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SIDNEY MARTIN

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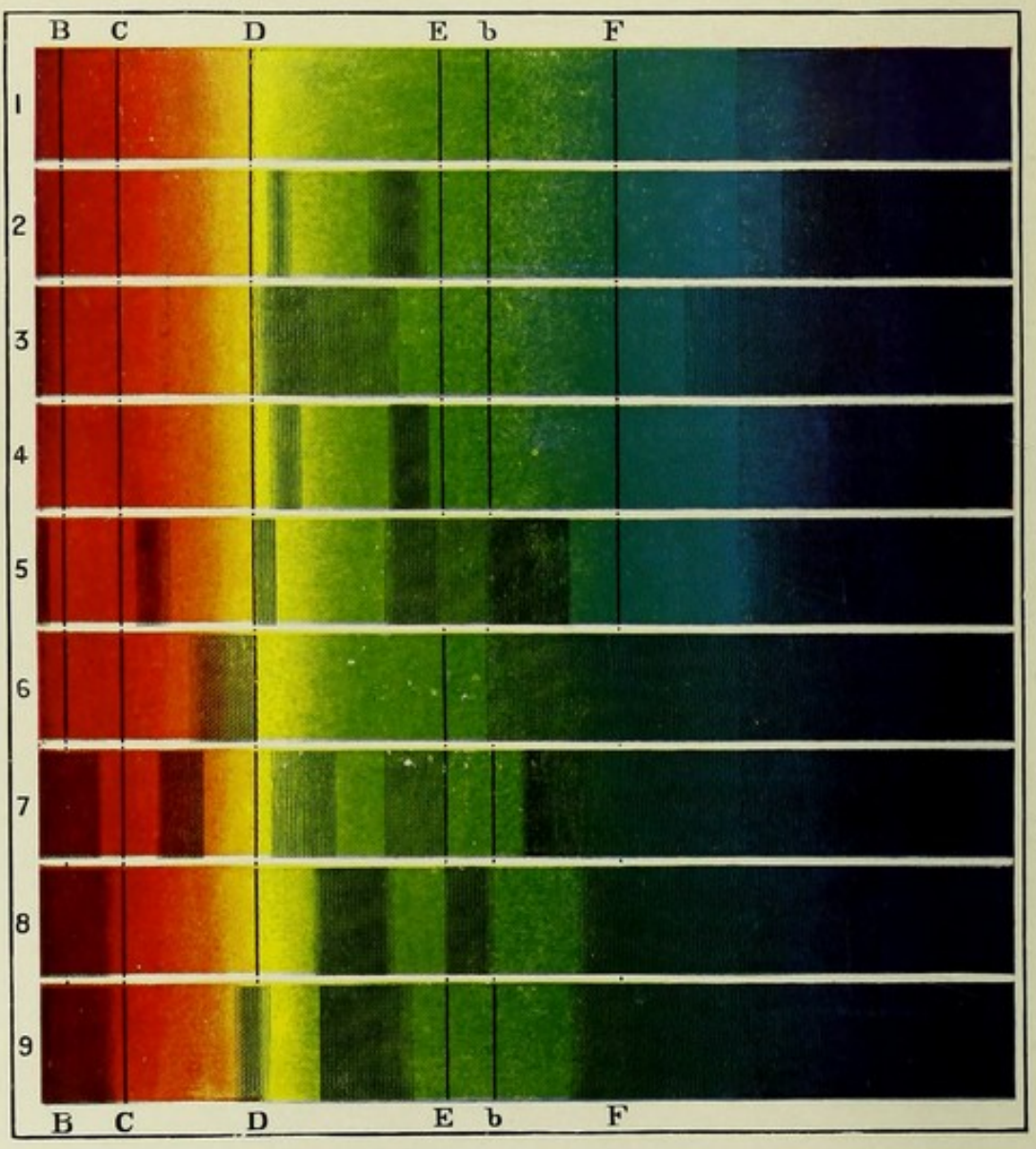
A MANUAL OF GENERAL PATHOLOGY

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FIG. 98.

BLOOD-SPECTRA COMPARED WITH SOLAR SPECTRUM (KIRKE).



1. Solar spectrum.
2. Spectrum of dilute solution of oxyhæmoglobin.
3. „ „ hæmoglobin.
4. „ „ carbonic oxide hæmoglobin.
5. „ „ acid hæmatin in ethereal solution.
6. „ „ alkaline hæmatin.
7. „ „ methæmoglobin.
8. „ „ hæmochromogen.
9. „ „ acid hæmatoporphyrin.

[*To face page* 323.

A MANUAL OF GENERAL PATHOLOGY

FOR STUDENTS

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1904

PREFACE

THE basis of this Text-book has been the Lectures on General Pathology delivered at University College during the past five or six years. It attempts to give in a short space a clear account of the processes of disease, which it is necessary for the student to appreciate in order to follow the study of scientific medicine. The study of General Pathology must go hand in hand with that of medicine and be preceded by practical work in Morbid Histology and Anatomy, and to some extent in Bacteriology. These subjects are in the book only dealt with as far as they have an evidently direct bearing on the processes of disease. Illustrations of some of the minute changes occurring in diseased processes have been included, in order to remind the student of the structural changes occurring with disordered function. These illustrations and descriptions are, however, not intended to take the place of a systematic study of Morbid Histology. References to the literature of the subject have been purposely omitted. I wish, however, to acknowledge my indebtedness more particularly to Cohnheim's *Vorlesungen iber allgemeine Pathologie;* Cohnheim's *Gesammelte Abhandlungen;* some articles in Clifford Allbutt's *System of Medicine;* von Noorden's *Lehrbuch der Pathologie des Stoffwechsels;* Cabot's *Clinical Examination of the Blood;* and Mott's *Croonian*

Lectures on the Degeneration of the Neurone. I am indebted to Professor J. Risien Russell, M.D., for valuable criticism of the Chapter on the Nervous System; to my Assistant, Dr D. N. Nabarro, Assistant Professor of Pathology in University College, for valuable help in reading the proofs; to Professor G. D. Thane, for the outline diagrams of Figs. 47 to 50 and Fig. 101; to Mr Renshaw for permission to use Fig. 125; to Dr F. W. Mott, F.R.S., for permission to use the figures illustrating the Chapter on the Nervous System. The remaining illustrations (unless where acknowledged in the text) are from photographs by Mr E. S. Worrall, Radiographer at University College Hospital.

SIDNEY MARTIN.

August 1903.

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INTRODUCTION

GENERAL PATHOLOGY is a study of the processes of disease; Pathological Histology deals with structural changes in the tissues in disease, and bears the same relation to General Pathology as Histology bears to Physiology. Gross Morbid Anatomy is a study, not only of the naked-eye characters of disease, but more particularly of the distribution of the lesions produced by disease; that is, of their regional pathology. By this means much information may be gained as to the locality of origin of disease and of its mode of spread. Bacteriology includes a study of the living agents which frequently are the causes of disease, and by the investigation of the life history of these agents, and of the chemical changes produced by them, much information is gained as to the processes of infective disease.

The study of General Pathology is carried out by the methods in use in Physiology; mainly by experiment with the view of elucidating the chemical, electrical, fermentative and other changes which occur during the processes of disease. Experiment is of prime importance in the study of Pathology. (1) By removal of healthy tissues or organs, not only is light thrown on their normal functions, but the study of the effects of their destruction by disease can be regulated. In this way great progress has been made in both Physiology and Pathology by removal of the thyroid, spleen, kidneys, liver and portions of the brain. The study of the functional defects produced by the removal of these organs has aided in elucidating diseased conditions. (2) A second class of experiment is one in which a study is made of the results of separating

important parts either from the central nervous system or from the vascular system. In this way a change is produced in the functions of the part. (3) Stimulation of normal organs, mechanically, chemically, or by electricity, is also a means of determining the functions of organs; as, for example, the brain, secretory glands and the heart. (4) The enormous advance made in the study of infective disease has occurred almost solely by experiment—namely, by the cultivation of the infective agent outside the body, by the study of its chemical life processes, and by the investigation of the effects of introducing the living agent itself or its chemical poisons into animals.

Disease is a variation from health or from the normal. It is produced by many different causes, the majority of which, however, are external agencies. A provisional classification of diseased conditions as to their causation is as follows:

1. *Congenital disease*, as in (*a*) Malformations and monstrosities; (*b*) Fœtal remnants.

2. *Acquired disease*, which is mainly due to the following external agencies: (*a*) Heat, cold and electric shock; (*b*) Mechanical injuries; (*c*) Chemical poisons; (*d*) Infective agents; (*e*) Alterations in the food; and (*f*) in the surroundings of life as affecting the amount of oxygen taken into the body and the amount of muscular and mental activity. Of a similar nature are such conditions as excessive activity of any tissue or organ which is induced by external conditions.

3. *Inherited disease.* (*a*) A defect in any particular tissue may be inherited, from which disease is brought out either by the surroundings of life or by the results of the process of infection. This particularly applies to the inheritance of defects in the nervous system. It is also shown, however, in the inheritance of defects in metabolism or in the tendency to specific infections, such as tuberculosis, (*b*) The disease itself may be inherited; either an infection such as syphilis, a defect in metabolism, or a special disease of the nervous system.

