of the still surviving connective-tissue cells of the infarction, a granulation tissue is formed which gradually replaces the latter, and is changed by subsequent contraction into a scar, which in the case of hæmorrhagic infarctions may still for a long time contain pigment.

The changes are otherwise, however, if the thrombus or embolus contains pathogenic bacteria, especially pyococci. There will then occur, first, a purulent softening of the thrombus or embolus, with consecutive vasculitis, and the bacteria will either soon grow through the wall of the vessel and penetrate into the tissue of the infarction, or their growth will first advance along the interior of the vessels of the latter, plugging them to a variable extent, and causing a necrosis of the vessel-wall (Fig. 111, *a*). Owing to the penetration of the

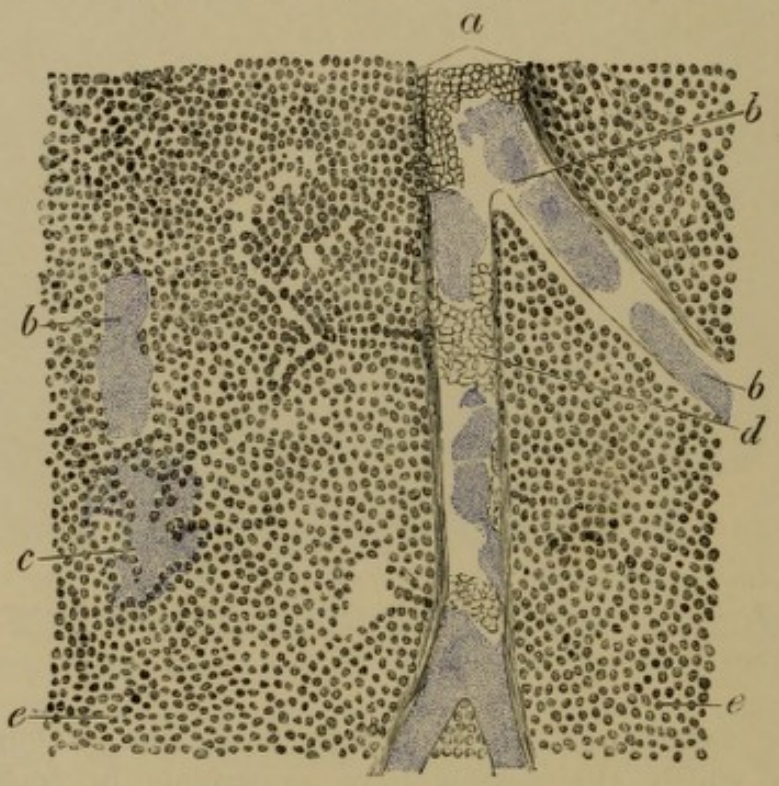

FIG. 111.—METASTATIC INFARCTION OF THE SPLEEN IN ULCERATIVE ENDOCARDITIS. × 240. (Weigert's modification of Gram's method.) *a*, Branched artery with necrotic walls; *b*, Embolus of cocci; *c*, Embolus of cocci growing into the tissue of the infarction; *d*, Red corpuscles; *e*, Necrotic cells of the infarction, no longer capable of being stained.

bacteria into the tissue of the infarction, there results a formation in it of small suppurative foci (Fig. 110, *b*), which by their subsequent coalescence finally change the infarction into an abscess (*metastatic abscess*).

Should the particles loosened from thrombi containing bacteria lodge in the capillaries or in any of the smaller-sized blood-vessels which are not terminal arteries, they will cause no infarctions, but will give rise in the neighbourhood of the occluded vessels to small rounded foci of inflammation not uncommonly bordered by a hæmorrhagic area, in which foci the tissue in immediate proximity to the

embolus is usually necrotic at the outset, while the suppuration commences at the circumference of the focus. The same effect will also be produced if the vessels affected are blocked with bacteria (such as pyococci) alone (Figs. 127, *b*, and 185, *d*). As the latter at the same time progressively increase, the vessels blocked with them take varicose forms (Fig. 127, *b*); and lastly the bacteria will also grow through the wall of the vessel and invade the surrounding tissue.

7. Dilatation of Blood-vessels. Aneurysms.—Dilatations may take place in *arteries*, *veins*, or *capillaries*, and may either extend with some regularity over a considerable section of the vessel, or else occur in the form of circumscribed protrusions. The latter are the more important, and are called *aneurysms* when they involve arteries.

These never[1] form except after rupture of the coats of the vessel, whether in consequence of trauma or of faulty development or disease of the wall, and most frequently in atheroma. The rupture sometimes involves the intima, at others the middle coat or even the adventitia, different forms of aneurysm being distinguished according to these variations. The aneurysmal sac may gradually increase in size, and thus cause the atrophy of adjoining structures, including even cartilage and bone. The cavity of the aneurysm is found to contain thrombi, much stratified and sometimes of very large size, the outer layers of which are usually already decolorised. Furthermore, not only does the aneurysm in most cases show upon its internal surface the appearances of the original disease atheroma, but inflammatory growths repeatedly form in its walls, in consequence of the increasing distension, and thus cause the development of new connective tissue. In spite of this, however, the termination is, sooner or later, rupture.

A special variety of the above is the *embolic aneurysm*, which is developed (most frequently at the bifurcations of arteries) either through injury done to the vessel-wall by emboli with sharp angles, such as calcified particles of valves, or by the action of emboli containing bacteria, which set up an inflammation starting from the adventitia and leading to rupture of the intima or media.

It has already been mentioned (p. 204) that an aneurysm may also occur in consequence of the *extension of a bacterial process* to an artery from the surrounding parts.

[1] [It is more usual, however, to distinguish a rarer form of aneurysm in which none of the coats are ruptured, and which is known in this country as *true aneurysm*, in contradistinction to that where one or more coats have given way, and which is termed *false aneurysm*. The former may be either *fusiform* (or *tubular*) when involving the whole, or *sacculated* when involving only a part, of the circumference of the artery. The latter is never fusiform.]—*Tr.*

The so-called *spurious* [or *diffused*] *aneurysm* is also frequently distinguished from those just described. This is formed by the bursting of all three coats and the formation by the blood-clot of a sac communicating with the lumen of the artery, the wall of which sac, however, may subsequently become fibrous by proliferation of the surrounding connective tissue.

III. LYMPHATIC VESSELS.

8. The most frequent **disease of the lymphatic vessels**—by which of course are meant only the larger lymphatics and the thoracic duct—is **inflammation (lymphangeitis)**, which occurs in an *acute* or a *chronic* form.

The *acute* inflammation is always caused by (pathogenic) bacteria, most frequently the micrococci of pus, which usually, however, merely penetrate into the lymphatic trunks from tissues already altered by them. In the former, the endothelial cells are then found in proliferation or cast off, the lumen is occupied by a fibrinous exudation or by pus, and the wall and immediate surroundings are infiltrated with small cells, whilst complete suppuration or necrosis of the wall may follow at a later period.

Chronic lymphangeitis often leads to fibrous thickening of the wall, and obliteration. Should the latter involve a large number of vessels, lymph-stasis and lymphangiectases occur in the neighbouring lymphatics, a condition which may develop not only as a result of recurring hyperæmic and inflammatory conditions of the skin and subcutaneous connective tissue in *elephantiasis Arabum*, but also in the chyle-ducts of the mesentery after obliteration of some of them or of the thoracic duct (by inflammation or tumours).

Examination of the Circulatory Apparatus.—*Brown atrophy*, *cloudy swelling*, and *fragmentation* of the muscular substance of the heart are examined by tearing up *fresh* preparations with needles, and the examination of *fatty degeneration* of the heart and the walls of blood-vessels can be carried out in the same manner. Addition of dilute acetic acid or of caustic soda solution brings the pigment and fat-drops out more distinctly, while the albuminoid granules of cloudy swelling dissolve in the former. Otherwise *hardening* in Müller's fluid followed by alcohol, and double staining with hæmatoxylin and eosin or with picro-carmine (or picro-lithium-carmine) are to be recommended.

Respecting the methods of examining for *fatty*, *amyloid*, and *hyaline degenerations*, see pp. 53, 55, and 57–8.

The *elastic tissue* in the blood-vessels may be characteristically stained after the method of Herxheimer by immersing the sections (best after previous hardening in Müller's fluid and alcohol) for three to five minutes in a staining fluid consisting of hæmatoxylin, 1 grm.; absolute alcohol, 20 grm.; distilled water, 20 grm.; and cold saturated aqueous solution of lithium carbonate, 1

c.cm. ; after which they are extracted for five to twenty seconds in 27 per cent. perchloride of iron solution, and rinsed in water. The elastic fibres are blue-black to black, the surrounding tissue grey to bluish.

Another method (that of Manchot) consists in staining the sections in concentrated aqueous solution of fuchsin (after freeing them from celloidin), washing in water, and allowing them to lie until they have become reddish-violet in an aqueous solution of sugar of the consistence of glycerin, to every 10 c.cm. of which three or four drops of sulphuric acid have been added. Finally they are examined in a plain solution of sugar. All the tissues lose their colour when so treated with the exception of elastic fibres (and hyaline material) which remain dark red. To distinguish the blood-platelets from fibrin in the thrombi, the method of staining given on p. 75 should be used. Whilst the fibrin is stained an intense violet colour by this process, the blood-platelets remain colourless.

Mycotic processes are examined for the individual species of *bacteria* by the methods given under the latter head (Part II., Chapter V.). The bacteria of endocarditic vegetations may also be examined in cover-glass preparations by rubbing down the vegetations. Careful rubbing is also necessary in preparing cultures. Alcohol must be employed for *hardening*, and the treatment with alkaline or carbolic methyl blue adopted for sections when the bacteria are unknown or are difficult to stain.

CHAPTER III.

THE SPLEEN, THE LYMPHATIC AND THYROID GLANDS, AND SUPRARENAL CAPSULES.

I. THE SPLEEN.

1. Degeneration, Disorders of Circulation, and Inflammation.—*Amyloid degeneration* attacks either the Malpighian follicles (*'sago spleen,'* which is the most frequent form), or the pulp. In the former case the arteries of the follicles are first diseased, after which the connective-tissue stroma becomes involved in the degeneration. In the second case also it is first of all the reticulum which swells up owing to the degeneration and becomes glassy, whilst the cells of the pulp usually perish by atrophy, but also perhaps partly by amyloid degeneration. The walls of the veins and capillaries of the pulp of course degenerate also.

Infarctions may be caused in the spleen, as in other organs, by either infective or non-infective emboli, and in other respects also show no deviations from the general course of events already depicted on pp. 210-213, except that in hæmorrhagic infarctions the centres of the Malpighian follicles usually remain free from extravasations.

Active hyperæmia and *acute inflammation* of the spleen do not admit of being sharply separated from one another; they form the *acute enlargement* of the spleen which is usually present in acute infective diseases. In these conditions at the outset not only are the veins and capillaries found to be dilated, but many red corpuscles are also seen in the pulp spaces (Fig. 66, *B*). At a later stage, when the spleen becomes paler, the colourless elements of the pulp are also increased, so that we see partly small leucocytes, partly large cells with vesicular nuclei, and in which red corpuscles are often enclosed (Fig. 66, *c*). Sometimes also the follicles are enlarged in consequence of growth of their cells. In this stage the capsule of the spleen often shows delicate fibrinous deposits upon its surface.

When the hyperæmia lasts longer, but especially when it is rather frequently repeated (which is a special feature of malaria, for example), it results in thickening of the trabeculæ and capsule, as well as abundant formation of pigment in the form of yellow, brown, or black granules and masses lying chiefly in the pulp, partly in the interior of the pulp cells and partly free, and only to the smallest extent in the cells of the follicles.

Passive hyperæmia occurs chiefly in cirrhosis of the liver and in cardiac lesions, and likewise leads, when lasting for any length of time, to fibrous thickening of the capsule, and of the trabeculæ as well as the reticulum of the pulp.

2. Hyperplastic Processes, Infective Granulomata, and New-formations.—The *chronic enlargement* of the spleen in leucæmia and pseudo-leucæmia (*hypertrophia or hyperplasia leucæmica or pseudo-leucæmica*) begins first with hyperæmia, especially of the cavernous splenic veins, and with the appearance of numerous red blood-corpuscles in the pulp. Next follows increase of the colourless elements in the pulp and multiplication of the cells in the follicles, but both to a fairly equal degree. Subsequently, however, the cell-growth in the follicles preponderates so markedly as to form large white nodes and bands, between which the pulp atrophies, its cells undergoing fatty degeneration, whilst at the same time much pigment appears, both free and in the interior of cells. Hæmorrhagic and anæmic infarctions may form at this stage. The destruction of the cells of the pulp is associated with a fibrous thickening of the reticulum, trabeculæ, and splenic capsule, whilst the cells of the follicles also gradually give way more and more before the advance of fibrous tissue.

The variety of splenic hyperplasia described may either be connected with a leucæmic condition of the blood (*splenic leucæmia*), or occur apart from the latter (*pseudo-leucæmia, Hodgkin's disease*). In the latter case, however, a hyperplasia of the lymphatic glands exists simultaneously, whereas in the former the affection of the spleen may either occur alone, though this is questionable, or may associate itself with similar changes in the lymphatic glands (*lymphatic leucæmia*) and in the marrow of bones (*myelogenic leucæmia*), and even with the formation of tumours composed of adenoid tissue in other organs, in which such tissue is not normally present; and here again either the splenic hyperplasia or the changes in the other organs may be the primary lesion.

Tubercle is the most frequently found of the *infective granulomata*, and is met with both in the acute and the chronic form. *Syphilomata* on the contrary are rare, but in hereditary syphilis a swelling of the spleen is sometimes observed, which depends on multiplication of

the connective tissue or of the pulp cells. Of the *tumours proper*, primary forms (fibroma, sarcoma, angioma, and lymphangioma) are very rare. Metastatic tumours are somewhat more frequently observed.

II. LYMPHATIC GLANDS.

3. Degeneration, Pigmentation, and Inflammation.—Here also *amyloid degeneration* involves the reticulum as well as the blood-vessels, the trabeculæ swelling irregularly and breaking down into homogeneous masses, whilst the nuclei remain for a considerable length of time intact. The actual lymph cells are destroyed only by process of atrophy. *Hyaline degeneration* is also frequently observed, and affects either the vessels or the cells lying in the reticulum.

Pigmentation may be due to absorption of extravasations of blood or to the introduction of coloured inorganic substances, as, for example, when dust is inhaled. In the pigmentation of the bronchial glands which occurs from the last-named cause, the pigment, most frequently coal-dust, is found enclosed partly in the lymph corpuscles, partly in the cells of the supporting tissue, or else free. In such glands the eventual result may be thickening of the reticulum and partial abolition of the lymphatic elements (*induration* and *atrophy*), or on the other hand *softening;* and the latter sometimes extends so as to involve the neighbouring tissue which has become adherent to the glands.

Acute inflammation of lymphatic glands is, certainly in the majority of cases, set up by bacteria, and will also show differences of behaviour according to the character of the latter. In all cases there first takes place (in addition to hyperæmia) a multiplication of the lymphoid elements in the follicles and medullary cords, and a rarefaction of the reticulum; and in these changes the new cells may be furnished by division of those already existing, or by emigration from the blood-vessels. There next ensues either necrosis (simple or coagulation necrosis, or granular disintegration of the nuclei) or suppuration. In the latter case small suppurative centres first form in the interior of the follicles and medullary cords, and these subsequently coalesce so that the entire gland even may be changed into an abscess, in which case the surrounding parts are usually also involved.

In *chronic inflammation* it is the reticulum and the capsule that are chiefly involved, both becoming progressively increased in thickness and finally changed, with simultaneous disappearance of the lymphatic elements, into a firm contracting tissue containing but few cells (*induration* and *atrophy*).

4. Hyperplasia, Infective Granulomata, and New-formations.—*Adenia*, or *hyperplasia* of lymphatic glands leading to the formation of tumours, may be divided into a *leucæmic* and a *simple* adenia, according as it is or is not accompanied by leucæmic changes in the blood, which in the latter case is either not altered at all, or shows oligo- and poikilocytosis. The two forms of adenia may perhaps pass one into the other, and they also correspond mutually in the fact that in both the process need not remain restricted to isolated lymphatic glands, but advances from one to the other, and that, moreover, analogous growths may also occur in the spleen, the lymphoid follicles and adenoid tissue of the digestive tract, and even in organs which normally contain no adenoid tissue.

In *leucæmic adenia* (*leucæmia lymphatica*) it is no longer possible to distinguish histologically between the cortex and medulla of the lymphatic glands, as these are alike changed into a tissue resembling that of lymphoid follicles, though the lymph-paths are still preserved in the process.

Simple adenia, also named *pseudo-leucæmia* or *Hodgkin's disease*, forms either soft and juicy or hard and sapless tumours. The histological structure in the former case is similar to that in leucæmic adenia, except that the growth in the glands advances very rapidly, and may also invade the neighbouring tissues, such tumours being entitled also *lympho-sarcomata* or *malignant lymphomata*. In the *hard* form of adenia the affected gland does indeed retain the structure of an adenoid tissue, but there are no longer follicles nor lymph-paths to be recognised in it. The reticulum is thickened and the spaces within its meshes narrowed. The hard and soft forms of adenia may also pass into one another.

Tuberculosis of the lymphatic glands occurs in two forms. In the one nodules develop (Fig. 60), consisting principally of epithelioid (*a*) but partly also of giant cells, and these compress the proper tissue of the lymphatic gland by their advancing growth, and do not undergo caseation until a late date. In the other form the nodules consist essentially of small round cells and caseate early. This form usually occurs in children, and is also described as *scrofulous lymphadenitis*. Should the diseased glands lie near the surface of the skin, they may soften and burst after caseation has occurred.

In *syphilitic adenitis* the swelling is due, not to hyperplasia of the reticulum, but to an even and not excessively abundant multiplication of the lymphoid cells, a condition which may persist unchanged for a long time, but may eventually retrograde owing to fatty degeneration of the proliferated cells.

Of *tumours proper*, the different forms of *sarcoma* may occur prim-

arily, but are upon the whole rather rare. The small-celled forms have so much similarity to simple adenia that they can scarcely be distinguished from it histologically.

Amongst secondary tumours, *carcinoma* is the most frequent. Regarding its mode of occurrence, see p. 102.

III. THE THYROID GLAND AND SUPRARENAL CAPSULES.

5. The Thyroid Gland.—The most important change is *hypertrophy* (*goitre*), which occurs in either a diffuse or a circumscribed form, and may be observed not only in the thyroid gland proper, but also in the so-called *accessory* thyroids. In addition to this form, an *adenoma* of the thyroid gland is distinguished by some authorities, but does not admit of sharp differentiation from hypertrophy.

Goitre depends chiefly upon a new formation of glandular tissue, in which there develop structures, some of which are rounded and

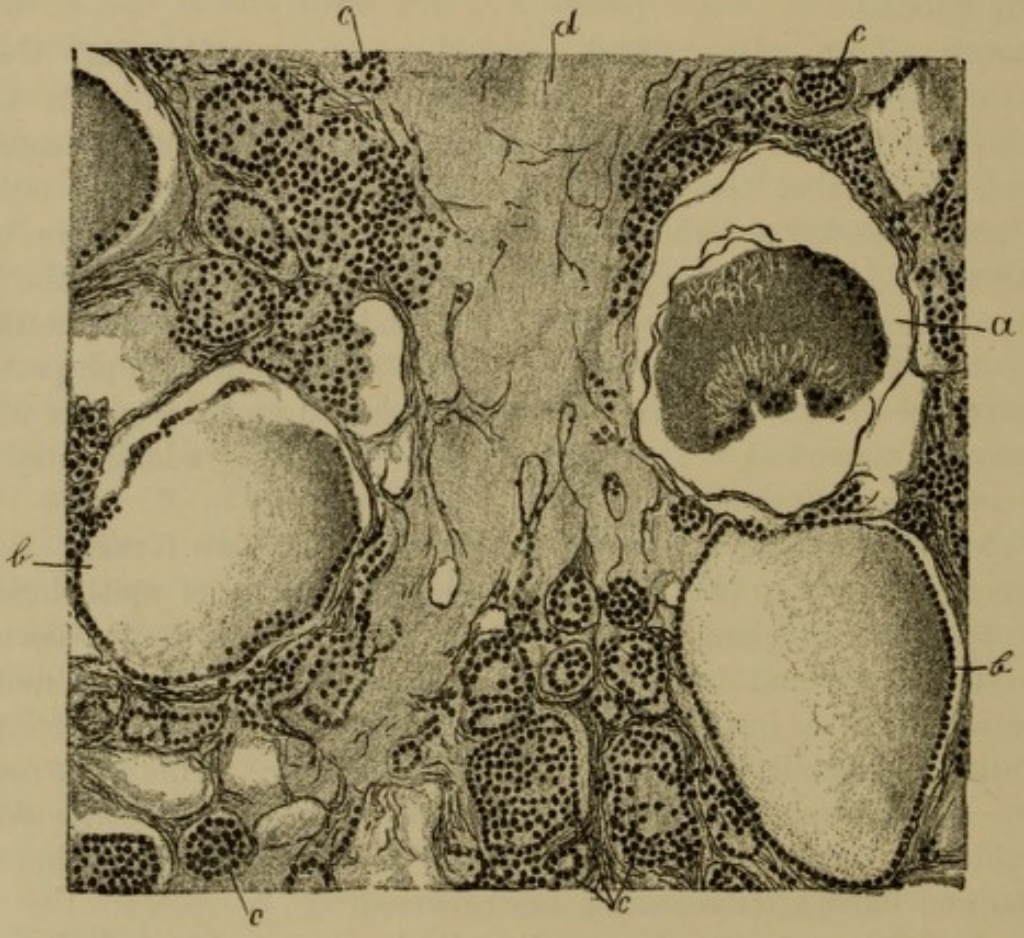

FIG. 112.—COLLOID GOITRE, WITH HYALINE DEGENERATION OF THE STROMA OF THE THYROID GLAND. × 200. (Hæmatoxylin and eosin.) *a*, Colloid cyst containing firm homogeneous-looking colloid matter, not filling up the entire space, with shed epithelial cells lying on its surface; *b*, Colloid cysts containing softer, and in part finely-granular-looking colloid material; *c*, Follicles of normal size or somewhat dilated; *d*, Stroma of connective tissue which has undergone hyaline degeneration.

follicular, or vesicular, others more cylindrical and solid or tubular (*parenchymatous goitre*). If an extensive colloid degeneration takes

place at the same time in the newly-formed glandular tissue, the term *colloid goitre* is used (Fig. 112). In this form the follicles, becoming progressively more distended in consequence of accumulation of colloid material, may coalesce after the connective-tissue septa have atrophied from pressure, the result being the formation of colloid cysts varying in size (*a* and *b*), the wall of which is lined with a greatly-flattened epithelium (*cystic goitre*). The cyst-wall may furthermore be pushed inwards by neighbouring follicles, or may bear papilliform processes clothed with cylindrical epithelium (*papilliferous cysto-adenoma*).[1]

In other cases of hypertrophy a considerable multiplication and enlargement of the blood-vessels also takes place (*vascular goitre, cavernous goitre*, etc.), giving rise to hæmorrhages. *Cysts* may likewise form owing to softening and liquefaction of the tissue destroyed by the hæmorrhages, and the contents of these may be variously coloured by the remains of the extravasated blood, whilst the interfollicular connective tissue may then also be increased (*fibrous goitre*). *Hyaline degeneration* of the connective tissue (Fig. 112, *d*) and blood-vessels may also set in, and by it the follicles may be finally destroyed, and cavities filled with clear fluid left in their stead (*myxomatous goitre*). At such spots, as well as in stroma which has become sclerotic, or in cysts, *calcareous deposits* are not uncommonly met with.

Of the *cause* of the development of goitre we are ignorant; it occurs endemically in many localities, with or without *cretinism*, and is then ascribed to miasmatic influences clinging to the soil.

Of the *primary new-formations, carcinoma* and *sarcoma* have been observed in the thyroid gland.

6. Suprarenal Capsules.—*Fatty degeneration* of the epithelial cells of the suprarenal capsules is normal in adults, as is *increased pigmentation* of the innermost cortical layer in later life. The most important pathological process in the suprarenal capsules is the *tubercular*. It begins with the formation in the medullary substance of small nodules, which coalesce and gradually change into larger caseous masses often replacing the entire organ, whilst at their periphery the round-celled tubercular tissue frequently becomes cicatricial, the latter change often giving the foci a great resemblance to syphilomata.

A change which is tolerably frequent, especially in old people, is the so-called *struma lipomatodes*. This consists of a circumscribed

[1] This form of goitre, as well as those in which the glandular tissue consists of solid or tubular cylindrical structures, may also be included amongst the *adenomata*.

hypertrophy of the cortical substance, with great fatty degeneration. *New-formations* are rare. *Ganglionic neuromata* (Fig. 27), *sarcomata*, and *carcinomata*, have been observed.

Examination of Spleen, Lymphatic and Thyroid Glands, and Suprarenal Capsules.—In the case of the *spleen* an examination in the *fresh* state is perfectly practicable, either by tearing up with needles in salt solution, or by making stained cover-glass preparations, the spleen pulp being smeared in a very thin layer upon the cover-glass. The staining of the cover-glass preparation, if a specific coloration of the different varieties of cells in the spleen is sought for, is conducted according to the methods given for the blood (pp. 189, 190).

For hardening the above organs immersion in Müller's fluid, and thereafter in alcohol, is to be recommended in the majority of cases, especially if it is intended to preserve the blood naturally present; and for staining the sections, hæmatoxylin and eosin, or picro-carmine (picro-lithium-carmine) may be used. In leucæmia of the spleen and lymphatic glands staining by Heidenhain's method (p. 190) may also be tried.

In examining *fatty*, *colloid*, *hyaline*, and *amyloid degeneration*, the rules given on pp. 53, 55, and 57–8 hold good, and for the methods of examining for *bacteria*, see Part II., Chapter V.

CHAPTER IV.

THE DIGESTIVE APPARATUS.

I. THE MOUTH, PHARYNX, AND ŒSOPHAGUS—THE TEETH.

1. Inflammatory and Hyperplastic Processes.—*Acute catarrh* does not present many peculiarities as compared with that of other mucous membranes. On the *lips* and *tongue* it shows a *desquamative* character; that is, it manifests itself chiefly by increased shedding of the epithelium. On the tongue the heaped-up epithelial cells then form the so-called 'fur,' which becomes brown by drying.

In the *œsophagus* also acute catarrh is principally characterised by desquamation of the epithelium, whilst in the *buccal cavity* it may often lead to the formation of vesicles. On the *tonsils* and the parts of the pharynx rich in adenoid tissue the passage of leucocytes through the epithelium is considerably increased during acute catarrh, and they, together with the shed epithelial cells and many bacteria (see p. 231), accumulate in the crypts of the tonsils in the form of white plugs (*follicular tonsillitis*), which subsequently may give rise to the formation of tonsillar calculi by condensation and calcareous deposit.

Certain *special* forms of acute inflammation of the mucous membrane also occur in the cavity of the mouth, viz.:—

(1) *Aphthous stomatitis*, especially in children, characterised by the presence of small white or yellowish-white spots, which cannot be wiped off, and which are formed by the deposit of a fibrinous exudation on the surface of the mucous membrane, with simultaneous necrosis of the epithelium, and are probably of mycotic origin;

(2) *Ulcerative stomatitis*, which affects the gums first and leads to hæmorrhagic infiltration and ulcerative destruction of the tissue. It occurs in individuals reduced in health, and under the influence of mercury, phosphorus, or lead;

(3) *Noma* or *cancrum oris*, occurring in children especially after infective diseases, and consisting of a gangrene of the mucous mem-

brane of the cheek which rapidly advances both in depth and superficial area.

Lastly, in *variola* little efflorescences may occur both in the buccal cavity and in the pharynx and œsophagus, which, like the variola pustules of the skin (see Part III., Chapter XI.), also owe their existence to necrosis of the epithelium and superficial layer of the mucous membrane, and are soon attacked by a secondary invasion of pyococci, especially *Streptococcus pyogenes*. The covering of

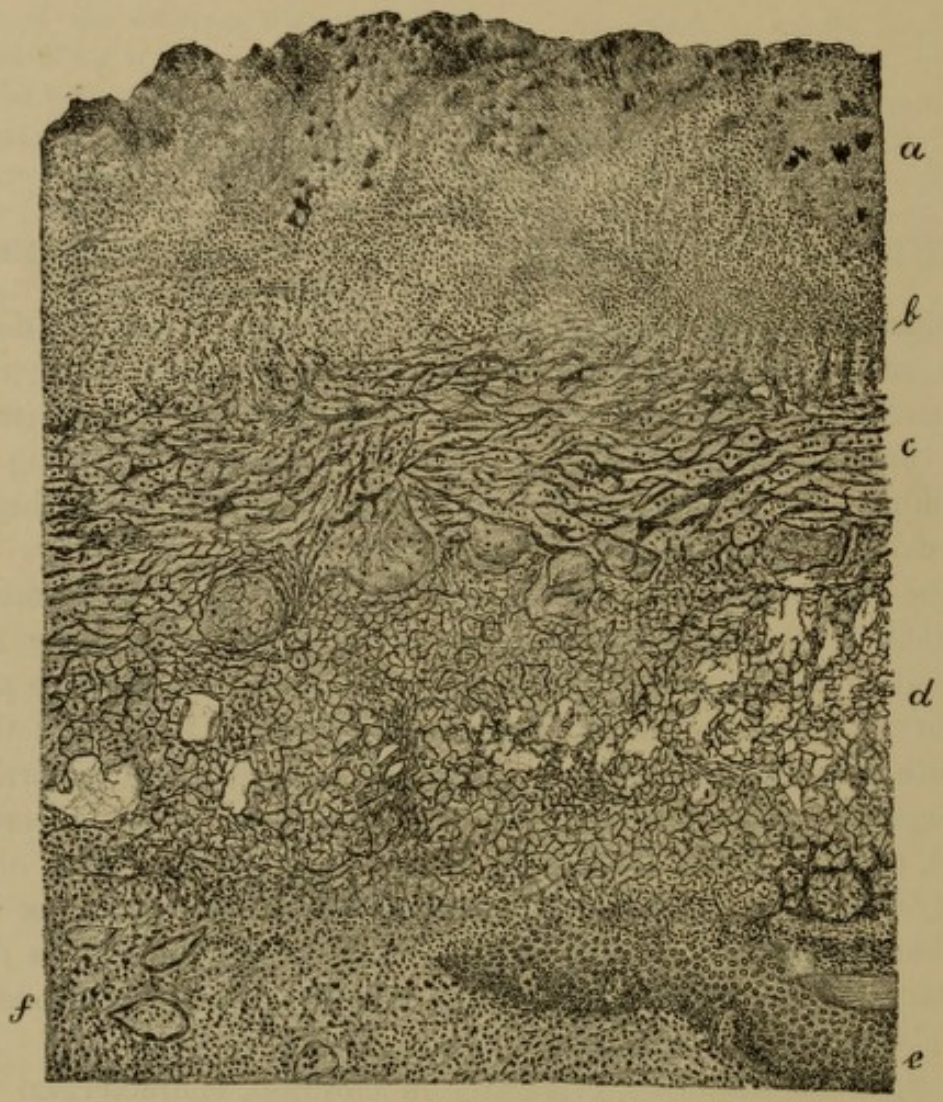

FIG. 113.—FALSE MEMBRANE ON THE UVULA IN DIPHTHERIA. × 70. (Alkaline methyl blue.) *a*, Most superficial stratum of the false membrane, with groups of diphtheria bacilli and streptococci embedded in it; *b*, Second stratum of the false membrane, consisting principally of pyococci, between which mere indications of an excessively delicate network are to be seen; *c*, Third stratum, consisting of a network of thick bands with the spaces of the meshes seen lengthwise; *d*, Fourth stratum, consisting of a very delicate network with rounded meshes; *e*, Vestiges of the epithelium covering the uvula; *f*, Mucous membrane of the uvula, with blood-vessels and small-celled infiltration.

the so-called pustules is soon destroyed, owing to the greater delicacy of the epithelial layer, and there are then formed shallow ulcers, the base of which is covered at first with masses of necrosed tissue and cocci, while the surroundings show a dense infiltration with mononuclear and polynuclear leucocytes.

To the group of *acute inflammations set up by specific bacteria* belong *diphtheria* and *phlegmon*. The former may at first be localised in different places—tonsils, uvula, soft palate, or pharynx—but may then advance not only downwards into the respiratory passages, but forwards and upwards into the buccal and nasal cavities, etc., and may occur under the form either of a simple *catarrh*, or of a *croupous* or *diphtheritic* exudation. In the latter cases the result is formation of *false membranes* of variable thickness which, as we have learnt, are divided into *croupous* and *diphtheritic* according as they merely lie loose upon the surface of the mucous membrane or are intimately connected with it, although this distinction cannot always be strictly carried out.

The formation of the false membrane usually begins with necrosis of the epithelium, which is followed by the deposition of a coagulable exudation in the substance of the latter and upon its surface, either at once or in several instalments. In this way the false membrane

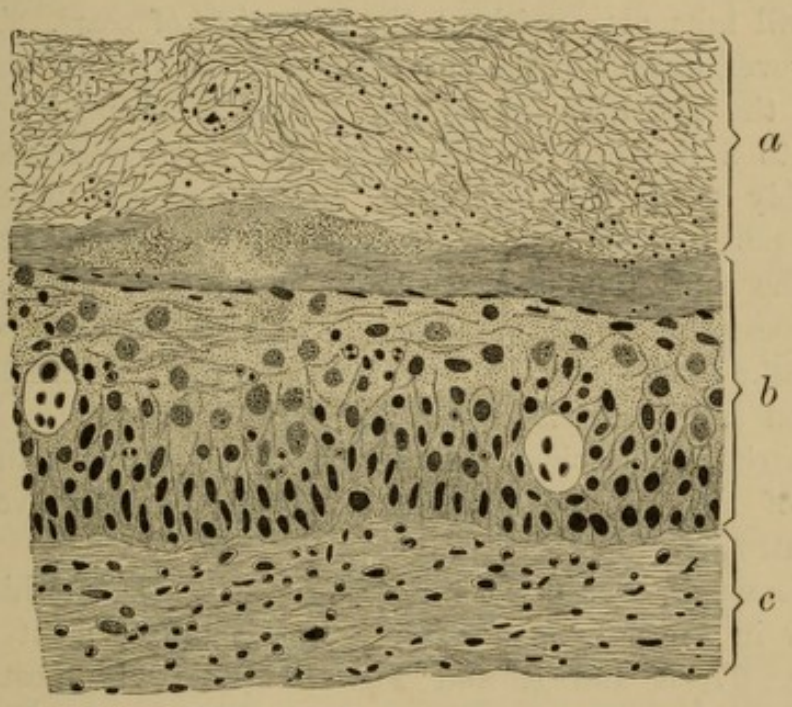

FIG. 114.—CROUPOUS FALSE MEMBRANE ON THE UVULA (the part *c* of the false membrane in Fig. 113, × 285). *a*, Delicate fibrinous reticulum; *b*, Stratified epithelium of the uvula partially infiltrated with pus corpuscles, the uppermost layer having become homogeneous; *c*, Mucosa, in which several leucocytes are visible.

may attain varying degrees of thickness, and in the latter case will be laid down in several layers (Fig. 113), which show certain differences from each other according as they are composed of a very delicate reticulum of fibrin (Fig. 113, *d*, and Fig. 114, *a*), or of a narrow-meshed network of tolerably thick shining bands (Fig. 113, *c*), and either contain many leucocytes (Fig. 113, *b*) in the spaces of the network, or are almost totally devoid of cellular

elements (Figs. 113, *d*, and 114, *a*). The uppermost layer of the false membrane, which as a rule harbours the greater part of the bacteria, is not uncommonly found already broken down into a granular detritus (Fig. 113, *a*).

The degenerated epithelium usually disappears entirely by solution or desquamation, but isolated vestiges may still be met with here and there beneath the false membrane, especially when the epithelial layer has not become necrotic in its whole thickness, and also when the exudation has spread over adjoining portions of mucous membrane the epithelium of which is not yet degenerated (Figs. 113, *c*, and 114, *a*). At such places the false membrane will then adhere but loosely to the surface beneath, and thus produce the impression of being a so-called croupous membrane. The mucous membrane itself also suffers changes, showing not only hyperæmia but small-celled infiltration (Figs. 113, *f*, and 114, *c*), and frequently also fibrinous exudation.

If the necrosis in diphtheria restricts itself to the epithelium only, healing will take place without the formation of scars. The necrosis may, however, extend to the mucous membrane also, in which case the tissue of the latter, including the vessels, is changed to a variable extent into a network, for the most part narrow-meshed, composed of tolerably thick shining bands, and it is only underneath this that the purely inflammatory changes (small-celled infiltration, etc.) begin. The separation of the necrotic portions of mucous membrane results necessarily in the formation of a deficiency, the floor of which either breaks down anew by coagulation necrosis or else fills up with granulation and cicatricial tissue and skins over.

Diphtheria is sometimes followed by local *paralyses* in which the muscles of the affected parts (soft palate, pharynx, vocal chords) undergo atrophy.

The disease is caused by the *Bacillus diphtheriæ*, which is found constantly in the false membranes at the commencement of the process (Fig. 67, *a* and *b*, and Fig. 113). It is most frequently accumulated in the superficial parts of the false membrane, where it usually forms rounded groups and clumps (Fig. 113, *a*); but it also penetrates into the deeper parts of the false and even into the superficial layers of the mucous membrane. In addition to this, however, the *Streptococcus pyogenes* very soon effects a lodgment (secondary infection, Fig. 67, *c*), and may then wander not only into the mucous membrane and deeper tissues, but also into the blood-vessels and lungs, thus causing certain *complications* of the disease (lobar pneumonia, nephritis).

From true diphtheria must be distinguished those diphtheritic or

croupous processes in the same localities and under a similar form, which may occur *secondarily* in different infective diseases (the acute exanthemata, typhoid and typhus fevers, and Bright's disease), but sometimes also *primarily*, and are probably due to the action of the *Streptococcus* or *Staphylococcus pyogenes*. In such the exudative processes seem, at least in many cases, to fall more into the background, so that the false membranes are then much thinner, and are not composed of many layers as in true diphtheria.

Phlegmon, which is due to the *Staphylococcus* and *Streptococcus pyogenes*, may occur in different localities, as in the tongue (*glossitis*), the tonsils, the floor of the cavity of the mouth (*angina Ludovici*), the entrance to the larynx, the retro-pharyngeal connective tissue, etc. The process always begins in the deeper layers of the tissue (the submucous coat, etc.), but then advances towards the surface, becoming particularly extensive wherever there is much loose connective tissue. The exudation, as in every phlegmon, is frequently serous at the outset, but later becomes fibrinous or fibrino-purulent. Should the pus finally burst into the cavity of the mouth or pharynx, the process often assumes a *gangrenous* character owing to a secondary lodgment of putrefactive bacteria.

Amongst the phlegmonous processes is ranked *acute inflammation of the salivary glands*, which may occur primarily as well as secondarily, and oftenest affects the parotid. As the excitants of the inflammation (*Staphylococcus pyogenes aureus* has hitherto been usually found in parotitis) make their way into the salivary glands for the most part from the mouth along their respective ducts, the ducts of the lobules and their ramifications are also found at first to be more or less completely filled with pus corpuscles, and later metamorphosed into small abscesses. The inflammation next advances from them to the acini themselves and the connective tissue of the gland, in which latter there is then set up a condition partly of cellular infiltration and partly of serous or fibrinous exudation.

Acute parotitis may also occur *epidemically*, and is then not uncommonly complicated with inflammation of the testicles in the male, and in many cases of the mammæ or ovaries in the female; but whether the same bacteria participate in these cases as in the non-epidemic form has not yet been ascertained.

The swallowing of *corrosive fluids* (mineral acids or alkalies) usually causes death merely of the epithelium in the *mouth* and *pharynx*, owing to the brief duration of their action here; but in the *œsophagus* (Fig. 115) a necrosis of the mucous membrane (*a*) or even of the muscular coat is often brought about, and this is followed then by extensive reactive inflammation in the deeper

parts (*c* and *e*), with fibrinous or fibrino-purulent exudations (*corrosive œsophagitis*). After the necrotic parts have been shed a formation

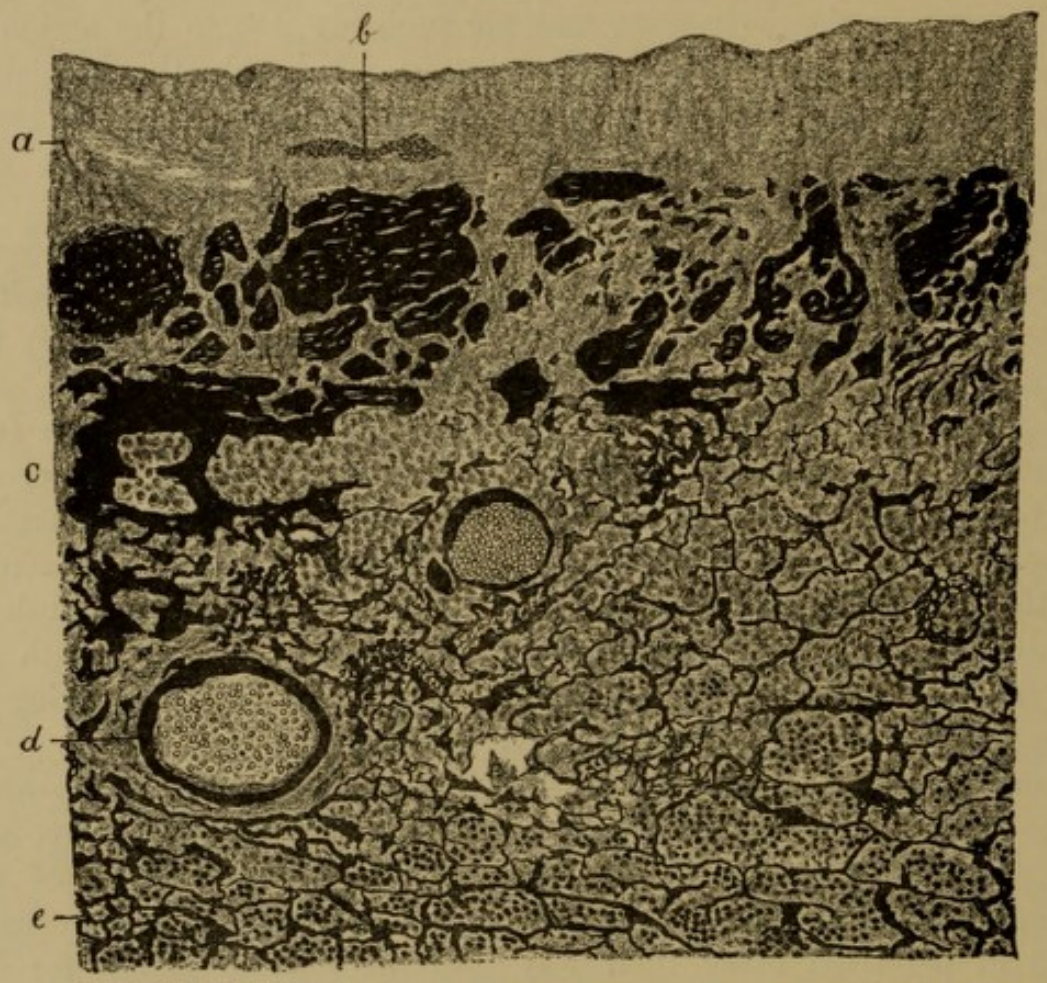

FIG. 115.—CORROSIVE ŒSOPHAGITIS AFTER SWALLOWING ALKALINE LYE. × 90. (Hæmatoxylin and eosin.) *a*, Necrosed mucous membrane; *b*, Bacteria embedded in *a*; *c*, Superficial portions of the submucous coat, infiltrated partly with homogeneous deeply-staining masses (fibrin ?), partly with a fibrinous reticulum, in the spaces of which, however, no stained nuclei are visible; *d*, Blood-vessel with necrotic wall; *e*, Deeper parts of the submucosa, permeated by a fibrinous network, in the meshes of which stained leucocytes are lying.

of cicatricial tissue follows, the contraction of which may give rise to *strictures*, with their usual consequences.

Chronic catarrh is very common, especially in the vault of the naso-pharynx. In this condition the adenoid tissue of the mucous membrane becomes considerably increased in quantity, especially in the areas surrounding the ducts (distended with secretion) of the mucous glands, so that the mucosa acquires a granular appearance (*granular pharyngitis*). The epithelium is also more or less infiltrated with leucocytes. In many places, particularly in the region of the pharyngeal tonsil, the growth of the adenoid tissue may be so considerable as to form actual tumours, the so-called *adenoid vegetations*. These then appear under the microscope (Fig. 116) as conical or papilliform elevations of the mucous membrane composed of a very vascular

round-celled tissue, with deep and much-branched fissures and sinuses lying between, into which the ducts of the mucous glands discharge.

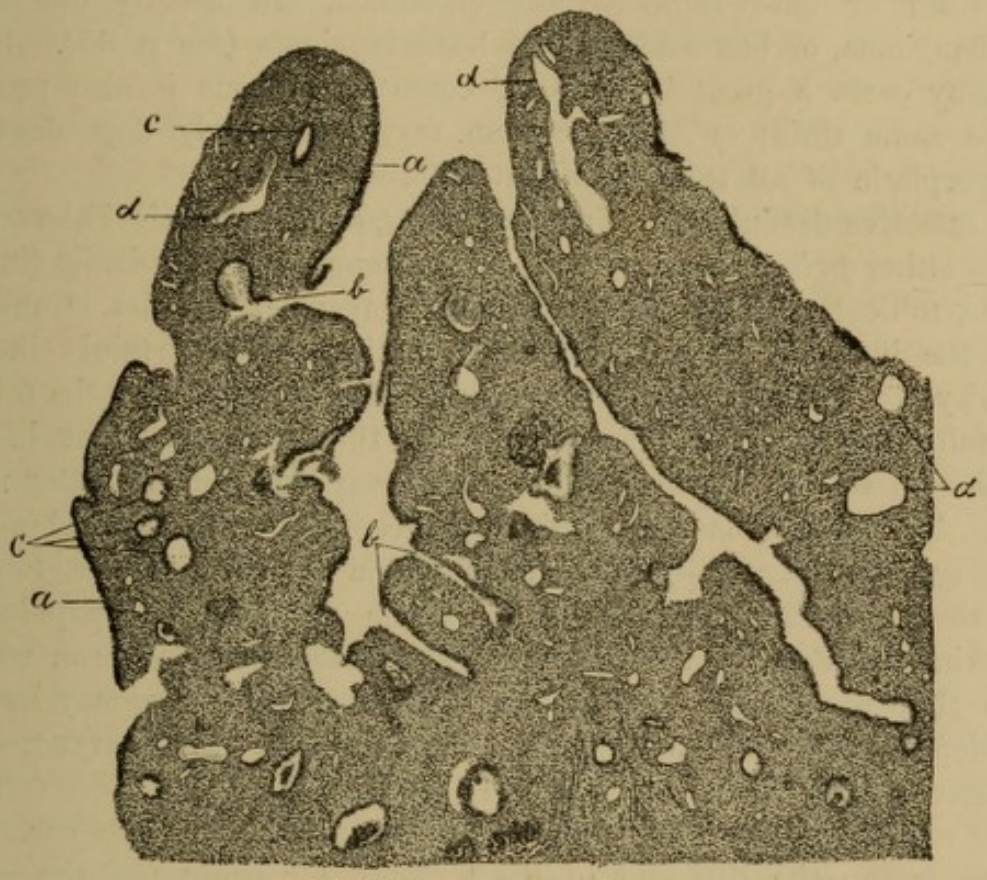

FIG. 116.—ADENOID VEGETATION OF THE PHARYNX. × 16. (Hæmatoxylin and eosin.) *a*, Epithelium; *b*, Epithelial depressions; *c*, Ducts of mucous glands, cut obliquely; *d*, Blood-vessels.

When the catarrh is of longer duration it may, however, lead to *atrophy* of the mucous membrane.

The *mucous glands in the œsophagus* may become diseased not only in catarrhal inflammations but independently; in either case their ducts are found to contain plugs composed of desquamated epithelial cells and leucocytes, while the surrounding mucous membrane is in a state of cellular infiltration. Under certain circumstances even suppuration with consequent development of small abscesses is observed.

By '*plaques opalines*' or *leucoplacia* are meant whitish patches which form in irritative conditions of a more protracted character, notably on the tongue and mucous membrane of the cheeks, and are due to a circumscribed thickening and superficial horny transformation of the epithelium.

A not infrequent consequence of repeatedly recurring inflammations of the tonsils is the so-called *tonsillar hypertrophy*, which

consists in a hyperplasia of the entire constituents of the tonsils, but especially in multiplication and enlargement of the follicles.

The conditions known as *macroglossia* and *macrocheilia*, which are congenital or date from earliest childhood, are usually due to a lymphangioma, or but seldom to a hæmatangioma (see p. 85). Still, in many cases a great increase of connective tissue is also present at the same time; or the condition may be entirely dependent on a hyperplasia of all the constituents of the tissue.

2. Infective Granulomata, New-formations, and Parasites.—*Tuberculosis* occurs either *primarily* (especially in the tongue) or *secondarily* (in the tonsils, follicular glands of the tongue, soft palate, angles of mouth, etc.), the infection in the latter case taking place, certainly in the majority of cases, by the agency of tubercular sputum. In the tonsils and follicular glands of the tongue the tubercles form first in the lymph-sinuses and follicles, and do not appear between the latter until later. The disease is often quite imperceptible to the naked eye.

In *syphilis*, *mucous papules* may exist on the lips, cheeks, tongue, etc., these having histologically the same characters as papules of the skin (see Part III., Chapter XI.); or *gummata* may form, which, when they are situated on the soft palate, and ulcerate, may lead to adhesion of the velum palati to the posterior wall of the pharynx.

Regarding *rhinoscleroma*, see p. 152.

Of *new-formations* those most frequently observed are *cavernous angiomata* (on the lips and in the tongue), *sarcomata* (on the gums and jaw, and in the parotid), *cystic tumours*, and *epitheliomata* (the latter on the lips and tongue, and in the lower third of the œsophagus). The sarcoma which occurs in the gums is also called *epulis*. It starts either from the periosteum or medullary spaces of the jaw, and is usually of the pigmented giant-celled variety.

Parotid sarcomata are frequently of *mixed* forms, as in addition to sarcomatous tissue they may also contain cartilage, bone, mucous or connective tissue. In many of them a network composed of bands of cells is also found, the cells sometimes even showing concentric stratification. These are probably formed by proliferation of the endothelial cells of the lymphatic vessels.

Cysts are of common occurrence, especially under the tongue (*ranula*), and are formed by dilatation of the ducts of the lingual mucous glands, or those of the salivary glands in the same situation. They may be lined with ciliated epithelium. Unilocular and multilocular cysts are observed also in the jaw-bone, where they develop from the sockets of mature, or the tooth-sacs of undeveloped teeth, rudimentary or deformed specimens of which are sometimes contained in them. *Adeno-cystomata* may also occur in the same situation.

Vegetable parasites, and especially *bacteria*, are always present in large numbers in the cavities of the mouth and pharynx, and are particularly abundant in the fur covering the tongue, and in the tartar of teeth. They gain entrance partly with the food, partly with the air. The majority are harmless saprophytes, but nevertheless pathogenic micro-organisms (*Diplococcus* and *Bacillus pneumoniæ*, *Streptococcus* and *Staphylococcus pyogenes* in the saliva, and *Actinomyces* in the crypts of the tonsils and in carious teeth) have been repeatedly detected as occasional inhabitants of these cavities.

The bacteria met with in plugs in the tonsils usually appear in the form of long jointed filaments, which stain bluish-red with iodine and potassium iodide, and are named *Leptothrix*. Under certain conditions these organisms continue to grow, and then cover the tonsils and their immediate vicinity superficially (*pharyngomycosis leptothricia*), so that they exhibit a certain misleading resemblance to the false membranes of diphtheria. Regarding *thrush*, see p. 164.

3. Addendum on Diseases of the Teeth.—*Caries* of the teeth is compounded of two processes, viz., a decalcification of the tissue due to acid fermentations in the mouth, and a solution of the softened substance brought about by the action of bacteria. No *specific* varieties of the latter have as yet been made out, but the enamel cuticle and the spaces between the enamel prisms, as well as the dentine tubules and cement canaliculi, are found filled with a dense mixed mass of cocci and bacilli. The canaliculi become more and more dilated by the crowding forward of the bacilli, until finally they coalesce after disappearance of the intervening substance. Sometimes thickening of the wall of the dentine tubules, or disintegration of the dentine fibrils into rod-like elements, is also observed in this process. Should the process penetrate as far as the pulp and into the root canals, *pulpitis* and *periodontitis* are set up, and the latter again may extend to the gum and lead to the formation of abscess in it (*parulis*). For *odontoma*, see p. 82.

Methods.—*Croupous* and *diphtheritic deposits* and *thrush patches* may be examined in the *fresh state*, the former after needling and addition, if necessary, of dilute acetic acid, the latter in glycerin, or, still better, after being subjected to the action of 5 per cent. caustic potash solution, which causes the epithelial cells to swell, and the filaments and spores of the fungus to come out more distinctly.

Fur from the tongue and *tartar from the teeth* are also examined fresh, as are tonsillar plugs and calculi. In the deposits on the tongue and teeth large quantities of bacteria will above all be met with, and in the former, in addition to these, and especially in catarrhal affections, the desquamated apices of the filiform papillæ, which are composed of densely packed horny epithelial cells.

In *tonsillar calculi* the lime can be dissolved by adding hydrochloric acid

(p. 7), whereupon large horny epithelial cells, often arranged in concentric layers, come into view. In the fluid from the mouth horny epithelial cells are present even under normal circumstances in the form of large thin plates, containing abundant bacteria, and, besides these, the so-called *salivary corpuscles*, *i.e.*, lymphoid cells, the protoplasm of which contains fine granules seen to be in a condition of active molecular movement. Both kinds of elements are multiplied in catarrhal processes.

For *hardening*, alcohol or Müller's fluid is used. If changes in the epithelium are to be examined, the objects must be placed in the fluid while as fresh as possible, and for cutting must be embedded in celloidin, as with sections made in paraffin epithelial cells may become loosened in dissolving out the medium, and so break away and be lost (see p. 13). The same is true also of the examination of deposits on the mucous membranes. Sections are *stained* in carmine solutions, or in hæmatoxylin and eosin. Heidenhain's method (p. 190) may also be tried in examining adenoid tissue.

For studying *caries of the dental enamel* it is necessary to make *grindings*, though in doing so certainly the greatest part of the diseased tissue becomes lost. For this purpose the piece selected[1] is first ground on a coarse grindstone or on a coarser kind of emery paper, and then on finer stone or finer emery paper respectively. When the grinding has become as thin as possible it is further rubbed and polished with filter paper, and lastly with smooth paper.

Grindings of *carious dentine* may also be prepared, or, which is preferable, the softened dentine is lifted out with an excavator, and sections are made from it by means of a freezing microtome, the freezing being done in an aqueous solution of gum arabic instead of water. For *staining*, picro-carmine or picro-lithium-carmine are used, by which the dentine fibrils and dental sheaths are stained red, the ground-substance pink, and the disintegrating portions yellow.

The examination for *bacteria* is carried out according to the methods given for the latter. The bacteria occurring in the plugs in the tonsils and in the deposits in pharyngomycosis leptothricia, the so-called *Leptothrix* filaments, stain blue with Lugol's solution, and the recognition of such micro-organisms guards against the possibility of mistaking the condition for croupous or diphtheritic membrane. The bacteria which occur in dental caries may be stained by Gram's method, or with alkaline or carbolic methyl blue. For the modes of examining *sputum*, see p. 288 *et seq.*

II. THE STOMACH.

4. Degeneration, Softening, Hæmorrhagic Erosion, and Circular Ulcer.—*Cloudy swelling* and *fatty degeneration* of the glandular epithelium are observed in many diseases due to infection and intoxication. *Amyloid degeneration* may also occur in the stomach (when simultaneously present in other organs). Histologically these processes differ in no respect from those in other organs.

Gastric softening, which only comes into existence *post mortem* as

[1] Owing to the hardness of the enamel, it is impossible to saw teeth through the crown, so that they must be filed away with a glass-file.

a rule, but sometimes (especially in diseases of the brain) during the actual death-agony, consists in solution (digestion) of the wall of the stomach by the acid gastric juice. In this process the red corpuscles are first destroyed and the hæmoglobin changed into hæmatin, which permeates the tissues and stains them brown or black. The wall of the stomach itself and also the surrounding tissues then undergo solution.

Hæmorrhagic erosions arise from little hæmorrhages in the mucous membrane, which are often caused by the act of vomiting, or by changes in the constitution of the blood or vessels. The hæmorrhagically infiltrated parts, which are reduced in vitality, are acted upon and dissolved by the acid gastric juice, and this is accompanied by the formation of a brown discoloration of the extravasated blood due to change of the hæmoglobin into hæmatin. Such erosions may either heal or, should the solvent action of the gastric juice continue, may change into the following:—

Circular or Chronic Ulcer.—This may also occur, however, in consequence of embolism or thrombosis of a small arterial twig, as well as after hæmorrhagic infarctions, hyaline degeneration of the walls of vessels, and corrosion or mechanical lesions of the mucous membrane, the affected portions of the membrane becoming impaired in their vitality, and consequently dissolved by the gastric juice. The extension of the chronic gastric ulcer is not usually due to an inflammatory process, but merely to progressive solution of the tissue by the gastric juice, and hence also the edges and floor of the ulcer are smooth and free from inflammatory infiltration. Only when the ulcer has penetrated as far as the serous coat can it lead to an inflammatory adhesion of its base to the neighbouring organs, but the digestive action of the gastric juice then extends to these also. Sometimes, however, inflammatory and necrotic changes (Fig. 117) may take place at the base of the ulcer even before this, probably in consequence of a settlement of bacteria, and these contribute to a more rapid enlargement, and may produce, on the one hand erosion of blood-vessels (*b*), on the other perforation of the base of the ulcer.

In addition to this, however, the walls (especially the intima) of the blood-vessels at the margins and on the base of the ulcer are usually found thickened and the lumen narrowed (sclerosis); and, moreover, the muscular coat of the stomach often shows fatty degeneration within the area of the ulcer.

5. Inflammation.—In *catarrhal inflammation* the cylindrical epithelium is found, in the *acute* stage, to have undergone a high degree of mucous degeneration, and accordingly the mucous membrane is covered with a thick layer of slimy material, consisting of de-

generated and desquamated epithelial cells and leucocytes, while, besides the mucous membrane, the submucosa itself also sometimes

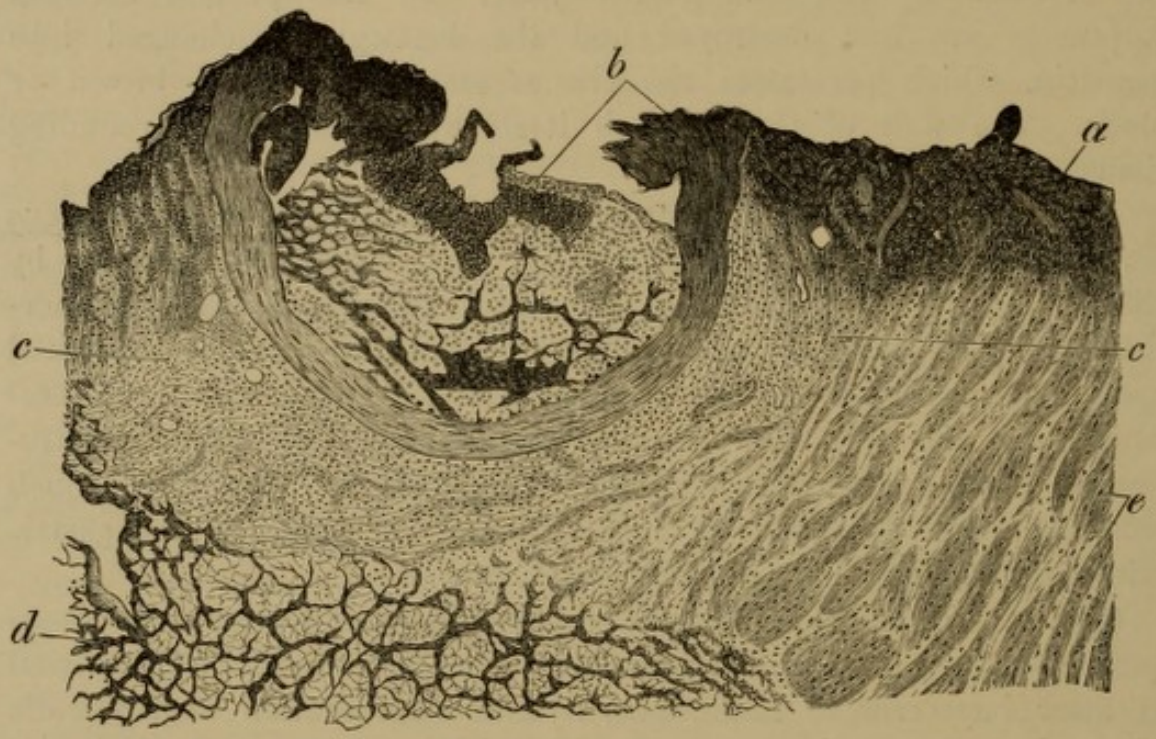

FIG. 117.—CHRONIC GASTRIC ULCER, WITH EROSION OF A THROMBOSED VEIN. × 77. (Alum cochineal.) *a*, Base of ulcer, consisting of tissue which is for the most part necrotic and stains intensely and evenly; *b*, Eroded and thrombosed vein, the wall and contents of which are likewise necrotic in the plane of the base of the ulcer; *d*, Fibrinous exudation in the deeper parts; *e*, Muscular coat.

shows a moderate degree of small-celled infiltration, and its blood-vessels become dilated.

In the *chronic* stage (Fig. 118) the prominent change is at first hyperplasia of the glands and connective tissue, in consequence of which the former become elongated and coiled, and often distended also with stagnating secretion, or changed into little cysts having mucous or colloid contents, the wall of which again may itself push out papillary excrescences. The hyperplastic connective tissue between the tubes appears at the outset very rich in small round cells (*d*), which may even form groups like follicles near the muscularis mucosæ. The hyperplasia of the connective tissue also produces an enlargement of the villous protuberances (*a*) normally present on the surface of the mucous membrane. Now, as those parts of the mucous membrane in which the connective tissue and glands have attained to a more considerable degree of hyperplasia project above the rest in the form of numerous small flat elevations (*A*), the result is the so-called '*état mamelloné*,' which, should the process become further intensified, may even end in the formation of isolated or numerous *polypi* of larger or smaller size. The glands of the mucous membrane covering the latter are very often found elongated or

dilated, and also increased in number, and are lined throughout with a cylindrical epithelium which assumes in places the form of goblet cells. *Cysts* not uncommonly develop from the dilated glands.

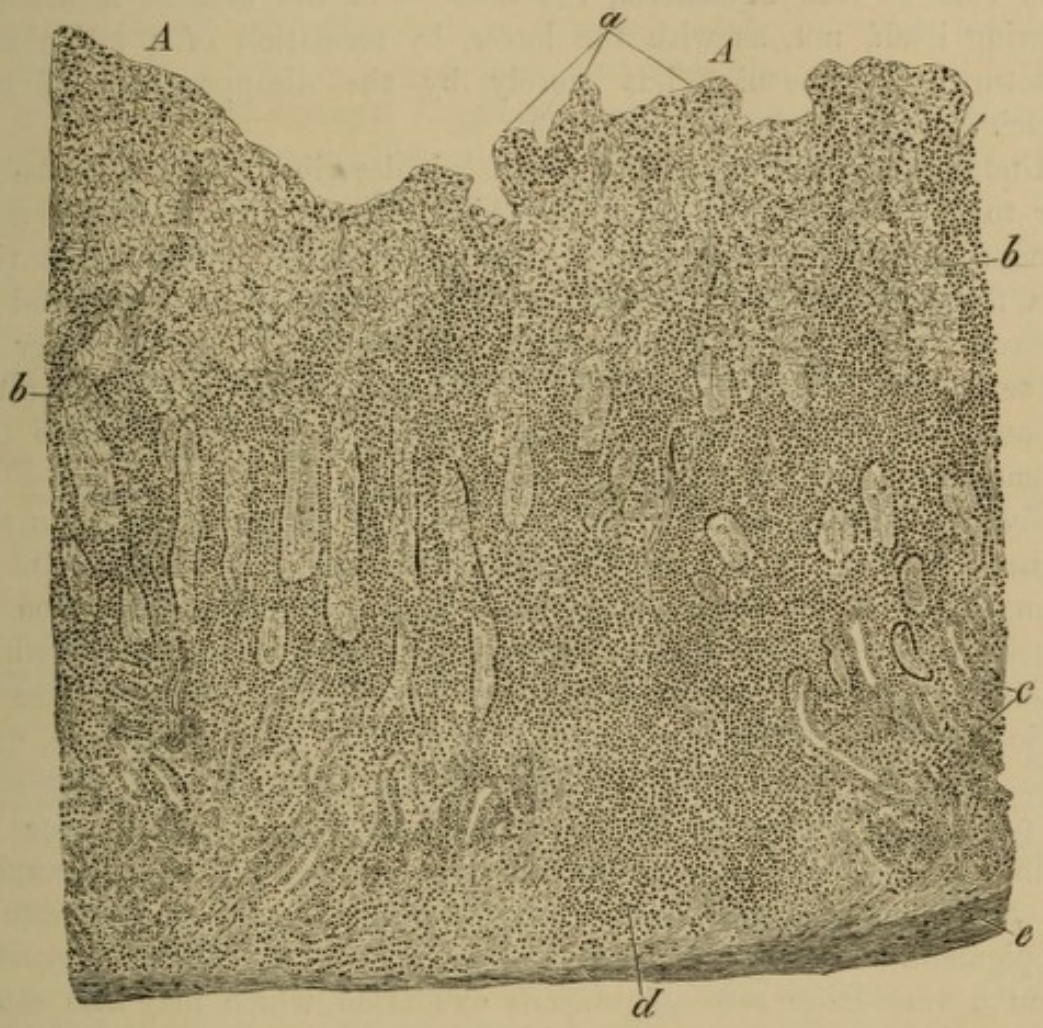

FIG. 118.—CHRONIC CATARRH OF THE STOMACH (*état mamellonné*). Vertical section through the mucous membrane, × 65. (Hæmatoxylin and eosin.) *A*, Two prominences of the mucous membrane separated by a depression, and constituting the *état mamellonné*; *a*, Enlarged villous processes of the surface of the mucous membrane; *b*, Upper segment of the pepsin glands, with mucous-degenerated epithelium; *c*, Lower segment of pepsin glands; *d*, Small-celled infiltration of mucous membrane; *e*, Muscularis mucosæ.

When gastric catarrh is of longer duration the intertubular connective tissue gradually becomes poorer in cells and firmer, and also frequently shows a deposit in its substance of little pigment granules derived from small hæmorrhages. As, moreover, the glands also gradually perish, a thinning and *atrophy* of the mucous membrane is thus brought about.

Several factors may act in the *causation* of gastric catarrh, amongst which especially abnormal fermentation of the gastric contents, chronic alcoholism, and venous congestion, play a frequent part.

Diphtheritic gastritis either develops in the course of a diphtheria,

when it is due to the same species of bacteria as the latter, or is caused by other micro-organisms which have not yet been discovered. In the latter case the histological character may deviate somewhat from that of true diphtheria, the necrosis of the mucous membrane showing itself, not, as with the latter, by formation of a reticulated structure of trabeculæ, but merely by the disappearance of the nuclei.

Under the name *phlegmonous gastritis* is described a process probably due to the *Streptococcus pyogenes*, which appears always in the submucosa, either in foci or far more frequently diffusely, and gives rise to a fibrino-purulent exudation. It may extend on the one hand to the submucous coat of the œsophagus or duodenum, on the other to the serous coat of the stomach, in the latter case leading to peritonitis. Suppuration of the tissue, followed by bursting of the pus into the stomach, may also take place.

Corrosive substances cause the occurrence of similar changes in the stomach to those in the œsophagus, except that they are much more intense in the former on account of the more prolonged action of the corrosives. Sulphuric and hydrochloric acids form greyish-white friable eschars, the alkalies brown, and less friable. In the case of nitric acid the eschar is yellow in colour, and with sublimate, carbolic acid, and arsenic, white. Under the microscope it may still be possible to recognise the several constituents of the tissue in outline in the substance of the eschar, but they are more granular and cloudy than normal, and the nuclei of the cells no longer take up pigment. Under the parts covered with eschar there is usually found a very large sero-sanguineous exudation, which may also cause an additional brown or black coloration of the eschar. Should the latter be cast off, scars may be formed, causing great contraction.

6. New Growths and Parasites.—The *new growths* most frequently met with in this situation are *polypi* and *carcinomata*, for the former of which see p. 234. Carcinoma occurs as *glandular* (adeno-carcinoma, cylinder-celled epithelioma), *scirrhous*, and *colloid cancer*. All three forms are usually situated at the pyloric end, take origin in the mucous membrane, and then extend chiefly in the submucosa. They may also extend by the lymphatics to the muscular and serous coats, or, on the other hand, by breaking into the blood-vessels, may give rise to metastases, which are most frequently found in the liver. Sometimes the cancer tissue may be so completely destroyed by ulceration that it can no longer be recognised even with the microscope.

The *glandular* is the softest and most vascular form of carcinoma, and in many cases shows a great resemblance to an adenoma in the

structure of its alveoli, but even in such cases quite atypical glandular spaces, *i.e.*, unmistakable cancer alveoli, will not fail to be found.

The *scirrhous* cancer frequently occurs as a diffuse fibrous-looking thickening of the coats of the stomach, which can still in most cases be clearly distinguished, so that here the diagnosis can only be rendered certain by microscopic examination.

In the *gastric contents* numerous *micro-organisms* are constantly present, mostly bacteria, but also yeasts (especially in gastric dilatation), which have gained entrance to the stomach with the food and saliva, and either exist there merely as indifferent parasites, or else may act as excitants of fermentation and putrid decomposition. The *Sarcina ventriculi* is very often found, and consists of small cocci arranged in fours or in combinations resembling bales of goods. Its significance is unknown.

Examination of the Stomach and its Contents.—The *gastric contents* and *vomited matters* are first examined microscopically according to the rules already laid down for investigating fluids (p. 5). There are then found *epithelial cells*, usually much altered, *isolated leucocytes* of which only the nuclei can be seen, and *constituents of the food*. Of the latter, particles of meat may be recognised by the transverse striation of the primitive muscular bundles; elastic and other connective-tissue fibres as well as fat-globules and fat-needles partly by their optical characteristics, partly by their behaviour towards reagents (p. 7); starch-granules by their concentric structure and the blue colour assumed on addition of Lugol's solution; and other vegetable constituents, such as spiral cells, by their form.

Blood mixed with the contents of the stomach may either be entirely unchanged, in which case the red corpuscles are still easy to recognise, or may already have become altered, when the red corpuscles are seen as colourless rings, or are replaced by pigment masses of variable size. In doubtful cases the recognition of blood may be effected by the demonstration of hæmin crystals (p. 191). In cases of ulcerating new growths of the stomach, *particles of tumour* may also be found in the vomited matter, and should be examined according to the rules given on pp. 110 and 111.

The examination of the gastric contents for *vegetable micro-organisms* and any *animal parasites* which may chance to be present is carried out by the methods given for these in Part II., Chapters V. and VI. Amongst the bacteria occurring in the gastric contents there are also some which stain blue with Lugol's solution, whilst the rest become brown. Yeasts may be recognised even in the unstained state as relatively large, round or oval, strongly refracting bodies. The stomach itself can be examined in a manner similar to the buccal cavity, pharynx, and œsophagus.

III. THE INTESTINAL CANAL.

7. Degenerations and Disorders of Circulation.—*Amyloid degeneration* occurs not uncommonly in the intestine, and here also it chiefly affects

the vascular and connective-tissue apparatus. *Fatty* and *hyaline degenerations* as well as *pigmentary deposit* may also be observed in the muscular coat of the intestine.

The *disorders of circulation* most calling for notice are those which occur in the wall of the protruded coil of intestine in strangulated hernia. In such cases we find all three intestinal coats, but especially the mucous and submucous, in a state of extreme venous hyperæmia, which is succeeded by extravasation of serum and red corpuscles into the tissue and lumen of the intestine, as well as into the hernial sac. The fluid collected in the latter will thus acquire a hæmorrhagic character. Should the strangulation last longer the hyperæmia increases to complete stasis, which is followed by a necrosis, first of the mucous membrane, later of the remaining intestinal coats also. In many cases the blood-supply may be *completely* cut off by the strangulation and a total anæmia thus caused, which also leads to necrosis when lasting for any length of time.

Migration of bacteria from the intestinal contents into the necrotic portions may cause *gangrene* and *softening* of the latter, and then *perforation* with consecutive *peritonitis*. It has already been mentioned above (p. 146) that a more important part is played in the causation of the latter by the *Bacterium coli commune* than by any other of the intestinal bacteria. But peritonitis may also occur without perforation, as the *Bacterium coli commune* is capable of making its way through the intestinal walls if their vitality is once reduced in consequence of venous stasis or total anæmia, and of penetrating into the sac of the peritoneum. Hence this bacterium is also found as a rule in the fluid of the sacs of strangulated herniæ.

8. Catarrhal Inflammation.—The *causes* of this disorder are very numerous, comprising firstly changes and decompositions of the intestinal contents brought about by abnormal multiplication of the ordinary intestinal bacteria (*Bacterium coli commune, Bacterium lactis aerogenes*, and others), or by micro-organisms which have only made their way into the intestine with substances already in a state of decomposition (*e.g.*, in so-called meat-, sausage-, and cheese-poisoning); secondly, different toxic bodies which have either been originally generated in the intestine by the agency of definite vegetable and animal parasites, or which, already fully formed, enter the intestine with the ingesta, or which act upon the intestinal mucous membrane from the circulation; while lastly, corrosive substances in a low degree of concentration, or mechanically irritant bodies, may also act in this way.

In *acute catarrh* of the intestine the finer changes in the mucous membrane are like those in gastric catarrh, except that at one time

mucous degeneration of the epithelium predominates, at another desquamation, and at a third suppuration, *i.e.*, a greatly increased emigration of colourless corpuscles; and the mucous layer upon the surface shows a somewhat variable consistence and composition corresponding to these differences. The accumulation of leucocytes in the intertubular tissue of the mucous membrane may under certain circumstances be so considerable that the Lieberkühn's glands are not only pushed widely apart, but their uppermost segments are also compressed (Fig. 119).

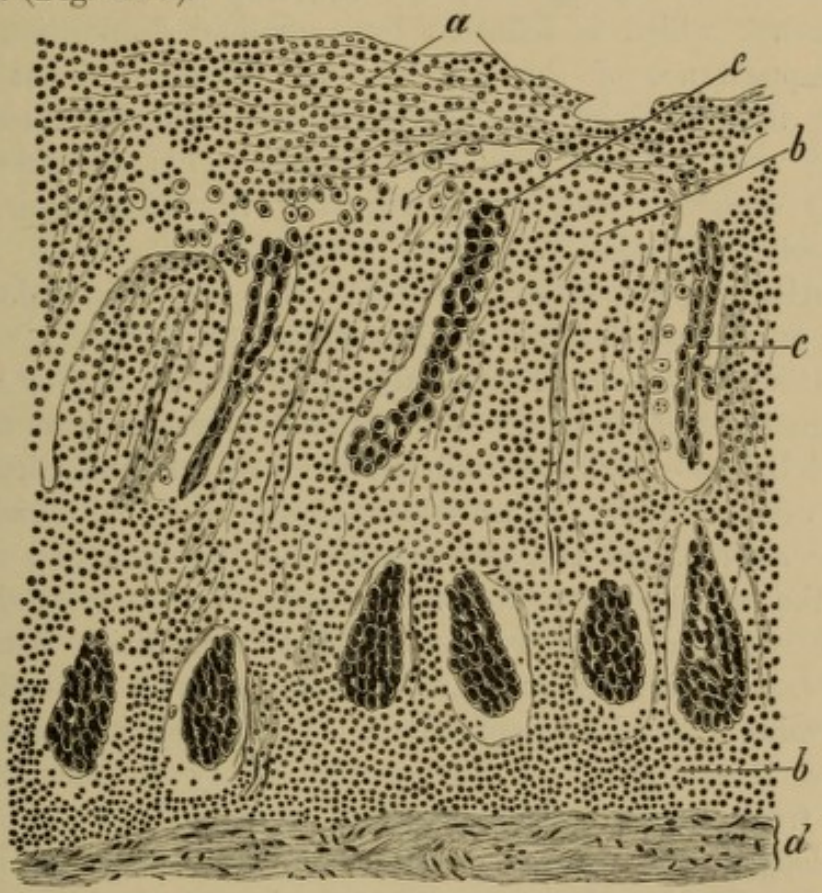

FIG. 119.—ACUTE CATARRH OF THE LARGE INTESTINE. × 240. (Alum cochineal.) *a*, Pus corpuscles (with scanty fibrin filaments) on the surface of the mucous membrane, which is stripped of epithelium; *b*, Small-celled infiltration of the mucous membrane; *c*, Upper compressed segment of the Lieberkühn's glands, which are separated from each other. Their epithelium is for the most part loosened from the membrana propria, and between the two a few pus-corpuscles are settled; *d*, Submucosa.

Similar conditions prevail in *chronic catarrh*. In it there sometimes ensues, as a consequence of narrowing or occlusion of the orifices of the glands, a formation of numerous small *retention cysts*, which still, however, often show a fine aperture from which glassy mucus oozes out. In many cases of chronic catarrh a mucus appears to be secreted which is not only very copious but very viscid, and which then, should it lie for any length of time in the intestinal canal, may form band-like or vermiform masses.

Deposits of brown and black pigment-granules in the mucous

membrane are also frequently found as consequences of previous hæmorrhages, especially in the apices of the villi and the neighbourhood of intestinal follicles. The submucous coat is usually not affected, but sometimes a moderate degree of serous or small-celled infiltration is observed in it also, and at a later stage even fibroid thickening.

Chronic intestinal catarrh leads to *atrophy* of the mucous membrane still more frequently than does chronic gastric catarrh. The regeneration of the superficial and glandular epithelium, which is continually undergoing desquamation, may soon become defective, an occurrence which is followed by a gradual diminution and ultimate disappearance of the Lieberkühn's glands, while at the same time the interglandular connective tissue somewhat increases and condenses, and the villi may also vanish. This atrophic condition is notably observed with great frequency in the cæcum. On the other hand, *hyperplastic* processes may also be set up, leading to the formation of polypoid excrescences. The glands included in these show the same characteristics as those in gastric polypi.

The *intestinal follicles* always participate to a greater or less extent in inflammations of the mucous membrane, whether by multiplication of their cells or by cellular infiltration of the circumfollicular tissue. In many cases, however, an actual suppuration of the follicles results (*follicular abscess*), and the pus bursts into the intestinal canal, thus forming the so-called *catarrhal ulcers*, defects of tissue having undermined edges (*follicular enteritis*). When this condition lasts for some time a *partial* skinning over may follow, the new epithelium sometimes forming gland-like depressions. The glassy mucus secreted in abundance from these will fill up the cavity of the follicle, and protrude from its orifice as a plug, and if such mucous plugs become dislodged, they appear in the intestinal contents as little sago-like bodies. The lymphatic vessels of the intestinal wall may likewise show certain changes, such as accumulation of leucocytes and fibrin in their lumen, or desquamation of the endothelial cells, which latter are then not uncommonly seen as large polynuclear cells lying in the lumen of the vessel.

Acute or chronic catarrh may affect various segments of the intestine *independently*. In the *duodenum* it not uncommonly leads to narrowing or closure of the orifice of the bile duct, and in consequence of this to *icterus*. In the *cæcum* inflammations of the mucous membrane (*typhlitis*) are often caused by accumulation and decomposition of fæces (owing to multiplication of the *Bacterium coli commune?*); but the inflammation may eventually invade all the layers of the intestinal wall, and lead to ulceration and perforation of the gut, with general or circumscribed peritonitis (*perityphlitis*).

The *Bacterium coli commune* is often found in the exudations of such processes, alone or in company with other intestinal bacteria. The *vermiform appendix* also is frequently the seat of an inflammation due to the presence of foreign bodies and fæcal calculi, or to extension from the mucous membrane of the cæcum. The results are similar. Catarrhal inflammation of the *rectum* (*proctitis*), which is likewise caused by lodgment of fæces, foreign bodies, and the like, may lead on the one hand to ulceration and phlegmonous inflammation of the surrounding tissue (*periproctitis*), and on the other, when of longer duration, to fibrous thickening of the mucous membrane and formation of polypi.

9. Specific Inflammations.—*Asiatic or epidemic cholera* is due to a specific bacterium (p. 153) which causes necrosis and desquamation of the epithelium of the mucous membrane and glands, most intense in those of the ileum; and which also produces an excessively copious watery transudation into the intestinal tube. The latter is accordingly found to be filled, in the *first* stage of the process, with a fluid mixed with abundant flakes (the shed epithelial cells) and resembling gruel or rice-water. The actual mucous membrane and in part also the submucous coat, more rarely the serous, are infiltrated to a moderate degree with round cells, and the follicles also are somewhat swollen owing to multiplication of their cellular elements. In the *second* stage (*cholera typhoid*) the mucous membrane shows on the contrary a diphtheritic inflammation not unlike that of dysentery, but this is no longer to be looked on as a direct consequence of the action of cholera bacteria, being probably due to the penetration into the mucous membrane, bared of its epithelium, of various other micro-organisms which have not yet been certainly recognised.

The *Spirillum choleræ Asiaticæ* is found in greatest abundance during the first stage of the process in the flakes floating in the intestinal contents, and in cases which run a rapid course it is present in enormous numbers, and to the exclusion of all other bacteria. It may further be detected also in the lumen of the Lieberkühn's glands, between their epithelial cells, and even in the sub-epithelial connective tissue. As the process runs its course the numbers of spirilla again diminish.

In *cholera nostras* the anatomical and histological changes are similar to those in Asiatic cholera, but their cause is still unknown.

In *typhoid fever*, which is to be regarded as caused by the *Bacillus typhosus*, there is found in the *first* stage a swelling of the Peyer's patches and solitary follicles which is usually very considerable and is accompanied by catarrh of the remaining mucous membrane.

These changes affect especially the lower part of the ileum and the cæcum, and are due to an abundant multiplication of the leucocytes and of the cells of the reticulum. In addition to this, a small-celled infiltration invades the mucous membrane covering the parts, as well as the villi and the submucous, muscular, and serous coats, in which latter it may even form nodular collections recalling the appearance of lymphoid tubercles (*typhoid lymphomata*). Lastly, there is also a very considerable dilatation of the capillaries and transitional vessels (Fig. 120, *c*).

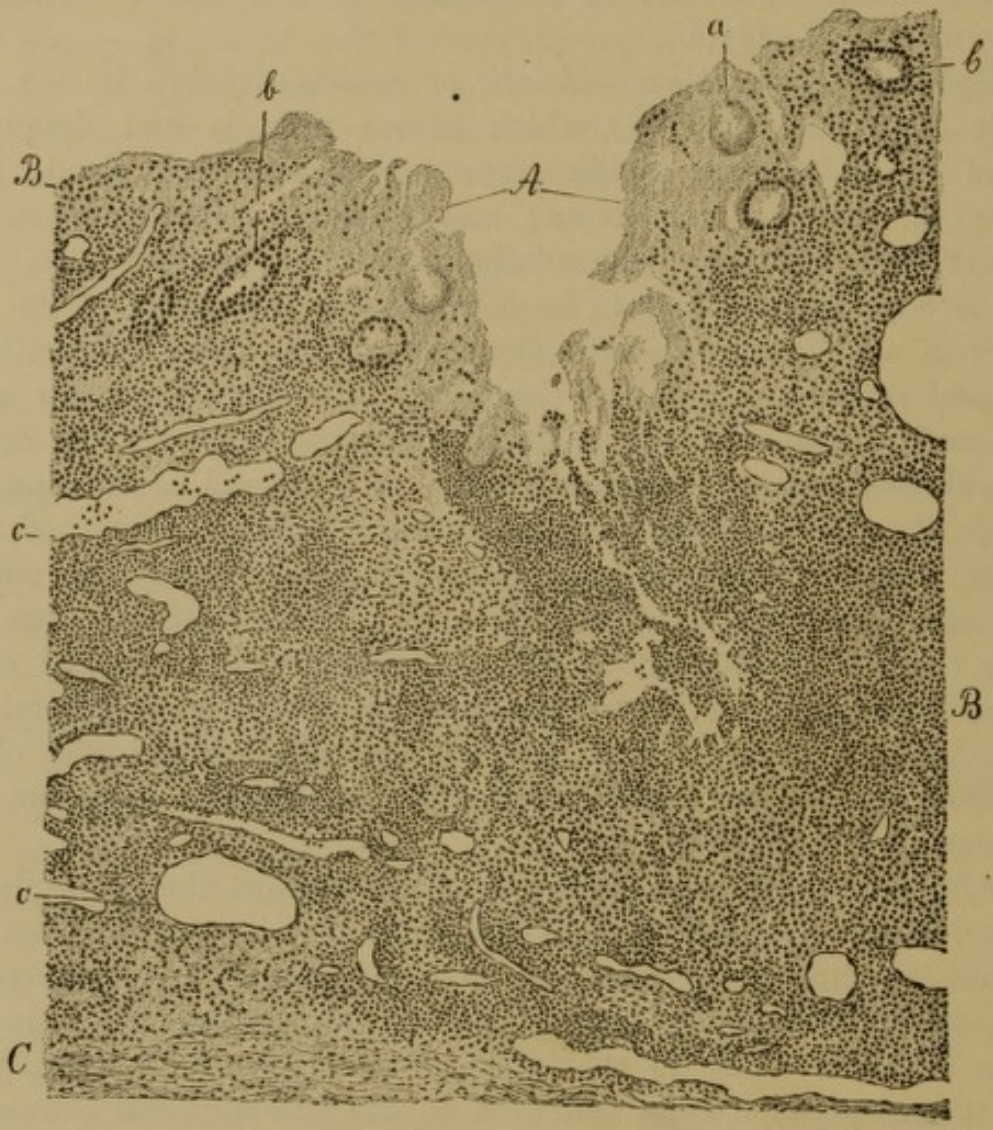

Fig. 120.—Commencing Necrosis of a Swollen Peyer's Patch in Typhoid Fever. × 77. (Hæmatoxylin and eosin.) *A*, Necrosis and breaking down of the most superficial portions of the patch; *B*, Non-necrotic part of the swollen Peyer's patch with hyperæmia and multiplication of the lymphoid cells; *C*, Lowest part of the submucosa; *a*, Necrosed Lieberkühn's glands in section; *b*, Unnecrosed Lieberkühn's glands; *c*, Distended blood-vessels.