In studying the processes of disease, although for convenience the subject is divided into chapters, defect in one organ affects the body generally. Special conditions arise in which the disease becomes *localised;* in other cases it becomes *generalised.* Disease of an organ may, however, be of such a kind and degree as to produce no effect on the body generally, in the majority of instances compensation occurring. The introduction into the body of a foreign agent, living or dead, may result in local disease, owing to the resistance of the tissues; or the diseased condition may become generalised. The diseased conditions produced, more particularly by the growth of living infective agents in the body, must be considered apart from other diseased conditions which result from injury to organs and tissues. The infective process lasts only a certain time in the body and may cease without leaving any permanent effect on the tissues. It may, however, lead to damage of one or other tissue; this damage persisting and producing its own effects on the body. The effect of damage to organs has therefore to be considered apart from infection. Thus the effects, both local and general, have to be considered, of disease and disorder of the circulatory system; of the respiratory system; of the glands of the body, of those with and of those without ducts; and of the nervous system, as well as of the changes which occur in the blood and other liquids in the body.

GENERAL PATHOLOGY

CHAPTER I

INFLAMMATION

INFLAMMATION has been defined in the following terms:—"The process of inflammation is the succession of changes which occurs in living tissue when it is injured, provided that the injury is not of such a degree as at once to destroy its structure and vitality" (Burdon Sanderson). Another definition considers inflammation "as the series of changes constituting the local manifestation of the attempt at repair of actual or referred injury to a part, or, briefly, as the local attempted repair of actual or referred injury" (Adami).

It is, however, impossible to give a succinct and complete definition of the process of inflammation, and to bring a definition into line with the researches which have been done of late years on the processes of infection, inflammation can most usefully be considered as *a reaction of the tissues to the irritant effect of an injury, mechanical, chemical, thermal, or bacterial.*

Changes in Inflammation.—For many years inflammation was considered only as a phenomenon occurring in vascular tissues and in the higher animals, but research has shown that some of the changes may occur in non-vascular tissues and in invertebrata, and the study of these changes has greatly aided in the explanation of the phenomena of inflammation in tissues supplied by blood vessels. The phenomena of inflam-

mation in vertebrata are well expressed in the four words, *rubor* (redness), *tumor* (swelling), *dolor* (pain), *calor* (heat) (Celsus). To these, which accurately describe the more obvious features of inflammation, must be added *functio læsa*, or diminished function. The predominance of one or other of these obvious changes depends on the intensity and character of the inflammation.

The minute changes in inflammation may be observed occurring in the frog's mesentery or tongue. In performing this experiment the frog must be curarised and pithed, and the mesentery drawn out through an incision in the body wall, and pinned on a flat piece of cork which has a round hole cut in it. It may then be placed on the stage of the microscope, and examined with a low power. The mere exposure of the delicate vascular membrane to the air excites inflammatory changes.

The first obvious change is a dilatation of the blood vessels, both arteries and veins, with an increase in the rate of the blood stream (active hyperæmia).

The second change is a slowing of the circulation, chiefly in the veins and capillaries, which ends in a condition of stasis, or stoppage in the capillaries.

The third change observed is the collection of the white corpuscles at the periphery of the blood stream. They collect in such numbers in the slowed stream as to present the appearance of what is called "pavementing."

The changes which occur in the visibility and arrangement of the blood corpuscles during the slowing of the blood stream are very characteristic. In the normal stream through a small vessel the current is seen to be divided into two parts. In the centre is the axial stream of red blood corpuscles, and between these and the vessel wall is the plasma of the blood, in which white corpuscles are moving along (Fig. 1). The red corpuscles are not visible, owing to the rapidity of the stream. When the stream becomes slowed, the first change, observed at the same time as the collection of white corpuscles along the vessel wall, is the individual distinctness of the red corpuscles (Fig. 2). They still, how-

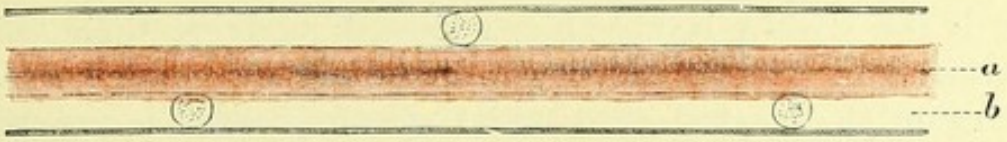


FIG. 1.

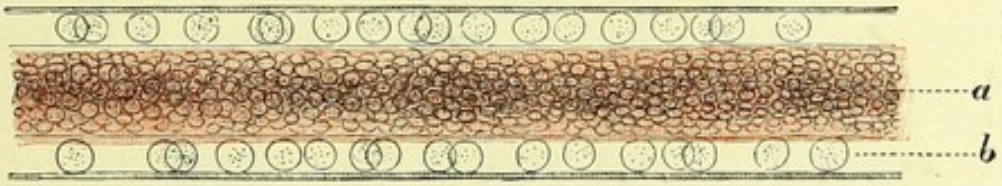


FIG. 2.



FIG. 3.

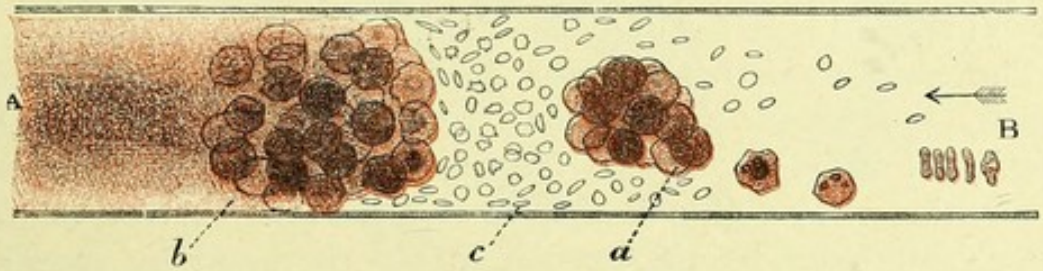


FIG. 4.

MICROSCOPICAL APPEARANCE OF THE BLOOD STREAM OF DIFFERENT VELOCITIES.

Fig. 1 represents a vessel in rapid circulation. There is a well-defined red axial stream (*a*), in which the individual red corpuscles are not distinguishable, and a peripheral plasma zone (*b*), in which a few leucocytes are present.

Fig. 2 shows slight slowing of the blood stream in a vein. In the axial stream (*a*) the individual red corpuscles are seen, but not distinctly. In the plasma zone (*b*) are numerous white corpuscles—pavementing of the leucocytes.

Fig. 3 shows great slowing of the circulation. The axial stream is still present, but the individual red corpuscles are distinguishable. In the plasma zone there are few leucocytes, but numerous blood plates.

Fig. 4 represents stagnation or stasis. At A, circulation has ceased; and at *a* and *b*, a red hyaline thrombus has formed. At B the vessel communicates with another, through which blood is still flowing, and from which come blood plates (*c*) into the stagnating blood. The red corpuscles and the blood plates are both undergoing changes in shape. (Eberth and Schimmelbusch.)

ever, if the stream is not much slowed, preserve their axial direction. In greater slowing of the stream, as well as in the condition of stasis, the axial stream breaks up so that the red corpuscles become irregularly distributed (Figs. 3 and 4). Some are seen flat, others sideways, and still others commencing to form rouleaux.

During this time two other phenomena have taken place, namely, the emigration of the white corpuscles and the exudation of liquid. The emigration of the white corpuscles, as far as can be seen in such an experiment, takes place chiefly where there is not complete stasis of the blood stream. The corpuscles are noticed to adhere to the inner side of the vessel wall, and, if one corpuscle be watched, it is seen in a short time to form a slight projection on the outside of the vessel wall, and then gradually to protrude more and more from the vessel, which it eventually leaves with a little jerk (Fig. 5). Outside the vessel wall it shows amœboid movement, and passes into the loose connective tissue between the folds of the peritoneum. The red corpuscles pass out of the vessel in small numbers. Their emigration is not of the active character of the amœboid corpuscle. As the process goes on the inflamed part swells, owing to the exudation of liquid.

The redness of the inflamed part is due to the increased quantity of blood which goes to it, and this increased quantity of blood, as well as the exudation of liquid, leads to the swelling. The pain is due to the irritation of the nerve endings, produced by the tension in the part and by specific poisons. The increased heat of the part is mainly due to the increased quantity of blood, the heat of which is not, as in normal conditions, distributed to other parts and so equalised, on account of the sluggishness of the blood stream. There is no increased formation of heat in the inflamed part. The rise of temperature in it is not more than 1° or 2° C.

Causes of the Changes in Inflammation.—Changes in the Blood Vessels.—The increased flow of blood in the inflamed part is frequently spoken of as active hyperæmia or as determination of blood to the part. The changes in the blood vessels

accompanying this phenomenon were the subject of extended research by Cohnheim and his pupils. As a result of this work it was concluded that the vessel wall was directly affected in inflammation, and that this accounted for the changes in the

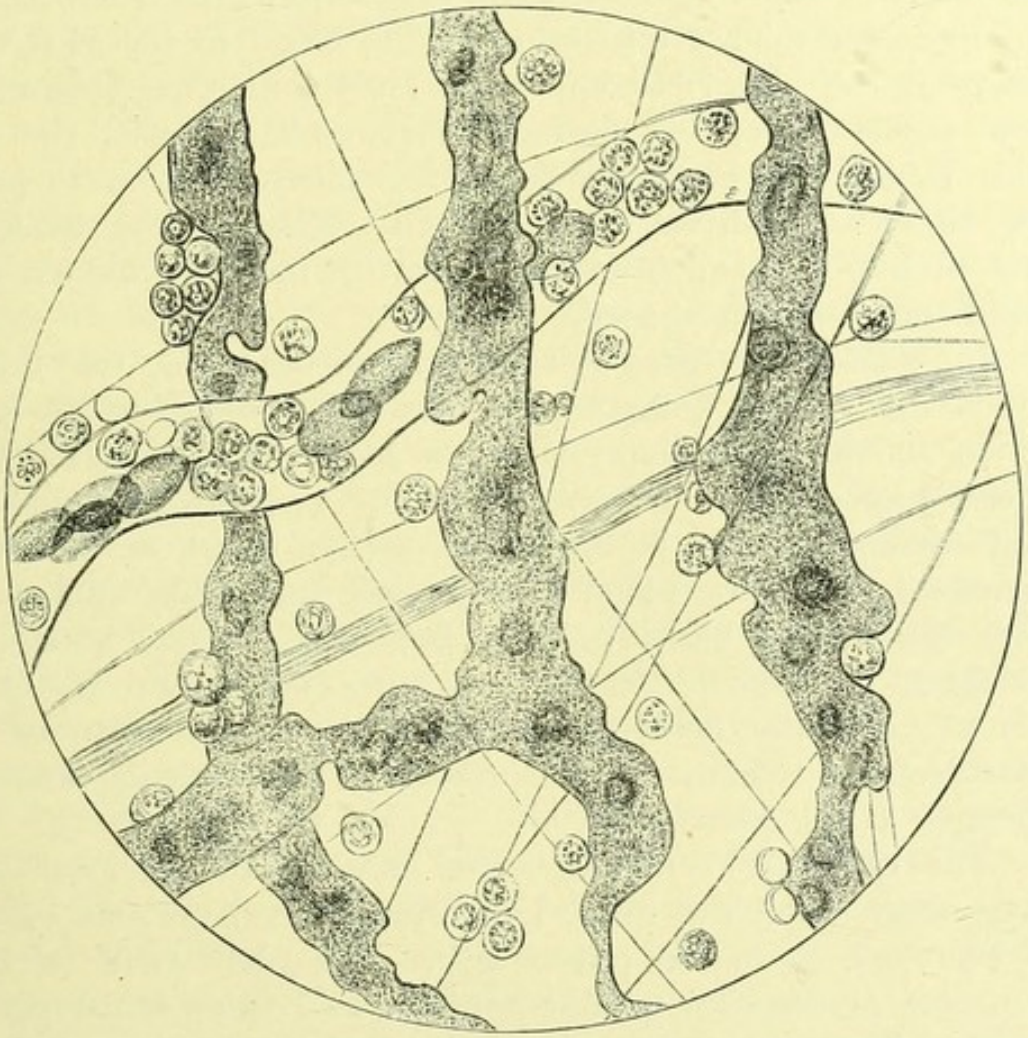


FIG. 5.—Emigration of leucocytes.

The reproduction of the drawing shows dilatation of the capillaries in the frog's tongue, with irregularity of their contour, owing to exposure to air. In one capillary individual red corpuscles can be seen, and outside the capillaries are to be seen numerous leucocytes, which have emigrated from the blood vessels. Some of these are free in the tissue, others are attached to the vessel wall, and still others are seen just separating from the vessel wall. (From the original figure by Aug. Waller, M.D., *Phil. Mag.*, 1846.)

blood vessels, the emigration of leucocytes, and the exudation of liquid. Arnold thought that stigmata formed between the endothelial cells, to allow of the emigration of the corpuscles. The endothelial cells undoubtedly undergo changes in inflammation. They show signs of irritation, as is evident

from their enlargement and the karyokinesis of the nucleus. Some of Cohnheim's experiments indicate that interference with the nutrition of the vessel wall may lead to some of the phenomena of inflammation. Thus, if the blood supply to the tongue of the frog be stopped for a short time, a temporary engorgement follows the return of the blood to the part. If, however, the vessel is compressed for a long time, inflammation ensues when the pressure is removed. Again, the ear of a rabbit was bandaged for a few minutes, so as to press the blood away from the part. On removing the bandage and placing the ear in warm water (50°-60° C.), sudden and rapid inflammation ensued.

In both these cases it may be supposed that the injury which led to the inflammation was the damage to the part which followed the deprivation of blood for a certain time. These experiments, however, do not explain why, in the first instance, there is dilatation of the blood vessels with increased rate of the blood stream, and, later, there is slowing and stasis. The blood vessels dilate and contract under the influence of their proper nerves, vaso-dilator and vaso-constrictor, and the influence of the nervous system must be considered in relation to the process of inflammation and the changes in the blood vessels.

The changes in inflammation may be purely local, and may occur when the influence of the central nervous system is removed, as in the pithed frog. The removal of nervous influence predisposes to inflammation, as is seen in the proneness of paralysed parts to inflammation. This is associated with a diminution in the natural reflex defence of the part, owing to the loss of sensation and of trophic influence (Chapter XIX.). Primary dilatation of the blood vessels must be considered as the result of a paralysis of the vaso-constrictor nerves, ascribable to the local injury. The subsequent slowing of the circulation is in part due to this dilatation.

The vessels of the rabbit's ear are supplied by vaso-constrictor fibres, which run in the sympathetic nerve, and vaso-dilator fibres, which run in the auricular nerve. Division

of the sympathetic nerve leads to great dilatation of the vessels of the ear. Division of the auricular nerve usually produces no obvious effect, though dilatation of the vessels is observed when the peripheral end is stimulated. If all the nerves in the rabbit's ear be divided, the vascular changes of inflammation occur when the ear is dipped into hot water (54° C.). Indeed, the changes are more rapid than when the nerves are not divided. The following experiments, however, show that division of one or the other nerve influences the processes of inflammation. Thus, if the auricular nerve be divided, and the inflammation started by dipping the ear in warm water, no hyperæmia occurs, but stasis and gangrene of the part may ensue. If, on the other hand, the sympathetic alone be divided, and the ear be dipped into hot water, well-marked congestion is seen, and the inflammation rapidly recovers. These experiments have been repeated, using the streptococcus of erysipelas instead of hot water as the excitant of the inflammation, and the results obtained were the same.

It might be concluded from the first experiment that the congestion of the part is mainly due to an active stimulation of the vaso-dilator fibres, and it is possible that this is the explanation of the phenomenon in a part with such a specialised nerve supply as the ear of the rabbit. In other parts of the body, however, in which there is no great evidence of the existence of vaso-dilator fibres, it must be concluded that the chief means by which congestion of the part occurs is by the paralysis of the vaso-constrictor fibres.

The slowing of the circulation which follows the dilatation of the blood vessels and the increase of the blood stream, is due partly to the dilatation itself, which causes a concentration of blood in the part. The adhesiveness of the white corpuscles to the vessel wall may also aid the slowing. The presence of blood is not necessary for the phenomenon to occur, as stasis is observed if milk or salt solution is substituted for blood in the frog.

Exudation of Liquid.—The amount and character of the liquid exuded from the blood vessels depends, to some

extent, on the nature of the irritant, but also on the looseness of the inflamed tissue, and whether inflammation occurs in a serous membrane or in a solid tissue.

The nature of the irritant will be more fully discussed when the invasion of the body by bacteria (*i.e.*, the process of infection) is considered, but it may here be said that although certain irritants usually produce a fibrinous exudation, others a clear liquid exudation, and still others a purulent exudation, yet one and the same bacterium may, according to its degree of virulence, produce either a serous, a fibrinous, or a purulent exudation. Thus, the anthrax bacillus, if not very virulent, will produce a large serous exudation, when injected subcutaneously in an animal. If more virulent, it will produce little or no exudation. Another example may be taken in the typhoid bacillus, which produces, as the result of intraperitoneal injection, liquid exudation without the formation of an abscess; whereas, in man and when injected subcutaneously in the rabbit, it produces an abscess. The same may be said of the bacillus coli communis. In other cases, again, the exudation is but slight, and the effect on the tissues great.

Composition of Inflammatory Effusions. — Clear effusions, such as are obtained from the pleura or pericardium in inflammatory conditions, are all alkaline and of a yellowish or yellowish-green colour, the colour being due to the presence of a lipochrome. The specific gravity is, on the average, 1018, and they clot spontaneously, not only when removed, but often in the body cavity. The specific gravity of non-inflammatory effusions is 1010 to 1015, and they do not clot spontaneously in the body, but a coagulum is produced on adding serum or blood, fibrin ferment, or myosinogen. The following table illustrates the composition of these fluids.

PERCENTAGE COMPOSITION (IN GRAMMES) OF INFLAMMATORY AND NON-INFLAMMATORY EXUDATIONS.