In the *second* stage a *necrosis* of the Peyer's patches and solitary follicles sets in from the surface downwards (Fig. 120, *A*), which may extend to various depths and makes itself perceived partly by granular

disintegration or disappearance of the nuclei (*simple necrosis*), partly by transformation into a reticulum (*coagulation necrosis*). Sometimes, however, the so-called eschar shows exactly the histological appearances of a croupous false membrane, under which the epithelium of the mucous membrane as well as a part of the glands and villi may still be retained in many places. As the necrosed parts are next cast off, *ulcers* are formed, and if in this process any blood-vessels of larger size are eroded, severe hæmorrhages also occur, while smaller hæmorrhages may take place in the course of the disease by diapedesis from the numerous greatly dilated blood-vessels. Should the ulcers not be very deep healing may follow, their base becoming covered with granulation tissue and skinned over. The slightly sunken scars, however, remain for a long time pigmented (the pigment originating from the previous hæmorrhages) and usually contain no glands or follicles; the villi are also absent as a rule, or present only in stunted form.

Besides the lymphoid apparatus of the intestine, the *mesenteric glands* belonging to the latter are also enlarged, as well as the *spleen*. In the former the swelling is likewise due to multiplication of the lymphoid cells as well as those of the trabeculæ, and to dilatation of the capillaries. In many cases partial necrosis and even suppuration of the lymphatic glands may also take place, and may eventually be succeeded by calcification. How much of the swelling of the *spleen* is due to hyperæmia, and how much to multiplication of the cells, is difficult to decide. There are found in the spleen, in many cases, as well as in the liver and kidneys, small nodules composed of round cells (typhoid lymphoma), which then also contain typhoid bacilli.

For all remaining particulars regarding the occurrence of typhoid bacilli and the complications in the disease, see pp. 144-5; and for the waxy degeneration of certain skeletal muscles which is often present in this disease, see Part III., Chapter X., II. In the sloughs of Peyer's patches, as well as in the ulcers, there are found, in addition to the typhoid, other bacteria which have wandered in from the intestine. These are mostly saprophytic, but may sometimes make their way thence into the circulation also (Fig. 66, *e*).

Dysentery is an inflammation which occurs in epidemics under certain circumstances, and is variable in its extent and intensity, but in the majority of cases is restricted to the large intestine. Its causation has not yet been ascertained, some holding that bacteria, others that amœbæ (*Amœba coli*), are the excitants of the disease. It is not improbable, however, that several processes, distinct both etiologically and anatomically, are at present comprehended under the name of dysentery.

The slighter degrees of the disorder appear in the form of catarrh, which is, however, accompanied by great sero-sanguineous infiltration of the mucosa and submucosa, and staining of the mucus with blood. Other cases again are characterised by suppuration and ulceration of the follicles, and it is precisely in this form of dysentery, which runs a chronic course and occurs sporadically, notably in sub-tropical and tropical regions, that amœbæ have hitherto most frequently been found. Severe degrees of dysentery, on the other hand, present the appearances of a croupous or diphtheritic inflammation, which is at first localised in the folds of the mucous membrane. In such cases the process often begins with a fibrinous exudation upon the surface of the mucous membrane, which however soon becomes associated with a necrosis of the membrane itself extending to a variable depth, in consequence of which the tissue of the latter either simply becomes devoid of nuclei, its individual elements still remaining partly

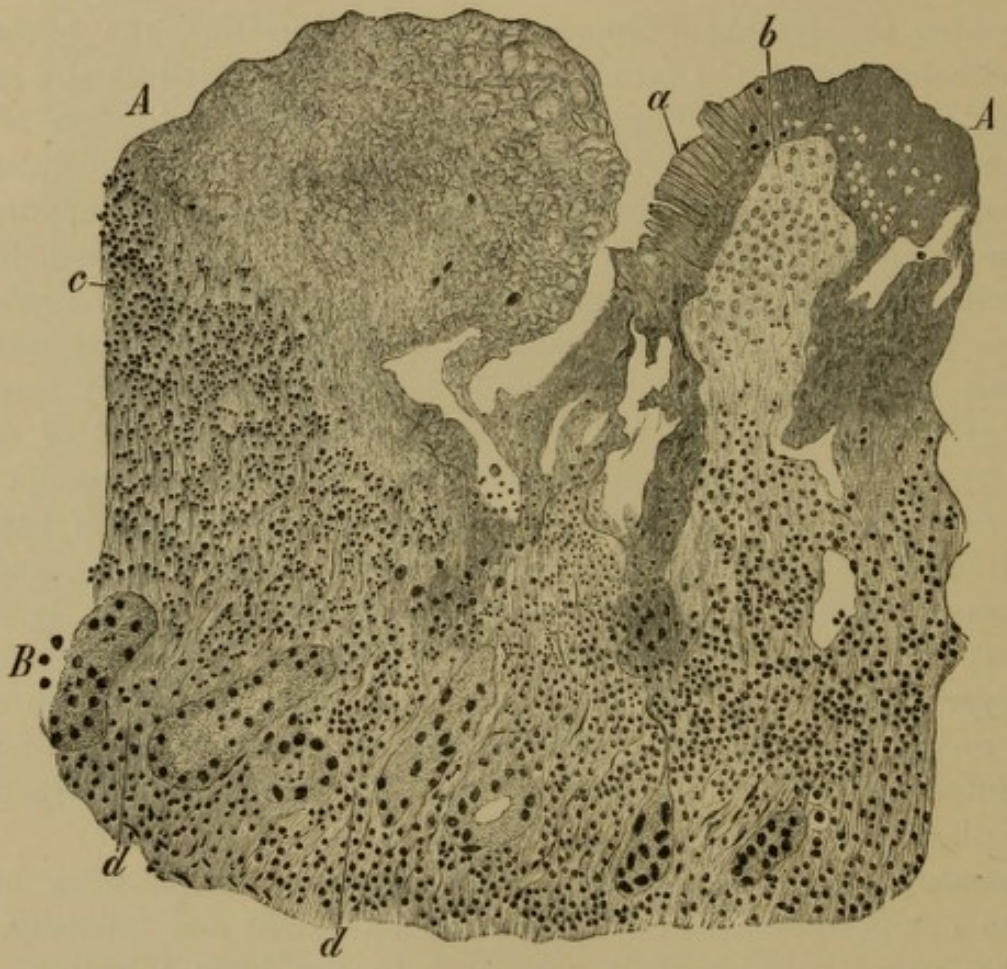

FIG. 121.—DIPHTHERITIC INFLAMMATION OF THE ILEUM IN DYSENTERY. × 265. (Alum cochineal.) *A*, Necrosed villi—the left showing indications of a reticulum in its right half; *B*, Glandular layer of the mucous membrane; *a*, Necrotic cylindrical epithelium; *b*, Necrotic round cells in the base of the villus; *c*, Leucocytes with nuclei undergoing disintegration; *d*, Intertubular small-celled infiltration.

recognisable in outline (Fig. 121, *A* and *a*), or changes into a more or less distinctly marked network.

Beneath the necrotic portions, into which numerous bacteria of different species penetrate, an intense and deep-reaching infiltration with leucocytes is always found (*d*), but those of the latter which immediately adjoin the necrotic tissue already, as a rule, show a disintegration of their nuclei (*c*). A considerable degree of venous hyperæmia is also usually present, together with extensive hæmorrhages, and the small arteries frequently show hyaline degeneration. When the necrosed parts have been cast off, ulcers of variable depth and extent are left, and in consequence of their cicatrisation may lead to constriction of the gut; whilst hyperplastic processes (polypoid growths) not uncommonly occur in the vestiges of mucous membrane that remain.

Diphtheritic and croupous inflammations also occur in the intestinal canal apart from dysentery, and are partly primary and partly secondary. They probably arise from various causes which may or may not be of a bacterial nature, and moreover they do not always quite agree with one another in their histological form. Thus, croupous inflammation may be caused by the *Diplococcus pneumoniæ*, while on the other hand many diphtheritic forms are to be set down to the account of the *Streptococcus pyogenes* or other bacteria. A diphtheritic intestinal inflammation may also occur in *poisoning with corrosive sublimate* as well as after *ptomain intoxication*.

For the intestinal form of *anthrax*, see p. 128.

The changes brought about in the digestive tract by *corrosive substances* may be recognised also in the intestinal canal, at least in its upper part, though of course with continually diminishing intensity, until at last nothing but small hæmorrhages or simple hyperæmia can any longer be found.

10. Infective Granulomata, New-formations, and Parasites.—*Tubercular* lesions in the intestine are usually localised in the same regions as those of typhoid fever. In the neighbourhood of the large caseous centres, as well as of the ulcers, small nodules are always found (Fig. 122, *b*), which develop chiefly in the lymphatic vessels or along their course, and often show the structure of epithelioid-celled or giant-celled tubercles. As the lymph-channels accompanying the blood-vessels extend transversely round the intestine from the mesentery, the ulcers will also spread principally in this direction, and hence assume the characteristic girdle form. Should tubercular ulcers develop in the rectum the process may also extend to the circumrectal connective tissue and then lead to the formation of so-called *rectal fistulæ*, the wall of the latter consisting of a granulation tissue in which tubercles, recognisable with the microscope, are embedded. A tubercular process sometimes develops also

in the cicatricial tissue which has formed after operative interference with the intestine (*e.g.*, extirpation of tumours). Should this take

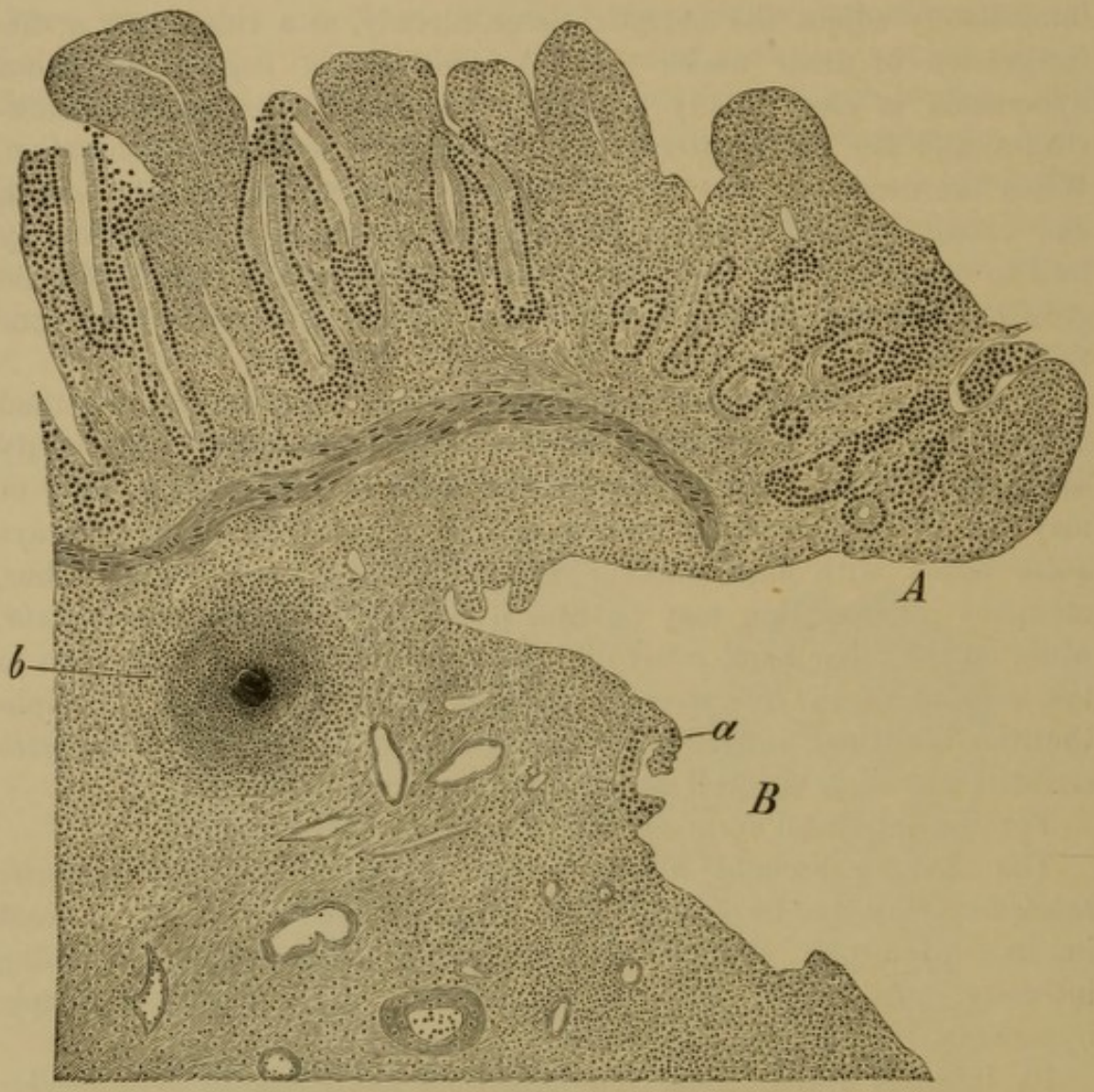

FIG. 122.—TUBERCULAR ULCER OF THE ILEUM. × 77. (Hæmatoxylin and eosin.) *A*, Overhanging margin of ulcer formed from the mucosa; *B*, Base of ulcer, composed of granulation tissue; *a*, Remains of a Lieberkühn's gland; *b*, Tubercle with commencing caseation in the centre.

the form of a diffuse infiltration, its recognition will in most cases be possible only by microscopic examination.

Syphilis is very rare in the intestine, with the exception of the rectum. Only in the inherited form are ulcerating gummata somewhat oftener found in the Peyer's patches or outside them, the vessels being at the same time strongly affected (p. 206). In the rectum, on the other hand, syphilitic processes occur with rather greater frequency even in adults, in the shape of initial scleroses, papules, and gummata. The ulcers which develop from them may attain a great size, and in cicatrising may give rise to the formation of a very

extensive and bulky cicatricial tissue, and hence to narrowing of the intestinal tube. For intestinal *actinomycosis*, see p. 159.

Of *new-formations* the *polypi* and *carcinomata* must be mentioned. The former may occur even in the absence of inflammation, and are most frequently found in the rectum. They have a structure similar to that of gastric polypi, *i.e.*, they are very rich in long and much-convoluted tubular glands, branched or dilated into cysts, and lined with cylindrical epithelium. If they prolapse from the anus the cylindrical epithelium of the surface changes into flat-celled epithelium.

Carcinoma appears in the form either of glandular or colloid cancer or, in the lowest segment of the rectum, of epithelioma.

Vegetable micro-organisms—mostly bacteria, but also yeasts—exist in large numbers in the intestinal canal even under normal conditions, but they are especially abundant whenever the intestinal contents become thin. Many of the bacteria seem to multiply to an extraordinary extent under certain conditions which are not yet accurately known, when they set up certain morbid disturbances, to which probably cholera nostras belongs.

Of *animal* parasites, *Amœba coli*, *Paramœcium coli*, and *Cercomonas* and *Trichomonas intestinalis*, all belonging to the class of Protozoa, are observed; and from that of Vermes, *Tœnia solium*, *mediocanellata*, *nana* and *cucumerina*, *Bothriocephalus latus*, *Ascaris lumbricoides*, *Oxyuris vermicularis*, *Anchylostomum duodenale*, *Trichocephalus dispar*, and *Trichina spiralis*; for particulars of which see page 166 *et seq.*

IV. THE PERITONEUM.

11. Ascites and Inflammation.—In the fluid of *ascites* are found scanty endothelial cells, for the most part fatty-degenerated, which are partly isolated, partly in membrane-like masses; also single (frequently swollen) leucocytes; and sometimes, in addition to these, very delicate fibrinous coagula, and minute droplets of fat. The last are in many cases tolerably abundant, *e.g.*, in carcinoma of the peritoneum and in chronic peritonitis (*hydrops adiposus*). In the so-called *chylous ascites* (effusion of chyle into the abdominal cavity) the fat is present in the form of extremely minute, feebly shining granules, surrounded by an albuminous envelope, and requiring the addition of acetic acid or alkalies before they will run together to form larger drops, which can be distinctly recognised as fat. If the fluid is stained with blood, more or less numerous red corpuscles are of course present; and lastly, in carcinoma or sarcoma of the peritoneum very minute particles or cells corresponding to the form of tumour may be found in the fluid, and in echinococcus

of the peritoneum cysts or free scolices, or, on the other hand, hooks or fragments of cyst-wall.

When the dropsy lasts for some time a proliferation of the endothelium often takes place, and also partial fatty degeneration and increased desquamation, together with growth of the connective-tissue cells of the serosa, which may then lead to circumscribed or more diffuse fibrous thickenings of the serous coat, and adhesions of the intestines to each other as well as to the abdominal wall.

Acute peritonitis may be *primary* or *secondary* according to its mode of occurrence. In the latter case it develops by extension of an inflammation, or importation of an exciting cause of inflammation, from the neighbouring parts, or from a distant centre of disease by means of the circulation. The cause referred to is either a definite bacterium (*Streptococcus* and *Staphylococcus pyogenes, Diplococcus pneumoniæ, Bacillus typhosus, Bacterium coli commune*, and possibly *Gonococcus*), or an agent producing its effects by chemical action (extravasation of gastric or intestinal contents, etc.). How and whence the excitants of *primary* peritonitis—up to the present the *Streptococcus pyogenes* and *Diplococcus pneumoniæ* have been recognised as such—gain entrance into the abdominal cavity has not yet been made clear.

When the peritonitis is due to extension of an inflammation from the neighbouring parts its character corresponds to that of the latter. In the remaining cases the exudation may be serous, fibrinous, purulent, or mixed, but most frequently fibrino-purulent; whilst in extravasations of fæces, gangrene of the gut, and so forth, it may also assume a putrid character.

When examined histologically, the serous coat is found to be not only hyperæmic but infiltrated with serum or with fibrin, as the case may be, and more or less numerous leucocytes. To this is further added proliferation and increased desquamation of the endothelium, and deposition of fibrinous or purulent exudations upon the surface of the serosa. The lymphatic vessels are also frequently dilated and filled with thrombi, while their endothelium is swollen or undergoing proliferation. Should healing set in, a vascular embryonic tissue grows out from the serosa after absorption of the exudation (compare p. 201), and this gradually changes into firm connective tissue, leading to thickenings of the serosa or adhesions (*adhesive peritonitis*), sometimes also to much shrinking of the great omentum and mesentery (*peritonitis deformans*).

Chronic peritonitis has the same termination. It either originates in an acute inflammation, or runs a lingering course from the outset.

12. Infective Granulomata and New-formations, etc.—In *tuberculosis* of

the peritoneum either the disease restricts itself merely to isolated patches of the membrane, or the tubercles are distributed over its entire area. In the latter case there is usually also a more or less intense chronic peritonitis, with a serous or sero-fibrinous and often blood-stained exudation. In this form there is found a particularly active proliferation of the endothelium accompanied by increased desquamation, as well as cellular infiltration of the serous coat, with emigration of red corpuscles and extravasations of blood (ecchymoses). In many cases the inflammation exhibits the character of adhesive peritonitis.

Of the *primary new growths* the *endothelial sarcoma* must especially be mentioned, which occurs in the form of flat nodules connected together by bands. In the connective-tissue stroma, which is usually firm, are found alveoli containing large epithelioid cells, which are, however, formed by proliferation of the endothelium of the lymphatic vessels or of the serosa itself. The alveoli not only frequently follow the arrangement of the lymphatic vessels, but sometimes still permit of the recognition of a lumen as well as of the proliferative processes in the endothelium of these vessels (Fig. 36). By disappearance of the cells in the alveoli and condensation of the stroma there may result, as in a scirrhus, a contraction of the nodules and serosa as well as of the intestines themselves.[1]

Of *animal parasites, Echinococcus* is frequently found.

Examination of the Intestine and Peritoneum, and of their Contents.—The microscopic investigation of the *intestinal contents* is in many cases materially assisted by a previous naked-eye examination, as in this way not only can the consistence and colour of the contents or stools be determined, but the larger undigested masses of food-constituents, animal or vegetable, such as tendon tissue, arteries, berries, fragments of vegetables, etc., may be detected, as well as certain pathological products such as pus, mucus, masses of necrosed tissue (from the intestinal mucous membrane or entire wall of the intestine, or the pancreas), not to mention particles of tumours, concretions, and, lastly, intestinal worms.

The microscopic examination itself is carried out on the same general principles as that of the contents of the stomach, and reveals first of all elements of food similar to those found in the latter, such as *vegetable cells*, *starch granules* (large quantities of which indicate morbid conditions of the intestine), *elastic tissue*, *muscle fibres* (stained yellowish, and with or without distinct transverse striation ; in great abundance in liquid stools), and *fat*. The latter is usually present as needle-shaped crystals (Fig. 13), which are found normally in infants at the breast, but otherwise occur in considerable quantities only in acholic stools, and in diseased conditions of the pancreas. Other crystals, such as those of *calcium carbonate*, *sulphate*, *phosphate*, and *oxalate*, and of *ammonio-magnesian*

[1] Many authorities class the new-formation described amongst the inflammations, and give it the name of *lymphangeitis carcinomatodes*.

[*triple*] *phosphate*, as well as *Charcot-Leyden* and *cholestearin crystals*, may also be found, but have no pathological significance.

In *intestinal hæmorrhages* (occurring in the course of dysentery, typhoid fever, etc.) intact *red corpuscles* are scarcely ever met with, but only masses of pigment and hæmatoidin crystals. Demonstration of Teichmann's crystals must be resorted to in doubtful cases (see p. 191).

If *mucus* is present in the intestinal contents it is often so intimately mixed with the latter that it can only be recognised by microscopic examination, by the granular striation which occurs on the addition of acetic acid. If, on the contrary, it occurs in larger masses, visible to the naked eye, the latter sometimes take an elongated ribbon-like or vermiform shape (p. 239). The use of the reactions peculiar to mucin (p. 54) will guard against any possible error. On the other hand, the mucus may also occur in the form of small lumps, recalling the appearance of grains of boiled sago (p. 240), and must not be confounded with swollen masses of starch. The latter, however, would stain blue on adding Lugol's solution.

Epithelial cells and *leucocytes* may be met with even in normal intestinal contents, but only isolated. Their occurrence in larger numbers indicates catarrhal, and suppurative or ulcerative processes respectively. The epithelial cells may then form coherent agglomerations of considerable size, or even appear as glove-like coverings from the villi. Particles of *tumours*, should such be found in the stools, are examined after the methods described on pp. 110 and 111.

The *contents of the abdominal cavity*, which consist of exudations or transudations, are examined respectively according to the rules which hold good for exudations (p. 75) and fluids (p. 5). If the fluid is very poor in solid elements it may be made to sediment by standing in a conical glass, or by means of Stenbeck's centrifugal machine, and the deposit then examined. In chylous ascites addition of dilute acetic acid or of caustic potash solution will dissolve the albuminous envelopes of the granules and allow the fatty nature of the latter to become distinctly apparent.

As a rule it will scarcely be possible to distinguish isolated *cancer cells* with certainty from endothelial cells, although the former are in general marked by their polymorphism and the strikingly large size of their nuclei. As, however, cancer cells frequently show the glycogen reaction on addition of Lugol's solution, whilst endothelial cells usually do not, a distinction may perhaps be found in this fact. Generally speaking, however, great caution is needed in making such a differential diagnosis.

The examination of the contents of the intestine and abdominal cavity for *animal and vegetable parasites* is conducted according to the rules given in Part II., Chapters V. and VI. Amongst the non-pathogenic intestinal bacteria there are also some which stain blue with Lugol's solution. Yeasts are present especially in the acid stools of children.

Examination of the *intestine* itself as well as of the *peritoneum* is carried out in a manner analogous to that of the stomach.

CHAPTER V.

THE LIVER, BILE-DUCTS, AND PANCREAS.

I. THE LIVER.

1. Degenerations, Pigmentary and Leucæmic Infiltrations, and Atrophy. —*Cloudy swelling* (*parenchymatous degeneration*) occurs very frequently in the liver in diseases due to infection and intoxication, and consists, as in other organs, in the deposition of small dark albuminoid granules in the protoplasm of the hepatic cells (Fig. 12, *d*), owing to which the latter swell, and the nucleus may even be concealed. In the diseases mentioned it frequently passes into *fatty degeneration*, which, however, is present in its most characteristic form in poisoning with phosphorus and arsenic, and in acute yellow atrophy of the liver.

In *acute yellow atrophy* (Fig. 123), which may probably be counted amongst the acute infective diseases, we find first of all, as in fatty degenerations of the organ due to other causes, the hepatic cells densely packed with fat-droplets of small and medium size (*a*), and which *do not coalesce;* and in consequence the cells and entire organ become somewhat enlarged. This is then followed by a disintegration of the hepatic cells, on the site of which we now observe merely collections of fat-drops, fatty detritus, yellow pigment-granules, and sometimes also crystals of bilirubin. Up to this point the liver is of an intense yellow colour, and is at first somewhat enlarged, but subsequently reduced in size (*yellow atrophy*); but with the disappearance of the fatty detritus the stroma and blood-vessels come into greater prominence, so that such spots appear red (*red atrophy*). In these portions the place of the acini is found to be occupied by connective tissue infiltrated more or less intensely with small cells (*d*), and in this, in addition to isolated survivors of the hepatic cells, mostly atrophic and filled with bile pigment (*b*) or undergoing fatty degeneration, there are also seen peculiar branching columns and tubes composed of epithelial elements (*c*), in which the latter are in

part of remarkable size and also contain large nuclei, sometimes two or more in a cell. These structures, which recall the appearance of

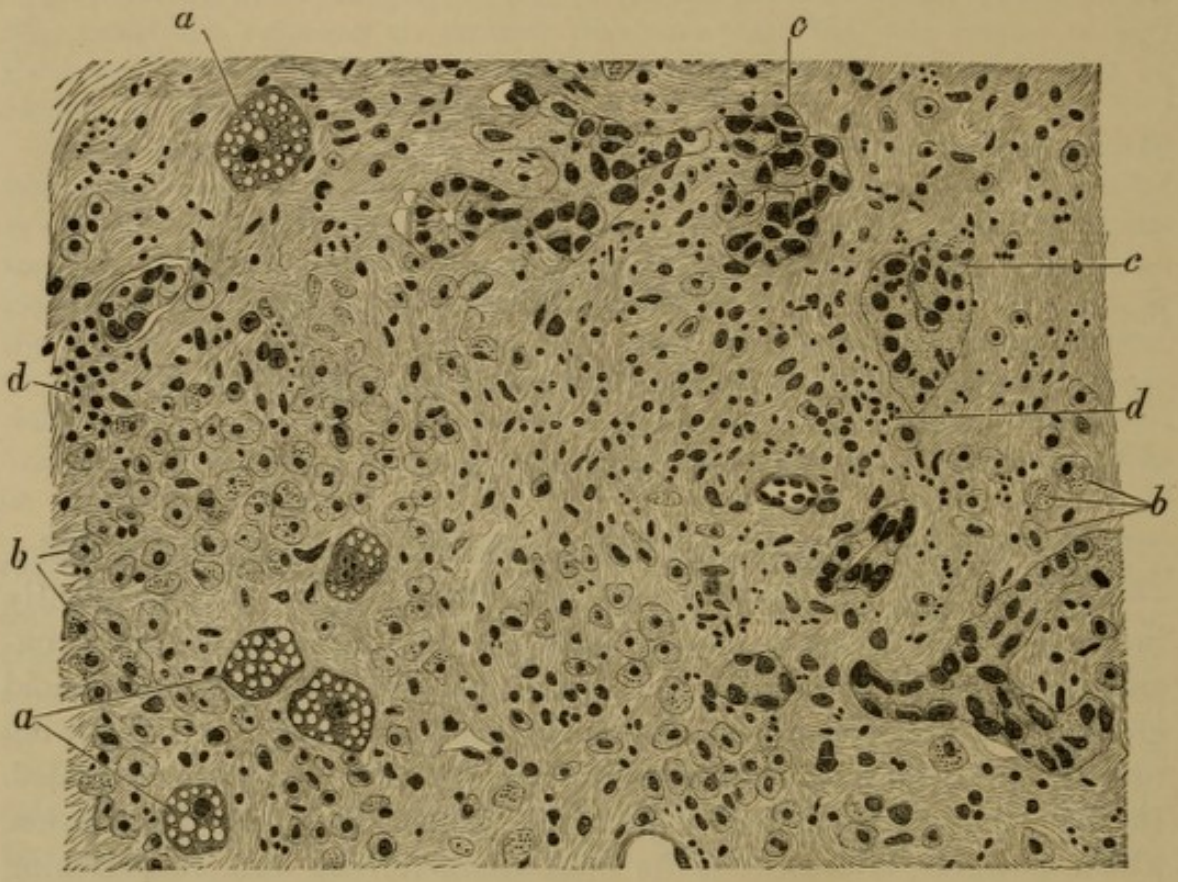

FIG. 123.—ACUTE YELLOW ATROPHY OF THE LIVER (from a spot showing RED ATROPHY). × 330. (Alum cochineal.) *a*, Fatty degenerated liver cells, some with and some without nucleus; *b*, Atrophic liver cells, partly filled with granular bile pigment; *c*, Newly-formed bile-ducts; *d*, Stroma, infiltrated with small cells.

bile-ducts, are probably to be regarded as the result of a *regenerative* growth on the part of the epithelium lining the old bile canaliculi.

Fatty degeneration must not be confounded with *fatty infiltration* of the liver (*fatty liver*, Fig. 128, *A*), which consists in an excessive storage of fat in that organ, and occurs in well-nourished individuals, in chronic alcoholism, and in tuberculosis. Since the fat is brought by the portal vein it is first deposited in the hepatic cells at the peripheral portions of the acini, and only extends over the entire organ when the condition is of a higher degree of intensity. At the beginning several minute fat-droplets are present in the cells, which subsequently *coalesce* to form *large* drops which fill the entire cell, but again break up into small drops as the process subsides.

Amyloid degeneration (Fig. 15) usually implicates the entire organ; more rarely it is merely circumscribed. It first of all affects the capillaries, usually those in the so-called "intermediate zone" of the acini (*i.e.*, approximately midway between periphery and centre of the acinus), the wall of the capillary becoming converted into a

homogeneous mass of unequal thickness, while its endothelium at first remains intact. The small arteries are next involved, and in these again chiefly the media; and lastly, the hepatic cells may also lose their nuclei and be changed into glassy masses. Usually, however, these cells merely disappear by atrophy (Fig. 15, *d*), or show fatty infiltration. In amyloid degeneration the organ is always very poor in blood, as the degenerated vessels, although still remaining pervious (that is to say, they can still usually be completely filled by artificial injection), are nevertheless considerably narrowed. Regarding *glycogen degeneration*, see p. 57.

In *icterus* the hepatic cells, chiefly those in the centre of the lobules, are found partly infiltrated with light yellow pigment in solution, and partly filled with yellow or brownish-red pigment-granules. More rarely there is a deposit of bilirubin crystals. If the icterus is very intense, in addition to the above we see many bile-capillaries distended in an irregular manner with homogeneous yellowish-brown or greenish masses.

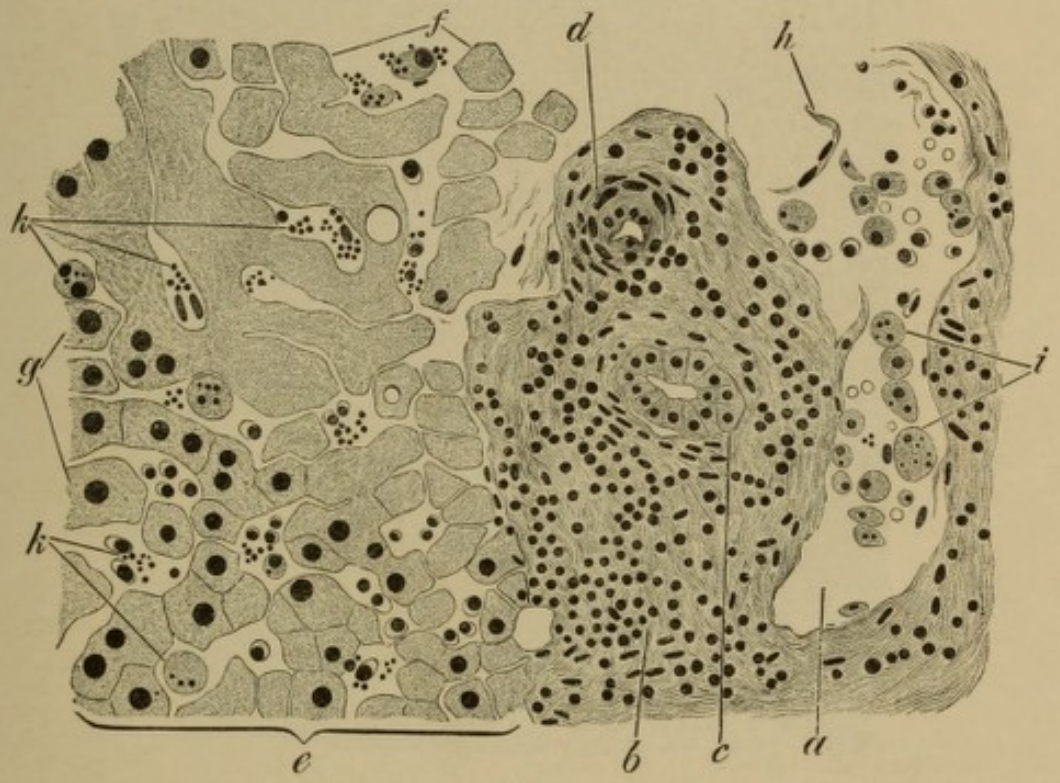

FIG. 124.—MELANOSIS OF THE LIVER IN INTERMITTENT FEVER. × 545. (Hæmatoxylin and eosin.) *a*, Branch of portal vein; *b*, Small-celled infiltration of Glisson's capsule; *c*, Bile-duct; *d*, Hepatic artery; *e*, Periphery of an hepatic acinus; *f*, Hepatic cells devoid of nuclei (necrotic?); *g*, Nucleated hepatic cells; *h*, Separated endothelial cells; *i*, Pigment-bearing leucocytes in a branch of the portal vein; *k*, Pigment granules and pigment-bearing leucocytes in the hepatic capillaries.

Pigmentary deposit in the liver takes place also in severe forms of intermittent fever in which the pigment (melanin) formed in consequence of the destruction of red corpuscles by the plasmodia

(see p. 168) first accumulates, like the fat in fatty infiltration, in the capillaries of the peripheral portion of the acini (Fig. 124, *e*). Here it appears in the form of brown or black grains and masses, partly enclosed in white corpuscles (which may be considerably increased in size thereby) and partly free (*i* and *k*). Later, it is found outside of the blood-vessels also, in the fixed cells of the circumportal connective tissue and in those of the liver. In intermittent fever of long duration besides the pigmentary deposit, there is usually also a cellular infiltration (*b*) and hyperplasia of Glisson's capsule even to its finest ramifications (*pigmentary induration*). Pigmentary deposit in the liver is found also in other diseases which are accompanied by extensive destruction of red corpuscles, such as pernicious anæmia. We then find in the actual hepatic cells granules which are partly yellow or brown, partly colourless, but which give the iron reaction (see p. 60).

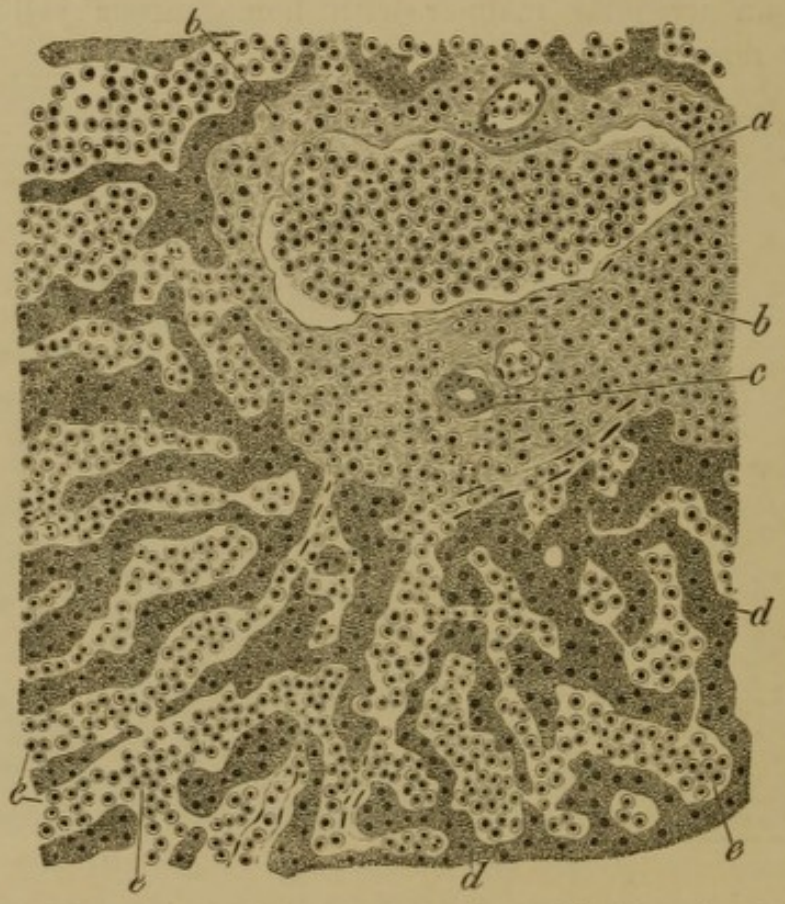

FIG. 125.—LEUCÆMIA OF THE LIVER. × 215. (Alum cochineal.) *a*, Branch of portal vein, containing white corpuscles almost exclusively; *b*, Capsule of Glisson, infiltrated with numerous leucocytes; *c*, Bile-duct; *d*, Bands of hepatic cells, partially atrophic; *e*, Capillaries filled exclusively with white corpuscles and in part greatly distended by them.

Leucæmic infiltration (Fig. 125) has a predilection for the liver. When it occurs we find extraordinarily large numbers of white corpuscles not only in the capillaries (*e*) and smaller blood-vessels (*a*), but also in the vicinity of the former as well as in the tissue of Glisson's

capsule, in which latter it is present either as a diffuse infiltration (*b*) or in the form of little nodules. A portion of the hepatic cells are destroyed owing to compression by the distended capillaries.

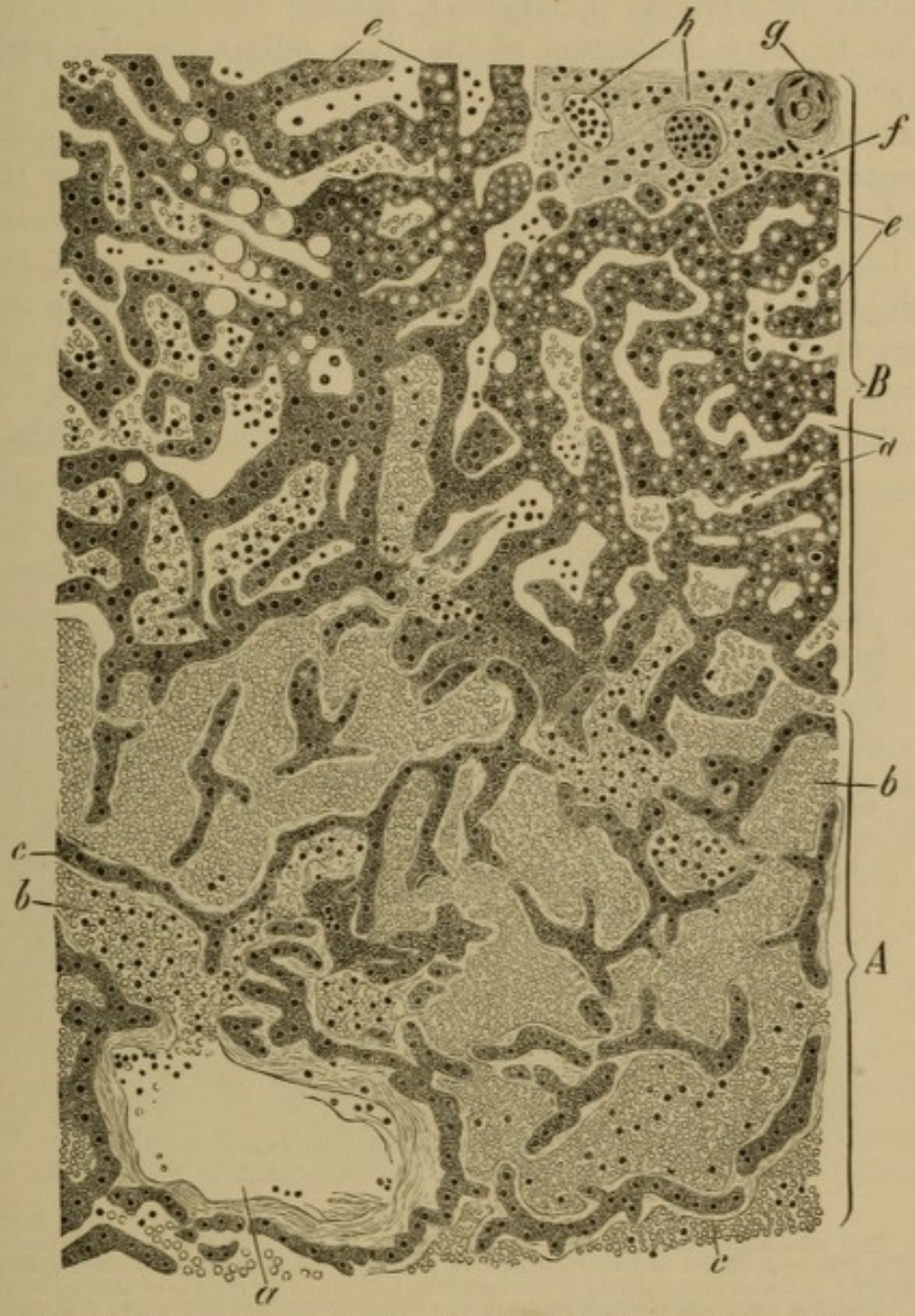

FIG. 126.—NUTMEG LIVER. × 240. (Hæmatoxylin and eosin.) *A*, Central portion of an acinus; *B*, Periphery of an acinus; *a*, Hepatic vein; *b*, Greatly dilated capillaries; *c*, Compressed bands of hepatic cells; *d*, Undilated capillaries; *e*, Uncompressed bands of hepatic cells, partly showing fatty infiltration; *f*, Capsule of Glisson; *g*, Hepatic artery; *h*, Bile-ducts.

In *cyanotic atrophy* (*nutmeg liver*, Fig. 126), which develops especially in obstructions to the pulmonary circulation, the central veins together with the adjoining capillaries (*b*) of the acini are seen to be distended and the hepatic cells thereby more or less compressed, atrophied (*c*), and usually full of yellow or brown granules of

pigment, which at last may alone remain, the hepatic cells having completely disappeared. The venous stasis sometimes leads to hæmorrhages, and, when it lasts longer, on the one hand to growth and small-celled infiltration of Glisson's capsule (*cyanotic cirrhosis*), on the other to fatty infiltration of the liver cells (*e*) at the periphery of the acini (fatty nutmeg liver).

2. Inflammations.—*Suppurative hepatitis* occurs when the causes of inflammation, usually pyococci, make their way into the liver through a wound, from one of the adjacent organs, or by the blood-vessels (vena portæ, hepatic artery, or more rarely the vena cava, and, in newborn children, the umbilical vein). A suppurative inflammation of branches of the portal vein or bile-ducts may likewise give rise to the condition.

The most frequent form is *metastatic inflammation* (Fig. 127),

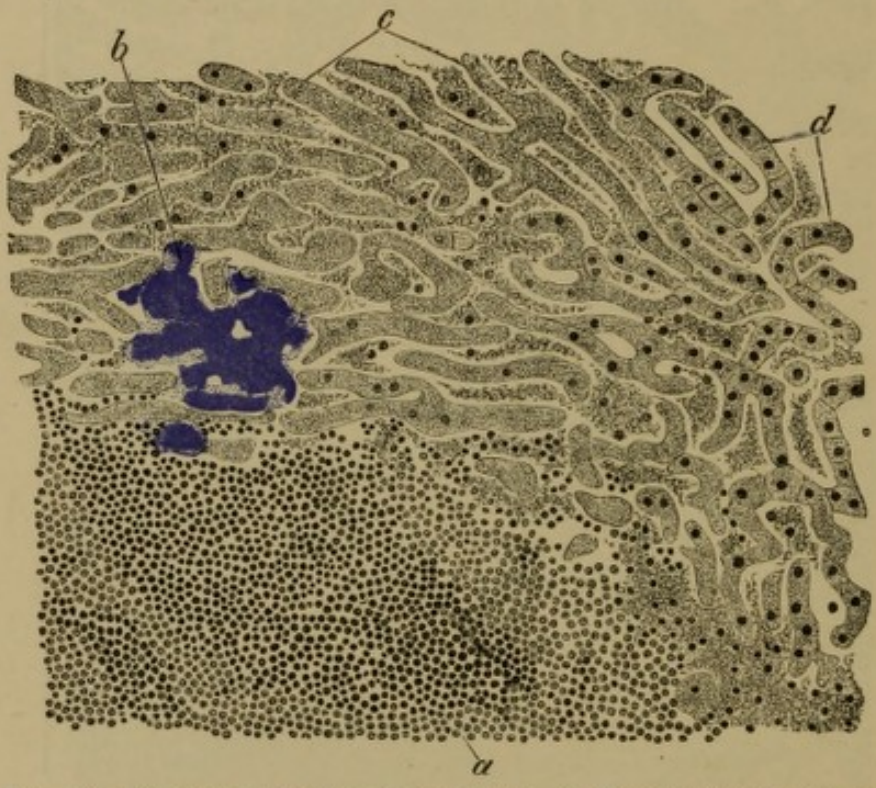

FIG. 127—METASTATIC ABSCESS OF THE LIVER IN PERIURETHRITIS SUPPURATIVA. × 285 (the cocci drawn in under a power of × 545). (Weigert's modification of Gram's method.) *a*, Dense accumulation of pus corpusles (abscess at the periphery of an acinus); *b*, Embolus of cocci in the hepatic capillaries; *c*, Necrotic bands of liver cells; *d*, Normal bands of liver cells.

i.e., that in which the excitants are brought to the liver by the circulation from an already existing focus of suppuration. In this case the pyococci settle in the capillaries (*b*) or small branches of the veins and arteries, which they fill more or less completely by their multiplication. If a small portal or arterial twig is completely stopped by them, the result is, first, an intense hyperæmia and stasis in the area supplied by the vessel, and ultimately necrosis

succeeded by suppurative inflammation. If the lodgment of cocci takes place only in the capillaries (*b*), there is no hyperæmia, but immediate necrosis (*c*), which then is likewise succeeded by suppurative inflammation (*a*). In this the walls of the vessel and the surrounding connective tissue are densely infiltrated with pus corpuscles, and by advance of this infiltration, and liquefaction of the necrotic or cell-infiltrated tissue, small *abscesses* are finally formed.

When a suppurative inflammation exists anywhere within the area drained by the radicles of the portal vein, there may first ensue a thrombo-phlebitis of the radicles and trunk of the vein (*pyle-phlebitis*), owing to extension of the inflammation to the former; and this may then advance into the branches of the portal vein in the interior of the liver, even as far as their finer ramifications. Here also there follows purulent infiltration of the wall of the vessel and of Glisson's capsule, with formation of abscesses; but the suppuration does not extend to the acini themselves, and the hepatic cells perish only from the pressure of the abscesses.

Chronic interstitial inflammation (*cirrhosis*) may be set up by various influences, such as alcoholism, disease of vessels, biliary stasis, etc., and may also begin in various ways, according as it is or is not preceded by degeneration of the hepatic cells. It is, however, always localised in Glisson's capsule, which in the first stage at least is more or less densely infiltrated with small round cells (Fig. 128, *c*). According to the extent and results of the inflammation two forms are distinguished, viz., *hypertrophic* and *atrophic* cirrhosis, and of the latter again a *granular* and a *lobular* form.

Hypertrophic cirrhosis, also called *biliary cirrhosis*, usually follows changes in the bile-ducts, and is distinguished by the fact that the capsule of Glisson for the most part continues permanently in the state of small-celled infiltration, and consequently no contraction and no considerable atrophy of the hepatic cells takes place, the liver thus remaining large and its surface smooth.

In *atrophic cirrhosis*, however, the small-celled infiltration leads to formation in Glisson's capsule of firm contracting connective tissue, poor in cells, while at the periphery of the capsule the small-celled infiltration may advance and even penetrate into the interior of the acini along the capillaries. Owing to the shrinking of the connective tissue the smaller twigs of the portal vein and also the capillaries in the interior of the acini become obliterated, but this again may be partially compensated for by a new formation of blood-vessels fed from the hepatic artery. At first the hepatic cells often show fatty infiltration (Fig. 128, *A*), and likewise (especially at the periphery of the acini) a copious deposit of yellow and brown pigment

granules, in consequence of stoppage of the flow of bile due to the obliteration of biliary ducts in the contracting capsule of Glisson.

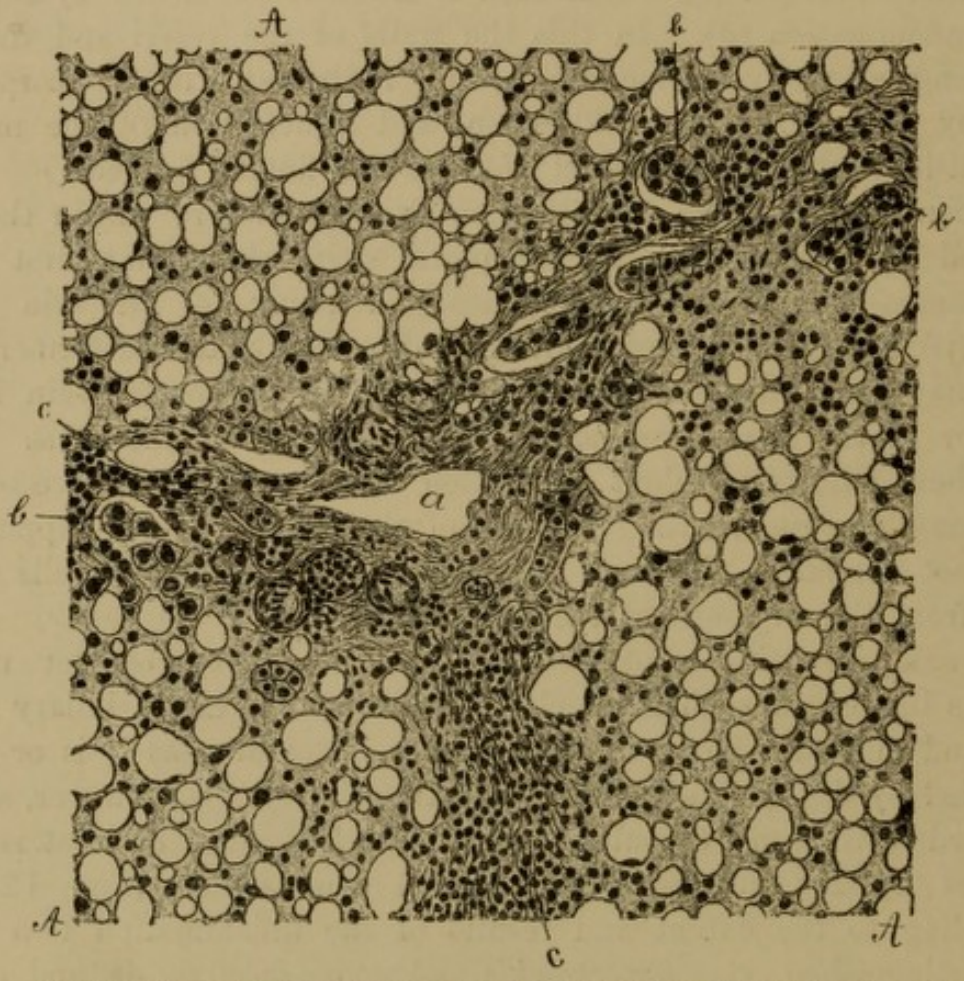

Fig. 128.—Commencing Cirrhosis of the Liver with Fatty Infiltration. × 240. (Hæmatoxylin and eosin.) *a*, Branch of portal vein; *b*, Bile duct; *c*, Capsule of Glisson with small-celled infiltration; *A*, Peripheral part of hepatic lobules, with fatty infiltration.

Later, the hepatic cells and acini atrophy (Fig. 129, *a* and *b*), partly in consequence of the abolition of numerous blood-vessels, but chiefly from the constriction exercised by the shrinking connective tissue. According as the process is restricted merely to the principal branches of Glisson's capsule, or involves also its finer ramifications and penetrates even into the acini, larger or smaller groups of the latter are constricted off, and these then project from the surface, as well as from the face of cuts into the substance, in the form of coarse bosses or lobules [*"hob-nail liver"*], or of fine granules, thus constituting respectively the *lobular* and *granular* forms of cirrhosis. If the atrophy of the hepatic cells is more considerable, rows of epithelial tubules and bands are found in the newly-formed connective tissue (Fig. 129, *d*) similar to those seen in acute yellow atrophy, and having also a like origin and significance.

3. Infective Granulomata, New-formations, and Parasites.—*Tuber-*

culosis of the liver occurs most frequently as a part of general acute miliary tuberculosis, the tubercles developing for the most part in

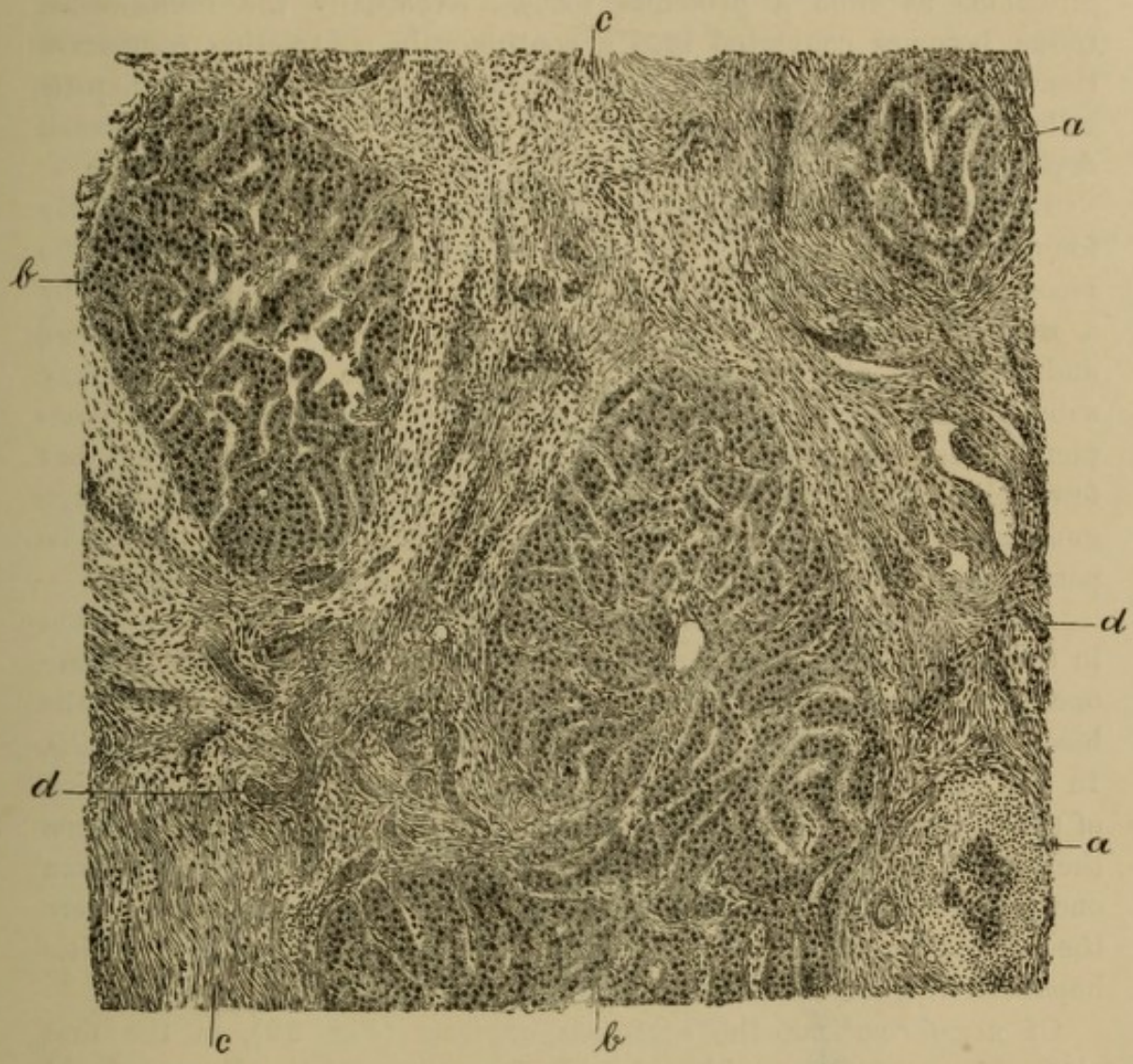

Fig. 129.—Cirrhosis of the Liver in the Stage of Atrophy. × 70. (Hæmatoxylin and eosin.) *a*, Small vestiges of atrophic acini; *b*, Constricted groups of acini undergoing atrophy; *c*, Greatly thickened capsule of Glisson, still partly infiltrated with round and spindle-shaped cells; *d*, Newly-formed bile-ducts.

the circumportal connective tissue, and but seldom in the interior of the acini also. It is sometimes further followed by a more or less extensive small-celled infiltration of the capsule of Glisson. When the tubercles develop in the vicinity of small bile-ducts, the epithelial cells of the latter may also take on growth and collect together in places into structures apparently composed of giant cells.

Syphilis in adults occurs in the liver rarely in the form of a hepatitis distributed evenly over the entire organ, and recalling the appearances of cirrhosis. Usually it takes a more focal form, in which case we find on one or more spots, widely separated from each other, an extensive small-celled infiltration involving not only the

capsule of Glisson, but also the connective tissue *within* the acini, the infiltration radiating out with diminishing intensity in various directions as from a principal focus. Eventually the round-celled tissue becomes converted into a continuously contracting connective tissue, poor in cells, which causes atrophy of the acini and hepatic cells which it encloses, and in this way produces deeply-retracted depressions of the surface of the organ.

Lying in the substance of the infiltration there are also frequently found nodes (gummata), the larger of which usually permit of the recognition of three strata, viz., a caseous centre, surrounded first by a zone of spindle cells (or, even already, of cicatricial tissue), and outside of all by a zone of round cells. The caseous centre may subsequently become absorbed, while the peripheral part is completely metamorphosed into firm connective tissue containing but few cells. It is not uncommon to find, in addition to the large gummata, other nodules which are quite small, in fact can only be perceived with the microscope, and consist of round cells solely.

Inherited syphilis may also give rise to the formation of gummata in the liver—nodules of some size as well as very numerous minute ones, which latter develop in the interstitial tissue surrounding the blood-vessels—but it much more frequently causes a *diffuse hepatitis*. In this case there occurs all over the organ a small-celled infiltration of the capsule of Glisson which also penetrates into the acini between the hepatic cells and capillaries, so that the latter are separated from one another by fairly broad lines of a highly cellular tissue. Here the liver is considerably enlarged, but there is also a form of syphilitic hepatitis which resembles atrophic cirrhosis.

Of *new-formations*, the *cavernous angioma* (Fig. 29), in the first place, is encountered with tolerable frequency in the livers of old persons. It is formed chiefly by dilatation of the capillaries of a circumscribed portion of the liver, with simultaneous atrophy of the hepatic cells. The septa of the angioma may be of varying degrees of thickness, and the spaces of different sizes. Obliteration of the cavities and cicatrisation may eventually take place, owing to a formation of thrombi which then become organised.

The *melanotic* is the most frequently observed of the *sarcomata*, but usually—perhaps always—as a metastatic tumour. Its cells may at first be round and non-pigmented, but later they become larger, flatter, and more like endothelial cells, and fill with pigment (Fig. 40). The tumour occurs either in the form of nodes or quite diffusely.

The *adenoma*, which is not uncommonly multiple, occurs in two forms: as adenoma of the *bile-ducts*, and as adenoma of the *hepatic*

cells. The former consists of tubes and of bands of cells, which in their configuration and in the form of their individual cells recall the appearance of bile-ducts, from the epithelium of which they have evidently originated. The liver-celled adenoma, on the other hand, more or less copies in its structure the acinous arrangement of the liver, its cells also corresponding for the most part with the hepatic cells, from which they may probably be derived. The adenoma differs from carcinoma above all in its sharp delimitation from the hepatic tissue, which may even find expression in the presence of a fibrous capsule.

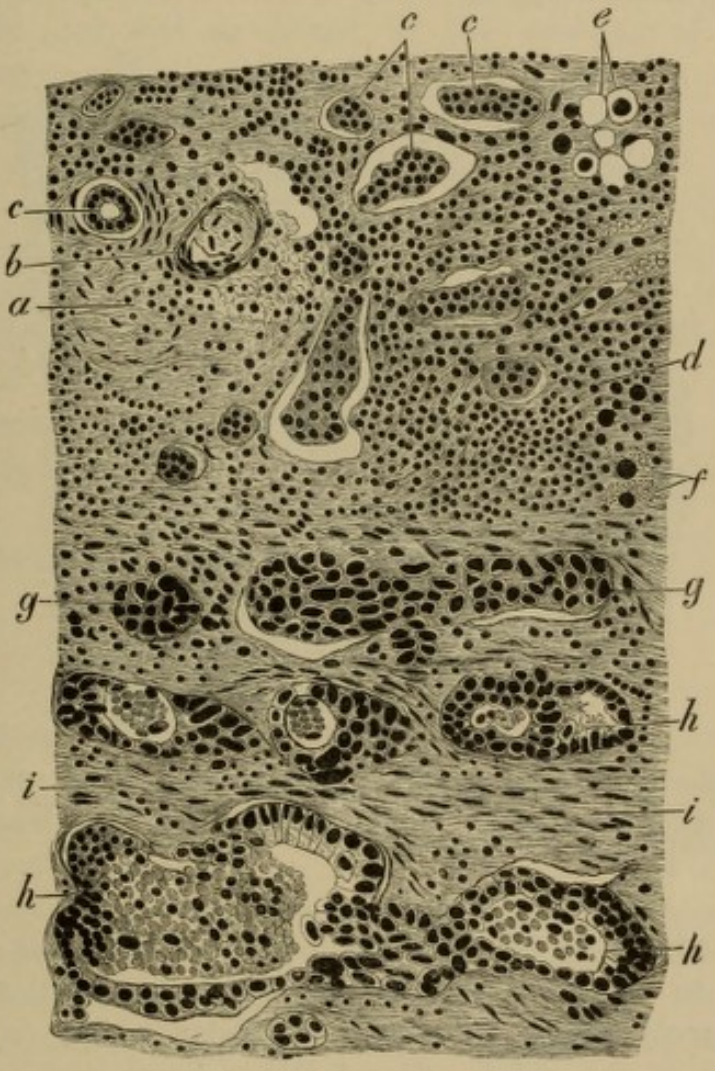

FIG. 130.—PRIMARY GLANDULAR CARCINOMA OF THE LIVER, originating in the bile-ducts. × 240. (Hæmatoxylin and eosin.) *a*, Capsule of Glisson; *b*, Portal vein; *c*, Bile-ducts, partly in proliferation; *d*, Small-celled infiltration of the hepatic connective tissue at the edge of the carcinoma; *e*, Hepatic cells with fat-drops; *f*, Atrophied and pigmented hepatic cells; *g*, Solid cylinders of cancer cells; *h*, Tubes of cancer cells, with partially cylindrical elements and lumen filled with desquamated and partly necrotic cancer cells; *i*, Connective-tissue stroma of the carcinoma, with spindle cells.

Cysts may form in the liver from the vasa aberrantia of the bile-ducts, owing to accumulation of the secretion derived from their

mucous glands. They are lined either with flat- or cylinder-celled epithelium, the latter either with or without cilia.

Carcinoma occurs both *primarily* and (much more frequently) *secondarily*. *Primary* carcinoma may start from the *epithelial cells of the bile-ducts*, or from the *hepatic cells*. In the former case alveoli are seen in the cancer (Fig. 130) which are usually elongated or cylindrical (*g* and *h*), and which not only recall the appearance of bile-ducts more or less by their form, especially when they show a central lumen (*h*), but whose cells may also resemble the cylindrical epithelium of the ducts.

Secondary carcinoma (Fig. 131) occurs most frequently in cases of

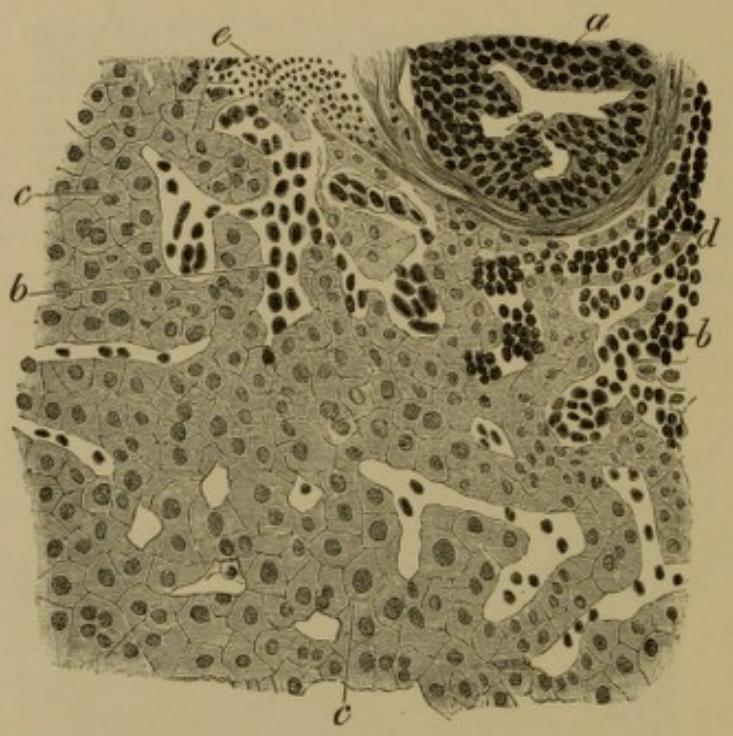

FIG. 131.—METASTATIC ADENO-CARCINOMA OF THE LIVER. × 285. (Hæmatoxylin and eosin.) *a*, Branch of portal vein, filled with cancer cells; *b*, Cancer cells in the capillaries of the liver; *c*, Bands of hepatic cells; *d*, Compressed bands of hepatic cells; *e*, Small-celled infiltration of Glisson's capsule.

cancer situated within the area drained by the radicles of the portal vein, owing to dissemination through the latter of the cancer cells, which ultimately lodge in the interlobular veins (*a*) or in the capillaries (*b*) of the acini. The further dissemination of the carcinoma then takes place by the interlobular veins first becoming distended with the proliferating cancer cells and thrombosed (*a*), the cells then breaking through their walls and displacing the hepatic tissue; or else the cancer cells first of all grow through the acini along the capillaries (*b*), and produce atrophy of the columns of hepatic cells (*d*) situated between the latter.

Of the *animal parasites* the *Echinococcus* is that most frequently

found in the liver, either in the form of simple cysts or parent and daughter cysts, or as a multilocular echinococcus. Besides this, however, *Distoma hepaticum*, *lanceolatum*, and *hæmatobium*, and *Coccidia*, may also be observed.

II. THE BILE-DUCTS.

4. Inflammation and New Growths.—The most frequent form of *inflammation* occurring in the bile-ducts and gall-bladder is the *catarrhal*, which is usually due to the advance of a gastro-duodenal catarrh into the ductus choledochus. If the orifice of the ductus choledochus is narrowed or closed by the swelling of the mucous membrane, the result is obstructive jaundice and in severe cases cholæmia, a condition in which the liver cells may undergo fatty degeneration and be destroyed just as in acute yellow atrophy.

Suppurative inflammation of the bile-ducts is due either to direct extension from the intestine or to the entrance of bacteria from the latter (*Bacterium coli*, pyococci). In the interior of the liver the suppurative inflammation usually extends to the adjoining hepatic tissue also, and then leads to the formation of abscesses. In *chronic catarrh* a gradual connective-tissue thickening of the wall of the bile-ducts takes place. *Gall-stones* cause the same changes, or lead to ulceration. Of *new-formations*, a *primary carcinoma* of the gall-bladder or common bile-duct is often observed.

III. THE PANCREAS.

5. Degeneration, Inflammation, and New Growths.—*Cloudy swelling* and *fatty degeneration*, which occur especially in infective diseases, show histologically the same features as in other organs. *Amyloid degeneration* is also observed.

Lastly, a peculiar species of *necrosis* (*fatty necrosis*) occurs in many cases from unknown causes in the interlobular adipose tissue. It is found in distinct foci, and begins in the fat-cells with a separation out of crystals of fatty acid, whilst the nuclei of the cells lose their capability of taking stain. The crystalline accumulations in the centres of the larger foci next assume a peculiar hyaline character, which is said to be due to formation of lime salts of the fatty acids. The necrotic nodes may eventually become loosened from their surroundings owing to a reactive inflammation.

Suppurative inflammation of the pancreas is certainly in the majority of cases due to the spread of an inflammation from the surrounding parts. It may be that here also, as in suppurative

inflammation of salivary glands, the causes of the process wander in (from the intestine) along the excretory duct, in which case the histological appearances will be like those in suppurative parotitis (p. 227). In the course of such inflammations *necrosis* of the pancreas may also take place, the cast-off portions being expelled through the intestine.

Chronic interstitial inflammation, which usually involves the head of the pancreas, most probably also occurs by extension in the majority of cases and is but seldom primary. The histological changes are analogous to those in cirrhosis of the liver.

Carcinoma is the most frequent of the *new growths*, and occurs as scirrhus in the head of the gland.

Examination of the Liver, Bile-Ducts, and Pancreas.—*Cloudy swelling*, *fatty degeneration*, and *fatty infiltration*, as well as to a certain extent *amyloid degeneration* and *pigmentary deposit*, may be examined in *fresh* preparations, observing the rules given on pp. 52-3, 57-8, and 60. The methods for studying the above changes in *hardened* preparations will also be found in the places mentioned, and on p. 58 the modes of examining *glycogen degeneration*. In general, Müller's fluid and alcohol are mostly used for hardening, and hæmatoxylin and eosin for staining; and in leucæmic infiltration of the liver Heidenhain's method may be tried if desired (p. 190). For the methods of examining for *vegetable and animal parasites* see Part II., Chapters V. and VI.

CHAPTER VI.

THE RESPIRATORY APPARATUS.

I. THE NOSE AND ITS ACCESSORY CAVITIES.

1. Diseases of the Nose.—*Acute catarrh* (*coryza*) sometimes occurs *primarily*, and is then probably due in most cases to micro-organisms, acting concurrently with certain predisposing influences. It may also be *secondary*, forming part of the symptoms of infective diseases. The secretion is at first serous, later muco-purulent, and in the latter case it contains, embedded in mucin, a larger or smaller number of epithelial cells undergoing mucous transformation, and of pus corpuscles. In the epithelium covering the mucous membrane are found many goblet cells, and between these also leucocytes; and the membrane itself shows a more or less intense cellular infiltration.

In *chronic catarrh* not only is this infiltration tolerably general, and particularly strongly marked over the inferior turbinated bone, but when the process lasts longer there not uncommonly results also a *hyperplasia* of the mucous membrane, which either affects the membrane equally or takes the form of polypoid growths (*nasal polypi*). The latter (Figs. 55 and 56) have in general a structure like that of the mucous membrane itself, and are also clothed with a similar epithelium, which consequently, in polypi of the anterior portions of the nasal cavity, shows the gradual transition from ciliated columnar to stratified squamous epithelium. The tissue of the polypi may be sometimes very rich in small round cells, either more evenly distributed or accumulated at circumscribed localities (Fig. 56, *e*), while at other times again it has the character of œdematous connective tissue or of mucous tissue (*mucous polypus*, Fig. 55); or it is very rich in glands (*glandular polypus*), which may also undergo cystic degeneration; or it contains numerous wide and thin-walled blood-vessels, so as to approximate to a cavernous tissue like that on the posterior extremity of the inferior turbinated

bone (*teleangiectatic polypus*). In the latter form hæmorrhages and accumulations of pigment (Fig. 55, *d*) may readily occur in the tissue of the polypus. In many cases the surface of the growths shows numerous indentations of varying depth, and they then approximate in appearance to papillomata.

Chronic catarrh may also, however, lead to an *atrophy* of the mucous membrane and even of the osseous framework of the turbinated bones. In such cases a foul-smelling decomposition is frequently observed (*ozæna*), due to the action of certain saprophytic bacteria on the nasal secretion, which is altered in consequence of the disappearance of Bowman's glands. It has already been mentioned that the mucous membrane of the nasal cavity may be affected in *diphtheria* in the same manner as that of the pharynx (p. 225). So also in *variola* efflorescences may occur here similar to those in the buccal cavity and pharynx (p. 224).

The *perforating ulcer* observed on the anterior portions of the nasal septum, and most frequently, as it would appear, in tuberculous individuals, is the result of a circumscribed coagulation necrosis which first affects the epithelium and most superficial parts of the mucous membrane, but (together with the reactive inflammation consequent on it) may subsequently penetrate gradually deeper until it reaches the cartilage, and, either alone or with the concurrence of a similar process in the mucous membrane of the opposite side, may lead to *perforation*. The disintegration of the cartilage does not begin merely at the moment when the actual coagulation necrosis has reached it, but earlier than this, *i.e.*, when the perichondrium, extensively infiltrated with small cells in consequence of the reactive inflammation, and softened, becomes loosened from it. As large numbers of cocci in chains and clusters (in addition to small numbers of other bacteria) can be found constantly in the necrotic parts as the process advances, and are present in greatest abundance in the portions quite recently attacked, the cause of the necrosis may lie in a lodgment of the *Streptococcus* or *Staphylococcus pyogenes*, which is probably favoured by previous lesions of the mucous membrane, hæmorrhages, etc. The ulcer seems capable of healing at any stage, by complete separation of the necrosed masses and filling up of the deficiency with granulation and cicatricial tissue.

In *tuberculosis* of the nasal mucous membrane there form in the latter caseating and, later, ulcerating nodes of the well-known histological structure. The process may also extend to the bones and be associated with a foul-smelling discharge (*tubercular ozæna*).

Syphilis gives rise either to papules or still more frequently to gummata, which may cause ulcerative destruction of the mucous

membrane, cartilage, and bone, and may also be accompanied with production of a foul-smelling secretion which forms crusts (*syphilitic ozæna*).

In *glanders* nodules develop with tolerable frequency in the mucous membrane and submucosa, which have the same constitution as in other localities, and also speedily suppurate and lead to the formation of ulcers (see pp. 141-142).

Regarding *rhinoscleroma*, see pp. 152 and 153.

Vegetable micro-organisms, especially bacteria of the most widely dissimilar species and forms, occur just as constantly in the nasal as in the buccal cavity, and the same species of pathogenic bacteria may also be met with even under normal circumstances in the nose as in the mouth (p. 231).

2. Diseases of the Nasal Air-Sinuses.—The *inflammatory processes* occurring in these are similar to those in the nasal cavity, except that here a still more abundant accumulation of exudation or secretion may take place in the cavities, and the inflammations, even when originally situated in the mucous membrane, in many cases speedily involve the lining of the cavities in its entire thickness, thereby approximating in character to phlegmonous inflammation. The secretion from the inflamed mucous membrane is either serous, in which case an evenly-distributed, or still more frequently a circumscribed and then tolerably bulky, serous exudation also exists in the membrane; or it may be more mucous or purulent.

Should the inflammation assume a distinctly *phlegmonous* character (Fig. 132), the lining membrane will not be equally infiltrated, but the exudation—which may be fibrinous or fibrino-purulent, and is sometimes also hæmorrhagic—gathers in particular abundance at circumscribed spots (*a*), which then project in the form of flat bosses above the level of the remaining mucous membrane. The epithelium over these prominences may be lost, whereas between them it is usually retained (*c*).

Acute inflammatory processes affecting the accessory cavities are, at least as a rule, propagated from the nose; but they may attain a higher degree of intensity than in the latter, and may become to a certain extent independent. Phlegmon of these cavities in its pronounced form also occurs primarily. Besides these, inflammations arise in the course of different infective diseases, and with especial frequency in pneumonia and influenza. In the former the *Diplococcus pneumoniæ* is then found in the secretion and tissue of the sinuses, and in the latter the *Streptococcus* or *Staphylococcus pyogenes*, alone or in company with the diplococcus. Sometimes inflammatory processes in the nasal air-sinuses also extend to the

meninges and brain, notably when situated in the frontal sinus or ethmoidal labyrinth.

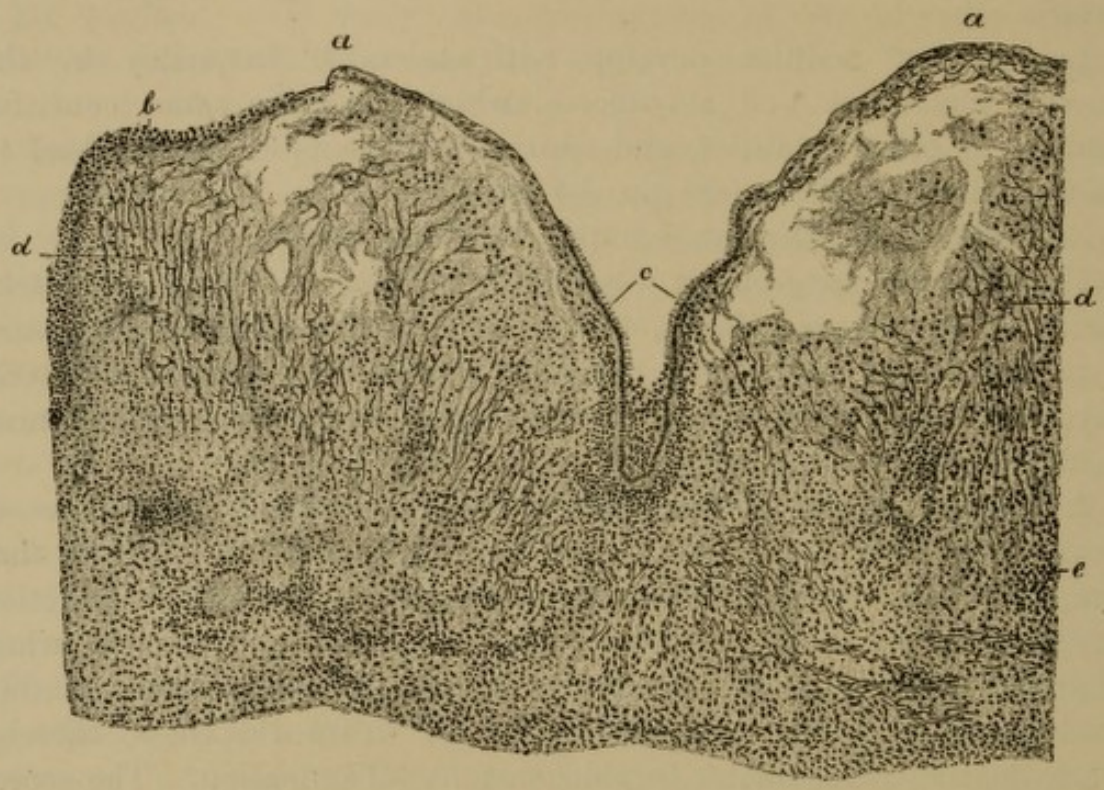

FIG. 132.—PHLEGMON OF THE ANTRUM OF HIGHMORE. × 70. (Hæmatoxylin and eosin.) *a*, Circumscribed protuberances of the mucous membrane, due to deposit of exudation; *b*, Pus-corpuscles on the surface of the mucous membrane; *c*, Epithelial covering of the fissure between the protuberances; *d*, Sero-fibrinous exudation; *e*, Small-celled infiltration of the deeper parts of the mucous membrane.

In *diphtheria*, *glanders*, and *variola*, the same changes may be found in the accessory cavities as occur in the nose itself.

II. THE LARYNX AND TRACHEA.

3. Inflammatory and Necrotic Processes.—The changes in *acute catarrh* are similar to those in catarrh of the nasal cavity. When the inflammation is more protracted, not only does the desquamation of epithelium increase, especially in places which either are normally covered with squamous epithelium or whose epithelium has become converted into this variety in the course of the catarrh, but a hyperplasia of the epithelium and cornification of its superficial layers (*pachydermia laryngis*) also sometimes takes place in these localities, notably on the vocal chords and anterior surface of the inter-arytenoid fold. The connective tissue of the mucous membrane may also become thickened and may even grow out into papillary excrescences. On the other hand, the mucosa may acquire a granular structure owing to enlargement or dilatation of the mucous glands (*granular laryngitis*). Lastly, should the process persist for very long, the mucous membrane may also become *atrophied*.

When *diphtheria* spreads to the larynx and trachea the changes which occur in these situations are analogous to those in the pharynx, except that the false membranes are usually of the so-called croupous character.

Phlegmon occurs in the larynx both primarily and secondarily (by propagation from the neighbouring parts), the excitants being most probably as a rule the pyococci. If the exudation is serous, and accumulates in the ary-epiglottic ligaments and false vocal chords, we speak of it as *acute œdema of the glottis*, the *chronic œdema* being due to a serous transudation consequent on venous congestion. Should the phlegmonous inflammation reach the perichondrium of the laryngeal cartilages (*perichondritis*), the result may be either total detachment of the former from accumulation of pus beneath it, leading to necrosis and speedy expulsion of the cartilage, otherwise little altered; or the latter itself undergoes purulent liquefaction, the spaces in the cartilage becoming gradually distended by the penetrating pus cells, until they finally coalesce.

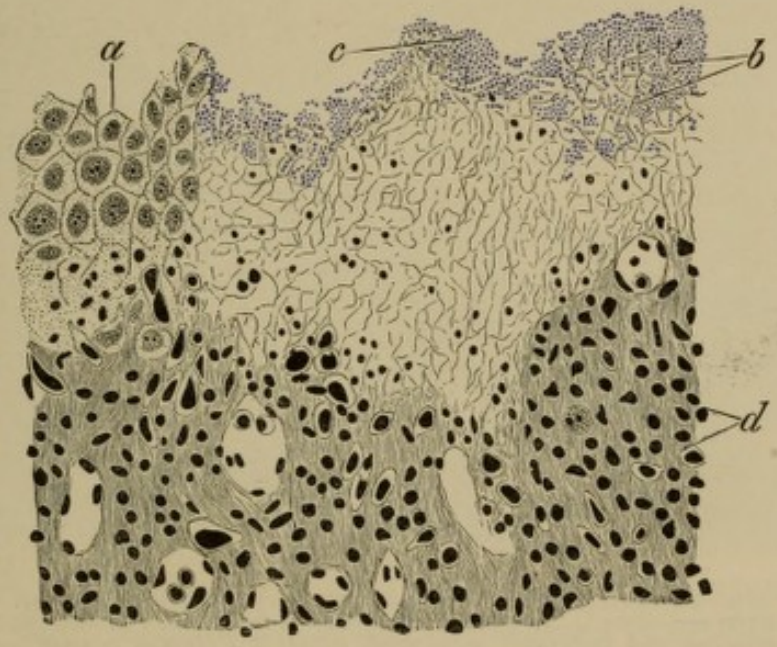

FIG. 133.—MYCOTIC ULCER OF THE LARYNX IN TYPHOID FEVER. × 545. (Weigert's modification of Gram's method.) *a*, Normal epithelium; *b*, Necrotic epithelium (coagulation necrosis); *c*, Cocci; *d*, Small-celled infiltration of mucotheus membrane.

In *typhoid fever* shallow ulcers covered with a delicate, firmly adherent coating occur with tolerable frequency on the margins of the epiglottis, the posterior wall of the larynx, and the processus vocales. The epithelium on these places, and even the most superficial layers of the mucous membrane, are then found to be changed into a mass in which no nuclei can be seen, and which is sometimes distinctly reticulated (coagulation necrosis) and encloses in its sub-

stance clusters of cocci (usually *Staphylococcus pyogenes aureus*), whilst the underlying portion of mucous membrane is in a state of small-celled infiltration (Fig. 133). Whether *true* typhoid ulcers (*i.e.*, ulcers caused by typhoid bacilli) also occur is somewhat doubtful.

Regarding the efflorescences which sometimes form also in the larynx in *variola*, see p. 224.

4. Infective Granulomata and New-formations.—*Tuberculosis* of the larynx and trachea, which usually occurs in the course of pulmonary tuberculosis in consequence of penetration of tubercle bacilli into the mucous membrane from the sputum, is localised most frequently on the processus vocales and vocal chords in the larynx, and in the trachea on the posterior wall in the neighbourhood of the ducts of mucous glands. There first form beneath the epithelium either

FIG. 134.—ULCERATING GUMMA OF THE TRACHEAL MUCOUS MEMBRANE. × 77. (Hæmatoxylin and eosin.) *A*, Mucous membrane of the trachea covered with cylindrical epithelium and infiltrated with small cells; *B*, Ulcerated gumma; *a*, Giant cell; *b*, Caseous and necrotic masses of the gumma.

small-celled foci and giant-celled tubercles, or else more diffuse cellular infiltrations (granulation tissue), which caseate and ulcerate. Later it is not uncommon also to meet with round- or epithelioid-celled tubercles lying scattered in the submucosa or in still deeper strata.

Leprosy causes affections in the laryngeal mucous membrane similar to those which are found in the skin; *glanders* and *rhinoscleroma* changes analogous to those in the nasal cavity.

In *syphilis* there form either erosions of the mucous membrane or

gummata. The latter usually develop in the submucosa, and may either subside again or protrude the mucous membrane continually more and more as their growth advances, until, the centre of the gumma having first undergone caseation, the membrane also falls victim to necrosis (Fig. 134). In this manner ulcers are formed which extend to variable depths and are followed later by cicatrisation and narrowing of the laryngeal or tracheal lumen.

The most frequent *new-formations* are *papillomata*, which develop in inflammatory conditions, but also apart from such, and are commonly situated on the true vocal chords. They consist as elsewhere of branched or less often simple papillæ, rich in blood-vessels and in cells, and covered with a thick stratified squamous epithelium. *Enchondromata* and *osteomata* are also observed.

Carcinoma may occur primarily in the larynx, and is then a flat-celled epithelioma.[1]

III. THE BRONCHI.

5. Inflammation.—In *acute catarrh* the character of the secretion and the alterations in the mucous membrane are in general identical with those in the same class of inflammation affecting the upper part of the air-passages. When the catarrh persists longer the process spreads to the ducts of the mucous glands also, which then become distended with desquamated epithelial cells in a state of mucous degeneration, as well as with leucocytes.

In *chronic catarrh* the cellular infiltration of the mucosa shows a tendency to pass deeper, and hence when the inflammation is protracted the exterior strata of the bronchial wall and even the peribronchial connective tissue are also found to be infiltrated with cells. The proliferative processes in the mucous membrane may lead to the formation of ridged or papilliform elevations of the surface (Fig. 135, *a*), and even the muscular bundles of the bronchi may take part in the hypertrophy. Later, however, when the glands, muscle, and even cartilage are destroyed by the pressure of the cellular infiltration, and the bronchial wall is thus rendered very yielding, dilatations of the bronchi may result which are known as *bronchiectases* (p. 272). When the bronchial secretion stagnates, a putrid decomposition is sometimes set up in it by the action of putrefactive bacteria (*putrid bronchitis*).