	Specific Gravity.	Total Proteids.	Fibrin.	Serum-Albumin.	Serum-Globulin.
Acute Pleurisy	1020-1023	3.5-5	0.016-0.1	1.24-3	1.18-2.1
Hydrothorax .	1012-1016	1.3-2.5	0.006-0.013	0.4-0.7	0.7-1.8
Subcutaneous Œdema .	1009-1012	0.3-0.6	Traces	0.13-0.19	0.45
Hydrocele Fluid . .	1016-1022	...	0.059	1.35	3.5
Pus Serum .	...	6.2-7.7	...	...	Lecithin 0.15-0.056
Peritoneal Fluid (ascites) .	1010-1018	2.9-3.5-4 or 0.6-0.7	..	0.2-2.9	0.5-2.6

The proteids consist of fibrinogen, serum globulin, and serum albumin; the extractives consist of cholesterin and sugar. Inflammatory effusions contain a smaller quantity of proteids than blood serum, but a much larger quantity than is present in non-inflammatory effusions. The salts are like those in the blood.

Besides these substances, inflammatory effusions frequently contain toxic agents, as well as the bacteria producing them.

The cause of the effusion of liquid is probably the effect of the irritant on the endothelial cells of the blood vessels, so that increased transudation occurs. The so-called nutrition theory (Virchow), which supposed that the increased exudation of fluid in inflammation was due to an increased local metabolism of the tissues, is not supported by facts, inasmuch as inflammation leads to a diminution, and not to an increase, of functional activity.

Diapedesis.—The emigration of white blood corpuscles was first observed by Dutrochet in 1824, next by Addison in 1843, and subsequently by Waller in 1846; but the most systematic study was published by Cohnheim in 1867. He

drew special attention to the amœboid character of the exuded leucocytes.

The diapedesis of the white corpuscle is mainly an active process, owing to the amœboid properties of the leucocyte, and the direct observation of the process of inflammation in the frog's mesentery or tongue, demonstrates that the passage of the white corpuscle out of the blood vessel is, in the main, an active process. Red corpuscles, however, also pass out of the blood vessels in the inflamed area, and this movement must be a passive one.

Cohnheim stated that arrest of the circulation of the part by compression of the vessel supplying it arrested diapedesis, and he did not consider that much, if any, diapedesis occurred in the area of stasis. Metchnikoff (and previously Waller), however, directly observed the emigration of the white blood corpuscle in the area of stasis. The leucocytes show amœboid movements both inside and outside the blood vessels, so that, at any rate at first, their vitality is not altered by the passage through the vessel. Subsequently, however, most of the leucocytes die. Some act as phagocytes, engorging not only bacteria, but pigment formed from hemoglobin and the débris of dead tissue. A very few may develop into the fixed cells of connective tissue, during the process of repair.

The question arises: Why do the leucocytes leave the blood vessels at all? Emigration varies enormously in extent in different cases of inflammation, and this variation is dependent on the nature of the irritant, not only on the particular bacterium causing the inflammatory change, but on the degree of virulence of the bacterium. The greatest amount of emigration is observed in the formation of abscesses, whether acute or slowly forming. In the case of a rapidly acting irritant, such as is produced by virulent bacteria, there is very little emigration, but there may be a great exudation of liquid; or, in other cases, there is but little liquid, and great necrosis of tissue. With less virulent bacteria more emigration occurs. The causes of this variation in the amount of emigration as a result of the action of different irritants has to be studied.

Primâ facie, there appear to be some irritants which conduce to the emigration, and others which diminish it. This process of the attraction or repulsion of leucocytes is referred to as *chemiotaxis*, positive and negative (see Phagocytosis, p. 27).

Effect of Inflammation on Tissues.—Although the main phenomena of inflammation are concerned with the vascular system, yet the changes which occur have an effect on the tissues in which the inflammation occurs, and these effects may be ascribed to two causes. The first is due to the deprivation of the part of a proper supply of oxygenated blood; the second is due to the direct action of the bacterial poisons on the cells of the tissue or organ, associated with the condition of pyrexia which is induced in such cases of infection.

1. *Effect on Connective Tissue.*—The primary effect of inflammation is to cause cloudy swelling of the connective tissue cells themselves, with some proliferation subsequently. Many of the cells degenerate. The fibres of the connective tissue swell, and ultimately may undergo hyaline degeneration. In chronic inflammation there is an increase of the connective tissue, mainly of the white fibrous tissue (p. 24).

2. *Cells of Organs.*—The primary effect here is to produce cloudy swelling of the cells, which may rapidly pass on to fatty degeneration, and these changes are observed, not only as the result of a local inflammation of the organ, but in many cases of general infection, where the effect is due to the circulation of poisons throughout the body Other forms of degeneration are also observed, but mainly as the result of chronic inflammation, or chronic infection; such, for example, as mucoid and dropsical degeneration of the cells. The cells which are more particularly observed to be affected by cloudy swelling or other changes, as the result of inflammation or of infection, are the secretory cells, such as those of the digestive glands and of the liver and kidney, while similar changes are observed in the heart muscle (Chapter VII.).

3. *Necrosis.*—Necrosis or death of a part, or of the cell

elements of a part, is one of the main results of the inflammatory, or more correctly speaking, the infective, process.

The degree in which necrosis occurs varies considerably in different inflammations, and is due to the nature of the irritant. In some but little necrosis occurs; in others, such as diphtheria, necrosis is well marked. The varying degrees of necrosis sometimes are described as a soft or colliquative necrosis, and as a dry, and sometimes fatty, necrosis (caseation).

4. *Pigmentation.*—Pigmentation may be considered as one of the effects of inflammation upon tissues, and results from the transformation of the hemoglobin of the exuded red blood corpuscles. The final result is the deposit of pigment both in and between the cells of the permanent tissue (Chapter XIV.).

Varieties of Inflammation.—Inflammation may be classified in two ways. A proper classification would be into divisions in which the nature of the irritant would be chiefly considered, but there is no advantage in such a division. An anatomical classification is more useful.

Inflammation is either acute or chronic. It may be chronic from the first, or a chronic form may follow the acute, but in either case it is simply a question of the process and degree of infection, and the degree of resistance offered by the tissues to the infective process.

For the present purpose, the varieties of inflammation may be classified according to the main feature of the process which is present, and this main feature may be one of three kinds: first, as regards the predominance of the leucocytic emigration; secondly, as regards the character of the liquid exudation from the vessels, and thirdly, as regards the effect of the inflammation on the tissues.

1. *Predominance of Leucocytic Emigration.*—(*a*) *Interstitial inflammation* (Fig. 6), in which the main feature is a leucocytic infiltration in the connective tissue, or between the cells of the organ. The inflammatory focus is dry, but little liquid being exuded.

(*b*) *Purulent inflammation* (Fig. 7), in which, in addition to a large leucocytic emigration, the cells of which degenerate, there is exudation of liquid, forming the so-called liquor puris or pus serum.

2. *Predominance of Exudation.*—(*c*) *Œdematous inflammation*, in which there is a large amount of liquid exudation, with a relatively small amount of leucocytic emigration.

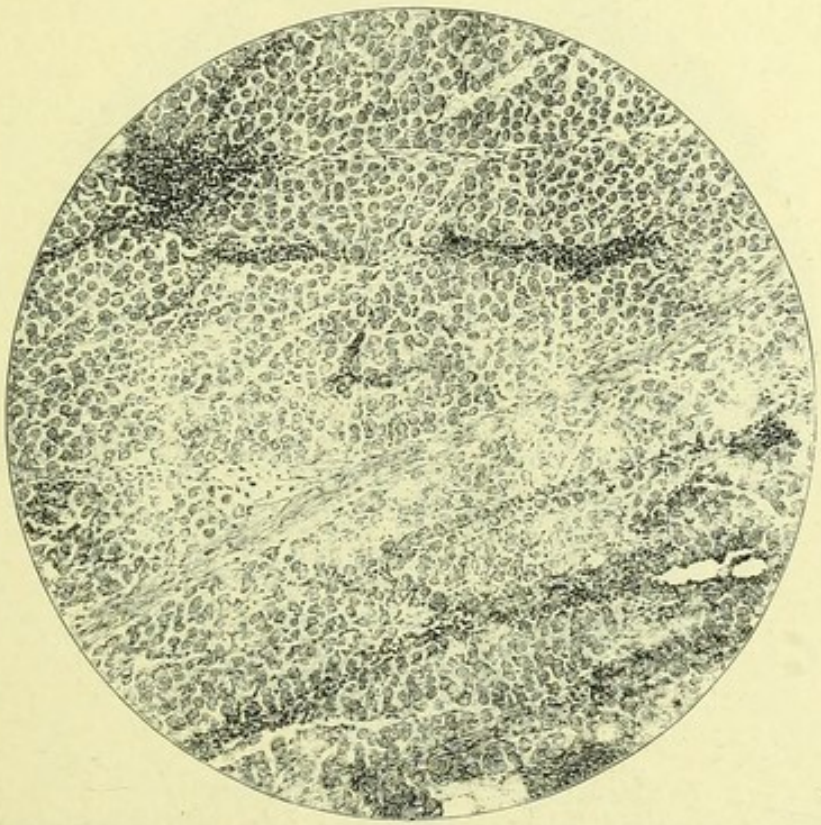


FIG. 6.—Interstitial myositis.

A transverse section of voluntary muscle under a low power, showing the muscle fibres cut transversely. In parts are to be seen radiating lines of round cells or leucocytes, showing an early stage of interstitial inflammation. (For the later stage, see Fig. 77.)

This form of inflammation occurs only in loose tissues such as connective tissue, or in cavities such as the pleura, pericardium, and peritoneum, or in the lungs, and does not occur in solid organs, such as the liver, kidneys, spleen and heart.

(*d*) *Croupous or fibrinous inflammation* (Figs. 8 and 9), in which there is but little liquid exudation. The main feature is the fibrin which is deposited in the inflamed area. There is an emigration of leucocytes, but the predominance of fibrin

constitutes a well marked variety. This inflammation occurs in the skin and the connective tissue, as in some kinds of carbuncles; on mucous membranes, as in diphtheria; in lung tissue, as in croupous pneumonia, and on the surface of serous membranes, pleura, pericardium and peritoneum.

3. *Predominance of Effect on the Tissues.—(e) Catarrhal*

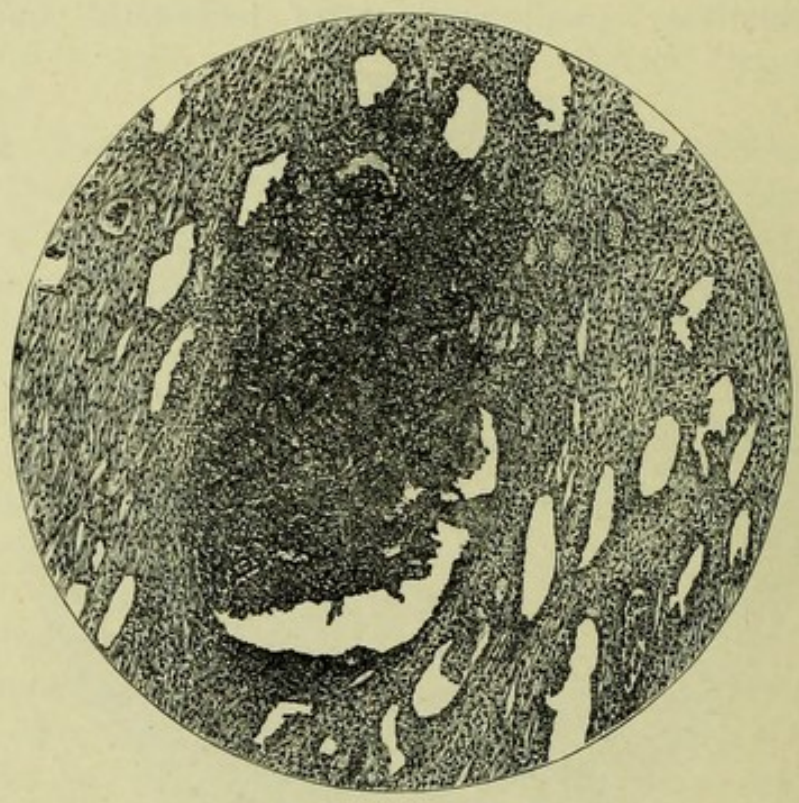


FIG. 7.—Purulent inflammation.

Section of a portion of kidney substance under a low power, showing a cavity containing a dark mass, composed mostly of pus corpuscles (leucocytes) in various stages of degeneration, and showing also a leucocytic infiltration of the kidney substance, the interstitial tissue of which is quickly increased, widely separating the tubules. These last are indicated in the figure only by clear spaces, irregular in shape, the epithelium having in great part fallen out of the tissue during the preparation of the specimen.

inflammation (Fig. 10). In this variety, in which the mucous membranes are affected, there are the general signs of inflammation, such as congestion, leucocytic emigration and transudation of liquid. There are, besides, two changes, the first of which is cloudy swelling of the cells of the glands; the second, which gives its name to the variety of inflammation, is the increased production of mucus by the epithelial cells and the cells of the glands. In the acute stages of the

inflammation, as well as in some forms of the chronic, there is a purulent, as well as a mucoid, discharge from the mucous membrane. Catarrhal inflammation may affect any of the mucous membranes of the body.

(*f*) *Ulcerative inflammation* (Fig. 11); *Desquamative inflammation.*—Ulcerative inflammation affects the surface of

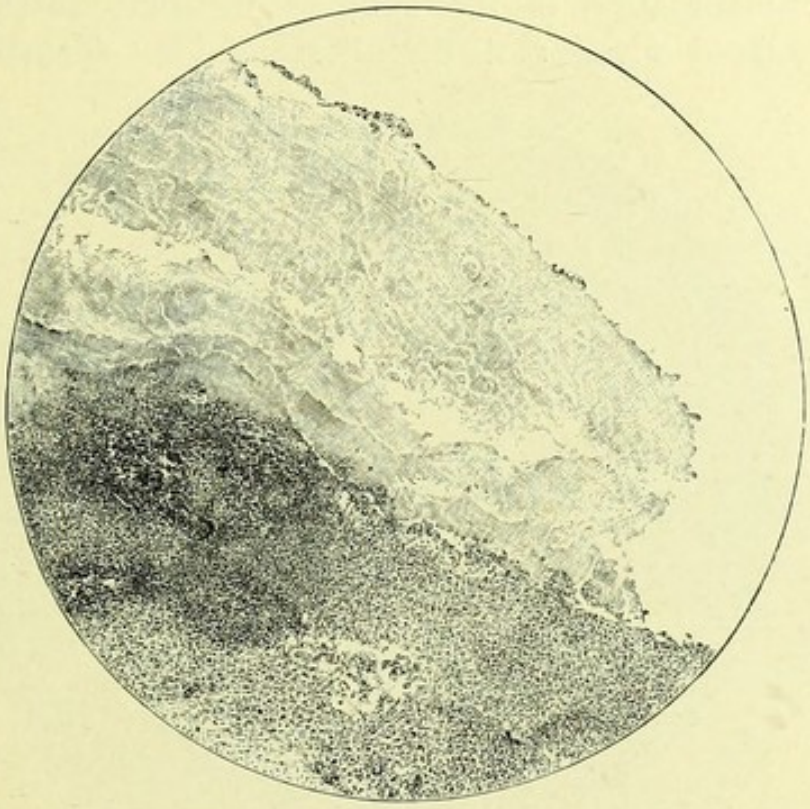


FIG. 8.—Croupous inflammation.

Section of a tonsil showing false membrane on the surface. The tonsillar tissue is in the lower part of the figure, and is composed of numerous cells, which, near the surface, are seen to be loosely attached to the tissue, and to be present partly in the false membrane. The false membrane is firmly attached to the tonsillar tissue; it contains a few leucocytes, and shows a faint fibrillation, due to the strands of fibrin, but no organised structure. At the surface small dark masses are present in the false membrane. These are groups of bacteria. (From a case of tonsillar diphtheria in a child.)

the body or mucous membranes, and consists of the usual changes in inflammation, with subsequent death of the superficial parts, and discharge of the necrosed inflammatory area.

The term desquamative inflammation is practically reserved for certain inflammatory conditions of the skin and other parts covered by stratified epithelium. Desquamation of this

epithelium may occur in acute inflammation, as, for example, in the gangrenous form, but it is also observed as the result of an acute congestion of the skin, after the congestion has passed off. This occurs, for example, as a sequence of several varieties of erythema, and is observed also in scarlet fever. It may also occur when there has been no obvious previous inflammation of the skin, as in some cases of influenza, typhoid fever and diphtheria. The desquamation,

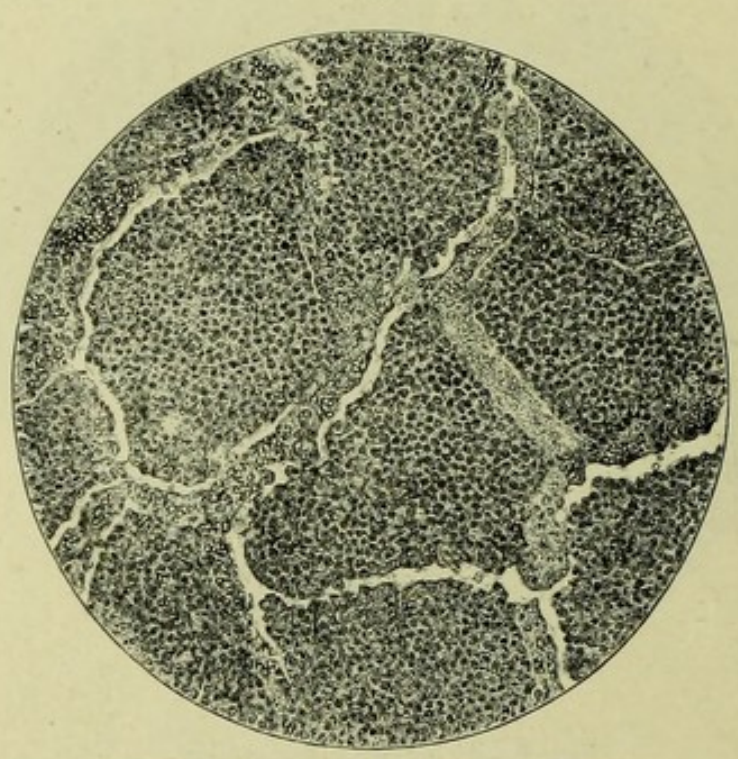


FIG. 9.—Croupous inflammation in the lung.

The figure represents the stage of grey hepatisation in croupous pneumonia. The alveoli are shown filled with leucocytes and a few larger cells coming from the epithelium, the cells being separated by strands of fibrin. The alveolar cells are larger than normal, owing to the distension of the capillaries.

which occurs as the result of inflammation, is, no doubt, directly dependent on the diminished nutrition of the epithelial cells of the skin.