[1] In rare cases the tissue of the *thyroid gland* may force its way into the larynx and trachea in consequence of adhesion of the gland to these organs. It enters the lateral wall between the cartilages, and then forms small nodes underneath the mucous membrane.

Croupous inflammation may be caused either by descent of the same process from the trachea, or by extension of the croupous exudation in a pneumonic lung to the smaller bronchi. There is also a *chronic* form of bronchial croup in which tubular croupous membranes are formed extending throughout the whole of the bronchial system or the greater part of it, and hence showing a branching arborescent figure (*plastic bronchitis*).

Peribronchitis.—As has already been partially explained, when a bronchitis is of longer duration the cellular infiltration and the new-formation of connective tissue arising from it may not only involve the entire thickness of the bronchial wall, but may also spread to the peribronchial connective tissue (Fig. 135, *e*) and adjoining

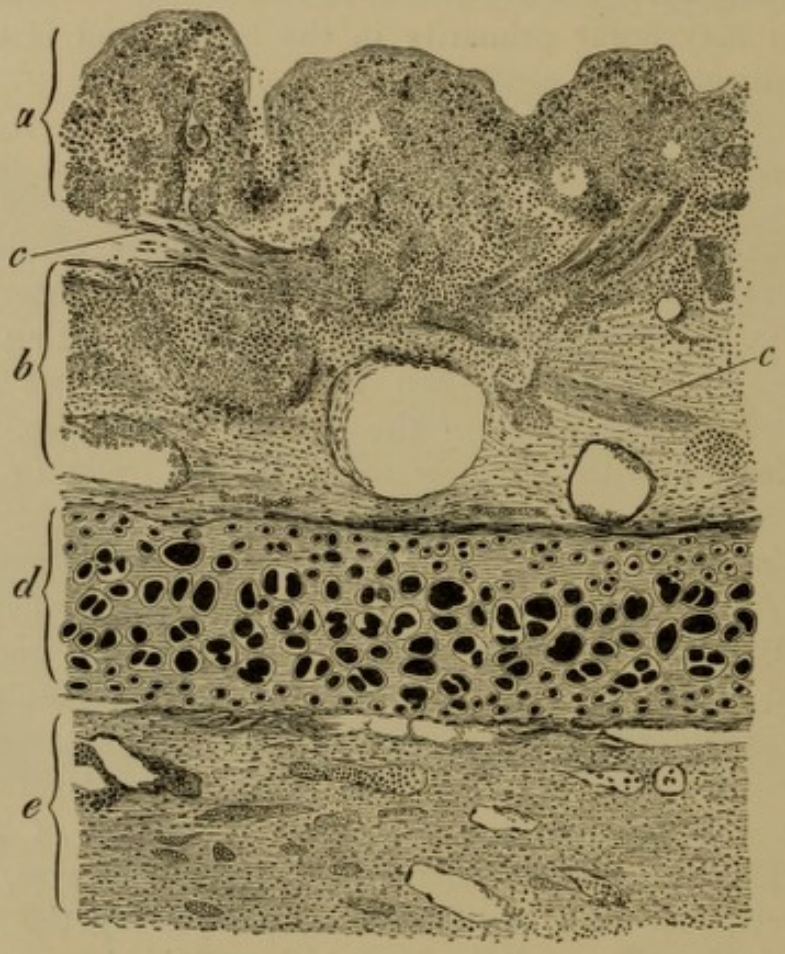

FIG. 135.—INDURATIVE PERIBRONCHITIS, WITH BRONCHIECTASIS. × 80. (Hæmatoxylin and eosin.) *a*, Mucous membrane of a dilated bronchial twig, swollen in ridges, vascular, and infiltrated with extravasations; *b*, Submucosa vascular, and infiltrated with cells; *c*, Bundles of smooth muscular fibres; *d*, Cartilage of the bronchus; *e*, Peribronchial connective tissue, infiltrated with round and spindle-shaped cells.

parenchyma of the lung. *Vice versa*, inflammatory processes may pass from the alveoli, or from the pleura and interlobular connective tissue, to the peribronchial tissue, alike whether they are of a purulent, indurative, or tubercular nature.

6. Bronchiectasis and Tuberculosis.—*Bronchiectasis* may occur after

long-protracted bronchitis, when, as observed above, the powers of resistance of the bronchial wall have become reduced in consequence of the inflammation; or it may also be due to retraction of the newly-formed connective tissue in a peribronchitis, or to accumulation of secretion in the bronchi. The mucous membrane of the dilated bronchus may appear more or less atrophied, as may also the cartilage (which may be partially replaced by connective tissue); or, on the contrary, not only the mucous membrane (Fig. 135, *a*) but the submucosa (*b*) and peribronchial connective tissue (*c*) are thickened owing to cellular infiltration and great dilatation of the blood-vessels, and sometimes papillary growths may even be present on the mucous membrane (*a*). The epithelium may remain perfectly intact, or low cubical cells may now alone be visible instead of the columnar ciliated elements.

A *gangrenous inflammation* of the bronchial wall and surrounding tissue of the lung is not uncommon in bronchiectases as a result of putrid decomposition of the stagnating secretion.

There is also a *congenital cystic* form of bronchiectasis which occurs in consequence of faulty development of the proper pulmonary tissue. The malformed portion of lung may finally be composed of *cysts* of different sizes lined with ciliated epithelium, the fibrous wall of which may still include islets of cartilage, whilst between the cysts lies a non-pigmented but sometimes very vascular connective tissue. Such bronchiectases may also, of course, be attacked by inflammation.

In *tuberculosis* of the bronchi the same products are formed as in the larynx and trachea, except that caseation of the secretion plugging the bronchioles may also result.

IV. THE LUNGS.

7. Emphysema, Hæmorrhagic Infarction, Fat-Embolism, Œdema, and Brown Induration.—*Emphysema.*—*Acute vesicular* emphysema merely consists in an abnormal distention of the alveoli and alveolar passages, whereas in *chronic* or *substantial* emphysema (Fig 136) an atrophy of the alveolar septa (*c*) is superadded, which again may be favoured by disturbances of nutrition or congenital weakness of the septa. The atrophy commences with an enlargement of the spaces between the capillaries, by which the elastic fibres of the septa are separated from one another and gradually destroyed, while the capillaries as well as the small arteries and veins become obliterated. Apertures then appear at the thinnest parts of the septa and gradually enlarge, thus causing coalescence of the alveoli and alveolar passages to form

cavities (*b*) which become progressively larger. The epithelium of the alveoli frequently shows fatty degeneration, whilst the muscular bundles at their entrance may even become hypertrophied

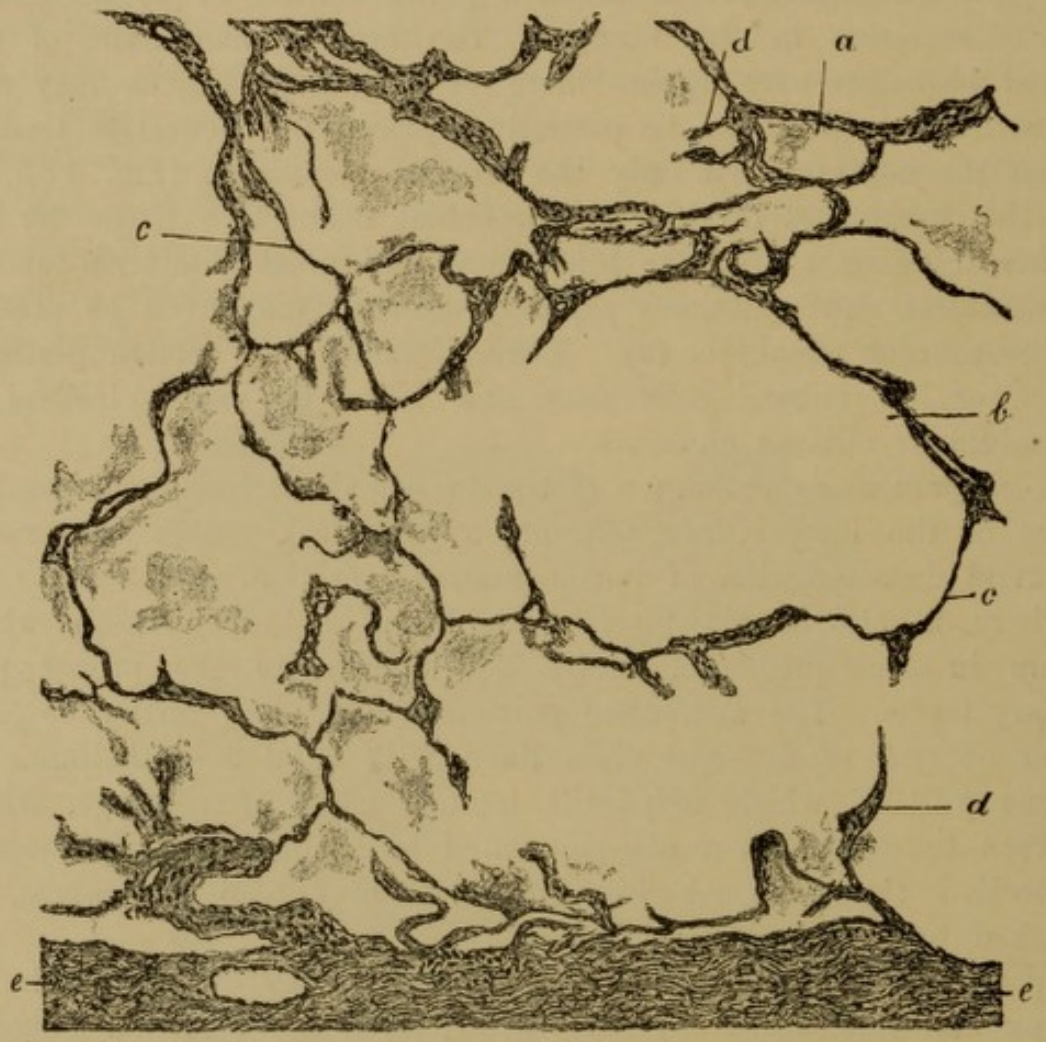

FIG. 136.—CHRONIC EMPHYSEMA OF THE LUNG. × 77. (Hæmatoxylin and eosin.) *a*, Slightly dilated alveolus; *b*, Cavity formed by coalescence of several alveoli; the alveoli partially filled with serum; *c*, Thinned alveolar septa; *d*, Vestiges of ruptured septa.

(compensatory hypertrophy). The emphysema which is due to old age is known as *senile emphysema*.

In *hæmorrhagic infarction*, which occurs after embolism or thrombosis of pulmonary arteries, or from the formation of hyaline thrombi in the capillaries, the alveoli (Fig. 110, *a*) and bronchioles are found evenly filled with red corpuscles, with which are mixed usually only a few leucocytes and filaments of fibrin, whilst the septa of the alveoli are sometimes also found to be ruptured, so that the latter unite to form large cavities full of blood. The further changes are the same as in hæmorrhagic infarctions in other organs (see pp. 211-212). Should the embolus contain pyococci or putrefactive bacteria, or should the latter find their way into the infarction with the inspired air, the results will be respectively

suppuration (Fig. 110) and gangrene of the infarction. (See also *Metastatic Pneumonia*, p. 281.)

Fat-embolism of the lungs, which may take place after destruction of adipose tissue, especially of the fatty marrow of bones (*e.g.* in fractures), but also in diabetic lipæmia (p. 188), consists in accumulation of fat in the capillaries, transitional vessels, and small arteries. In the larger vessels the fat usually appears in the form of drops, whilst in the capillaries it is apt in most cases to run together into band-shaped or retiform masses.

Œdema of the lungs either is the result of venous congestion, or constitutes the first stage of an inflammation. In both cases the alveoli and bronchioles contain a serous fluid which appears in

FIG. 137.—BROWN INDURATION OF LUNG. × 240. (Hæmatoxylin and eosin.) *a*, Thickened interlobular connective tissue, vascularised, and infiltrated with cells; *b*, Brown pigment, partly free and partly in the interior of connective-tissue cells; *c*, Alveolus filled with extravasated red corpuscles; *d*, Alveoli with shed epithelial cells (*e*), and isolated red corpuscles (*f*); *g*, Larger epithelial (or perhaps wandering) cells with brown pigment granules; *h*, Coagulated serum; *i*, Much-convoluted hyperæmic capillaries in the walls of the alveoli.

hardened preparations in the form of a more or less distinctly fine-granulated mass (Fig. 140, *b*), and which in *congestive* œdema en-

closes partly-swollen shed epithelial cells, and sometimes red corpuscles, but in *inflammatory* œdema also contains leucocytes in variable number (Fig. 139, *c*). When the œdema persists for some time the epithelial cells and leucocytes undergo fatty degeneration.

Brown induration (Fig. 137) develops in venous congestion of the pulmonary circulation, especially in insufficiency of the mitral valves. The first change here is dilatation and lengthening of the capillaries (*i*), which project into the alveoli much further than before, and narrow them. The interlobular vessels are also found dilated. This is followed on the one hand by a moderate degree of cellular infiltration and hyperplasia of the interlobular connective tissue (*a*) and of the muscular bundles wound round the alveolar passages; on the other hand by hæmorrhages into the alveoli (*c*). The effused blood is taken up by wandering cells (and desquamated epithelial cells?), which become pigmented cells (Plate I., Fig. 1, *c*) owing to change of the hæmoglobin into yellow or brown granules. These cells are then found partly in the interior of the alveoli (along with desquamated non-pigmented epithelial cells) as round elements (*g*), tolerably large in the main, which also appear in the sputum and are known in German as "*Herzfehlerzellen*" (heart-failure cells). They also occur partly in the form of stellate and spindle-shaped cells in the peribronchial and perivascular connective tissue; but here free pigment may also be met with (*b*).

8. Inflammation.—The *acute inflammations* of the lungs are primarily divided into *lobar or croupous pneumonia*, *lobular or broncho-pneumonia*, *metastatic or embolic pneumonia*, and *interlobular or pleurogenous pneumonia*.

Lobar or croupous pneumonia, also known as *true* pneumonia, is in the great majority of cases caused by the *Diplococcus pneumoniæ*, and only in a few instances by the *Bacillus pneumoniæ* or *Streptococcus pyogenes*, or by a combination of two of the bacteria named.[1] Even the lobar pneumonia which occurs in the course of other diseases, notably those of infective origin, may be due to the *Diplococcus pneumoniæ*, or to such bacteria (*Streptococcus* or *Staphylococcus pyogenes*, and perhaps also *Bacillus typhosus*) as are already present in some other organ in the particular disease. The latter bacteria then exist in the pneumonic lung either alone or along with the *Diplococcus pneumoniæ*.

The form of pneumonia caused by the sole action of the *Diplococcus pneumoniæ* has a tendency to spread rapidly over considerable sections of the lungs, but may sometimes also take a more focal form, especially when occurring in the course of other infective

[1] Other bacteria also may possibly play a causative part in some cases.

diseases. The latter mode of appearance is especially characteristic of pulmonary inflammations caused by the *Streptococcus* or *Staphylococcus pyogenes*.

In all these pneumonias we find in the alveoli, alveolar passages, and bronchioles, an exudation of somewhat variable composition. At the commencement it is merely serous, *i.e.*, in sections of hardened preparations a finely granular mass is found with which are mingled isolated leucocytes, as well as desquamated epithelial cells, either large and squamous or small, and not uncommonly containing fat-droplets. The capillaries in the walls of the alveoli are also turgid with blood at this stage. Later (Fig. 138), not only do the leuco-

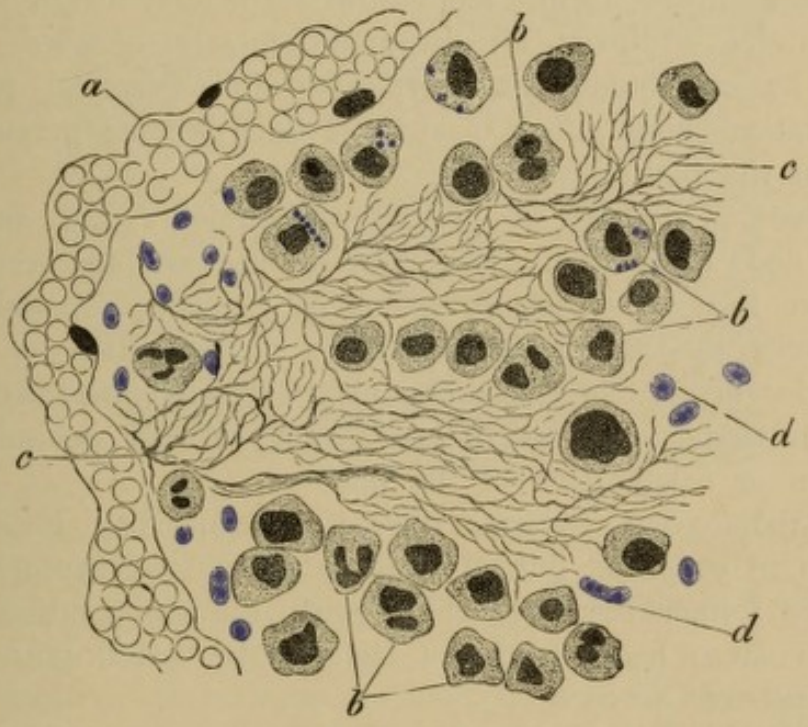

Fig. 138.—Croupous Pneumonia in the stage of Red Hepatisation. Portion of a pulmonary alveolus. × 975. (Weigert's modification of Gram's method.) *a*, Capillary of the alveolar wall, filled with blood; *b*, Mononuclear and polynuclear leucocytes, some of them containing pneumococci; *c*, Fibrinous network; *d*, Round and elongated pneumococci, with capsules.

cytes (*b*) in the exudation increase in numbers, but besides red corpuscles there appear more or less abundant fibrin-filaments (*c*), delicate and difficult to recognise, or thick and with sharp outlines; and this is especially the case in pulmonary inflammations due to the *Diplococcus pneumoniæ*, whereas in pneumonia excited by the *Streptococcus* or *Staphylococcus pyogenes* the exudation is much less rich in fibrin. The red corpuscles in the exudation and the hyperæmic condition of the capillaries (*a*) give the inflamed pulmonary tissue its red colour, whilst the granular appearance of the cut surface of the lung is due to the richness of the exudation in fibrin (*red or brown hepatisation*). An exudation similar to that in the alveoli is

also found in the lymphatics of the lungs, and further, the fibrinous mass which forms in the bronchioles may sometimes advance into the nearest branches of the bronchi, though the latter are not usually completely blocked by the exudation. The still larger bronchial ramifications show as a rule the appearances of an acute catarrh.

In the next stage the emigration of white corpuscles is still further increased, these now infiltrating the septa also and compressing their blood-vessels, whilst the red corpuscles in the exudation become decolorised and the fibrin ceases to be prominent (*grey hepatisation*). Here the acme of the process is reached, and fatty degeneration of the leucocytes (formation of granule corpuscles) and solution of the fibrin then follow. The detritus of the exudation is under ordinary circumstances mostly *absorbed* by being taken up by emigrated white corpuscles and conveyed partly into the lymphatics, should these meanwhile have become pervious again, partly into the blood-vessels.

Less common results of croupous pneumonia are *suppuration*, *gangrene*, and *induration*. *Suppuration* appears to occur chiefly when there is a secondary lodgment of pyococci, especially of the *Staphylococcus pyogenes*, and then leads to formation of abscesses which under favourable conditions may become encapsuled off with granulation tissue and heal, either leaving a scar behind, or after inspissation or calcification of the pus.

The *Staphylococcus pyogenes aureus* or *albus* has hitherto been found also in *gangrene*, but in addition to various saprophytic bacteria. The former seem (probably with the co-operation of other factors) to cause necrosis of the tissue; the latter, putrefaction of the dead masses.

When the issue is *induration* (*carnification*, Fig. 139), not only does the cellular infiltration of the septa (*d*), as well as of the perivascular and peribronchial connective tissue increase, but a granulation tissue develops on the wall of the alveoli, also owing to growth of the fixed cells and blood-vessels, and this permeates the plugs of exudation, gradually fills up the lumen of the alveoli, and then, together with the perivascular and peribronchial infiltrations, changes by the formation of fibroblasts into a connective tissue which becomes continually firmer and is for the most part pigmented (*cirrhosis*). The new connective tissue in the alveoli is frequently developed only from a portion of the alveolar wall, and then pushes itself more and more into the alveolus (*b*) in the form of a polypoid protuberance. Owing to shrinkage of the connective tissue developed around the bronchi, with simultaneous adhesion of the lung, bronchiectases may result. The same effect may also be produced should

the connective-tissue hyperplasia which occurs during the healing of a pleurisy extend to the interlobular and peribronchial connective tissue of the lung.

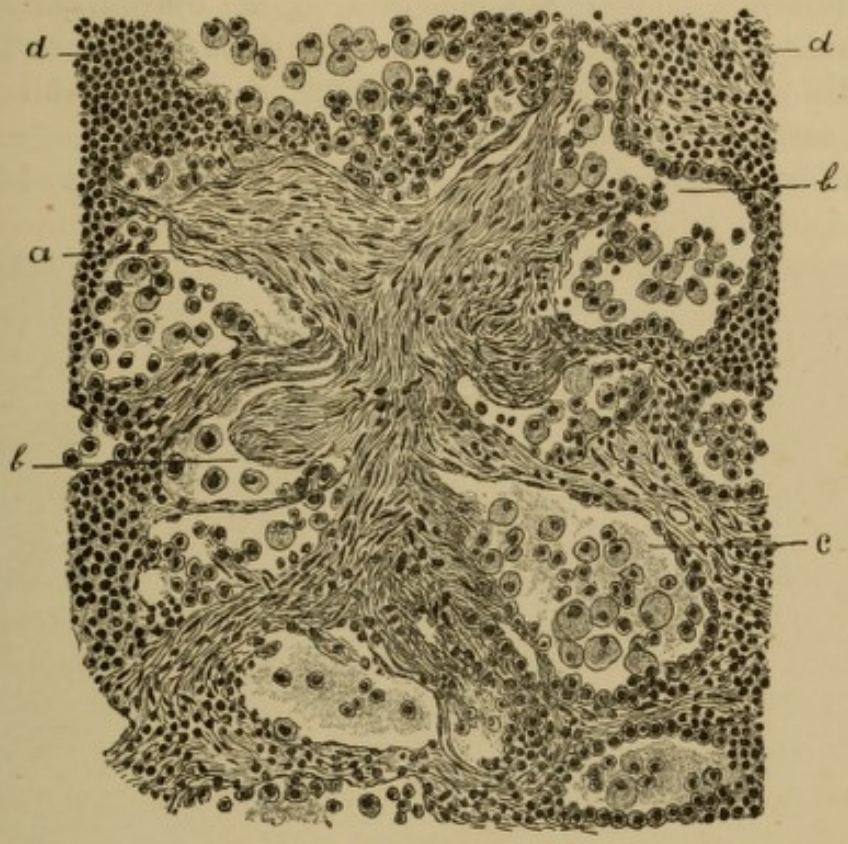

FIG. 139.—COMMENCING INDURATION OF THE LUNG IN PNEUMONIA OF TWENTY DAYS STANDING. × 285. (Alum cochineal.) *a*, Newly formed connective tissue; *b*, Alveoli into which the newly formed connective tissue is growing in polypoid form; *c*, Exudation in the alveoli consisting of leucocytes, desquamated epithelial cells, and serum; *d*, Alveolar septa infiltrated with small cells.

The *Diplococcus pneumoniæ* is found in greatest abundance in those parts of the lung in which the disease is still most recent, and hence especially in the œdematous portions bordering on the area of hepatisation, where it also frequently shows an easily-stained capsule (Fig. 138, *d*); whereas in the actual area of hepatisation, especially the grey, it may be completely or for the most part dead. It is furthermore found in the exudation of those processes which are apt to complicate pneumonia, such as pleurisy, pericarditis, endocarditis, peritonitis, and so forth.

Not uncommonly there also occurs in pneumonia an acute serous infiltration of the mediastinum, of the connective tissue in the neck and thorax, or of the submucous coat of the pharynx; or there may be an acute inflammation of the nasal air-sinuses, the tympanic cavity, the meninges, the kidneys, or the joints; and abscesses may even form in different localities. The *Diplococcus pneumoniæ* is then found also in the products of these inflammations. Lastly, in

pneumonia it may be further recognised at times in the blood and spleen, the latter being often in a state of acute enlargement.

Should the *Bacillus pneumoniæ* be present, it is usually found in great abundance, and the same is true of the *Streptococcus* and *Staphylococcus pyogenes;* and inasmuch as these varieties of bacteria do not die so quickly as the diplococcus, their successful detection is much easier.

Acute lobular pneumonia or broncho-pneumonia (Fig. 140) often

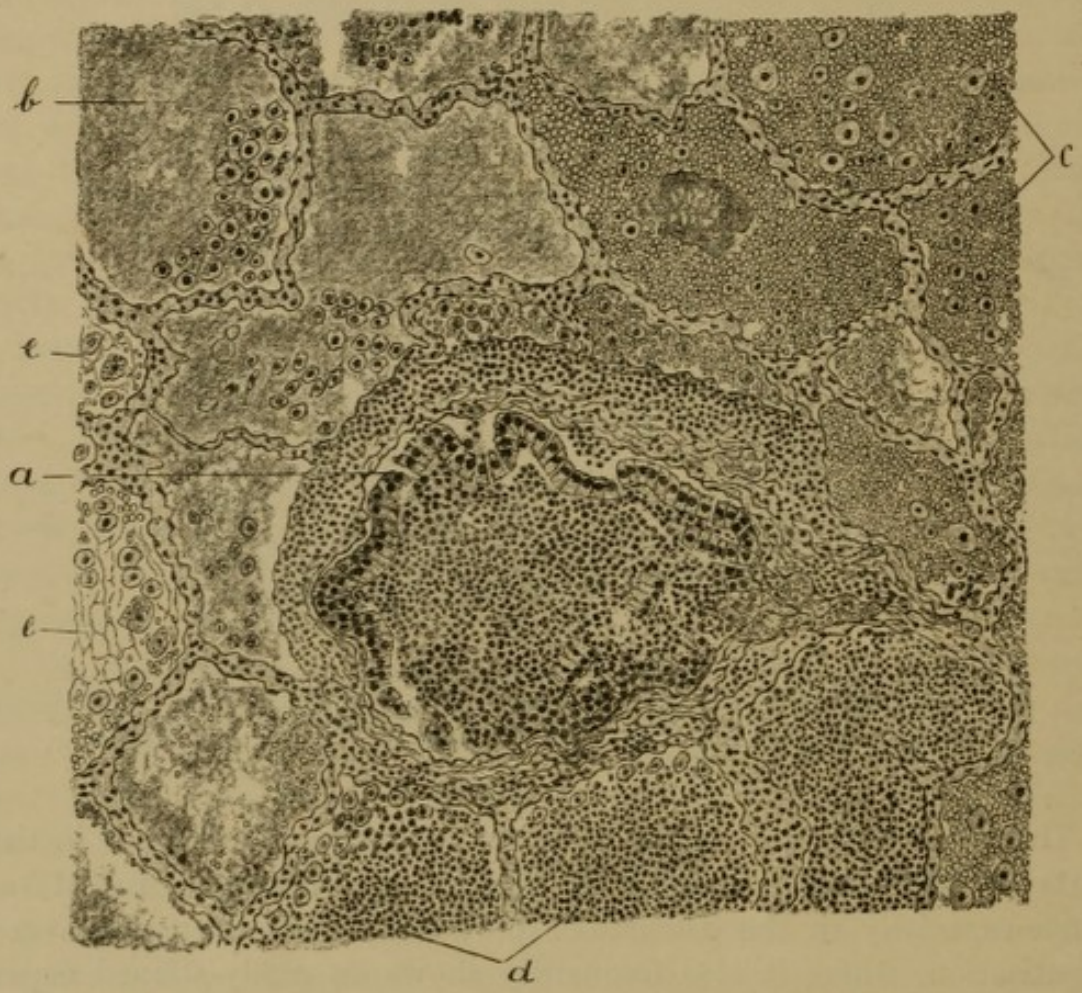

Fig. 140.—Acute Lobular Pneumonia. × 200. (Alum cochineal.) *a*, Small bronchus filled with pus; *b*, Alveoli containing serum and desquamated epithelial cells; *c*, Alveoli containing blood and desquamated epithelial cells; *d*, Alveoli filled with pus corpuscles and desquamated epithelial cells; *e*, Alveoli containing red corpuscles, cast-off epithelial cells, some of which contain pigment, and a scanty amount of fibrin.

forms the termination of an acute bronchitis or bronchiolitis, especially in certain diseases of infective origin, such as the acute exanthemata, diphtheria, typhoid fever, etc., and is caused by the same bacteria in general as lobar pneumonia, but most frequently, as it appears, by the *Streptococcus pyogenes.* If, however, the lobular pneumonia occurs as a sequel of putrid bronchitis, or owing to aspiration of fluid from the mouth, or of other contaminated matters, the organisms found in the exudation are naturally in great variety.

The exudation into the alveoli may be preceded by *atelectasis* of the latter, *i.e.*, when the small bronchial twigs are blocked by abundant secretion.

The inflammation always occurs in scattered foci, and only in the groups of alveoli belonging to the affected bronchial branch (*a*), but it may extend by little and little so as to involve a whole lobe. In broncho-pneumonia there also takes place at the commencement of the inflammation an increased desquamation of the alveolar epithelium, which consequently, in the form of roundish cells having vesicular nuclei, fills the alveoli to a greater or less extent, in company with a highly albuminous fluid (*b*). At a later period the character of the exudation depends essentially on the nature of the inflammatory excitant, and since the latter is most frequently the *Streptococcus* or *Staphylococcus pyogenes*, the epithelial cells very soon become replaced, in greater part or altogether, by pus corpuscles (*d*). Fibrin (*e*) is usually not present at all, or but sparingly. Lastly, the exudation may also be of a hæmorrhagic (*c*), or, in the presence of putrefactive bacteria, of a putrid, character.

Metastatic or embolic pneumonia develops owing to the entrance into the lungs in considerable quantity, by the circulation, of the bacteria from an inflammatory process existing elsewhere in the body, the pyococci being those usually found. This may take place alone or in association with an embolus plugging a terminal artery, in which latter case a hæmorrhagic infarction is first developed, and this changes into an abscess owing to the suppurative inflammation which soon follows; or, should putrefactive bacteria at the same time be present, into a gangrenous patch. In the former case, *i.e.*, when only capillaries or vessels other than terminal arteries are blocked by the bacteria, small roundish inflammatory foci form in which the exudation is frequently hæmorrhagic at first, but later becomes purulent or putrid.

Interlobular or pleurogenous pneumonia, which is rare in man, occurs in consequence of the entry into the pleura of certain inflammatory excitants which are as yet unknown, and which make their way thence by the lymph channels into the interlobular, peribronchial, and perivascular connective tissue of the lung, giving rise to a fibrino-purulent or purulent exudation in this tissue. The adjoining alveoli are thus compressed, or are likewise attacked by the inflammation.

9. Diseases due to Inhalation of Dust (Pneumonoconiosis).—When dust of a mineral, vegetable, or animal nature is inhaled, the particles which reach the alveoli are taken up by wandering and epithelial cells (dust cells); or, should they wound the alveolar epithelium,

as may be the case for instance with sharp-cornered particles of coal-dust, they pass directly into the alveolar frame-work and the lymphatic vessels in this situation, in which they are then either carried to the bronchial glands, or deposited at once in the peribronchial, perivascular, and interalveolar connective tissue, especially at spots where small lymphatic follicles usually exist. Here they lie free or in the interior of round, spindle-shaped, and stellate cells, causing, when they are coloured, a corresponding *pigmentation* of the lung—black in the case of coal-dust (*anthracosis*), red or black with metallic dust containing iron (*siderosis*), and so on. If the quantities of dust inhaled are larger, slight inflammatory changes are set up, such as proliferation and desquamation of the alveolar epithelium, emigration of white blood-corpuscles, and sometimes even an indurative broncho pneumonia, in which pigmented nodules of larger or smaller size are formed, consisting of connective tissue arranged concentrically round one or more centres.

10. Infective Granulomata, and New-Formations.—*Tuberculosis of the lungs* is due either to inhalation of tubercle bacilli or to their importation by way of the blood or lymph. In all these cases the pulmonary connective tissue, *i.e.*, the interalveolar, interlobular, perivascular, or peribronchial connective tissue, seems to be the first seat of development of the tubercles, and it is chiefly the fixed cells of the connective tissue and of the vessels that, by their growth, produce the elements of the tubercle. Soon, however, changes are also set up in the adjoining alveoli, alveolar passages, and bronchioles, the lumen of which becomes filled with proliferated epithelial cells and emigrated leucocytes, so that such tubercles, especially those occurring in the interalveolar and interlobular connective tissue (Fig. 141), really constitute very minute broncho-pneumonic patches, in which the outlines of the individual alveoli (*a*) can often still be distinguished. The blood-vessels within the area of these patches are then abolished, whether by compression or by becoming occluded owing to the growth of their cells; whilst caseation sets in at the centre of the focus. If the tubercle bacilli have been brought to the lung by the circulation, numerous tubercles usually form very speedily in all parts of the organ, whereas after introduction of the bacilli by the inspired air or the lymphatics only isolated tubercles grow at first.

The tissue of the lung immediately surrounding the tubercles usually shows inflammatory appearances; that is to say, the alveoli contain partly fluid exudation and partly proliferated epithelial cells and leucocytes (Fig. 141, *b*), and not uncommonly also fibrin or red corpuscles, whilst the septa are more or less intensely infiltrated

with small cells. Owing to these inflammatory changes, which may be of variable extent, the neighbourhood of the tubercle frequently

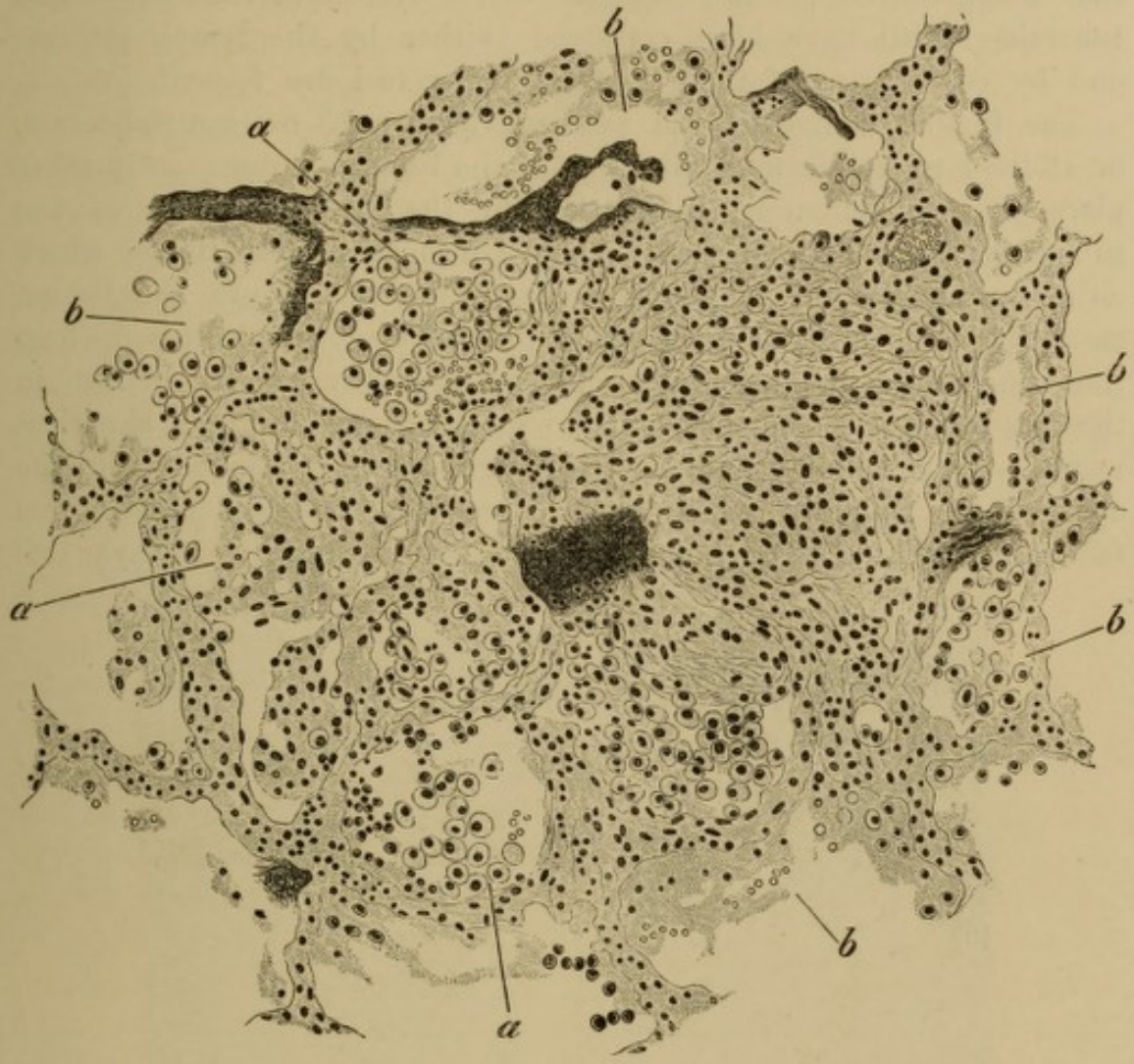

FIG. 141.—A MILIARY TUBERCLE OF THE LUNG with commencing caseation in the centre. × 240. (Alum cochineal.) *a*, Peripheral portion of the tubercle in which the individual alveoli with their cellular contents are still recognisable; *b*, Alveoli adjoining the tubercle, partially filled with serum, shed epithelial cells, leucocytes, and red corpuscles.

acquires a gelatinous look to the naked eye (*gelatinous infiltration*). How far they are to be set down to the account of the tubercle bacilli and their toxins, and how far to the simultaneous presence of other causes of inflammation, especially *Streptococcus pyogenes* and *Diplococcus pneumoniæ*, has not yet been determined; but it may at all events be looked upon as tolerably certain that the last-named bacteria play a causative part in the more wide-spread inflammatory infiltrations, such as may accompany not only the acute miliary but also the chronic form of tuberculosis. In such cases we have a so-called *mixed infection*, and the character of the exudation also will then be determined, at least partially, by the nature of the inflammatory excitant. The tubercle enlarges owing to the inflammatory

involvement of the alveoli surrounding it, and the caseation gradually invades this zone. On the other hand, new nodules may form in the neighbourhood, and also in more remote localities, should tubercle bacilli have been conveyed thither by the lymph stream; and by coalescence of these nodules larger foci are formed.

The further course of the process varies. If no multiplication, or at least no active multiplication, of the bacteria subsequently takes place, the inflammatory infiltration in the neighbourhood of the tubercular focus may gradually change into connective tissue, which either encapsules or completely replaces the latter. In the former case the caseous portion of the tubercle may remain for a long time unchanged and also infectious, or else may calcify; whilst in the latter, fibrous and frequently pigmented nodules and cicatrices result. Such nodules and cicatrices are especially frequent in the apex of the lung, in which they cause the condition named *grey induration* (Fig. 142), though this is not necessarily always due

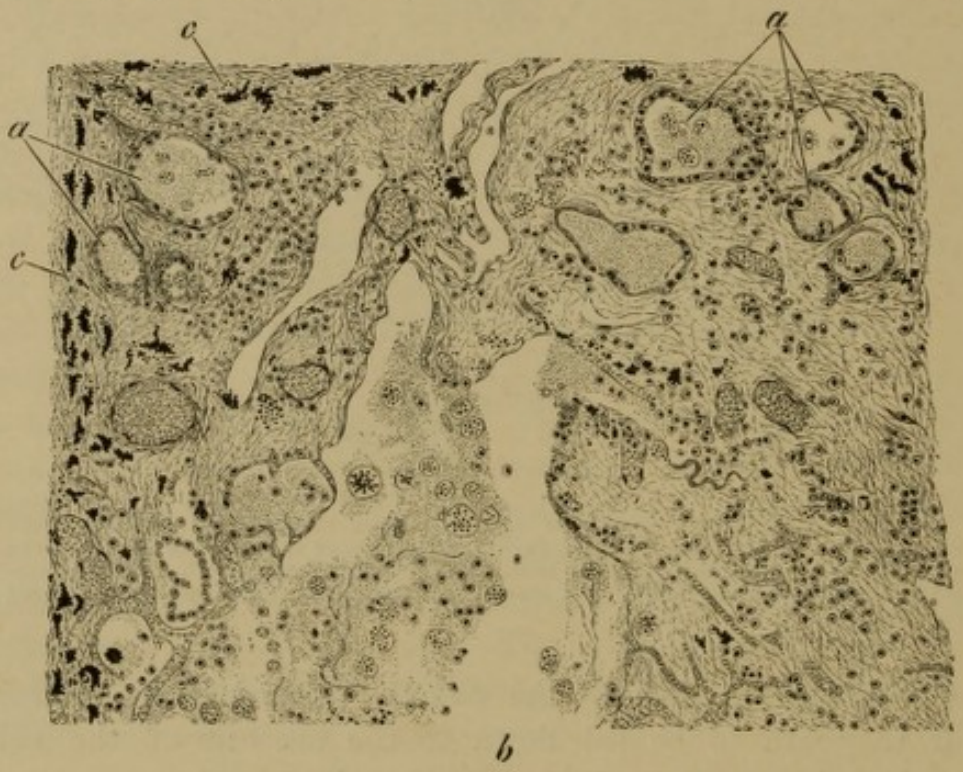

FIG. 142.—GREY INDURATION OF THE APEX OF THE LUNG FOLLOWING TUBERCULOSIS. × 95. (Hæmatoxylin and eosin.) *a*, Compressed bronchioles and alveoli, partially filled with a finely granular mass and pigmented cells, the wall lined with cubical epithelium; *b*, Greatly dilated alveolus with similar contents; *c*, Cicatricial tissue rich in carbon pigment.

to the healing of tubercular disease, but may also be the consequence of indurative broncho-pneumonic processes (see p. 282) occurring as the result of inhalation of dust. In such spots, besides a more or less cellular connective tissue, usually infiltrated with abundant black pigment (*c*), we still find also alveoli and bronchioles, some of which (*a*) are compressed or plugged with exudation (or secretion),

while others have undergone emphysematous distension (*b*). The exudation consists of finely-granular masses, and round cells of variable size, some of them containing pigment. The walls of such alveoli not uncommonly show a thick cubical epithelium, which gives the alveoli a certain resemblance to glandular cavities (*a*).

In contrast to this *indurative* form of tuberculosis, with its tendency towards recovery, stands the *ulcerative* form, which speedily results in softening of the caseous tubercles and formation of cavities. The latter form in those instances where a tubercular focus extends to the wall of a bronchial twig, which in consequence undergoes caseation and ulceration. The contents of such a cavity consist of caseous pus enclosing particles of necrotic tissue, and its wall is composed of a granulation tissue, the innermost layers of which are caseating (Fig. 143, *A* and *B*). The cords and bands existing in the larger cavities

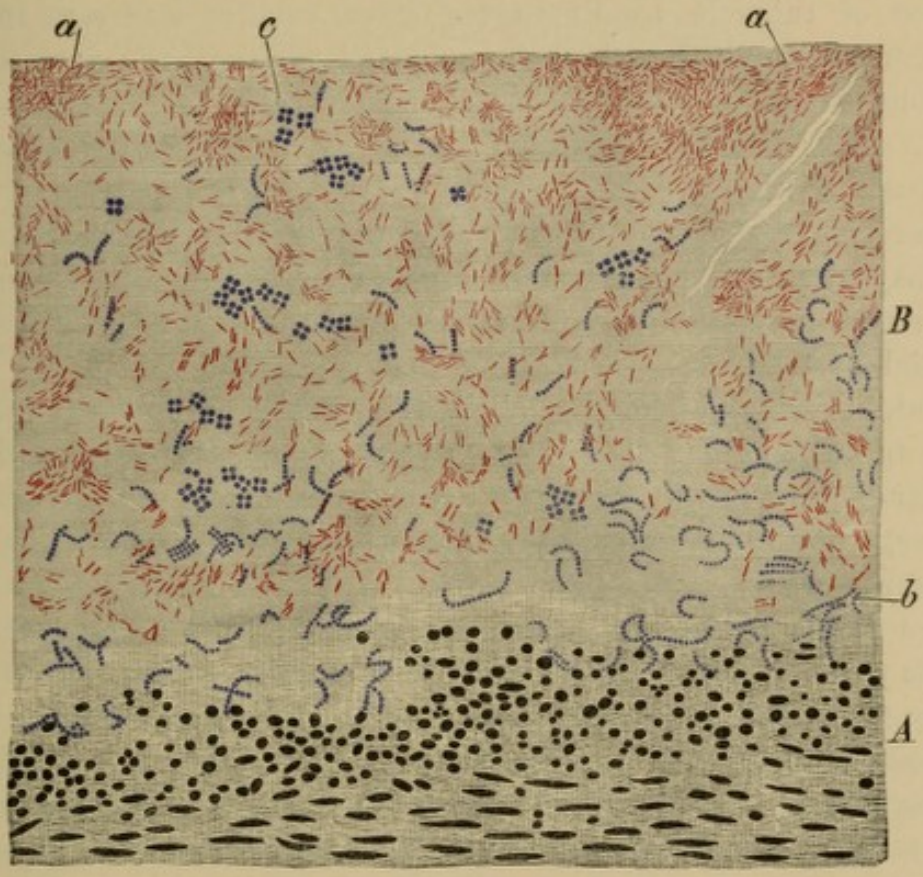

FIG. 143.—WALL OF A TUBERCULAR CAVITY IN THE LUNG. × 545; the bacteria drawn in under a power of × 925. (Koch-Ehrlich method.) *A*, External portion of wall of cavity, composed of round-celled and spindle-celled tissue; *B*, Inner caseous portion of wall; *a*, Tubercle bacilli; *b*, *Streptococcus pyogenes*; *c*, *Micrococcus tetragenus*.

frequently contain arterial twigs, the lumen of which is in most cases narrowed or even closed by fibrous thickening of the intima. Sometimes, however, the arteries show aneurysmal dilatations, which may then lead to rupture of the vessel.

If the tubercular process ceases to advance, the walls of the

cavities become transformed into connective tissue, by the contraction of which the cavity may gradually be reduced in size or entirely closed, while its contents calcify. Frequently, however, new tubercles form in the vicinity of the cavity, and by their disintegration contribute to its enlargement.

Since tubercle bacilli may make their way into the air-passages by the breaking of a tubercle into a bronchial twig, they may be aspirated into other parts, and thus give rise to the formation of new foci in the lung. When the foci lie very close together and extend over considerable portions of the lungs, the process acquires the appearance of a lobular or even of a lobar caseous pneumonia.

When tubercular foci encounter blood-vessels, tubercles may develop in the walls of the latter, and having undergone caseation may burst into the lumen of the vessel, thus affording opportunity for the entrance of tubercle bacilli in larger or smaller numbers into the blood-current, and for the consequent formation of more or less numerous tubercles in different organs (*general acute miliary tuberculosis*). This issue is, however, frequently frustrated by antecedent thrombosis of the vessel.

Tubercles may also occur in the walls of bronchial twigs, where they may eventually ulcerate if situated in the mucous membrane. The process may then spread further upwards or downwards in the bronchial system.

Should tubercular foci extend so as to reach the pleura, a *pleurisy* is set up, which may be either circumscribed, eventually leading to partial adhesion of the lung; or else general, and accompanied by a serous, a fibrinous, or, notably after rupture of cavities, a purulent exudation.

The tubercle bacilli themselves are found with the greatest certainty in those parts of the tubercles which have not yet undergone caseation, and are more abundant the quicker the process; hence they are most numerous in the acute ulcerative form of tuberculosis (*florid phthisis*), and scantiest in the indurative form. They are often present in large numbers in the contents and innermost layers of the walls of cavities, but frequently in association with other bacteria such as *Micrococcus tetragenus*, *Streptococcus pyogenes*, etc. (Fig. 143, *a*, *b*, and *c*).

Syphilis of the lungs is very rare in adults, but occurs with somewhat greater frequency in new-born infants, either in the form of gummata or as a more diffuse infiltration. The former (Fig. 144) show the same characters as gummata in other organs, *i.e.*, when of a certain size they allow the three zones described on page 139 to be made out. The surrounding pulmonary tissue is usually the seat of an indurative inflammation.

The second form of pulmonary syphilis occurs in new-born children as the so-called *white pneumonia*, which depends, on the

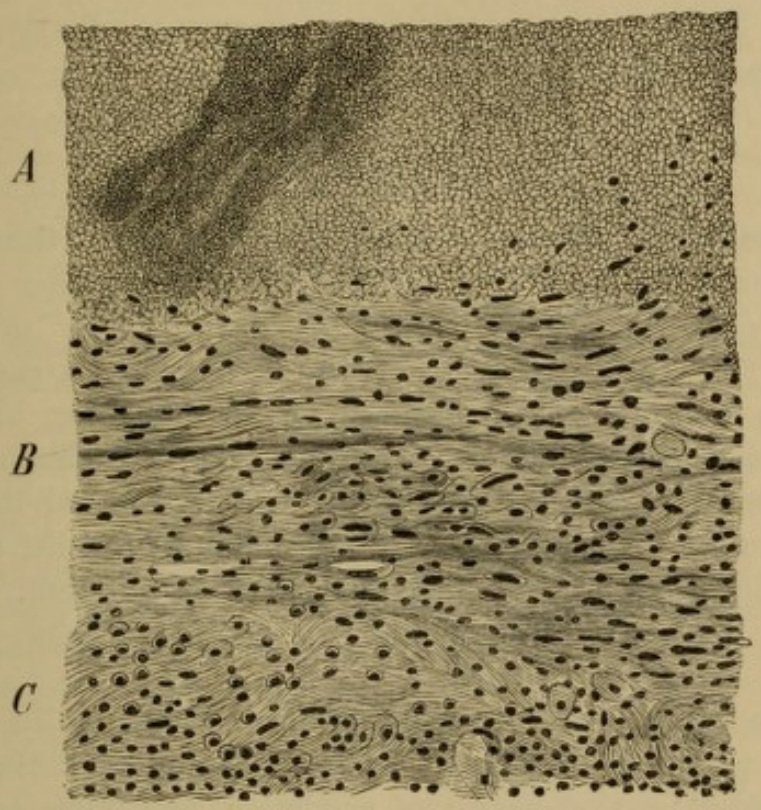

FIG. 144.—SYPHILOMA OF THE LUNG. × 285. (Alum cochineal.) *A*, Cascated centre; *B*, Layer of spindle cells; *C*, Layer of round cells.

one hand, upon intense cellular infiltration of the alveolar septa or of the connective tissue of the lung in general, especially in the vicinity of the blood-vessels, the intima and adventitia of which are likewise thickened; and, on the other hand, upon accumulation of desquamated and fatty-degenerated epithelial cells in the alveoli.

In *glanders*, isolated or coalescing nodules may form, within the area of which the alveoli mostly contain pus corpuscles undergoing granular disintegration, whilst those in the immediate neighbourhood are filled for the most part with a hæmorrhagic exudation.

For *actinomycosis* of the lung, see p. 159.

Primary *new-formations* are very rare in the lung, but secondary, on the other hand, are more frequent. Secondary carcinoma may spread in the lung along the course of the lymphatics, a condition in which the lumen of the latter is found distended with cancer cells to a variable degree, but mostly irregularly, whilst the endothelial cells of the lymphatics may still be retained, and show absolutely no proliferative processes—a point of distinction from endothelial sarcoma of lymphatics (Fig. 36, and p. 91).

Of *vegetable parasites*, besides the specific excitants of disease already dealt with, the *Aspergillus* must also be mentioned (Fig. 70).

Of *animal parasites*, *Echinococcus* occurs with greatest relative frequency. Scolices, or their hooks or fragments of cyst, may then be found also in the sputum.

V. THE PLEURA.

11. Inflammation, Infective Granulomata, and New Growths.—The same statements hold good for *hydrops pleuræ* as for ascites (p. 247).

Acute pleurisy may, like peritonitis, occur either primarily or secondarily. In the latter case it is due to the extension of an inflammation from the neighbourhood, or to embolism, and it then also corresponds in character with the primary inflammation.

In *primary* pleurisy the *Diplococcus pneumoniæ* and the pyococci have hitherto been found, apart or in combination with each other, the exudation being either chiefly fibrinous or purulent. The finer changes in the serosa are similar to those of acute peritonitis (p. 248).

When the pleurisy is of longer duration it results in the formation in the pleura of a highly vascular granulation tissue, which gradually permeates the deposit of exudation, and, after being transformed into connective tissue, leads either to mere localised thickenings, or to cord-like and membranous adhesions of the two layers of the pleura. This newly-formed connective tissue is sometimes extraordinarily dense, and then shows a perfectly homogeneous appearance under the microscope. Deposits of lime-salts may occur in it later.

Tuberculosis frequently exists primarily in the pleura, but it is most commonly secondary. The exudation in the former case is usually sero-fibrinous, and at the same time stained with blood; whilst in the latter, notably after the perforation of cavities, it may also be purulent, though without pyococci being necessarily present in it. In general, a purulent exudation in the pleural cavity, *without* bacteria (including tubercle bacilli), points with great probability to tuberculosis.

Primary new growths are very rare. The most important of them is the *endothelial sarcoma*, which corresponds in structure to that occurring in the peritoneum (p. 249).

Examination of the Entire Respiratory Apparatus, including the Sputum and Contents of the Pleural Cavity.—(1) The microscopic examination of the *sputum* should always be preceded by a naked-eye inspection, since even in the latter way certain diagnostic indications may be obtained. Thus, a thick greenish-

yellow sputum indicates the presence of a large proportion of cellular elements, especially pus cells; a fœtid greenish-brown sputum, putrid bronchitis or gangrene of the lungs, in the latter of which the expectoration, besides the colour, shows three separate layers, an upper frothy, a middle watery, and a lower opaque—the last sometimes containing shreds of tissue. Separation of the sputum into an upper watery and a lower purulent layer points to pulmonary abscess; into an upper frothy, a middle watery, and a lower thick layer, to bronchiectasis; a rusty or lemon-yellow colour to pneumonia; and so on. Furthermore, macroscopic examination of the sputum—spread in a thin layer upon a black surface—gives information regarding the presence of coarser impurities, such as particles of food, fibrinous coagula, shreds of tissue, Curschmann's spirals, and plug-like or caseous fragments derived from the walls of cavities and usually containing elastic fibres and numerous tubercle bacilli. Actinomyces granules or fragments of echinococcus cysts may also be detected by this means, and any increase in the amount of pigment contained in the sputum may likewise be recognised. Some preliminary information having been gained in this way, suitable particles of sputum are transferred to a slide and examined, usually without any further addition.

In searching for indications of *elastic fibres*, we should restrict ourselves to the plugs already mentioned, which can be rendered so transparent by the addition of acetic acid that the elastic fibres come out very distinctly; or a sample of the sputum may first be examined under a low power without addition, and any suspicious-looking places then tried with a stronger power, adding acetic acid. The sputum may also be boiled with ten per cent. caustic potash solution, allowed to settle in a conical glass, and the sediment then examined. Since elastic fibres may also be derived from the food, they are of pathological import only when they can be recognised, from their alveolar arrangement, as parts of the pulmonary alveoli. They are found in abscesses and cavities of the lungs, as well as in pneumonia, but seldom, on the other hand, in pulmonary gangrene, probably because they are dissolved in this condition.

Fibrinous coagula occur in croupous bronchitis and in pneumonia, in the former as dichotomously-branching casts of the larger bronchial ramifications, whereas in the latter they come only from the finer bronchi. Microscopically they show a feltwork of fine filaments which dissolves in acetic acid.

Curschmann's spirals are spirally-coiled whitish structures, probably composed of mucin, in which are frequently embedded Charcot's crystals (p. 187) and eosinophil leucocytes (p. 186). They are found in asthma and bronchitis, and sometimes also in pneumonia.

Of *cellular* elements, in the first place *epithelial cells*, mostly of the squamous variety, are found in all sputum, being usually derived from the saliva mixed with it, or from the pharynx and uppermost portions of the larynx. Less frequent are *ciliated epithelial cells* (usually without their cilia), from the nasal cavity or deeper parts of the respiratory passages. If present in considerable quantity, it may be concluded with certainty that there is catarrh of the parts referred to. Further, cells also occur which are round like leucocytes, but larger, and resemble the epithelial cells in possessing a vesicular nucleus which does not stain deeply. These are commonly believed to be cells of the alveolar epithelium, though this can scarcely be always the case, and are met with in a variety of morbid processes, such as chronic bronchitis, tuberculosis, and pneumonia. The characteristic nucleus is brought

out distinctly by adding acetic acid. Furthermore, they often contain pigment in their protoplasm (Fig. 137, *g*, and Fig. 142, *a* and *b*), and sometimes also droplets of fat. The former is usually carbon in the form of black grains and masses, but may also consist of other kinds of dust which have been inhaled (iron filings, stone-dust, and the like), or may be blood pigment, in which case it consists of yellow or brown granules and is found in the affected cells after hæmorrhages or in the brown induration which follows cardiac lesions, such cells being hence called by the Germans *Herzfehlerzellen* (Fig. 137, *g*). *Leucocytes*, both mononuclear and polynuclear, are likewise found in all sputum, but in greatest abundance in purulent bronchitis and pulmonary abscesses. Their protoplasm is for the most part highly granular, or may contain fat-drops in variable quantity (*granule cells*), in which case the nuclei as a rule only become visible on addition of acetic acid. Besides these, leucocytes with eosinophil granulations (p. 186) occur not uncommonly in catarrhal affections. Isolated *red corpuscles* are very often encountered in sputum. They are present in large quantity in pulmonary hæmorrhages and hæmorrhagic infarctions, and are then either still unchanged or have become in part transformed into pigment or hæmatoidin crystals.

Crystals of *cholestearin* may also be found in tuberculosis or after bursting of abscesses; of *margarin* in gangrene of the lung, putrid bronchitis, and bronchiectasis; and of *leucin* and *tyrosin* after the bursting of abcesses. Lastly, hooks and vestiges of the cysts of *Echinococcus* may be present.

For the examination of sputum and nasal secretion for *vegetable parasites*, especially for the bacteria of tuberculosis and pneumonia, see Part II., Chapter V.

(2) The *contents of the pleura* are examined in a similar manner to those of the abdominal cavity (p. 250).

(3) The *lungs and pleura* themselves are best examined in the *fresh state* in cases of *fat-embolism* or *inflammatory processes*. In fat-embolism sections are cut with the freezing microtome and examined either without reagents or after addition of dilute acetic acid or caustic potash solution; or they may be treated with osmic acid (p. 53). In the inflammatory processes we must be content with examining respectively the juice obtained by scraping the tissue, and the exudation coating the pleura. This is done according to the rules given for fluids and exudations (pp. 5 and 75-6).

Lastly, tissue from the respiratory tract is *hardened* in alcohol if fibrin or bacteria are to be demonstrated, otherwise usually in Müller's fluid and alcohol. In *pulmonary œdema*, however, the boiling method (see p. 8) may also be employed. For *embedding* the objects it will in most cases be necessary to use celloidin, as in the paraffin method the contents of spaces, *e.g.*, of the alveoli of the lungs, would fall out. Hæmatoxylin and eosin may advantageously be employed for staining the sections: but for *fibrin* the methods given on p. 75, and for *vegetable parasites* those in Part II., Chapter V., may be adopted.

CHAPTER VII.

THE URINARY APPARATUS.

I. THE KIDNEYS.

1. Degenerations.—*Cloudy swelling*, which principally affects the epithelium of the convoluted tubules, manifests itself, as in other organs, by the presence of abundant dark granules in the cells, causing the latter to swell and thus fill the lumen of the tubules more or less completely. The outline of the epithelial cells also becomes less distinct, and their connection with the membrana propria is loosened.

This condition not uncommonly terminates in *fatty degeneration* or in *necrosis*. In the first case, fat-droplets of larger and smaller

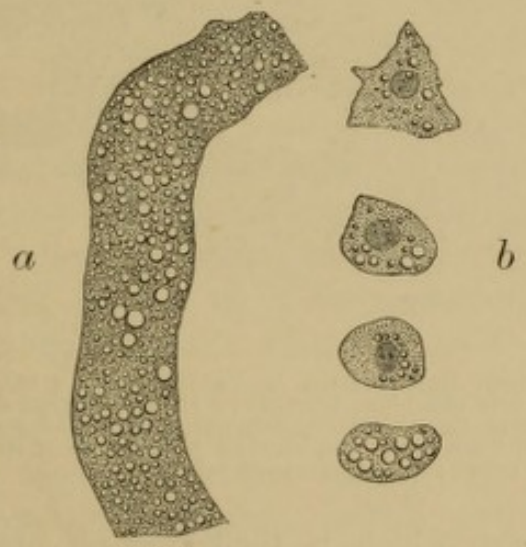

FIG. 145.—FATTY DEGENERATION OF THE KIDNEY.—Fresh torn-up preparation, treated with acetic acid. *a*, Portion of a convoluted tubule thickly covered with larger and smaller fat-droplets. × 285. *b*, Isolated fatty-degenerated epithelial cells from a urinary tubule. × 545.

size (Fig. 145, *b*) appear in the bodies of the epithelial cells lining the canaliculi and glomeruli, and sometimes also in the endothelial cells of the blood-vessels and in the connective-tissue cells, whilst

in the latter case the nuclei vanish and the cells either become cloudy or are reduced to homogeneous masses, and frequently the degenerated epithelial cells of the tubules also separate from the membrana propria. When urinary tubules which have undergone a high degree of fatty degeneration are examined in the fresh state, neither the outlines of the epithelial cells nor their nuclei can be recognised, owing to the surface of the tubules appearing thickly covered with fat-droplets (Fig. 145, *a*).

Cloudy swelling, as well as fatty degeneration and necrosis, may occur both idiopathically (in various intoxications and infective diseases) and also as part of the phenomena of nephritis. The necrosis at times affects chiefly or exclusively the epithelium of

Fig. 146.—Amyloid Degeneration of the Kidney. × 545. (Gentian violet.) *a*, Urinary tubules with membrana propria in a state of amyloid degeneration; *b*, Vas afferens of a glomerulus in amyloid degeneration; *c*, Amyloid-degenerated parts in the glomerular loops; *d*, Small artery with amyloid degeneration of its wall; *e*, Waxy cast in lumen of urinary tubule; *f*, Normal urinary tubule.

the glomerular loops, which is then cast off and blends with the exudation escaping from the loops (in consequence of the necrosis) to form a finely-granular mass. The loops of the glomeruli, deprived of their epithelium, appear pale, swell up, and may finally lose their endothelium also. Necrosis much more rarely affects the epithelium lining Bowman's capsules, or the endothelial cells of the capillaries and veins.

Amyloid degeneration (Fig. 146) first and foremost attacks the glomeruli, of which single loops (*c*) are involved at the outset, but afterwards the entire coil is transformed into homogeneous masses. The process next attacks the vasa afferentia (*b*) of the glomeruli, and the arteriolæ ascendentes, then the membrana propria (*a*) of the urinary tubules in the medulla, and finally most of the remaining blood-vessels and tubules. It is frequently accompanied by fatty degeneration, especially of the epithelium of the convoluted tubules, by the shedding of which epithelial and granular casts are formed. In addition to these, however, hyaline and waxy casts (*e*) also occur. Not uncommonly the interstitial connective tissue is also found in places in a state of cellular infiltration, or increased in amount, a condition which may result at a later date in shrinking and partial atrophy of the kidney. For *glycogen degeneration*, see page 57, and for *hyaline degeneration*, page 55.

2. **Atrophy.**—*Senile* and *arteriosclerotic atrophy* of the kidney, which occurs in advanced life or in atheroma of the renal arteries (with or without simultaneous disease of the rest of the arterial system), first manifests itself, in consequence of the deficient blood supply, in an obliteration of the glomeruli which is usually of focal distribution, the vascular loops in the tufts becoming transformed (perhaps after hyaline thickening of their walls or formation of hyaline thrombi) into an almost homogeneous tissue, which contains few or no nuclei, is sometimes concentrically laminated, and still at first allows the lobular formation to be recognised. The capsules of the glomeruli, meanwhile, either remain unchanged or are merely slightly thickened. A consequence of this change is atrophy (narrowing) of the corresponding urinary tubules, the epithelium of which becomes much lower while at the same time acquiring a deeper colour, and sometimes also undergoes fatty degeneration or disappears altogether. There frequently follows a deposit in the lumen of such tubules of homogeneous colloid masses, in many cases stratified, which probably have their origin in the epithelial cells (Fig. 149, *k*), and which, when they accumulate to any great extent, transform the tubules into larger or smaller *colloid cysts*, lined with flattened epithelium. The connective tissue between the tubules is often in a state of small-celled infiltration, but is not otherwise increased in bulk. The greater the number of glomeruli with the tubules belonging to them that are destroyed, the more conspicuous does the atrophy of the cortex and the granular structure of its surface become. The interlobular arteries also then necessarily take an extremely convoluted course.

Hydronephrotic atrophy.—Whereas in senile (and nephritic) atrophy

it is chiefly and primarily the cortical substance that is affected, in the atrophy produced by *hydronephrosis, i.e.*, stagnation of fluid in the pelvis and calices of the kidney, the condition begins in the medullary substance (first of all with flattening of the papillæ), and only invades the cortex at a later date. At the commencement of the hydronephrosis the urinary tubules are still dilated, and there is likewise usually a condition of passive hyperæmia. The epithelium in the collecting tubes is flattened out by the pressure of the retained urine, whilst in the other tubules, as well as in the glomeruli, it usually appears in a state of fatty degeneration. Hyaline tube-casts are also found in the tubules, as well as albuminous coagula, which occur too in the cavities of Bowman's capsules. As the hydronephrosis progresses the urinary tubules and the blood-vessels become more and more compressed, the interstitial connective tissue in cortex and medulla increases, and finally the glomeruli also are obliterated. At this stage the microscopic appearances are very like those in chronic interstitial nephritis (p. 301).

3. Infiltrations.—*Leucæmic infiltration* consists in an accumulation of white corpuscles between the urinary tubules, and in its higher degrees may even assume the form of wedge-shaped foci or of nodules. After *hæmorrhages* in the kidney, yellow or brown pigment granules, which lie for the most part in epithelial cells, are found in the urinary tubules, especially in Henle's loops (*pigmentary infarction*). In conditions in which large numbers of red corpuscles are dissolved, hæmoglobin and methæmoglobin are not only excreted through the kidneys in solution, but also deposited in the efferent tubules in the form of dark yellow or brown drops and grains (which sometimes unite to form cylindrical structures), and in many instances even as red crystals (*hæmoglobin infarction*).

The *bile-pigment infarction* in severe icterus consists of yellow, greenish, or brown grains and masses of bile-pigment, which partly lie in the epithelial cells of the tubules and in the adjoining tissue, and partly fill the lumen of the former to a greater or less extent. In slighter degrees of icterus, however, only a diffuse yellowish tinging of the cells is usually found. On the other hand, in icterus neonatorum not only granules and irregular masses of pigment occur, but also needle-shaped and rhombic crystals of bilirubin, of a ruby-red colour, which are seen especially in the substance of the cortex (*bilirubin infarction*).

Calcareous infarction, which occurs in senile atrophy of the kidneys, in poisoning with corrosive sublimate and sometimes with other substances also, and in certain diseases of infective origin, usually gives rise to formation of clustered or cylindrical brightly-glancing masses

of calcium carbonate or phosphate, which stain reddish-brown with hæmatoxylin. These usually lie in the convoluted or straight tubules, in which the lime is only as a rule precipitated after the epithelial cells have previously undergone necrosis. The calcareous infarction may, however, consist in a deposit of finely-granular masses in the capsules of the glomeruli and in the membrana propria of the urinary tubules, as well as in the intertubular connective tissue. This form, together with the preceding, is found especially in old people and in the so-called metastatic calcification (p. 61)—in the former by preference in the region of the papillæ.

In the *uric acid infarctions* of new-born infants a mass can be squeezed out of the apices of the papillæ which under the microscope is seen to be composed of little balls of uric acid usually possessing a spiny surface, like ammonium urate. These globules form as far up as the convoluted tubules, but accumulate in the collecting tubes of the papillæ.

Gouty deposits in the kidney consist of rhombic tablets of acid sodium urate, which lie partly in the lumen of dilated collecting tubes of the medulla, partly in the epithelial cells and interstitial connective tissue. The tissue immediately surrounding these deposits is destitute of nuclei (*i.e.*, necrotic).

4. Hypertrophy, Disorders of Circulation, and Tube-casts.—The *compensatory hypertrophy* which occurs in one kidney when the other is *congenitally* deficient either depends solely on multiplication of the glomeruli and urinary tubules, or there is also an enlargement of these structures in addition; whereas that which develops in consequence of *acquired* defect of one kidney depends on enlargement of the urinary tubules and glomeruli and multiplication of their cells. In this condition the diameter of the urinary tubules increases, in the case of the convoluted, from the normal 49–79 μ to 49–141 μ; in the straight tubules from 26–49 μ to 49–89 μ; and the diameter of the glomeruli from 135–225 μ to 188–402 μ.

In *venous hyperæmia*, especially when the result of cardiac and lung disease, not only are the veins and capillaries greatly dilated, especially in the labyrinth of the kidneys; but in the cavities of many of the Bowman's capsules and in the urinary tubules an albuminous fluid is found (appearing as a finely-granular mass in preparations made by boiling or hardening in alcohol), as well as more or less numerous red corpuscles, and grains of yellow or brown pigment,[1] the latter especially in the epithelial cells of Henle's loops. Isolated tubules also contain hyaline casts. When the

[1] Apart from this, pigment-granules are almost always found in the kidneys of elderly persons.

hyperæmia is of longer duration the intertubular connective tissue appears somewhat thickened and at the same time distinctly fibrillated, and here and there even infiltrated with small cells (*cyanotic induration*). Isolated glomeruli become obliterated and transformed into a homogeneous tissue, whilst the epithelium of the tubules, especially in the medulla, undergoes a greater or less degree of fatty degeneration.

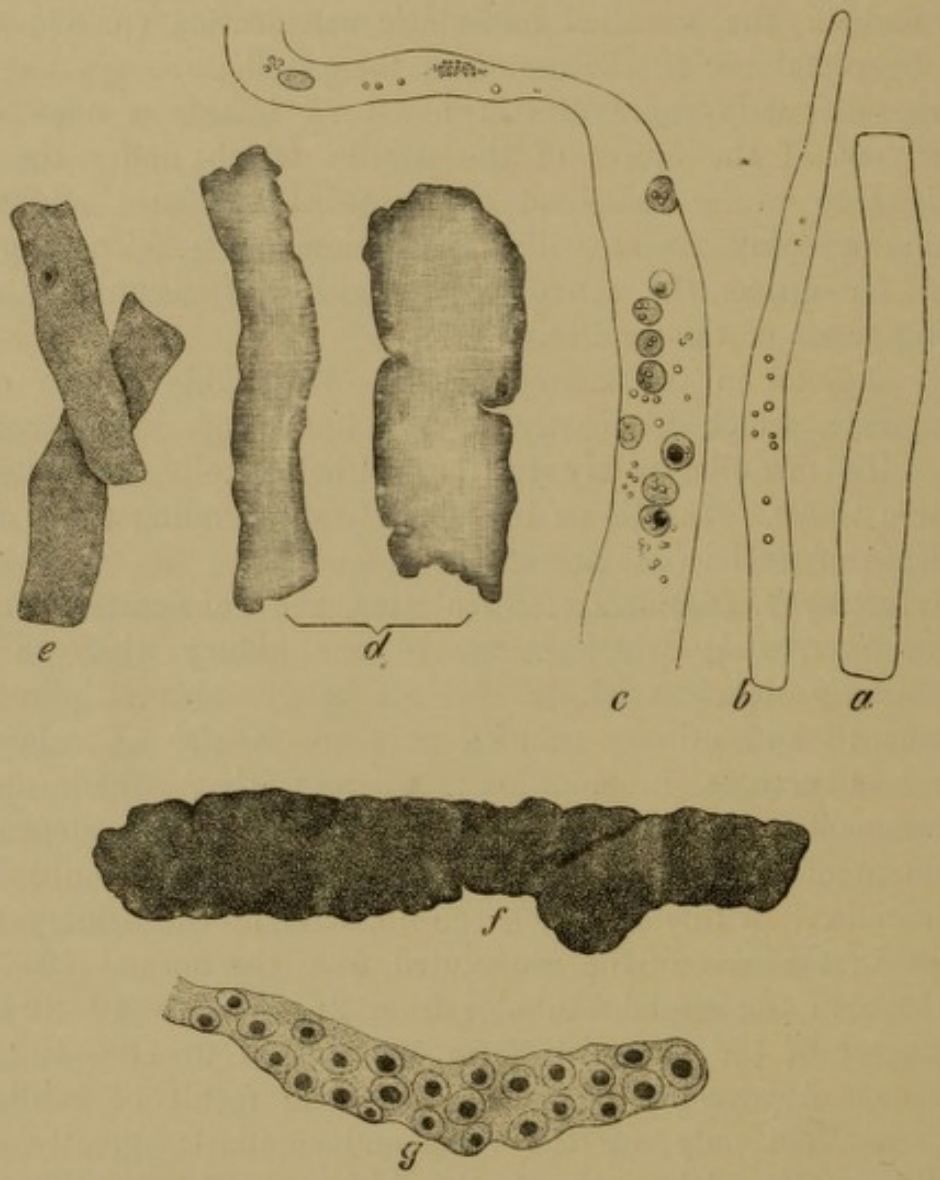

FIG. 147.—TUBE-CASTS FROM URINARY SEDIMENT IN CHRONIC PARENCHYMATOUS NEPHRITIS. × 440. *a*, Hyaline cast; *b*, Hyaline cast with isolated droplets of fat; *c*, Hyaline cast with fat droplets, leucocytes, and epithelial cells; *d*, Waxy casts; *e*, Finely granular cast; *f*, Granular cast with coarse granules; *g*, Epithelial cast.

Following *occlusion* (embolism or thrombosis) of the renal arteries there form *anæmic*, or more rarely *hæmorrhagic*, *infarctions*. But the anæmic infarctions also show a zone of redness at the margin, which is partly due to extreme distension of the capillaries and partly to extravasations of blood between and into the urinary

tubules, and it may still be possible to follow isolated vessels filled with blood even deep into the infarction itself. The further changes in the latter are analogous, whether the thrombi and emboli are indifferent or contain bacteria, to those which have already been depicted in a general manner on pp. 211 and 212.

We have still to mention *fat-embolism*, which occurs in the loops of the glomeruli under the same conditions as in the lung (p. 275), and in which the fat also appears in the form of drops or cylindrical cord-like masses.

Of *tube-casts* (Fig. 147), which are found in the lumen of the urinary tubules and in the urine in disorders of circulation and nephritic processes, we distinguish *hyaline* (*a*, *b*, *c*), *waxy* (*d*), and *granular* (*e*, *f*) varieties, and lastly, casts consisting solely of cells (*g*), which may be more or less degenerated cast-off elements of the renal epithelium (*epithelial casts*), or leucocytes or red corpuscles which have made their way into the lumen of the tubules (*blood casts*). The granular casts are composed of *finer* (*e*) or *coarser* (*f*) granules, produced by the disintegration of the cells of the renal epithelium. When they are entirely made up of fat drops they are also called *fatty casts*. The hyaline casts (Fig. 147, *a*, *b*, *c*) are very pale, transparent, homogeneous, and often very narrow structures, and the *waxy casts* (*d*) are merely somewhat firmer and of a wax-like sheen.

5. Inflammation.—According as the principal changes are seen in the epithelial cells or the interstitial connective tissue we distinguish a *parenchymatous* and an *interstitial nephritis;* and again either may run an *acute* or a *chronic* course.

1. In *acute parenchymatous nephritis* it may at times be the *glomeruli* which are chiefly involved (*glomerulo-nephritis*). We then observe swelling or proliferation of the endothelial cells of the glomerular loops; accumulation of leucocytes or cast-off degenerated endothelial cells in the lumen of the vessels in the loops;[1] and swelling, fatty degeneration, necrosis and desquamation, but on the other hand also proliferation, of the epithelium lining the capsule and covering the glomerulus. The shed epithelial cells are found in the cavity of the capsule, sometimes in concentric layers (Fig. 148, *b*), either alone or along with red and white corpuscles or with a finely-granular or sometimes more homogeneous exudation, and in

[1] It is, however, often very difficult to distinguish in particular cases between accumulated leucocytes and desquamated endothelial cells in the vascular loops, and it may even be hard to decide whether the proliferated nuclei of the vascular loops are inside or outside the lumen of the latter, that is, whether they belong to leucocytes, endothelial, or epithelial cells.

this way the coil may be compressed to a variable degree (Fig. 148, *c*), or may even be obliterated. On the other hand, the vascular loops of the glomerulus may be occluded by proliferation or desquamation of the endothelial cells or by the accumulation of leucocytes, but also by hyaline thrombi and hyaline swelling of the vessel-walls, and may then likewise suffer obliteration (p. 293).

Very often changes in the *urinary tubules* and *interstitial connective tissue* are added to the glomerular affection. In the former, and especially the convoluted tubules, we may find cloudy swelling, fatty degeneration (Fig. 145), necrosis, and desquamation, but sometimes

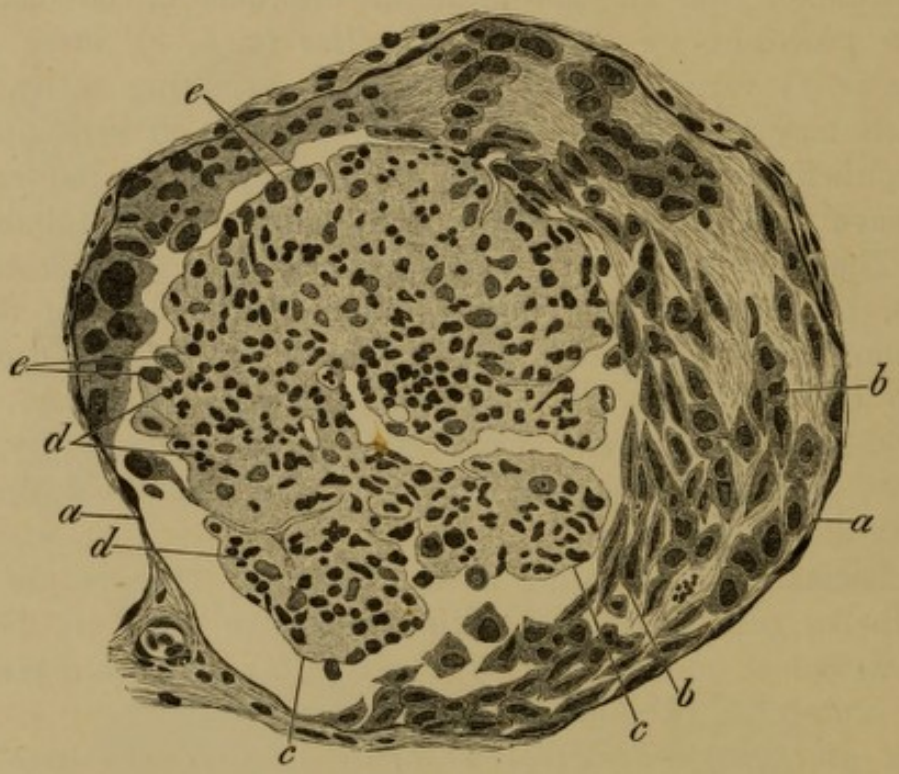

FIG. 148.—GLOMERULO-NEPHRITIS IN SCARLATINA. × 500. (Alum cochineal.) *a*, Capsule of glomerulus; *b*, Desquamated capsular and glomerular epithelium, concentrically stratified; seen partly from the side, partly on the flat; *c*, Compressed glomerular loops partly robbed of their epithelium; *d*, Polynuclear leucocytes; *e*, Nuclei of epithelial or endothelial cells of the glomerular loops.

also proliferation, of the epithelium; hyaline, granular, and epithelial casts (Fig. 147); and, after hæmorrhages, also red corpuscles or masses of pigment.

The *changes in the interstitial tissue* consist in a thickening of the interstitial spaces between the tubules from serous absorption, and in small-celled infiltrations which occur especially in the cortex corticis in the neighbourhood of the stellate and interlobular veins, and around the glomeruli. When the cellular infiltrations are particularly strongly developed the condition is spoken of as an *acute interstitial focal nephritis*. Within the area of the round-celled nodules leucocytes can be found in the interior of the tubules also.

In many cases a *hyaline degeneration* of the glomerular loops or other small blood-vessels is also found.

Acute parenchymatous nephritis occurs either primarily or secondarily, the latter in intoxications and acute diseases of infective origin. In the latter case we are not uncommonly able to recognise in the kidney also the bacteria (*Diplococcus pneumoniæ*, *Streptococcus pyogenes*, *Bacillus typhosus*, *Bacillus pneumoniæ*) which give rise to the particular infective disease or its complications, if any. There these bacteria are found in the vascular loops of the glomeruli as well as in other small blood-vessels, in the round-celled patches, and even in the urinary tubules; and it is then not improbable that they have caused the nephritic changes. If, however, no bacteria have been met with in the kidney in nephritis occurring in the course of infective diseases, it must be assumed that the nephritic changes in such cases are to be ascribed to the action of the toxic products alone, which have been generated outside the kidney by the bacteria of the particular infective disease and have traversed the organ in order to be eliminated. In general, however, one is inclined to the view that the changes which usually occur in elimination of toxic substances through the kidney are mainly *degenerative*, whereas in the presence of bacteria in the organ they are mainly *inflammatory*, occurring especially in the form of interstitial infiltrations; though degenerative changes also are not entirely absent in the second case, nor inflammatory changes in the first.

The *causes* of *primary* nephritis have not as yet been made clear. In some cases a streptococcus could be demonstrated in the urine, but it has remained undecided whether this was the cause of the nephritis or not.

2. In the *chronic parenchymatous nephritis*, which either begins insidiously or develops from the acute form, the changes are the same in general as in the latter, except that sometimes one, sometimes the other becomes more prominent. Thus in one case we find the changes in the glomeruli very marked, in another again the œdema and cellular infiltration of the interstitial connective tissue, or the fatty degeneration of the epithelium, or both the last-named changes at once. When copious hæmorrhages occur (into the spaces of Bowman's capsules, the urinary tubules, etc.), we speak of a *hæmorrhagic nephritis*, a condition in which grains of yellow and brown pigment are also found in the epithelial cells of the tubules. The predominant changes, however, in chronic parenchymatous nephritis are in general *degenerative*, consisting especially in *fatty degeneration* of the epithelium lining the tubules and glomeruli, and of the endothelium of

the blood-vessels, which is the cause of the white colour of the kidney seen in many cases (*large white kidney*). The interstitial connective tissue also shows fat-drops, which are free as well as in the interior of cells, especially of the round cells of the small-celled foci; and the endothelial cells of the intertubular capillaries may also be in a state of fatty degeneration.

When the changes enumerated are of long standing they result in atrophy of the kidney and cicatricial depressions of its surface. Thus, the urinary tubules collapse in consequence of degeneration and desquamation of their epithelium, but especially after obliteration of the glomeruli, a condition which is ushered in by the changes already described (p. 293). Later, the capsules of the glomeruli and the interstitial tissue may also become thickened.

The *ætiology* of chronic parenchymatous nephritis is not known; perhaps in this instance also an important part is played by the elimination of noxious matters which have been partly taken into the organism from without, partly formed in it by an abnormal metabolism.

3. *Acute suppurative interstitial nephritis* usually occurs metastatically (apart from pyelonephritis) in pyæmic processes, and is consequently always due to bacteria, mostly pyococci, which plug the glomerular loops or other small blood-vessels. This leads, in the first place, to necrosis of the latter and of the epithelium of the adjoining urinary tubules, but next to "reactive" suppurative inflammation in the neighbourhood, in which the pus corpuscles penetrate into the urinary tubules also, and finally little abscesses are formed owing to liquefaction of the tissue. These abscesses then lie in groups upon the surface of the kidney, or permeate cortex and medulla in rosary-like stripes along the interfascicular vessels and vasa recta.

The most frequent form of acute suppurative nephritis is, however, *pyelonephritis*, which usually occurs as a termination of purulent cystitis and pyelitis, in consequence of penetration of the micro-organisms causing the last-named inflammations (p. 305) into the renal papillæ and the tubules of the medullary substance. Hence in this form we find the first and principal changes in the medullary substance, though they eventually spread to the cortex also. The presence of the above-mentioned micro-organisms in the collecting tubes of the medullary substance causes changes analogous to those produced by the occlusion of the small blood-vessels with bacteria in the metastatic form of suppurative nephritis. Here also there results necrosis in the immediate neighbourhood of the tubules blocked by the bacteria, and at a greater distance accumulation in

the interstitial connective tissue and the tubules of pus-corpuscles, which, however, eventually penetrate into the necrotic zone also and change the patch into a small abscess. Such abscesses form in large numbers and have the same arrangement as in metastatic nephritis, except that they occur first in the medullary substance.

The subsequent extension of the process to the cortex takes place either by progressive growth of the bacteria inside the urinary tubules, or by their penetration into arteries, by which they are carried to the cortex. In the latter case the foci in the cortex show the same microscopic characters as in metastatic nephritis. By union of the suppurative foci not only may larger abscesses form in the kidney, but the suppuration may spread also to the renal capsules and surrounding connective tissue (*perinephritis* and *paranephritis*).

4. *Chronic interstitial or indurative nephritis* (Fig. 149), which possesses great similarity to arteriosclerotic atrophy, begins with small-celled infiltration of the interstitial connective tissue (*c*), leading to increase in the amount of the latter. Hence, when it has lasted for some time we find the intertubular and circumglomerular connective tissue thickened and of a distinctly fibrillated structure, but at the same time still more or less rich in cells. The capsules of the glomeruli also appear thickened and composed of concentrically stratified connective tissue (*g*). In other respects the glomeruli may exhibit changes (*f*) similar to those in parenchymatous nephritis, though not in so high a degree; but finally they also become obliterated and transformed into homogeneous or concentrically laminated globules (*b*), in which also lime may sometimes be deposited in the form of finely-granular masses. The remaining blood-vessels are frequently likewise altered, either the adventitia or intima becoming thickened (*e*), or the affected vessel being even obliterated. The epithelium of the tubules shows changes similar to but not so intense as those in parenchymatous nephritis, and the formation of tube-casts is also not so frequent (*i*).