(*g*) *Gangrenous inflammation* is applied to cases in which there is extensive destruction of the tissues of the inflamed part. It is due to particular forms of bacterial infection, and is sometimes associated with thrombosis of the vessels.

(*h*) *Parenchymatous inflammation.*—The term parenchymatous inflammation is a misnomer, inasmuch as inflam-

matory changes have to do with an alteration in the circulation of the blood, and not primarily with any change in the parenchyma or proper tissue of the organ; that is, the cells of the liver, kidney, or connective tissue do not, of themselves, undergo inflammation, without the vascular changes occurring.



FIG. 10.—Catarrhal inflammation.

The figure shows a transverse section of a small bronchus in a patch of broncho-pneumonia. The epithelium of the bronchial mucous membrane has proliferated, and some of it has disappeared, leaving the mucous membrane irregular on the surface. Around the bronchus there is great thickening of the tissue, due mainly to leucocytic infiltration. The alveoli are for the most part obliterated, and there is great dilation of the blood vessels.

The term parenchymatous inflammation is sometimes made interchangeable with interstitial inflammation. This, however, is a mistake. The only parenchymatous change which can properly come under this heading is one which affects the cells of the solid organs in the course of certain infections, namely, the cloudy swelling of the heart, liver, and kidney,

the changes in parenchymatous nephritis, as well as, perhaps, a similar change going on to fatty degeneration, which occurs in phosphorus and some other forms of poisoning.

(*i*) *Chronic Proliferative inflammation* (Figs. 12 and 13).—This is observed mainly in the skin, and parts of the body covered by stratified epithelium: it also occurs in glands.

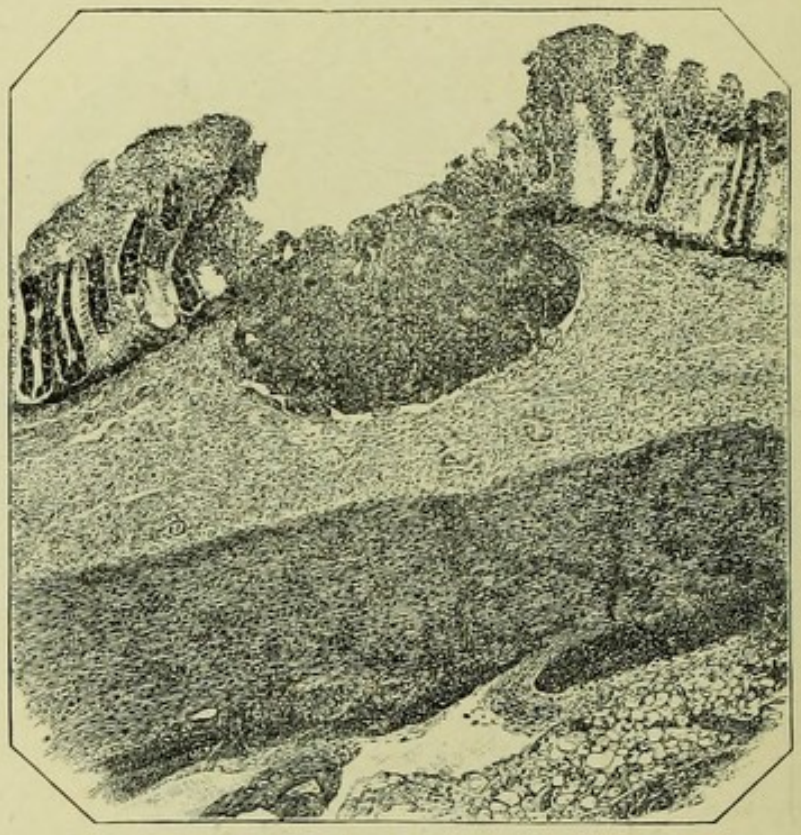


FIG. 11.—Ulcerative inflammation.

The figure shows a transverse section of an ulcerating solitary follicle in the large intestine. The mucous membrane is thickened by a leucocytic infiltration. The glands are degenerated, and remains of them are seen on the base of the ulcer, which is mainly occupied by the inflamed follicle. The submucous coat, the muscular coat, and peritoneal coat are all thickened, mainly by the leucocytic infiltration.

The inflammatory process is usually chronic, and leads to a great proliferation and heaping up of the epithelium, sometimes in the form of warts. Examples of this form of inflammation are observed in the skin, as in gonorrheal warts which may show, on section, no deep suppurating foci, and in post-mortem warts (*verruca necrogenica*), which are the result of post-mortem wounds, and show chronic inflamma-

tion with foci of suppuration and great proliferation of the skin and epithelium. This same variety of inflammation is also seen as the result of syphilis, either in the skin, nose, or buccal cavity. It also occurs in the œsophagus in some cases of dilatation very chronic in duration, and, as a rule, not due

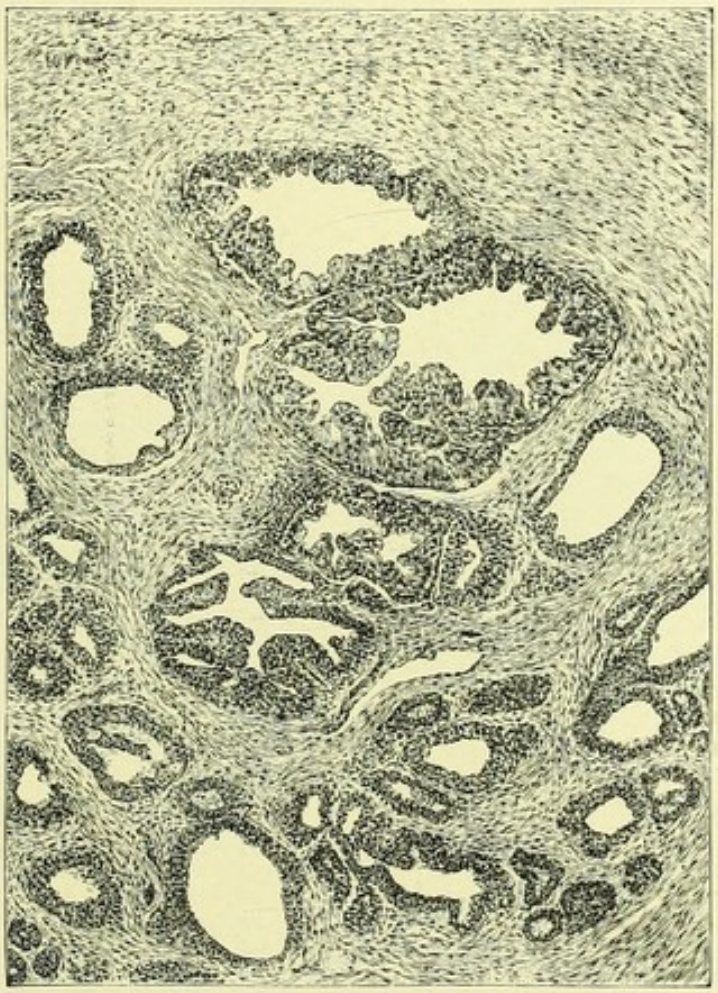


FIG. 12.—Proliferative inflammation.

The figure shows a transverse section of the mamma, in which the acini are irregular in shape, and in which the epithelial cells are greatly proliferated. There is an increase of fibrous tissue between the acini, and there is a tendency to cyst formation in the affected acini.

to obstruction at the cardia. It is observed in chronic inflammation of the mamma.

Nature of the Irritant.—Many different kinds of agents will produce the changes observed in inflammation. Bacteria and their products are, in disease, the main agents in producing inflammation. Other irritants will produce a local

inflammation which subsides, but the result of the action of bacteria is to produce a progressive inflammation. When this increases up to a certain point, it ends in death of the part or resolution.

Irritant poisons, such as croton oil, turpentine and corrosive sublimate, as well as mineral acids, will produce the changes observed in inflammation: but the action is not progressive.

The Course of Inflammation.—1. *Resolution and Repair.*—A slight inflammation, in which there are well marked vascular changes, and in which there is no formation of pus or destruction of much of the proper tissue of the part, may be recovered from, resolution taking place. The congestion diminishes; the blood current is restored; the exuded liquid is absorbed; the leucocytes usually dying, and the débris being carried away by the phagocytes. Such a slight degree of inflammation may be recovered from without any permanent damage to the tissue.



FIG. 13.—Chronic proliferative inflammation.

The figure shows a vertical section of a gonorrhœal wart. At the surface is seen thickening of the horny layer of the epithelium, which above is structureless, and below is composed of flattened cells. Beneath this layer is a greatly proliferated Malphighian layer, forming the greater part of the wart. The epithelium is arranged in a digitate manner, the body of the finger or the core of the wart being composed of connective tissue, in which are a few blood vessels.

In more severe cases, however, damage is done to the

tissue, and *repair* takes place. The process of repair has to be considered in the following circumstances: whether epithelium, columnar or stratified, has been destroyed, so that there is an erosion or ulcer; whether there has been more or less extensive destruction of the cells of an organ; whether the inflammation has occurred on the surface of a serous membrane, and lastly, whether there has been great destruc-



FIG. 14.—Granulation tissue.