In consequence of the changes in the glomerular and other blood-vessels, as well as probably owing to shrinkage of the newly-formed connective tissue, there results an atrophy of the urinary tubules (*a*), which become narrower and their epithelial cells lower, until finally the latter are entirely destroyed. The external tokens of this atrophy are numerous depressions (*B*) on the surface of the organ, between which little granules project (*A*), the latter containing tubules which are still normal or even hypertrophic, *i.e.*, dilated (*h*) and lined with enlarged epithelial cells. Furthermore, the capsule of the kidney is greatly thickened and

permeated by large blood-vessels and lymphatics. At this stage, owing to partial compression of the tubules by the shrinking connective tissue, retention of urine in the canaliculi (perhaps also in the cavities of the Bowman's capsules) not uncommonly results, and ultimately a formation of *cysts*, sometimes very numerous, which

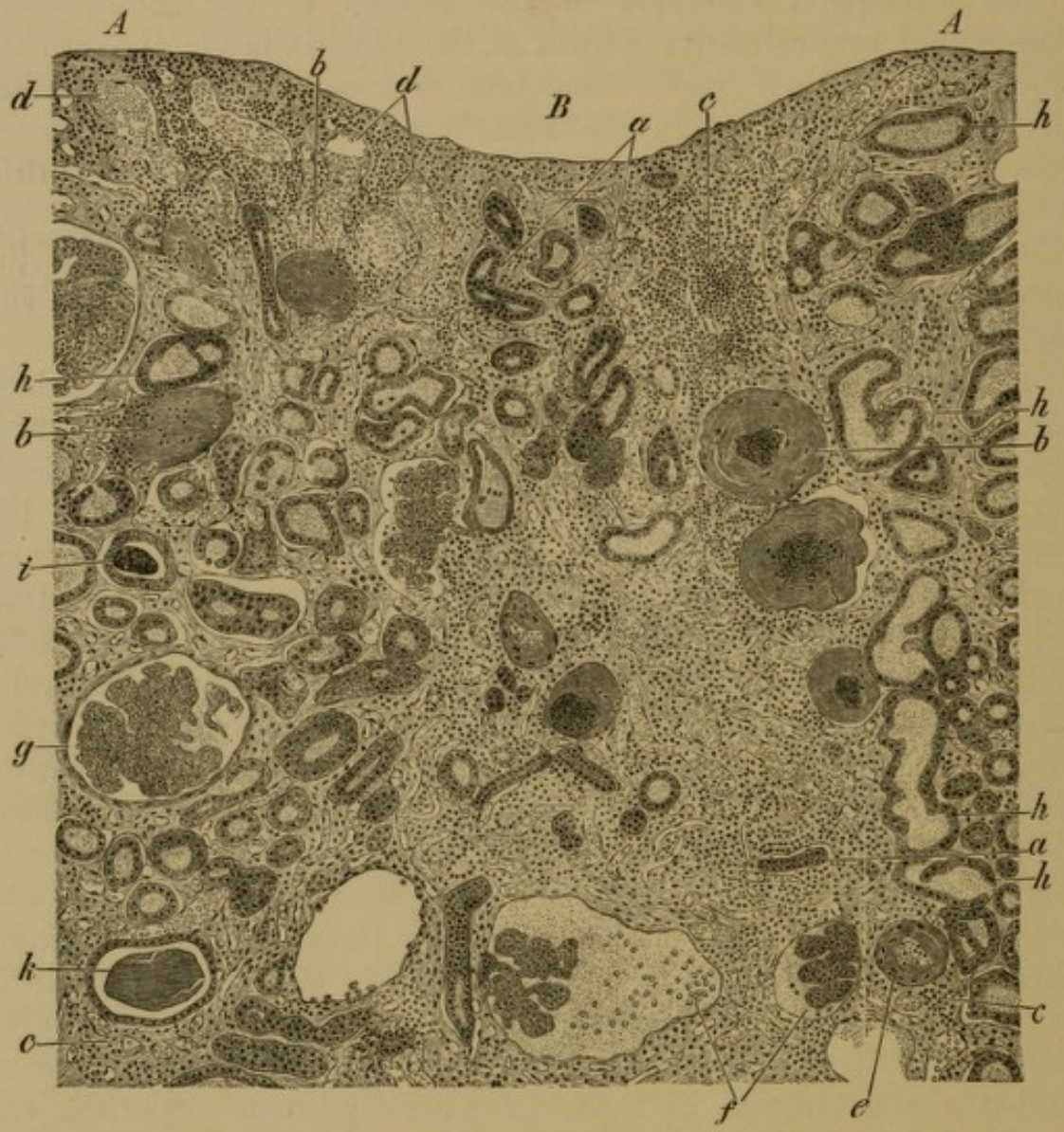

FIG. 149.—CHRONIC INTERSTITIAL NEPHRITIS in the stage of atrophy. × 77. (Hæmatoxylin and eosin.) *A*, Superficial granules; *B*, Depression of surface; *a*, Atrophied and partially compressed urinary tubules; *b*, Obliterated glomeruli, partly with concentric lamination of their connective tissue; *c*, Thickened interstitial connective tissue, in part infiltrated with small cells; *d*, Dilated blood-vessel; *e*, Artery with thickened (hyaline degenerated?) wall; *f*, Glomeruli in the cavities of whose capsules are collected a finely-granular exudation, and partly also red corpuscles; *g*, Glomerulus with thickened capsule; *h*, Dilated urinary tubule containing finely granular masses; *i*, Hyaline cast in a urinary tubule; *k*, Dilatation of a urinary tubule with colloid matter (small colloid cyst).

when very small may have *colloid* contents (*k*) but otherwise are filled with a thin fluid, and which are lined with low cylindrical or flattened epithelial cells. (See also p. 304.)

The *ætiology* of chronic interstitial nephritis is unknown. In many cases it develops immediately after diseases of infective origin.

6. Infective Granulomata, New-formations, and Parasites.—*Tuberculosis* occurs either in the acute miliary or in the chronic local form. In the former case it can often be observed with the microscope that the tubercles are situated around small vessels or glomeruli. In other respects their structure is the same as in other organs, but the epithelial cells of the tubules and even of the glomeruli may also by their growth take part in the formation of the elements of the tubercles, and even give origin to giant cells. *Chronic local tuberculosis* often develops in a way similar to pyelonephritis, *i.e.*, by ascent of the process from the lower urinary passages. It may lead to extensive caseations and to the formation of cavities, in which tubercle bacilli arranged in **S**-shaped groups are at times found in great numbers.

Of *new-formations*, *fibromata* commonly occur as small nodes in the medullary substance. *Sarcoma* is frequently *congenital*, and is then usually distinguished by the presence of transversely striated muscular fibres and of large spindle cells, also with transverse striation, which are young muscle fibres (*rhabdomyoma*). The *acquired* sarcoma may also in many cases occur in diffuse form.

The *adenoma* occurs especially in the kidneys of old persons, in the cortical substance as a rule, and may even be multiple. It appears in two principal forms. The *first* form may be described as *papillary adenoma*, since the tumour in its fully-developed state consists, like a papilliferous cystoma, of cavities with papillary excrescences, the walls of the cavities as well as the surface of the excrescences being usually covered with a cylindrical epithelium. This form appears to develop from the epithelium of the renal tubules, which proliferates in such a manner that folds of variable depth are formed in the tubules, and then assume more and more the look of papillary excrescences.

The *second* form probably always originates in detached portions of suprarenal capsule adherent to or embedded in the cortex of the kidney, and forms tumours which not uncommonly possess a great resemblance to the struma lipomatodes of the suprarenal capsule (p. 221). They consist of cylindrical masses of cells of variable thickness, usually coiled, and separated by a scanty amount of stroma. The cells also resemble those of the epithelium of the suprarenal capsule in assuming, like them, a yellowish or brownish tinge after hardening in Müller's fluid. The adenomata belonging to this group may sometimes attain a considerable size, may be divided up by fibrous septa into several lobes, and may undergo various retrograde changes. The most frequent of the latter is fatty degeneration, in which the adenoma-cells become filled with

droplets of fat, and appear when hardened in alcohol and examined in a balsam as scale-like, transparent, wrinkled structures. In other cases, however, some of the cells become dry and brittle, and finally crumble to pieces, whilst the remainder are pressed together and elongated, and then range themselves in lamellar rows; this change producing a resemblance to spindle-celled or fibro-sarcoma.

When the adenomata have attained a certain size they become separated off from their surroundings by a fibrous capsule formed by compression and condensation of the adjoining renal tissue, and hence frequently still containing atrophic urinary tubules and obliterated glomeruli. In this capsule, as well as in the septa of the adenomata, are sometimes found numerous very wide, varicose, and thin-walled blood-vessels, which readily burst and give rise to the formation of large hæmorrhagic cavities in the tumour, so that the latter comes to resemble a cavernous angioma.

Cysts occur in variable numbers in arteriosclerotic atrophy and in chronic interstitial nephritis; but they play a pre-eminent part in the so-called *cystic kidney*, since here the parenchyma may be almost entirely replaced by cysts of different sizes. These probably likewise originate merely in urinary tubules, and like the others their internal surface is covered with a single layer of flattened cells resting, at least in the smaller cysts, upon a distinct tunica propria, whilst the larger cysts in many cases want even a wall of their own. The contents are urinary fluid more or less diluted, but sometimes mixed with fat, cholestearin, blood, or masses of pigment. Vestiges of renal parenchyma may still be present between the cysts, or the latter may now be separated from each other only by fibrous tissue. Since the partition walls of the cysts are sometimes remarkably thin, there can be no doubt that a coalescence of the smaller cavities into large cysts may occur by the divisions being worn through. The cystic kidney may be congenital or acquired, and in the former case is ascribed to an inflammatory obliteration of the urinary tubules in the papillæ.

Carcinoma of the kidney usually presents no peculiarities. The mistake of confounding a large adenoma with a carcinoma will be guarded against by the presence of a fibrous capsule in the former case. Regarding the extension of a cancer of the renal pelvis to the kidney, see p. 309.

The only *animal parasites* requiring mention are *Echinococcus*, and *Distoma hæmatobium*.

II. THE URINARY DISCHARGING APPARATUS (RENAL PELVES, URETERS, BLADDER, AND URETHRA).

7. Inflammation.—*Inflammation of the renal pelvis and calices, pyelitis*, most frequently occurs as a complication of cystitis, and like it may be of a simple catarrhal, a suppurative, or a diphtheritic type. Its histological character is also like that of cystitis.

Acute cystitis occurs either primarily or secondarily (*i.e.*, by spread of an inflammation from the surrounding parts, or hæmatogenously, *e.g.*, in acute infective diseases), bacteria being usually the cause in both cases. In the *primary* form these are introduced into the bladder by instruments (catheters), but also under certain circumstances (where the urine drips away continuously, or in severe stricture of the urethra near the ostium vesicæ) from the urethra, which even normally contains bacteria. Several species of bacteria have been found in cystitis, amongst them, of the known pathogenic species, the *Staphylococcus pyogenes aureus*. They all seem to possess the property of decomposing urea, and either exercise an inflammatory action from this cause alone (*catarrhal cystitis*) or attack the mucous membrane itself (*purulent* and *diphtheritic cystitis*). In many cases stagnation of urine in the bladder or lesions of the mucous membrane constitute an essential or at least a favouring factor in the development of cystitis.

In the *catarrhal form* of cystitis swelling and desquamation of the epithelium is present, together with a moderate degree of small-celled infiltration of the mucosa; whilst the urinary sediment contains cells of bladder epithelium, crystals of triple phosphate and ammonium urate (p. 312), isolated red and white blood corpuscles, and numerous bacteria.

In *purulent cystitis* not only are pus-corpuscles present in and between the epithelial cells of the mucous membrane, but the surface of the latter itself, after shedding its epithelium, becomes covered with a layer of pus, and the tissue of the membrane is also more or less densely infiltrated with polynuclear and mononuclear leucocytes (Fig. 150, *a*). Sometimes the inflammation passes deeper, and centres of suppuration may then form in the muscular and subserous coats; indeed the inflammation may also extend to the connective tissue surrounding the bladder (*paracystitis*) or to the serosa (*pericystitis*). The urinary sediment, which forms a thick greyish-white deposit, contains in general the same constituents as in catarrhal cystitis with the addition of numerous pus cells.

Diphtheritic cystitis localises itself on the folds of the mucous membrane, appearing first in the trigone of the bladder in the form of small plaques, which show under the microscope a reticulated band-work formed by coagulation necrosis of the epithelium and in some cases also of the subjacent layer of mucous membrane, with more or less abundant pus-corpuscles deposited in and upon it (Fig. 151, *A*). These plaques may eventually coalesce, and may further become incrusted with "gravel," which consists mostly of ammonio-magnesian

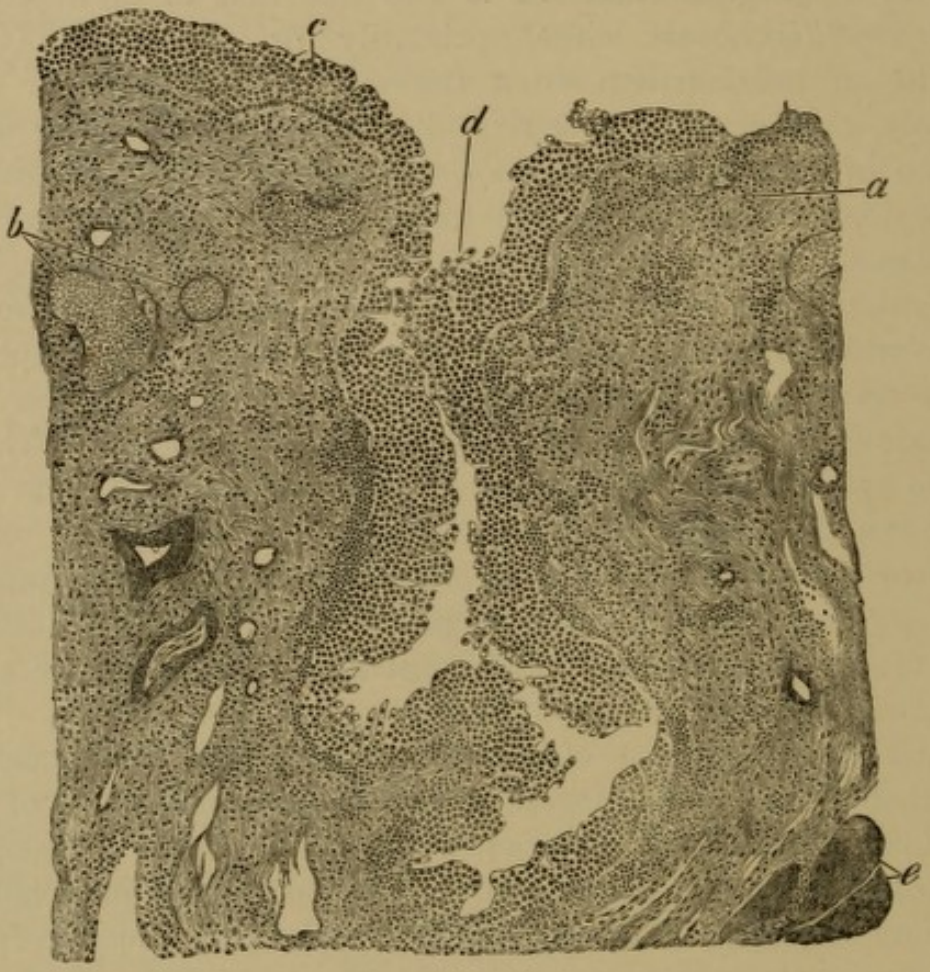

FIG. 150.—PURULENT CYSTITIS WITH COMMENCING FORMATION OF DIVERTICULA. × 65 (Hæmatoxylin and eosin.) *a*, Mucous membrane infiltrated with small cells; *b*, Dilated blood-vessels; *c*, Stratified epithelium of the mucous membrane; *d*, Small diverticulum with two secondary offshoots; *e*, Bundle of smooth muscular fibres cut transversely.

phosphate. Beneath the diphtheritic deposits the mucous membrane shows cellular infiltration (*C*), and sometimes also extravasations of blood (*a*).

In the *chronic* forms of cystitis the lymphoid nodules normally existing in the mucous membrane may enlarge and multiply, and a further result, especially where there is obstruction to micturition, may be *hypertrophy of the muscularis*, and subsequently also formation of *diverticula*, which may either remain simple, or may acquire secondary bulgings in their floor (Fig. 150, *d*). The mucous

membrane in the area of the diverticulum shows inflammatory changes the same as (or even still more intense than) that elsewhere.

The most frequent of the *inflammations of the urethra* is that caused by the *Gonococcus* (*gonorrhœa*). This may also spread to perhaps all the other parts of the urinary discharging apparatus, as well as to the vas deferens and the epididymis, and possibly may even cause metastases in the joints. The histological changes in the

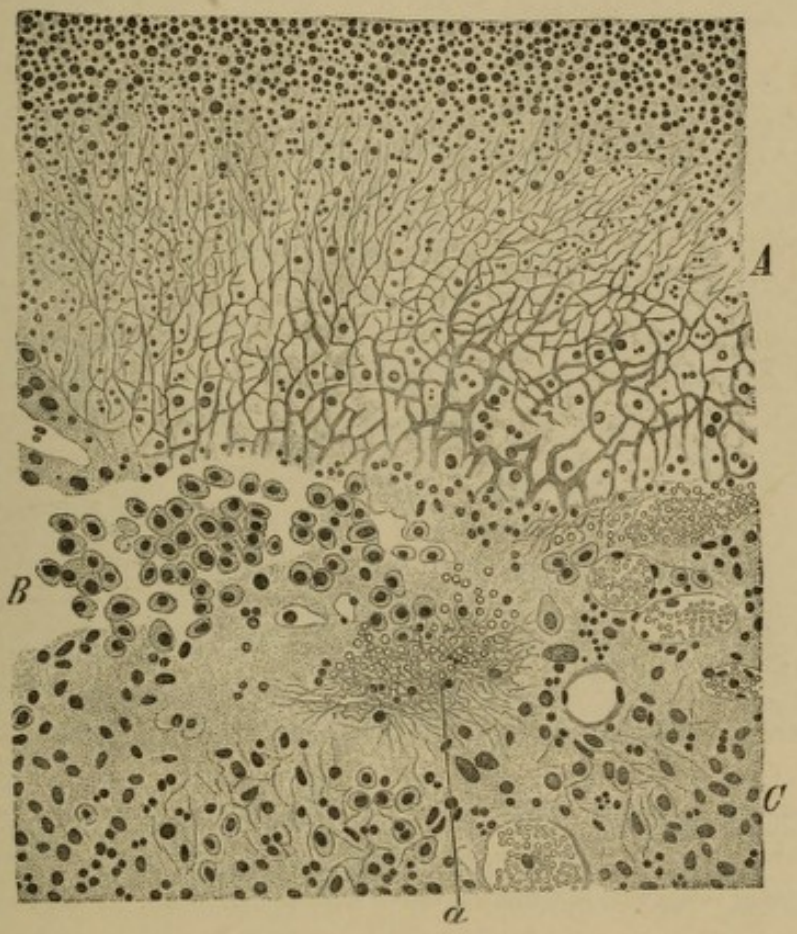

FIG. 151.—DIPHTHERITIC CYSTITIS. × 285. (Hæmatoxylin and eosin.) *A*, Focal diphtheritic exudation composed in its superficial segment of partially disintegrated pus-corpuscles, in its lower segment of a net-like bandwork, which below and to the right passes directly into the tissue of the mucous membrane, but below and to the left is still separated from this by remains of epithelium (*B*); *C*, Mucous membrane with cellular infiltration which consists of polynuclear and large mononuclear round cells; *a*, Small extravasation of blood.

acute stage of *gonorrhœal urethritis* are like those in purulent cystitis; the secretion is composed solely of pus corpuscles, in the protoplasm of which the gonococci are usually situated, although the latter may also occur free (perhaps after bursting of the pus cells). The *acute* very often passes into a *chronic* stage, in which the secretion becomes very scanty, is composed principally of young epithelial cells, and also contains but few gonococci. At this stage an infiltration is found in the superficial layers of the mucous membrane which

consists of mononuclear round cells and of epithelioid cells, and which also penetrates deeper along the lacunæ and the ducts of Littre's glands, even reaching into the corpus cavernosum, and eventually changes into shrinking connective tissue (Fig. 152, *b*). The epi-

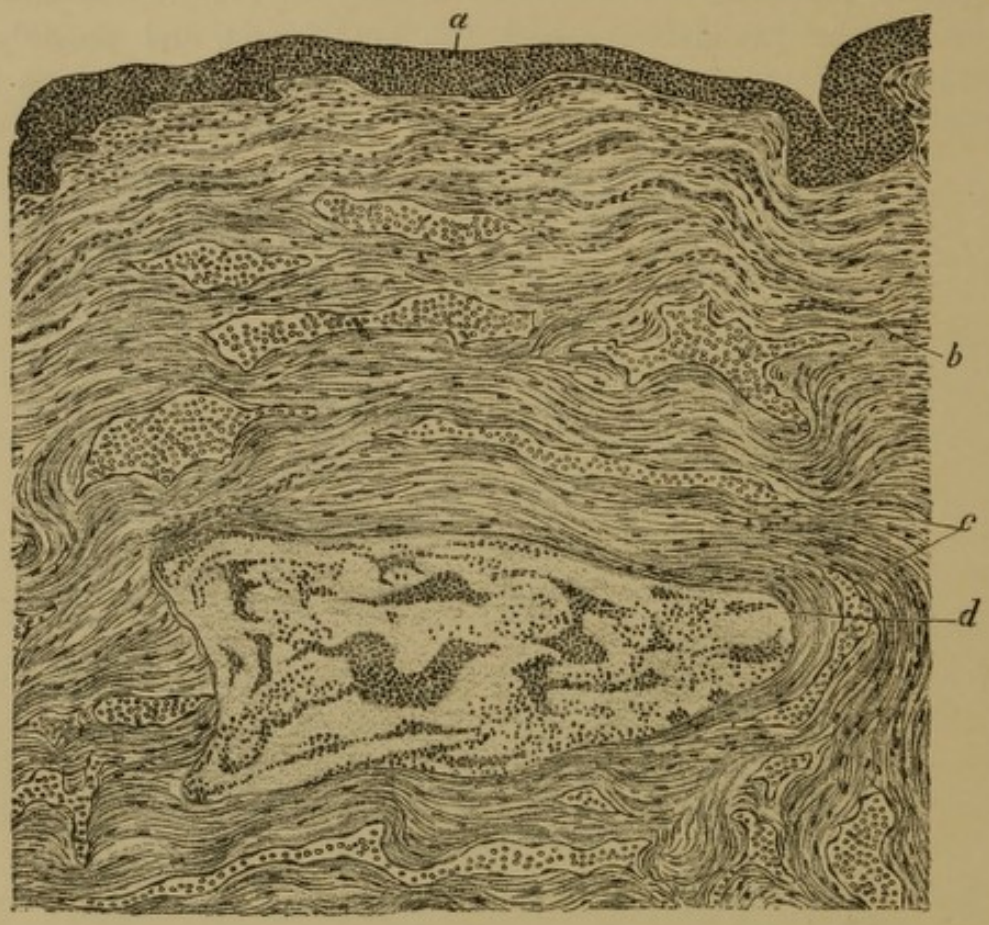

FIG. 152.—CICATRICIAL STRICTURE OF THE PARS PENDULA URETHRÆ IN CHRONIC GONORRHŒAL URETHRITIS. × 77. (Alum cochineal.) *a*, Stratified squamous epithelium; *b*, Connective tissue in contraction, but still containing a fairly large number of spindle cells; *c*, Narrowed spaces of the corpus cavernosum; *d*, Remains of a Littre's gland destroyed by contracting periglandular and interstitial infiltrations.

thelium is at first in a state of proliferation and desquamation, and partially also of mucous degeneration; later it is transformed into squamous epithelium (*a*). At the same time the lacunæ and Littre's glands may be destroyed (*d*), owing to the change of the cellular infiltration situated immediately around them and between the acini of the glands into a contracting cicatrix. Under certain circumstances, notably when the cicatricial tissue extends into the corpus cavernosum, a narrowing or *stricture* of the urethra may even result.

If in the presence of strictures wounds of the urethra have been caused in passing a catheter (*false passages*), the entrance of the urine and the bacteria existing in it into the wounded tissue (urinary infiltration) may lead to the setting up of a suppurative or putrid inflammation of the periurethral connective tissue (*periurethritis*).

Croupous and *diphtheritic inflammations of the urethra* are rare. They are most likely to occur with strictures, in consequence of wounds caused in passing catheters.

8. Infective Granulomata, New-formations, and Parasites.—*Tuberculosis of the renal pelves and ureters* usually occurs in diffuse form, in which the greatly thickened wall of the pelvis and ureter appears changed in greatest part into a superficially-disintegrating caseous mass, tubercles (usually of the giant-celled kind) being recognisable only in its outermost portions. In the *bladder*, tuberculosis begins with the formation in the mucous membrane of nodules showing the typical structure, which coalesce, soften, and break down into ulcers. They must not be confounded, as might happen, with the lymphatic follicles normally present in the mucous membrane. Besides these, more diffuse caseous infiltrations may also occur. As tubercular infection of the bladder usually takes place by the urine (which conveys the tubercle bacilli from the upper urinary passages and the kidneys), or is due to extension of tubercular disease from the sexual organs, the earliest nodules are usually found near the openings of the ureters or at the cervix of the bladder.

The *carcinomata* which occur in rare cases in the *renal pelvis* or *calices*, and then extend to the *kidney* also, originate from the so-called transitional epithelium covering the mucous membrane of the parts in question, and may under certain conditions assume the character of a flat-celled epithelioma, in a manner analogous to that in which the epithelium of the mucous membrane of the urinary discharging apparatus in general may attain an epidermoid appearance in chronic inflammations, in consequence of horny transformation of its uppermost layers.

Amongst the *new-formations of the bladder*, the *papilloma* (also wrongly called *villous cancer*) is the most frequent. It is usually situated in the trigone, and is made up of very long, narrow, and much-branched villi or papillæ (Fig. 153), whose bodies sometimes contain almost no connective tissue at all, but only wide blood-vessels (*c*) with delicate walls and enveloped in round cells, and are covered with a stratified epithelium (*e*) like that of the bladder. Owing to the thinness of the walls of the blood-vessels hæmorrhages are frequent. Portions of the villi may also be cast off and evacuated with the urine. The tumour may indeed exist in the bladder in multiple form, but it does not advance in depth, differing in this respect from *carcinoma villosum* (Fig. 49), which, although it also forms villous outgrowths, at the same time produces characteristic cancerous alveoli in the mucous membrane or in still deeper layers of the bladder wall.

Polypoid and *papillary growths* may also be observed in the *urethra,* notably in chronic inflammations, the latter being also known as *acuminate condylomata.*

As regards the presence of *vegetable micro-organisms* in the *urine;* in the first place, in diseased conditions of the urinary apparatus due to bacteria, the corresponding pathogenic species (pyococci, gonococci, tubercle bacilli, typhoid bacilli, and others) may be found. Furthermore, in isolated individuals certain saprophytic bacteria which have not yet been accurately determined may also

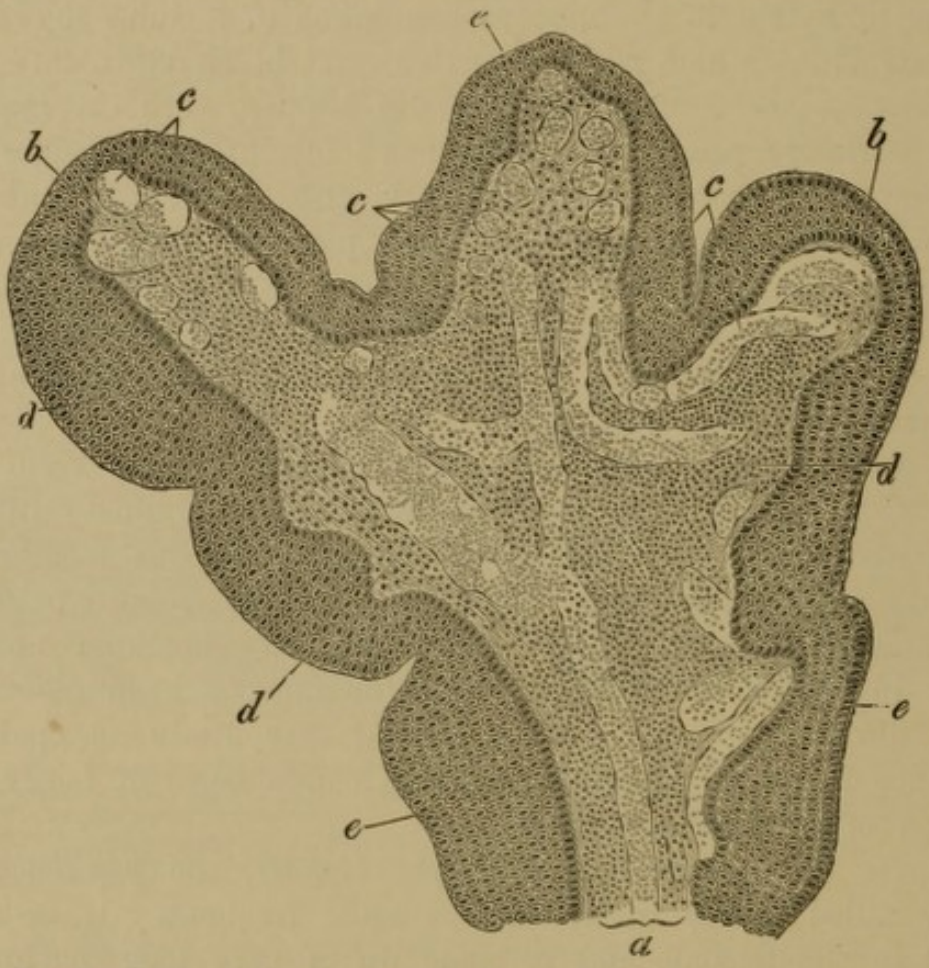

FIG. 153.—PORTION OF EXCRESCENCE OF A VESICAL PAPILLOMA, EVACUATED WITH THE URINE. × 95. (Alum cochineal.) *a*, Trunk of the papilla; *b*, Branches of papilla; *c*, Loops of blood-vessels cut longitudinally and transversely; *d*, Stroma of the papilla infiltrated with small cells; *e*, Stratified squamous epithelium.

occur without recognisable disease of the urinary system (*bacteriuria*). Otherwise, when freshly passed and caught aseptically, the urine is usually free from bacteria, whereas when left to stand for some time exposed to the air it becomes continually richer in saprophytic species, which also induce ammoniacal decomposition. In *diabetes* yeast-fungi are also present in the urine, in which they may cause an alcoholic fermentation.

Of *animal parasites* must be mentioned the *Echinococcus* and also *Filaria sanguinis* and *Distoma hæmatobium.*

Examination of Urinary Apparatus and Urine.—The *degenerative processes* in the kidney, *cloudy swelling*, and *fatty* and *amyloid degenerations*, as well as *pigmentary*, *calcareous*, and *uric acid infarctions*, and *fat-embolism*, can all be examined in the *fresh* state, according to the directions given on pp. 52-3, 57-8, 60, 62, and 290. The methods for examining the above processes in *hardened* preparations are also detailed at the places referred to. It should further be noted that the uric acid deposits do not give the peculiar colour in staining with hæmatoxylin which is characteristic of calcareous masses.

Otherwise, except in examining for bacteria, Müller's fluid followed by alcohol is used for *hardening*, and hæmatoxylin with eosin, or the simple carmine solutions, for *staining*. For the demonstration of albuminous fluids in the Bowman's capsules, urinary tubules, and interstitial tissue of the kidney, the boiling method may also be used (p. 8). As regards the choice of the *embedding* medium, what has been said with reference to the examination of the buccal cavity (p. 232) and of the lungs (p. 290) holds good here also.

The microscopic examination of the *urine* is usually conducted by leaving the latter up to twenty-four hours to settle in a conical glass[1] in a cool place (an antiseptic such as thymol being added if necessary), and then taking a minute drop of the sediment by means of a pipette. The following are the most important constituents :—

1. *Epithelial cells.*—Isolated epithelial cells are present even in normal urine, and are then principally of the squamous kind, being derived from the urinary passages. Only when they are present in large numbers is one justified in concluding that catarrh exists. Since, however, the renal pelves, the ureters, and the bladder possess a like epithelium, it is impossible to decide from the form of the cells as to which of their mucous membranes is the seat of the catarrh. In the case of women the possibility must also be borne in mind that epithelial cells from the vagina (squamous cells) may be mixed with the urine.

Of much greater importance is the occurrence of cells from the *renal* epithelium, which are smaller than the foregoing, of polyhedric figure, and frequently in a state of degeneration, and which are found lying either isolated or on the surface of casts, or even themselves moulded into cylindrical structures (epithelial casts). They then afford conclusive evidence of nephritis.

2. Isolated *leucocytes* may likewise be present even in normal urine. Should they occur in larger quantity they indicate a suppurative inflammation of the urinary passages, or the rupture of an abscess. They are most numerous in purulent cystitis, in which they form a bulky puriform sediment visible even to the naked eye. In women they may also come from vaginal blennorrhœa, should its secretion have mixed with the urine. In nephritis cylindrical structures also occur which consist solely of leucocytes, or isolated specimens of the latter may lie upon the surface of other tube-casts. If the nuclei of the leucocytes or epithelial cells are not visible, half per cent. acetic acid should be applied to the preparation.

[1] To bring about sedimentation more rapidly we may avail ourselves of Stenbeck's sedimentator, which works by centrifugal force. It is of service especially in those cases in which the urine is very poor in solid elements (cells, casts, bacteria, and so forth), and hence yields no distinct sediment on standing.

3. *Red corpuscles* may likewise be found in acute nephritis, in the form of cylindrical structures (blood-casts), or else lying more scattered and then usually as colourless or pale yellow rings; and they also occur in venous hyperæmia, the so-called congestive kidney, though only in very small numbers.[1] In hæmorrhages from the bladder and urethra not only is the quantity of the red corpuscles much larger, but they are not intimately mixed with the urine, so that in sedimentation of the latter they form a layer readily recognisable from its red colour, which is not the case in hæmorrhage from the kidney, renal pelvis, or ureters, owing to the intimate mixture of the red corpuscles with the urine in these affections.

4. The different varieties of *tube-casts* have already been discussed (p. 297). The *hyaline casts* may be present in non-inflammatory disorders of the renal circulation also, so that the existence of a nephritic process must not be at once assumed from their presence in the urine, especially if they occur in small numbers and are not covered with any layer of renal epithelial cells, leucocytes, or red corpuscles. On the other hand, such a conclusion is as a rule allowable in the presence of *epithelial*, *leucocyte-*, or *blood-casts*, all three of which are frequently present together; or of *granular casts*, to which also cells of renal epithelium, white corpuscles, fat-drops, and fatty crystals may adhere.[2] To render the very pale hyaline and waxy casts more distinctly visible, Lugol's solution, picrocarmine, or a watery solution of a basic anilin colour may be added. Under this treatment the waxy casts in many cases show a similar reaction to amyloid substance.

Those constituents of the sediment which consist of *crystals* and *amorphous precipitates* are of less importance. In *acid* urine can be found crystals of *uric acid* (readily recognisable from their yellowish-brown colour); *calcium oxalate* (envelope crystals); *triple phosphate* (prismatic crystals with bevelled ends); *hæmatoidin* (after antecedent hæmorrhages); in many cases also *leucin* and *tyrosin* (in acute yellow atrophy of the liver, and phosphorus poisoning); and furthermore, very frequently amorphous precipitates of *sodium urate* in the form of very small granules lying singly or in mosslike groups. In *alkaline* urine, on the other hand, crystals of *triple phosphate* and of *ammonium urate* (thorn-apple or morning-star form) are especially apt to occur. Sodium urate when present in quantity forms, as is well known, a brick-red sediment even after standing but a short time.

Amongst the less common constituents of the sediment *fat drops* have still to be mentioned, which may be found in small quantity in chronic nephritis and in fractures, in larger quantity in the chyluria caused by *Filaria sanguinis* or *Distoma hæmatobium*; *hæmoglobin* in the form of brown drop-like figures (in hæmoglobinuria);[3] *scolices*, *hooks*, or *vestiges of cysts* of *Echinococcus*, in cases

[1] Stenbeck's apparatus is particularly well adapted for the demonstration of very small quantities of red corpuscles.

[2] Granular casts must not be confounded with finely-granular precipitates of urates or cocci, which may also at times arrange themselves in the form of casts. The urates, however, dissolve on warming the urine or on addition of acids, whilst the cocci are very resistant to acids and alkalies, and stain intensely with anilin colours.

[3] By using Stenbeck's centrifuge *hæmoglobinuria* can be distinguished from *hæmaturia* even with the naked eye, since in the latter the fluid standing above the sediment is colourless, but in the former of a reddish-brown tint.

where the latter ruptures into the urinary passages ; and lastly (but only in the tropics), *Filaria sanguinis* and *ova* of *Distoma hæmatobium*. Sometimes also small *particles of tumours* pass away with the urine, usually derived from tumours of the bladder or urethra. They are in general examined according to the directions on pp. 110 and 111. If they originate from a *papilloma* or *villous carcinoma*—and this is most usually the case—the papillary structure of the tumour may often be recognised even in torn-up preparations ; and in case of villous cancer it will also be possible to make out that the epithelium on the surface of the villi is composed of remarkably large and polymorphic cells (see Fig. 49, *b*). For *certain* diagnosis between papilloma and carcinoma, however, the further examination of sections is essential, and even this will only permit a perfectly positive conclusion of the existence of carcinoma to be arrived at when characteristic cancerous alveoli can be recognised in the particles of tumour. Should only *cells* of tumours, *e.g.*, of carcinomata, be found in the urinary sediment, their recognition will be much more difficult still, especially as the epithelial cells of the urinary passages also recall the appearance of cancer cells by their polymorphism.

For the methods of examining the urinary apparatus and urine for *vegetable micro-organisms*, see Part II., Chapter V.

CHAPTER VIII.

THE GENERATIVE APPARATUS.

I. THE MALE GENERATIVE ORGANS.

1. Inflammation and Hypertrophy.—*Acute inflammation of the testicle and epididymis* (*orchitis* and *epididymitis*) is most frequently caused by the spread of an inflammation, especially that of gonorrhœa, from other parts of the urogenital apparatus. Less often it arises metastatically in pyæmia, parotitis, etc. In the *epididymis* the canals are found distended with a mass composed of desquamated epithelial cells, leucocytes, and mucus, or exclusively of pus-corpuscles. The epithelial layer is infiltrated with leucocytes or is already cast off, and the interstitial connective tissue shows serous exudation and foci of small-celled infiltration.

In the *testicle* the chief changes are in the interstitial connective tissue, and here the process more readily goes on to formation of abscesses. In *variola* there very often occur in the testicle peculiar foci which are mostly visible even to the naked eye, being of a yellowish colour (*orchitis variolosa*), and in which two or three zones can be distinguished by microscopic examination. The innermost zone consists of necrotic tissue, and is succeeded, first by a layer of densely-packed leucocytes partially in a state of granular disintegration, and frequently also by a stratum of larger or smaller round cells with filamentous exudation lying between them, which forms the third zone. In these foci streptococci can sometimes be met with, but probably merely effect a lodgment there secondarily, whereas the foci themselves are plainly due to the specific contagium of the small-pox. Should inflammation of the testicle last for a greater length of time it may assume an *indurative* character, *i.e.*, the interstitial connective tissue and fibrous tunica propria of the seminiferous tubules undergoes thickening, in consequence of which the lumen of the tubules is narrowed and the epithelial cells—the

semen cells first—undergo fatty degeneration and are destroyed. The thickened interstitial tissue gradually becomes sclerotic or takes on the character of mucous tissue, and then encloses merely isolated bands of epithelial cells as relics of the atrophied tubules, bands which are not unlike cancer-cell cones, especially when, as is often the case, there is in addition atypical proliferation of the epithelium.

In *inflammation of the tunica vaginalis propria* of the testicle, which occurs in either acute or chronic, primary or secondary form (the last especially in inflammations of the testicle and epididymis), the sac of the tunica is found in most cases to contain a serous, less often a fibrinous or purulent, exudation. The serous exudation at first is still more or less clouded with delicate filaments of fibrin and with white, sometimes also with red, blood corpuscles; but later it becomes perfectly clear. If it is present in large quantity the condition is spoken of as a *hydrocele*. Sometimes the fluid in the latter shows a milky turbidity from the presence of cholestearin crystals, or is inspissated to a pultaceous mass, and it may also contain spermatozoa should a vas aberrans open into the vaginal sac (*spermatic hydrocele*). When a hydrocele is of longer standing we often find lamelliform thickenings consisting of parallel-striped connective tissue poor in cells, or villous and even branched arborescent outgrowths from the tunica, or adhesions of its two layers to one another. The outgrowths alluded to may tear off and appear as *free bodies* in the cavity, in which case they usually calcify at their centre. In many hydroceles not only does a very considerable and constantly increasing new-formation of connective tissue take place in the walls, but this connective tissue is also very rich in wide blood-vessels, the bursting of which gives rise to hæmorrhages into the tissue and into the cavity of the tunica vaginalis (*hæmatocele*). *Inflammations of the vas deferens and vesiculæ seminales* usually occur as the result of inflammatory processes in the urogenital apparatus and have a character similar to the latter processes.

Inflammation of the prostate, prostatitis, also occurs as a rule only by extension of an inflammatory process to the organ from the neighbouring parts. When the inflammatory excitants wander in along the prostatic duct, *e.g.*, in urethral inflammations, we see the first changes within the area of the glandular portion of the prostate, *i.e.*, we find the ducts and acini filled with pus-corpuscles, which afterwards make their way thence into the fibro-muscular tissue of the organ. In this manner small abscesses form corresponding to the glands, but may eventually coalesce. Besides this, in the rare *embolic prostatitis* the suppuration may also commence first in the gland

canaliculi, since the blood-vessels extend close up to the glandular epithelium.

The inflammatory processes occurring in the *skin of the penis and scrotum* correspond with those in other parts of the skin (see Part III., Chapter XI.). On the *glans penis* an acute inflammation may develop from decomposition of the smegma or owing to purulent discharge from the urethra (*balanitis* and *posthitis*). In *inflammatory phimosis* and *paraphimosis* the primary condition is an acute œdema of the subcutaneous connective tissue of the prepuce. It may, however, subsequently lead to gangrene.

In the *hypertrophy of the prostate* which often occurs in later life, a *fibrous* form and an *adenomatous* form are distinguished, the former consisting in an increase of the fibro-muscular portion of the prostate

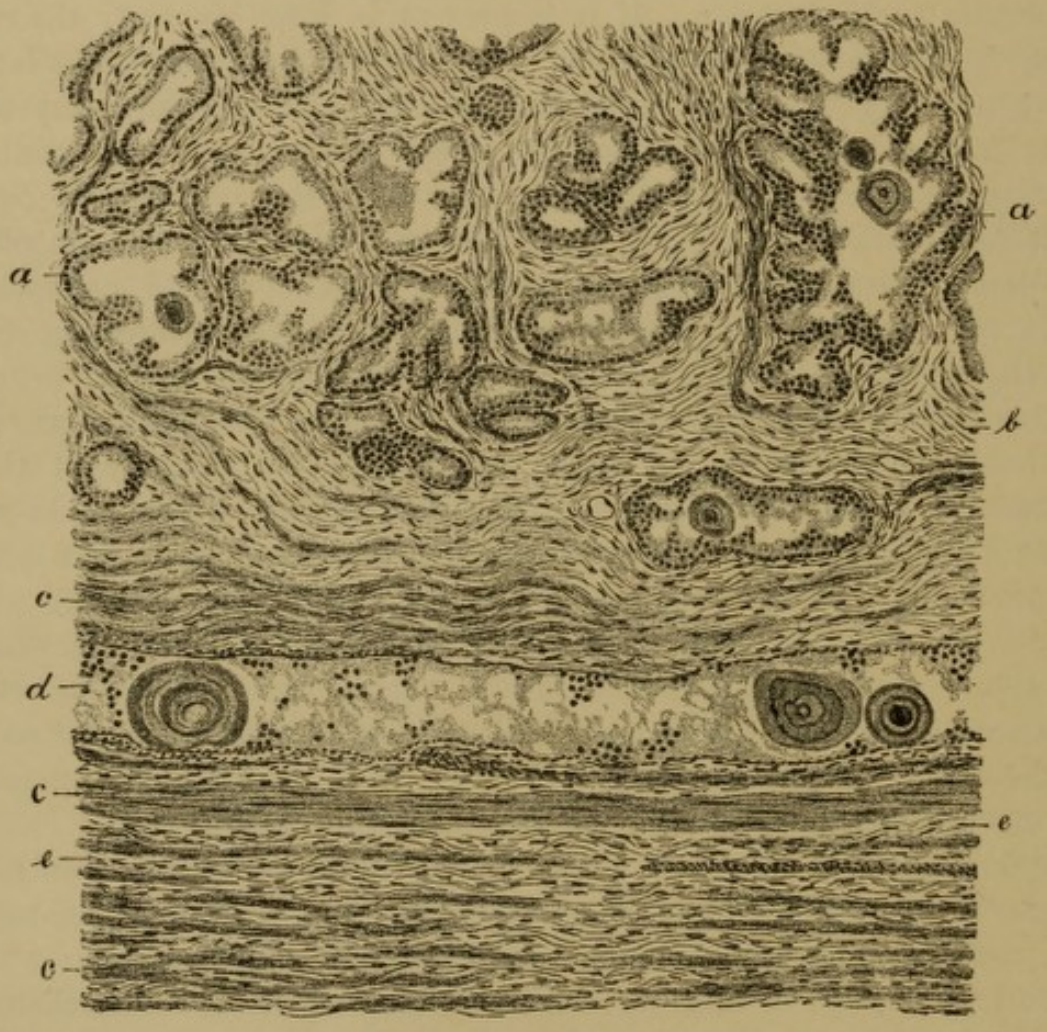

FIG. 154.—HYPERTROPHY OF THE PROSTATE, ADENOMATOUS FORM. × 70. (Hæmatoxylin and eosin.) *a*, Acini, some of them dilated and containing small corpora amylacea; *b*, Interacinous connective tissue; *c*, Bundles of smooth muscle; *d*, Gland duct with larger laminated corpora amylacea; *e*, Intermuscular connective tissue.

with simultaneous atrophy of the glands, whilst the latter, which is characterised by the occurrence of nodules (Fig. 154), depends

chiefly upon a growth of the glands, with which a dilatation of the gland tubes may also be associated (*a*). In the ducts (*d*) and acini (*a*) of the glands, corpora amylacea (see p. 57) of variable size and usually laminated structure are often found, not only in prostatic hypertrophy, but in elderly individuals generally.

2. Infective Granulomata and New-formations.—*Tuberculosis* in the *testicle* and *epididymis* occurs more rarely in the acute form as a part of general miliary tuberculosis, being usually chronic. In the latter case it commonly develops by the ascent of a tuberculosis from the prostate or vesiculæ seminales, although the possibility of its independent development in the testicle cannot be denied, in the face of the fact that on some occasions tubercle bacilli have been found in phthisical persons in the tubules of the testicle while the latter was still intact.

In the majority of cases the process begins in the epididymis, and produces both in this organ and the testicle compound tubercles, which are frequently distinguished by the presence of giant cells of remarkable size. The elements composing the tubercles are derived, at least in chief part, from the cells of the interstitial connective tissue; still, the epithelial cells of isolated seminal tubules, as well as the cells of their walls, may also bear a part in the formation of tubercles, whilst, however, the other tubules become compressed, or their epithelial cells undergo fatty degeneration.

Syphilis is met with in the testicle in two forms. The *first*, which is only found in congenital syphilis, consists in growth of the connective tissue, first in the mediastinum and septa, later also between the seminiferous tubules and in their walls. Owing to the shrinkage of the newly-formed connective tissue the tubules are narrowed, and at length quite closed. The blood-vessels also commonly show the appearances of syphilitic vasculitis (p. 206). The *second* variety of syphilis of the testicle leads to the formation of gummata, which later subside again or ulcerate. A growth of connective tissue usually takes place also in the neighbourhood of the gummata, perhaps in the same manner in which it accompanies the first form.

The *new-formations of the testicle and epididymis* which deserve chief notice are *cysts*, *adenomata*, and *carcinomata*. The *cysts*, which may form by retention of secretion in the tubules of the testicle and epididymis, as well as in the vasa aberrantia, not uncommonly include spermatozoa in their contents (*spermatocele*). They are unilocular or multilocular, and their walls are covered with ciliated, columnar-celled, or squamous epithelium, and sometimes also bear papillary protuberances (*papilliferous cystoma*). In *adenomata* also

there frequently results a formation of simple or papilliferous cysts, whose contents are either mucous (*mucous cysto-adenoma*) or pultaceous (*atheromatous cysto-adenoma*). In the former case the cyst-wall has a cylindrical, in the latter a stratified squamous, epithelium. Not uncommonly combinations of the adenoma with sarcomatous, mucous, cartilaginous, bony, or adipose tissue are observed; while carcinoma may likewise combine with sarcoma or enchondroma. Cysts may also form in carcinomata owing to colloid degeneration of the cancer cells. Lastly, *leiomyomata* and *rhabdomyomata* have been observed.

Of *new-formations in the penis, carcinoma* and *acuminate condyloma* require notice. The former is usually an epithelioma containing many pearls, but whose stroma often exhibits an exact papillary structure, so that the tumour then resembles a villous carcinoma. The *acuminate condylomata*, which so frequently exist on the glans and prepuce of the penis, have the structure of the papilloma (p. 108).

II. THE FEMALE GENERATIVE ORGANS.

A. DISEASES OF THE OVARIES AND FALLOPIAN TUBES.

3. Inflammation and Infective Granulomata.—*Acute inflammation of the ovary, oöphoritis* or *ovaritis*, usually develops by the advance of an inflammation from the neighbouring parts, the primary inflammation being usually puerperal, but sometimes also gonorrhœal. The tissue of the ovary is infiltrated with serous or sero-fibrinous exudation or riddled with suppurative foci, with or without hæmorrhages; and partial necrosis may even result. More intense inflammations leave certain changes behind which are also described as *chronic ovaritis*, and consist in adhesions, cicatricial retractions, and diminution in size of the ovary. Some of the Graafian follicles are changed into fibrous bodies, whilst others may be in a state of cystic degeneration. Sometimes also isolated foci of round cells are found in the tissue of the ovary. The blood-vessels may in part undergo hyaline degeneration or become obliterated.

Inflammation of the Fallopian tubes, salpingitis, always develops exclusively by the advance of an inflammatory process occurring in the neighbouring parts (uterus, ovaries, peritoneum), and is therefore caused mostly by pus bacteria or gonococci. In the slighter degrees of the inflammation, if the secretion is mucous, the epithelium is found in a state of mucous degeneration and desquamation, whilst the folds of the mucous membrane may form more or less thick villus-like outgrowths in consequence of small-celled

infiltration. In inflammation of higher degree the contents of the tube consist of pus and the mucosa is transformed into granulation tissue. Owing to partial adhesions of the folds of mucous membrane one to another irregular and sacculated cavities may form in positions where the epithelium of the folds is still retained, and these cavities also may then become distended with secretion. When the inflammation is of longer standing it may also advance to the deeper parts and to the serosa, leading on the one hand to fibrous thickening of the wall, on the other to adhesions of the tube to neighbouring parts, to closure of its abdominal aperture, and consequently to accumulation of the secretion in the external portion of the tube. If at the same time its uterine aperture is narrowed (by swelling of the mucous membrane, kinking of the tube, inspissation of the secretion, or other cause), the tubes may sometimes be very considerably distended with purulent, mucous, or serous fluid.

In *tuberculosis* of the female generative apparatus the *tubes* are often the first parts to be affected (perhaps by infection with semen containing tubercle bacilli). The tubercles which form in the mucosa very soon fuse to a granulation tissue the surface of which is undergoing caseation, whilst the outer layers of the wall of the tube may thicken by hyperplasia of the connective tissue.

4. Cystic Degeneration and New-formations.—In the *ovary*, a *cystic degeneration of the Graafian follicles, hydrops folliculorum*, is very frequent. It may affect either isolated follicles only or a very large number, the cavities becoming filled with a thin fluid like serum, whilst the theca folliculi becomes the cyst-wall, and the follicular epithelium is transformed into a simple parietal border composed of low, or more rarely high, cylindrical cells. The ova are usually destroyed in the process, and it is only in the smaller cysts that they can still be recognised. If several cysts are present they may coalesce by the wearing through of their dividing walls. Should the cyst become very large, the remaining portion of the ovary may atrophy away; otherwise isolated follicles can always still be recognised.

If besides a hydrops folliculorum there also exists a *hydrops tubæ* (distension of the Fallopian tube with serous fluid, as above) and adhesion of the ovary to the tube, as the distension of the latter and of the ovarian cyst advances, there sometimes results a communication between the two cavities (*tubo-ovarian cyst*). *Dermoid cysts* are also met with in the ovary with tolerable frequency, both the simple form and those containing teeth, bones, and so forth. *Fibromata* and *sarcomata* of the ovary may likewise be combined with formation of cysts.

The *cystomata*, also called *adeno-cystomata*, differ from mere retention cysts. They develop by cystic dilatation from newly-formed simple or bulging gland-tubes, which are derived from the follicles of the ova or their primitive germs; but they may also perhaps form from mere retention cysts by papillary growth of the walls of the latter. The cystomata are unilocular or multilocular, but the latter may become unilocular in time by the disappearance of the dividing walls. According as the wall of the cyst-cavity is smooth or shows papillary growths (Fig. 46, *b*) of variable size, sometimes even filling up the entire space, we speak of a *simple cystoma* and a *papilliferous cystoma*, or *proliferous cysto-adenoma*. Gland-like structures or smaller cysts are, however, often found in the wall even of the simple cystoma. Otherwise the walls of both varieties of cystomata consist of laminated connective tissue, the innermost stratum of which is richest in cells and forms the papillary outgrowths in the papilliferous cystoma. This stratum as well as the outgrowths in question are covered with a simple high or low cylindrical epithelium, sometimes ciliated, which is not uncommonly in a state of mucous transformation (Fig. 46, *c*), and then also contains goblet cells.

The *contents* of the smaller cystic cavities consist of a clear or turbid mucous fluid, which is for the most part a product of the mucous degeneration of the epithelial cells, and which besides the latter may also show round, partly fatty-degenerated cells, nuclei, and droplets of fat, and sometimes also red corpuscles and pigment-granules. In larger cysts, however, the contents more and more lose their mucous character.

Papillary cystomata often take on a malignant character, in which case the excrescences not only break through the walls of the cysts and grow out to the surface of the tumour, but may also lead to metastatic growths on the peritoneum.

Carcinoma is tolerably often observed in the ovary, and sometimes shows a structure recalling the appearance of tubular glands. In many instances the cancer alveoli contain deposits resembling brain-sand (*carcinoma psammosum*).

B. DISEASES OF THE UTERUS.

5. Inflammation.—During *menstruation* not only is the mucous membrane of the uterus very hyperæmic, but extravasations take place into its substance and upon its surface, in which the escaped blood raises the epithelium, and even the superficial layers of the mucous membrane, and causes them to desquamate. In *membranous dysmenorrhœa* membranes or pieces of such are evacuated with the menstrual blood. These have the structure either of a fibrinous

exudation (fibrinous reticulum with leucocytes and red corpuscles entangled in it), or of an inflamed uterine mucous membrane (connective tissue rich in cells and partially infiltrated with red corpuscles, containing blood-vessels and tubular glands); or else they may consist merely of flat-celled epithelium in a single layer or in several layers, which may be perforated in a cribriform manner to correspond with the openings of the glands. In the latter case the epithelium is derived from the cervix, in women in whom the cylindrical epithelium has become transformed into squamous during the course of a chronic inflammation, or in whom, at all events, the latter epithelium extends higher up than usual. *Endometritis* is regarded as the cause of the desquamation of such membranes (*endometritis exfoliacea*).

Inflammation of the uterine mucous membrane, endometritis, may (apart from the *puerperal* form) occur *primarily* or *secondarily*—in the latter case either by extension of a vaginitis or hæmatogenously—and is probably always caused by bacteria, of which up to the present it has been possible to demonstrate the *Gonococcus* and the *Diplococcus pneumoniæ* as excitants. As regards the *character* of the inflammation, it may be *catarrhal* (in which form the secretion may be mucous or purulent), *croupous,* or *diphtheritic,* the catarrhal being the most frequent. The histological changes are in general similar to those in inflammations of the same kinds affecting other mucous membranes. It need only be remarked that the normal mucous membrane of the uterus is already very rich in cells, so that the cellular infiltration of the mucosa set up by the inflammation is not very easy to recognise with certainty; and that in catarrhal endometritis the glandular epithelium also may share in the epithelial desquamation.

If the inflammation becomes *chronic,* it not uncommonly results in hyperplastic growth of the connective tissue of the mucous membrane, giving rise to fine villous excrescences, composed of a tissue very rich in cells and blood-vessels (Fig. 155). The uterine glands may also take part in the hyperplasia by becoming elongated and pouched, or by branching and multiplying (*b*). Very often little retention cysts form at such spots, especially in the cervix, owing to plugging of the glands with secretion (*ovula Nabothi*). These project above the surface wherever the mucous membrane is coated with cylindrical epithelium, but in places covered with flat-celled epithelium they lie more in the deep parts (*cystic endometritis,* Fig. 156). It has already been intimated earlier that transformation of cylinder-celled into stratified squamous epithelium may take place as a general consequence of inflammation. Should the hyperplasia

remain circumscribed while reaching a considerable degree, *polypi* form, which are covered with cylindrical or stratified squamous epithelium, or with both, according to their position, and are composed of connective tissue usually very rich in cells, glands, and blood-vessels, the glands being frequently changed into small cysts.

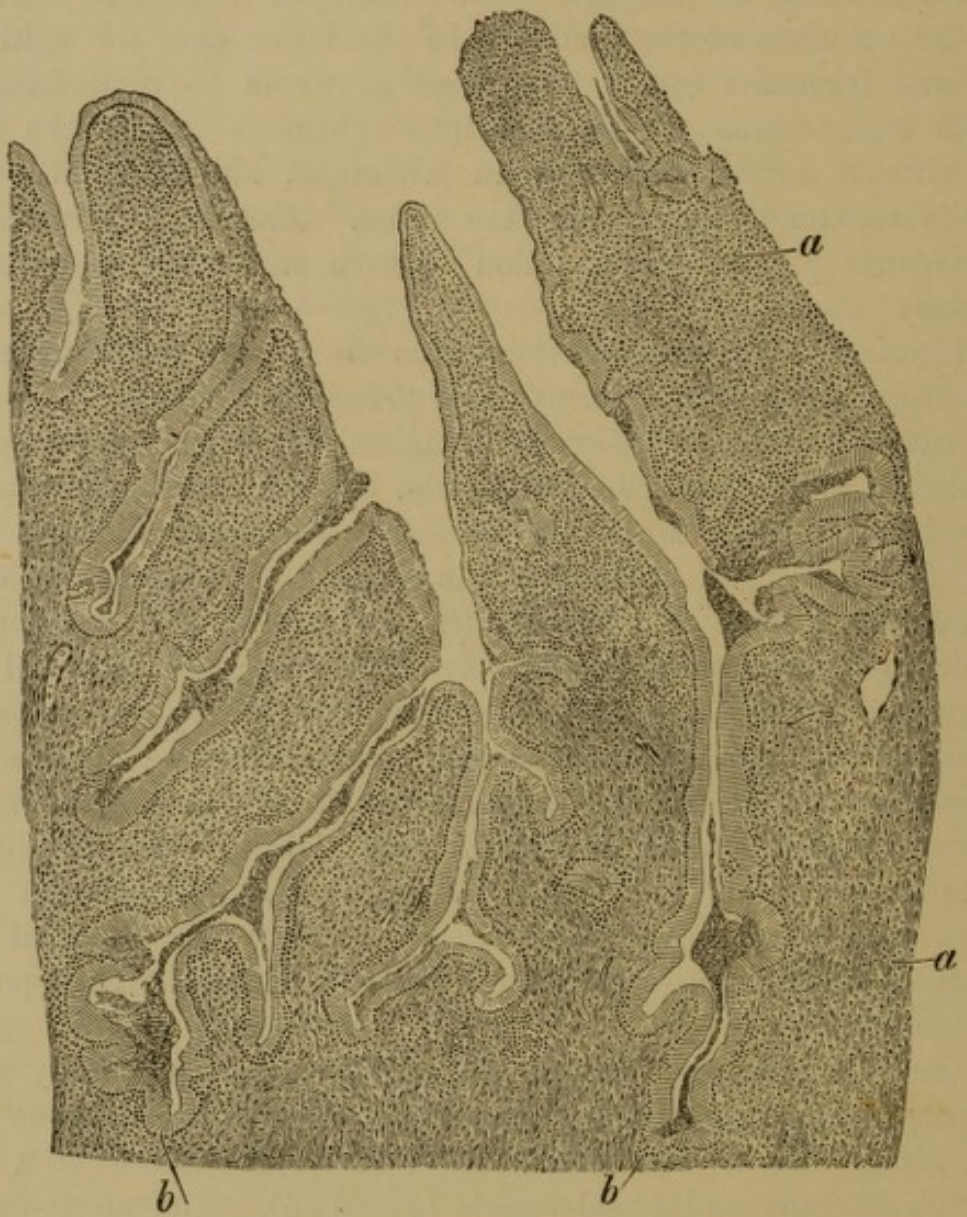

FIG. 155.—CHRONIC ENDOMETRITIS, showing formation of villous outgrowths and hyperplasia of the glands. × 77. (Hæmatoxylin and eosin.) *a*, Mucous membrane, the villous outgrowths infiltrated with small round cells, the deeper parts with spindle cells; *b*, Elongated and branched uterine glands.

Should the latter burst, or the apertures of the glands be dilated, dimples and fissures are visible on the surface of the polypi even to the naked eye. In the *vaginal portion of the cervix* the hyperplastic growth may lead to the formation of delicate papillary excrescences resembling acuminate condylomata, or of larger cauliflower-like *papillomata*.

In other cases chronic inflammation terminates in *atrophy* of the

mucous membrane, which becomes poorer in cells and glands whilst its epithelium is shortened. The atrophy may be combined with cystic degeneration of the glands, and, furthermore, hyperplastic growths may occur side by side with atrophic spots.

It is not uncommon in inflammations to see on the vaginal portion *erosions*, which come into existence either by the previous formation of vesicles in consequence of a serous exudation into the epithelium,

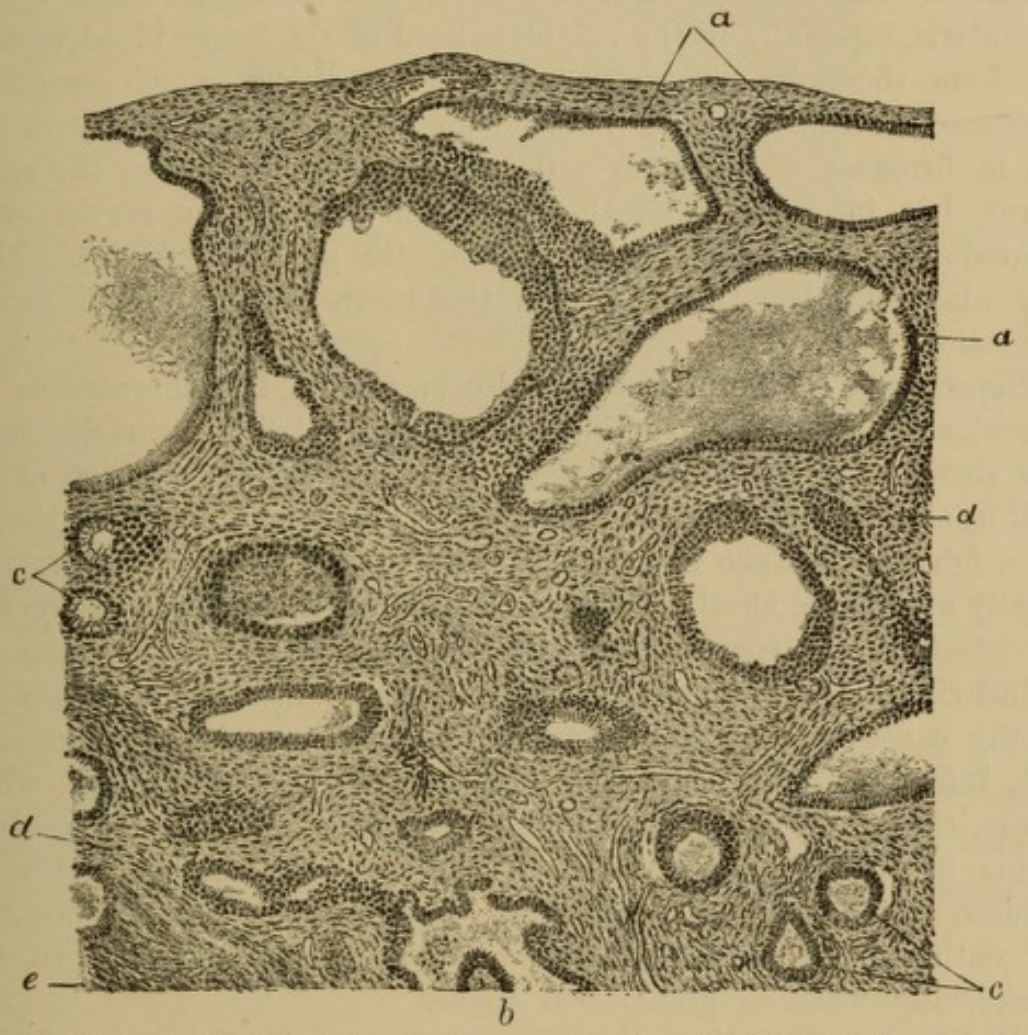

FIG. 156.—CYSTIC ENDOMETRITIS OF THE CERVIX UTERI. × 65. (Hæmatoxylin and eosin.) *a*, Glands of the mucous membrane dilated into cysts, partly filled with mucus (*ovula Nabothi*); *b*, Commencing dilatation of the glands; *c*, Normal glands in transverse section; *d*, Connective tissue of the mucous membrane; *e*, Muscularis.

which vesicles afterwards burst; or from the epithelium having become dissolved by the down-flowing secretion in endometritis. The tissue of the mucous membrane which forms the floor of all such erosions not only becomes very cellular when the process is of any considerable duration, but may also be elevated into fine papillary and villous outgrowths (*papillary erosions*). If a partial skinning-over with cylindrical epithelium takes place between the latter, and if this epithelium also sends simple and branching shoots into the

deeper parts, structures may be formed which recall the appearance of tubular glands, or even of cancer-cell cones.

Inflammation of the substance of the uterus, metritis, is, except in the puerperal form, rather rare, and in most cases occurs as a sequel of acute or chronic endometritis. In the former case the connective tissue in the uterine muscularis is infiltrated with small cells and saturated with serum, and suppuration but seldom results. In *chronic* metritis we also find foci of round cells in the connective tissue of the muscularis, especially in the neighbourhood of the larger blood-vessels; but from these is formed new connective tissue, which gradually becomes poorer in cells, so that the uterus increases not only in size but in firmness. The changes described may extend over the entire uterus, but in other cases they are restricted to the cervix or to isolated sections of it (*hypertrophy of the portio vaginalis*). They may also establish themselves in the uterus in protracted venous congestion.

Hypertrophy of the uterus may also be produced by increase in the muscular tissue, as is sometimes observed in deficient involution of this tissue in a puerperal uterus. *Perimetritis* (inflammation of the peritoneal covering of the uterus) and *parametritis* (inflammation of the neighbouring loose connective tissue in the broad ligaments, etc.) usually occur secondarily in inflammations of the generative tract or its vicinity. The parametritis shows the character of a phlegmon, the perimetritis that of inflammation of a serous membrane. They are usually caused by pyococci, parametritis perhaps also by gonococci.

6. Infective Granulomata and New-formations.—*Tuberculosis*, which occurs either primarily or as the sequel of a tubal tuberculosis, begins in the uterus also with formation in the mucosa of small nodules, which eventually ulcerate. In the severer cases, however, the entire inner surface of the uterus is seen to be changed into superficially-caseating granulation tissue.

Of the *new-formations* the *fibro-myomata* (*fibroids*) are the most frequent. The subserous tumours usually contain connective rather than smooth muscular tissue, and are very scantily supplied with vessels, whereas the interstitial tumours are composed chiefly of smooth muscular fibres, and are tolerably rich in blood. The submucous fibro-myomata (*fibrous uterine polypi*) also are often distinguished by numerous large and wide vessels. The smooth muscle fibres usually form bundles which are separated from one another by connective tissue (Fig. 157, *a* and *b*), but in many instances they lie more irregularly, or are even isolated (*f*). The connective tissue between the muscular fibres either appears distinctly fibrillated (*d*), or is more homogeneous (*e*). The muscular fibres themselves sometimes

undergo retrograde changes, such as fatty or waxy degeneration, or destruction by mucous softening and liquefaction (*f*, in the lower half of the figure). Lastly, calcification is observed with tolerable frequency in uterine fibro-myomata. *Sarcomata* are rare, and consist

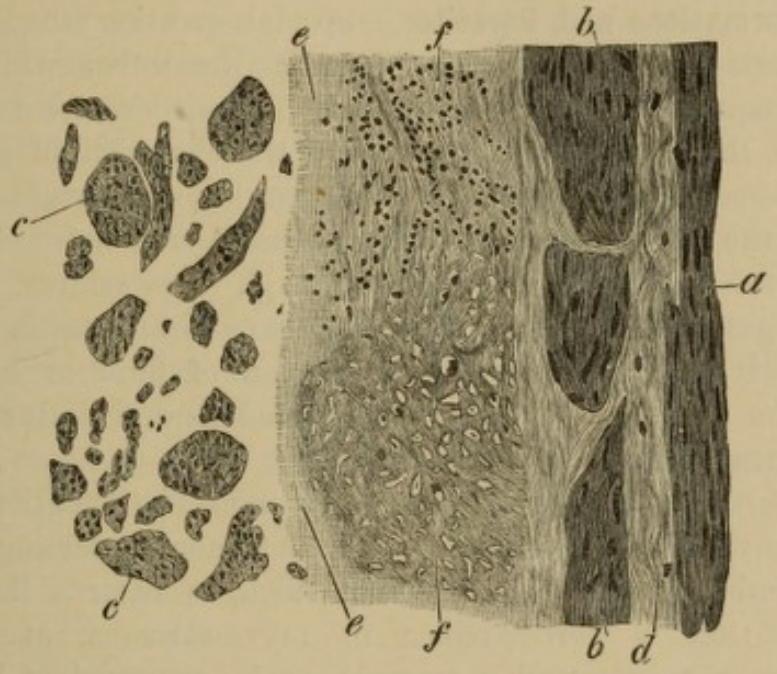

FIG. 157.—FIBRO-MYOMA OF THE UTERUS. × 160. (Hæmatoxylin and eosin.) *a* and *b*, Bundles of smooth muscle fibres in longitudinal and oblique section; *c*, Bundles of smooth muscle fibres in transverse section, with perfectly homogeneous interstitial substance; *d*, Fibrillary connective tissue; *e*, Connective tissue of more homogeneous character; *f*, Transversely-cut muscle fibres, partly (in the lower half of the figure) in a state of mucous degeneration.

of round or spindle-shaped cells. *Carcinomata* are far more frequent, especially in the cervix and portio vaginalis. They may take the form of glandular cancers, epitheliomata, or villous carcinomata.

C. DISEASES OF THE VAGINA AND VULVA.

7. Inflammation of the *vagina, vaginitis* or *colpitis*, may be catarrhal (with desquamation of epithelium, and perhaps with formation of pus) or diphtheritic. The former variety is frequently caused by the *Gonococcus;* the latter occurs (apart from the puerperal form) in the presence of putrefying tumours, in the acute exanthemata, etc. In many cases of vaginitis little vesicles form in the epithelium. The *chronic inflammations* when of longer duration lead to hyperplasia of the connective tissue of the mucosa in general, or that of the papillæ in particular. In many cases small-celled foci, resembling lymphatic follicles, are found in the sub-papillary stratum, and protrude the surface of the mucous membrane somewhat (*granular colpitis*).

Inflammatory processes affecting the vulva do not differ essentially in any respect from those of the skin in other parts of the body (see Part III., Chapter XI.). It need only be noted that in gonorrhœa the inflammation not uncommonly extends to Bartholin's glands.

8. New-formations and Parasites.—Special mention should also be made of certain *hyperplastic* growths in the vulva which are of tolerably frequent occurrence, and may be either circumscribed or diffuse. In the former case they have the character of *papillomata* (*acuminate condylomata*) or of *fibromata* (or *myxo-fibromata* and *myxomata*); in the latter case that of *elephantiasis* (Part III., Chapter XI.). In the *vagina* there occur, though but seldom, *cysts* with serous or gaseous contents, which perhaps originate in lymphatic glands and lymph-fissures by accumulation of fluid or by entrance of air. The air-cysts contain proliferated endothelial cells which are partly transformed into giant cells.

Of *new-formations proper* the *sarcoma* must be mentioned, which usually occurs in the form of polypoid tumours starting from the mucous membrane of the vagina, and which, as regards its structure, is at one time a fibro-sarcoma or myxo-sarcoma, at another a round-celled or spindle-celled sarcoma, or is composed of both round and spindle cells. The frequent occurrence of transversely-striated muscular tissue in the tumour must, however, be noted as a special peculiarity of vaginal sarcoma. Whilst the healthy uterus is free from bacteria, these occur in large numbers in the vagina even under normal circumstances, on account of its communication with the outer world. They are in most cases merely saprophytic bacteria, but still pathogenic forms (*Staphylococcus* and *Streptococcus pyogenes*) have also been observed occasionally in the normal vagina. Besides these the *thrush-fungus* is sometimes met with, especially in lying-in women. Of *animal parasites*, *Oxyuris vermicularis* may be present in the vagina. It then comes from the rectum.

D. DISEASES OF THE PLACENTA AND MEMBRANES, AND OF THE PUERPERAL UTERUS.

9. The Placenta and Membranes.—Of the diseases of the *placenta*, which have otherwise been little studied as yet, *syphilis* alone requires special mention. It occurs first as a small-celled infiltration in the sheathes and walls of the chorionic and umbilical vessels, which, however, may subsequently lead to the formation of gummatous caseating nodes, or to fibrous thickening of the vessel-walls with development of thrombi on the intima. The other changes which

may also occur, such as *fatty degeneration* (chiefly in the cells of the decidua), *calcareous deposits* (in the neighbourhood of the chorionic villi), and formation in the maternal sinuses of infarction-like *thrombi* consisting of stratified hyaline fibrin permeated with fissures, or filamentous fibrin, appear to have a morbid significance only when occurring at a very early date, or when of considerable extent. Should vestiges of the placenta or of the membranes remain behind in the uterus after delivery, they may gradually increase in size owing to hæmorrhages which take place into their tissue and upon their surface, and may assume the form of polypi, being then called *placental polypi*. These consist in great part merely of masses of clotted blood, more or less distinctly laminated; but in rare cases the chorionic villi of such placental remains begin to grow, penetrate into the uterine veins, and may even cause the substance of the uterus to atrophy.

In the *chorionic villi*, *hypertrophy* and *mucous degeneration* often occur. If the former alone is present the free ends of the villi swell into small nodes composed of fibro-cellular tissue, which may be regarded as fibromata (*fibrous mole*). If, however, mucous degeneration occurs in addition to this, the heads of the villi become still larger, and assume the appearance of vesicles, or resemble the grapes in a cluster (*cystic* or *hydatid mole*), whilst their tissue shows the microscopic character of œdematous or mucous tissue.

10. Puerperal fever is a traumatic infection which is caused as a rule by the *Streptococcus pyogenes*, and most frequently originates in raw places (fissures and the like) of the cervix, vagina, and vaginal entrance. When this takes place the injured spots are changed into suppurating, diphtheritic, or gangrenous ulcers, from which the process may extend out in all directions; or these spots serve merely as portals of entry for the cocci, which only settle at other places in the genital tract. The raw internal surface of the uterus with its lochial secretion likewise forms a favourable substratum for the entrance and multiplication of the bacteria, which produce, in the first place, an endometritis with purulent, diphtheritic or croupous exudation, and a decomposition of the lochial secretion. Most frequently the endometritis has a diphtheritic character, the superficial layers of the inner surface of the uterus being changed into a tissue devoid of nuclei, or into a more or less distinct retiform and trabecular structure with streptococci in its substance and upon its surface, whilst the deeper layers show a dense small-celled infiltration (Fig. 158). The process either remains restricted to the spot first attacked, or, in consequence of the penetration of the cocci into the interstices of the connective tissue and into the

blood-vessels and lymphatics, it also invades the neighbouring parts, viz., the uterine muscularis (*metritis*), in which it causes hyaline degeneration and necrosis of the smooth muscle fibres, and the broad ligaments and pelvic cellular tissue, as well as the serosa of the uterus (*parametritis* and *perimetritis* respectively), where it produces a serous or more frequently a fibrinous or purulent exudation.

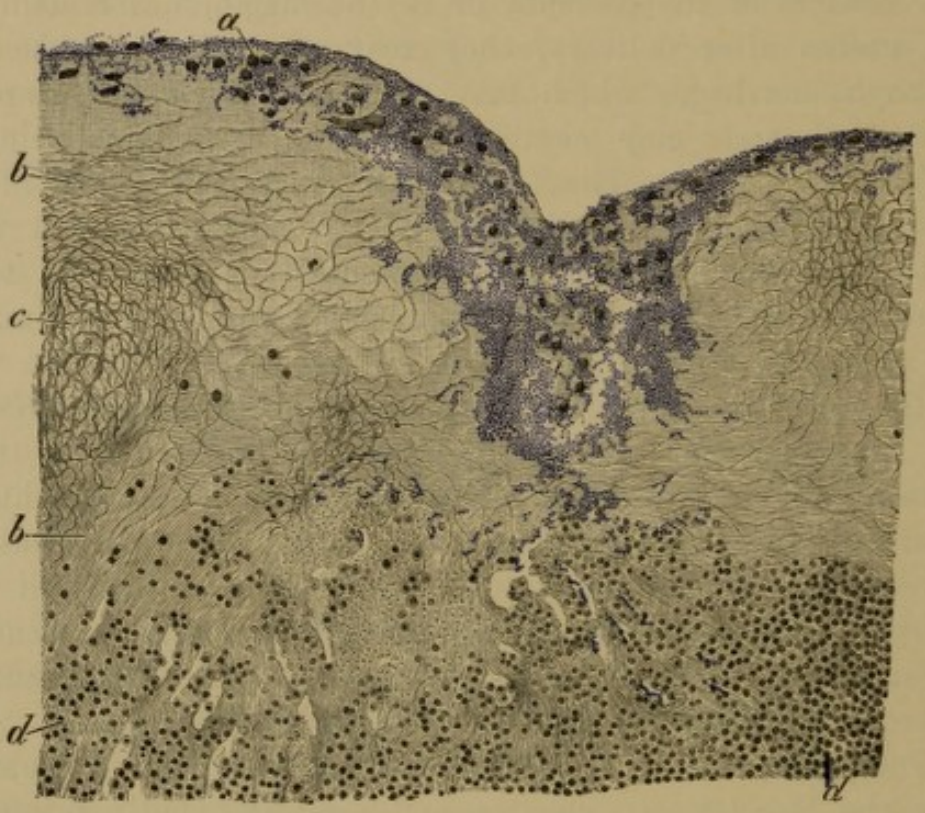

FIG. 158—PUERPERAL ENDOMETRITIS DIPHTHERITICA. × 240; the cocci drawn in under a power of × 545. (Weigert's modification of Gram's method.) *a*, Pus-corpuscles partly covered with cocci (*Streptococcus pyogenes*); *b*, Necrotic tissue, in places showing a reticular structure (diphtheritic exudation); *c*, Necrotic blood-vessel transformed into a reticular band-work; *d*, Small-celled infiltration.

The inflammation may further extend on the one hand to the ovary (*ovaritis*) and tubes (*salpingitis*), on the other to the rest of the peritoneum and to the pleura.

The affected lymphatics and blood-vessels of the uterine wall and broad ligaments contain respectively pus, and thrombi in a state of purulent softening, and also show in addition to this the changes characteristic of acute lymphangeitis (p. 214) and vasculitis (pp. 202-4)—*metro-lymphangeitis* and *metro-phlebitis*. Should particles be loosened from the thrombi, pyæmic metastases may also result in other organs.

E. DISEASES OF THE MAMMARY GLANDS.

11. Inflammation and New Growths.—*Acute inflammation of the mammary glands, mastitis,* occurs almost exclusively during the puerperium, and is caused by the *Staphylococcus* or the *Streptococcus pyogenes.* These cocci either effect an entrance into the gland from without (along the lactiferous ducts or from abrasions on the nipples), or, in persons suffering from puerperal fever, make their way from the circulation through the membrana propria into the secreting acini and the ducts. Acute mastitis usually ends in suppuration and the development of abscesses.

The most frequent pathological process in the mammary glands is the formation of *adenomata* and *carcinomata.* The former (*adenomata*) always contain a stroma in addition to the proper glandular tissue, and according as this stroma resembles in its structure the tissue of a fibroma, a myxoma, or a sarcoma, or forms intermediate between them, we use the terms *adeno-fibroma, adeno-myxoma,* or *adeno-sarcoma;* or again *adeno-fibro-myxoma,* or *adeno-fibro-sarcoma.* The glandular tissue itself may have the character either of an acinous or a tubular gland (*acinous* and *tubular adenoma*); but the tubular form may also develop from the acinous, the acini becoming pulled out lengthwise and distorted into clefts in consequence of increased growth of the interacinous connective tissue (Fig. 42).

By the dilatation of isolated or numerous ducts and acini in adenomata, formation of *cysts* (*cysto-adenoma*) frequently results, the walls of these cysts either remaining smooth, or pushing out papillary and nodulated excrescences of variable size and shape (*papilliferous* or *proliferous adeno-cystoma*), which may even grow through the cyst-wall. The latter is especially apt to happen when the growth of the epithelial elements is so luxuriant that they cover the membrana propria of the gland-ducts and the surface of the papillæ several layers deep. The tumour then also approximates to a carcinoma in its histological structure. Cysts may also develop, however, by dilatation of the ducts of the mamma itself. Should this happen in a breast during lactation, the cyst will contain a fluid resembling milk (*galactocele,* or milk cyst); otherwise, however, its contents are a thin watery or more mucous fluid (with crystals of fat and cholestearin), or, though seldom, a substance like cream or butter. If a growth of the mammary connective tissue sets in, whether before or after the formation of cysts, there thus form *cysto-fibromata, cysto-myxomata,* or *cysto-sarcomata.* Lastly, the connective tissue surrounding the glandular portions of a normal mamma or of an adenoma may also grow into the ducts in the form

of papillary protuberances, in which case we speak of an *intracanalicular fibroma*, *myxoma*, or *sarcoma*, as the case may be.

Carcinoma occurs in *acinous*, *tubular*, and *scirrhus* form. The *acinous* form gives rise to large cancer alveoli, approximately round, and recalling the appearance of acini. It yields the softest cancers. In the *tubular* form, which is the commonest, the alveoli are smaller and more elongated (Fig. 159, *a*).

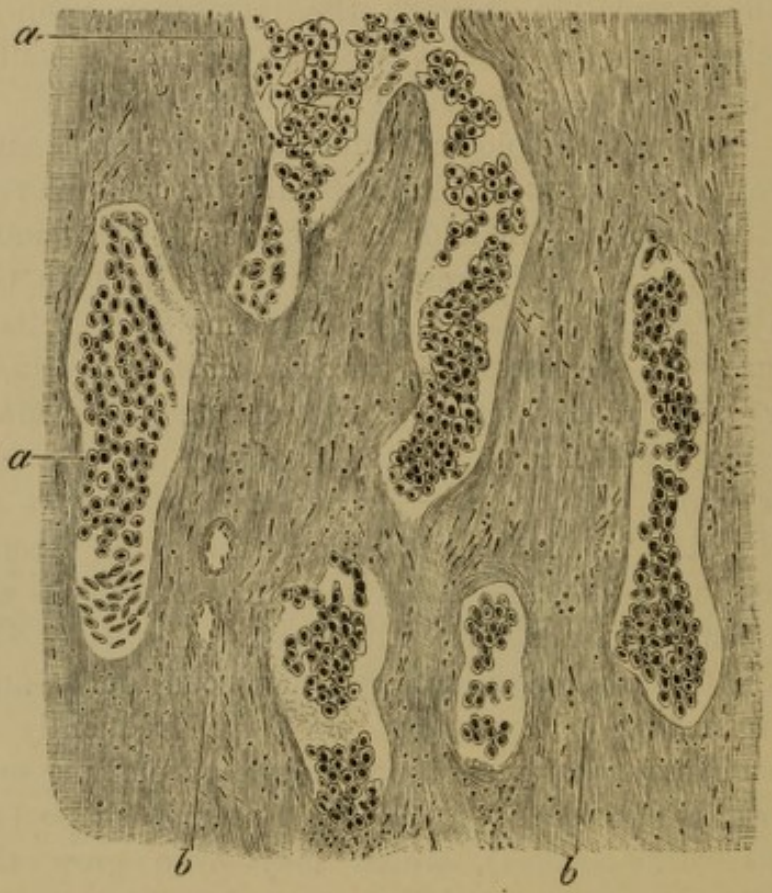

FIG. 159.—CARCINOMA OF THE BREAST (TUBULAR FORM). × 95. (Hæmatoxylin and eosin.) *a*, Longitudinal tubes of cancer cells (some of the cancer cells have fallen out of the alveoli); *b*, Connective-tissue stroma.

The *scirrhus* is characterised not only by the smallness of its alveoli, but especially by the supervention of fatty degeneration in the centre of the nodules, whereby the cancer cells are destroyed and only the stroma remains behind, which then becomes further condensed and shrunken.

Methods.—*Hardening*, *embedding*, and *staining* are done in the same way as in the case of the urinary apparatus. The examination of the *secretions* as well as of the contents of ovarian cysts is carried out in general according to the directions given for fluids on p. 5. In the *semen*, which is compounded of the contents of the seminal vesicles, the secretion of the prostate, and that of Cowper's glands, there are found, besides the spermatozoa, round mononuclear or polynuclear cells of variable size from the seminiferous tubules; scanty cylindrical, squamous, and

transitional epithelial cells from the seminal vesicles, prostate, and urethra; isolated leucocytes; Charcot's crystals (when the semen has stood for some time), globules and grains of lecithin, and corpora amylacea (the three last-named structures being derived from the prostatic secretion); and lastly, especially in elderly persons or after previous inflammations, masses of yellow pigment. The spermatozoa also may be altogether absent from the semen (*azoospermia*), or only their heads may be present, or they may no longer show any movement, even immediately after evacuation. If the semen is already dry it can be again made available for examination by softening with distilled water.

The *secretion of the uterus and vagina* in inflammation of these organs, since the latter is mostly of a purulent character, will consist chiefly of pus corpuscles; but besides these it will contain cylindrical epithelial cells if coming from the uterus, and squamous epithelial cells if from the vagina. In cases of ulcerating carcinomata, red corpuscles, and cells or even particles of the tumour, may also occur. The recognition of isolated tumour-cells will of course be very difficult. *Particles* of tumour are examined according to the directions given on pp. 110-11. Sometimes, in order to clear up the diagnosis in the living, it is advisable to excise little pieces from the uterine tumour or ulcer in question, which are then to be examined after preliminary hardening. In interpreting them, the atypical epithelial growths that sometimes occur in papillary erosions (p. 323) must not be forgotten; hence it will be possible to decide with *complete certainty* on the presence of carcinoma only when portions of the uterine muscularis are also present in the piece along with cancer alveoli.

The *menstrual fluid* consists principally of blood. Should membranous structures be mixed with it, their nature is determined either by making torn-up preparations with addition of acetic acid, or still more certainly after previous hardening. In doing this it is to be observed that any shreds of decidua may be distinguished from uterine mucous membrane by their peculiar remarkably large polygonal or rounded cells, the membrane containing only *small* round cells in its tissue. The presence of the former would indicate *abortion*. The *lochial secretion*, besides red corpuscles and squamous epithelial cells, likewise contains decidual cells derived from the deepest layer of the decidua, which is left behind in the uterus after delivery. Any portions of placenta which may remain will be easily recognisable in the lochia by the branching placental villi. The normal lochia contain neither pus-corpuscles nor bacteria.

The *secretion of the mammary glands* in the first week after delivery shows, in addition to isolated epithelial cells and leucocytes, very numerous droplets of fat, partly free, partly arranged in groups of variable size [in cells] (*colostrum corpuscles, granule cells*). Later the latter only occur isolated. In suppurative mastitis numerous pus-cells may be present in the secretion, and also pathogenic bacteria, the *Streptococcus* and *Staphylococcus pyogenes*. Apart from this, bacteria may be demonstrated even in the milk of healthy mothers, especially after prolonged retention of the secretion in the mammary glands; chiefly *Staphylococcus albus*, which evidently wanders in from without into the milk ducts, though in many diseases of infective origin (puerperal fever, pneumonia) the specific excitants also make their way out from the blood into the milk glands and their secretion. The examination for *bacteria*, especially for pyococci and gonococci and for tubercle bacilli, is carried out by the methods given in Part II., Chapter V.

CHAPTER IX.

THE NERVOUS SYSTEM.

I. THE CENTRAL NERVOUS SYSTEM.

1. Atrophy and Softening.—Amongst the *atrophic* conditions are included, in the first place, those changes in the *spinal cord* and *medulla oblongata* which are found in some of the morbid conditions designated on the one hand *chronic anterior poliomyelitis* or *progressive muscular atrophy*, and on the other, *progressive bulbar paralysis*. The lesion here is an atrophy of the *anterior horns* of the spinal cord (in chronic anterior poliomyelitis), or of the *motor nuclei of the medulla oblongata* (in progressive bulbar paralysis), in which the ganglion cells first lose their processes, and then gradually become smaller, and sometimes at the same time richer in pigment (the so-called *pigmentary atrophy*); or else, their nuclei simultaneously disappearing, they assume a shining homogeneous appearance (*sclerosis* or *hyaline degeneration*), to vanish altogether at last (Fig. 160). The atrophy next involves the nerve-fibres between the ganglion cells as well as the nerve-roots and the nerves passing out, the medullated fibres losing their medullary sheaths first; and finally it invades also the muscles supplied by the diseased nerves. This peculiar atrophy, regarding which it has not yet been made out whether it is or is not really the result of an inflammatory process, most frequently begins either at the upper or the lower end of the spinal cord, and then gradually advances downwards or upwards as the case may be.

Early destruction or division of peripheral nerves or peripheral end organs, as in amputation of extremities or destruction of the globe of the eye or optic nerve, is also apt to be followed by an atrophy in the corresponding portions of the central nervous system, an atrophy which may involve the ganglion cells as well as the

paths of conduction. Lastly, a *primary atrophy of nerve-fibres* also occurs in the brain under certain circumstances, as after insolation and in general paralysis (see p. 342).

Softening of the brain and spinal cord is a necrosis due to disorders of the circulation setting in either suddenly or gradually (embolism, vascular disease, compression), or to mechanical destruction, and the process is called *white* or *red* (or *yellow*) softening according as it runs its course without or with hæmorrhages. (The softening brought about in the spinal cord by compression is also called *compression* or *contusion myelitis*.) In the first instance the ganglionic cells and the nerve-fibres undergo necrosis (the former not uncommonly swelling up and becoming hyaline, or vacuoles

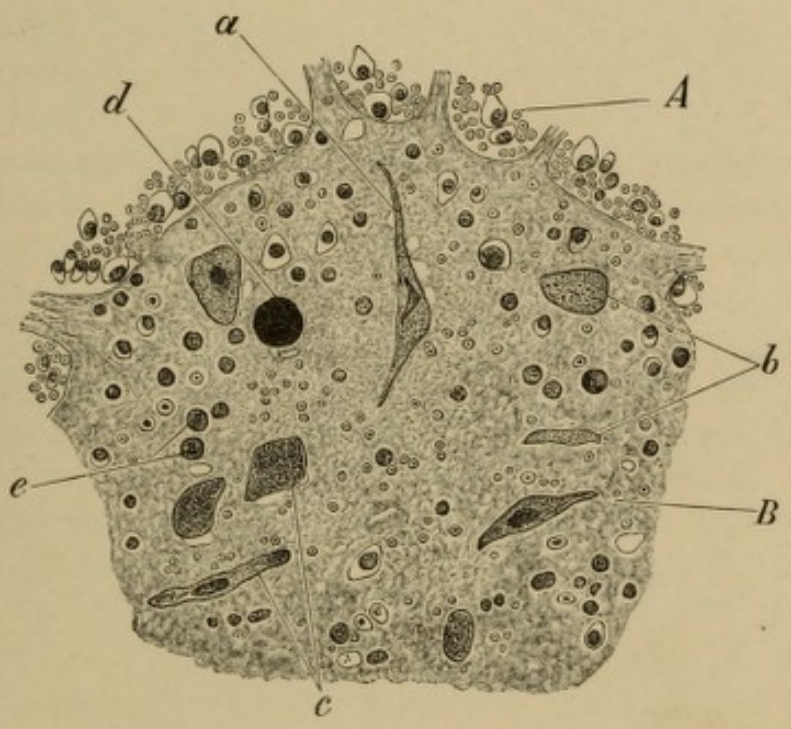

FIG. 160.—ATROPHY OF THE ANTERIOR HORNS OF THE SPINAL CORD IN CHRONIC ANTERIOR POLIOMYELITIS. × 545. (Alum cochineal.) *A*, Anterior column; *B*, Anterior horn; *a*, Ganglion cell with processes; *b*, Atrophic ganglion cells; *c*, Atrophic ganglion cells with pigment; *d*, Corpus amylaceum; *e*, Nuclei of neuroglia cells.

forming in them), whilst finally they dissolve altogether. The ganglion cells may also, however, undergo fatty degeneration, and when once dead, may even calcify.

In the nerves it is the medullary sheath which is most sensitive. It breaks up into drops of variable size and of very numerous and strangely outlined forms, these drops being still at the outset composed of myelin, though later, as they become smaller and smaller, it is impossible to distinguish them from fat-droplets. The axis cylinders may remain unaltered for a longer time, or may swell up or become varicose. Within the limits of the softened portions there next

follows a transudation of fluid from the still pervious blood-vessels, and emigration of white corpuscles (Fig. 161, *c*). By the former the neuroglia fibres and the processes of the cells of Deiters are

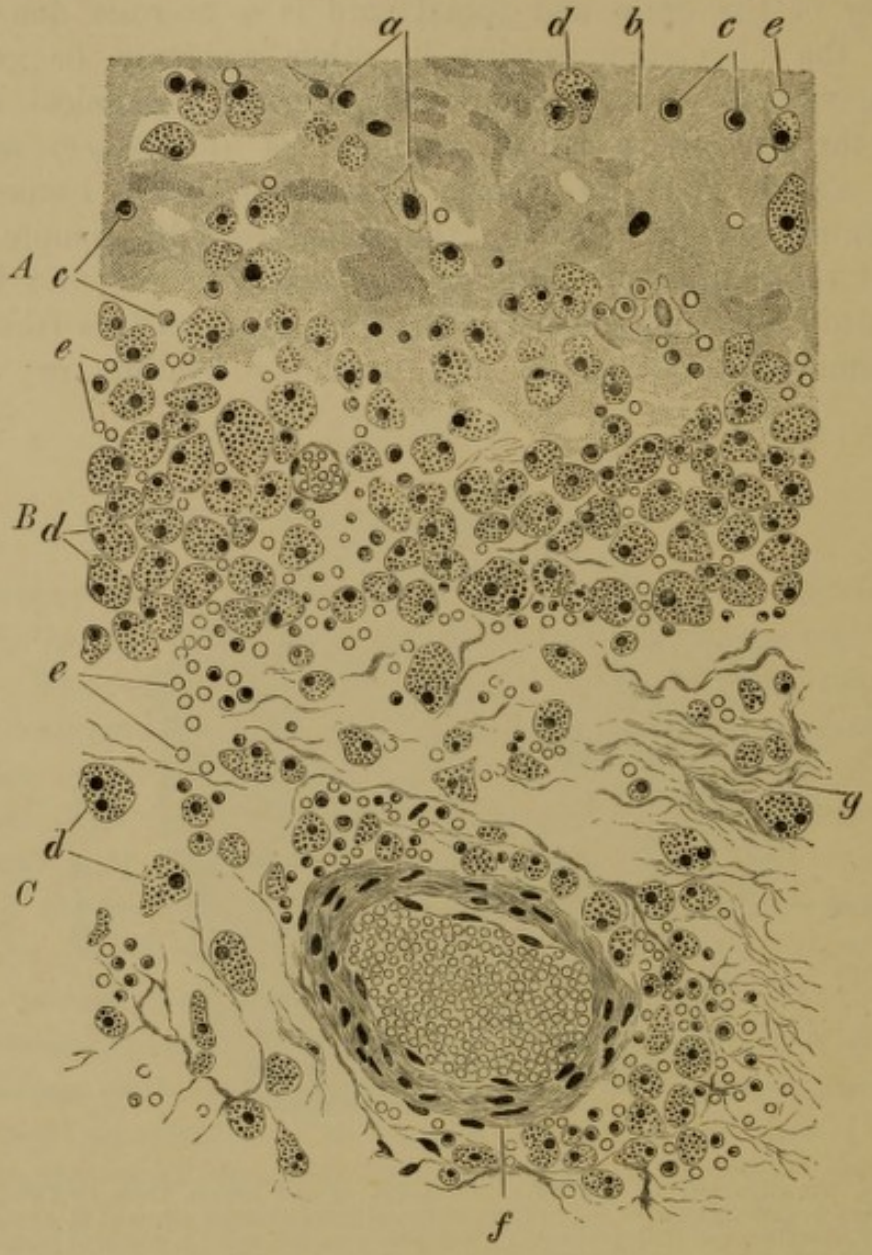

FIG. 161.—RED AND YELLOW SOFTENING OF THE CORTEX OF THE TEMPORAL LOBE, after embolism of the Arteria fossæ Sylvii. × 535. (Hæmatoxylin and eosin.) *A*, Cerebral cortex with commencing softening; *B*, Accumulation of granule cells and red corpuscles; *C*, Extreme softening and liquefaction of the substance of the brain; *a*, Ganglion cells; *b*, Neuroglia; *c*, Mononuclear leucocytes; *d*, Leucocytes filled with myelin and fat-droplets (granule cells); *e*, Extravasated red corpuscles; *f*, Blood-vessel with accumulation of granule cells in its adventitia; *g*, Neuroglia fibres not yet liquefied.

thrust asunder, or partially destroyed, whilst the emigrated leucocytes become charged with the fatty detritus resulting from degeneration of the ganglion-cells and nerve-fibres, being thereby expanded into large granule corpuscles (*d*), and transport it into the neighbouring perivascular lymph-spaces (*f*). At this stage the still-remaining blood-vessels (*f*) form with the relics of the neuroglia fibres (*g*) and of the processes of the glia-cells a meshwork (*C*),

containing in its spaces a fluid which is of a milky turbidity from the presence of granule corpuscles, but gradually becomes clearer in consequence of advancing reabsorption.

Should the necrosis be accompanied by hæmorrhages, the extravasated blood undergoes the well-known changes (see page 58), and causes a red, brown, or yellow coloration of the softened patch. We then find yellow and brown pigment both inside and outside cells, and sometimes also crystals of hæmatoidin (Plate I., Fig. 1). The final result of softening is the development either of a *cyst* traversed by a network of fine vessels, or of a *cicatrix* formed by growth of the neuroglia and of the sheaths of the vessels. If the foci of softening lie superficially, a cellular infiltration is established in the overlying parts of the inner meninges, which eventually leads to fibrous thickening of the membranes. The free space left by the sinking inwards of the softened portions of brain is partially filled up with transuded serum.

2. Degenerations.—Of these, *primary and secondary system-degenerations* are distinguished. The *secondary* system-degeneration is a degeneration restricting itself to definite systems of fibres, and occurring after destruction of certain parts of the brain and spinal cord—probably the trophic centres of the systems in question.

In the anterior, lateral, and posterior columns of the spinal cord the following special tracts of fibres are, as is well known, distinguished, viz., the *anterior* (*direct*) *pyramidal tracts*, the *lateral* (*crossed*) *pyramidal tracts*, the *direct cerebellar tracts*, and the *columns of Goll and of Burdach*. The anterior and lateral pyramidal tracts consist of nerve-fibres, running centrifugally, which connect the anterior horns of the spinal cord with the cortex of the parietal lobes. The fibres of the *direct pyramidal tracts* (Fig. 164, *b*) take no share in the decussation of the pyramids, and consequently run downwards on the same side in the median portion of the anterior columns of the cord, to cross lower down in the anterior commissure. They may end as high up as the middle of the dorsal part of the cord, but descend somewhat lower in many cases; or they may be entirely absent. The fibres of the *crossed pyramidal tracts* (Fig. 164, *a*) pass across to the opposite side in the pyramids themselves, and in the spinal cord course downwards in the posterior segment of the lateral column. The *direct cerebellar tracts* occupy the peripheral part of the posterior segments of the lateral columns, and extend as far down as the lower end of the dorsal region of the cord. They connect the superior vermiform process of the cerebellum with the columns of Clarke in the spinal cord. The remaining bundles in the anterior columns are called the *basis bundles* of the anterior columns,

and those in the lateral columns the *mixed zones*. Lastly, the median portion of each posterior column is named the *column of Goll* or *funiculis gracilis*, and the lateral portion the *column of Burdach* or *funiculus cuneatus*.

Secondary degeneration may be *ascending* or *descending*. The latter (Fig. 162) most frequently affects the pyramidal tracts, occurring in cases where the motor centres in the cerebral cortex, or the system of motor fibres passing downwards from them through the corona radiata, internal capsule, crusta of the crura cerebri, and pyramidal tracts, are destroyed at any spot. The *ascending* degeneration occurs after destruction of the cord or posterior spinal nerve roots. Immediately above the site of the lesion it affects the whole of the posterior columns, but further up the column of Goll only.

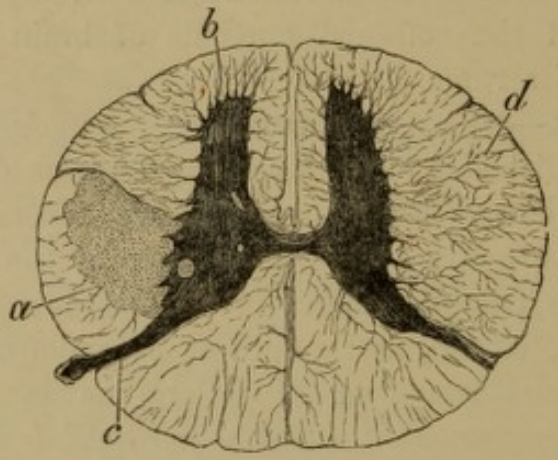

FIG. 162.—SECONDARY DESCENDING DEGENERATION OF THE RIGHT CROSSED PYRAMIDAL TRACT IN THE CERVICAL REGION OF THE CORD, in cerebral softening due to embolism of the Left Arteria fossæ Sylvii. About × 5. (Ammonia carmine.) *a*, Grey degeneration of the crossed pyramidal tract; *b*, Anterior horns; *c*, Posterior horns; *d*, White substance.

When the lesion has occurred in the upper dorsal region, the direct cerebellar tracts also degenerate above it. The more minute processes in secondary degeneration, which make themselves perceptible as early as the second week, are not unlike those in softening, as they also consist in disintegration of the nerve-fibres and formation of granule corpuscles, whilst the empty spaces thus left are filled up partly with fluid and partly with growing neuroglia. At the earliest period the degenerated tracts still contain many of the products of disintegration, and hence to the naked eye are white and softer than normal. Later the supporting tissue gradually increases in amount, and its spaces become progressively smaller, but isolated granule corpuscles are always still present. At this stage the affected tracts appear grey to the naked eye.

As regards *primary degeneration*, the histological conditions are analogous to those in the secondary variety. Here also we have an

atrophy of the nerve-fibres ushered in by disintegration of the medullary sheaths, and accompanied by formation of granule corpuscles and growth of the neuroglia. It is only questionable whether the latter or the disappearance of the nerve-fibres is the primary lesion.

Primary degeneration occurs with greatest frequency in the *posterior columns*, and is then called *tabes dorsalis*, or grey degeneration

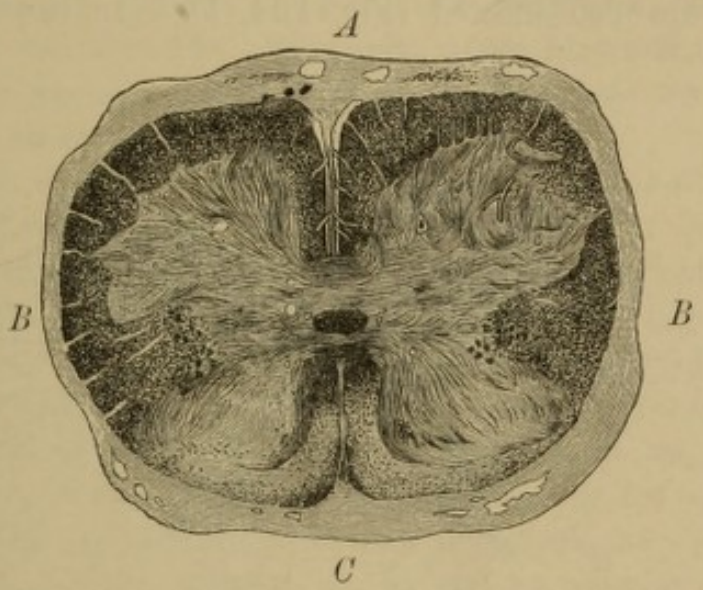

FIG. 163.—TRANSVERSE SECTION THROUGH THE SPINAL CORD IN TABES DORSALIS. Very low power. (Weigert's hæmatoxylin.) *A*, Normal anterior columns; *B*, Normal lateral columns; *C*, Posterior columns, for the most part in a state of grey degeneration.

of the posterior columns (Fig. 163). In this disease the first parts to be affected are the central portions of the columns of Burdach in the lumbar and dorsal regions of the cord, and the median portions of the columns of Goll in the dorsal and cervical regions, as well as also the posterior nerve-roots. Subsequently the other parts of the posterior columns are also involved, especially in the lumbar and dorsal segments, only the most anterior parts immediately adjacent to the posterior commissure appearing almost always intact, or at all events less altered. The degeneration may spread, on the one hand upwards along the funiculi graciles to the fossa rhomboidalis, on the other to the columns of Clarke in the spinal cord. Grey foci also occur frequently in the optic and other cranial nerves. It must also be mentioned that so-called corpora amylacea are often found in the degenerated posterior columns of the spinal cord, especially in their peripheral parts, though the presence of these bodies seems to be connected much less with the atrophy of the nerve-fibres than with the more or less advanced age at which tabes usually comes on (see p. 56).

Less common is a second form of primary tract-degeneration,

viz., *amyotrophic lateral sclerosis*. This begins in the lateral columns and then extends to the anterior horns, especially in the cervical region, and to the motor nuclei of the fourth ventricle, notably those of the hypoglossal, facial, and spinal accessory nerves. In many cases the lateral columns are not affected in their entire thickness, but merely the crossed pyramidal tracts (Fig. 164, *a*); and, in case the cord still contains undecussated anterior pyramidal tracts, these are also affected (Fig, 164, *b*). In the anterior horns

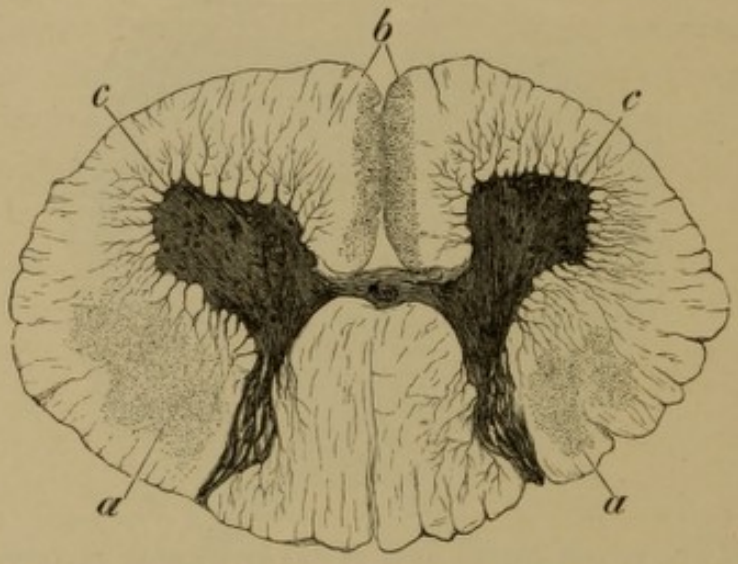

FIG. 164.—AMYOTROPHIC LATERAL SCLEROSIS. About × 5. (Ammonia carmine.)
a, Degenerated crossed pyramidal tracts; *b*, Degenerated direct pyramidal tracts; *c*, Anterior horns, with atrophy of the ganglion cells.

it is the ganglion cells of the most anterior parts that are chiefly destroyed. It need hardly be said that the atrophy also involves the nerves springing from the nuclei, as well as the muscles which these nerves supply. Under certain circumstances the degeneration may even ascend as high as the pons and crura cerebri.

3. Hæmorrhage and Œdema, etc.—The *hæmorrhages* are either punctiform (capillary apoplexies) or larger effusions (hæmorrhagic foci). The former take place in inflammations, in embolism or atheroma of the smallest cerebral arteries, in acute infective diseases (diphtheria, anthrax, etc.), in morbus maculosus Werlhoffii, in phosphorus poisoning, and so forth; whilst the latter only occur in chronic endarteritis, in which case also rupture of the diseased arteries is frequently preceded by the formation of small ampullary aneurysms. The punctiform hæmorrhages consist either of accumulations of blood in the sheath of the vessel or of roundish patches about the latter, and in general go through the same transformation as the large effusions. In the latter the serum of the coagulated blood is carried off by the lymphatics and blood-vessels, whilst the hæmoglobin is partly dissolved, staining the surroundings yellowish, and partly

leads to the formation of amorphous yellow and brown pigment, or of hæmatoidin crystals. The further changes are like those in softening; *i.e.*, the portions of nervous tissue destroyed by the hæmorrhage break down into a detritus which is taken up by leucocytes and swept away into the perivascular lymph-spaces, until finally a so-called *apoplectic cicatrix*, or still more frequently an *apoplectic cyst*, is left behind. Both the wall of the latter and the cicatrix usually contain pigment, and sometimes also amorphous or crystalline hæmatoidin. Similarly, after hæmorrhages into the sheaths of the vessels yellow pigment-granules are for a long time found in this situation.

Œdema occurs both in the cerebral substance and also in the meninges of the brain and spinal cord, and may be either circumscribed or more equally distributed. In the choroid plexus circumscribed collections of fluid are often found in the form of *cysts*, the cavity of which is lined with endothelium and is not uncommonly traversed by vessels and by bands of connective tissue.

Accumulations of fluid in the *cerebral ventricles* are described as *internal hydrocephalus*, and in the *central canal of the spinal cord* as *hydromyelia*. In these conditions the ependyma is found more or less thickened, either evenly or by finely-granular aggregations [*granulations*], which latter, however, may also be found under other circumstances, especially in the fourth ventricle. Both these aggregations and the thickened ependyma consist of a dense finely-fibrillated connective tissue rather poor in cells. In the higher degrees of hydromyelia there may result atrophy of the grey, and even of the white, substance.

Hydromyelia must not be confounded with *syringomyelia*, which depends upon a circumscribed growth of the neuroglia in parts of the spinal cord which are probably malformed, and which are situated most frequently in the grey commissure or the posterior columns. This condition subsequently results in partial liquefaction of the tissue, and formation of fissures and cavities.

4. Inflammation of the Brain and Spinal Cord.—*Acute inflammation of the brain, encephalitis*, is usually *secondary*, occurring in the course of various acute infective diseases (pyæmia, ulcerative endocarditis, etc.), or by extension from neighbouring parts (in meningitis), and hence is most frequently caused by the pyococci (Fig. 165, *c*) or the *Diplococcus pneumoniæ*. Should a cerebral artery become blocked by an embolus containing bacteria, the softening which first occurs (p. 333) will also be succeeded by an inflammation, usually of a suppurative character. Encephalitis always occurs in circumscribed form, either giving rise to foci which are only visible under the microscope, and

which consist of accumulations of leucocytes in the perivascular lymph-spaces or their immediate neighbourhood (Fig. 169, *d*, *e*, and *f*), or appearing in the form of somewhat larger patches, which are then usually accompanied by small hæmorrhages (Fig. 165, *b*). Should suppuration ensue (which usually takes place in the course of pyæmic processes), circumscribed abscesses may sometimes form (Fig. 166), in the immediate neighbourhood of which the brain-substance is permeated not only with more or less numerous pus cells (*a*), but usually also with punctiform hæmorrhages (*b*). The blood-vessels meanwhile in many cases show a necrotic inflammation, their walls being transformed into a network of bands which radiates into the

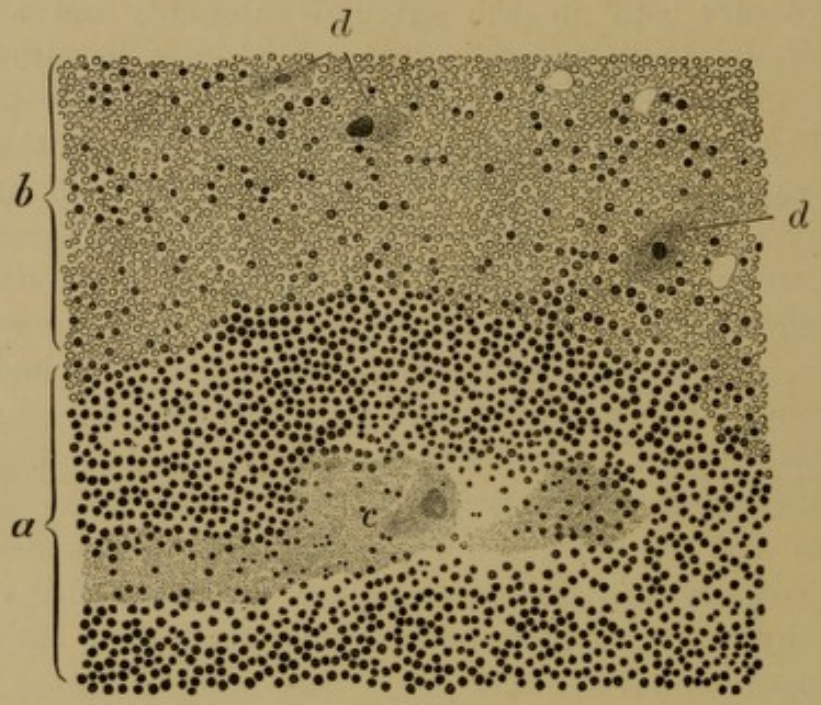

FIG. 165.—METASTATIC ENCEPHALITIS OF THE CEREBELLAR CORTEX IN PYÆMIA. × 285. (Hæmatoxylin and eosin.) *a*, Encephalitic focus consisting of leucocytes; *b*, Hæmorrhage in the neighbourhood of the focus; *c*, Masses of cocci (*Staphylococcus pyogenes aureus*) in the centre of the focus; *d*, Purkinje's ganglion cells, which are separated from one another by the hæmorrhage.

surrounding parts (*c*). Only very small abscesses are capable of healing by cicatrisation; for though larger abscesses soon become encapsuled in granulation tissue, the outer layers of which even change subsequently into connective tissue, notwithstanding this enclosure no healing takes place, but on the contrary the abscess cavity may continue to enlarge by gradual increase in the pus.

Acute inflammation of the spinal cord, myelitis, appears to occur frequently under analogous conditions and in like manner as does acute encephalitis. It may be divided, according as its seat is in the *grey* or the *white* substance, into a *poliomyelitis* or *central myelitis*, and a *leucomyelitis;* but if the entire transverse section of the cord, or at least the greater part of it, be involved, the condition is

designated *transverse myelitis*. The inflammation is likewise characterised by small-celled infiltrations in and around the perivascular spaces of the blood-vessels, as well as by small hæmorrhages, but it is rare for it to lead to suppuration. Besides these purely inflammatory changes, degenerations may also be met with in the ganglion-cells and nerve-fibres to a variable extent. Should the inflammation affect the anterior horns, we speak of *anterior polio-*

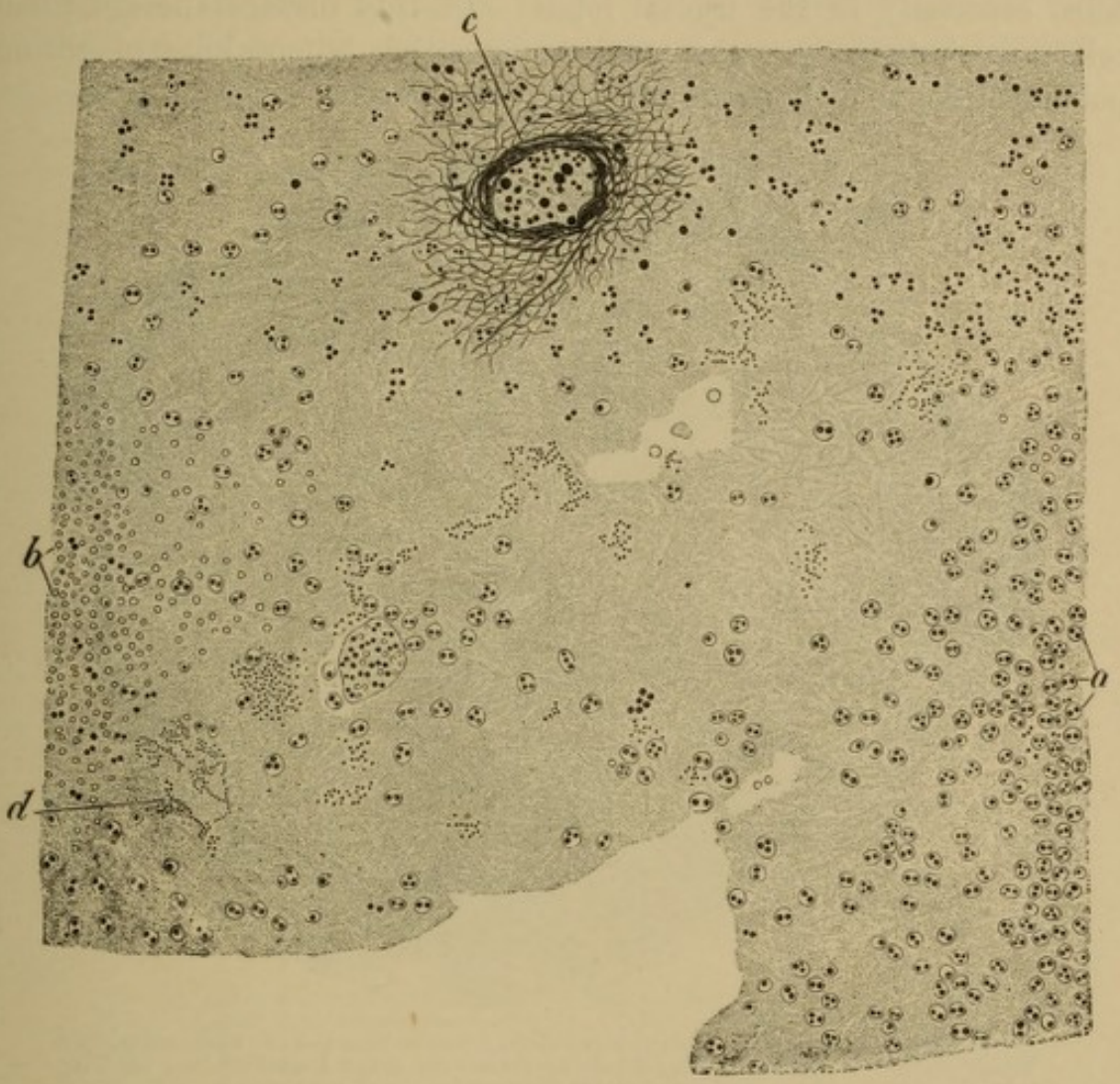

FIG. 166.—WALL OF A RECENT CEREBRAL ABSCESS. × 285. (Hæmatoxylin and eosin.)
a, Pus-corpuscles; *b*, Small hæmorrhagic focus; *c*, Necrotic blood-vessel, the wall of which is transformed into a network of bands; *d*, Minute aggregation of cocci.

myelitis, a form which lies at the root of spinal *infantile paralysis* amongst other diseases, and leads as a final result to *atrophy* of the anterior horns, in which we find the place of the destroyed ganglion-cells and nerve-fibres occupied either by condensed neuroglia or by a gelatinous tissue composed of branched cells and vessels. Sometimes the neuroglia also may disappear, and in this case there ensues, by accumulation of fluid, a formation of small *cysts* traversed by delicate vessels. The microscopic appearances in this atrophy have already

been sketched above (p. 332), under the head of Chronic Poliomyelitis.

Amongst the *chronic inflammations* many authorities reckon the process underlying *dementia paralytica* [or *general paralysis of the insane*] and *multiple cerebro-spinal sclerosis*. In *dementia paralytica*, however, the primary element seems to be, not inflammatory change, but atrophy of the medullated nerve-fibres and of the ganglionic cells, especially in the frontal lobes. In this disease the ganglionic cells are destroyed in the manner described in speaking of chronic poliomyelitis, though irregularly, all disappearing in some places, but

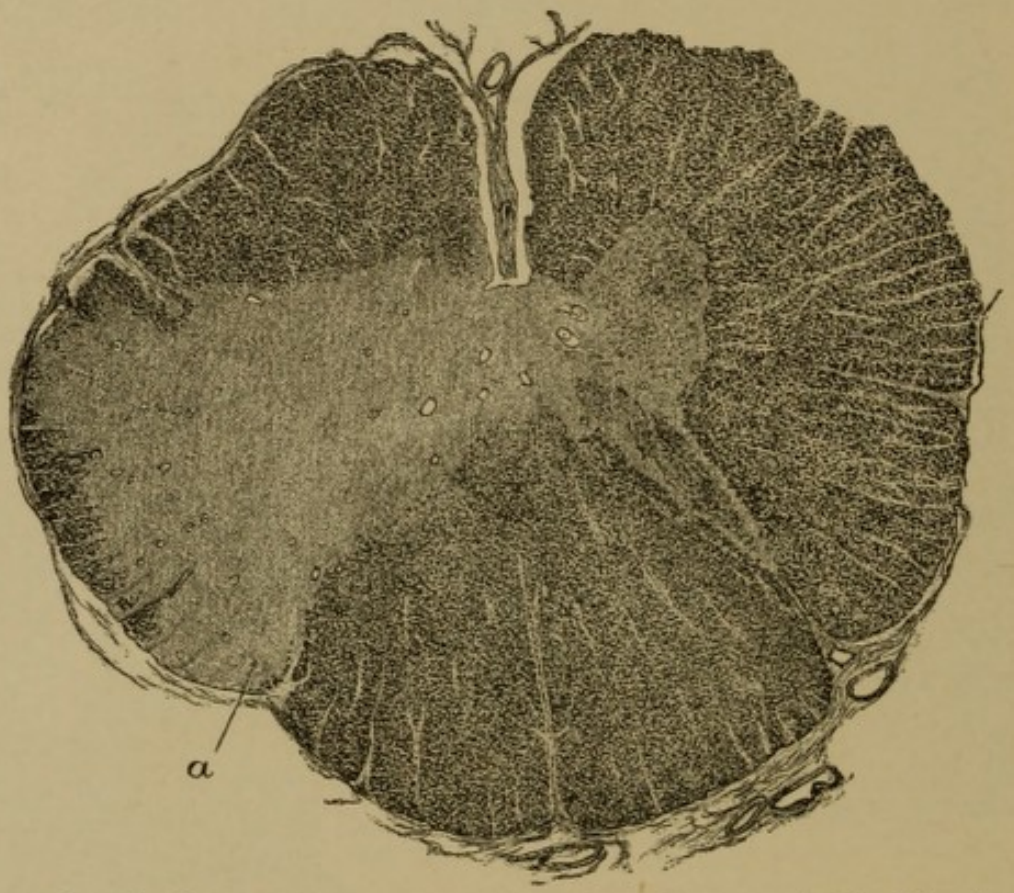

FIG. 167.—MULTIPLE SCLEROSIS OF THE SPINAL CORD. Low power (×16). (Weigert's hæmatoxylin.) *a*, Sclerotic focus involving almost the entire lateral column, together with the anterior and posterior horns of the same side.

few in others; whilst the nerve-fibres, not only in the cortex but in other parts of the brain also, undergo atrophy to a greater or less extent. The larger the amount of nervous elements destroyed, the more conspicuous becomes a growth of the neuroglia, the cells of the latter increasing in number and partly also in size, and the fibres becoming not only more numerous but thicker. There next appear further changes which are undoubtedly of an inflammatory nature, viz., aggregations of leucocytes and sometimes also of red corpuscles and grains of pigment in the perivascular spaces of the vessels of the cortex, and in many cases in those of the medullary

centre also, together with small-celled infiltrations in the inner meninges which are either confined to the immediate neighbourhood of the blood-vessels or show a more diffuse distribution.

Multiple cerebro-spinal sclerosis is marked macroscopically by the occurrence of more or less numerous grey or reddish-grey patches of firmer or softer consistence in the white and grey substance of the brain and spinal cord (Fig. 167, *a*); and histologically, on the one hand by proliferative processes in the neuroglia and in the adventitia of the vessels, on the other by atrophy of the nervous elements. If

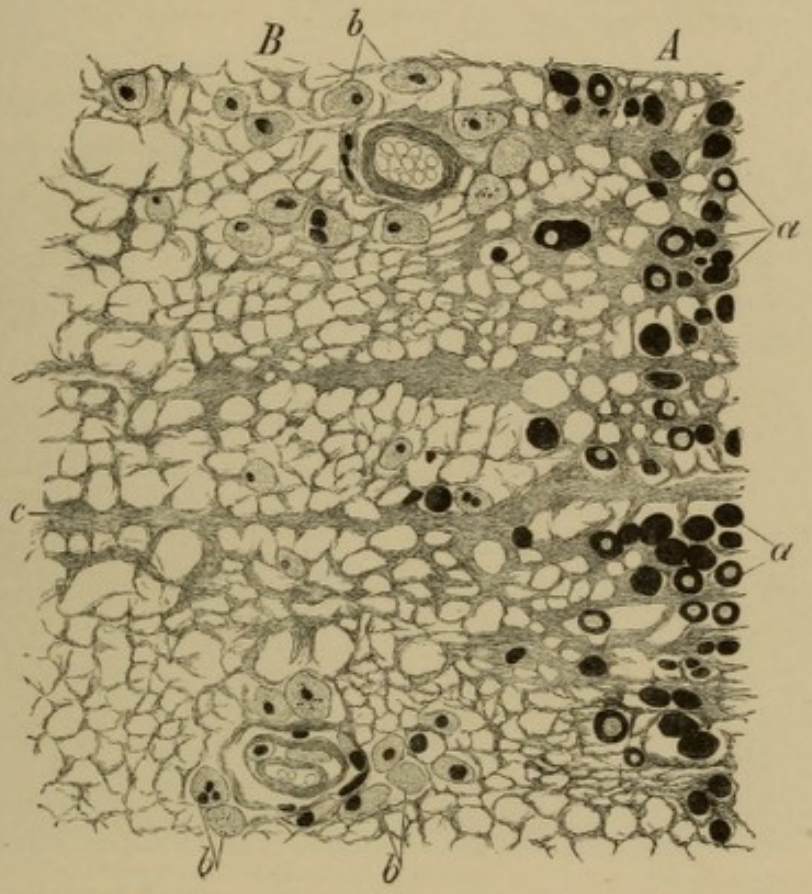

FIG. 168.—MULTIPLE SCLEROSIS OF THE SPINAL CORD. A portion of the superficial parts of the right antero-lateral column. × 500. (Weigert's hæmatoxylin.) *A*, Normal part of the lateral column; *B*, Sclerotic part of the lateral column; *a*, Nerve-fibres not yet degenerated, seen in section; *b*, Granule cells, mostly in the immediate neighbourhood of the sheath of blood-vessels; *c*, Thickened bands of neuroglia.

somewhat younger and softer patches be examined, the sheath and adventitia of the blood-vessels (which latter are usually a little dilated) are found to be infiltrated with round cells and partially also with granule cells (Fig. 168, *b*). Besides this the neuroglia forms a feltwork of fine shining fibres, which radiate out from the frequently polynuclear neuroglia-cells, and still contain more or less numerous round cells entangled amongst them. Later, when the patches become firmer, the round cells disappear, the fibrous feltwork of neuroglia increases in density, and its bands appear thickened (Fig. 168, *c*). The nervous elements in these patches are

destroyed in like manner as in the system-degenerations, or perhaps as in chronic poliomyelitis. Even when they have become older, however, *non-medullated* nerve-fibres are often still found in them in large numbers, although medullated nerve-fibres may by this time have entirely disappeared. Corpora amylacea are usually but sparingly present.

5. Inflammation of the Meninges.—*Acute inflammation of the membranes of the brain or spinal cord, cerebral or spinal leptomeningitis,*

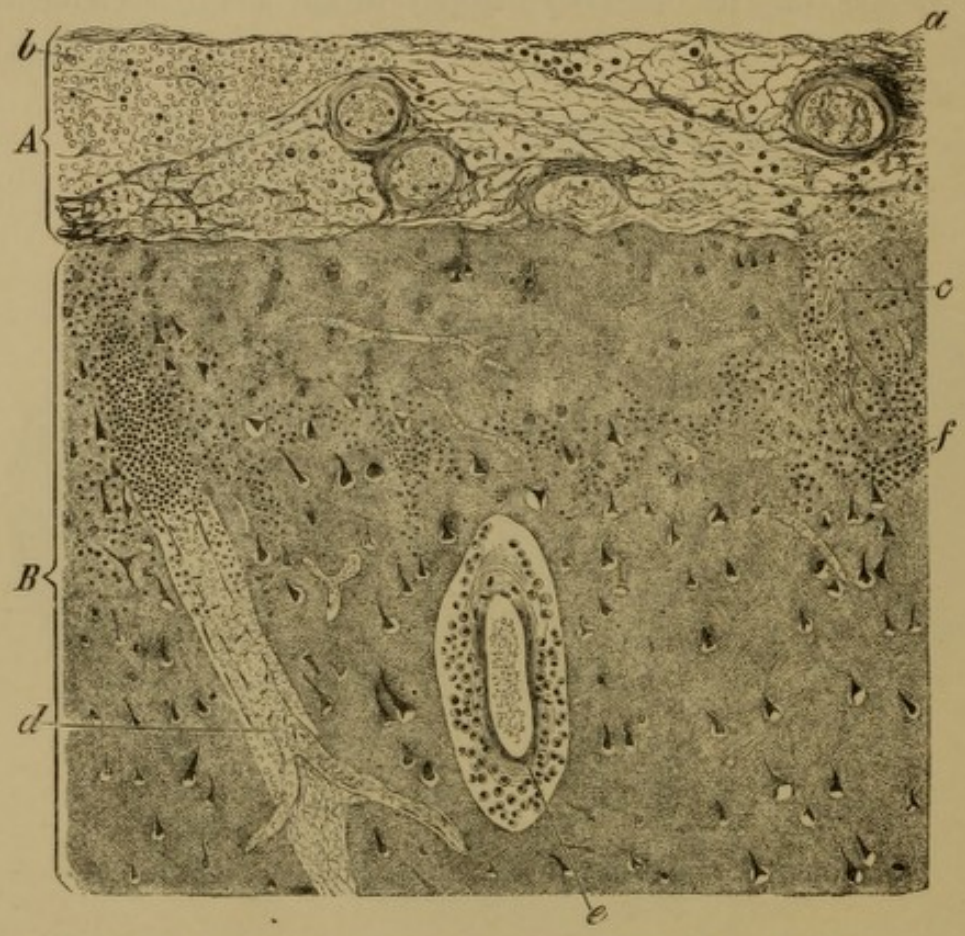

FIG. 169.—ACUTE TRAUMATIC MENINGITIS AND ENCEPHALITIS. × 95. (Hæmatoxylin and eosin.) *A*, Inner membranes of brain; *B*, Cerebral cortex; *a*, Fibrinous exudation; *b*, Hæmorrhagic exudation; *c*, Blood-vessel passing into the cortex. It contains coagulated fibrin, and its surface is partially covered with leucocytes; *d*, Small artery cut longitudinally. Its upper segment is covered with leucocytes, which are heaped up partly in the invisible perivascular space and partly in the immediate neighbourhood; in the lower segment of the vessel the perivascular space is visible and is filled partly with emigrated leucocytes and partly with red corpuscles; *e*, Obliquely-cut blood-vessel, in the perivascular space of which are many leucocytes; *f*, Circumscribed accumulation in the brain-substance of leucocytes which are partly in a state of granular disintegration.

is in the majority of cases *secondary* (if that of traumatic origin be disregarded), either occurring by metastasis in the course of various acute infective diseases (pneumonia, acute endocarditis, etc.), or by the direct extension of inflammation from neighbouring parts (brain, dura mater, cranial bones, orbit, nasal cavity, and nasal air-sinuses). Even in cases where the meningitis is apparently *primary* an inflammation in the nasal air-sinuses or tympanic cavity can often be

detected, so that in many cases these cavities form the gates of entry for the excitants of the meningeal inflammation. The bacteria which have hitherto been recognised most frequently in the latter capacity are the *Diplococcus pneumoniæ* and the pyococci, whilst in some cases still other species could also be found.

The *exudation* of meningitis (Fig. 169) is rarely serous, and is so only at the commencement; otherwise it is fibrinous (*a*), fibrino-purulent, or altogether purulent. It may, however, also be hæmorrhagic in places (*b*). The inflammation not uncommonly propagates itself along the sheaths of the vessels into the substance of the brain and cord, in which case accumulations of leucocytes and

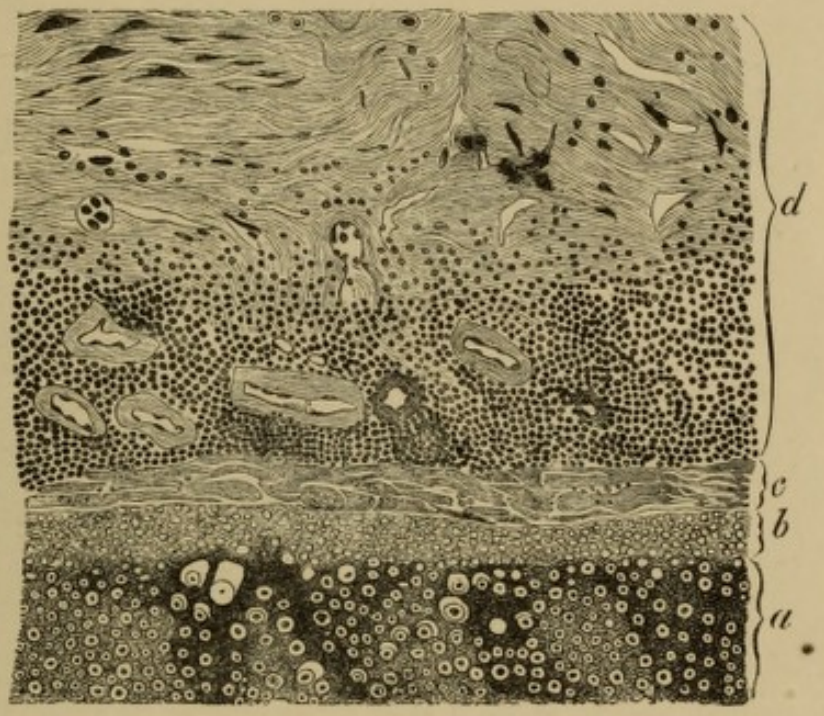

FIG. 170.—SUBACUTE CEREBRO-SPINAL MENINGITIS. × 285. (Hæmatoxylin and eosin.) *a*, Normal part of the spinal cord; *b*, Atrophic cortical layer of the spinal cord; *c*, Spinal pia mater in a state of sclerotic thickening; *d*, Thickening and mutual adhesion of the pia, arachnoid, and dura mater of the cord; the former still in a state of cellular infiltration. The walls of the blood-vessels are also thickened and sclerotic.

sometimes also of red corpuscles are found (*d* and *f*) either inside the perivascular spaces of the blood-vessels only (*e*), or also outside in their immediate neighbourhood. If the process is of longer duration, and the spinal membranes are involved (Fig. 170), the nerve-fibres of the superficial stratum of the cord may suffer degeneration and atrophy (*b*). Furthermore, in spinal as well as cerebral meningitis there gradually occurs a more or less considerable fibrous thickening of the pia mater and arachnoid, and in spinal meningitis even an adhesion of these membranes to the dura mater (*d*), which again may give rise to atrophy of the nerves enclosed in the shrinking connective tissue.

Acute inflammation of the dura mater, acute pachymeningitis (Fig. 171), is always set up by extension from the surrounding parts. The exudation has the same character as in leptomeningitis, except that it is situated chiefly upon the surface (*a* and *b*), internal or external, whilst the tissue of the dura (*c*) merely shows a comparatively slight degree of small-celled infiltration.

Much more frequent is the *chronic inflammation, pachymeningitis interna chronica seu hæmorrhagica,* in which a formation of delicate membranous deposits takes place on circumscribed patches or over the entire extent of the internal surface of the dura mater, these deposits consisting at first of fibrin and isolated round cells, but

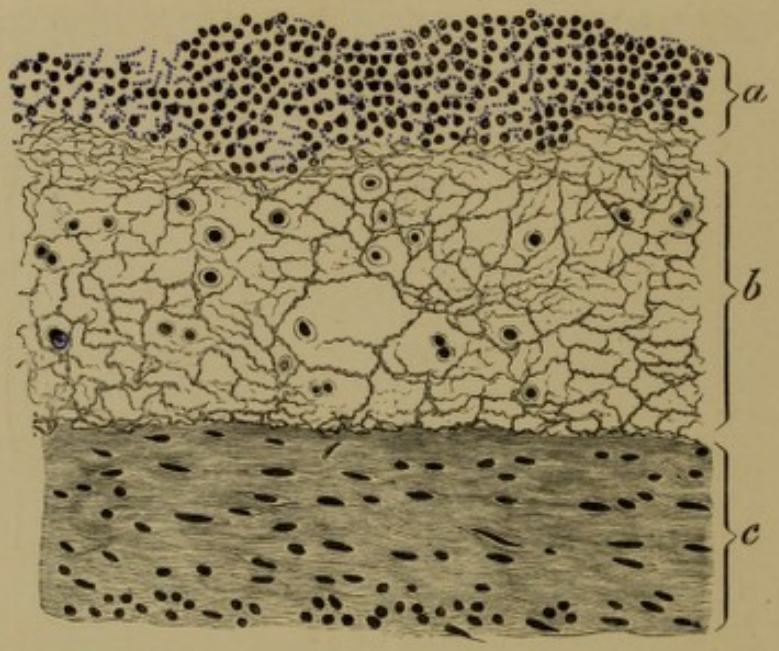

FIG. 171.—FIBRINO-PURULENT INTERNAL PACHYMENINGITIS IN OTITIS INTERNA. × 440; the cocci, however, drawn in under an amplification of × 925. (Weigert's modification of Gram's method.) *a*, Pus-corpuscles, between which lie chains of cocci (*Streptococcus pyogenes*); *b*, Fibrinous exudation; *c*, Dura mater, with cellular infiltration.

later of a highly vascular embryonic or connective tissue. As the blood-vessels of the latter are very thin-walled, hæmorrhages and deposits of pigment are also usually found.

6. Infective Granulomata and New-Formations.—*Tuberculosis* usually occurs in the brain and spinal cord in the form of rather large, solitary, completely caseous nodules, only surrounded at their periphery by a narrow zone of granulation tissue, which, however, may still enclose typical epithelioid-celled or giant-celled tubercles. In the inner *meninges* of the brain and cord, tuberculosis (Fig. 172) gives rise to the formation of minute nodules, mostly in large numbers, which usually lie in the immediate neighbourhood of the blood-vessels (*a* and *b*). The latter also are soon implicated

in the process, either by the extension to their walls of the caseation occurring in the tubercles (*c*), or by the vessel itself becoming the seat of a pronounced tubercular vasculitis, in which its wall is at first infiltrated, and its lumen filled, with round and epithelioid cells, whilst later the entire tubercular new-formation caseates (Fig. 107). The development of tubercles is very often associated with an inflammatory exudation (Fig. 172, *e*) in the cerebro-spinal membranes, and at the same time the process may

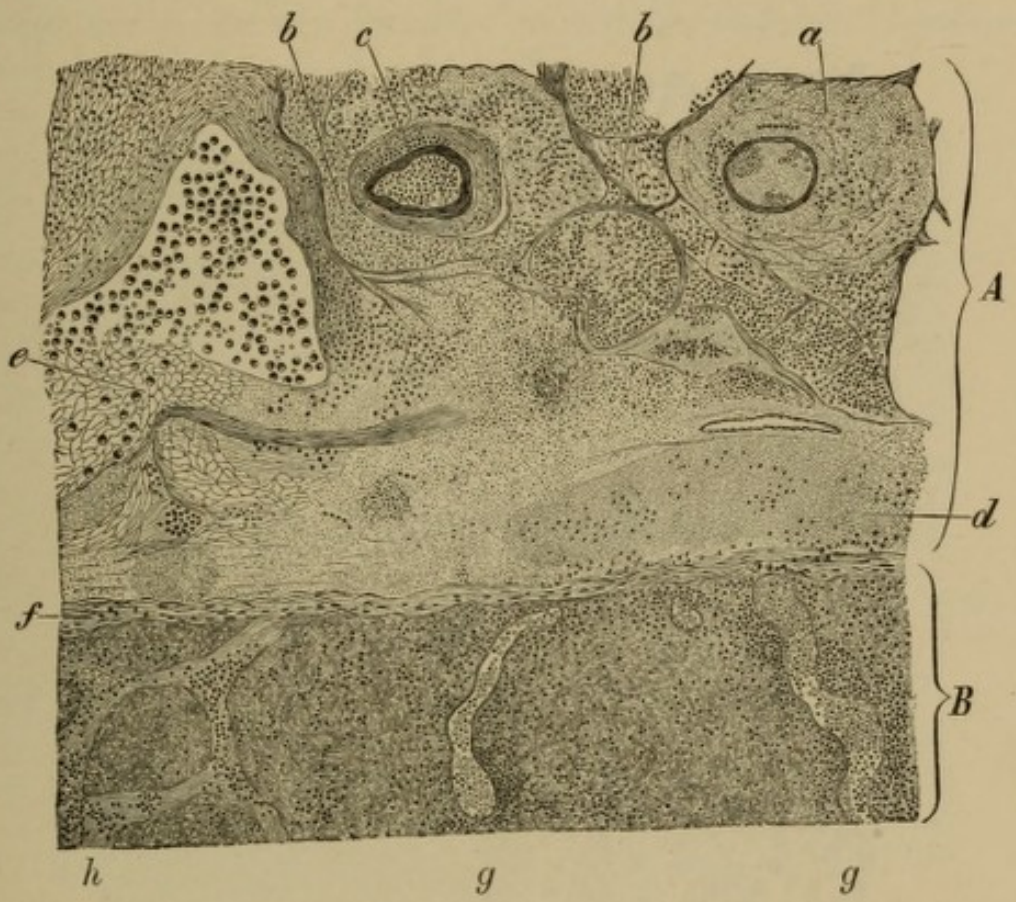

FIG. 172.—TUBERCULAR LEPTOMENINGITIS AFFECTING THE OPTIC CHIASMA, TOGETHER WITH NEURITIS. × 95. (Hæmatoxylin and eosin.) *A*, Internal meninges; *B*, Optic nerve; *a*, Caseous tubercle surrounding a partially caseous vessel in the form of a ring; *b*, Partially caseous tubercle; *c*, Artery in transverse section, with partially caseated walls; *d*, Caseous infiltration formed by the coalescence of tubercles; *e*, Fibrinous exudation; *f*, Perineurium; *g*, Blood-vessels of the endoneurium surrounded with small-celled infiltration; *h*, Interstitial connective-tissue of the nerve, with small-celled infiltration.

also extend along the vessels into the actual substance of the brain and cord, where it either restricts itself to the vessel-sheaths, or attacks the actual nervous substance.

Syphilis occurs not only in the brain and spinal cord themselves, but in the meninges and the nerves issuing from them, taking on the one hand the form of gummata, on the other that of syphilitic vasculitis. As the gummata usually attain a more considerable size, especially in the brain, parts as a rule are found in them which are

already more or less caseated (Fig. 173, *c*), and in the immediate neighbourhood of which the tissue of the syphiloma consists entirely or at least partially of spindle cells, whereas in all other places it is composed exclusively of round cells. Isolated giant cells (*b*) may also be found. It is not uncommon to meet with gummata and syphilitic vasculitis side by side.

Amongst the *new-formations* of the brain and spinal cord, the *glioma* and the *ganglionic neuroglioma* must be mentioned. The former (Fig. 174) usually occurs as a diffuse growth, which either

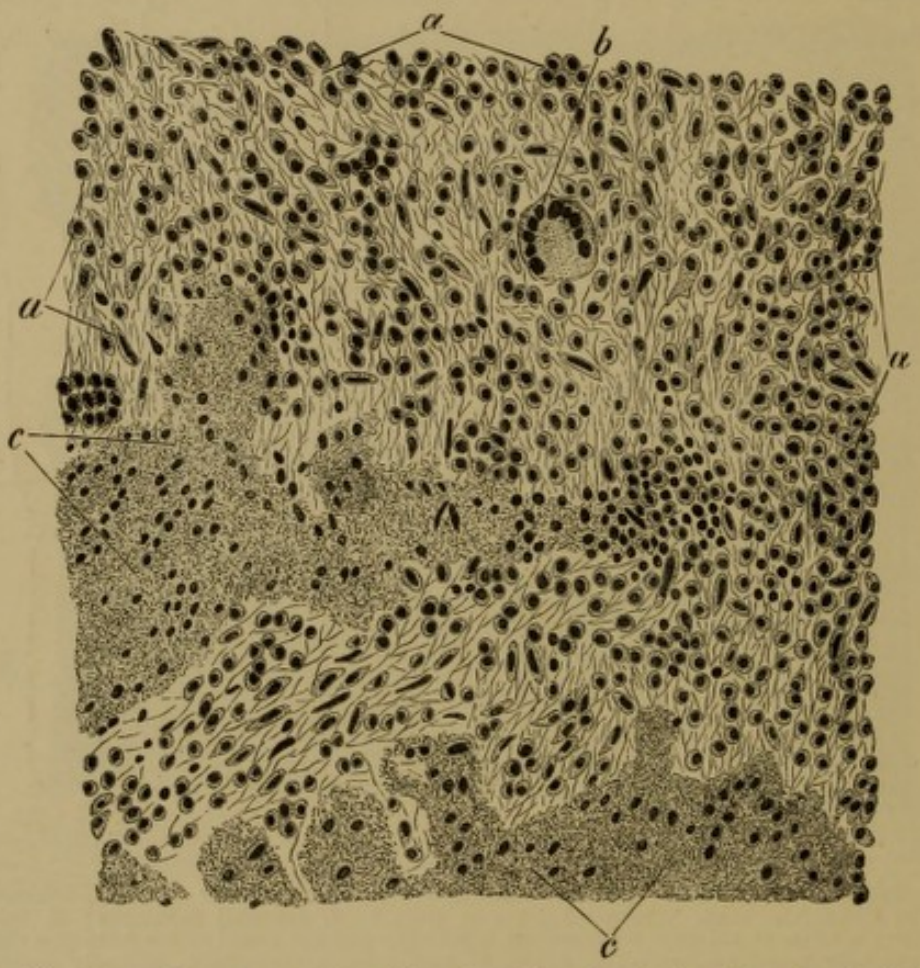

FIG. 173.—GUMMA CEREBRI. × 285. (Hæmatoxylin and eosin.) *a*, Round and spindle-shaped cells; *b*, Giant cell; *c*, Caseous portions.

resembles the normal neuroglia, *i.e.*, contains relatively few and small cells, provided with numerous processes, in an interstitial substance of fine fibres (*b*); or is composed, after the fashion of a sarcoma, of densely-packed cells of larger size, in which latter case we may speak of it as a *glio-sarcoma*. Besides this, *pure sarcomata* also occur, and these as well as the gliomata are frequently very vascular, and show numerous hæmorrhages. In the gliomata softening, liquefaction, and formation of cavities (*d*) may also result. Should nerve-fibres also exist in a glioma (*c*), the latter forms a transition stage to the

ganglionic neuroglioma, which differs from the simple glioma in containing in its glia-like tissue ganglion cells of variable size, and medullated and perhaps also non-medullated nerve-fibres.

The *new-formations in the inner meninges* mostly belong to the connective-tissue tumours, and are oftenest *sarcomata*. In these there not uncommonly occur concentrically laminated calcareous concretions resembling brain-sand (Fig. 37, *b*), which are probably formed by the calcification of flat endothelioid cells arranged in strata like the coats of an onion (*psammomata*). In the *arachnoid of the spinal cord* small *osteomata* are frequently found in elderly persons, the development

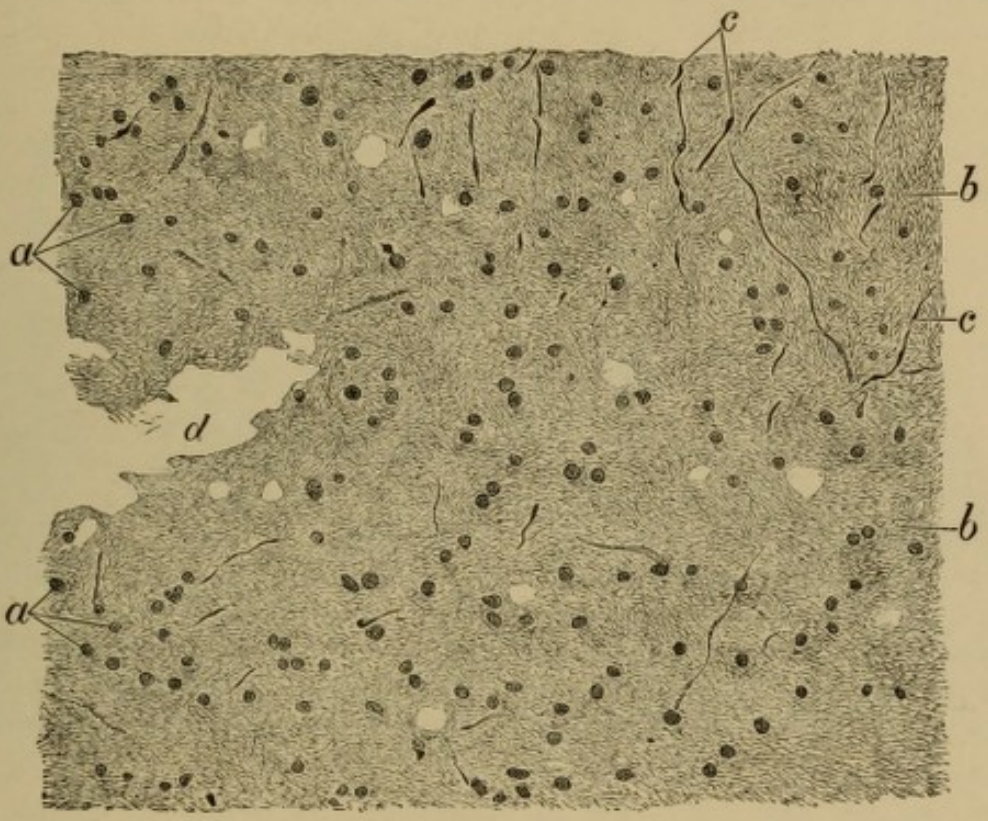

FIG. 174.—GLIOMA OF THE CORTEX OF THE FRONTAL LOBE. × 285. (Weigert's hæmatoxylin—after-staining with alum cochineal.) *a*, Nuclei of the glioma-cells; *b*, Finely fibrous intercellular substance; *c*, Fine medullated nerve-fibres, usually of a varicose character; *d*, Commencing formation of cavities.

of which is ascribed to degenerative processes in the connective tissue. Lastly, the *cholesteatoma* must also be mentioned. It is especially apt to occur at the base of the brain (see p. 99).

Amongst the *new-formations met with in the pituitary body*, those most frequently observed are the *adenoma* (*struma*) and small *cysts* lined with ciliated epithelium. The latter develop from the cavities situated between the anterior and posterior lobes, whilst in the former case we have to do with new-formation of a tissue resembling the normal substance of the anterior lobe, but in which in most instances small colloid cysts are also prone to occur.

II. THE PERIPHERAL NERVOUS SYSTEM.

7. Degeneration, Atrophy, Inflammation, and New-formation.—The *degeneration and atrophy* of the nerves which may occur in consequence of mechanical injury (section or bruising), compression, and inflammation, and after destruction of the central organs (*e.g.*, of the anterior horns of the spinal cord), as well as in infective diseases and intoxications, manifests itself first in a clouding and coagulation of the medullary sheaths. The latter then break down into a detritus consisting of larger and smaller droplets and granules, which are taken up by leucocytes (Fig. 175, *e*) and carried away.

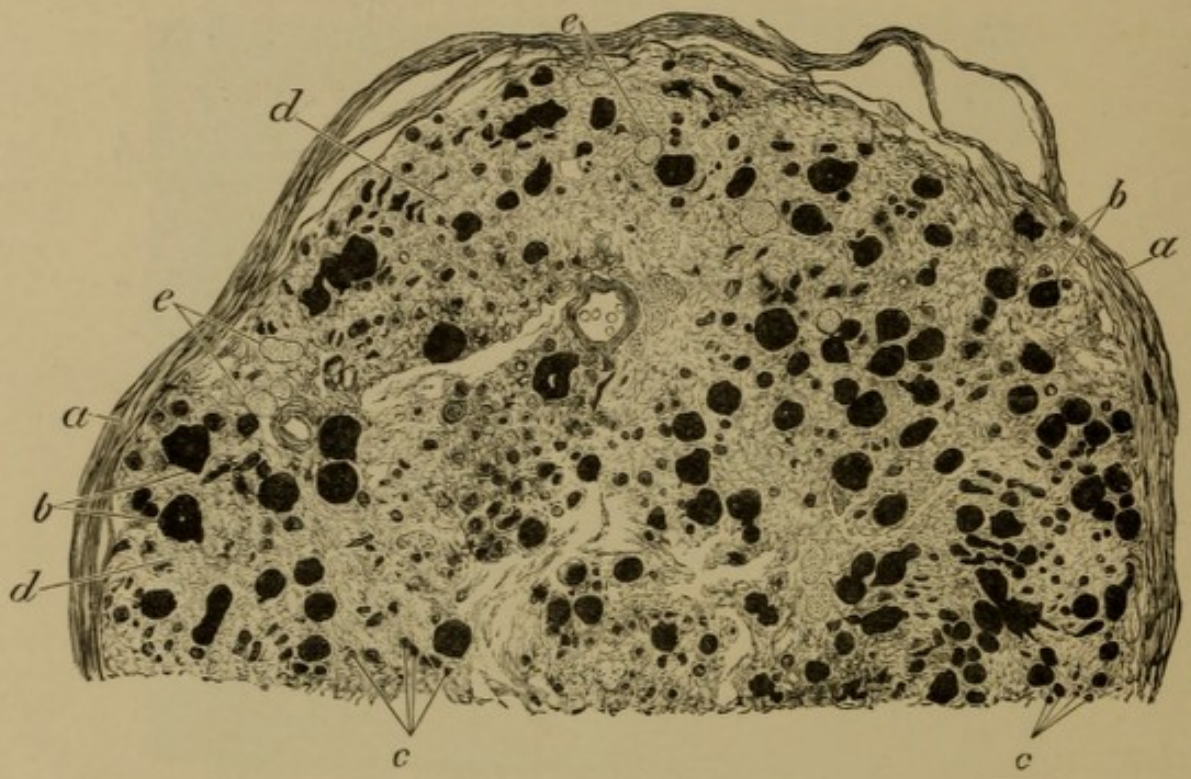

FIG. 175.—COMMENCING ATROPHY OF THE SCIATIC NERVE IN PARAPLEGIA. Half of a transverse section through a nerve-bundle. × 330. (Weigert's hæmatoxylin.) *a*, Perineurium; *b*, Thick and *c*, Thin medullated nerve-fibres in transverse section; *d*, Proliferated endoneural connective tissue; *e*, Granule cells.

The axis cylinders swell up, or disappear by crumbling to pieces. The endoneurium and perineurium either suffer no change or become thickened (Fig. 175, *d*) and sclerosed (Fig. 205, *b*); and the nerve corpuscles may be involved in proliferation.

In *inflammation of the nerves, neuritis*, which may occur as a sequel of infective diseases, intoxications, disorders of circulation and nutrition, or by extension of an inflammation from the surrounding parts, the endoneurium and perineurium are the seat of exudation and cellular infiltration (Fig. 172, *g* and *h*). In severe cases, however, degeneration of nerve-fibres also follows, bearing out the general rule that degenerative and inflammatory processes in the

nerves often cannot be sharply distinguished from one another. If the inflammation runs a *chronic* course, a hyperplasia of the connective tissue of the nerves also gradually sets in (*neuritis prolifera*).

For *neuroma*, see pp. 82-4.

Methods.—The nervous system may be partially examined even in *fresh* preparations, made by teasing out after immersion in macerating fluid (p. 6).

[A useful method for examining degenerative and other changes in the cells of the cerebral cortex, is the *modified fresh method* of Bevan Lewis, which with slight alterations is as follows:—Sections are cut with the freezing microtome from fresh brain, the knife being kept dry on its lower surface, but moistened above with iced water. The sections having been floated off the knife singly, as cut, into iced water are next immersed for a quarter of a minute in 0·25 per cent. osmic acid, washed in water, stained for three quarters of an hour in a 0·25 per cent. aqueous solution of anilin blue-black,[1] thoroughly washed for five minutes, allowed to dry on slides for twenty-four hours, and then mounted, without clearing, in Canada balsam. This method, however, is not applicable to the spinal cord.]

For *hardening*, alcohol is used when examining for bacteria, otherwise Müller's fluid followed by alcohol is most advantageous, but the brain and spinal cord must usually remain in the fluid for several months. In examining processes which extend over considerable portions of the nervous system, notably degenerations and atrophies, it is necessary to make *serial sections*.

The methods given in Part II., Chapter V., suffice for the demonstration of *bacteria* in sections. In all other cases (except the following) the sections should be stained with ammonia carmine, or with alum cochineal or alum carmine, by which the degenerated parts are stained a much deeper red than the normal parts; or with hæmatoxylin and eosin. For the *degenerative* changes, however, *Weigert's hæmatoxylin method* is to be recommended above all others. The pieces having been hardened in Müller's fluid and then (without previous soaking in water, though this is not always injurious) in alcohol, are embedded in celloidin and kept for a day or two at incubation temperature in a saturated solution of copper acetate diluted to half strength with water, and next for one day in 80 per cent. alcohol. Sections cut from the pieces so prepared are then treated during fifteen minutes to twenty-four hours with a staining mixture composed of the following:—Hæmatoxylin,[2] 1 grm.; alcohol, 10 c.cm.; distilled water, 90 c.cm.; and saturated aqueous solution of lithium carbonate, 1 c.cm. The spinal cord and peripheral nerves in general stain more quickly than brain. The sections, which appear evenly black, are then washed in water and decolorised in a fluid consisting of borax, 2 grm.; potassium ferricyanide, 2·5 grm.; distilled water, 200 c.cm.; which can also be further diluted with water according to need. In this the sections are left until a lighter colour becomes sharply differentiated from the original black, after which they are rinsed in water and further treated in the usual way.

[1] [All samples of anilin blue-black are not equally good for this purpose. That made by Messrs. J. Woolley, Sons & Co., of Manchester, will, however, be found satisfactory.]—*Tr.*

[2] Extract of logwood may be substituted for the costly hæmatoxylin.

If the decolorisation is correct, the medullated nerve-fibres appear bluish-black, as also do (to a certain degree) the products of disintegration formed when they degenerate, and which consist of myelin and possibly fat; and this is true even when they have already been taken up by leucocytes. Everything else is yellowish. The degenerated parts (that is, all those in which the nerve-fibres have lost their medullary substance) consequently contrast even to the naked eye, by their yellowish tint, with the normal black-coloured parts. When, however, the decolorisation has been insufficient, the red corpuscles and cell-nuclei also retain the black pigment. If it is desired to stain these latter specially, the decolorised sections should be further immersed in alum carmine or alum cochineal, but their colour will not be very intense. If preparations or sections refuse to take Weigert's hæmatoxylin stain well, whether from having been previously kept too long in alcohol, or from having been soaked in water after the hardening in Müller's fluid, the difficulty may be met by returning the preparations to Müller's fluid again, until they have assumed a dark green colour.

A *modification*, by Weigert himself, of the method just described, whereby the decolorisation in borax and potassium ferricyanide can usually be omitted, consists in first leaving the pieces embedded in celloidin for twenty-four hours at incubation temperature in a mixture of a cold saturated aqueous solution (filtered) of neutral copper acetate with equal parts of 10 per cent. aqueous solution of sodio-potassic tartrate, and then for twenty-four hours more, likewise at incubation temperature, in the copper solution originally given on p. 351, *i.e.*, diluted to half strength with water. Thereupon the preparations, after superficial washing with water, are transferred to 80 per cent. alcohol, and sections from them are stained in a fluid for the preparation of which two solutions are required, the one consisting of a gramme of hæmatoxylin in 10 c.cm. alcohol, and the other of 7 c.cm. of a saturated aqueous solution of lithium carbonate and 93 c.cm. of distilled water. The second solution is always added to the first immediately before staining, in the proportion of 9 parts by volume of the second to 1 part by volume of the first. In this mixture the sections remain for four or five hours, or even longer, and are then simply washed in water, by which means the desired differentiation is usually at once attained; that is to say, the medullated nerve-fibres now appear from dark blue to black, and the ground becomes a pale rose. Should, however, no differentiation follow, for any reason, the sections may be decolorised in the borax and potassium ferricyanide solution given above, which must, however, be further diluted with water for this purpose.

Another modification of Weigert's method is that introduced by Pal, in which good counter-staining of the cell-nuclei is possible. The sections having been stained in Weigert's hæmatoxylin during twenty-four to forty-eight hours, are washed in water to which, in case the sections do not appear deep blue, is added 1 or 2 per cent. of a saturated solution of lithium carbonate. Thereupon the sections are transferred to a $\frac{1}{4}$ per cent. aqueous solution of potassium permanganate for half a minute or longer, until they have become brownish-yellow, and then for a few seconds to a fluid composed of oxalic acid, 1 grm.; potassium sulphite, 1 grm.; distilled water, 200 c.cm. They are then washed in water, and counter-stained with some one of the carmine solutions.

Another method of examining *degenerative* conditions is that of Heidenhain

(p. 190), by which the normal medullated fibres are stained orange-yellow, the degenerated fibres diffusely red, and the cell-nuclei blue. For the same purpose the mode of hardening in Flemming's solution with subsequent saffranin staining may be recommended, which was given in dealing with the examination of fatty degeneration and of karyokinesis (pp. 53 and 69).

Lastly, the method of Adamkiewicz for this purpose, improved by Nikiforoff, must also be mentioned. After hardening in Müller's fluid and (without previous soaking in water) in alcohol, the sections are stained for twenty-four hours in a concentrated aqueous solution of saffranin, or in anilin saffranin, or saffranin 5 per cent. carbolic acid. The differentiation is now accomplished by first moving the sections to and fro in alcohol, until the grey substance stands out from the white by its lighter tint, after which they are transferred to a $\frac{1}{3}$ per cent. aqueous solution of gold chloride until the grey substance passes permanently into violet, and finally, after careful washing out in water, are dehydrated in absolute alcohol until the grey substance appears pure violet, and the medullary substance red. By this method the cell-nuclei are stained violet, the medullated nerve-fibres red; but if the latter are diseased, though only in slight degree, they no longer take the red colour.

CHAPTER X.

THE ORGANS OF LOCOMOTION.

I. THE OSSEOUS SYSTEM (INCLUDING THE MARROW, THE CARTILAGES, AND THE JOINTS).

1. Retrograde Changes.—*Atrophy of bone* is termed *concentric* or *eccentric* according as it begins from the surface or from the medullary cavity, whilst that which occurs in the substance of the bone is known as *osteoporosis*. According to the *causes*, again, there are distinguished a *senile* atrophy and a *pressure* atrophy, and, further, an *atrophy of inactivity* from disuse of the bones, a *neurotic* atrophy in

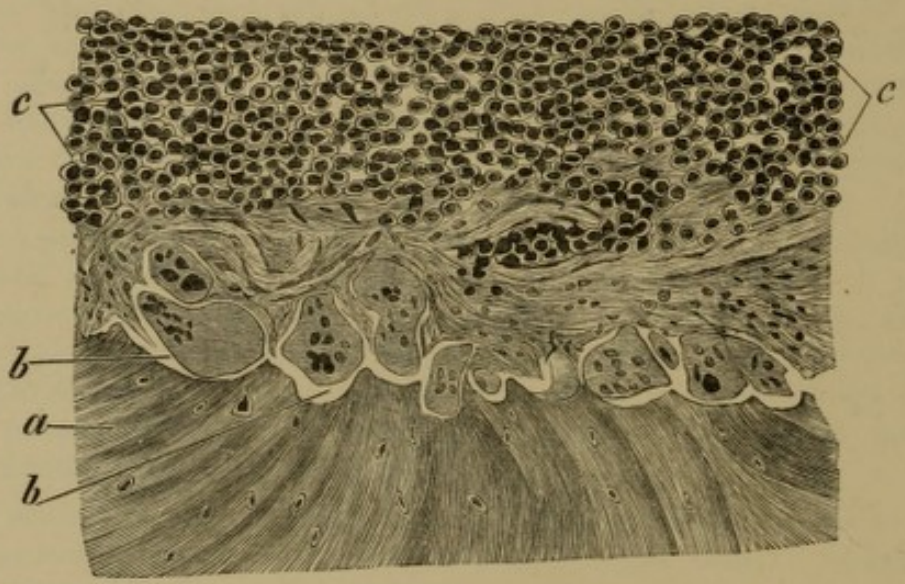

FIG. 176.—LARGE-ROUND-CELLED SARCOMA OF THE CRANIUM, WITH ABSORPTION OF THE BONE. × 240. (Hæmatoxylin and eosin.) *a*, Bone with bone-corpuscles; *b*, Howship's lacunæ, with osteoclasts; *c*, Large round cells of the sarcoma.

certain morbid conditions of the nervous system, and an atrophy due to inflammation of the marrow and periosteum. In all these varieties the atrophy advances, like physiological absorption of bone, by the formation of pitted depressions, semicircular lacunæ (*Howship's lacunæ*), wherein lie large polynuclear cells (*osteoclasts*, Fig. 176, *b*)

which show their activity by solution of the bone-substance. Should this solution take place over a wider extent, and be complete, *cysts* may even form in the bone.

Osteomalacia (Fig. 177) is a special variety of atrophy which occurs in more advanced life, but is most frequent in women during pregnancy and child-bed, and which consists in a decalcification of

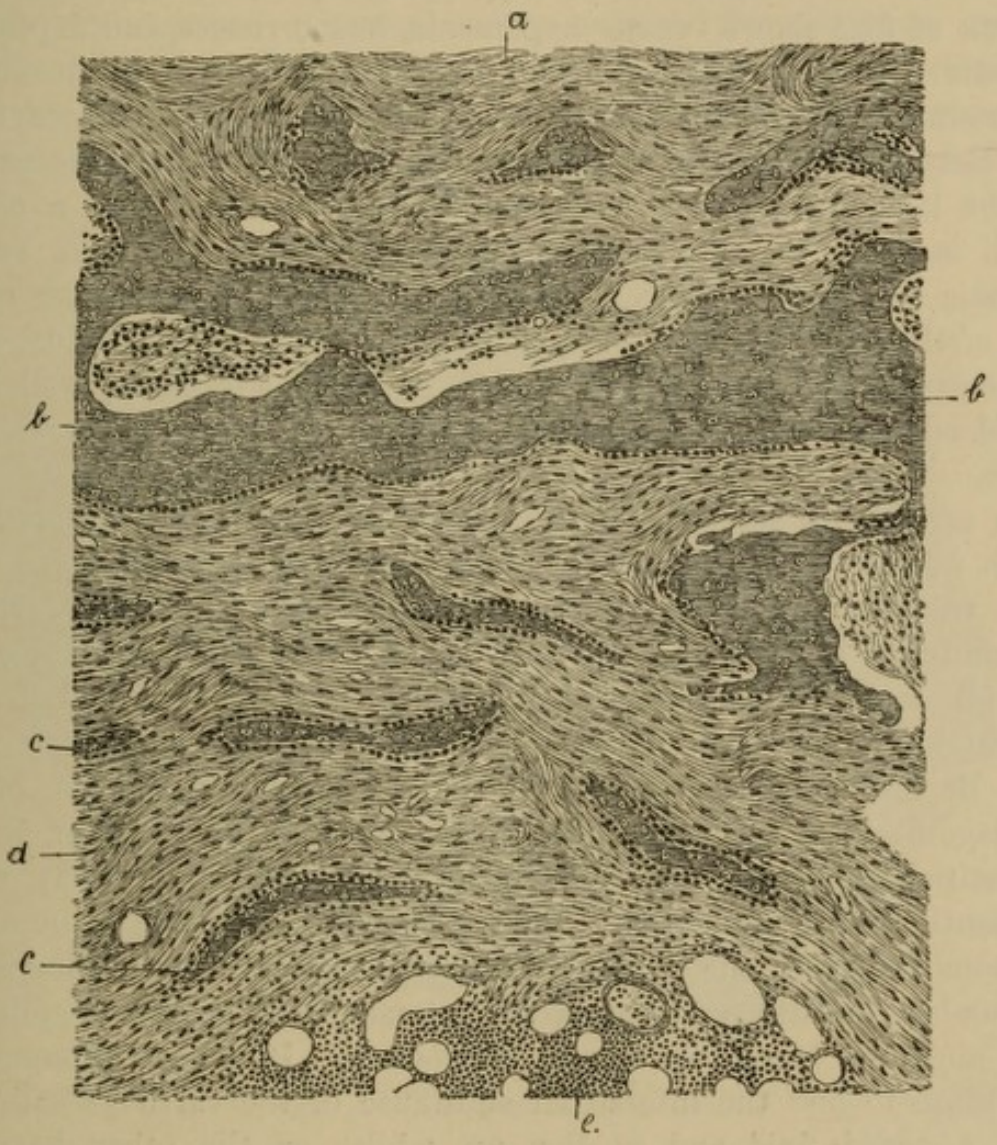

FIG. 177.—SENILE OSTEOMALACIA OF THE RIB. × 70. (Hæmatoxylin and eosin.) *a*, Periosteum; *b*, Thicker calcified trabeculæ of bone; *c*, Very thin bony trabeculæ in process of decalcification; *d*, Decalcified osseous tissue, rich in cells; *e*, Marrow composed of round and fat-cells.

the bone. This always begins from the medullary cavity or from the cancellous spaces and Haversian canals, *i.e.*, at the periphery of the bony trabeculæ, and gradually advances towards the axis of the latter. The decalcified part (*d*) shows a striped or fibrous interstitial substance, in which the earlier lamellar stratification can sometimes still be made out, whilst the bone corpuscles are in part retained, but in part have lost their processes or even entirely disappeared. The

line of demarcation between the decalcified and normal bone is very sharp, but sometimes shows incurvings resembling Howship's lacunæ. When the decalcifying process steadily progresses, and the parts affected by it finally dissolve completely, cystic spaces of variable size may be formed, which contain a clear fluid. However, recovery may also take place, the decalcified parts being again transformed into osseous tissue by taking up lime-salts. The *bone-marrow* at first shows venous hyperæmia, hæmorrhages, and deposits of pigment in its substance, as well as a multiplication of its colourless round cells (marrow-cells) at the expense of the adipose tissue (*e*); but later it is changed into the so-called *gelatinous marrow.* By the latter designation (*gelatinous marrow*) is understood a change which is prone to occur in later life generally, as well as in various marastic conditions, and consists in the diminution in number of the cells of the marrow and their replacement by a mucinous fluid. *Fatty degeneration* may also be observed in the marrow-cells, as well as in the blood capillaries of the marrow, in typhoid, typhus, and relapsing fevers.

In *cartilage* a series of *retrograde changes* occurs in advanced life, which we may group together under the name of *senile changes.* The most frequent of these is *fissuring* and *fibrillation* of the cartilage, especially of articular cartilage, which may begin in the superficial as well as in the deeper parts, and which shows a preference for certain joints and also for certain localities in those joints. It probably depends on a solution of the cementing substance of the cartilage-fibrils, in consequence of which there first appear in the interstitial substance fine clear lines and fissures (Fig. 178), which frequently radiate out from the cartilage cells and effect numerous anastomoses with one another (*fissuring*). These fissures increasing in number, breadth, and depth, the interstitial substance is split into finer and finer bands and fibres (*fibrillation*). It is not uncommon at this stage to find the interstitial substance of the cartilage saturated with a viscid fluid and swollen up, whilst on the other hand the cartilage cells are engaged in proliferation, and then constitute large parent cartilage-cells filled with numerous young elements. The fibrillated portions of cartilage becoming in the next place rubbed away by the movements of the joint, deficiencies are formed which continually increase in depth (*attrition*), but which, in case they lie near the margins of the cartilage or near the bone, may be again filled up by the ingrowth of processes rich in cells and vessels from the synovial membrane or the bone-marrow.