The tissue is composed mainly of small round cells, chiefly leucocytes, with other elongated cells not well shown in the figure, owing to the low power of magnification. At two parts of the figure can be seen areas which contain nuclei in an apparently amorphous mass. These areas are masses of epithelial cells of the skin which are undergoing degeneration. (The specimen was taken from a wound of the skin.)

tion of tissue by abscess formation or by the occurrence of gangrene. Wherever there is an ulcer or great destruction of the tissue, or where the inflammation occurs on the surface of a serous membrane, granulation tissue is formed.

Granulation tissue (Fig. 14) is composed of cells among which numerous blood vessels ramify and anastomose. The

cells are, in part, leucocytes, but also consist of elements derived from the fixed cells of the part. These elongate, forming the so-called fibroblasts, which ultimately develop into connective tissue, the tissue of the scar. The vessels are at first mere channels in the tissue. They subsequently become lined with endothelium and are connected with the surround-

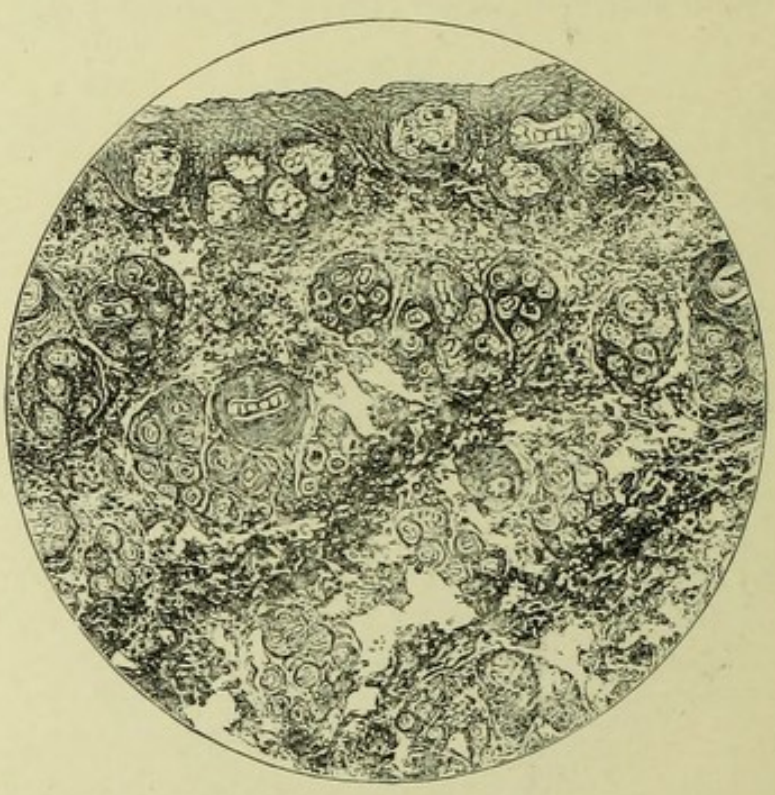


FIG. 15.—A healing wound.

This figure shows groups of epithelial cells beneath the epithelium of the skin, which is covering the wound. The groups of cells are separated by tissue, which contains a large number of leucocytes (granulation tissue). The epithelial cells are seen in all stages of division. They are the normal epithelial cells which grow from the edge of the wound in the process of healing, and are covered by the epithelium growing above them, mixing with the granulation tissue below. Eventually they disappear.

ing vessels. Most of the cells of the granulation tissue ultimately disappear; the remainder aid in forming connective tissue, and some remain as permanent connective tissue corpuscles.

Repair of epithelium takes place by means of the subdivision of the epithelial cells at the periphery of the lesion (Fig. 15). Epithelial cells can only develop from similar cells. The same is true of cells of organs and of muscle fibre, and

in any case in which there is a great amount of destruction of the heart muscle, the liver, kidney, or other cellular organs, no reproduction of the cell structure takes place, a connective tissue scar alone resulting. Such damage to the cell as cloudy swelling and slight fatty changes may be recovered from.

In cases where there is inflammation of the liver and kidney, subdivision of the cells is observed in parts. This subdivision, however, is hardly to be considered an attempt at repair, but is more correctly described as a result of irritation, similar to the subdivision of the endothelium of the blood vessels which sometimes occurs in an inflamed area.

Where there is a solution of continuity of tissue by means of a knife or other cause of wound, the process of repair differs according as to whether the wound is infected by a bacterium or not, whether the edges of the wound are apposed or not, and thirdly, whether the wound itself has caused much destruction of tissue.

The process of repair in infected wounds need not be specially considered, as repair takes place by granulation tissue. In non-infected or aseptic wounds, repair differs according to whether the edges of the wound are clean cut and apposed, and whether there is much destruction of tissue and bruising. In clean cut, aseptic wounds, with edges apposed, the healing is by primary union. In these the amount of tissue killed by the action of the knife is but small. Leucocytes emigrate from the blood vessels to the edges of the wound, some liquid is exuded, and healing takes place by means of the division of the cells of the part, the leucocytes being mainly employed in removing the dead tissue and the small amount of exuded blood.

When there is much destruction of tissue, as well as effusion of blood into the part, more evident granulation tissue is formed than in the first case, leucocytes act as phagocytes, removing the dead tissue and the effused blood; repair takes place by the granulation tissue in the manner previously described. A similar process takes place if the edges of the wound gape, and

still remain aseptic, the epithelium spreading from the edges of the wound.

2. *Chronic Inflammation.*—The term chronic inflammation is sometimes employed in two different senses. In true chronic inflammation the process is progressive, although slow. This means that the infective agent is still acting as an irritant. But the term is also applied to conditions in which there has been a profound change in an organ or part, caused by a previous inflammation in which there was destruction of cells with the formation of fibrous tissue. A typical chronic inflammatory process occurs in a chronic abcess, especially in those forms which occur in the skin, and in which there are multiple foci of suppuration, as well as in the lesions of tuberculosis, syphilis and leprosy.

With regard to internal organs, however, chronic inflammation shows itself in three different forms, which may all be associated with a small-celled, interstitial infiltration, an increase of fibrous tissue (fibroid hyperplasia) and degeneration of the cells of the organ. Thus, in the kidney, in chronic interstitial nephritis, both small-celled infiltration and fibrosis are observed, and in many cases these are associated with a fatty degeneration of the cells of the tubules. In the stomach, in chronic inflammation, the interstitial fibrosis may be slight, while the degeneration of the cells of the glands is great. In the liver, fibrosis is, as a rule, predominant, the degeneration of the cells being secondary (Chapter VII.).

Inflammation of Non-vascular Tissues and in Invertebrata.—*In Non-vascular Tissues of Warm-blooded Animals.*—The changes which result from the injury of non-vascular tissue depend on the strength of the irritant and the duration of exposure to the irritant, and are according to the degree of injury. Experiments were performed by Senftleben on the cornea, the irritant used being a solution of zinc chloride (66 per cent.), with a little chloride of sodium added. This caustic solution was applied to the centre of a rabbit's cornea for a greater or less length of time. Results varied in the two following ways (Figs. 16 and 17). If the caustic solution

was applied for so short a time that there was no solution of continuity of the corneal surface, a certain number of cells were killed by the caustic and a slight opacity of the cornea resulted. Repair took place by means of division of the corneal corpuscles, which lie, with their branched processes, between the layers of corneal tissue. The daughter cells passed from the healthy tissue to the injured; the dead cells



FIG. 16.—Repair of non-vascular tissue.

The figure is a drawing, under a high power, of a horizontal section through a lesion of the cornea made by the application of chloride of zinc, no solution of continuity occurring. The corneal corpuscles are seen. *b* and *c* represent those which have been killed by the caustic; *a* represents the normal corneal corpuscles, which are seen to send projections into the damaged area, these projections being nucleated, and eventually replacing the damaged cells. (Senftleben.)

were partly removed by means of these new cells, which eventually developed into adult corneal corpuscles (Fig. 16). As the result of this injury, there was no leucocytic infiltration, and no congestion of the vessels of the conjunctiva at the periphery of the cornea.

If, however, the injury to the centre of the cornea were such as to produce a solution of continuity (Fig. 17), in addition to the changes above mentioned, there ensued deep congestion

of the vessels of the conjunctiva, and emigration of leucocytes, which travelled from the periphery towards the central part which was injured. It is probable that, in this case, some of the caustic solution was absorbed by the cornea, and travelled in the corneal spaces to the conjunctiva, where it produced inflammatory effects. There could be no reflex nervous

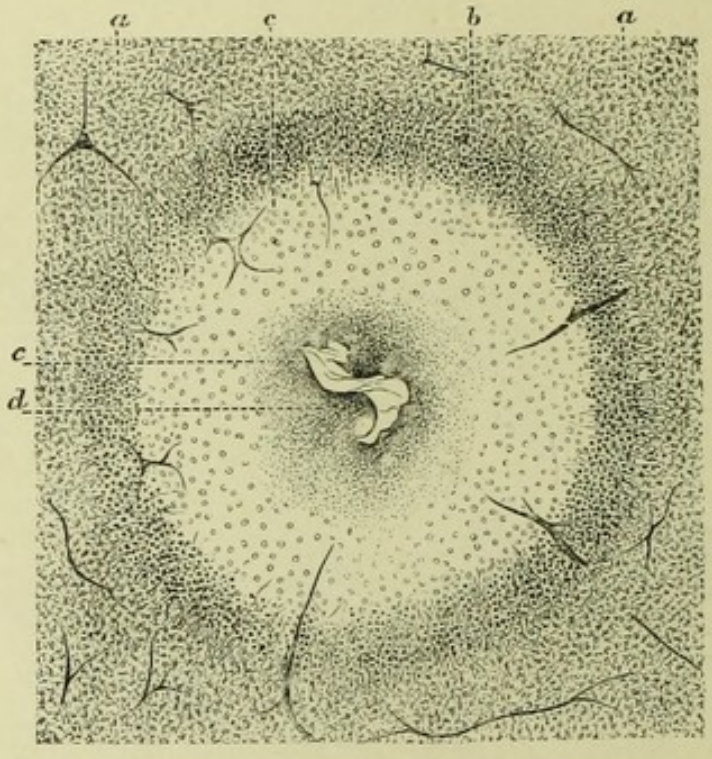


FIG. 17.—Inflammation of non-vascular tissue.