A further senile change, at least in the articular cartilages, consists in an *absorption* which sets in at the edges, and which here also,

as in bone, occurs with formation of dimples and lacunæ harbouring elements derived from the cells of the synovial membrane, and which are of variable outline, very rich in processes, and in many cases also polynuclear (*chondroclasts?*). Furthermore, *amyloid degeneration* may be observed in the cartilages of old people, not only in joints but synchondroses, and especially at the fibrillated parts. It first affects the capsules of the cartilage cells, which swell up unequally and assume a glassy sheen, and it then extends, on the one hand to the cells themselves, on the other to the interstitial substance of the cartilage, so that finally irregular crumbling masses are left. Lastly, *deposits of lime* also occur in advanced life,

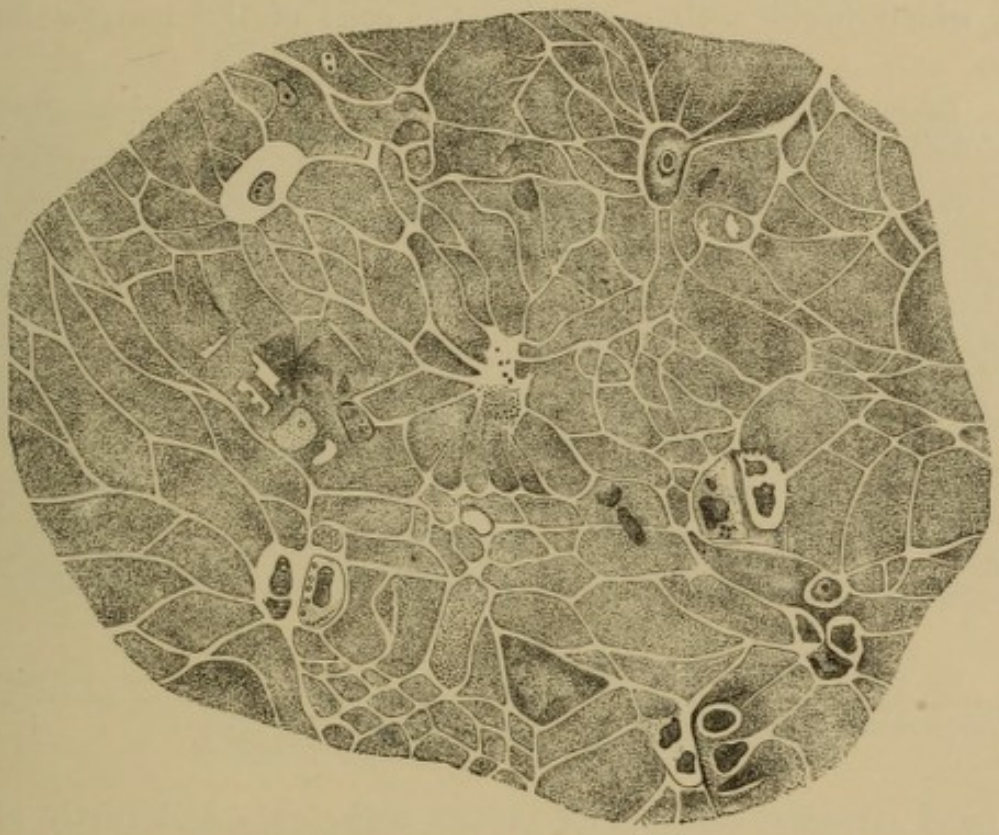

FIG. 178.—SENILE FISSURING OF CARTILAGE. Horizontal section through the superficial parts of the cartilage encrusting the head of the humerus. × 400.

by preference at the border of the articular cartilages and at the fibrillated spots. The salts precipitated in this process are for the most part calcium carbonate and calcium phosphate, which are deposited in the form of finely granular masses, first in the capsules of the cartilage cells, later also in the cells themselves and in the interstitial substance of the cartilage; in contrast to *gout*, in which a deposit of needle-shaped crystals of urates takes place.

The *synovial membranes* and *fibrous capsules* of joints may in advanced life show similar retrograde changes to cartilage, viz., fibrillation, amyloid degeneration, and deposit of lime.

2. Regenerative and Hyperplastic Processes.—The *regeneration of osseous tissue*, as it takes place after fractures, resections, and the like, always commences from the periosteum and the marrow, and follows the type of the physiological development of bone. In simple fractures it is only in the first few days that the regenerative processes are accompanied by inflammatory changes, which are inconsiderable in degree and consist partly in the outpouring of fluid exudation into the injured tissues (the bone-marrow, the periosteum, and the adjoining soft parts), and partly in the immigration of leucocytes in moderately large numbers, which take up the detritus of tissue left by the lesion, together with the extravasated blood, and convey them away. The principal changes, however, are the *regenerative*, which begin with growth of the cells of the marrow on the

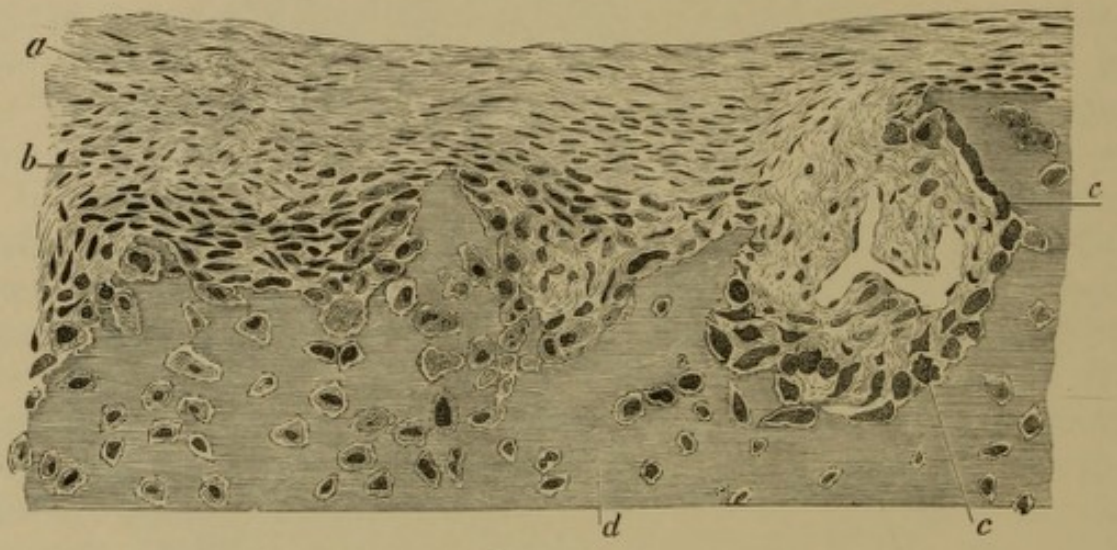

FIG. 179.—DEVELOPMENT OF BONE FROM THE PERIOSTEUM. × 285. (Alum cochineal.) *a*, Outer layer of periosteum, containing few cells; *b*, Inner (osteoplastic) layer, rich in cells; *c*, Osteoblasts; *d*, Osteoid tissue.

one hand (*internal callus*), and of the periosteum and partly also of the immediately adjoining soft parts on the other (*external callus*).

In the periosteum it is especially the inner (*osteoplastic*) layer (Fig. 179, *b*) in which the connective-tissue cells and those of the endothelium lining the vessels are engaged in proliferation by karyokinesis, and thus produce a highly vascular tissue, composed of largish cells of variable shape embedded in a homogeneous interstitial substance. By this means, as well as by the simultaneous growth of the cells of the marrow, there results an extensive absorption of the bone at the broken ends and a smoothing of the latter. Later, however, the new tissue in the periosteum and in the internal medullary spaces becomes differentiated, either by the union of the cells lying nearest the old bone to form an epithelium-like layer of

osteoblasts (Fig. 179, *c*), which then produce new trabeculæ of bone in the ordinary manner (a part of the osteoblasts forming the osseous ground-substance, whilst another part develops into bone corpuscles which are at first plump and provided with few processes); or by the formation in the first place of islets of osteoid tissue or cartilage (Fig. 180, *a*) in the proliferated periosteum, whilst the remaining cells assume the rôle of marrow-cells. In the osteoid tissue the interstitial substance at first appears homogeneous, and the cells are enclosed in

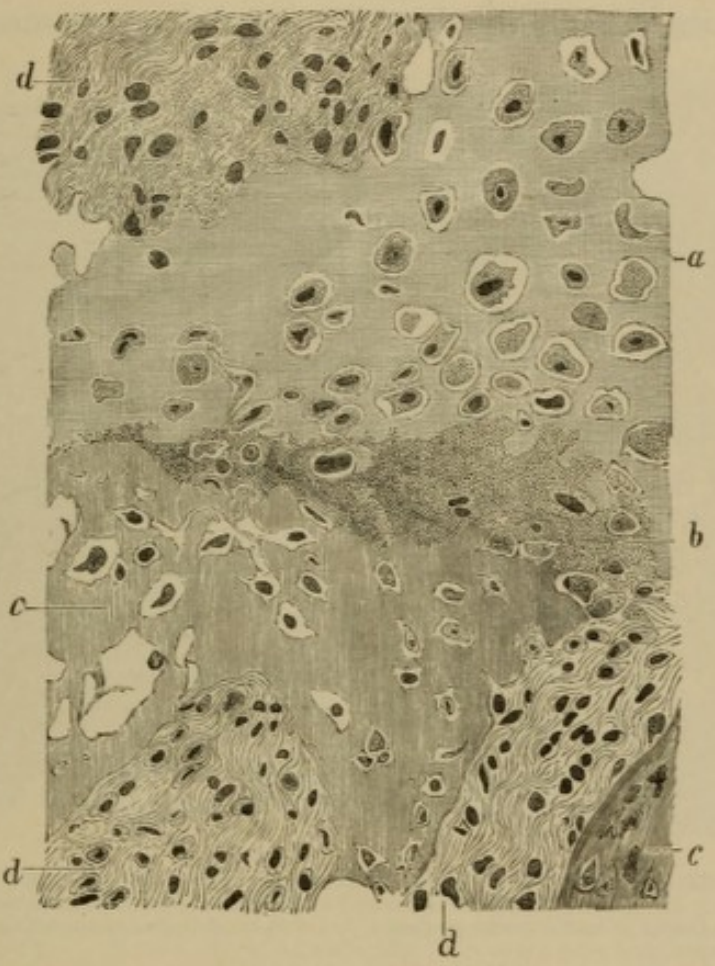

FIG. 180.—CARTILAGINOUS AND BONY CALLUS FOUR WEEKS AFTER FRACTURE OF THE CORONOID PROCESS. × 285. (Alum cochineal.) *a*, Cartilaginous callus; *b*, Commencing calcification of the cartilage and direct change into bone; *c*, Bony callus; *d*, Cancellous spaces.

serrated spaces (Fig. 179, *d*); at a later period, however, the tissue becomes transformed by deposit of lime-salts into actual bone.

The islets of cartilage, which are of the hyaline variety, are also transformed subsequently into bone either directly or indirectly. In the *direct* transformation, on the one hand the cartilage-cells at once become bone-cells by acquiring processes while their cavities assume serrated forms; and on the other, lime is deposited in the interstitial substance (Fig. 180, *b*). In the *indirect* transformation, however, the cartilage dissolves, whilst its cells first become marrow-cells,

and only subsequently bone-corpuscles. Besides this, a portion of the newly-formed tissue may also change first into fibrillated connective tissue, this subsequently becoming bone.

In the manner just described new bone (*external and internal callus*) is formed not only on the surface of the broken ends, but between them [*definitive callus*], being most strongly developed in the immediate neighbourhood of the seat of fracture, and gradually decreasing in bulk as it recedes from the latter. This bone is at first very spongy, *i.e.*, it still contains numerous and relatively large cancellous spaces, filled with a medullary tissue rich in cells

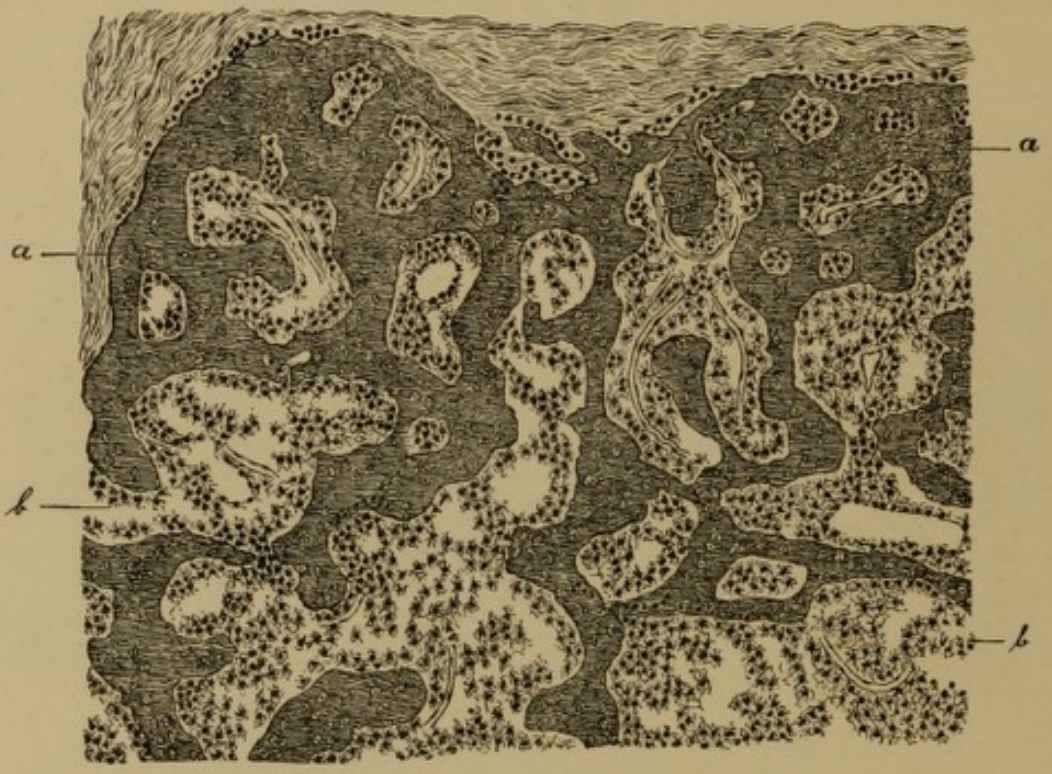

FIG. 181.—EXTERNAL CALLUS OF A FOUR-WEEKS-OLD FRACTURE OF THE CORONOID PROCESS OF THE ULNA. × 70. (Hæmatoxylin and eosin.) *a*, Narrow trabeculæ of bone, with numerous bone-corpuscles, more or less densely packed; *b*, Large cancellous spaces, containing tissue rich in cells and vessels.

and blood-vessels (Fig. 181, *b*); but later it becomes more and more compact owing to the continual deposition from both periosteum and medullary spaces of new bony trabeculæ upon the old. After a still longer time (in the course of years) a partial reabsorption of the callus takes place, all parts not required for the function of the bone being in this way removed.

If the broken ends are widely separated, or are continually shifting one on the other, or are insufficiently nourished, the bone either remains altogether ununited, or there ensues a mere union by *fibrous masses* (*pseudarthrosis*). In the former case a kind of joint may be developed by the smoothing off of the fractured ends and condensation of the neighbouring connective tissue, and there may even be

secretion of a fluid resembling synovia, whilst finally the fractured ends may actually become coated with newly-formed cartilage.

After *resection* of articular ends or in the continuity of the bone changes and results are observed analogous to those which follow fractures.

The *regenerative processes in cartilage* are much slighter than in bone. Fractures of cartilage unite not by a cartilaginous, but by a connective-tissue or bony callus. When pieces of cartilage become chipped off in joints, the deficiency is entirely or partially filled up with connective tissue derived from the overgrowing synovial membrane, or from the tissue of the exposed Haversian canals and medullary spaces, whilst the piece broken off may suffer certain

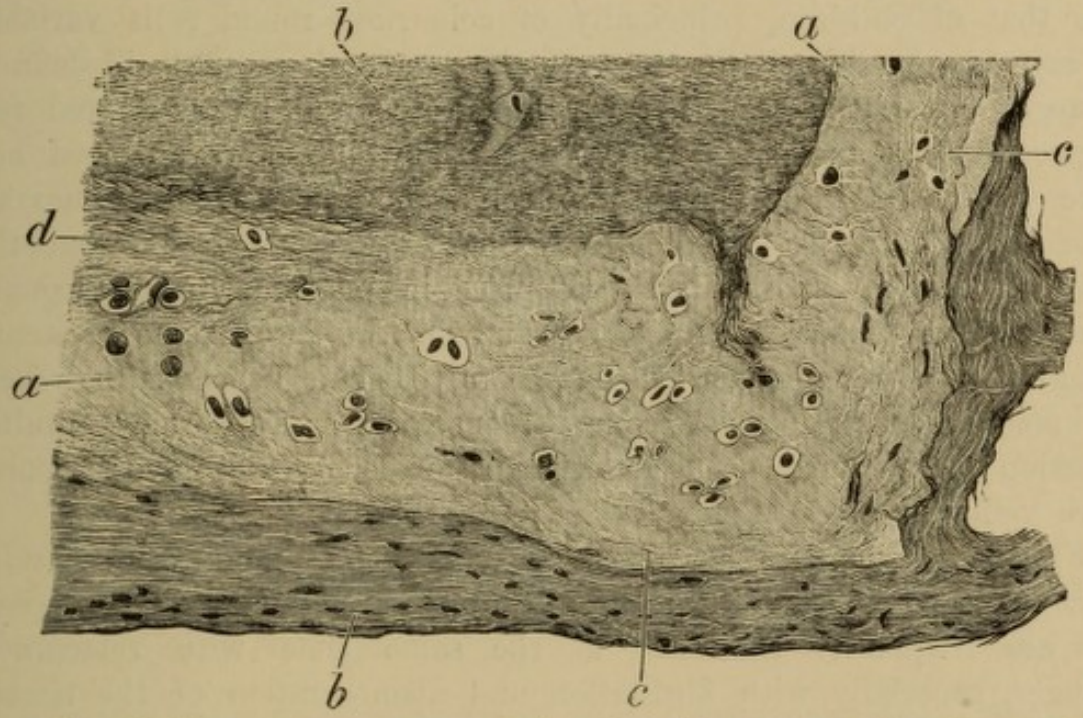

FIG. 182.—VERTICAL SECTION THROUGH A FLAT LOOSE BODY FROM THE KNEE-JOINT. ×285. (Alum cochineal.) *a*, Cartilage, the ground-substance of which is fissured in places, and at *d* is fibrous; *b*, Old fibrin encapsuling the cartilage, homogeneous in structure, and partly permeated with fissures and cells; *c*, Clefts in the interstitial substance of the cartilage.

further changes as a *loose body* in the joint, a portion of its cartilage becoming fissured and fibrillated (Fig. 182, *c* and *d*), and also calcifying, or else being transformed into osteoid tissue and finally into actual bone.

After *luxations* which have not been reduced, a new joint may form by the creation of a new socket and a new articular capsule as the result of processes of growth in the connective tissue and bone at the spot upon which the dislocated articular end rests. The socket may even become coated with cartilage in the same way as in pseudarthrosis following fractures, and the capsule may secrete a synovia-like fluid, whilst the old joint becomes obliterated.

Hyperplasia or new-formation of bone occurs usually as a con-

sequence of chronic inflammation, but also in the neighbourhood of absorptions of bone (*e.g.*, in tumours in bone), and follows the same type as regeneration. If the process consists in an even increase in bulk of the old bone, it is spoken of as a *hyperostosis*; if the old bone merely gains in density, as *osteosclerosis*. Circumscribed osseous new-growths in the interior of the bone are known as *endostoses*, but if such growths are on the surface they are called *osteophytes*, or, when larger, *exostoses*.

In the *marrow*, *hyperplastic* growths frequently occur in which the proper marrow-cells are involved, the fat-cells of the marrow at the same time disappearing; and which end in the formation of the so-called *lymphoid* or *red* marrow, *i.e.*, a marrow consisting, like that of children, principally of colourless round cells variable in size (some with distinctly vesicular and others with ill-defined homogeneous nuclei), together with nucleated and non-nucleated red corpuscles, and pigmented cells. All the cells, however, need not have originated in the marrow itself; they may also be derived from the blood. In such marrow Charcot's crystals are frequently seen. The changes described take place in oligæmia, in myelogenic leucæmia, in cachectic conditions, and in the later stage of acute infective diseases. In high degrees of myelogenic leucæmia, however, the marrow loses its red colour in consequence of enormous multiplication of the white corpuscles within the blood-vessels, and becomes more yellowish-green like pus.

Hyperplastic growths are observed in *cartilage* and in the *capsules of joints* in advanced life, in chronic inflammations, and in paralyses, but are frequently combined at the same time with retrograde changes, especially with fibrillation and disintegration of the tissue.

In the *articular capsule* the hyperplasia shows itself on the one hand by enlargement and multiplication of the synovial villi and their non-vascular appendages, as well as by gradual growth of the synovial membrane over the edges of the cartilage after the manner of a pannus; on the other hand, by new formation of cartilaginous tissue, which originates from the cells of the synovial membrane. The synovial villi may attain so considerable a size in this process that they may properly be regarded as pedunculated fibromata, or, when much adipose tissue is present in them, as lipomata (*lipoma arborescens*).

The *new-formation of cartilaginous tissue* manifests itself most in the parts of the synovial membrane which abut on the edges of the cartilage, not only the enlarged villi but also the remaining tissue of the membrane. In the latter case, warty or more diffuse fibro-cartilaginous outgrowths form at the margins of the articular surfaces (*ecchondroses*), whereas in the former the newly-developed

masses of cartilage lie in the heads of the villi, and after the latter have been torn away form loose articular bodies, which may also occur (apart from the traumatic separation of a piece of articular cartilage as mentioned on p. 361) by the chipping off or loosening of ecchondroses or newly-formed plates of cartilage in the synovial membrane.

3. Inflammation.—*Inflammations of bone* run their course in the periosteum or the marrow, whilst only a passive rôle in the process is assigned to the proper substance of the bone.

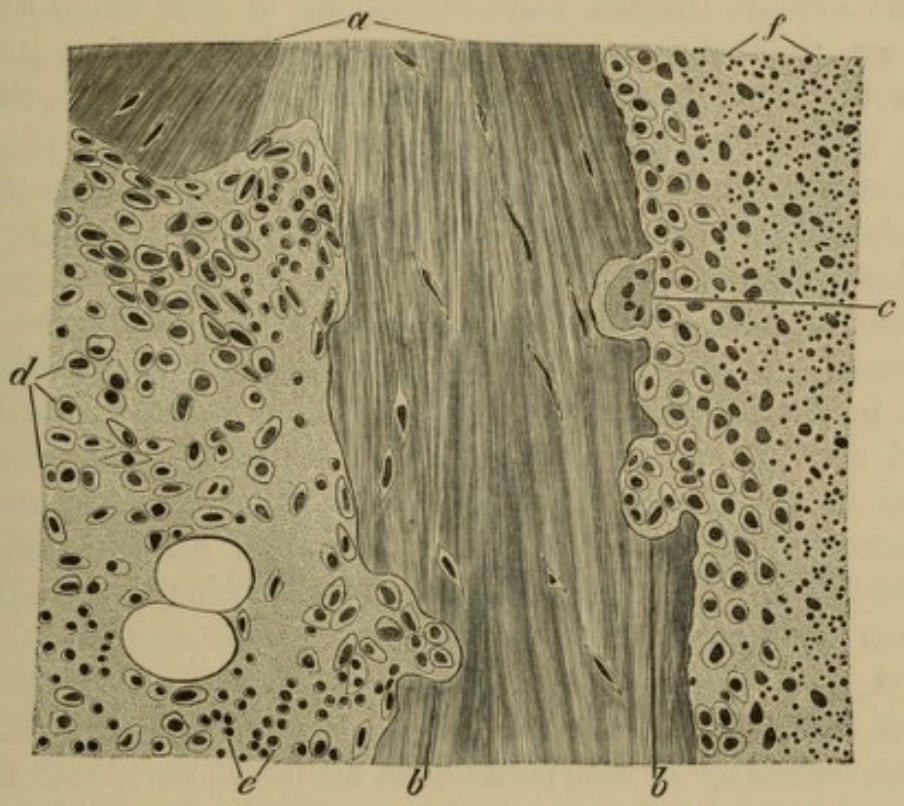

FIG. 183.—SUPPURATIVE OSTEOMYELITIS. × 440. (Alkaline methyl blue.) *a*, Bone; *b*, Howship's absorption lacunæ; *c*, Giant cell (osteoclast); *d*, Larger proliferated medullary cells; *e*, Small mononuclear round cells; *f*, Pus-corpuscles, the nuclei of which have in part undergone granular disintegration.

Acute inflammation of bone, *acute osteitis*, may be *primary* or *secondary*, the primary inflammation, again, occurring either idiopathically or after an injury, when the latter has been accompanied by infection with pyococci.

Idiopathic osteitis, also known as *acute infective osteomyelitis and periostitis*, is usually due to the *Staphylococcus pyogenes aureus*, but sometimes also to the *Streptococcus pyogenes*, or to both together. Probably *traumatic* influences may also play a part in the process, in so far as they give rise to disorders of circulation or extravasations of blood in the affected bones, and by so doing create a favourable soil for the lodgment of any specific bacteria that may chance to be already circulating in the blood. The inflammation (Fig. 183) occurs

oftenest in the femur, and begins either in the periosteum or the medulla. The one or the other, as the case may be, is found infiltrated with larger and smaller mononuclear round cells and pus corpuscles (*d*, *e*, and *f*), which in the marrow compress the fat-cells more and more, and soon also cause a lacunar liquefaction of the bone (*b*), usually by the intervention of osteoclasts (*c*). The pus-corpuscles in the immediate neighbourhood of the settlement of cocci frequently show a granular disintegration of their nuclei (*f*). With further increase of the pus-corpuscles, there become visible to the naked eye on the one hand collections of pus under the periosteum, on the other suppurative foci in the medullary tube and spaces of the bone. The former produce a *superficial necrosis* of the diseased bone owing to rupture of the vessels passing to it from the periosteum: the latter a *central necrosis*, in consequence of the compression of the blood-vessels favoured by the unyielding nature of the bony substance; and these necroses, again, may be *partial* or *total* according to the extent of the suppuration. With the setting-in of necrosis, however, what is known as a *limiting inflammation* develops in the periosteum and bone at the boundary line between the dead and the living tissue, giving rise in the first instance to formation of granulation tissue and of numerous osteoclasts. The latter cause a lacunar liquefaction of the dead bone in the manner with which we are acquainted, the result being either complete destruction of the bone in question (*insensible exfoliation*), or its separation from the living tissue as a *sequestrum*. The osteoplastic properties of the granulation tissue now come to the front, the latter producing, especially in the periosteum, abundant new bony tissue in the form of osteophytes, after the mode already described in speaking of fractures (pp. 358-9). In total necrosis these osteophytes may coalesce to form a bony case which encloses the sequestrum. If the latter is very small it may entirely disappear by progressive lacunar liquefaction; otherwise it keeps up a permanent chronic inflammation, which does not cease until the sequestrum has been removed. Should this eventually be done, processes partly of liquefaction and partly of new formation of osseous tissue will persist in the bone covered with osteophytes which remains behind, until its original shape has been approximately restored.

The *second* variety of primary osteitis, viz., the inflammation occurring after *injuries* with simultaneous entrance of pus bacteria, as for example after compound fractures, may in general lead to changes similar to those in spontaneous osteitis.

Secondary osteitis is set up either by the extension of an acute inflammation from the neighbouring parts, in which case it takes on

the same character as the latter, or metastatically in different acute infective diseases (pyæmia, typhoid fever, scarlatina, and so on), in which case it is excited by the specific micro-organisms of the primary infective disease or its complications. Hence pyococci are most frequently found in this kind of osteitis also, though in the osteitis and periostitis which often occur in the course of typhoid fever, typhoid bacilli, alone or in association with pyococci, may be the cause of the inflammation. The histological processes in secondary osteitis are in general not different from those of the primary form.

Acute inflammation of the joints may also be *primary* or *secondary*. The former occurs as the so-called *articular rheumatism* (*acute polyarticular rheumatic arthritis*), and is not improbably always due to bacteria. It usually affects several joints, and gives rise to either a serous, a fibrinous, or a purulent exudation. In the serous exudation no micro-organisms have as yet been found, but in the others it has been possible to demonstrate the *Diplococcus pneumoniæ* and the pyococci. Acute articular rheumatism in its further course tolerably often leads to an *acute endocarditis*. An acute arthritis may also occur after *injuries*, should the bacteria of pus at the same time gain entrance.

Another disease belonging to the primary form of acute inflammation of joints is *uratic arthritis* [*gout*], which most frequently affects the metatarso-phalangeal joint of the great toe and the finger joints, and is characterised by mortary-looking deposits of sodium or calcium urate in the cartilage, bones, and soft parts [*tophi*]. In the cartilage it is chiefly the cells and their capsules in which the urates are precipitated, in the form of stellate tufts of crystals, whereas in the soft parts the interstitial substance is also affected. Uratic arthritis may also take a more *chronic* course.

The *secondary* form of acute arthritis occurs either by extension of an inflammation from the neighbourhood, *e.g.*, in acute infective osteomyelitis, or (which is most frequent) metastatically, as happens in pyæmia (including puerperal fever), scarlatina, measles, cerebro-spinal meningitis, gonorrhœa, and so forth. *Metastatic arthritis* may attack one joint or several, and is usually of a suppurative nature. It is, of course, excited by the micro-organisms of the primary diseased condition or of its complications.

The *histological changes* in the primary and secondary forms of acute arthritis are the same. In slighter degrees the synovial membrane is found to be alone affected, its villi especially being enlarged by vascular dilatation and moderate small-celled infiltration; but in the severer degrees and when the disease is of longer duration, especially in the suppurative form, all parts of the joint are sympa-

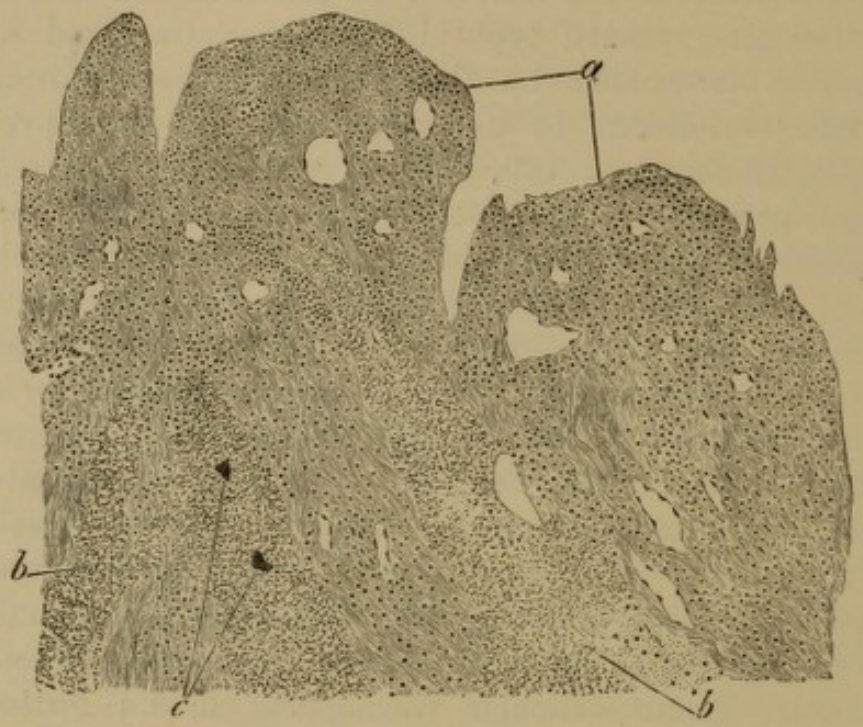

FIG. 184.—SUPPURATIVE POLYARTHRITIS (KNEE-JOINT). × 95. (Alum cochineal.) *a*, Synovial villi, swollen and infiltrated with cells; *b*, Necrotic parts in the synovial membrane; *c*, Aggregations of cocci.

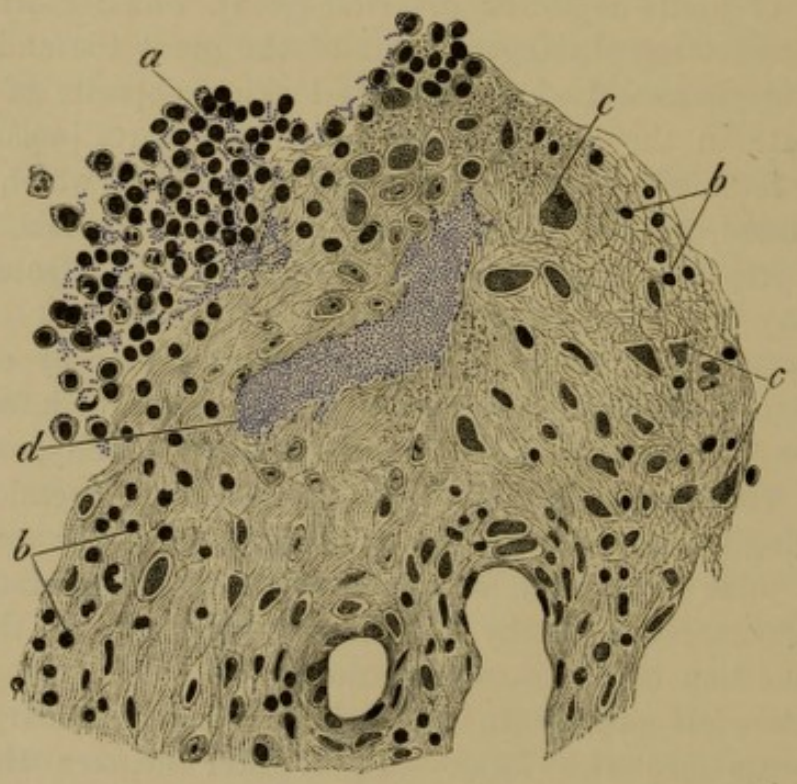

FIG. 185.—SWOLLEN SYNOVIAL VILLUS OF THE KNEE-JOINT IN SUPPURATIVE POLYARTHRITIS. × 545, the cocci drawn in under a power of × 975. (Weigert's modification of Gram's method.) *a*, Mononuclear and polynuclear leucocytes on the surface of the villus, with streptococci in and between them; *b*, Round cells in the villus; *c*, Swollen or newly-formed connective-tissue cells of the villus; *d*, Blood-vessel filled with streptococci, in the neighbourhood of which the cells have stained badly, indicating commencing necrosis.

thetically involved. It is then found not only that the epithelium of the synovial membrane is cast off, the surface of the latter and its villi covered, and their tissue infiltrated, with mononuclear and polynuclear leucocytes (Fig. 185, *a* and *b*), whilst the tissue is even necrotic in places (Fig. 184, *b*, and Fig. 185, *d*), but that the cellular and purulent infiltration extends into the fibrous capsule of the joint, or even into the periarticular connective tissue.

In the articular cartilage the active processes fall more into the background. Growth of the cartilage-cells and penetration of pus-corpuscles into the cavities of the cartilage may indeed take place, but in most cases it is by degeneration or necrosis that the cartilage is destroyed, its interstitial substance undergoing a finely-granular clouding, or becoming fibrillated, as a preliminary to complete solution. The cartilage may also die *en masse* over considerable areas, whereupon its cells lose the power of staining; or it may be pressed upon and absorbed by the synovial membrane growing into it from the margin. After the destruction of the cartilage the inflammation may also extend to the bone. Should *recovery* take place at this stage, regeneration of the destroyed articular cartilage does not follow, but the articular ends of the bones become coated with granulation tissue, which develops from the synovial membrane and the tissue of the medullary spaces in the bone, and acquires connections by means of processes with the like tissue covering the opposed articular surface. Subsequently it passes through the process of transformation into connective tissue, with the result that a fibrous adhesion is formed between the two articular surfaces (*fibrous ankylosis*). If, however, ossification of this connective tissue sets in, an *osseous ankylosis* is the result.

Of the *chronic inflammations of bone* most prominence must be given to that caused by *inhalation of the vapour of phosphorus*, and to the *tubercular* and *syphilitic* varieties. The first attacks the jaw-bones as a rule, leading partly to new formation of bone from the periosteum and marrow, and partly to suppuration, by which a more or less extensive necrosis of the bone, even of that newly formed, is caused. Regarding *tubercular* and *syphilitic osteitis*, see p. 372 *et seq.*

Amongst the *chronic inflammations of the joints* we reckon first of all *arthritis deformans* (*chronic rheumatoid arthritis*). Its occurrence is conditioned above all by advanced age, but we also find it as a so-called trophic neurosis in diseases of the spinal cord accompanied by paralysis, especially in tabes; as the result of certain influences, traumatic and possibly rheumatic, which cannot be more accurately defined; and, lastly, also after too prolonged rest of a joint.

Two forms of arthritis, a *monarticular* and a *polyarticular*, may

be distinguished. The former affects chiefly the large joints, one only, or at least but few, being involved, and most frequently the knee or hip. The second form, however, affects many joints, and first those of the fingers and toes, especially in women; but it may then extend to other joints also (*arthritis nodosa*). Both forms are in general distinguished by the fact that in them those retrograde and hyperplastic changes, which have already been described (pp. 356 and 362) as appertaining to advanced life *per se*, attain an especially high degree of development.

In the *polyarticular* form (Fig. 186), however, it is the proliferative

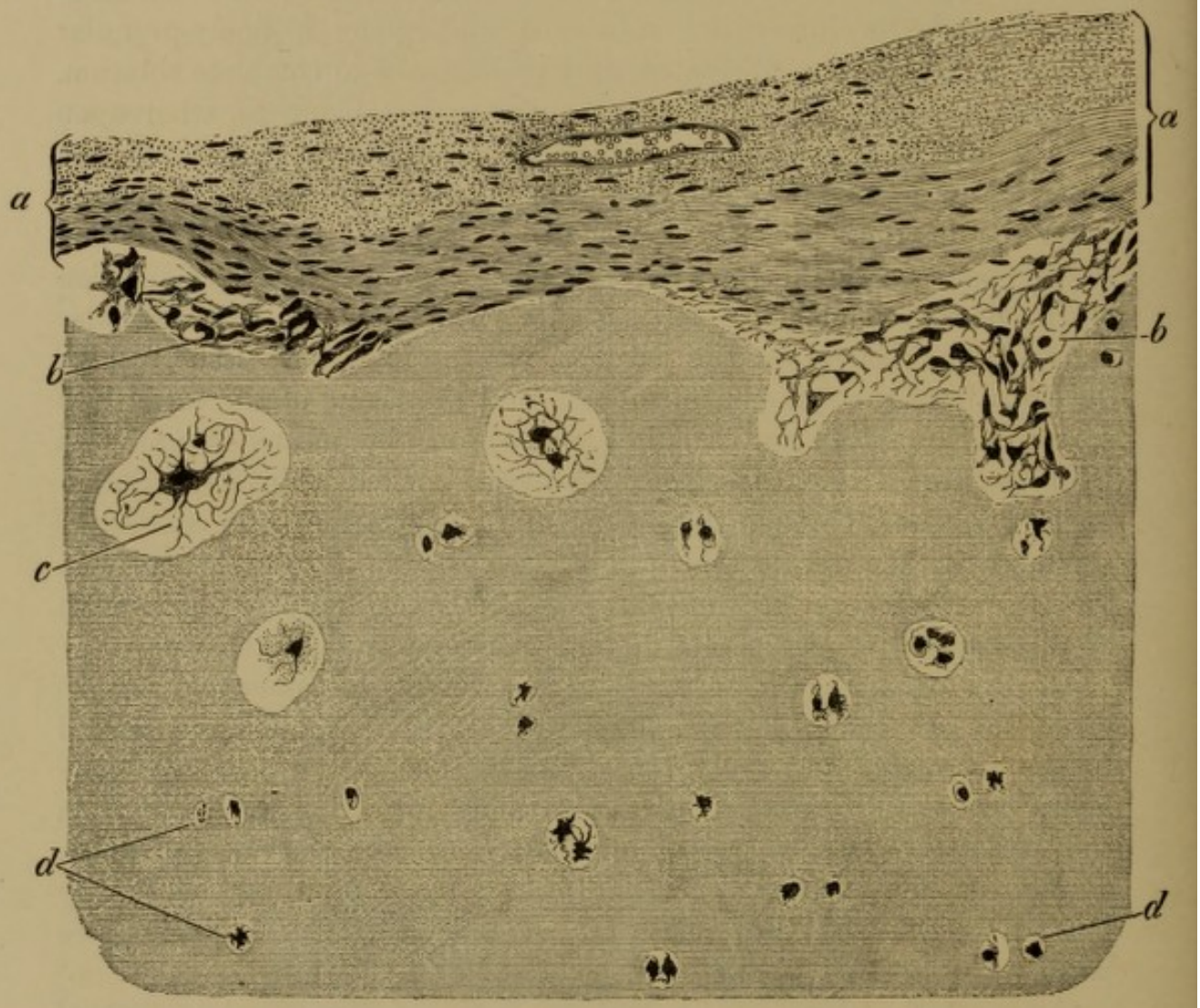

FIG. 186.—ARTHRITIS DEFORMANS, POLYARTICULAR FORM. × 285. (Hæmatoxylin and eosin.) *a*, Growing synovial membrane overspreading the surface of the articular cartilage; *b*, Pitted depressions on the surface of the cartilage; *c*, Enlarged cartilage cavities, both occupied by cells having numerous processes; *d*, Normal cartilage cavities.

processes in the synovial membrane that are especially prominent. Not only does the tissue of this membrane become richer in cells and blood-vessels, and permeated with extravasations of blood and masses of pigment, but the membrane overgrows the edges of the

joints, and thus covers more and more of the surface of the articular cartilage in the form of a pannus-like layer (*a*), leading to the gradual destruction of the latter (*arthritis pannosa*). The disappearance of the cartilage in this process is effected by the penetration in the first place of the growing synovial membrane into the cartilage cavities, converting the latter into pitted depressions (*b*), which progressively enlarge and finally coalesce. In the dilated cavities of the cartilage, instead of the normal cartilage cells large cells (*c*) are seen having an extraordinary number of processes, and regarding which it is only doubtful whether they are altered cartilage cells, or whether we have to do with cells of the synovial membrane that, having first penetrated into the cavities of the cartilage, are now enlarging them in all directions (chondroclasts?). In addition to this peculiar growth of the synovial membrane, there may certainly also exist fibrillation of the cartilage and formation of warty cartilaginous and bony excrescences at the margins of the articular surfaces, but these changes as a rule are only subordinate in degree.

A further peculiarity of the polyarticular form is that the synovial membrane not only covers the surface of the cartilage, but also sends highly-vascular processes to the articular cartilage opposite, in consequence of which the surfaces of the joint become partially or completely adherent to one another (fibrous ankylosis). The affected joint thus becomes fixed in a definite faulty position (flexion or hyperextension), and more or less immovable. Finally, the fibrous coating of the articular surfaces may ossify, and the fibrous then develops into an osseous ankylosis.

In the *monarticular* form of arthritis deformans, the retrograde and hyperplastic changes in the articular ends of bones and the capsules of joints are combined in the most manifold fashions. In the first place, the fibrillation of the cartilage and synovial membrane here becomes prominent, attaining a very advanced degree, and being accompanied in the cartilage by a considerable growth of the cells, and by their transformation at the same time into large parent-cells. The fibrillated portions of cartilage are next rubbed off in the movements of the joint, so that deficiencies are left which are either filled up again by processes of the synovial membrane, or become deeper and deeper, and finally lay bare the bone. The latter may then sclerose, owing to processes of ossification in its medullary spaces (*eburnation*), whilst its denuded surface is as it were polished by the movements of the joint, and may even have grooves ground on it. In other parts of the articular ends of bones, again, a very extensive lacunar liquefaction may take place, in consequence of which there may result an extensive destruction of the

bone, diminution and flattening of the articular ends, and so forth. The marrow itself either becomes gelatinous (p. 356), when it may even liquefy and give rise to formation of cysts, or it is converted into lymphoid marrow (p. 362).

In the synovial membrane the principal morbid change is the at times very excessive enlargement and multiplication which the villi undergo, owing to new formation of connective tissue and blood-vessels and partly also of adipose tissue, so that, as has already been mentioned (p. 362), structures may be formed resembling pedunculated fibromata or lipomata. A partial change of the cells of the synovial fringes into cartilage cells, and the consequent appearance of nodules of cartilage in the enlarged villi, are also very common. These nodules may go on to ossify, and may become loose bodies in the joint, the villi being torn away. Formation of plates of cartilage may also occur in the other parts of the synovial membrane, and these may eventually ossify likewise. In the same way there forms at the margins of the articular cartilage a great multiplicity of partly-ossifying ecchondroses, which, in conjunction with the partial destruction of the bone, cause very strange deformities of the articular ends, whilst on the other hand abnormal mobility and subluxations result from the changes in the capsule of the joint.

Another form of chronic inflammation in joints is *hydrarthrosis or chronic serous arthritis*, which is distinguished above all by the presence of a large quantity of thin synovial fluid. Later, a slight fibrous thickening of the synovial membrane, with enlargement of its villi, may also take place, as well as fibrillation of the cartilage and growth of the synovial membrane over its edges. This process most frequently affects the knee-joint. It either forms the termination of an *acute* serous arthritis, or runs an insidious course from the beginning.

4. Rachitis or Rickets.—This disease (Figs. 187 and 188) probably depends upon an insufficient supply of lime-salts to the bone, and is marked on the one hand by an extensive absorption of osseous tissue, on the other by formation of a bone devoid of lime (*osteoid tissue*). Here also the bony absorption is lacunar, and is caused by osteoclasts which may disseminate themselves over the entire skeleton. As the result of it the bones sometimes become so porous that certain of them, for example the flat bones of the skull, come to consist merely of a few bony trabeculæ.

The development of the osteoid or limeless tissue takes place not only from the periosteum but from the marrow, both of which, during the disease, are composed of a very vascular fibrillated con-

FIG. 187.—RACHITIS OF RIB. × 77. (Hæmatoxylin and eosin.) *a*, Normal hyaline cartilage; *b*, Medullary spaces in the cartilage, containing vessels; *c*, Growing hyaline cartilage (shortened in the drawing); *d*, Calcified cartilage; *e*, Large highly-vascular medullary spaces; *f*, Trabeculæ of osteoid tissue; *g*, Vestiges of calcified cartilage in the osteoid tissue; *h*, Deposits of lime in the centre of the trabeculæ of osteoid tissue.

nective tissue with stellate and spindle cells (Figs. 187, *e*, and 188, *c*), the osteoid tissue forming directly from these cells (Fig. 188, *g*), or by the intermediation of osteoblasts (Fig. 188, *f*). The trabeculæ of the osteoid tissue (Fig. 188, *e*), which possess a finely fibrillated interstitial substance staining intensely in carmine, and large plump bone-cells, are partly deposited on vestiges of the old bone still remaining *in situ*, and partly cover its surface as a soft spongy mass.

In the portions of the skeleton represented by *cartilage* still other changes are seen. Even with the naked eye the enlargement of the cartilage and its translucent character can be made out at the limit of ossification, and, on the other hand, the absence of a zone of calcification which otherwise manifests itself as a white line. Corresponding to this there may be recognised microscopically, in the first place, a considerable enlargement of the growing zone of the cartilage, this zone containing long rows of cartilage cells of 30-40 elements, and a scanty interstitial substance (Fig. 187, *c*), but nowhere in this area, or at least in but a few places (*d*), is calcification perceptible. On the other hand, the cartilage is found to be permeated partly with medullary spaces pushed far in advance in an irregular manner, partly with numerous blood-vessels derived from the perichondrium. The cells in the cartilage cavities thus opened up change into marrow-cells, whilst the rest of the cartilage partly remains unaltered, partly is developed into osteoid tissue (Fig. 188, *b*). To the cartilage there then succeeds an abnormally broad layer of osteoid tissue (Fig. 187, *f*), and only lastly the proper osseous zone. The osteoid tissue is altogether atypical in the arrangement and form of its trabeculæ, between which, in addition to isolated vestiges of cartilage (Fig. 188, *a*), lie large irregular medullary spaces with a very vascular tissue composed chiefly of fibrillated interstitial substance and large stellate or spindle-shaped cells (Figs. 187, *e*, and 188, *c*). The osteoid trabeculæ arise partly from these cells (Fig. 188, *g*) and partly from osteoblasts (Fig. 188, *f*).

In the adjoining osseous zone, osteoid trabeculæ are also still seen at first, but they already contain new bone in their axis as the result of deposit of lime (Fig. 187, *h*). Only after these follow the trabeculæ consisting entirely of bone. When the diseased bone returns to the normal condition, the deposition of lime always takes place first in the centre of the osteoid trabeculæ.

5. Infective Granulomata, New-formations, and Parasites.—*Tuberculosis* affects by preference the short bones and the epiphyses of the long. It begins either in the marrow or the periosteum, whither the tubercle bacilli make their way in most cases probably by the

blood-stream, less often along the lymphatic channels, its first manifestation being the occurrence of little nodules which show the well-known structure. This is followed by inflammatory growth of the marrow or of the periosteum, resulting in formation of granulation tissue, the so-called *fungous granulations,* whilst at the same time leading to lacunar liquefaction of the bone. By the continual cropping up, coalescence and caseation of fresh tubercles, larger

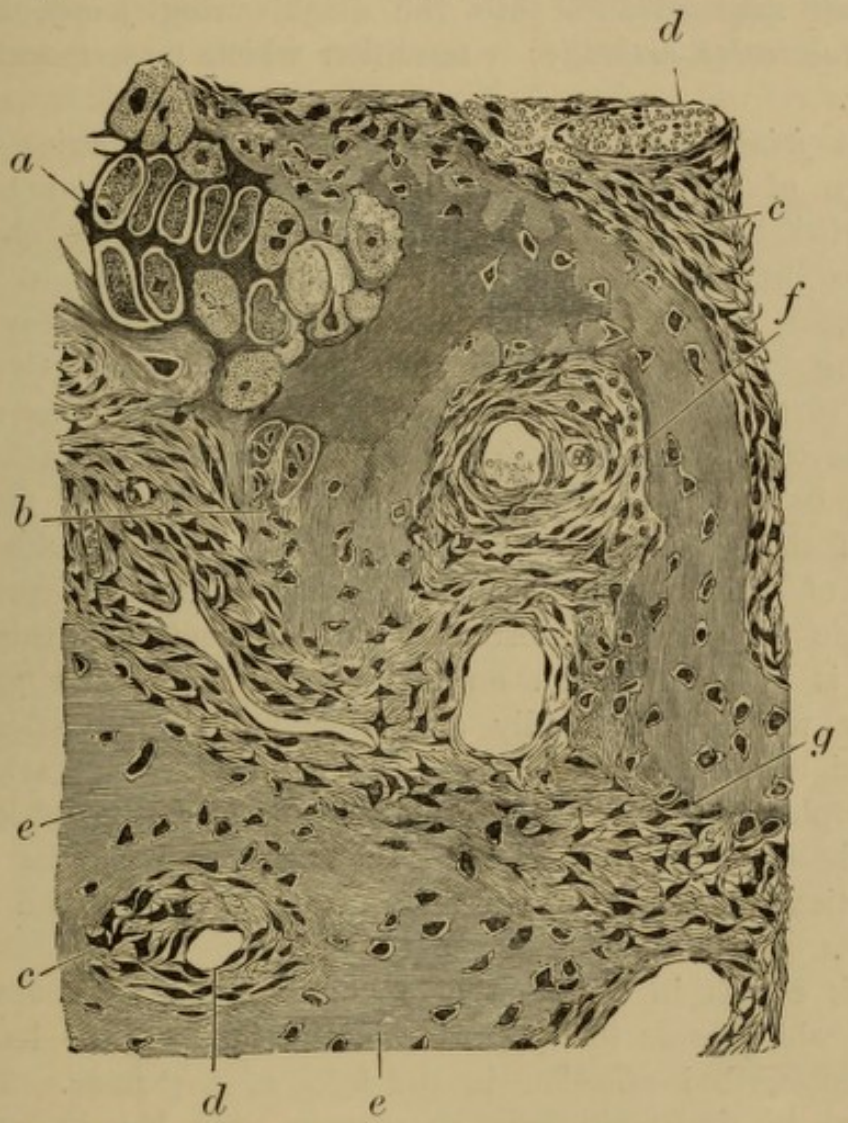

FIG. 188.—ZONE OF OSSIFICATION IN RICKETS (COSTAL CARTILAGE). × 390. (Hæmatoxylin and eosin). *a*, Growing cartilage, partly calcified; *b*, Transition of cartilage into osteoid tissue; *c*, Medullary spaces; *d*, Dilated blood-vessels; *e*, Osteoid tissue; *f*, Osteoblasts; *g*, Direct transformation of the cells of the medullary spaces into cells of osteoid tissue.

caseous patches are formed, which enclose necrotic trabeculæ of bone and later, by softening, give rise to cavities filled with caseous pus and separated fragments of bone.

The inflammatory growth in the neighbourhood of the tubercles sometimes spreads to greater distances, and there also leads, on the one hand to liquefaction of the osseous tissue in the interior, on the other to osseous new-formation upon the surface of the bone

in the shape of osteophytes. Should osseous new-formation take place also in the medullary spaces of the bone, an *osteosclerosis* is the result. When the tubercular process set up in the interior of the bone reaches the surface of the latter, it may next give rise to formation of gravitation abscesses or may break its way outwards or into adjoining organs, leaving fistulous tracts lined with a granulation tissue which secretes caseous pus. On the other hand, the process may advance into the neighbouring joints, and there cause a *tubercular arthritis;* a condition which may, moreover, arise *primarily.*

In the *joints* the tubercular process likewise begins with the appearance of miliary tubercles in the synovial membrane. This is succeeded by a chronic inflammation which partly changes the membrane into granulation tissue, partly gives rise to a serous, sero-fibrinous, or purulent exudation in the articular cavity. The granulating synovial membrane then grows over the edges of the articular cartilage and pushes into its interior as the membrane does in arthritis deformans (pp. 368-9); whilst at the same time, owing to extension of the process to the subchondral marrow, ingrowth of the latter may take place from below into the cartilage, the cells of which meanwhile are likewise engaged in proliferation and mingle with those penetrating from without. In this way the cartilage is broken through on all sides by tubercular granulation tissue, by which it is finally altogether replaced. The soft parts in the neighbourhood of the joint also are involved at a later stage in a hyperplastic growth which usually yields an indurated lardaceous-looking tissue (*tumor albus*), whilst at the same time the exudation in the articular cavity may effect a rupture outwards with formation of sinuses.

Syphilis causes in bone either a more evenly-distributed morbid condition which leads to hyperostosis (especially in the long bones), or a circumscribed affection in the form of a gumma. The latter is situated in the periosteum or marrow, and has in general the same structure as in other localities, except that at the outset it is poorer in cells but richer in fluid, whence also its gelatinous character. Subsequently, when it has become larger, patches of caseation occur in it in the same way as in other syphilomata (Fig. 64), whilst the remainder of the granulation tissue is gradually changed into cicatricial tissue. The syphiloma further causes an absorption of the bone at the spot where it is situated, in consequence of which more or less considerable defects occur, especially over the cranium. Considerable portions of the bone may also become necrotic. On the other hand a very abundant new formation of bone in the

form of osteophytes often takes place in the neighbourhood of the syphilitic focus.

The changes which are frequently found in the epiphysial cartilages of new-born infants in *congenital syphilis* (*osteo-chondritis syphilitica*) consist chiefly of irregularities in the deposition of lime and in the formation of the medullary spaces in the cartilage, together with thickening of the growing zone of cartilage cells and of the transitional zone between the latter and the complete bone. Sometimes there may even be a separation of the epiphysial cartilage.

The majority of the *primary new-formations* in bone belong, as

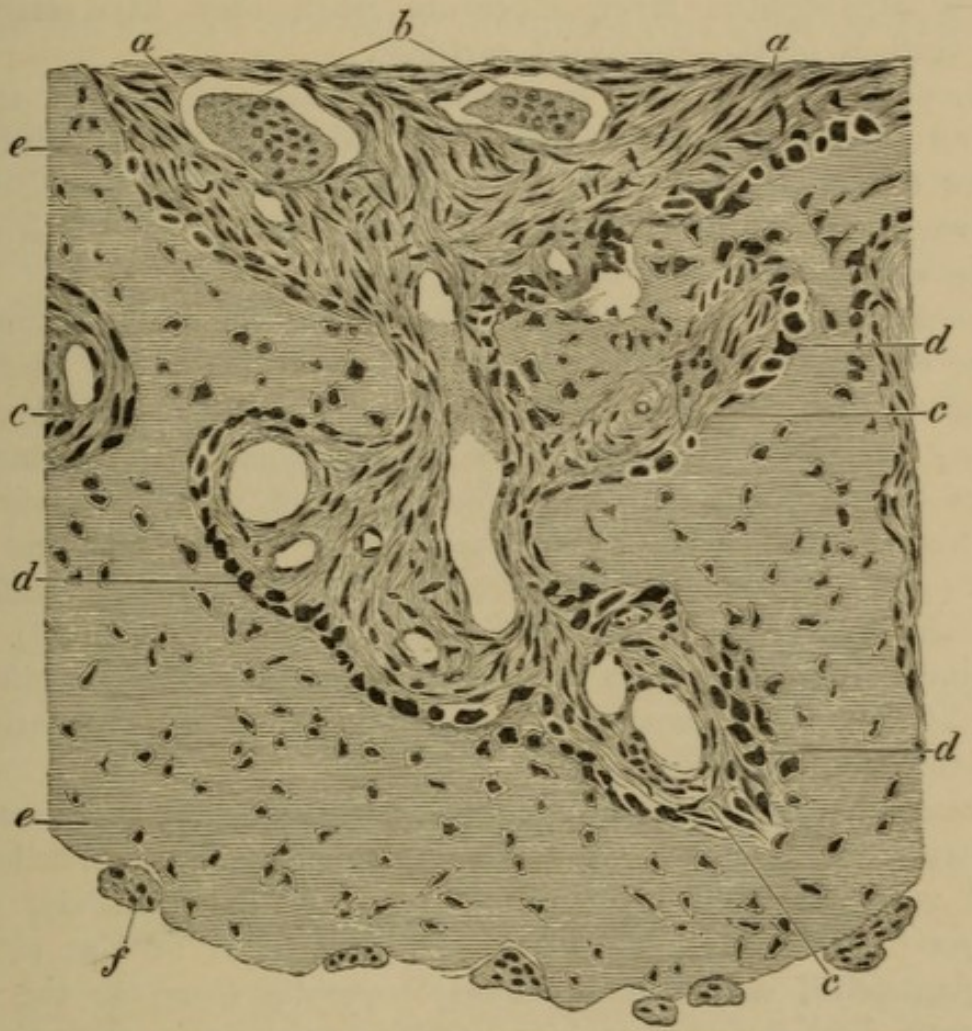

FIG. 189.—OSTEO-FIBRO-SARCOMA (GIANT-CELLED SARCOMA) OF THE LOWER JAW, WITH NEW FORMATION AND ATROPHY OF BONE. × 285. (Alum cochineal.) *a*, Sarcomatous tissue; *b*, Giant cells of the sarcoma; *c*, Medullary spaces in the bone of the lower jaw; *d*, Osteoblasts; *e*, Osseous tissue; *f*, Howship's lacunæ, with osteoclasts.

regards their structure, to the connective-tissue series; that is to say, are *osteomata, chondromata, fibromata,* or *sarcomata.* Their starting-point is either the periosteum (very frequently its inner osteoplastic layer) or the medullary tissue.

In their growth the adjoining bone is usually destroyed to a variable extent by lacunar absorption (Figs. 176, *b*, and 189, *f*),

whilst, on the other hand, new bone may be formed from the periosteum or medulla (*c*) in the neighbourhood of the new growth by means of osteoblasts (*d*). Besides this, osseous tissue may develop in the tumours themselves, especially in those of the periosteum, either after the type of regenerative new-formation of bone (p. 358 *et seq.*, Fig. 26, *a*, *b*, and *c*), or still oftener by direct transformation of the connective tissue or cartilage into bone.

Osteomata occur most frequently in the periosteum (*exostoses*), less often in the medulla (*endostoses*), and may be composed either of compact or of spongy bone. Besides this they may also be covered with a cartilaginous layer, especially when they have originated from vestiges of the epiphysial cartilage.

Fibromata usually start from the periosteum, especially that of the vertebræ and cranial bones. Should they project into the cavities of the nose or pharynx, they are also called *polypi*, whilst it is customary to give the name *epulis* to the fibroma which occurs on the alveolar processes of the maxillæ.

The favourite site for *chondromata* is on the phalanges of the fingers, especially in children, and the tumours are then frequently multiple. They perhaps have their origin in relics of the rudimentary cartilaginous ground-work of the bone. Development of osseous tissue frequently takes place in them, or the tumour may even from the outset consist of a mixture of cartilaginous and bony tissue (*osteo-chondroma*), in which case the latter occupies chiefly the inner, the former the outer portions of the tumour (Fig. 26). But retrograde changes are also frequently observed, such as calcification (Fig. 26, *d*), and mucous softening leading even to solution of the tissue and formation of cysts.

Sarcomata start either from periosteum or medullary tissue. In the former case they are of the spindle-celled, round-celled, or mixed varieties, whilst in the latter—when they are also called *myelogenic sarcomata*—they are either giant-celled or else alveolar. The giant-celled sarcomata are most frequently found on the upper and lower jaws (being here also named *epulis*), or in the epiphyses of the large long bones. When they have attained some size, they usually possess a bony shell and sometimes also trabeculæ of bone in their interior, and are frequently so vascular that hæmorrhages and pigmentation may readily take place, or even destruction of the tissue with subsequent formation of cysts. The alveolar sarcoma is most frequently observed in the bones of the skull and of the trunk.

We have still to mention that sub-variety of sarcoma of bone which is usually known as *myeloma*. This occurs in the form of

multiple tumours, not sharply defined and but slightly prominent, which are situated in the cranial bones and vertebræ, or in all parts of the skeleton, especially in old people, and contain only small round cells. It is very doubtful, however, whether the myeloma is still to be regarded as a neoplasm, and not perhaps as a diseased condition of the bone-marrow appertaining to leucæmia or pseudo-leucæmia.

Of *animal parasites*, *Cysticercus cellulosæ* and *Echinococcus* have been observed in the bones.

II. THE MUSCULAR SYSTEM (INCLUDING SHEATHS OF TENDONS AND BURSÆ).

6. Atrophy and Hypertrophy of Muscle.—*Atrophy* of the muscles may occur from the most widely different causes; as in consequence of disuse (*atrophy of inactivity*), of diseased conditions of the nervous system (*neuropathic atrophy*), of various local and general disorders of nutrition and circulation, and lastly as a primary disease (*e.g.*, *juvenile muscular atrophy*). Of the *neuropathic atrophy* again special

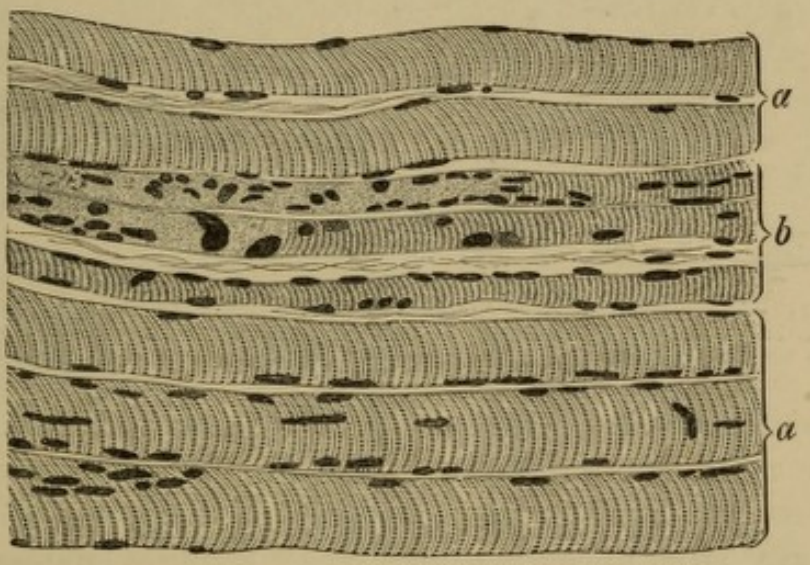

FIG. 190.—COMMENCING SIMPLE ATROPHY OF THE SUPINATOR LONGUS MUSCLE. × 545. (Hæmatoxylin and eosin.) *a*, Primitive bundles of normal thickness, with commencing proliferation of the nuclei in places; *b*, Three atrophic primitive bundles, showing partly multiplication and partly enlargement of the muscle-nuclei.

prominence must be given to the *spinal* form, the atrophy due to progressive degeneration of the ganglion cells in the anterior horns of the spinal cord (p. 332), and known as *progressive muscular atrophy, amyotrophia spinalis progressiva;* the *bulbar* form (in *progressive bulbar paralysis*); and, lastly, that caused by *multiple* nervous diseases.

Microscopically the atrophy may also manifest itself in different forms. Thus it may be either a *simple* atrophy, *i.e.*, may consist in

a mere gradual reduction in thickness of the primitive muscular bundles (Fig. 190, *b*); or a *pigmentary* atrophy, when yellow and brown pigment-granules (Fig. 192, *c*) are deposited in the atrophying muscular fibres (sometimes also in the endomysium); or it may take the form of a *parenchymatous* or *fatty degeneration*, when numerous fine albuminous granules or fat-droplets (Fig. 94) respectively appear in the primitive bundles. Lastly, there are also distinguished a *vacuolar degeneration* in which appearances resembling vacuoles become visible in the muscular fibres, and a *waxy degeneration*. The latter (Fig. 191) is met with most frequently in typhoid fever, affecting the diaphragm, the abdominal recti, and the adductors of the thigh; but it also occurs after injuries and inflammations, and

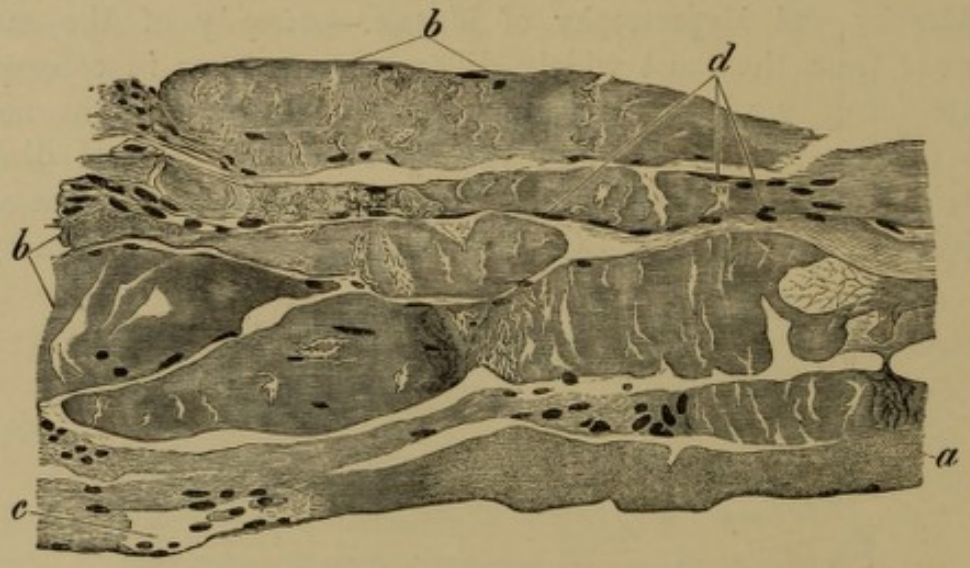

Fig. 191.—Waxy Degeneration of the Rectus Abdominis Muscle in Typhoid Fever. × 285. (Alum cochineal.) *a*, Fairly normal primitive muscle bundle; *b*, Degenerated primitive bundles; *c*, Piece of empty sarcolemma tube; *d*, Nuclei of the sarcolemma.

in progressive muscular atrophy. It is characterised by the coagulation of the contractile substance of the primitive bundles to a brittle hyaline mass, which afterwards (probably as the result of contraction of the fibres still remaining unaltered) acquires numerous transverse fissures (*b*), then breaks up into irregular masses, and finally crumbles away altogether.

The perimysium often appears to contain more cells than normal in this degeneration, whereas in all other forms of atrophy it may be either unaltered, in a state of cellular infiltration, or transformed into adipose tissue (Fig. 192, *g*). The fatty metamorphosis in some cases sets in even *before* the atrophy of the muscle-fibres, the latter being afterwards destroyed merely by the pressure of the growing adipose tissue, a phenomenon which is observed especially in the muscles of the thigh and leg in certain forms of juvenile muscular atrophy, and in which the muscles apparently increase in volume—

hence the designation of *pseudo-hypertrophic paralysis*, or, more correctly, *pseudo-hypertrophic lipomatous atrophy of muscle.*

As regards the *muscle corpuscles*, in the forms of atrophy just described they are either at once destroyed, or, on the contrary, take on active growth, giving rise to mononuclear or polynuclear cells lying in rows or in large aggregations, and which sometimes have nuclei of remarkable size (Figs. 190, *b*, and 192, *d* and *e*). The

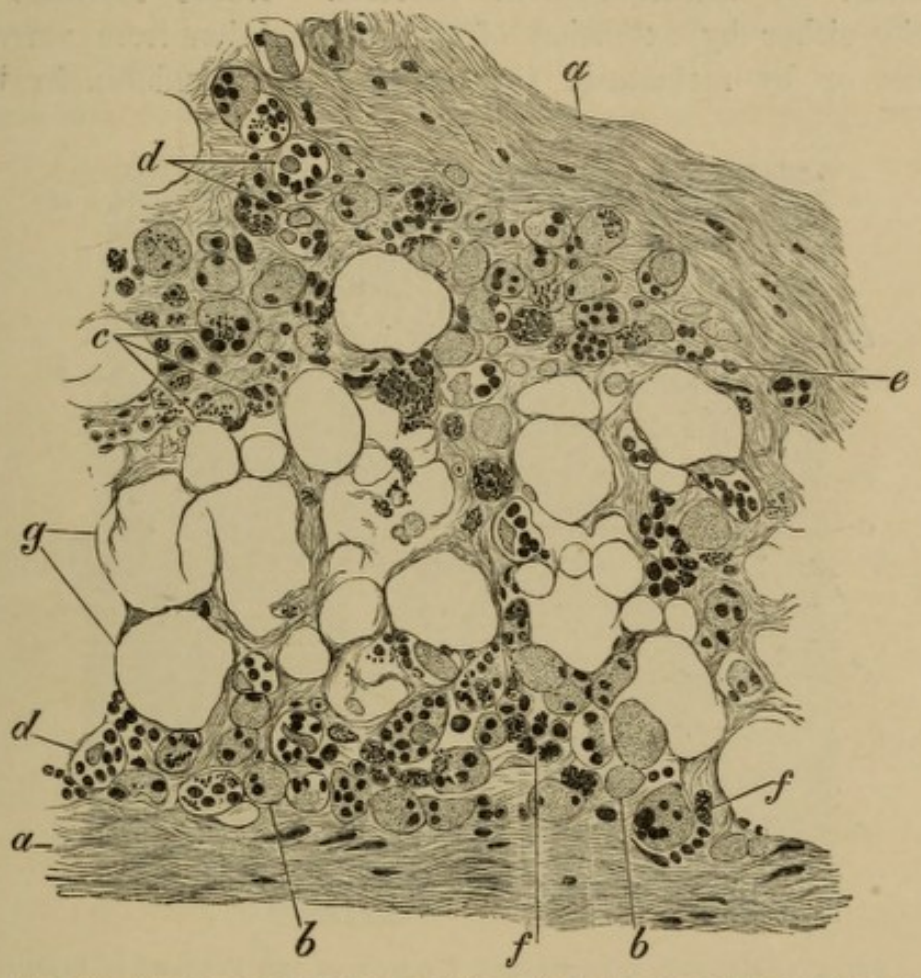

FIG. 192.—PIGMENTARY ATROPHY AND FATTY GROWTH OF THE SOLEUS MUSCLE IN CHRONIC ANTERIOR POLIOMYELITIS. Part of transverse section through a muscle bundle. × 285. (Hæmatoxylin and eosin.) *a*, Interstitial connective tissue; *b*, Atrophic primitive muscle bundles; *c*, Atrophic primitive bundles, with accumulation of pigment, and partly also showing growth of the nuclei of the sarcolemma; *d*, Tubes of sarcolemma, with proliferated nuclei and atrophied remnants of the contractile substance; *e*, Sarcolemma tube, now filled only with proliferated nuclei; *f*, Collapsed sarcolemma tubes containing nothing but pigment; *g*, Fat cells.

latter process appears to be of a regenerative nature, since it also develops after injuries and necroses of the muscles. Thus long spindle cells may then develop from the proliferated muscle-corpuscles, from which spindle cells new muscle-fibres are formed, the nuclei continuing to multiply, and transverse striation appearing.

Hypertrophy of muscle consists in thickening and elongation, and perhaps also multiplication, of the primitive bundles, and affects those muscles which have a greater amount of work to perform. In the

disease known as *Thomsen's disease—congenital myotonia*—there also occurs a hypertrophy of the muscular fibres together with multiplication of their nuclei, while the striation becomes indistinct.

7. Inflammation, Infective Granulomata, New-formations, and Parasites of Muscle.—*Inflammation of muscle, myositis*, may be acute or chronic, primary or secondary. *Acute primary myositis* can scarcely occur except as the result of injuries, especially when these are accompanied by infection with bacteria. Acute myositis occurs *secondarily* either by extension of an inflammation from surrounding structures, or by metastasis (in pyæmia and glanders), in both of

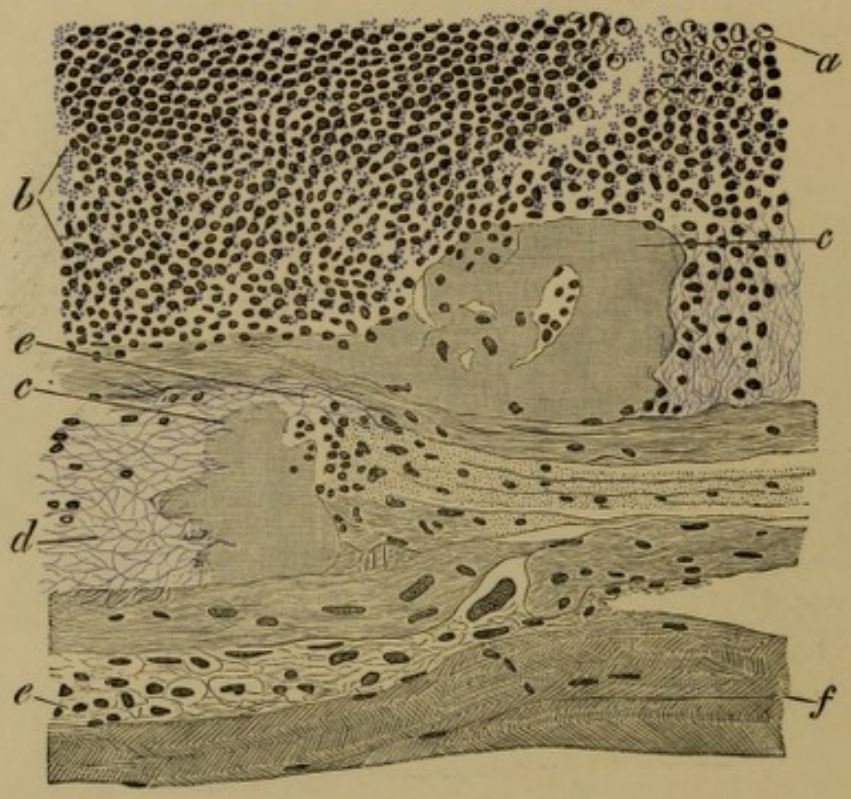

FIG. 193.—METASTATIC SUPPURATIVE MYOSITIS OF THE FOREARM IN PYÆMIA. × 545, the cocci drawn in under a power of × 925. (Weigert's modification of Gram's method.) *a* and *b*, Pus corpuscles, in and between which lie staphylococci; *c*, Necrotic primitive muscular bundles; *d*, Network of fibrin; *e*, Interstitial connective tissue, with small-celled infiltration; *f*, Normal primitive muscular bundles.

which cases the character of the myositis will be determined by that of the primary process. The inflammation runs its course chiefly in the intramuscular connective tissue (Fig. 193), where it may set up the same changes as in other parts of the connective-tissue system. The actual muscle-fibres behave more passively, either remaining entirely unaltered or undergoing cloudy swelling, fatty or waxy degeneration, or even necrosis (*c*). Should suppuration take place (*a* and *b*), the defect which is thereby formed in the muscle is in healing usually filled up merely with granulation tissue, which subsequently changes into cicatricial tissue. In

isolated cases, however, a restoration of the destroyed muscle-fibres by regeneration does seem to take place, at least partially.

A special form of chronic muscular inflammation is *myositis ossificans*, which results in new formation of bone in the muscles and tendons after the model of periosteal bone-development (pp. 358-9). It may occur spontaneously, or as the result of injuries, in isolated muscles (the deltoid, biceps of the arm or adductors of the thigh, the condition being then spoken of respectively as *drill-bone* or *rider's-bone*), or it may affect most or even all of the muscles of the body in succession.

Tuberculosis occurring primarily in muscle is certainly very rare.

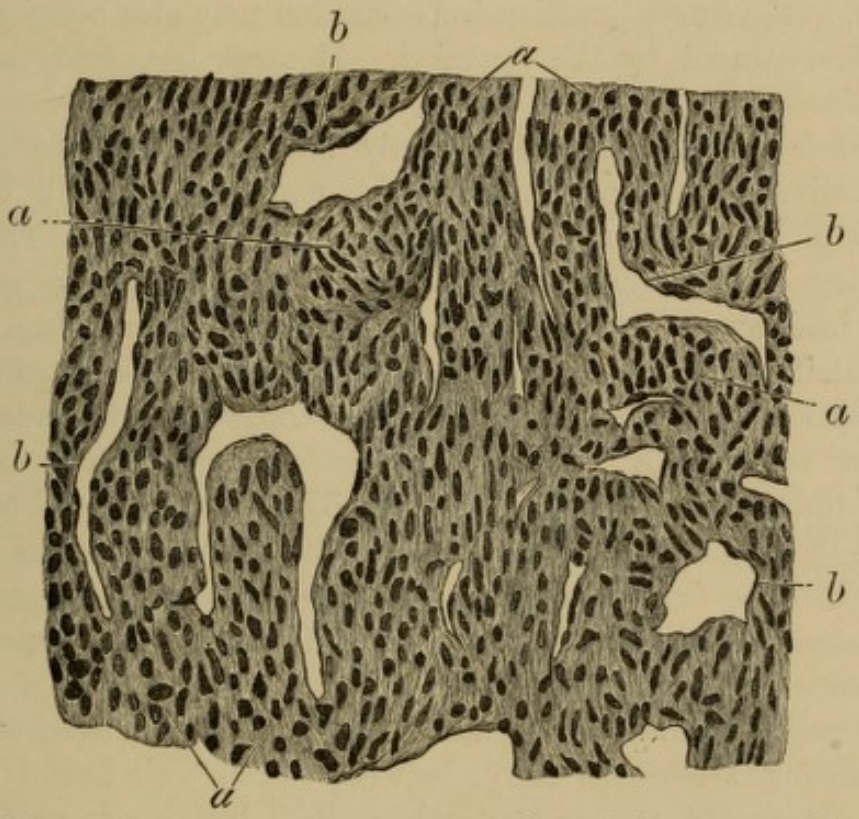

FIG. 194.—SPINDLE-CELLED SARCOMA OF THE MUSCULAR TISSUE OF THE THIGH. × 285. (Alum cochineal.) *a*, Bundles of spindle cells, in longitudinal and transverse section, usurping the place of the primitive muscle bundles; *b*, Blood-vessels.

Most frequently it spreads to the muscular tissue from the surrounding parts, in which case it takes the form of caseous nodes, abscesses, fistulæ, and so forth.

Syphilis may exist in the muscles in the form either of gummata or of a more diffuse affection. In the latter case the endomysium in the neighbourhood of the blood-vessels is found infiltrated with small cells, and the muscle corpuscles are also seen to be undergoing proliferation. These changes either subside again or lead eventually to cicatricial thickening of the intramuscular connective tissue and to atrophy of the muscular fibres.

Of *primary new-formations* the *sarcomata* occur most frequently.

Many of them so far copy the coarser structure of the muscle that their cells (spindle cells) are arranged in bundles in a manner analogous to the primitive bundles of muscle (Fig. 194).

Of *animal parasites, Trichina spiralis, Cysticercus cellulosæ,* and *Echinococcus* must be mentioned.

8. Diseases in the Sheaths of Tendons and in Bursæ.—*Inflammations* of these structures show many points of analogy with those affecting the joints. Here also in *acute* inflammation the exudation may be either serous, fibrinous, or purulent, and in the latter case, when affecting the *tendon-sheaths,* has usually extended from the neighbouring parts, and may lead to necrosis of the tendons. In the *bursæ,* however, suppurative inflammation may also occur *primarily,* and is then caused by the pyococci. It most frequently affects the patellar bursa.

In *chronic* inflammation we usually have accumulation of a fluid which is slimy at the outset, but later more watery, and distension, due to it, of the affected cavities (*hydrops* or *hygroma*). The chronic inflammation is not uncommonly the termination of an acute one, and may lead eventually to considerable fibrous thickening and even partial calcification of the wall, as well as to villous growths and new formation of plates of cartilage in the walls of tendon-sheaths and bursæ respectively. In the free ends of the villous outgrowths it is not uncommon to find structures like grains of rice (*corpuscula oryzoidea*—melon-seed bodies), which subsequently become torn off and may then be found free in the fluid, sometimes in large numbers. Loose bodies may also form as in joints, by the separation of cartilaginous plates from the wall.

The so-called *melon-seed bodies* are composed of homogeneous masses in part arranged concentrically, between which cell-nuclei may also be seen. It would appear that when these bodies are present there is not uncommonly a chronic (primary) *tuberculosis* of the affected bursa (which is most frequently the large bursa of the carpus) leading to the formation of villous outgrowths, and to a peculiar "fibrinoid" degeneration in many of the latter. The melon-seed bodies then form by the separation of such degenerated pieces, and in these cases may also contain tubercle bacilli.

The so-called *ganglion* is a cyst with colloid or mucous contents occurring in the tendon-sheaths of the hand, and which has arisen by the nipping off of a diverticulum from the affected sheath.

Methods.—In diseased conditions of *cartilage,* and partly also of *bone,* an examination may under certain circumstances be made even in the *fresh* condition. Thus it is possible to prepare tolerably fine sections of cartilage with a razor, and these can be examined either unstained in salt solution or after

staining. Anilin colours or Lugol's solution may be used for hasty staining, and the stained sections, having been washed in water (with anilin colours in acidulated water if need be), are examined in glycerin or potassium acetate. The reactions for *amyloid degeneration* and *calcification* (pp. 57-8, and p. 62) may likewise be tried with sections of fresh objects. Unstained and stained preparations of *bone-marrow* may also be made by needling and pressure; likewise cover-glass preparations, which latter may be stained in the same manner as preparations of blood (pp. 189-191). Furthermore, in the processes accompanied by liquefaction of bony tissue, very small splinters of bone may be picked with a forceps from the diseased part of the fresh preparation, and these may be examined either unstained or stained, at least under a medium power.

Lastly, the *muscles* can also be perfectly well examined in the fresh state (in torn-up preparations). For the methods of examining *cloudy swelling*, *fatty degeneration*, and *atrophy* of the muscles, see pp. 52-3 and 62; and for the demonstration of *Trichina spiralis*, p. 181. In all other cases *hardening* should be carried out, and with bones and calcified tissues, *decalcification*. The former is done in alcohol if bacteria are to be sought for, but otherwise in Müller's fluid and alcohol. If, however, it is wished to retain the lime-salts in calcified tissues, hardening must be done in alcohol only. *Decalcification* is never carried out until the objects have been previously fixed in alcohol, or still better, in Müller's solution. One of the decalcifying fluids given on page 9 is used.

For *staining* the sections the methods of contrast staining given on pp. 20 and 21 are the most useful if bacteria have not to be sought for. In order to differentiate the various stages in the development of cartilage and bone (*e.g.* in rickets) the contrast staining with ammonia carmine and hæmatoxylin (p. 21) is to be recommended. By the latter pigment the ground-substance of the growing cartilage, as well as of cartilage which was calcified but has been artificially deprived of its lime-salts, is tinged bluish-violet, whilst by the former osteoid tissue and decalcified bone are stained an intense red.

In order to bring out in a proper manner the difference between portions of bone which do and do not contain lime, *e.g.* in osteomalacia, the preparations should be decalcified in Müller's solution, and the process only continued until they can just be cut with a razor. The sections may then be stained with carmine. For the characteristic staining of *deposits of lime* see p. 62.

In *leucæmic affections* of the bone-marrow an attempt may also be made to stain the sections after Heidenhain's method (p. 190). For examining sections for *bacteria*, the standard rules given for the latter hold good (see Part II., Chapter V.). In *grinding bone preparations* the methods given on p. 232 for the preparation of grindings from teeth may be resorted to.

CHAPTER XI.

THE SKIN.

1. Degeneration, Atrophy, and Hæmorrhage.—In persons advanced in years a *degeneration* occurs affecting the *elastic fibres* of the skin, which at first show shining globules, but later assume a perfectly homogeneous and hyaline character either in circumscribed spots or more diffusely, and may even fuse one into the other, the fibrillated connective tissue between them having disappeared.

Amongst the *atrophic* processes occurring in the skin, *xeroderma* deserves mention. This may occur in a *progressive* form, being then accompanied on the one hand by shrinking of the papillæ, on the other by dilatation of vessels and glands, elongation of the cones of the rete Malpighii, and irregular accumulation of pigment (*xeroderma pigmentosum*), whilst at the same time it affords a very favourable soil for the development of cutaneous sarcoma or carcinoma. The disease may also, however, take the form of a *stationary* atrophy of the skin, in which the latter becomes in addition very deficient in pigment, and the epidermis is very greatly thinned.

The non-traumatic *hæmorrhages* occur as little spots (*petechiæ*), stripes (*vibices*), and nodules (*lichen hæmorrhagicus*), or in large patches, and are mostly situated in the papillary body and sub-papillary layer. Such hæmorrhages, which are usually described under the comprehensive name of *purpura*, either take place in the course of certain diseases (variola, scarlatina, endocarditis, septicæmia, and other infective diseases and intoxications), and may sometimes be due to the occlusion of small cutaneous vessels by pathogenic bacteria; or they are supposed to be symptoms of diseases (*purpura rheumatica, hæmorrhagica,* and *scorbutica*) whose ætiology is still unknown to us, but which perhaps also depend on infection or intoxication. At least in some such cases bacteria have been found in the extravasations or in the blood, partly belonging to known

pathogenic species (*Streptococcus pyogenes, Bacillus pyocyaneus*) and partly to new species (mostly bacilli).[1]

2. Abnormalities of Pigmentation.—In the morbid *pigmentations* we have to do either with an increase in the normal pigment of the skin, or with deposit of pigment from the blood and bile or of colouring-matter derived from without.

To the *former* category belong in the first place *nævus pigmentosus, ephelides, lentigines*, and *xanthelasma*. These are congenital or depend upon a congenital predisposition, and consist of collections of cells in patches and bands lying in the papillæ or corium; whilst the yellow or brown pigment peculiar to them lies in the cells of these patches and in the rete Malpighii. In *xanthelasma*, however, the characteristic coloration does not appear to be due to such pigment, but to an abundant deposit of fat-droplets in the cells in question, which cells also show variability in size and shape and are partly polynuclear. Furthermore, we find an increase of pigment in various parts of the skin in women who are pregnant or suffering from diseased conditions of the organs of generation (*chloasma uterinum*).

In *Addison's disease* the skin assumes a bronze-like colour, especially over the uncovered parts, the papillæ of the breasts, and the generative organs. In these localities not only is the epidermis then very rich in pigment—even the stratum corneum containing it—but in the neighbourhood of the blood-vessels of the cutis, especially in the papillæ, there exist very numerous pigmented cells, of which those situated near the rete Malpighii send out processes between the cells of the epidermis. As isolated blood-vessels are sometimes blocked by thrombi, whilst on the other hand little hæmorrhages may occur in the skin, the pigment in Addison's disease is considered by many to be hæmatogenous. Regarding the pigmentary deposit after *hæmorrhages*, in *icterus*, and in *argyria*, see pp. 58-60.

Deficiency of pigment in the skin (*leucopathia*) is either congenital (*albinism*) or does not occur until a later period (*vitiligo*). In the latter case the pigment is found to have disappeared from the affected spots, but it is frequently increased in their neighbourhood.

3. Inflammation.—The slightest degrees of *dermatitis* which are marked during life by redness and swelling (erythematous inflammation), or by formation of papules and vesicles, show microscopically a more or less abundant accumulation of small round cells in the

[1] These cases are also described as "*hæmorrhagic infection*." In them hæmorrhages are found not only in the skin, but also in serous membranes and in the lungs, intestine, capsules of the kidneys, etc.

papillæ and sub-papillary layer, mostly in the neighbourhood of the smaller blood-vessels and of the gland-ducts and hair-follicles; together with slight serous infiltration of the same parts of the cutis, and sometimes also small hæmorrhages. To this category belong the dermatitis or eruption in *scarlatina* and *measles*, the *traumatic erythema* resulting from the action of mechanical, chemical, and thermic agencies, *erythema exudativum multiforme*, *erythema nodosum*, *urticaria*, and *erysipelas*.

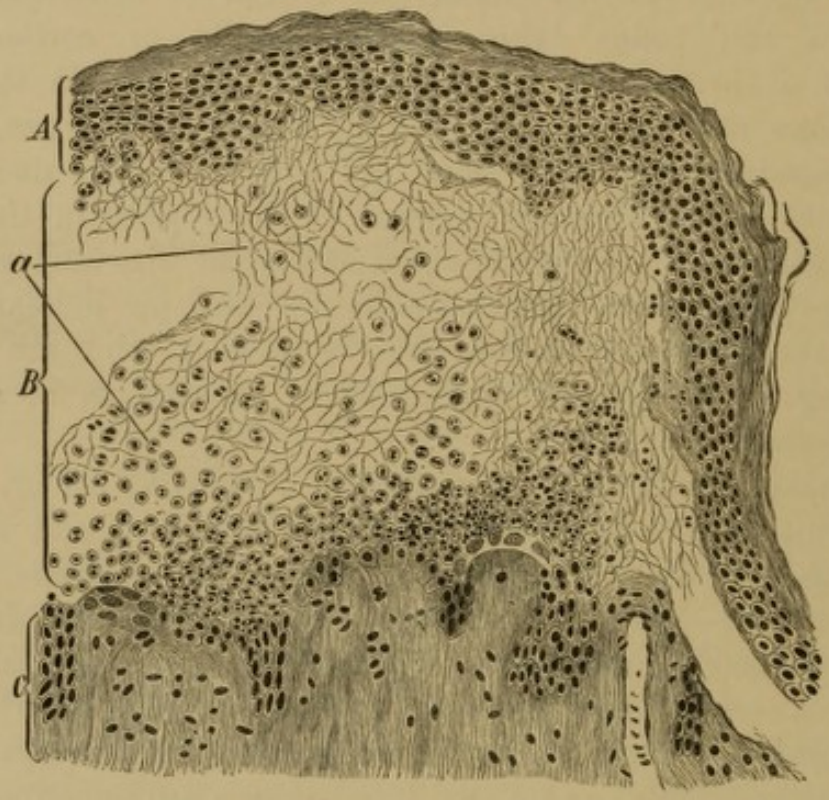

FIG. 195.—CUTANEOUS VESICLE IN PEMPHIGUS. × 285. (Alum cochineal.) *A*, Raised layer of epidermis; *B*, Vesicle; *C*, Remains of the epidermis, with the papillæ of the cutis; *a*, Pus corpuscles and fibrinous reticulum.

Measles and *scarlatina* give rise at the stage of subsidence to increased production and shedding of the horny layer of epidermis (desquamation). In *erysipelas* the small-celled infiltration restricts itself as a rule to the immediate neighbourhood of the smaller blood-vessels and lymphatics (Fig. 57, *c*) in the cutis and superficial portions of the subcutaneous tissue, but in addition to this the lymphatics may be distended with lymph and leucocytes (Fig. 57, *a*). In many cases, also, the epidermis is raised into vesicles (*erysipelas bullosum*). For the other particulars see pp. 121-2.

In the severer degrees of dermatitis both the cellular and the fluid exudation in the above-mentioned parts of the skin are increased. The fluid exudation then forces its way into the epidermis also, and the cells of the latter (except in the most superficial

layers) being thereby partly pushed asunder or elongated, partly swollen and liquefied, *vesicles* and *bullæ* are formed (Figs. 195 and 197). The existence of these, however, may also be due to a coagulation necrosis of the epidermic cells, which are transformed into a network of trabeculæ (Fig. 198, *c*), the meshes of the network becoming distended with fluid exudation. The vesicles are multilocular (Fig. 198) at the commencement and as long as any isolated epidermic cells drawn out to form septa are left within their area; but should these cells also disappear, the small cavities coalesce to form a single bulla. The contents of the latter usually consist at first of an almost clear fluid containing but few leucocytes, and which is seen under the microscope in hardened preparations as a very finely granular mass. At a later period, and also in many cases at the very beginning, the fluid appears cloudy and purulent, and then shows many pus-corpuscles (Fig 198, *c*), with which fibrinous coagula may also be mingled (Fig. 195, *a*). To this condition the name *pustule* is given. Should the fluid contained in a vesicle or pustule push its way outwards through the uppermost layer of epidermis, or should the latter likewise be destroyed, *crusts* and *scabs* are formed by the evaporation or drying up of the contents. In stained microscopic preparations these are seen as homogeneous masses (Fig. 196, *a*), in which the dried pus-corpuscles appear greatly shrunken or caked together, but very intensely stained. In the class of cutaneous inflammations just described we may include *herpes*, *miliaria*, *burns* of the second degree, *pemphigus*, *eczema*, *acne*, and *variola*.

In *herpes* the vesicles occur in groups and at definite parts of the body (labial, facial, præputial, and progenital herpes). In *herpes zoster* they follow the course of definite cutaneous nerves, and are probably caused by diseased conditions of the latter or of the corresponding centres. Whereas *burns of the first degree* merely give rise to an erythematous inflammation, those of the *second* (Fig. 197) cause partial necrosis of the epidermic cells (*a*) with liquefaction of the dead cells by a fluid exudation derived from the corium, and consequent formation of vesicles (*B*). In burns of the *third* degree the cutis itself is destroyed. Like changes, however, may also be set up by the action of great *cold*.

In *extensive* burns thrombi, consisting chiefly of blood-platelets, also form in numerous small cutaneous vessels. Small particles may then become detached from these and cause occlusion of numerous capillaries in internal organs, especially the kidneys, liver, and spleen, in consequence of which stasis and thrombosis also occur in somewhat larger vessels, whilst at times even small hæmorrhages

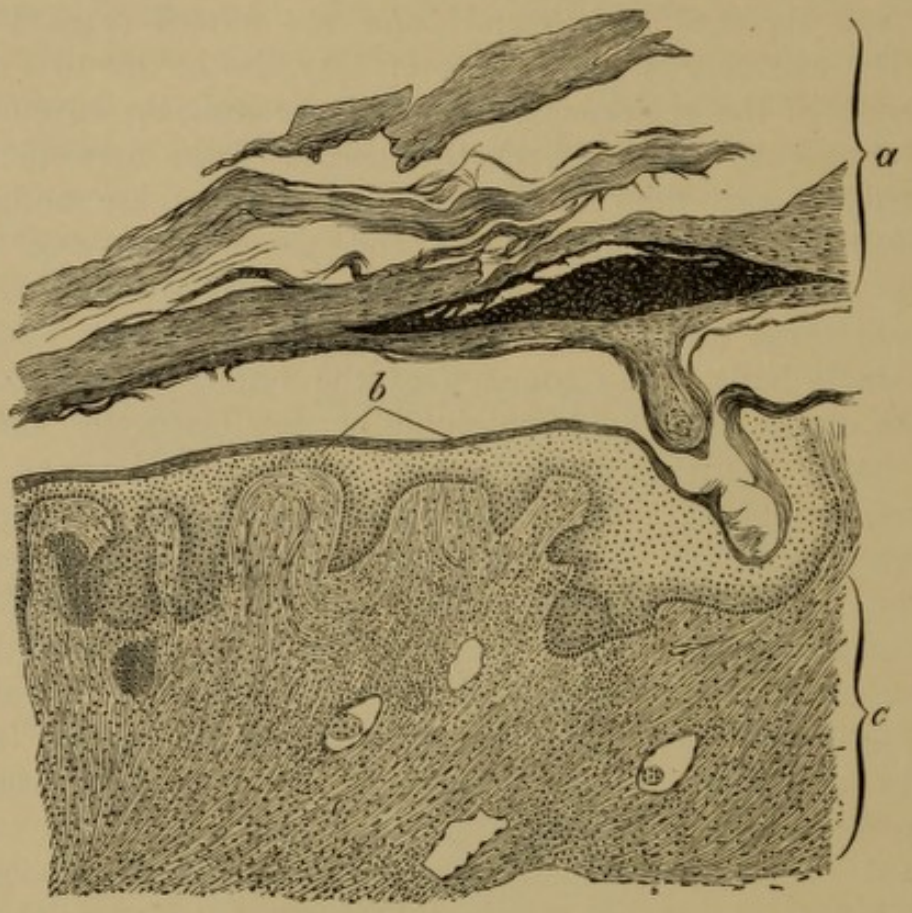

FIG. 196.—VARIOLA IN THE STAGE OF DRYING UP. × 95. (Alum cochineal.) *a*, Crust or scab; *b*, Narrowed rete Malpighii; *c*, Cutis infiltrated with round and spindle cells.

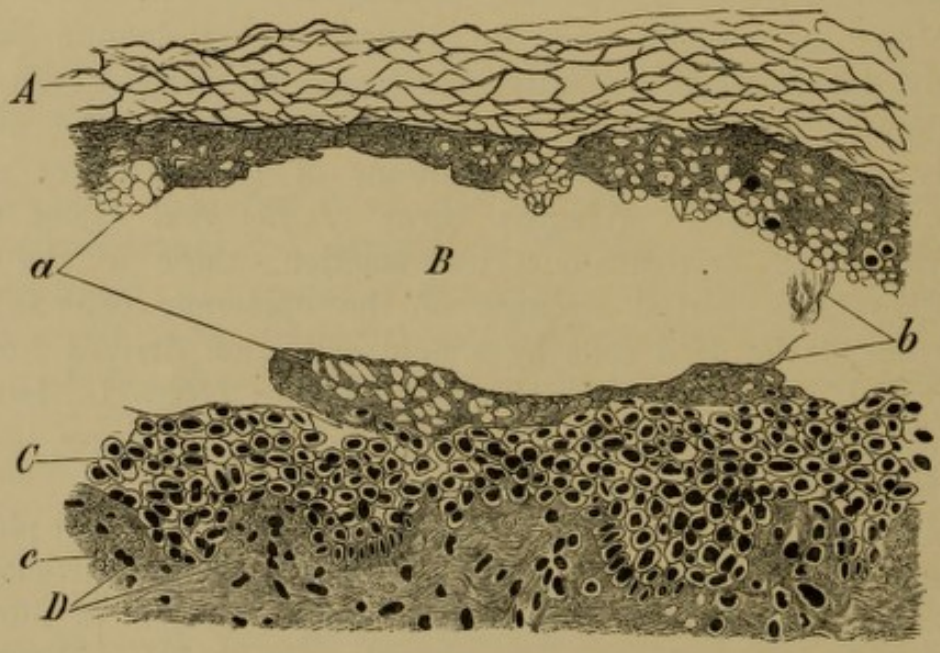

FIG. 197.—CUTANEOUS BURN OF THE SECOND DEGREE. × 240. (Hæmatoxylin and eosin.) *A*, Stratum corneum; *B*, Formation of vesicle in the upper layers of the rete Malpighii; *C*, Under layer of rete Malpighii; *D*, Papillæ of cutis; *a*, Necrotic cells of rete Malpighii; *b*, Elongated necrotic cells; *c*, Extravasated red corpuscles.

and circumscribed necroses are produced in the neighbourhood of the occluded vessels. In this manner is also to be explained the formation of the *duodenal ulcers* which are not uncommonly observed in extensive burns.

In *pemphigus* (Fig. 195) a very large portion of the corium may in time be laid bare by progressive vesication and destruction of epidermis (*pemphigus foliaceus*). Furthermore, isolated parts of the corium may actually die (*diphtheritic pemphigus*), whilst in other cases papillary growths may even arise from it (*pemphigus vegetans*). *Eczema* runs either an acute or a chronic course. In many forms (*eczema pustulosum* and *eczema impetiginosum*) the cellular infiltration is very abundant and may even pass down into the subcutaneous connective tissue. After chronic eczemas a pigmentation of the skin is frequently left, and in many cases there is also thickening of the epidermis and of the cutis. In *acne* we have to do with a pustular inflammation in the vicinity of the hair-follicles and sebaceous glands. The *Staphylococcus pyogenes* may be found in the pus from acne and eczema pustules, and hence the suppuration is probably caused by it.

Variola (Fig. 198), by the action of the virus on circumscribed spots in the rete Malpighii (above the apices of the papillæ), gives rise to a coagulation necrosis in which the epidermic cells become in part transformed into a network of trabeculæ (*c*). The meshes of the latter are then distended with a fluid exudation derived from the vessels of the papillæ, and this takes place more at the periphery of the focus than in its centre, so that *umbilicated* multilocular vesicles are formed. The contents of these are at first clear, but as more and more pus-corpuscles now wander in the fluid in the vesicles becomes cloudy, the dividing walls of the loculi tear through, the umbilication disappears, and we have finally *unilocular pustules*. Usually the papillæ (*c*) and subjacent layers of the corium are also infiltrated with small cells. When, eventually, the contents of the pustules dry up, *scabs* are formed (Fig. 196, *a*) under which the regeneration of the destroyed parts goes on. If the destruction is confined merely to the epidermis, no scars are left behind; but when the suppuration has spread to the cutis also, the deficiency is filled up with cicatricial tissue.

In *variola hæmorrhagica* (Fig. 199) either numerous small hæmorrhages occur in the skin from the very commencement of the process, or else nodules first form into which hæmorrhage afterwards takes place; whilst at the same time hæmorrhages occur upon different mucous membranes and in internal organs. The extravasations in the skin appear under the microscope partly in the form of

rounded or band-like patches, partly more diffused (*d*). Besides these extravasations, small-celled infiltrations are also seen in the skin in the immediate neighbourhood of the vessels (*c*).

As little is known of the *contagium* of variola as of those of scarlatina and measles. Usually, however, *secondary* infection with

FIG. 198.—SMALLPOX PUSTULE IN THE SKIN. × 285. (Alum cochineal.) *a*, Stratum corneum and stratum lucidum of epidermis; *b*, Uppermost layer of rete Malpighii, necrotic in the right half; *c*, Middle layer of rete Malpighii transformed into a network of trabeculæ, in the meshes of which lie finely granular masses (serum), pus corpuscles, and broken-down nuclei; *d*, Undermost part of the rete Malpighii; between the partially necrotic epithelial cells, which have lost their nuclei, lie pus-corpuscles and their broken-down nuclei; *e*, Papillæ of cutis infiltrated with small cells.

pyococci takes place in these diseases, and the micro-organisms in question can then be detected in the complicating morbid conditions and in the blood, whilst in variola they are also found in the pustules.

To the *inflammations which affect not only the cutis but also*

the subcutaneous connective tissue belong *phlegmon* and *furuncle*. The former, which is caused by the pyococci, always begins in the subcutaneous connective tissue (or in still deeper connective-tissue strata), only reaching the cutis at a later period. An abundant exudation is always present, which collects chiefly in the spaces of the connective tissue, and is in most cases fibrinous or fibrino-purulent. Here and there necrosis of tissue may result, or formation of abscesses, and the epidermis may also become elevated into bullæ.

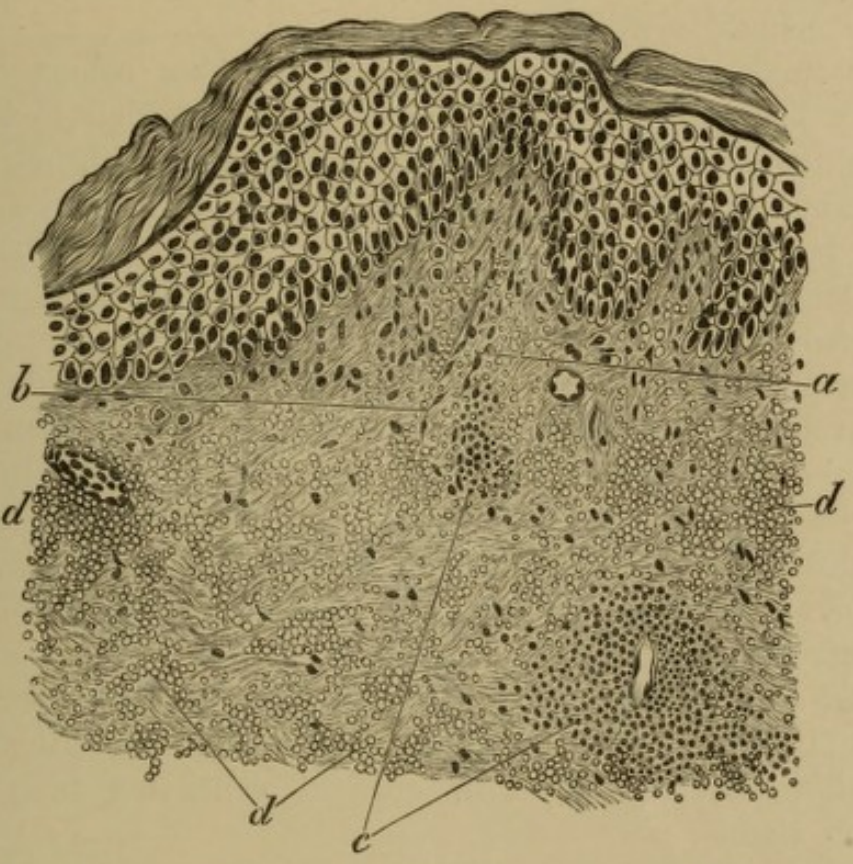

FIG. 199.—VARIOLA HÆMORRHAGICA. × 285. (Hæmatoxylin and eosin.) *a*, Capillary vessel in a cutaneous papilla; at *b*, the endothelial cells of the vessel are raised; *c*, Small-celled infiltration in the neighbourhood of blood-vessels; *d*, Extravasation of blood, partly divided into rounded or band-like groups, partly more evenly distributed.

The cocci are not, as in erysipelas, confined to definite localities, but may be present everywhere and in large numbers. Under certain circumstances they also penetrate into the lymphatics and blood-vessels, in which they may then give rise to inflammations, and may even cause pyæmia. (See also p. 119.) The *furuncle* is really a circumscribed phlegmon. It invariably develops in the vicinity of hair-follicles and cutaneous glands, by which the inflammatory excitants (usually *Staphylococcus pyogenes*) have gained entrance, and begins by causing necrosis of a small portion of tissue, which is then extruded in the form of a plug by the subsequent suppuration. When of greater extent the furuncle is termed a *carbuncle*.

Psoriasis occupies a peculiar position amongst the cutaneous inflammations, as in it not only are the papillæ and adjoining layers of the corium in a state of small-celled infiltration, but the cells of the stratum corneum are continually being cast off in the form of dry white scales. The latter phenomenon perhaps depends upon a peculiar disturbance in the process of horny transformation, owing to which the cells undergo a kind of desiccation and are loosened in their attachments. With longer duration of the process there also ensues a growth of the rete Malpighii and elongation and thickening of its cones.

To the *rarer chronic inflammations* of the skin belong *lupus erythematosus*, *prurigo*, and *lichen ruber*. The histological changes in these conditions are not very significant; they consist in circumscribed and sometimes nodular infiltrations of small cells in the papillary bodies and in the vicinity of the glands. In lupus erythematosus the cellular infiltration is most intense at the points where the sebaceous glands open into the hair-follicles.

4. Hyperplastic processes.—Amongst those hyperplastic growths which develop in immediate consequence of inflammation may be reckoned the *granuloma* and the *cicatricial keloid* [*false keloid*].

The *granuloma* forms a tumour-like growth composed of a very cellular and highly-vascularised granulation tissue. It may develop after various inflammations and even after quite insignificant lesions, and occurs in adults most frequently on the head. *Mycosis fungoides* and *dermatitis papillomatosa capillitii* are also reckoned amongst the granulomata, inasmuch as in these rare morbid conditions of the skin we have also to do with growths consisting in general of granulation tissue.

The *cicatricial keloid* (Fig. 200) depends on a tumour-like growth of cutaneous scars, and therefore consists of younger or older (*i.e.*, more or less cellular) cicatricial tissue (*B* and *C*), over which the newly formed epidermis (*A*) stretches in a straight line. In many cases tumours of like structure, *i.e.*, composed of cicatricial tissue, also develop *spontaneously*. They are then called simply *keloid* [or *true keloid*], and differ from the false keloid in that their tissue is covered with normal cutaneous papillæ and normal epidermis with rete-cones.

The remaining hyperplastic processes, which have either no connection at all or but a loose one with inflammation, involve, some the *epidermis*, others the *cutis* and *subcutaneous connective tissue*. In the former category we may place *ichthyosis*, a disease which is as a rule congenital and inherited, and in which peculiar scales and plates are formed owing to enormous thickening and fissuring of the stratum corneum. In *ichthyosis hystrix* the papillæ are also enlarged.

To this class also belong *tyloma, clavus,* and *cutaneous horns* (*cornu cutaneum*). In the *tyloma* or *callus* we have to do with a circumscribed hypertrophy of the stratum corneum over places (most frequently on the hands and feet) which have been exposed to repeated or somewhat prolonged pressure. If, under these circumstances, the thickened horny layer at the same time extends downwards in the form of a cone towards the papillæ and compresses them, the result is a *clavus* or *corn*; but if this hypertrophic layer

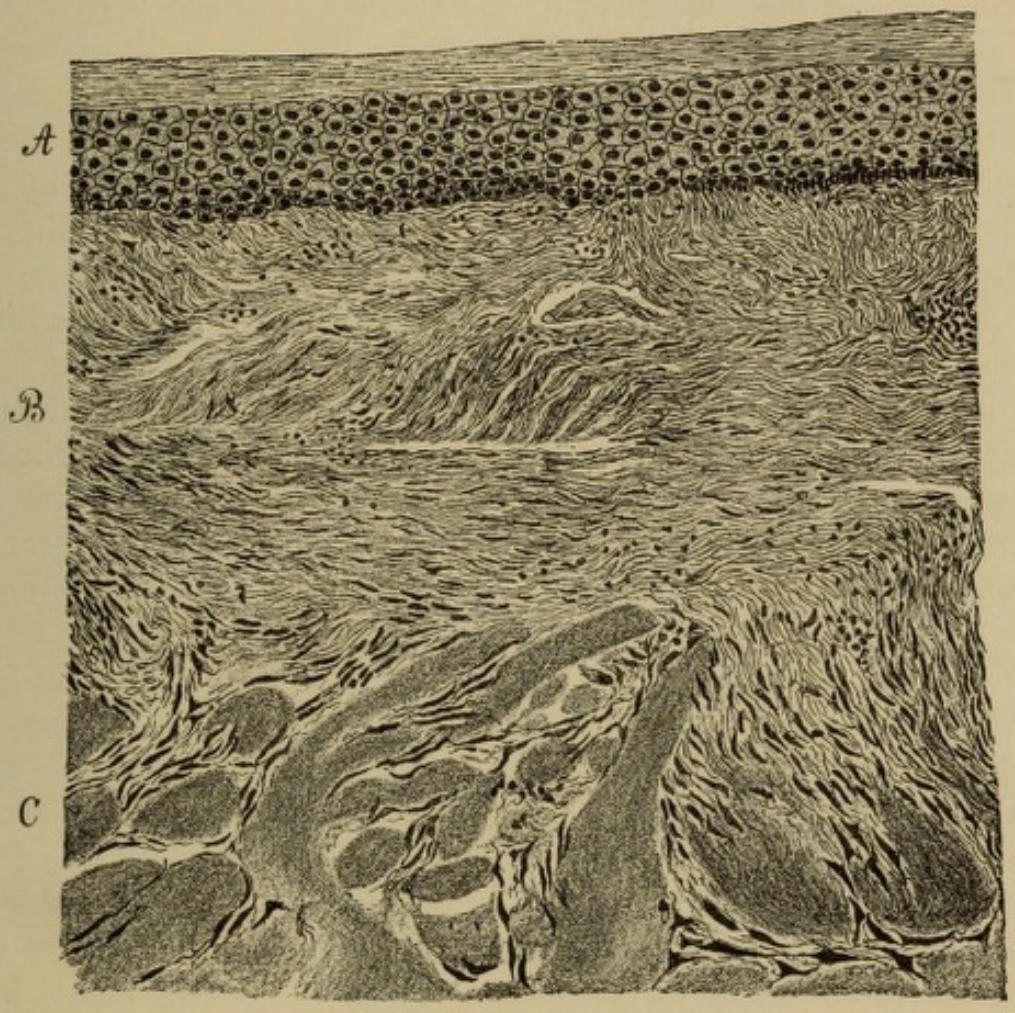

Fig. 200.—Cicatricial Keloid of the Skin. × 200. (Hæmatoxylin and eosin.) *A*, Newly-formed epidermis with rectilinear lower border; *B*, Cicatricial tissue, fairly rich in cells; *C*, Cicatricial tissue, with broad homogeneous bands of connective tissue.

rises above the surface of the skin like a claw or horn, a *cornu cutaneum.*

To the *second* category (*i.e.*, the inflammations affecting the cutis and subcutaneous tissue) belongs *elephantiasis Arabum,* which is only seen sporadically with us, but occurs in epidemics in many tropical and sub-tropical regions. It frequently develops after repeated attacks (which in the tropics are often caused by *Filaria Bancrofti*) of lymphangeitic or erysipelatoid or other chronic forms of inflammation, but apparently may also occur spontaneously. It most frequently

affects the lower extremities and external genitals, and consists in a bulky thickening of the cutis and subcutaneous connective tissue, and not uncommonly also of the epidermis. The newly-formed connective tissue, to which is due the increased thickness of the skin and subcutaneous tissue, is variable in its composition. Thus, it may either be rich in cells throughout, and even show here and there the characters of a granulation tissue; or cellular and non-cellular parts may alternate with one another, the aggregations of cells usually adhering to the blood-vessels; or the connective tissue is everywhere firm and poor in cells. The blood-vessels may be unaltered in the process, or may, together with the lymphatics, be greatly dilated. Thickening of the epidermis, if present, chiefly affects the stratum corneum, and if in such cases, in addition to the thickening, the papillæ are greatly elongated and branched, the surface of the skin acquires a warty or papillomatous appearance.

5. Infective Granulomata.—Of the *infective granulomata*, *tuberculosis* is found in the skin in several forms. One of these consists in the development of shallow cutaneous ulcers which in advanced tuberculosis of other organs occurs in the immediate neighbourhood of orifices clothed with mucous membrane, such as those of the nose, mouth, anus, and genitals, in consequence of the outflow of secretion containing a large number of tubercle bacilli. These ulcers do not differ histologically from other tubercular ulcers, and usually contain very numerous tubercle bacilli. A second form is the so-called *scrofuloderma*, occurring especially in children, and characterised by the formation of nodular foci in the subcutaneous connective tissue (especially of the face and neck), which eventually break and form sinuous ulcers. Here isolated or conglomerate tubercles are found, of microscopic size and embedded in a granulation tissue, and which usually exhibit the structure of giant-celled tubercles. In most cases tubercular processes also exist in the lymphatic glands, bones, joints, and so forth (*scrofula*). A third form is *lupus vulgaris* (Fig. 201), which occurs most frequently on the face or extremities in young persons. Small nodules, consisting of round cells alone or of epithelioid and giant cells (*d*), form in the cutis, while between them a more or less abundant granulation tissue also develops. The superficially situated nodules usually break outwards, the result being a shallow ulcer covered with pus and crusts, at the borders of which the rete Malpighii is not uncommonly in a state of growth, and pushes cones of variable length into the cutis (*a*). Lastly, as a fourth form, we must mention the *dissecting-room porter's wart*, *tuberculosis cutis verrucosa* [or *verruca necrogenica*], which is observed in persons who have frequently to handle tuberculous corpses. It differs essentially

from the preceding form in that to the tubercular alteration in the cutis there is further added growth of the papillæ and thickening of the epidermis. The last three forms described are also distinguished by their very chronic course and great poverty in tubercle bacilli.

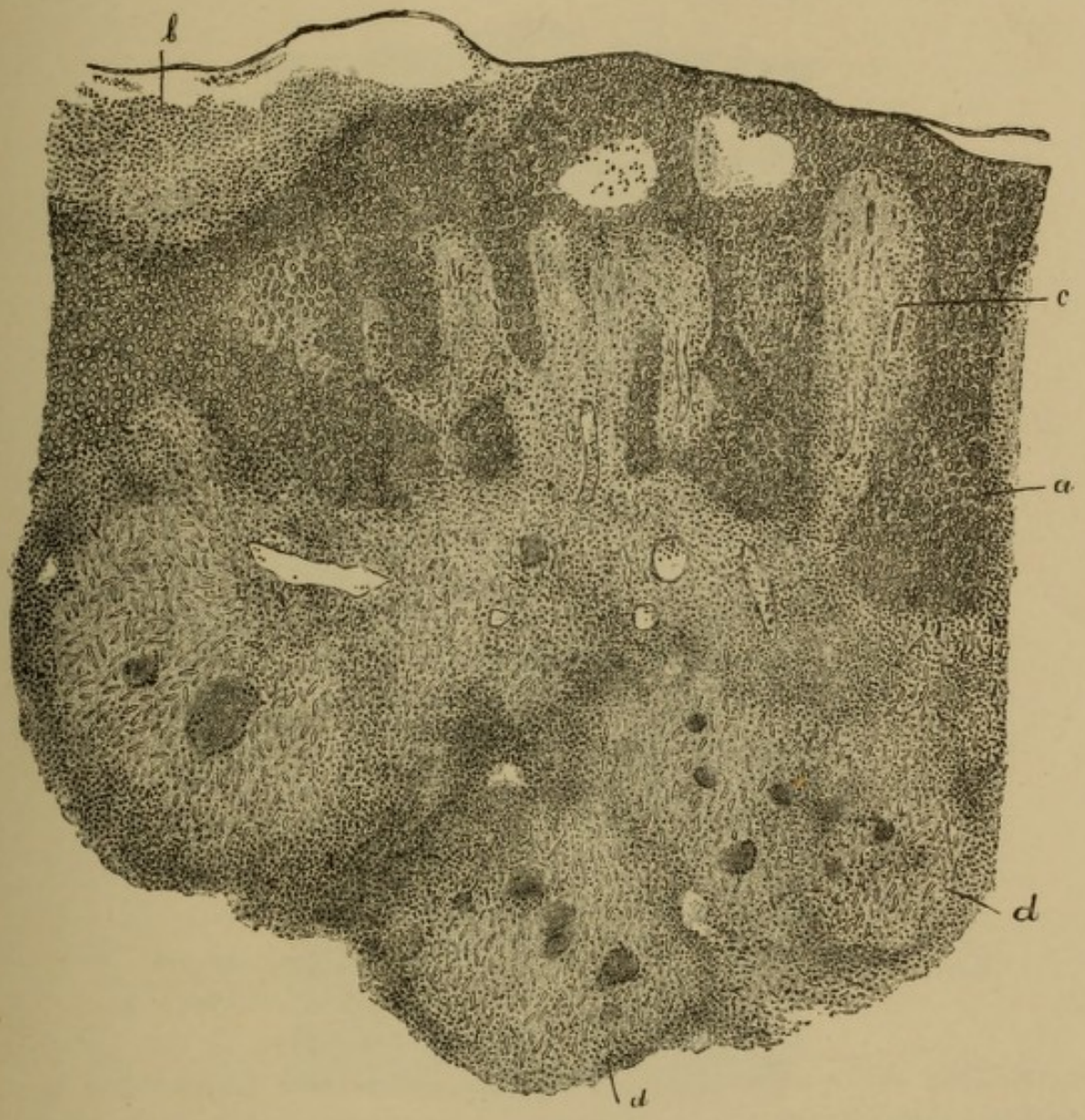

FIG. 201.—LUPUS OF THE SKIN in the stage of reaction after injection of Tuberculin. × 77. (Alum cochineal.) *a*, Epidermis with hypertrophy of the rete Malpighii; *b*, Elevation of the stratum corneum by pus (formation of pustule), which is to be regarded as indication of an inflammation set up in the lupus by the tuberculin (reaction); *c*, Enlarged papillæ; *d*, Epithelioid-celled tubercle containing giant cells.

Syphilis occurs in the skin either as *primary induration*, or in the form of the so-called *cutaneous syphilide*. The former (Fig. 202) develops at the point of entrance of the syphilitic virus, and is characterised by a tolerably sharply circumscribed aggregation of lymphoid cells in the cutis (*b*), between which epithelioid elements and even isolated giant cells may sometimes also be present. Further,

in the immediate vicinity of this infiltration the tissue of the cutis is somewhat richer in cells (*c*), and, above all, the small blood-vessels (*d*) show characteristic changes, their walls being densely infiltrated with small round cells (*syphilitic vasculitis*). The process may eventually subside again, the cellular infiltration undergoing a

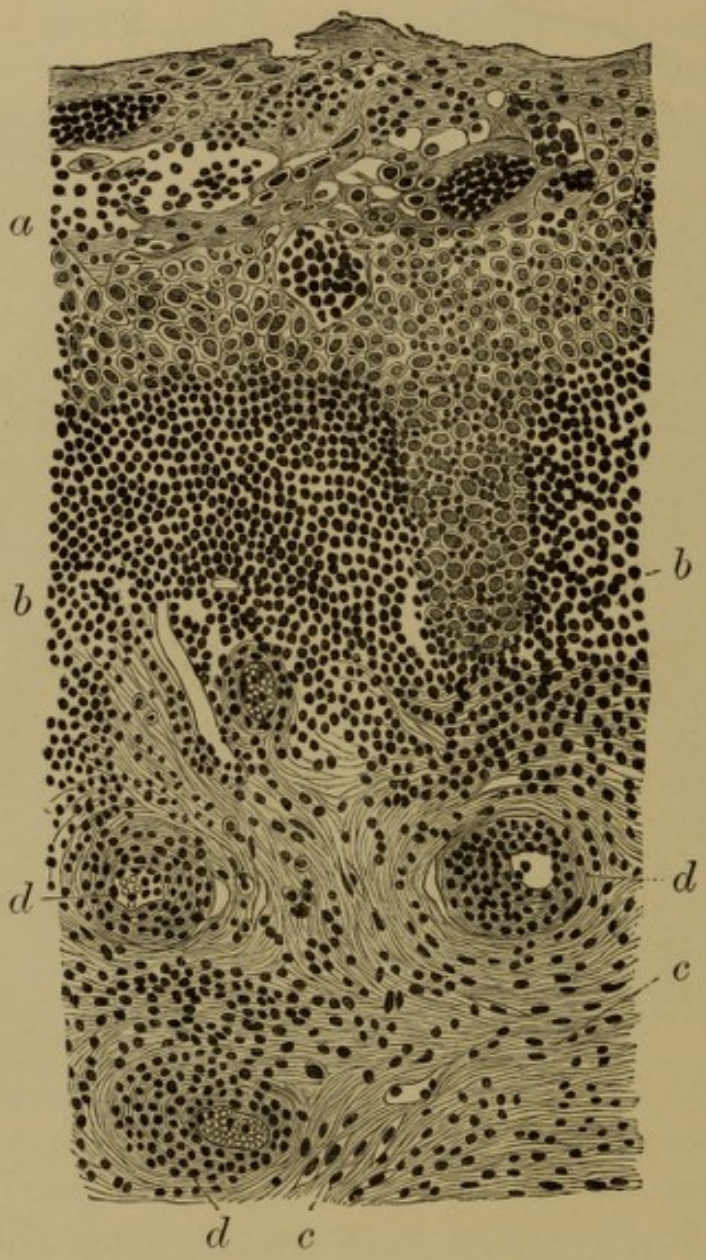

FIG. 202.—ULCERATING SYPHILITIC PRIMARY INDURATION OF THE PREPUCE. × 240. (Alum cochineal.) *a*, Epidermis partially infiltrated with leucocytes (commencing ulceration); *b*, Round-celled tissue; *c*, connective tissue rich in cells; *d*, Blood-vessels, the walls of which are infiltrated with round cells (syphilitic vasculitis).

gradual transformation into connective tissue, or it may go on to ulceration (*a*), giving rise to the *hard chancre* (*ulcus durum*). The *cutaneous syphilide* only develops after the syphilitic virus has passed into the circulation, and may take a macular, papular, pustular, or gummatous form.

In the *macular* syphilide small red spots appear, whilst in the *papular* form little nodules (*papules*) develop from the spots, and on parts of the skin which are continually in a moist condition (anus, organs of generation, and the like) also attain a considerable superficial extent, being then named *condylomata lata* (Fig. 203). In both forms of cutaneous syphilide the histological changes consist

FIG. 203.—CONDYLOMA LATUM. × 95. (Alum cochineal.) *a*, Stratum corneum; *b*, Rete Malpighii with thickened and elongated cones; *c*, Elongated papillæ; *d*, Small-celled infiltration of the sub-papillary layer of the cutis.

in small-celled infiltration of the walls and immediate neighbourhood of the blood-vessels, especially those in the papillæ and the sub-papillary stratum, but also those which twine round the hair-follicles, sebaceous and sweat glands, and arrectores pili muscles. Even the small blood-vessels in the deeper layers of the cutis and in the panniculus adiposus may be implicated in the changes described, whilst the endothelium of the diseased vessels may also take on growth. In addition to this the wall and immediate neighbourhood of the sebaceous glands and hair-follicles, as well as of the sweat-glands and their ducts, are found infiltrated with small round cells.

In the *papular* form of syphilide the changes described are of greater extent and intensity than in the macular form. Not only do the small-celled infiltrations attain a higher degree in places, notably in the upper layers of the cutis and in the papillæ, and even, it may be, contain isolated giant cells, but round cells also penetrate into the rete Malpighii, whilst the superficial cells of the epidermis swell up and are cast off. In the condylomata the cones of the Malpighian layer may also increase in length and thickness (Fig. 203, *b*). If the cellular infiltration of the papules breaks down into pus, and at the same time the stratum corneum is raised by abundant accumulation of pus-corpuscles in the epidermis, and thus a pustule is formed, we have the *pustular* syphilide. Should the pustules become large the condition is spoken of as *syphilitic pemphigus*, and when the pus dries up into scabs, as *rupia syphilitica*. After the scabs have been shed little ulcers come to view, which can only heal by cicatrisation. The cellular infiltrations in the skin which lie at the basis of the macular and papular syphilides disappear only very gradually as the process heals, the round cells in the first place changing to spindle cells. Vestiges of the infiltrations can be made out microscopically even several months after the process is apparently well, but these in most cases then consist solely of spindle cells, and occupy chiefly the walls of the blood-vessels.

The *gummatous* form of syphilis of the skin is characterised by the development partly of small gummata in the cutis, partly of large ones in the subcutaneous connective tissue. Eventually they either subside again—the larger after central caseation—or ulcerate. (For further particulars, see also p. 138.)

A more or less abundant *formation of pigment* occurs in all cutaneous syphilides, the pigment, which takes the form of yellow or brown granules, or of a diffuse staining, being situated in round cells in the recent syphilides, but when the process has lasted longer, in the cells of the connective tissue. It is present in greatest abundance in the papillæ and in the adventitia of the blood-vessels. This pigment may still persist for a considerable length of time after the subsidence of the syphilide, or may even remain permanently; whilst in many instances, on the contrary, especially after papular syphilides, a *deficiency of pigment* (*leucoderma syphiliticum*) may be observed in the skin of certain localities (on the nape of the neck). On such spots, however, only the epidermis appears unpigmented, whereas numerous cells containing pigment are present in the cutis, especially in the papillæ at the periphery of the leucoderma.

For *lepra*, *glanders*, *rhinoscleroma*, and *actinomycosis* of the skin, see pages 136, 140, 152, and 157.

6. New-formations and Parasites.—Of the more frequent *new-formations* of the skin must be mentioned *fibroma*, *lipoma*, *angioma*, *sarcoma*, *cystic tumours*, *carcinoma*, and *papilloma*. Concerning the fibroma which starts from the cutaneous nerves (*neuro-fibroma*), see p. 83. When the last-named tumours are multiple, the cutaneous and subcutaneous connective tissue between them in many cases also shows a diffuse growth of the nature of elephantiasis (*neuromatous elephantiasis*). A similar diffuse growth may also accompany *lymph-angiomata* and *hæmatangiomata* of the skin (*lymphangiectatic*, *tele-angiectatic*, and *cavernous elephantiasis*).

Most varieties of *sarcoma* are met with in the skin, where they occur either in solitary or multiple form, the latter especially in the case of *melanotic* sarcoma. Cutaneous *carcinoma* as regards its histological structure usually takes the form of a squamous-celled epithelioma, starting from the epidermis or from the epithelium of the sebaceous glands and hair-follicles; but in the case of carcinomata on the neck the epithelium of still-persisting relics of the visceral clefts may also form the starting-point. Lastly, there are cancers of the skin which arise from the epithelium of the sweat-glands, and which then also approximate more nearly to an *adeno-carcinoma* in their structure.

The *flat-celled epithelioma* of the skin occurs in two forms, a flat and a deep-growing, according to the depth to which the cones of cancer cells penetrate, the *first* form being less malignant, but seldom giving rise to metastases, and usually forming shallow ulcerations, which may even cicatrise in the centre [*rodent ulcer*].

Places where the skin passes into a mucous membrane form the favourite seat of carcinoma; but, in addition, warts, scars, ulcers, and especially lupous ulcerations not uncommonly form the starting-point for cutaneous cancer. Regarding the other new-formations of the skin (*lipomata*, *angiomata*, *cystic tumours*, and *papillomata*), compare Part II., Chapters III. and IV.; for the skin diseases excited by the *Hyphomycetæ*, see p. 162, and for *Acarus scabiei* and *Acarus folliculorum*, pp. 181 and 182.

Molluscum contagiosum should also be mentioned here. It forms nodules of lobular structure, consisting of agglomerations of epithelial cells which are separated from one another by fibrous septa. In the centre of these agglomerations lie oval structures with a dull gloss, partly free, partly in the interior of horny epithelial cells. These are the so-called *molluscum corpuscles*, which are regarded by some as coccidia (p. 169), but by others as being merely degenerated epithelial cells. The adherents of the first view believe molluscum contagiosum to be an epithelial growth excited by coccidia, and

starting from the rete-cones and hair-follicles; whilst the supporters of the second view consider it merely the result of a distension of sebaceous glands with proliferated and peculiarly altered epithelial cells.

Methods.—The *fresh* method of examination is suitable only for the contents of blebs, pustules, and cystic tumours, and for the crusts and scales in morbid conditions of the skin due to Hyphomycetæ. For the more detailed mode of procedure in the last case, see p. 165. In all other cases *hardening* is done in alcohol, or, more advantageously for many purposes, in Müller's fluid and alcohol, and in the latter instance the contrast stains (pp. 20 and 21) are used for sections. Celloidin will frequently be necessary for embedding, especially when the preparations contain scales, crusts, pustules, or cysts and other cavities.

For staining *elastic fibres* the methods described on p. 214 are to be used, and for the examination for *vegetable and animal parasites*, see Part II., Chapters V. and VI.

CHAPTER XII.

THE EYE.

1. Degenerative and Atrophic Processes.—The riband-like or zonular *nebulosity of the cornea*, which is observed in the region of the palpebral fissure, usually in atrophic bulbs, is due to thickening of the epithelium and deposit of calcareous granules or crystals, or, less frequently, of masses resembling colloid matter, in the superficial layers of the cornea; whilst the pathological change in the so-called *arcus senilis* is a fatty degeneration of the cells and intercellular substance at the margin of the cornea.

Posterior staphyloma consists of a bulging outwards of the three coats of the eye which occurs in the posterior half of the bulb in high degrees of myopia. It surrounds the optic papilla in a sickle-shaped or annular form, and within its area not only is the sclerotic greatly thinned, but the choroid is also partially or completely atrophied, and in the retina the pigmented epithelium, the rods and cones, and the outer granule layer, are wanting. In the *scleral staphyloma* [or *anterior staphyloma*] which occurs at the equator or in the anterior hemisphere of the eye after chronic inflammations, the choroid and retina are also atrophied in the area of the protrusion, and are adherent to each other and to the thinned and bulging sclerotic.

In *senile* eyes transparent lobulated and sometimes concentrically stratified deposits, probably composed of hyaline or colloid substance, are found upon Descemet's membrane as well as upon the inner surface of the anterior capsule of the lens, and are especially frequent on the innermost layer of the choroid.

The retrograde changes occurring in the *lens* are of importance, especially those included under the name of *cataract* (Fig. 204). The nucleus (*d*) of the lens is attacked at an early period by a gradually increasing process of sclerosis, in which the lens-fibres lose their nuclei and fuse into a homogeneous horny substance. The

conditions in cataract, of which various species are distinguished, are in general cloudiness and swelling of the tissue of the lens; changes usually restricted to those parts of the lens which still remain soft, and hence in advanced life affecting the cortical layer (*c*)—*cortical*

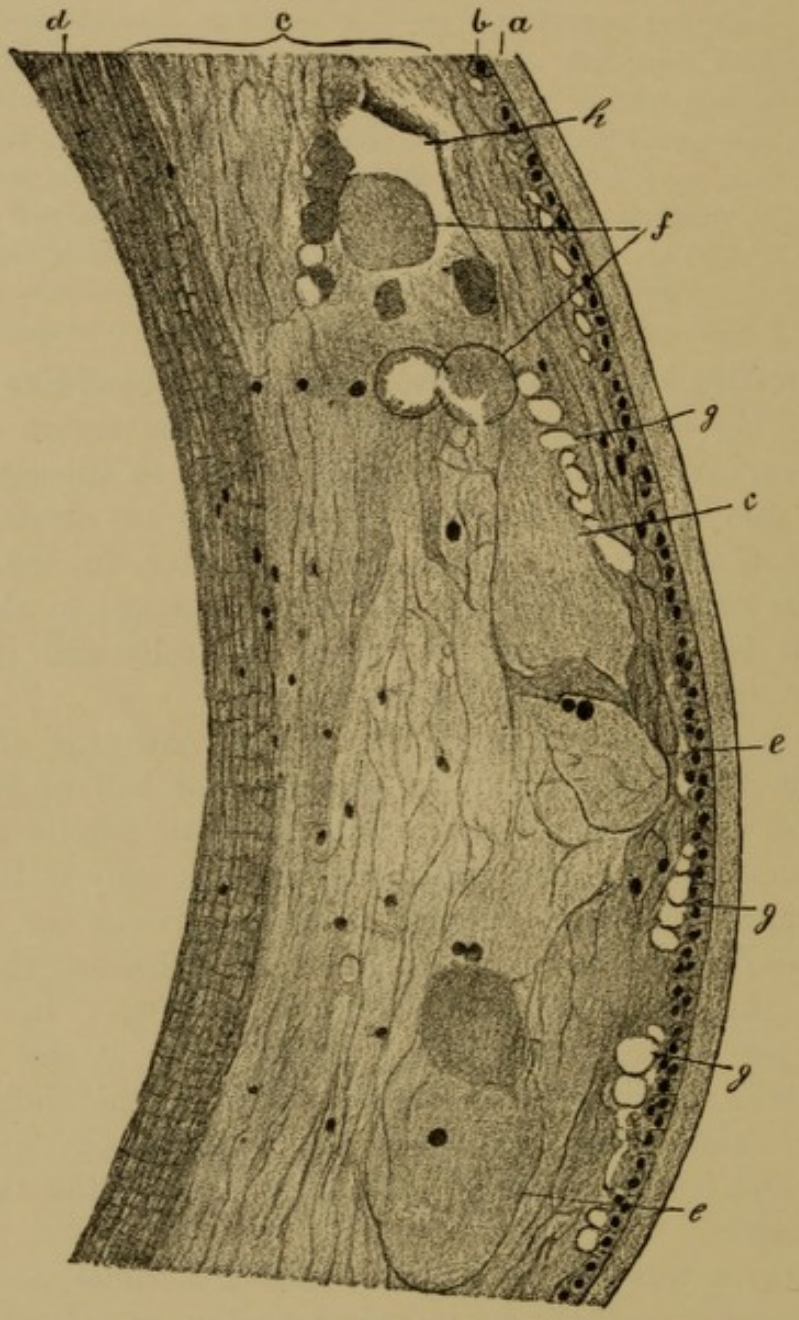

FIG. 204.—SENILE CATARACT. × 200. (Hæmatoxylin and eosin.) *a*, Capsule of lens; *b*, Capsular epithelium; *c*, Cortical layer of lens; *d*, Nucleus of lens; *e*, Vesicular cells, some with one nucleus and some without any; *f*, Spheres of Morgagni; *g*, Vacuoles; *h*, Complete liquefaction of the lens-substance.

cataract. The lens-fibres at first show fat-drops and vacuoles (*g*) in their interior, but later a more granular opacity. They next swell up, so that vesicular structures form which are still nucleated (*vesicular cells, e*), but which gradually increase in size and finally lose their nuclei. Meanwhile homogeneous globular masses, the so-

called *spheres of Morgagni* (*f*), have become visible between the lens-fibres, which latter finally break down completely into a pulp composed of droplets of fat and myelin, cholestearin crystals, and sometimes also masses of lime. This pulp becomes more and more inspissated in course of time, and thus causes a shrivelling of the lens (*over-ripeness* of the cataract).

In *anterior capsular cataract*, which may be superadded to congenital as well as to acquired cataract, we either find plate-shaped or acuminate outgrowths upon the inner surface of the anterior capsule, or else a more diffuse granular opacity of the capsular epithelium; the former, which are at first clear as glass but later become clouded, probably originating by proliferation of the epithelium. In addition to this, the epithelial elements of the anterior capsule may grow by dropsical degeneration into large vesicular cells, the contents of which break down into fatty granules at a later period; whilst the outer lens-fibres likewise may swell to a spindle shape by absorption of fluid. Sometimes also very slender spindle-shaped cells form in large numbers by proliferation of the capsular epithelium, and unite to form a tissue of lamellar structure, which may still be separated from the lens-fibres by a layer of normal epithelium and later may become opaque by deposit of lime and crystals of cholestearin. The much rarer *posterior capsular cataract* differs from the preceding in that its pathological products are developed, not from the capsular epithelium, but from the fibres of the lens.

A quite constant *senile* change in the anterior portions of the *retina* is the development in the external reticular layer of oval cystoid spaces communicating with one another. These spaces gradually increase in size as we pass forwards, and are separated from one another by thickened radial fibres arranged in arcades.

Atrophy of the optic nerve is a rather frequent lesion (Fig. 205), and may be either *primary* or *secondary*. It is ushered in by disappearance of the medullary sheaths, and a narrow-meshed network of very delicate fibres (*c*) finally forms on the site of the destroyed nerve-fibres, whilst the endoneurium (*b*) and the walls of the vessels become thickened and sclerotic. Corpora amylacea are also usually met with, as are granule corpuscles, especially at the commencement.

By the name *xerosis* is understood a peculiar change of the *conjunctival epithelium* in the vicinity of the cornea associated with fatty degeneration and horny transformation, the affected spots becoming covered with small fatty-looking scales, between which a special variety of bacillus, the so-called *Bacillus xerosis*, has also been found. The change described always accompanies *xeroph-*

thalmus, a disease which consists in cicatricial shrinking of the conjunctiva, and obliteration of the superior and inferior conjunctival sacs. *Amyloid degeneration* often occurs in the *conjunctiva* with formation of nodular or diffuse growths, the blood-vessels and connective-tissue fibrils being especially the seat of degeneration. Sometimes these growths or a portion of them fail to give the reactions of amyloid substance, although corresponding to it in appearance. They seem then to be composed of hyaline substance.

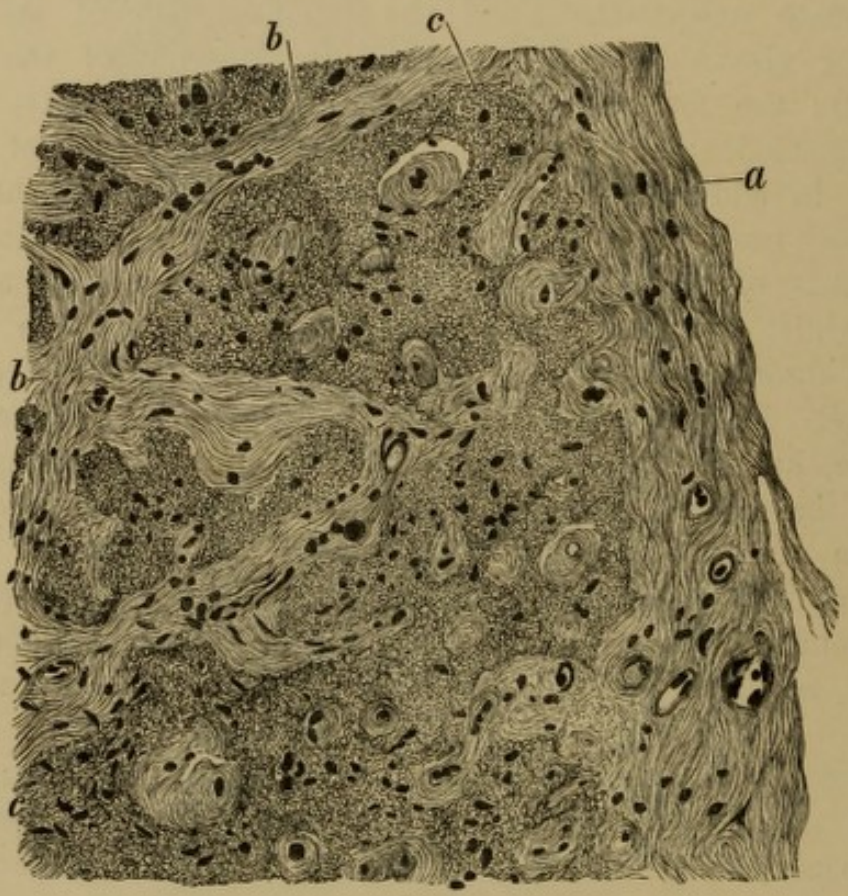

FIG. 205.—ATROPHY OF THE OPTIC NERVE. Segment of a transverse section through the nerve. × 285. (Weigert's hæmatoxylin.) *a*, Perineurium; *b*, Broadened and condensed endoneurium; *c*, Finely fibrous narrow-meshed network on the site of the destroyed nerve-fibres. (By Weigert's method of staining the latter appears darker than the endoneurium.)

2. Inflammation of the Cornea and Sclerotic.—*Acute inflammation of the cornea, keratitis* (Fig. 206), of which oculists distinguish various forms and which is sometimes circumscribed and sometimes more diffuse, is certainly in the majority of cases, if not invariably, caused by bacteria, amongst which the pyococci play a prominent part. Histologically it is characterised first by immigration of leucocytes, mostly of the polynuclear variety, which are derived chiefly from the hyperæmic vascular network of the conjunctival limbus (*a*), and collect more or less abundantly in the juice-lacunæ of the cornea. If the latter are narrow, the leucocytes may also become flattened, so as to assume a spindle shape. If the inflamma-

tion is superficial it gives rise to loosening (*b*), degeneration, and even shedding (*d*) of the epithelium. In the latter case a *corneal ulcer* is formed, which in its further course may attain variable dimensions. If, however, the deep-lying parts of the cornea are affected, a fibrinous or purulent exudation (*hypopyon*) is very often found in the anterior chamber of the eye (Fig. 209, *a*).

For *diphtheritic keratitis*, see p. 415.

In *keratomalacia infantum* an infiltration occurs in the part of

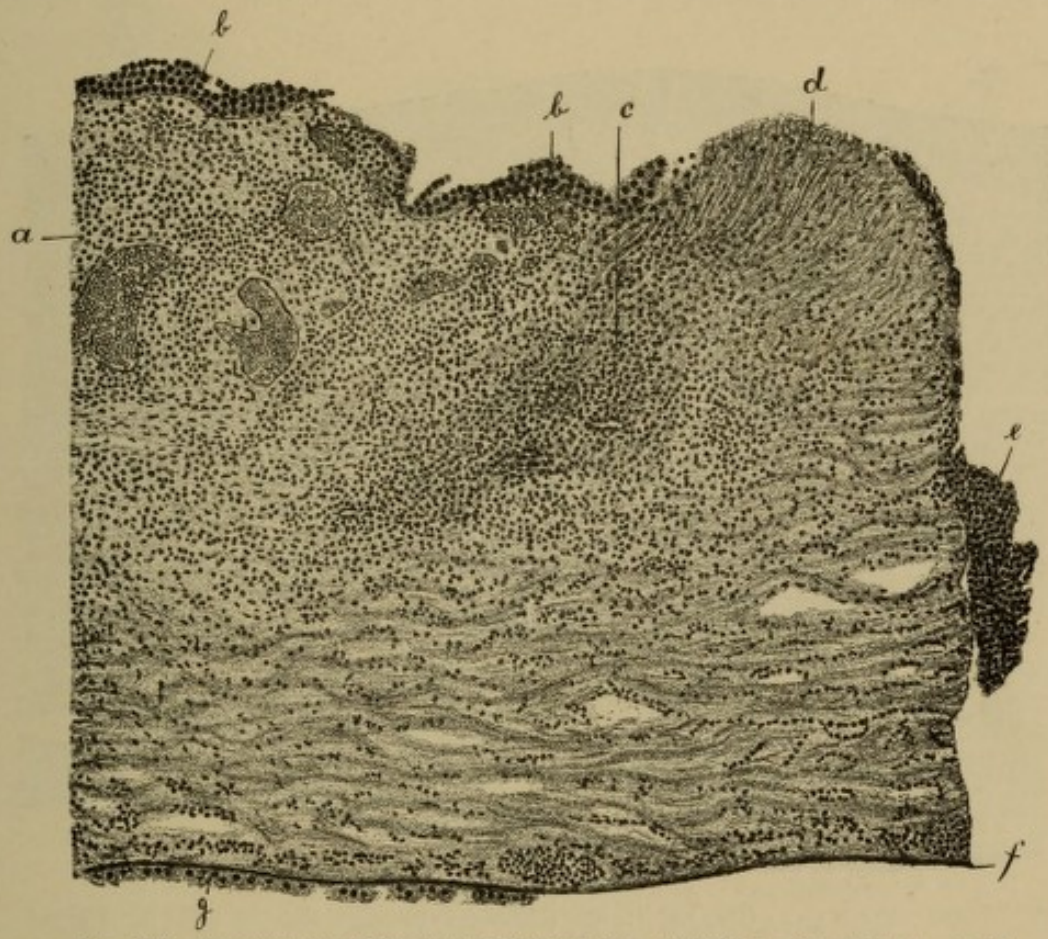

FIG. 206.—SUPPURATIVE KERATITIS following flap extraction of a cataract. × 70. (Hæmatoxylin and eosin.) *a*, Limbus corneæ with hyperæmia of the ciliary vessels, extravasations, and purulent infiltration; *b*, Vestiges of epithelium; *c*, Purulent infiltration of the peripheral part of the cornea; *d*, Necrotic part of the cornea; *e*, Little mass of pus on the surface of the corneal wound; *f*, Descemet's membrane; *g*, Endothelium of the anterior chamber.

the cornea corresponding to the palpebral fissure which quickly changes into an ulcer enlarging in all directions. The juice-canaliculi in the vicinity of the ulcer are found densely packed with bacteria, consisting partly of *Staphylococcus pyogenes* and partly of other as yet unknown species. In corneal as in conjunctival *herpes* small vesicles develop, the coverings of which are formed from the epithelium and most superficial layers of the cornea, and which quickly become converted into ulcers. The cornea is infiltrated with small cells in the neighbourhood of the latter.

Although at the commencement of keratitis the corneal corpuscles behave passively or even undergo degeneration, at a later stage they are involved in proliferation, and thereby give rise to a tissue which serves to replace the portions destroyed. This tissue, like all young cicatricial tissue, is at first fairly rich in cells (Fig. 207, *b*); later it loses indeed a large part of its cells, but it never becomes quite like the normal corneal tissue and also remains more or less cloudy to the naked eye (*macula corneæ*). No regeneration of Bowman's membrane ever takes place. If an ulcer existed it often becomes

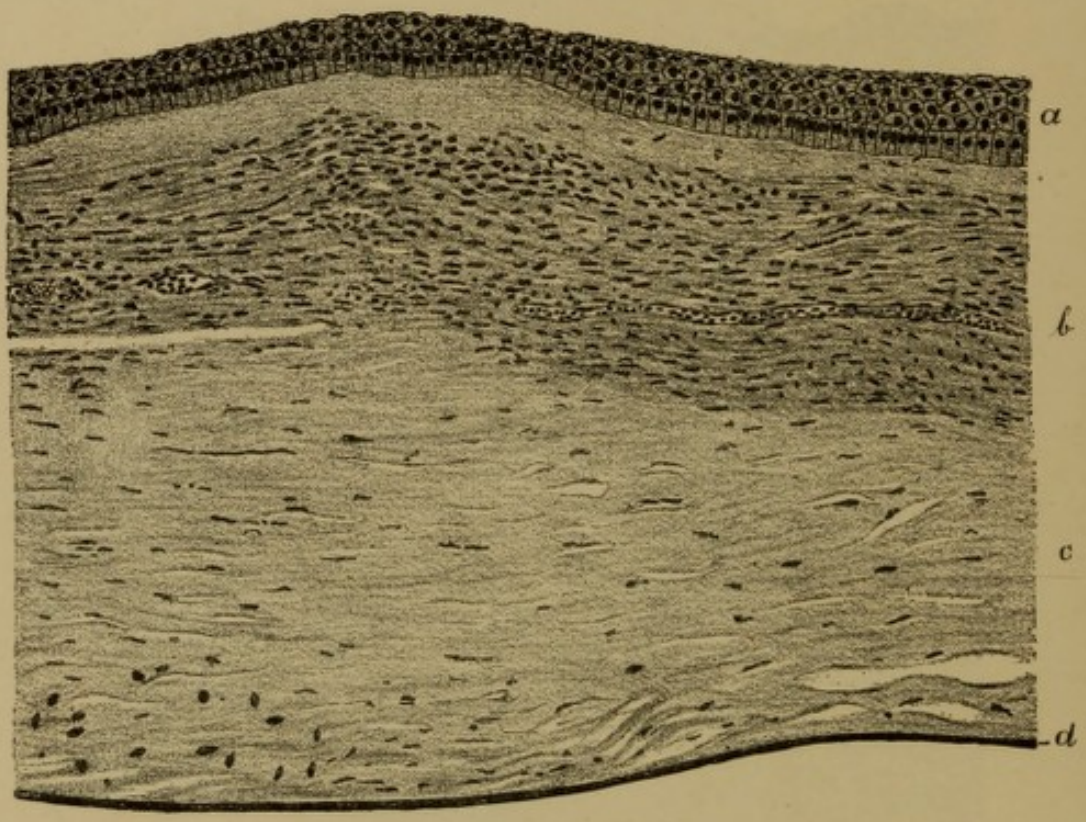

FIG. 207.—MACULA CORNEÆ. × 90. (Hæmatoxylin and eosin). *a*, Epithelium of the cornea; *b*, Cicatricial tissue still tolerably rich in cells and also containing isolated blood-vessels; *c*, Normal corneal tissue; *d*, Descemet's membrane.

skinned over by the regenerating epithelium even before the deficiency has yet been filled up by the growth of the corneal cells. In the cicatrisation of larger ulcers there is also in all cases a new formation of blood-vessels (Fig. 207, *b*), which run to the ulcer from the conjunctival limbus. They may again disappear in the subsequent course of the process, but granular brown pigment is often left behind in the scar.

New formation of blood-vessels also takes place, however, should the keratitis become more *chronic* or frequently recur. The cornea may then eventually become permeated with vessels in its entire extent, the condition being spoken of as *pannus tenuis* or *pannus*

crassus according as the vessels occupy the superficial parts only or the deeper parts as well. The vessels run a radiating course, and are always embedded in a connective tissue more or less rich in cells.

When a corneal ulcer of smaller size perforates into the anterior chamber, the iris becomes adherent, and forms a permanent attachment to the site of the perforation (*anterior synechia*, Fig. 208, *g*),

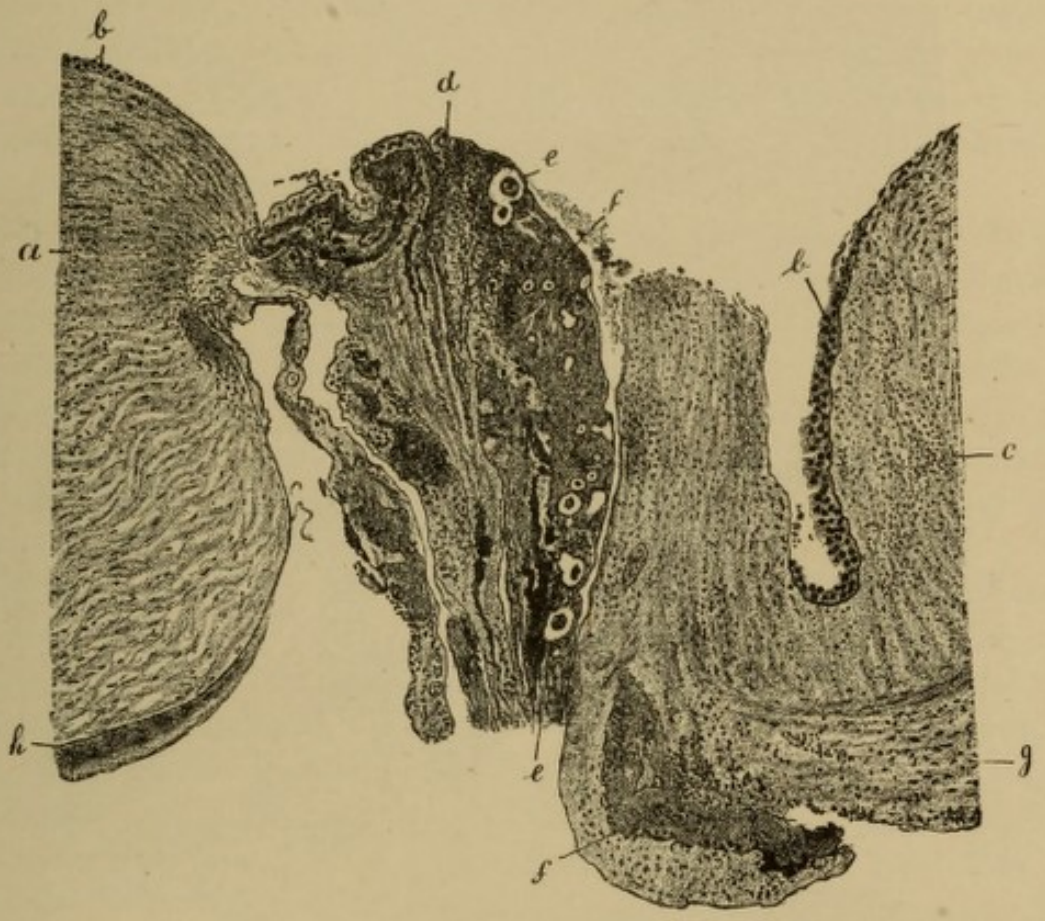

Fig. 208.—Cicatrised Perforation of the Cornea after Suppurative Keratitis and Prolapse of the Iris. × 50. (Hæmatoxylin and eosin.) *a*, Cornea; *b*, Corneal epithelium; *c*, Part of cornea thrown into folds and infiltrated with cells; *d*, Prolapsed portion of iris healed into the corneal cicatrix; *e*, Blood-vessels with sclerotic walls, in transverse section; *f*, Hæmorrhages in the iris; *g*, Iris adherent to posterior surface of cornea (anterior synechia); *h*, Membrane of Descemet.

the tissue of the iris often growing into the corneal cicatrix. If, however, a larger ulcer ruptures, the result is *prolapse of the iris*, and here also the prolapsed part (Fig. 208, *d*), whilst at the same time becoming atrophic, contracts adhesions to the corneal cicatrix, its fibres merging quite imperceptibly into the tissue of the scar. Not only do corneal cicatrices gradually become poorer in cells and firmer, but lime-salts or colloid masses may eventually be deposited in them. On the other hand, the scars resulting from perforating ulcers are sometimes protruded by the pressure of the aqueous humour, giving rise to *partial or total cicatricial staphyloma of*

the cornea. From this condition we must distinguish the *keratoglobus* or *keratoconus* [*conical cornea*] which mostly occurs as the result of a previous inflammation, and consists in a bulging outward and thinning of the entire cornea, either everywhere simultaneously or commencing in the centre.

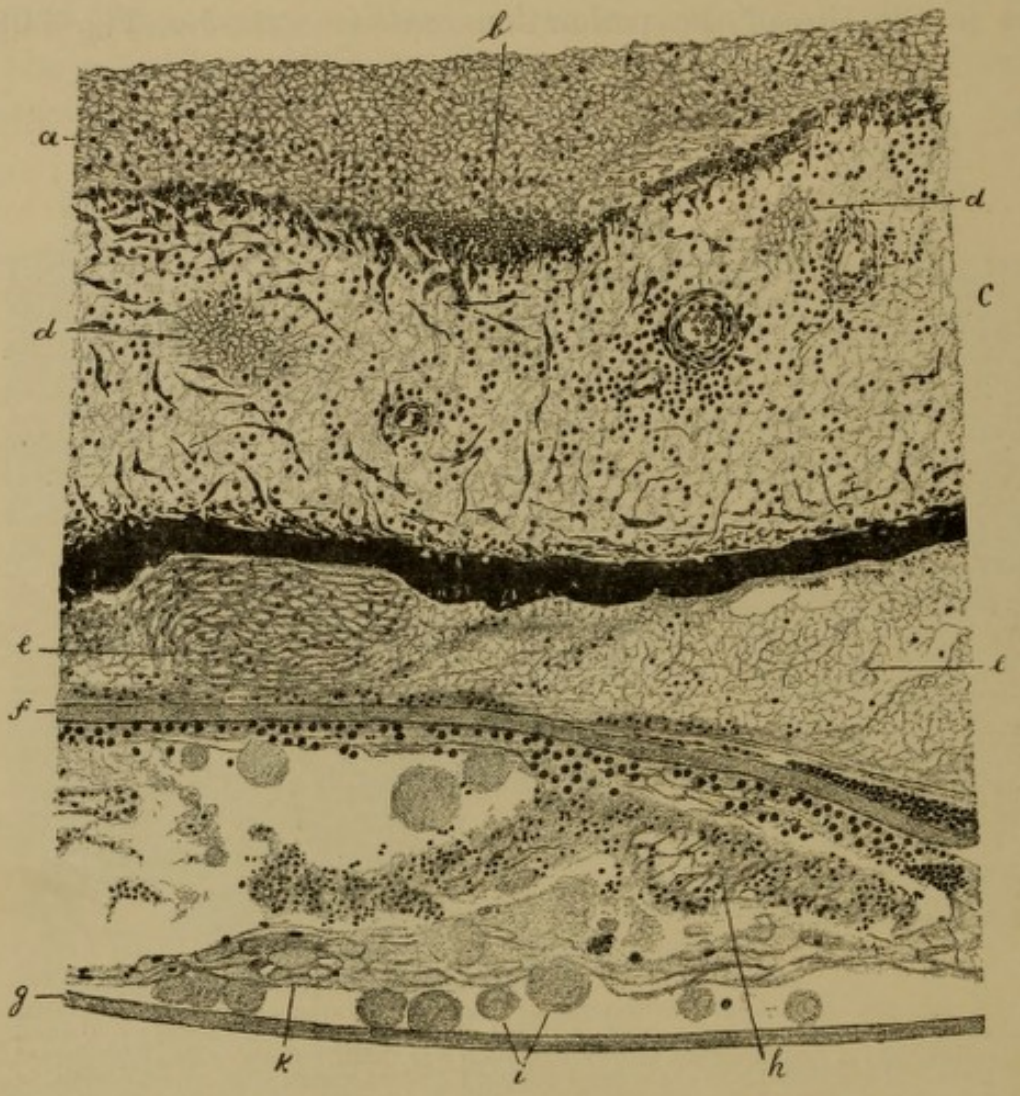

Fig. 209.—Acute Iritis with Exudation into the Anterior and Posterior Chambers following cataract extraction by flap operation. × 90. (Hæmatoxylin and eosin.) *a*, Fibrinous exudation in the anterior chamber, lying immediately upon the anterior bounding lamella of the iris; *b*, Small hæmorrhage; *c*, Iris; *d*, Delicate fibrinous network in the iris, which latter is also infiltrated with mononuclear and polynuclear round cells, especially in the immediate neighbourhood of the vessels; *e*, Fibrinous exudation in the posterior chamber, composed partly of delicate filaments and partly of somewhat thicker bands; *f*, anterior, and *g*, posterior, capsule of lens, between which are remains of the cataract, and fibrinous exudation, *h*; *i*, Spheres of Morgagni; *k*, Swollen lens-fibres in the remaining vestiges of the cataract.

Inflammation of the sclerotic, scleritis, which is much less frequent than keratitis and is usually associated with inflammation of the neighbouring parts (cornea, iris, and choroid), is characterised by small-celled infiltration of the tissue (Fig. 210, *h*), especially in the vicinity of the blood-vessels. The sub-conjunctival tissue is also frequently implicated.

3. Inflammation of the Iris, Ciliary Body, Choroid, and Vitreous Humour.—In *acute iritis* (Fig. 209), according to the degree of the inflammation, we either find mere small-celled infiltration of the tissue of the iris (sometimes only in scattered foci and in the sheaths of the vessels), or in addition to this the endothelium covering the anterior surface of the iris is raised by a fibrinous exudation, while a similar exudation, to which the pupillary margin is then adherent, is also present in both anterior and posterior chambers of the eye (*a* and *e*). Sometimes small hæmorrhages (*b*) are also observed in the tissue of the iris, whilst on the other hand the cellular infiltration in the latter may even take on the character of a purulent exudation.

Even in acute inflammations a part of the iris-pigment is destroyed, especially that in the spindle cells. In the *chronic* inflammations, however, this destruction is much more extensive (though again, on the other hand, growths of pigmented cells may occur), whilst in addition the iridal connective tissue and the sphincter pupillæ also undergo fatty degeneration and atrophy. In chronic inflammation the *pupil* may be partially or completely closed by vascular connective-tissue membranes (*atresia pupillæ*).

In *inflammation of the ciliary body, cyclitis*, the ciliary processes are found to be especially involved. If the inflammation is of a suppurative character, not only are the processes infiltrated with pus corpuscles, but there is also a collection of pus in the chambers of the eye. In other cases the inflammation has a more plastic character, *i.e.*, it leads gradually to the formation of fibrous excrescences and membranes, which extend on the one hand into the posterior chamber of the eye and to the iris, on the other into the vitreous. By their contraction not only is the iris dragged backwards, but detachment of the retina and cataract may also be caused. The inflammatory changes in the *ciliary muscle* are less marked, consisting mainly in small-celled infiltration of the interstitial connective tissue. Should the inflammation become chronic, the muscle-fibres may be destroyed by fatty degeneration.

Cyclitis frequently occurs *secondarily* as a complication of iritis or choroiditis as well as after wounds, especially those caused by foreign bodies such as metallic splinters. In the latter case cyclitis of the other eye also may follow after a variable length of time (*sympathetic ophthalmitis*), due, as is alleged, to the agency of bacteria, which are said to make their way from one eye to the other by the lymphatics of the optic nerves.

Whilst the causation of acute iritis and cyclitis by pathogenic bacteria can only be assumed provisionally, such an origin has now

been pretty certainly established for *acute choroiditis*. This occurs, that is to say, after bacterial infection of wounds and ulcers of the cornea, and also in the course of cerebro-spinal meningitis and in pyæmic processes, especially puerperal fever and acute endocarditis. In cases which occurred in the latter way it has been possible also to detect emboli of cocci in the choroidal vessels. In *acute* inflammation of the choroid, fibrinous exudation is frequently found

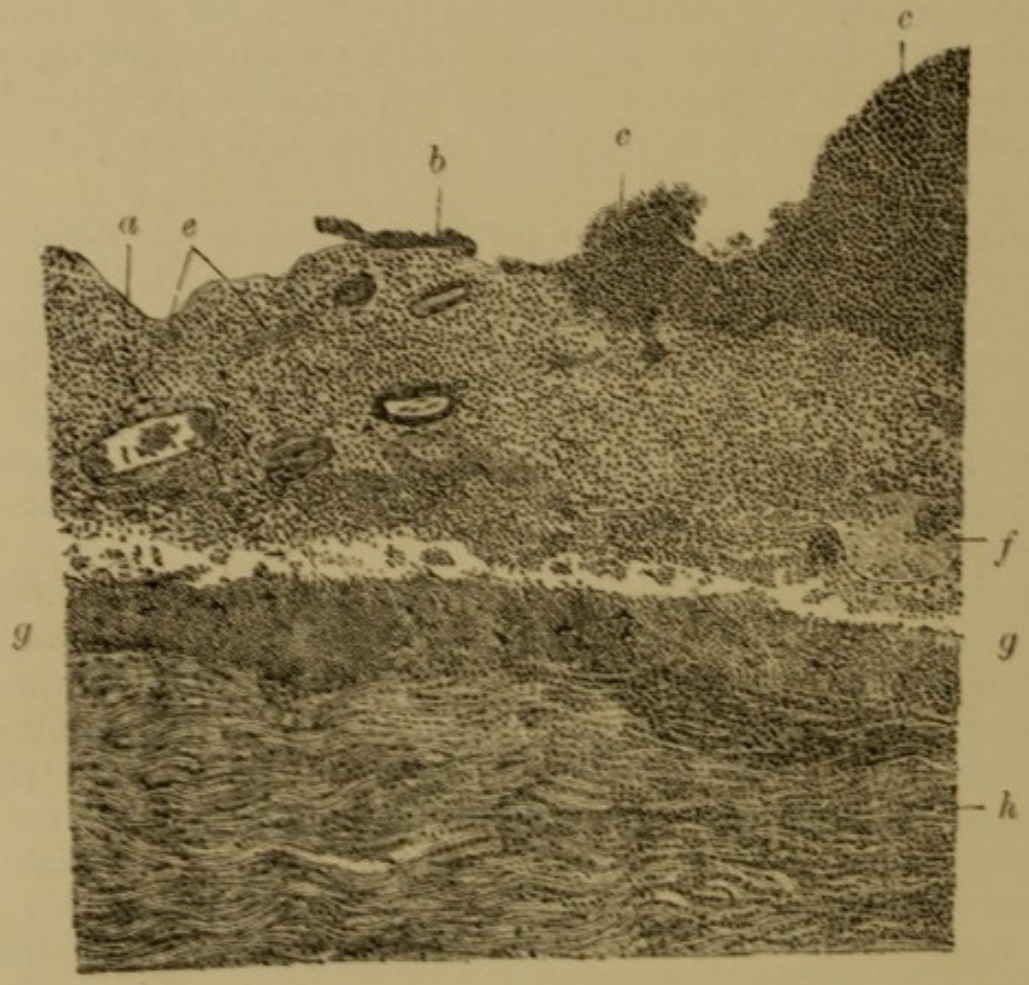

FIG. 210.—ACUTE CHOROIDITIS AND SCLERITIS IN METASTATIC PANOPHTHALMITIS. × 70. (Hæmatoxylin and eosin.) *a*, Vitreous layer of the choroid; *b*, Pigmented epithelium of retina; *c*, Purulent infiltration of the chorio-capillaris, with nodular elevations of the internal surface of the choroid; *d*, Small-celled infiltration of all three layers of the choroid; *e*, Hæmorrhages in the chorio-capillaris; *f*, dilated vein in the outer layer of the choroid; *g*, Severe hæmorrhage in the lamina suprachoroidea and lamina fusca, with detachment of the choroid from the sclerotic; *h*, Cellular infiltration of the sclerotic.

in the outer pigmented layers, in the inner layers chiefly cellular exudation. Still, a fibrinous or even a purulent exudation (Fig. 210, *c*) may sometimes be present also in the chorio-capillaris, causing a total detachment of the retina if it collects in any great quantity.

Chronic inflammation of the choroid gives rise mostly to focal products, which at the commencement consist of a vascular tissue of round or spindle cells, but later change into fibrous nodules. The latter are usually situated on the internal surface of the choroid,

and then contract adhesions with the retina or penetrate into it, the rods and cones and outer granule layer of the latter becoming for the most part destroyed, whilst the pigmented epithelium frequently begins to grow, but is in many cases transformed into a layer of colourless cells. The choroid also atrophies in the area of the nodular foci, and sometimes to such a degree that nothing is left of it but a connective tissue almost devoid of pigment. Event-

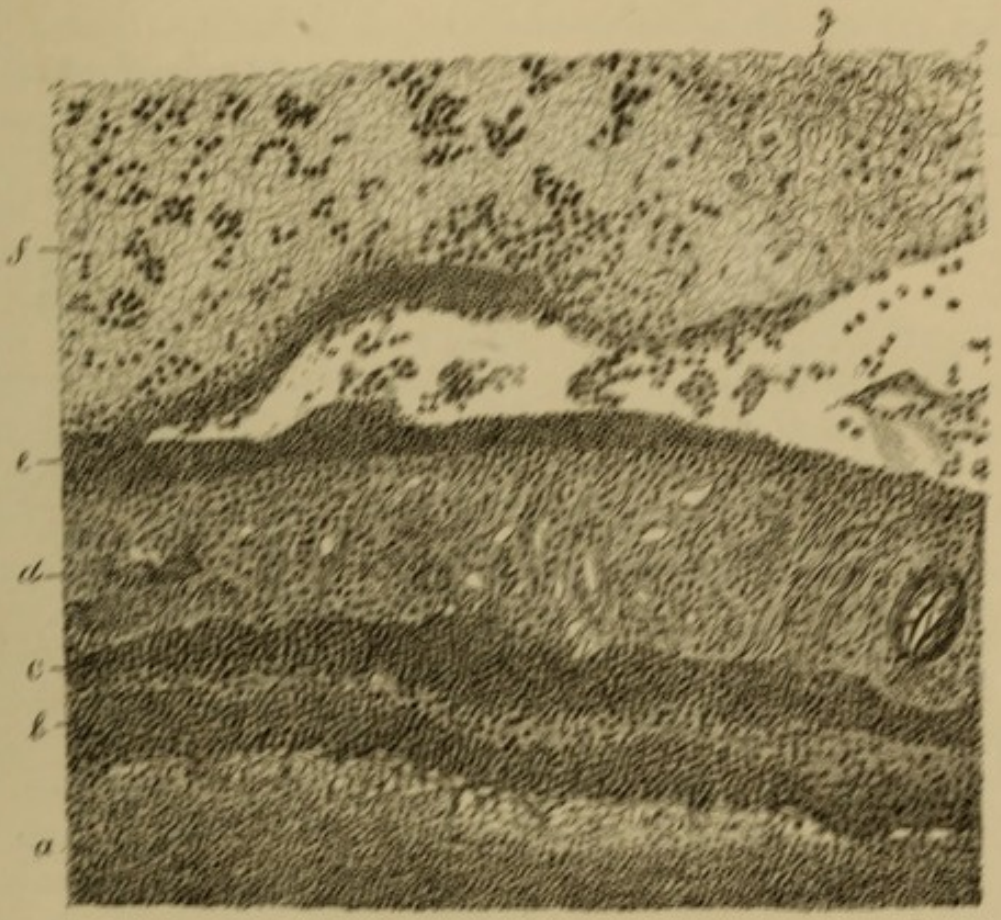

FIG. 211.—ACUTE INFLAMMATION OF THE RETINA AND VITREOUS HUMOUR IN METASTATIC PANOPHTHALMITIS. × 90. (*Weigert's modification of Gram's method.*) *a*, Collection of pus between choroid and retina, with destruction of the rods and cones of the latter; *b*, Outer, and *c*, Inner, granule layer of the retina; *d*, Hæmorrhages into the inner reticular and the ganglion-cell layers of the retina; *e*, Purulent infiltration of the nerve-fibre layer of the retina; *f*, Fibrinous exudation in the vitreous—the latter partially raised from the retina; *g*, Streptococci.

ually a formation of osseous trabeculæ or plates of spongy bone, or else merely deposits of lime, may take place in the fibrous outgrowths, especially when the choroiditis has also led to atrophy of the bulb. Besides the connective-tissue outgrowths, colloid grains, or lobulated homogeneous concentrically laminated excrescences, which may also calcify, are further found on the elastic membrane of the choroid at times.

Inflammation of the vitreous humour is practically always *secondary*, *e.g.*, as the result of a cyclitis, or in a panophthalmitis. In either case the exudation may be fibrinous (*Fig.* 211, *f*) or purulent.

4. Inflammation of the Retina.—*Acute retinitis* arises from causes similar to those of acute choroiditis, and also readily assumes a suppurative character (Fig. 211), in which case it often leads to *panophthalmitis*. In the *embolic* form of retinitis it has also been possible to recognise cocci in the blood-vessels of the retina. Amongst the *chronic inflammations* of the retina that form is of the greatest frequency and importance which is apt to occur in

FIG. 212.—ALBUMINURIC RETINITIS. × 200. (Hæmatoxylin and eosin.) *a*, Layer of rods and cones; *b*, External granule layer; *c*, External reticular layer; *d*, Internal granule layer; *e*, Internal reticular layer; *f*, Part of the ganglion-cell and nerve-fibre layers cut obliquely; *g*, Fibrinous exudation in the external reticular layer, in the form of elongated foci, by which the two granule layers are pushed widely asunder; *h*, Homogeneous masses in the external reticular layer; *i*, Small extravasations of blood in the external and internal reticular layers.

nephritis, especially in the *chronic interstitial* variety, and usually affects both eyes (*nephritic or albuminuric retinitis*). The following are the changes found in this condition:—Larger or smaller (Fig. 212, *i*) extravasations of blood, rounded or in stripes, probably the consequence of a sclerosis of the small arteries which is commonly present; small-celled perivascular infiltrations, and partly also fibrinous exudation (*g*); homogeneous globules and masses (*h*) in the external reticular layer; granule cells in the region of the macula lutea; and fatty or hyaline degeneration of the ganglion cells. In addition to

this, a chronic retinitis may also be observed in uveal inflammations (*choroido-retinitis*), in which case the process either occurs diffusely in the inner retinal layers, leading to increase in the interstitial connective tissue and atrophy of the nervous elements, or else attacks the outer layers focally and then coexists more or less with the disseminated chronic choroiditis described on pp. 410-11.

Retinitis pigmentosa, which usually affects both eyes and spreads from before backwards, is distinguished above all by the presence of abundant pigment in the wall and also in the lumen of the blood-vessels, where it lies in cells of variable shape; and furthermore, by gradually increasing thickening of the connective-tissue stroma, by sclerosis and obliteration of the blood-vessels, by progressive atrophy of the pigmented epithelium, and, at last, of all the nervous elements of the retina. Under the name of *hæmorrhagic retinitis* we describe the occurrence of retinal hæmorrhages, which are especially apt to take place in the external reticular and nerve-fibre layers in pernicious anæmia, leucæmia, degenerations of the blood-vessels, and so forth.

5. Inflammation of the Optic Nerve, Optic Neuritis.—*Inflammation of the optic papilla, papillitis*, may accompany any more intense retinitis, but especially the nephritic form. It may also, however, be the consequence of a so-called *choked disc, i.e.*, a venous stasis in the papilla such as is apt to occur when the venous return is impeded in consequence of disturbances either inside or outside the eyeball. In this case not only do we find great dilatation of the blood-vessels and small extravasations of blood in the papilla, but the nerve-fibres are also forced apart by serum, and small round cells are accumulated along the blood-vessels. Eventually hyperplasia of the interstitial connective tissue and atrophy of the nerve-fibres may result.

Inflammation of the trunk of the optic nerve either attacks the sheaths (*perineuritis*) or the nerve itself (*interstitial neuritis*). In the former case serous or fibrinous exudation is found in the intervaginal space of the nerve; in the latter, small-celled infiltration of the interstitial connective tissue, which may then lead to thickening of it and atrophy of the nerve-fibres.

6. Inflammation of the Entire Eyeball, Panophthalmitis.—*Suppurative panophthalmitis* commences in the cornea, uveal tract, or retina, and is probably always of bacterial origin. As by degrees all three coats of the eye (especially the choroid, Fig. 211, *e*), as well as the vitreous humour, become densely infiltrated with round cells, the bulb is transformed into an abscess-cavity. The pus eventually bursts out through the cornea or sclerotic, whereupon shrivelling of the bulb (*phthisis bulbi*) ensues; that is to say, the cavity of the

eye fills up with granulation tissue, which gradually changes into a partially pigmented cicatricial tissue, and may still include isolated atrophic vestiges of the coats of the eye; whilst the sclerotic is usually greatly thickened. Formation of osseous tissue, or deposit of calcareous concretions, in the interior of phthisical bulbs is not uncommon.

Glaucoma may be regarded as a chronic inflammatory morbid condition, the essential symptom of which is increase in the intra-ocular pressure. According as the eye attacked by the process was previously normal or already diseased we distinguish a *primary* and a *secondary* glaucoma, and according as the process itself occurs with or without pronounced inflammatory phenomena, an *inflammatory* and a *simple* glaucoma respectively. The *causes* of glaucoma have not yet been fully made clear. While some lay chief stress on an inflammatory tissue-growth in the neighbourhood of the canal of Schlemm, in consequence of which obliteration of the so-called spaces of Fontana and soldering of the periphery of the iris to the cornea are alleged to take place with the result of raising the intra-ocular pressure, others see the cause of the rise of pressure in a chronic choroiditis, or in an obstruction of the venæ vorticosæ by blood-platelet thrombi or proliferating endothelial cells. The most significant phenomenon resulting from the increase of pressure is *excavation or cupping of the optic papilla.* The lamina cribrosa being the weakest part of the bulbar capsule is the first to give way before the increased pressure, and this is then followed by atrophy of the nerve-fibres of the papilla. At a later period the nervous layer of the retina and the optic nerve itself are attacked by atrophy, whilst sclerosis or hyaline degeneration occurs in the blood-vessels. In the cornea there results in many cases a very transitory œdema, which manifests itself by the presence of droplets arranged in succession in rosary form between the epithelial cells, and of fissure-like cavities in the corneal substance.

7. Inflammation of the Eyelids.—*Inflammation of the margin of the lids, ciliary* (or *marginal*) *blepharitis,* may take the form of acne, eczema, or seborrhœa. In the first form of disease the focus of inflammation involving the sebaceous glands and hair-follicles is known as *hordeolum*; in the second, purulent infiltrations occur in the papillæ, which on the one hand advance into the epidermis, giving rise to minute ulcers with formation of crusts, on the other penetrate into the root-sheaths of the cilia and cause the latter to fall out.

Amongst the *inflammations of the conjunctiva* that described by some as *phlyctenular* or *lymphatic conjunctivitis,* by others as *eczema*

of the conjunctiva, is the most frequent. In this disease there form in the ocular conjunctiva, especially at the conjunctival limbus, small vesicle-like efflorescences, which consist of circumscribed subepithelial aggregations of small round cells, and soon change into minute flat ulcers. They may be present at the same time on the cornea also.

Acute catarrhal conjunctivitis is characterised by increased secretion and by small-celled infiltration of the subepithelial tissue of the conjunctiva. The secretion contains desquamated epithelial cells in a state of mucous degeneration, and leucocytes. If the latter are met with in great abundance, the secretion is said to be *blennorrhœic*.

Gonorrhœal conjunctivitis, which is most frequently observed in new-born infants (*opthalmoblennorrhœa neonatorum*), is caused by the *Gonococcus*. The tissue of the conjunctiva appears more or less densely infiltrated with leucocytes, especially in the superficial layers, and the epithelium is desquamated and replaced by a layer of pus corpuscles, which are partially laden with gonococci. The latter are restricted in their distribution in the conjunctiva to the superficial layer of the subepithelial connective tissue, in which they are arranged in rows or rounded aggregations between the bundles of fibres. The inflammation frequently extends to the cornea, and then leads to the formation of ulcers, which readily break through into the anterior chamber.

Croupous and *diphtheritic conjunctivitis*, which practically never occur except in the course of diphtheria, lead to the formation of false membranes having the same structure as those on other mucous membranes attacked by this disease. The diphtheria bacillus can be recognised constantly in them, at least at the commencement of the process, whilst in addition to this the *Streptococcus pyogenes* also effects a lodgment at a later period. In this form of conjunctivitis the cornea likewise is frequently implicated in the process (Fig. 213). Its tissue (*b*) is then not uncommonly found to be necrotic to a considerable depth, whilst the juice-canaliculi (*a*) of the superficial layers are filled with bacteria (diphtheria bacilli and streptococci), and the portions of the cornea adjacent to the necrotic tissue are infiltrated with pus cells, the nuclei of which partially show granular degeneration (*c*).

Amongst the *chronic inflammations* of the conjunctiva the most important is *trachoma* or *granular conjunctivitis*, whose limits as a morbid entity are certainly not quite stationary, some describing every hypertrophic conjunctivitis as trachoma, whereas others see the essence of the process in the existence of the so-called *trachoma-granules*. Micro-organisms, and of various kinds, have already been found repeatedly in trachoma, but whether they have a causal

import or not is absolutely uncertain. The process first attacks the palpebral conjunctiva, afterwards also the tarsus, bulbar conjunctiva, and cornea. Histologically we find not only a diffuse small-celled infiltration of the conjunctiva and subconjunctival tissue, but in addition to this, especially in the conjunctival fornices, sharply circumscribed small-celled growths resembling follicles—the so-called *trachoma-granules*. With regard to these, of course, it must not be forgotten that follicle-like structures may sometimes be present normally in the lower fornix. The epithelium is next thickened, and sometimes forms very deep depressions, between which the papillæ, enlarged and infiltrated with cells, jut forward more or less prominently. Should the epithelial depressions become closed over,

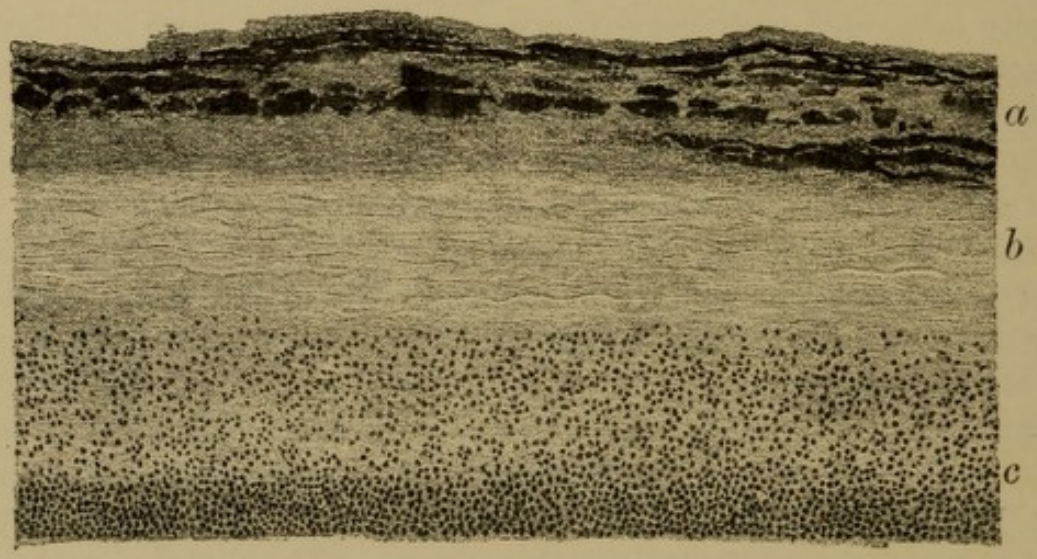

FIG. 213.—DIPHTHERITIC KERATITIS (in diphtheria of the naso-pharynx). × 265. (Weigert's modification of Gram's method.) *a*, Juice-canaliculi in the superficial parts of the cornea, filled with bacteria (diphtheria bacilli and cocci); *b*, Necrotic portion of the cornea; *c*, Posterior part of the cornea infiltrated with pus corpuscles, the nuclei of which are partly broken down into granules.

cysts are formed. The trachoma-granules may eventually change into connective tissue, and the conjunctiva in general gradually assume a cicatricial character. If now the tarsus and the Meibomian glands also atrophy, the final result is a drawing inwards of the cilia, or even the formation of an *entropion*. The cornea participates in the process by the development of a pannus, which gradually advances from the margin towards the centre.

8. Infective Granulomata, New-formations, and Parasites.—*Tuberculosis* most frequently takes the form of miliary tubercle of the choroid, an almost constant phenomenon in general acute miliary tuberculosis. Besides this, the *chalazion* should also be mentioned, which is a small tubercular new-growth in the area of the Meibomian glands, and consists of a granulation tissue composed in larger part

of epithelioid cells and in smaller part of leucocytes, in which may also be embedded discrete epithelioid-celled tubercles containing giant cells. The *syphiloma* is observed with greatest frequency in the iris, where it forms nodules perceptible with the naked eye, or at all events with the microscope, and which consist of vascularised granulation tissue. Giant cells and syphilitic disease of the vessels (p. 206) can also be made out at times in the larger nodules.

Of *tumours proper* should be mentioned the *epithelioma*, which is most frequently situated at the junction of conjunctiva and cornea; the *glioma*, which is commonly wont to occur in the retina, though only at the earliest age; and, finally, the *sarcoma*. The last is found chiefly in the choroid, when it is usually pigmented, and is composed either of spindle-cells alone or of spindle-cells and round cells. Less frequently it forms at the margin of the cornea, when its growth spreads all over the area of the latter beneath the epithelium, constituting, when it has reached a larger size, the so-called *staphyloma racemosum*.

Of *animal parasites*, *Cysticercus cellulosæ* is met with in the eye.

Methods.—The *degenerative changes* (fatty, colloid, and amyloid degeneration, calcification, etc.) may be partially examined even in *fresh preparations* after the usual methods (see Part II., Chapter I.). In other cases *hardening* is done as a rule in Müller's fluid, followed by alcohol. When the globe of the eye is immersed in its entirety, a cut should be made into its capsule at one spot, in order that the hardening fluid may be able to penetrate into the interior.

In *embedding*, if the relative positions of the individual parts are to be retained as far as possible, celloidin must be used; otherwise paraffin embedding is also admissible. For examining the degenerative process in the *optic nerve* the methods given on pp. 351-3 suffice. Otherwise the sections are stained with hæmatoxylin and eosin, or picro-lithium-carmine. For examining for *bacteria* the methods detailed in Part II., Chapter V., are to be employed.

CHAPTER XIII.

THE EAR.

(By Dr. B. Gomperz.)

I.—THE EXTERNAL EAR.

1. Diseases of the Auricle.—The morbid changes in the *skin* of the auricle are analogous to those in the skin of other parts of the body. The commoner *tumours* of the auricle, *fibroma* and *keloid* in the lobule, as well as *carcinoma*, also present no peculiarities.

The chief histological changes calling for notice are those in the *auricular cartilage*. This cartilage, normally of the reticular variety, is not at all uncommonly found in a state of *hyaline* or *mucous degeneration* in old persons, or in younger individuals reduced by exhausting diseases. In this condition the intercellular fibrous network has completely disappeared, and the cartilage capsules are no longer distinct from the interstitial substance, which latter has become hyaline and may go on to softening, usually after undergoing fibrillary cleavage. Fissures and cavities now frequently develop, which are filled with a mucinous mass and in many cases contain vascular connective tissue advancing from the perichondrium, as well as villous outgrowths on their walls. A further pathological process described as taking place in the auricle is the new formation of vessels in the otherwise non-vascular cartilage, but this only occurs in combination with hyaline degeneration or with development of enchondromata.

The name *enchondroma* is given to small nodules in the auricular cartilage, having a lobulated structure, and in the lobes of which hyaline tubes may be present similar to those in the so-called cylindroma. Instead of these tubes there are often found aggregations of cells ranged lengthwise, or a network of delicate stellate cells, which are embedded in a hyaline interstitial substance. All three changes have been spoken of as influences predisposing to the formation of *othæmatomata*—a supposition which seems confirmed by the

discovery in the latter of disintegrated portions of enchondroma and pieces of cartilage in a state of hyaline degeneration, as well as of growth of the vessels in the portions of cartilage adjoining. At the same time, however, it is certain that the aural hæmatoma may also form, as the result of injury, when the cartilage is healthy. Formation of *cysts* in the auricle has likewise been held to be connected with softening in the cartilage.

In the auricular cartilage of persons suffering from gout, nodules composed of deposited urates have been found (*tophi*). Furthermore, *calcifications* in the auricular cartilage are not rare, and, lastly, *ossification*, in which well-formed bone with medullary spaces and Haversian canals may be found, appears partly as a senile change and partly as a sequela of inflammatory processes—such, for example, as perichondritis.

2. **Inflammation of the External Auditory Meatus, Otitis externa.**—Inflammations in this situation correspond, at least in their histological details, with those in other parts of the skin. At the commencement there is dilatation both of the superficial vessels and lymphatics and of those running in the periosteal and perichondrial layers, together with emigration of white blood-cells; whilst in severer cases there may be hæmorrhages into the subcutaneous connective tissue, and later abundant infiltration with round cells, and dilatation also of the blood-vessels which pass into the bone. In the formation of hæmorrhagic vesicles, which occurs exclusively in the bony part of the meatus, we find the upper layer of the epidermis raised from the rete Malpighii by a copious effusion of blood, and the layers of cells in the rete broken up. As excitants of the *furuncular inflammation* of the meatus, *Staphylococcus pyogenes aureus* and *albus* have been found in the pus, and in one instance also *Bacillus pyocyaneus*.

In the diseased condition known as *croupous inflammation of the meatus* fibrinous exudations are present, which take the form partly of tubular deposits on the bony wall of the meatus, partly of solid plugs completely filling up its lumen. These consist of a delicate fibrinous network, in the meshes of which are entangled abundant round cells and finely-granular masses, together with flat epithelial cells and cocci. These exudations usually occur in connection with perforative inflammation of the middle ear and with furuncles, also after removal of cholesteatomata of the meatus, and in otomycosis.

Diphtheritic inflammation of the meatus, which develops in some cases by extension of a naso-pharyngeal diphtheria to the tympanic cavity, in others by infection of the meatus through a wound, is accompanied by formation of similar but firmly adherent deposits,

which are seen under the microscope to be composed of fibres felted together to form a network, and interspersed with round cells.

The products of inflammation deposited in the soft part of the external auditory meatus are for the most part reabsorbed, but may also cause thickenings in the lining of the meatus and constrictions, by the new formation of connective tissue. It is not uncommon for a growth of granulations, which may increase into polypi, to take place in the course of inflammations of the meatus; and by contact of the granulating surfaces in the narrow canal, bands, strings, and septa of connective tissue may form, and *atresia* of the meatus even may be the result. Formation of new bone under the periosteum may lead in some cases to *osseous atresia*, in others to formation of *exostoses*. Besides these, *osteomata* have also been observed, which had developed by osseous transformation of the proliferated connective tissue of the skin lining the meatus, or by ossification of polypoid tumours.

Cholesteatomatous plugs are often found in the external meatus with a perfectly intact tympanum. They are cylindrical or globular white masses, with the gloss of mother-of-pearl, and consisting of lamellæ of horny epidermis in which masses of crystals of cholestearin and fatty acid are embedded, the lamellæ being cased one inside the other like the scales of an onion. On their removal the wall of the meatus is found either lined with a delicate scar-like membrane, or granulating and covered with fibrinous exudation. The majority of these formations owe their existence to a desquamative inflammation of the lining of the meatus, marked by abundant proliferation as well as speedy cornification and shedding of the epidermis.

Little is known of the changes in the *cartilage of the meatus*. Normally of the reticular variety, there are often found in it hyaline spots and fibrillary degeneration going on to formation of cavities. Further, in elderly persons calcification and new-formation of true bone (partly as the result of perichondritis, partly as a senile change) have frequently been observed.

3. New-formations and Parasites of the External Meatus.—Amongst the *new-formations* most frequently met with in the external meatus are the *polypi*, which usually have their roots in the dermic covering of the osseous portion. The polypoid new growths situated in the cartilaginous meatus are granulation-tissue tumours proceeding from abscesses or sinuses which lead to carious or necrotic bone. The *true* polypi, *i.e.*, the polypoid tumours clothed with epithelium, consist partly of a round-celled tissue and partly of compact or loose, frequently œdematous connective tissue. Cystic cavities often exist

in them near the surface, being formed by partial adhesion of the edges of depressions. The epithelium covering these polypi is mostly horny at the surface and often pushes bulky cones towards the centre; but in the deep parts of the meatus, on the contrary, it is more delicate and is cylindrical. The vascularity of polypi of the meatus is in most cases less than that of polypi which have their root in the tympanic cavity.

Adenomata of the sebaceous glands are rather rare. They are tumours in which there is extensive new formation of glandular elements showing all the characters of normal glands.

Of *vegetable parasites, moulds* are not uncommonly present in the external meatus, both under normal and pathological conditions, and either behave quite indifferently, or else excite inflammation. They belong for the most part to the genus Aspergillus, less often to the genera Eurotium and Mucor, whilst in very rare cases representatives of still other varieties of moulds have also been found. Disregarding some quite isolated cases where the membrana tympani was permeated by the mycelium of the moulds, the latter do not penetrate into the living tissue, but merely form a coating over, or occur in the interior of, plugs of cerumen; or they rest on the surface of the denuded rete or of the corium, without entering the latter. On the other hand, the cells of the rete Malpighii may grow so as to include the deeper layers of the mycelium.

II. THE MEMBRANA TYMPANI.

4. Inflammation.—The inflammations of the tympanic membrane do not at all stages form subject-matter for histological investigation, but usually only in the more advanced grades and in membranes which have been attacked by an inflammation starting from the tympanic cavity. In the outer or cutaneous layer there speedily sets in proliferation and desquamation of the uppermost strata of the epithelium, with thickening of the rete Malpighii and especially of the cutaneous and subcutaneous tissue, the latter of which is seen to be infiltrated with round cells and traversed by dilated vessels filled to distension with blood. The inner or mucous layer shows the like changes together with dilatation of the lymphatics, so that the thickness of the tympanic membrane is many times increased. The substantia propria of the latter, however, is found unchanged in moderate degrees of inflammation, and it is only in more intense degrees that its fibres appear thickened, swollen, and separated into bundles by the deposit in its substance of nests of round cells, which, with further increase in the intensity

of the process, also break down into masses (Fig. 214). Micro-organisms, which are the specific excitants of the inflammation, may be found in all the layers, those demonstrated up to the present being *Bacillus pneumoniæ* and *Staphylococcus pyogenes aureus*.

The highest degrees of inflammation lead to the formation of hæmorrhagic vesicles on the tympanic membrane, owing to hæmorrhage between the cutis and epidermis; to the development of abscesses, sometimes in all the layers, sometimes only between cutis and epidermis; and finally to *perforation of the membrane* by necrotic breaking down of circumscribed patches, in which latter

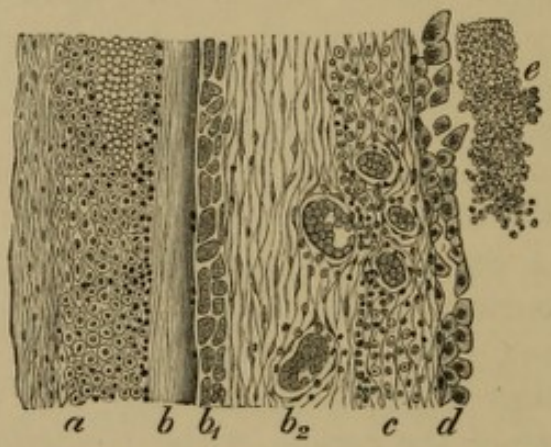

FIG. 214.—RADIAL SECTION OF A TYMPANIC MEMBRANE IN ACUTE SUPPURATIVE OTITIS MEDIA. × 440. (Alum cochineal.) *a*, Thickened epidermic layer, partially infiltrated with round cells and red corpuscles; *b*, Part of the substantia propria remaining intact; b_1, Radial fibres of substantia propria broken down into masses; b_2, Proliferation of the connective-tissue cells of the substantia propria; *c*, Mucous layer of membrana tympani, with hyperæmia and small-celled infiltration; *d*, Epithelium of mucous membrane becoming loosened and cast off; *e*, Pus lying upon the latter.

process the inflammatory excitants are also in every case concerned, having wandered into the tissue and multiplying there. In sections through the membrane which include the edge of the perforation, the substantia propria is found in acute cases to be projecting beyond the dermic and mucous layers, and to be fibrillated, the apices of the fibres being broken down into fine granules. In old perforations, on the other hand, the substantia propria is usually turned inwards and skinned over by the regenerating rete Malpighii. In the course of those inflammations the apertures may close, or else may enlarge and lead to almost complete destruction of the membrana tympani, which takes place with especial rapidity in the otitis of scarlatina. After the arrest of the inflammation, complete restoration to the normal condition is no rarity. More frequently, however, there are left thickenings of all the layers, increase in the bulk of the epidermic layer, augmentation of the submucous and subcutaneous connective tissue, varicose dilatations of the lymphatics, and deposit of little masses of fat in the epithelium of the mucosa

and in the fibres of the substantia propria. On the *outer surface* of the membrane also there remain, as residua of chronic inflammations, villi measuring 0·037 to 0·25 mm. in length and 0·045 mm. in breadth, which are seen to be composed of fibrillated connective tissue with a capillary loop and covered sometimes with cylindrical and sometimes with squamous epithelium. On the *inner surface* of the membrana tympani similar changes of the mucous membrane of the middle ear are often found as the result of chronic inflammation, and are described as *polypoid hypertrophy*. In this condition we have polypi of extraordinary minuteness, not more than 1 mm. in length, connected with the mucous membrane by a stalk or by a broad bridge, and which always originate in the subepithelial layer and contain abundant lymphoid cells in a connective-tissue network.

In the tympanic membranes of ears which have been demonstrably the seat of chronic inflammation a thick layer of finely fibrillated wavy connective tissue may often be observed, replacing the broad band-like radial fibres of the substantia propria, with their glassy homogeneous appearance. By deposit of lime-salts in inflammatory foci plate-like patches of *calcification* may form in the membrane, involving merely any one of the layers, or two, or all of them. These patches take a particularly deep stain, and contain calcium carbonate and phosphate in the form partly of dust or granules, and partly of crystals. They also contain black or blackish-brown pigment, which is accumulated in stripes or rounded clusters, or in stellate and spindle-shaped cells. Only rarely does the entire membrane undergo calcification. Bone-corpuscles with numerous fine processes have also been met with in the tissue of the tympanic membrane, but not as yet Haversian canals and systems of lamellæ such as exist in normal bone.

Perforations of the membrana tympani, when they are small and when the inflammatory process has lasted only a short time, may heal up without leaving a trace. They may, however, persist for life independently of their size, of which fact an explanation has been discovered in a growth of the epidermic layer to the tympanic side of the membrane. Too strong traction by the tensor tympani, involving increased tension of the membrane and therewith less favourable nutritive conditions, may also participate. In many cases the apertures heal with formation of distinct cicatrices, which mostly consist of a dermic and a mucous layer having a scanty amount of connective tissue interposed between them, whilst the substantia propria is restored only in the rarest cases (Fig. 215).

5. Infective Granulomata and New-formations.—In *tuberculosis* of

the middle ear the tympanic membrane is implicated almost as a rule. At the earliest stages miliary tubercles infiltrate the mucous layer, and soon not only does the mucous membrane over them ulcerate, but, as the tubercle bacilli wander outwards through the substantia propria, destruction of the entire membrane is in most cases brought about. Its disintegration may be complete within a few days.

New-formations of the tympanic membrane, apart from polypi, are rather rare. Usually the membrane merely shares in tumours of the meatus or tympanic cavity, or the tumours originate in the handle of the malleus. The *polypi* which arise from the membrane may have their root in any of its layers. They are chiefly soft

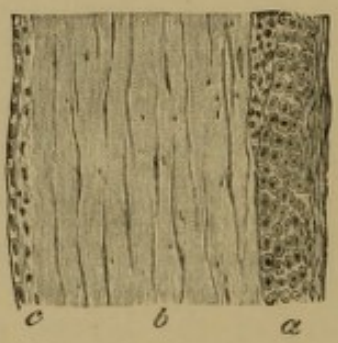

FIG. 215.—RADIAL SECTION THROUGH A CICATRIX OF THE TYMPANIC MEMBRANE. × 440. (Hæmatoxylin and eosin.) *a*, Epidermic layer; *b*, Regenerated substantia propria; *c*, Layer of mucous membrane.

fibromata, which are marked by their peculiar benignity and by the ease with which they can be made to shrivel up. The cause of the latter has been found to be growth of the endothelium in the vessels supplying them, leading to obliteration.

The so-called *pearl-formations* on the tympanic membrane consist of brightly-shining white globules in the epidermic layer of the size of millet-seed, which are usually multiple—as many as eight may be situated on the membrane—and are composed either of horny epithelial cells only, or of cholestearin crystals and molecular detritus. Genuine *cholesteatomata* in the substance of the membrana have also been described. The majority of the cholesteatomatous formations observed in the membrana may be considered connected with the occurrence of growths of the Malpighian layer. Cones grow from the latter into the deeper parts, and may there become constricted off and then undergo horny transformation.

III. THE MIDDLE EAR.

6. Diseases of the Middle Ear.—The mucous membrane of the middle ear, which, beginning from the Eustachian tube, forms a

continuous lining for all the cavities of this section, is the structure primarily attacked by the excitants of inflammation, the cartilaginous and bony walls beneath it only becoming affected secondarily. The morbid conditions come into existence either by continuity, extending from the naso-pharyngeal mucous membrane to that of the Eustachian tube, and thence into the tympanic cavity; or in consequence of the entrance of specific micro-organisms into the tympanum through the *canal* of the Eustachian tube. Less commonly they develop owing to access of infective germs by way of the circulation or from the external meatus.

7. Diseases of the Eustachian Tube.—In the *cartilage* of the tube *calcification* and *ossification* may take place as sequelæ of long-protracted disorders of nutrition and inflammations. The presence of fibrous instead of hyaline cartilage should probably not be regarded as pathological.

All *inflammations* in the mucous membrane of the naso-pharynx may spread to that of the Eustachian tube by extension through the pharyngeal orifice of the latter, inducing great congestion of the vessels, as well as multiplication of the lymphoid cells (which are present in abundance in the mucous membrane even under normal circumstances), and also small-celled infiltration of the submucosa. The epithelial layer at the same time becomes thickened and shows partly fatty degeneration and partly desquamation of its cellular elements. As the process runs its course, thickening or condensation of the submucous connective tissue often occurs, resulting in constrictions of the lumen of the tube; though *widening* of the lumen may take place, owing to shrinkage of the connective tissue, in which case, the ducts of the mucous glands being also compressed, dilatation and atrophy, and finally complete destruction, of the glandular cavities are found. In cases of *chronic* diffuse inflammation the normal ciliated cylindrical is changed into a stratified squamous epithelium, infiltrated with droplets of fat.

In *tuberculosis*, tubercles with giant cells and tubercle bacilli have often been found in the mucous membrane of the bony, more rarely of the cartilaginous, part of the tube. Of *new-formations*, *polypi* of the mucous membrane have been recognised in the tube; and in carcinoma of the tongue and upper jaw, *cancerous nodules* have been observed in the membranous part and in the vicinity of the cartilage.

8. Inflammation of the Tympanic Cavity, Otitis Media.—In inflammations of the *mucous membrane* the subepithelial layer is the part most extensively affected, whilst the periosteal layer does not show itself implicated until later. *Acute* inflammations are accompanied

by dilatation of the vessels, by small extravasations of blood in the vicinity of the latter, and by serous infiltration of the subepithelial layer. In their further course we find round-celled infiltration of this layer and then also of the entire mucous membrane, and in many cases outpouring of a fibrinous exudation into the tissue of the latter and upon its surface. The epithelial layer is thickened by proliferation of the basal stratum, and partially undergoing desquamation; and lastly a great increase takes place in the thickness of the mucosa in consequence of abundant formation of cells in its tissue, in which no stroma can any longer be recognised. At this stage the epithelium desquamates in its greater extent.

The *contents* of the tympanic cavity, when the inflammation is of slight degree, consist of a serous or mucous fluid containing but few cells. In more intense inflammation, however, this fluid is at first rich in red corpuscles, but later contains chiefly pus cells, desquamated epithelial elements, and the specific bacteria. Again, in particularly violent inflammation, and in Bright's disease, scurvy, morbus maculosus Werlhoffii, leucæmia, etc., the exudation may have a pronounced hæmorrhagic character. Hence, according to the composition of the secretion, we speak of a *catarrhal*, a *suppurative*, or a *hæmorrhagic otitis media*. The *suppurative* variety is distinguished by the speedy occurrence of perforation of the membrana tympani, the histological details of which have already been discussed above.

The following are the *pathogenic micro-organisms* which have been demonstrated up to the present in the purulent secretion of acute suppurative otitis media:—*Bacillus* and *Diplococcus pneumoniæ*, *Streptococcus pyogenes*, *Staphylococcus pyogenes albus* and *aureus*, *Micrococcus tetragenus*, *Bacillus pyocyaneus*, and the thrush-fungus. In the tissue of the mucous membrane, however, only *Bacillus pneumoniæ* and the pyogenic staphylococci and streptococci have hitherto been found.

Inflammations of the mucous membrane become especially important should they extend to the structures which it clothes, viz., the membrana tympani, auditory ossicles, fenestræ of the labyrinth, and bony walls of the tympanum. As the mucous membrane of the tympanic cavity subserves at the same time the function of periosteum to the bone covered by it, its inflammations, by extending to the nutrient vessels of the bone, often produce as sequelæ rarefying osteitis, caries, and necrosis. In such cases the Haversian canals and medullary spaces are found to be widened, the vessels thrombosed, and the tissues surrounding them in a state of round-celled infiltration. Penetration of pathogenic bacteria even into the bone-corpuscles has also been observed. Subsequently the spaces just mentioned are seen to be filled with granulation tissue,

which in particular causes rapid solution of the delicate auditory ossicles; whilst Howship's lacunæ with osteoclasts are everywhere found. From extension of the inflammation to the ligamentous apparatus by which the auditory ossicles are attached to each other and to the walls of the tympanum, there results destruction, or, after they have become loosened, falling out, of the incus and malleus, less readily of the stapes. Where there is excessive growth of the mucous membrane covering the auditory ossicles, polypoid tumours may form, and vestiges of the ossicles are often found unattached in the tympanic cavity, embedded in these tumours.

In the niches of the fenestra ovalis and fenestra rotunda there also occurs cellular infiltration of the delicate fibres so frequently present, or purulent or fibrinous exudation in the meshwork formed by them; and the conduction of sound is greatly interfered with by the resulting new formation of connective tissue. It may also be mentioned that the *chorda tympani* probably always suffers in suppurative otitis media. Thus we find the sheath and the septa passing therefrom into the substance of the nerve infiltrated with pus cells, which may accumulate in such quantities that the nerve-fibres are compressed. In more intense degrees of inflammation the chorda is destroyed over considerable tracts.

The *catarrhal* forms of *chronic* inflammation are marked by the gradual formation and shrinkage of new connective tissue in the mucous membrane and ligamentous apparatus of the tympanic cavity, whilst little papillary wrinklings of the surface, and cystic formations due to adhesion between such papillæ, have often been observed. The serous or mucous secretion, usually of a yellowish colour, contains scanty epithelial cells in a state of mucous or fatty degeneration, or isolated white corpuscles.

In the forms known under the name of *sclerosing catarrh* there is likewise found a new formation of connective tissue in the mucosa, especially in its periosteal layer, which new formation however restricts itself to circumscribed portions of the tympanic cavity, especially the articulations of the auditory ossicles and above all the stapedio-vestibular articulation. In these forms deposition of lime-salts in the ligamentous apparatus of the joints and ossification follow with especial frequency.

In the *chronic suppurative inflammations* the mucous membrane undergoes the most deep-reaching changes. The increase in thickness due to round-celled infiltration and partial new formation of connective tissue exceeds what is seen in acute inflammations so far that the lumen of the tympanum may be almost completely abolished. At such stages the mucous membrane shows itself transformed into a

dense granulation tissue, the epithelium of which in many cases remains in good preservation, retaining its cylindrical and ciliated form, whilst in other cases it undergoes fatty degeneration, and in others again is enormously thickened and has lost its cylindrical character owing to desquamation of its uppermost layers. Networks of lymphatics in a state of varicose dilatation, as well as cystoid cavities, are frequently met with in the subepithelial layer. Excessive growth of the cushion of granulation tissue leads to excrescences which make their way into the meatus through the apertures existing in the tympanic membrane, and are there found as polypi.

As regards the *terminations* of tympanic inflammation, it is quite possible for perfect recovery to take place in acute cases which run their course rapidly. But in the case of such as attained a high degree of intensity, or lasted a longer time, there result permanent changes in all layers of the mucous membrane. The suppurative inflammations, when they heal, lead to changes similar to those in chronic catarrh and sclerosis, but with the differences, that the new formation of connective tissue is much more considerable, and the destruction of the newly-formed blood-vessels much more extensive, and that subsequent calcifications, which affect chiefly the periosteal layer, are usually more widespread and penetrate deeper. Ossification of the membrane closing the fenestra rotunda has also been several times observed as the result of suppurative inflammation (in leucæmia and osteomyelitis). In rare cases, *e.g.*, in leucæmia, the new formation of connective tissue may take place very rapidly, and lead to obliteration of the tympanic cavity.

Changes of greater importance occur when the epidermic covering of the membrana tympani grows into the tympanic cavity through perforations, as the result of which the lining of the tympanum loses its character of mucous membrane, and changes into a dermic layer having a well-formed rete Malpighii covered with horny epithelial cells. This change most frequently affects the upper segment of the tympanic cavity (into which the epidermis can pass through apertures in Shrapnel's membrane), and the mastoid antrum. Should inflammation occur, whether it be acute or chronic, this dermis will shed lamellæ of epithelium, which become encased one inside the other like the scales of an onion, and may at last completely fill up the tympanic cavity, including its upper segment, and the antrum.[1]

[1] The supposition (which is certainly authorised) may also be borne in mind here, that the advance of the epidermis to the tympanic mucous membrane may give the first impulse to the formation of primary carcinoma of the tympanic cavity.

In such a manner are formed collections to which the name *cholesteatoma* has been given. They consist principally of polygonal cells, partly nucleated and partly non-nucleated, which far surpass the cells of the epidermis in size, and between which are found fat-droplets. In addition to these they are partly composed of embedded

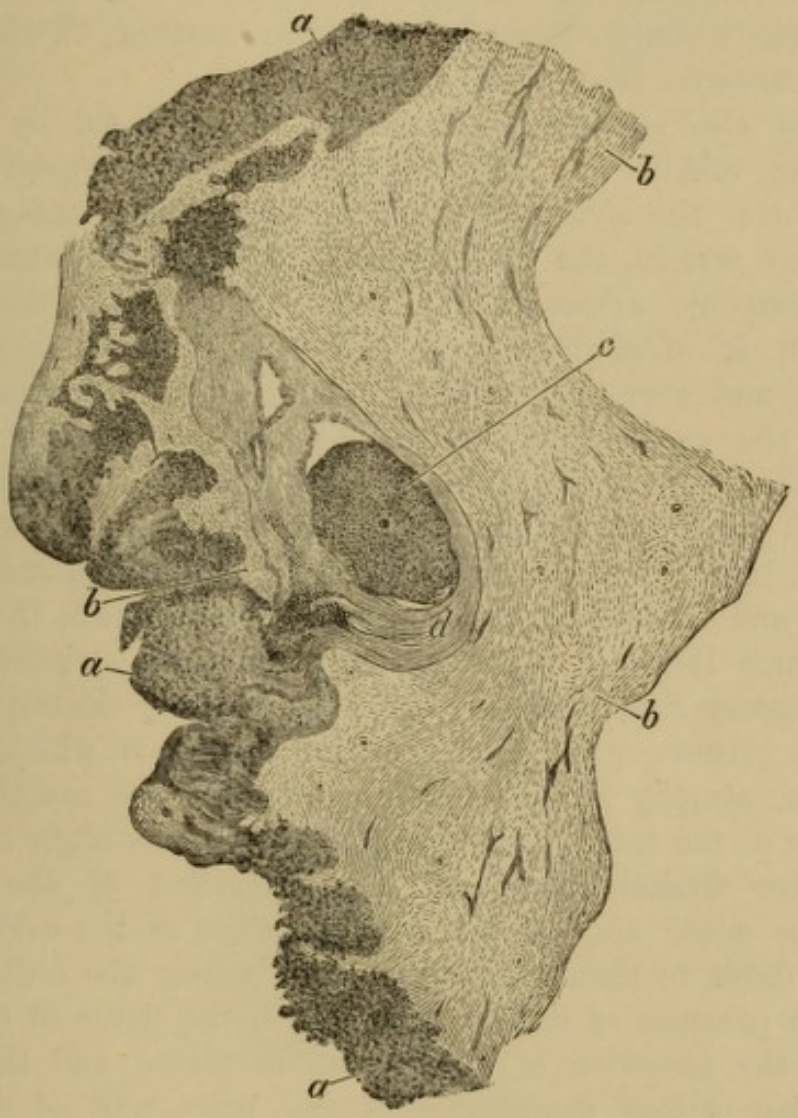

FIG. 216.—FRONTAL VERTICAL SECTION THROUGH THE INTERNAL WALL OF THE TYMPANUM IN THE REGION OF THE AQUEDUCT OF FALLOPIUS, in tubercular inflammation of the Middle Ear. × 25. (Hæmatoxylin and eosin.) *a*, Mucous membrane of the internal wall of the tympanum, transformed into caseating granulation tissue; *b*, Bone; *c*, Facial nerve, infiltrated with round cells; *d*, Very greatly thickened sheath of the facial nerve, broken through by round-celled tissue in places.

cholestearin crystals, and sometimes elongated giant cells of irregular shape and extraordinary size, having many large nuclei, are contained in them. In the central parts, which are usually broken down into crumbling masses, there can in most cases be recognised, besides the formed constituents mentioned, detritus, micro-organisms, crystals of margaric acid, or, though but very rarely, pus-corpuscles. The cones of epidermis which often push into the deeper parts from the

above-mentioned rete Malpighii, may grow into the bone along the nutrient vessels with the bundles of connective tissue, and lead to widening of the Haversian canals. The osseous substance of the auditory ossicles is also worn away or permeated by the cones of the rete, should the epidermic transformation extend to the mucous membrane covering them. As growth advances the cholesteatomata readily break through towards the outer surface of the mastoid process, or towards the cranial cavity.

Here may also be mentioned the changes induced by inflammations of the middle ear in the *aqueduct of Fallopius* where it extends above the fenestra ovalis, and in the *tensor tympani and stapedius muscles*, the bony sheaths of which likewise are lined with the tympanic mucosa. In the aqueduct, when the tympanic inflammation is of slighter degree, the nerve-sheath alone undergoes serous and round-celled infiltration. Only in intense inflammation of the mucosa does cellular infiltration of the connective tissue in the nerve (Fig. 216, *c*) take place with osteitis of the canal itself, and finally suppurative destruction of the former. In the muscles there is found in acute cases round-celled infiltration of the sheaths and delicate connective-tissue septa between the primitive bundles, which latter finally lose their transverse striation, undergo granular degeneration, and may even be entirely destroyed by the suppurative process. In middle-ear inflammations which have run their course, atrophy or waxy degeneration of the muscle bundles, with growth of the interstitial connective tissue, has often been found.

9. Infective Granulomata and New-formations of the Tympanic Cavity.—The acute and chronic inflammations of the middle ear in *tuberculosis* differ in their histological details from the ordinary forms only by the presence of miliary tubercles in the tissue of the mucous membrane, the caseation of the mucosa in places, and the more or less extensive carious destruction of the bony wall of the cavum tympani. The conditions which have been found in *syphilis* are partly changes in the vessels of the tympanic cavity (syphilitic vasculitis, p. 206), partly small bony deposits on the promontory.

Polypi are amongst the most frequent *new-formations* in the tympanum, and consist in most cases of a more or less vascular round-celled tissue. Next in frequency to these round-celled polypi come the *fibrous* varieties, into which the former may pass by an organisation of the granulation tissue, which begins along the vessels in the central parts of the tumours. Less common are the *cavernous* polypi, which develop out of the two first-named forms when the new formation of vessels prevails at the expense of the interstitial substance; whilst the *myxomatous* polypi are the rarest of all.

The epithelium of the small polypi is mostly cylindrical and stratified, and only passes into a stratified squamous form when the tumours grow further into the external meatus. If we then examine such polypi from the root to the apex of the portion lying in the meatus, we find in the first place a stratified ciliated epithelium, then a stratified cylindrical epithelium without cilia, which gradually becomes cubical, and finally passes into a stratified

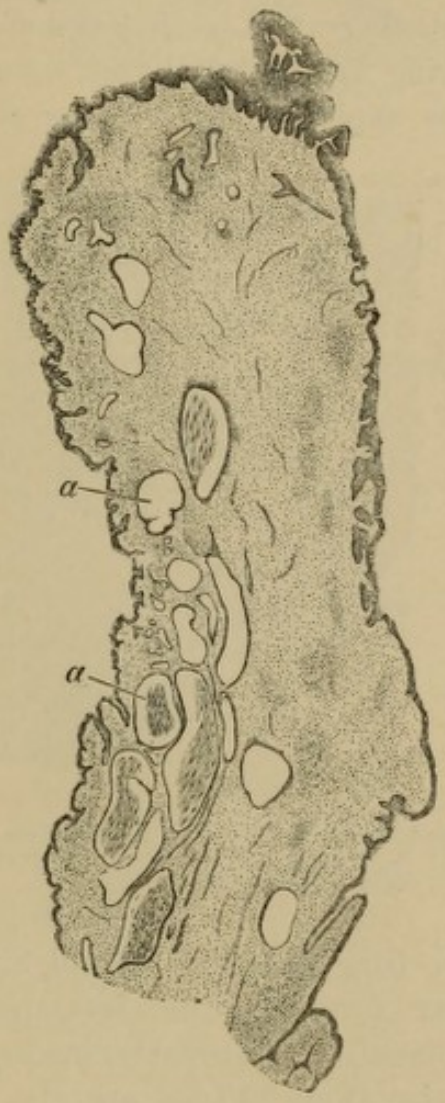

FIG. 217.—LONGITUDINAL SECTION OF A CYSTIC POLYPUS OF THE TYMPANIC CAVITY, with papillary surface. × 12. (Alum cochineal.) *a*, Cysts.

squamous epithelium. This, becoming considerably thickened in its lower layers, may assume the form of a rete Malpighii, sending into the substance of the polypi cones which readily undergo horny transformation. In the tubular depressions, which have often been taken for glands, the epithelium however remains mostly of the stratified cylindrical variety and is also provided with cilia.

The surface of the polypi is smooth only in the rarest instances; usually it recalls the surface of a papilloma (Fig. 217), and the

strangest forms may develop owing to the presence of deep indentations, as well as to secondary and tertiary formation of papillæ. A lobule often grows to a smooth polypus of larger size and usually fibrous in structure, whilst the papillary excrescences remaining at its base preserve the type of granulation tissue. Frequently in the centres of round-celled polypi are found interspersed groups or entire strata of horny epidermic cells (Fig. 218, *b*), as well as a large-meshed stroma in which such cells had existed at an earlier period. These so-called *central cholesteatomata*, which are chiefly found in polypi growing from the upper segment of the tympanic cavity, may mostly be explained as sections of cornified cones sent

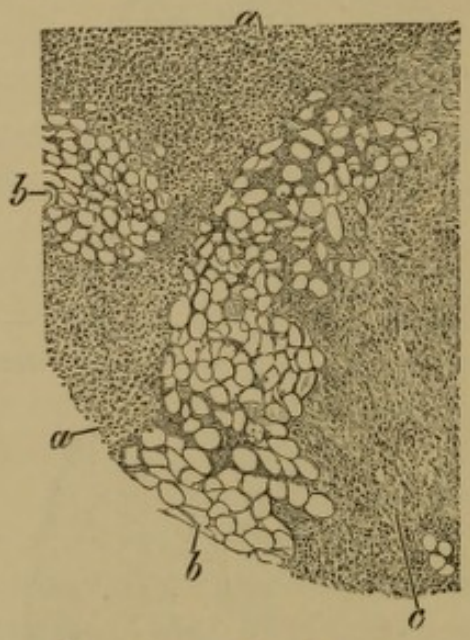

FIG. 218.—TRANSVERSE SECTION THROUGH A POLYPUS OF THE TYMPANIC CAVITY. × 65. (Alum cochineal.) *a*, Round-celled tissue; *b*, Horny epidermic cells (so-called central cholesteatoma); *c*, Spindle-celled tissue.

into the deeper parts from the rete Malpighii. Not uncommonly, however, the irregular form of the interspersed aggregations of cells renders this explanation apparently inadequate.

Cysts of variable size (Fig. 217, *a*) are also found in polypi, the formation of which is to be ascribed to the adhesion of the apices of adjacent papillary outgrowths, as well as to closure and dilatation of the tubular depressions already mentioned above. Enlargement may take place by disappearance of the septa of neighbouring cysts. Their epithelium is mostly cylindrical, often ciliated, but considerable tracts of it are sometimes desquamated. It is not uncommon to find in the interior of cysts peculiarly-formed cellular structures which certainly owe their origin to the epithelial layer. In the first place there are round finely granular cells with a diameter of as much as 0·1 mm. and nuclei measuring up to 1 μ

in breadth. Many of these cells bear either one or two spine-like processes, homogeneous and glassy, and measuring up to 0·04 mm. in length (Fig. 219); others are branched in a stellate manner or

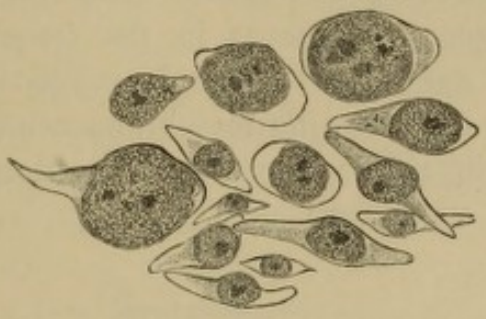

Fig. 219.—Cells from Cyst in a Polypus of the Tympanic Cavity. × 440. (Alum cochineal.)

fringed with cilia. Furthermore, fibres of a glassy clearness form in cysts, often filling them, but having no organic connection with their walls. These fibres show a parallel stratification, are interspersed with scanty nuclei, and are not unlike the tissue of tendons, though merely epithelial products (Fig. 220).

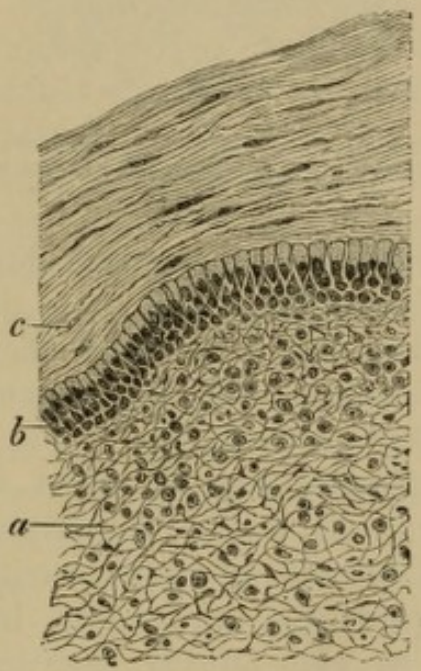

Fig. 220.—From the Wall of a Cyst in the Polypus of the Tympanic Cavity shown in Fig. 217. × 440. (Alum cochineal.) *a*, Tissue of the polypus; *b*, Stratified cylindrical epithelium; *c*, Fibres in the interior of the cyst, resembling connective tissue.

The connective tissue of which *fibrous polypi* are composed is but seldom dense; usually it is œdematous, owing to interference with the return of the blood in consequence of compression of the tumour by the wall of the meatus. The denser polypi consist of wavy connective tissue with scanty cells, which is arranged in densely fibrous bands especially along the blood-vessels. In the œdematous

polypi is seen a very delicate network of connective-tissue fibrils running a wavy course, at the nodal points of which lie round, spindle-shaped, and stellate cells (Fig. 221).

The *cholesteatomata* (*margaritomata, pearl-tumours*) which often occur as true heteroplastic tumours in the *temporal bone* correspond in their histological details with the desquamative products already described (p. 429). An investing membrane connected with the bone has been made out in them, from the rete Malpighii of which the cornifying epithelial layers are shed.

Fig. 221.—From a Fibrous Polypus of the Tympanic Mucous Membrane, composed of œdematous connective tissue. × 440. (Alum cochineal.)

Sarcomata and *carcinomata* in some cases develop primarily in the tympanic cavity, in others grow into it from the neighbouring structures. A *psammoma* has also been observed, which had penetrated into the tympanic cavity from that of the cranium after the tegmen tympani had been broken through.

10. Diseases of the Mastoid Process.—Most of the morbid conditions of this segment of the middle ear develop in connection with pathological processes in the tympanic cavity. In *inflammatory* changes the same appearances are present in the muco-periosteal lining of the air-cells as were already described in the case of the tympanic mucous membrane, with the addition only of abundant desquamation of the flat epithelial cells. In acute inflammations we find the air-containing lumen of the mastoid cells sometimes narrowed, and sometimes filled up with pus cells, fibrinous exudation or by abundant growth of the tissue of the mucous membrane. The thin bony septa then undergo liquefaction by rarefying osteitis very rapidly and in large numbers. As the inflammation subsides, new formation of connective tissue results, or eburnation by the development of compact osseous tissue on the old bony trabeculæ.

In *tuberculosis*, caseation of the mucous membrane is found, whilst the underlying tissue is evenly infiltrated with miliary tubercles, by the growth of which towards the bone caries is set up. The granulations which here fill the lumen of the air-cells and have replaced the bone are also frequently found caseated. *New-formations* are very rare in the mastoid process. *Osteomata* have been observed taking origin not only from the periosteum but from the diploe. In the former case they consist of compact osseous tissue with scanty vessels. Further, the *cholesteatomata*, which have already been more particularly dealt with, are frequent, *dermoid cysts* rarer. *Sarcomata* and *carcinomata* may form primarily in the mastoid process.

IV. THE INTERNAL EAR OR LABYRINTH.

11. Congestion, Hæmorrhage, Inflammation, Atrophy, and New Growths.—Most morbid conditions of the labyrinth arise as the result of inflammations of the middle ear, which extend from the tympanic mucous membrane to the membranous structures of the labyrinth through the fenestra rotunda or ovalis or the bony wall, or by way of the vessels anastomosing between the tympanic mucous membrane and the endosteum of the labyrinth.[1] These conditions include the inflammations which are set up in cerebro-spinal meningitis by propagation through the internal auditory meatus or aquæductus cochleæ, and lastly the inflammations due to entrance, by way of the circulation, of the specific morbid excitants in diphtheria, measles, syphilis, tuberculosis, and osteomyelitis, and the inflammations which occur in leucæmia.

Hyperæmia of the membranous structures of the labyrinth has hitherto been but seldom recognised under the microscope. Its having existed is in most cases inferred from the presence of pigment in unusual abundance, which however must not always be regarded as pathological. *Extravasations of blood* in the membranous structures and on their surface are more frequently found, in cases where congestion had existed in the cranial vessels, after injuries, meningitis, various infective diseases, suppurative otitis media, hæmorrhagic pachymeningitis, etc.

Inflammations in all sections of the labyrinth are accompanied at the commencement by great congestion and dilatation of the vessels. In hæmatogenous inflammations we find early thrombosis of the

[1] Lastly, the spread of middle-ear inflammations to the internal ear may also take place by passage through the petro-squamous fissure to the dura, and thence by the vasa subarcuata to the medullary spaces in the vicinity of the labyrinth.

vessels in consequence of fatty degeneration and necrosis of the endothelial cells; changes which have been observed above all in measles and diphtheria, and are due to the action of the micro-organisms which have gained entrance. Abundant emigration of lymphoid cells into both perilymphatic and endolymphatic spaces follows, in consequence of which the lymph acquires a turbid whey-like appearance. At the same time there takes place serous and, later, cellular infiltration of the periosteal lining of the semicircular canals, vestibule, and cochlea, as well as of the membranous semicircular canals, the utricle and saccule, and the structures of the ductus cochlearis. At this stage all the cavities may be filled with fibrinous exudation, or with a delicate network of coagulated lymph, in the meshes of which are entangled lymph cells, red and white corpuscles, and shed epithelial cells, the last sometimes of remarkable size. The epithelium of the membranous structures is swollen or in a state of granular disintegration, and is being abundantly desquamated. On the maculæ, the hairs of the neuro-epithelium are found reduced in numbers, and broken by products of inflammation lying upon them.

As the inflammation increases an active emigration of leucocytes occurs. Not only the membranous structures of the labyrinth are now infiltrated with them, but also the periosteum, which is raised in places, this being the commencement of the demolition of the membranous structures. Granulation tissue is not uncommonly found in the cavities, the perilymphatic and endolymphatic spaces are filled with pus cells, and finally, owing to the further spread of the suppurative process, there results complete destruction of the membranous labyrinth, whilst the extension of the process to the bone causes bulgings outwards and changes in the configuration of the cavities bounded by the latter. Just as suppurative inflammation advances along the auditory nerves and ductus perilymphaticus from the cranial cavity to the labyrinth, so it may extend in the reverse direction along these two paths of communication to the interior of the skull. Purulent infiltration, degeneration, and destruction, of the cochlear, vestibular, and ampullary nerves in their bony canals as far as the termination in the lamina spiralis ossea, are found in the most variable degrees up to total annihilation of the nervous elements. In the inflammations which have extended from the cranial cavity to the labyrinth it is, in the cochlea, usually the lower turns that are most strongly affected.

Further, disintegration of the ganglion cells in the spiral canal of the modiolus has been many times observed, apertures or a very fine network of connective tissue being found in the ganglion spirale on

the site of the destroyed cells. Lastly, accumulation of pus and growth of granulation tissue have been found in the aqueducts also.

The *termination* of labyrinthine inflammation varies according to the duration and intensity of the diseased condition, and also according to the variety of the specific excitant. Thus, for example, in the diseased conditions of the labyrinth following measles the changes hitherto found have been chiefly *degenerative*—hyaline and fatty degeneration, and necrosis of the membranous structures; whilst in cerebro-spinal meningitis, again, the products of *reactive inflammation* come markedly to the front. It is certain that moderate inflammations of the internal ear may pass off without leaving a trace, whilst in advanced cases there usually results a *new formation of connective tissue*, replacing the products deposited in the labyrinth or formed by reactive inflammation. This latter fact has been demonstrated in all the diseased conditions originally mentioned (p. 435), including tuberculosis, and it has been shown that the transformation into connective tissue may take place within a few weeks. In some cases only the periosteum and perilymphatic spaces are affected by these changes, in others the endolymphatic spaces also, and to a very variable extent; whilst according as single parts or several parts at once of the membranous labyrinth are implicated the most manifold results are produced. The organ of Corti is usually involved in the process, and frequently no trace whatever of it can any longer be found, or its site may now be occupied merely by vestiges of cells, flat epithelial deposits, or compact structureless formations, which recall the earlier outlines of the organ.

Many conditions found in the labyrinth of *deaf mutes* may be assumed to be the relics of inflammations which have run their course during the earlier periods of extra-uterine life. Such especially are low organs of Corti, in which the pillars are in part merely indicated, in part totally invisible; inclusion of the membrane of Corti in the cells of the internal spiral groove; connective-tissue bridges between the latter and the stria vascularis, etc.

The results which may occur from *ossification* of the newly-formed connective tissue are partly deposits of bone in the several sections of the labyrinth, and partly filling up of single cavities, or of them all, with newly-formed compact bone. The remarkable *multiplication of the otoliths*, which have often been found along with the relics of labyrinthine inflammations, has also been regarded as connected with the same process.

Mention should also be made in this place of certain conditions found in the *cochlea*, above all in the ductus cochlearis, the external contour of which is especially influenced by changes in the tension

of the membrane of Reissner. Besides wrinkling of this membrane as the result of atrophy, depressions of it have been observed, in consequence of which it was so closely applied to the organ of Corti that only a fine fissure was left; also attachment of its inner end to the crista spiralis and membrane of Corti, and fibrous adhesions to the wall of the scala. The membrane of Corti may show a peculiar resistiveness to inflammation, still remaining intact even at a time when the membrane of Reissner is already densely infiltrated with round cells and the organ of Corti implicated to a very intense degree. In the latter, when affected by degenerative processes, the individual cell-elements are said to show unequal degrees of resistiveness, the external supporting cells proving most resistant. The spiral ligament is often found to be in a condition of *atrophy*, showing numerous apertures in its connective-tissue substance. Of greater importance, however, are the atrophies of the nerves in the lamina spiralis which are observed as sequelæ of middle-ear inflammations, and also following intense auditory impressions. Either fissures or delicate networks of connective tissue are found in their place.

New-formations have been seldom observed in the labyrinth, and but little investigated microscopically. All of them which have been noted (*cholesteatomata, sarcomata, carcinomata*) had penetrated secondarily into the labyrinth from the tympanic or cranial cavities. An alleged *neuroma* has been found in the temporal bone of a deaf mute, in whom cochlea and vestibule were wanting. On the site of the nerve-end apparatus was situated a hard apparently fibrous mass of tissue, which consisted of narrow nerve-fibres crossing in the most various directions and of exactly the same appearance as the fibres in the nerve-trunk passing to it. Between these fibres was contained a small amount of loose connective tissue.

V. THE AUDITORY NERVE.

12. Hæmorrhage, Atrophy, Inflammation, New Growths, etc.—*Effusions of blood* into the sheath of the nerve and between its fibres have been seen in all the morbid conditions already mentioned under the head of labyrinthine hæmorrhages.

Atrophy of the auditory nerve has frequently been observed microscopically, and was sometimes *descending* as a consequence of cerebral disease, sometimes *ascending* (in which case it usually affected only the fibres in the interior of coils of the cochlea) as the result of faulty or abolished action of the sound-conducting apparatus, less often after inflammations. In this condition is found atrophy of

the medullary sheaths, and later also disappearance of the axis cylinders, whilst the connective tissue in the nerve may be proliferated and contain many nuclei, and the surviving nerve-fibres often show thickening as well as varicose swellings of the axis cylinders. The ganglion cells of the vestibular nerve are found partly atrophied and partly in a state of hyaline degeneration.

Concretions of calcium phosphate or carbonate are very common in the sheath of the auditory nerve. They are of microscopic size, have a round, oval, dumb-bell, or club shape, and are often concentrically laminated. *Corpora amylacea* are also found. Both appearances are believed to be connected with previous inflammation and atrophy.

In the *inflammations* of the auditory nerves (which have been found after fractures of the temporal bone, cerebral or cerebro-spinal meningitis, as well as following on suppurative processes in the middle ear) the nerve bundles and fibres are at first forced apart by leucocytes, whilst at a later period the nerve-fibres swell up and are finally destroyed by granular degeneration. Of *new-formations*, fibromata, gliomata, neuromata, sarcomata, and gummata have been recognised microscopically.

Methods.—For microscopic examination of the organs of hearing it is essential that the tissue of the temporal bone which contains them should be rendered capable of being cut, while at the same time the more delicate tissues are as far as possible preserved. In order to shorten as much as may be the period required for the action of the acids in decalcifying, all superfluous portions must be removed from the temporal bone and adherent soft parts. For this purpose, the cartilaginous meatus having been removed, the membrana tympani is laid bare by nipping away the pars tympanitica of the bony meatus. The squamous portion of the temporal bone, with the glenoid fossa and root of the zygomatic process, is next separated by means of a saw-cut,[1] taking with it also as much of the part of the squamous portion forming the roof of the meatus as can be removed without opening the upper segment of the tympanic cavity. By a saw-cut passing obliquely from without and in front inwards and backwards immediately behind the osseous meatus the mastoid process may also be removed. The apex of the pyramidal portion is next sawn off transversely in front of the internal auditory meatus, preserving the auditory nerve and the Eustachian tube; and after nipping off the styloid process, and removal of all soft parts except the Eustachian tube, the bulb of the jugular vein, and the auditory and facial nerves, the preparation[2] may be deposited in the fixing fluid. Before doing so, however, it is well, for the purpose of inspecting the tympanic cavity and examining any secretion that may be present in it, to remove with small bone-forceps the roof of the mastoid antrum and then that of the tympanum, and also to open the summits of the superior and posterior semi-

[1] For sawing it is best to use only fret-saws.

[2] Many also saw away as much as possible of the lower surface of the pyramidal portion.

circular canals. If it is intended to examine the tympanic cavity more thoroughly while still in the fresh condition, the joint between the stapes and the incus is severed and then the tendon of the tensor tympani divided with a fine knife, and the membrana tympani with malleus and incus is separated from the pyramidal portion by means of a saw-cut parallel to the inner wall of the tympanum, any further damage to the continuity of the auditory ossicles being carefully avoided.

The *fresh method* of histological examination, which, however, is but seldom necessary and may usually be restricted to isolated portions, is applicable to all the soft structures of the organs of hearing. From the *membrana tympani* the epidermic layer may readily be torn away in patches, and it is also possible, by careful preparation (under water if necessary) of the membrane, released from its groove, to separate the radial from the circular layer of the substantia propria, but the latter is so intimately adherent to the mucosa that no further separation is attainable. The *mucous membrane of the tympanic cavity* is loosened most easily from the inner wall, and may then be spread out and examined, or teased with needles. The *internal muscles* of the ear may readily be laid bare by breaking open the pyramid and the canal for the tensor tympani with a pointed bone-forceps. Lastly, the *membranous structures of the labyrinth* are rendered accessible by carefully clipping away the bony capsule, and thus material can be obtained for teased-out and flat preparations.

Incomparably more important than the microscopic examination of the ear in the fresh state is that in hardened *sections*, by which method alone, especially by following entire series of sections, comprehensive pictures of the pathological changes are to be obtained. For the preparation of sections, it is necessary that hardening should be preceded by fixation of the soft parts, followed by decalcification of the osseous constituents of the ear. For *fixing*, Müller's fluid is best adapted, or, for preparations of the labyrinth, osmic acid in ½ to 2 per cent. solution. Besides these, solutions of chromic acid and its salts are in use for this purpose. The preparation is immersed, if necessary after a short washing with 0·6 per cent. solution of common salt, for two or three weeks in Müller's fluid, which should be changed daily during the first week, after that only when it becomes turbid. If it is desired to use osmic acid, the following method of Katz may be adopted with much advantage:—Sufficient of a freshly-prepared ½ per cent. solution to cover the preparation is poured over it, and after ten hours four times the volume of the following solution is added:—Chromic acid, 5 grm.; glacial acetic acid, 10 c.cm.; distilled water, 1000 c.cm. In three or four days the preparation is transferred to a fresh quantity of the last-mentioned solution, in which it is left for four days longer.

After treatment by one of these methods the temporal bone, having been washed in water—which, however, is not necessary when Katz's method is used—is now immersed in the *decalcifying fluid*. The following solution has often been found satisfactory for this purpose:—Pure concentrated nitric acid, 35 c.cm.; common salt, 7·5 grm.; distilled water, 1000 c.cm. The solution must be repeatedly changed until the bone is fully decalcified, which is certainly effected when no resistance is any longer encountered on cutting the bone with a sharp knife close to the internal auditory meatus perpendicularly to the axis of the pyramidal portion. Decalcification is usually complete in two or three weeks, but may require longer. The preparation is now thoroughly soaked in water,

and *hardening* is completed in alcohol of increasing concentration up to 95 per cent. Prolonged immersion in absolute alcohol renders the bone too hard. When the preparation is hardened, it must be cut in pieces with a sharp razor for *embedding*. The separation of the membrana tympani with the malleus and incus must be carried out with the knife in the manner described above, should it not already have been done with the saw before decalcification.

The *membrana tympani* is best examined attached to its bony groove, the sections being cut radially, and, in the upper half, horizontally in a direction transverse to the handle of the malleus. To show the spaces lying above the processus brevis of the malleus, sections made in the line of the handle are best; for the examination of the joint between malleus and incus, horizontal and also sagittal sections; for that between incus and stapes, sections in the frontal direction, made from preparations in which the membrana tympani and auditory ossicles are still in position. To show the connection between stapes and vestibule, and also the walls of the tympanum, the vestibule, and the semicircular canals, the sections should be made in the frontal plane perpendicular to the inner wall of the tympanum. The best sections of the *cochlea* are obtained by cutting from within and in front outwards and backwards, beginning in front of the internal auditory meatus. For the *Eustachian tube* the most useful sections are those directed perpendicularly to its long axis. The parts thus reduced to a convenient size are then embedded in celloidin.

Staining of the sections of decalcified ear requires a somewhat prolonged action of the staining fluid when carmine solutions are used, but on the other hand a fine colour is obtained in a few minutes with Delafield's alum hæmatoxylin solution, which is very particularly suitable for preparations of the labyrinth fixed in osmic acid. A staining in all respects satisfactory is obtained by the use of alum carmine or alum cochineal, if the sections be left lying in it for twenty-four hours.

The secretions are examined for *bacteria* by the methods detailed in Part II., Chapter V. If, however, it is desired to examine the membrana tympani, mucous membrane of the tympanum or Eustachian tube, or the soft parts of the labyrinth, for bacteria, it is advisable to do so before decalcifying, the objects being hardened in alcohol, and sections from them treated according to the methods given in Part II., Chapter V.

INDEX

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THE following seven plates, II.-VIII., are photographs made from cover-glass preparations which were in every instance stained with fuchsin (carbolic or alkaline anilin) and mounted in Canada balsam. The amplification is × 1000. All the photographs were taken by direct sunlight (using erythrosin plates and the green Zettnow filter) with Zeiss' 2 mm. apochromatic system, aperture 1·30, and No. 2 projection eyepiece.

Plate II.

Fig. 1. *Staphylococcus Pyogenes Aureus.* Cover-glass preparation from a two-days-old culture on glycerin agar.

Fig. 2. *Streptococcus Pyogenes.* Cover glass preparation from a two-days-old culture in bouillon.

S. Lister-of. M.

Taf. II.

(Plate II.)

Fig. 1.

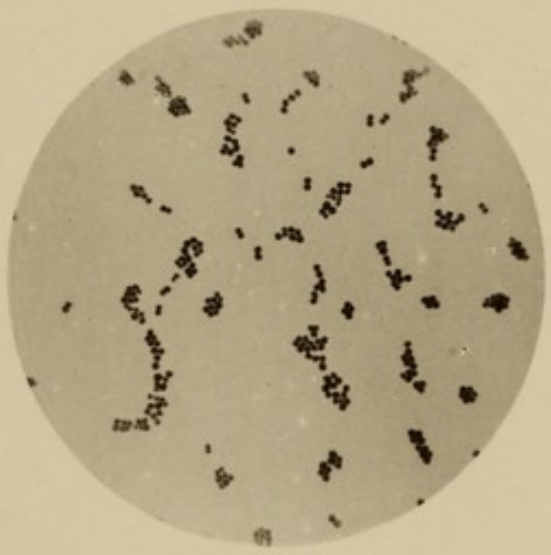


Fig. 2.

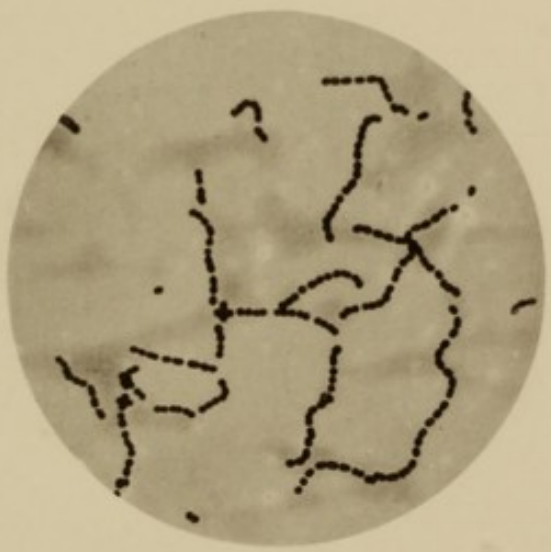


Fig. 1.

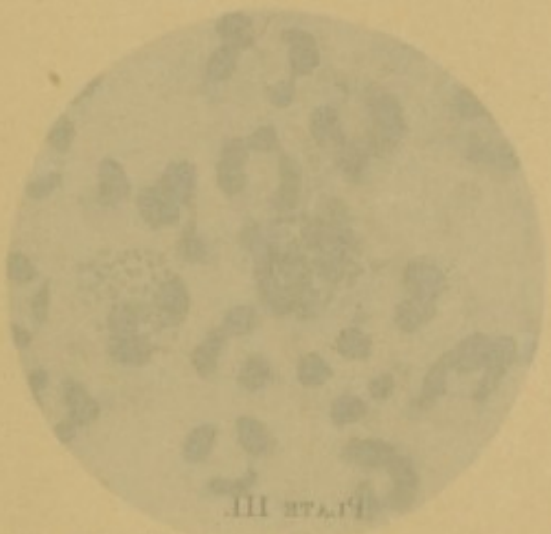


PLATE III.

FIG. 1. Gonococcus. Cover-glass preparation from the pus of an acute gonorrhœal urethritis. The gonococci are lying in the protoplasm of two pus-corpuscles.

FIG. 2. Bacillus typhosus. Cover-glass preparation from a two-days-old culture on glycerin agar.

Fig. 2.

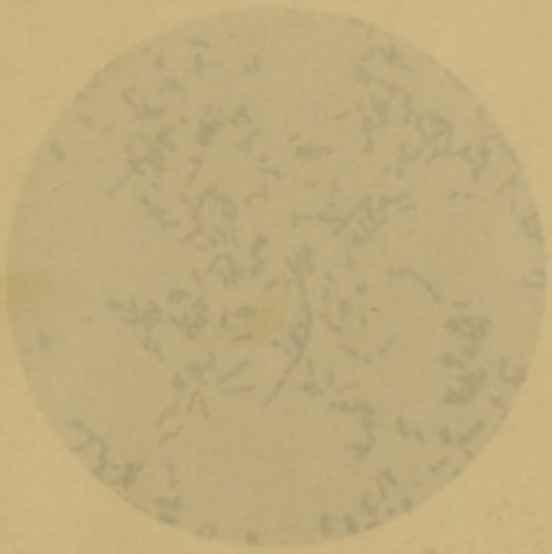


Plate III.

Fig. 1. *Gonococcus.* Cover-glass preparation from the pus of an acute gonorrhœal urethritis. The gonococci are lying in the protoplasm of two pus-corpuscles.

Fig. 2. *Bacillus typhosus.* Cover-glass preparation from a two-days-old culture on glycerin agar.

Fig. 1.

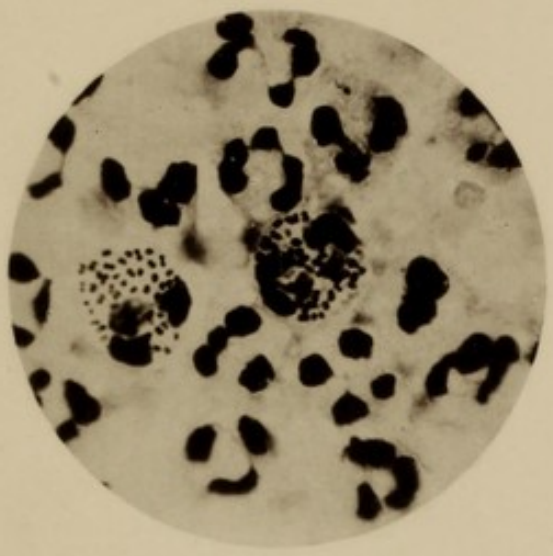


Fig. 2.

Taf. IV.

(Plate IV.)

Fig. 1.

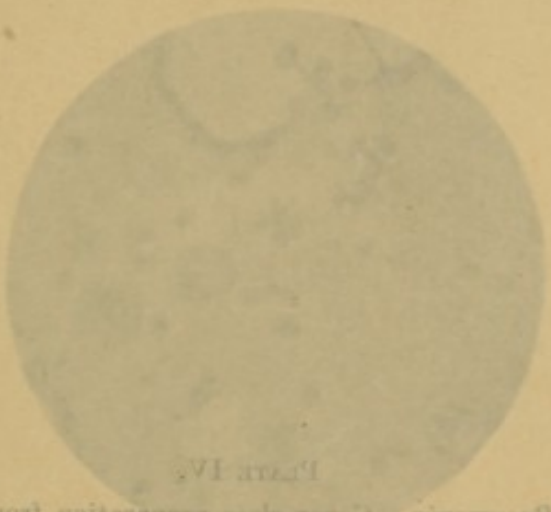


Fig. 2.

Plate IV.

Fig. 1. *Diplococcus Pneumoniæ.* Cover-glass preparation from the blood of a mouse. The cocci are surrounded with a capsule.

Fig. 2. *Bacillus Pneumoniæ.* Cover-glass preparation from the exudation of human lobar pneumonia. The bacilli show a narrow capsule.

Fig. 1.

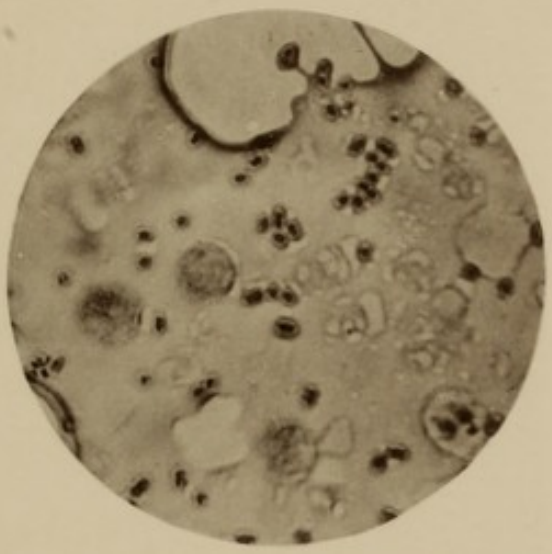


Fig. 2.

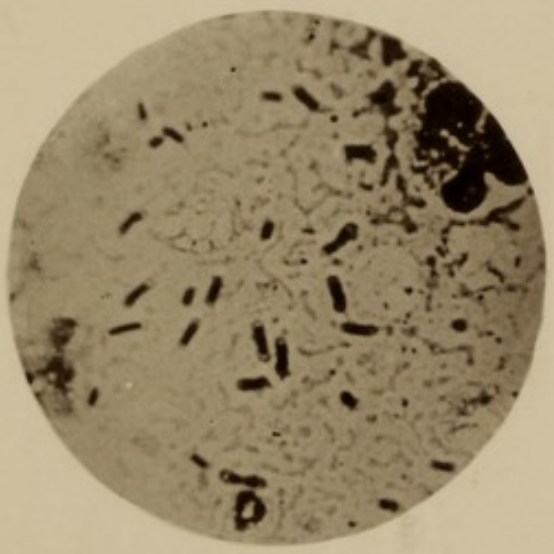


Fig. 1.

PLATE V.

FIG. 1. *Bacillus tuberculosis*. Cover-glass preparation from the spleen-pulp of a mouse.

FIG. 2. *Bacillus tuberculosis* with commencing spore-formation. Cover-glass preparation from a two-days-old culture on glycerin agar. The spores are present only in isolated bacilli.

Fig. 2.

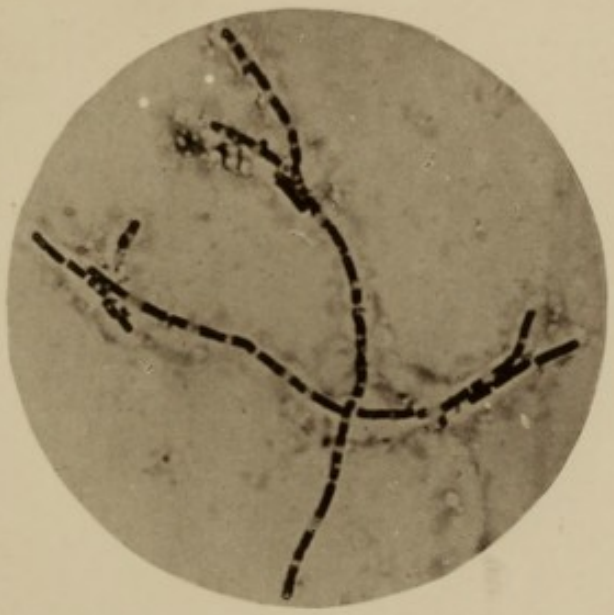
Plate V.

Fig. 1. *Bacillus Anthracis.* Cover-glass preparation from the spleen-pulp of a mouse.

Fig. 2. *Bacillus Anthracis* with commencing spore-formation. Cover-glass preparation from a two-days-old culture on glycerin agar. The spores are present only in isolated bacilli.

Fig. 1.

Fig. 2.



Taf. VI.

(Plate VI.)

Fig. 1.

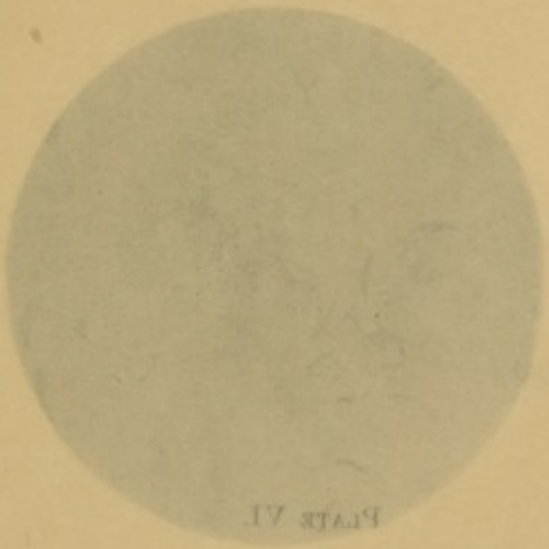


PLATE VI.

FIG. 1. Bacillus Tuberculosis. Cover-glass preparation from tuberculous sputum. Several filaments of bacilli show a granular structure.

FIG. 2. Bacillus Tetani. Cover-glass preparation from a culture, several days old, in grape-sugar agar. Several bacilli show terminal spores, stained or unstained.

Fig. 2.

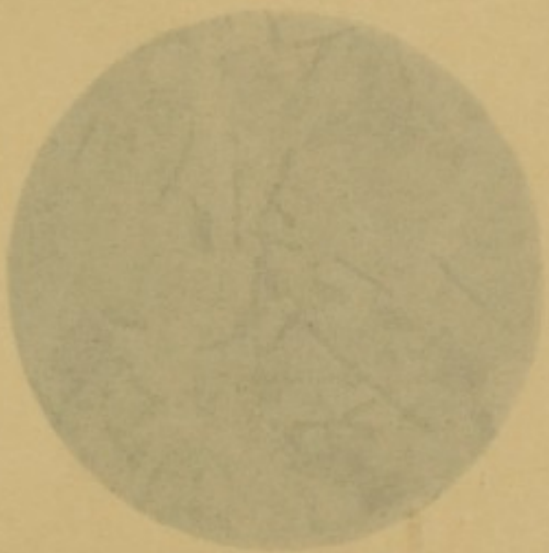


Plate VI.

Fig. 1. *Bacillus Tuberculosis.* Cover-glass preparation from tuberculous sputum. Several filaments of bacilli show a granular structure.

Fig. 2. *Bacillus Tetani.* Cover-glass preparation from a culture, several days old, in grape-sugar agar. Several bacilli show terminal spores, stained or unstained.

Taf. VI.

(Plate VI.)

Fig. 1.

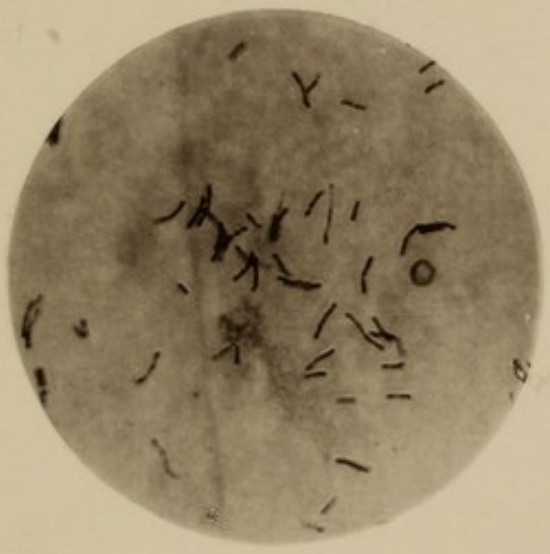


Fig. 2.

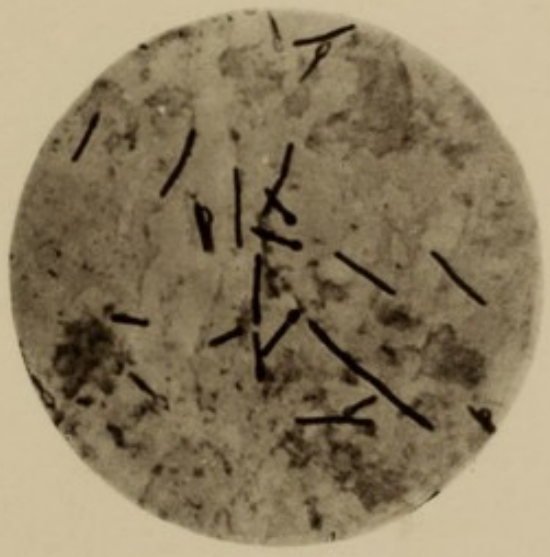


Fig. 1.

Fig. 2.

Plate VII.

Fig. 1. *Bacillus Mallei.* Cover-glass preparation from a two-days-old culture on glycerin agar. In some of the bacilli or filaments spots are seen which have remained unstained, and may possibly be spores.

Fig. 2. *Bacillus Diphtheriæ.* Cover-glass preparation from an eight-days-old culture on glycerin agar. Many involution and degenerative forms are already present.

Fig. 1.

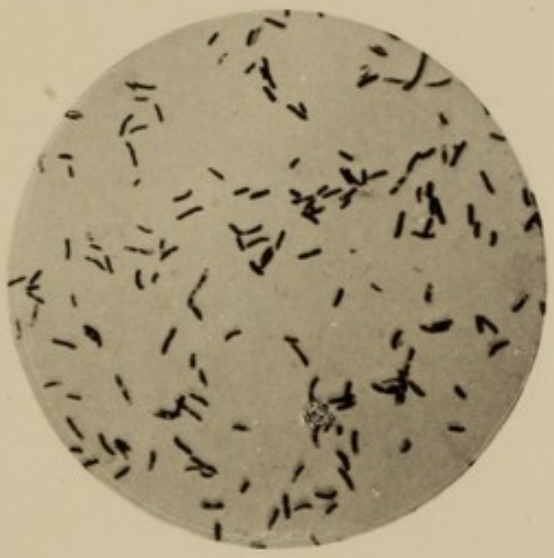


Fig. 2.

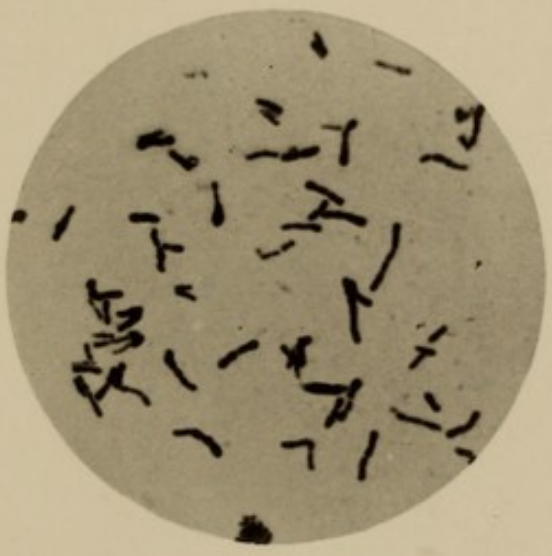


Fig. 1.

PLATE VIII.

Fig. 1. Spirillum Obermeieri. Impression-preparation from a gelatin plate-culture.

Fig. 2. Spirillum Febris Recurrentis. Cover-glass preparation from the blood in a case of relapsing fever.

Fig. 2.

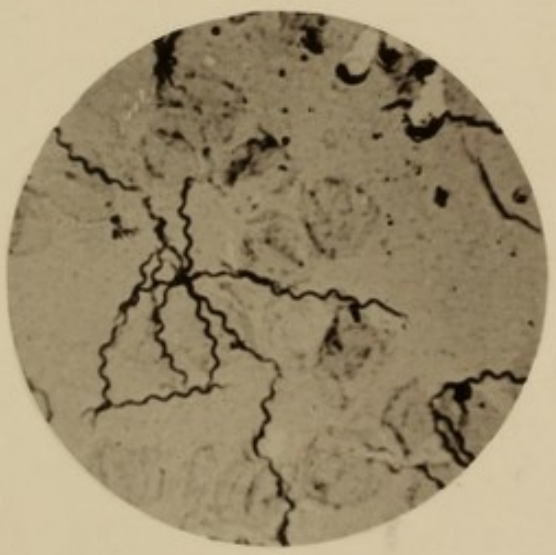
Plate VIII.

Fig. 1. *Spirillum Choleræ Asiaticæ.* Impression-preparation from a gelatin plate-culture.

Fig. 2. *Spirillum Febris Recurrentis.* Cover-glass preparation from the blood in a case of relapsing fever.

Fig. 1.

Fig. 2.



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