The figure represents a horizontal section, under a low power, of the cornea, which has been damaged by the application of chloride of zinc; a solution of continuity has occurred (*c*). Outside this is seen (*d*) a collection of dots, which represent leucocytes. Then comes a clear zone, in which the circles represent corneal corpuscles, most of which have been destroyed by the caustic. Then comes a third zone of leucocytes, and, finally, a zone (*a*) of normal corneal corpuscles. (Senftleben.)

mechanism concerned in such a case as this. The repair of the solution of continuity takes place by means of non-vascular granulation tissue, and if complete healing takes place, the leucocytes disappear for the most part. Some of these, however, may be transformed into corneal corpuscles, but most of the latter are reproduced from pre-existing corpuscles. In bacterial inflammation of non-vascular tissues similar phenomena are observed, but the process is intensified,

so that the leucocytes are distributed throughout the whole of the tissue (Fig. 18).

Inflammation in Invertebrata. — *Phagocytosis.* — The explanation of the emigration of white blood corpuscles in the process of inflammation in vertebrate animals has, to a great extent, been made clear by the researches of Metchnikoff into phagocytosis, and into the changes which occur in invertebrate animals in response to a mechanical injury or the invasion of micro-organisms.

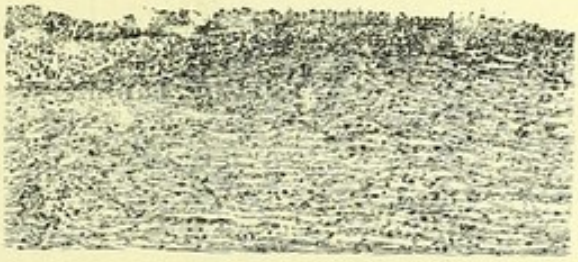


FIG. 18.—Inflammation of non-vascular tissue.

The figure shows part of a vertical section of the cornea, which is inflamed (bacterial corneitis), and is in reality an exaggeration or advanced stage of Fig. 17. The surface of the cornea is irregular from the destruction of the epithelium, and beneath this layer is one of leucocytes, which are also scattered irregularly through the corneal tissue.

Phagocytosis may be defined as the process by which animal cells take in solid particles, living or dead, some being digested, others discharged, others again, if living, capable of destroying the cell. This is a process that is very extensively observed in the animal kingdom, and may be discussed under the heading of physiological and pathological phagocytosis.

Physiological phagocytosis is observed in many of the lower animals, in which it is one of the means of obtaining and digesting food. The amœba takes in bacteria and diatoms from the water in which it lives, digesting some of these, rejecting others. Some of the living organisms taken in by the amœba may actually increase within its body, causing the death of the cell. In such a case as this there is no sharp line between physiological and pathological phagocytosis. The hydra, which is a simple double cellular organism with an elementary digestive cavity, by means of the cells lining in this cavity takes its food in the form of solid particles. A uni-cellular organism, like paramœcium, also receives its food in this manner.

Amongst warm-blooded animals, the process of absorption of fat in the small intestine is an example of physiological phagocytosis. The minute globules of fat are taken up by the epithelial cells, and then by the leucocytes, by which they are conveyed to the lymph stream. The absorption of bone during ossification, by which the secondary areolæ are formed, is another example of the physiological process, as well as the absorption of bone in old age by means of the osteoclasts. The absorption of the branchiæ in the tadpole during its transformation into a terrestrial animal is also an example of phagocytosis.

Pathological phagocytosis is observed when a living organism is injured mechanically, infested by a parasite, or when an inert foreign body is introduced into its substance. In many cases it is a battle between the host and the parasite, in which, in some cases the host, in others the parasite, gains the upper hand. The parasite itself may produce an injurious effect on the host in two ways: either (1) mechanically, by its mere increase destroying the vitality of the tissue or of the host if this be a lowly formed animal or if the parasite destroy a vital organ; or (2) by its secretion of toxic substances, which destroy the vitality of the host. In the latter case the action of the parasite is usually much more deleterious.

Metchnikoff has described the following chain of events as occurring in lowly organised animals, either as the result of injury or parasitism. With the uni-cellular organisms, such as the amœba, some of the living particles taken in serve, as has been stated, as food. Others again, instead of being digested or rejected, may produce a fatal disease. Metchnikoff has observed such a disease in the amœba, which takes into its substance a microsphæra, an organism composed of nucleated round cells multiplying by division (Figs. 19 and 20). This organism may multiply to such an extent as to kill the amœba. In other instances, in uni-cellular organisms, the parasite taken in may, after a short period of life and subdivision, be killed and digested by its host. There is evidence, then, even in these lowly organ-

isms, of a struggle for existence between the parasite and its host.

In multi-cellular organisms, phagocytosis becomes more complicated, owing to the progressive differentiation of function in the cells. These organisms are composed of three layers, ectoderm, endoderm and mesoderm, and it is to the cells composing the last of these that the property of phagocytosis becomes eventually mainly limited in the progress of evolution. The sponges protect themselves against harmful bodies by means of their contractile ectoderm cells, but the cells of the mesoderm and endoderm also act as phagocytes. By thrusting a small tube of glass into the body of spongilla, Metchnikoff observed that the tube became surrounded by mesoderm cells, which eventually fused together, forming a primitive giant cell (Figs. 21 and 22).

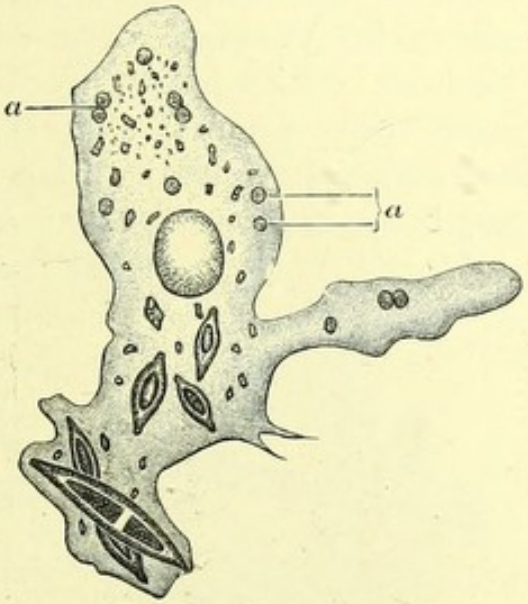


FIG. 19.—Phagocytosis.

Drawing of an amœba showing commencing invasion by the microsphæra. In the lower part of the figure diatoms are seen in the substance of the amœba. These are subsequently digested and utilised as food. Above this is a vacuole, and at *a* are seen the spores of the microsphæra. The later stage is shown in Fig. 20. (Metchnikoff.)

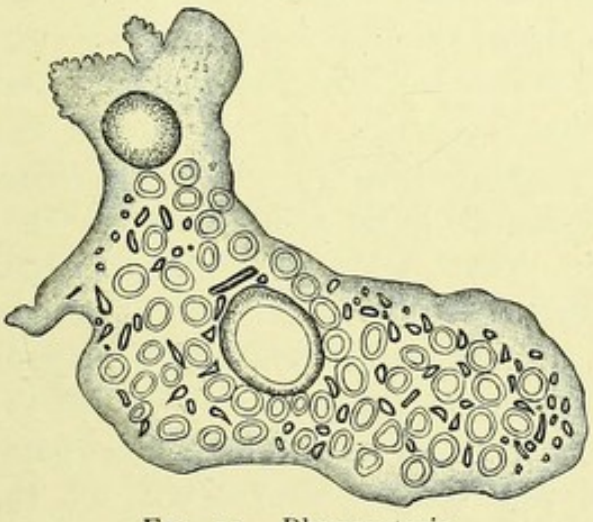


FIG. 20.—Phagocytosis.

This shows the advanced stage of the invasion of the amœba by the microsphæra. The animalcule is now becoming quiescent, slowly dying from the great growth and division of the invading micro-organisms. These are shown scattered throughout the protoplasm as spherical bodies. (Metchnikoff.)

In the simple animals which possess no mesoderm (cœlenterata), the endoderm cells, and sometimes the ectoderm cells, play the rôle of phagocytes; but in all animals which possess a mesoderm, it is the cells of this layer which are mainly the phagocytes. They sur-

round and attack harmful substances introduced into the body of the animal, and frequently fuse together, forming plasmodes or giant cells. This has been observed in the medusæ, echinoderms, worms and vertebrates. The mesoderm cells, which are at first a more or less fixed layer of the embryo, eventually in part become the wandering cells of the body, and are present in the fluid which fills the body cavities of the lower animals and the vascular system of such animals as molluscs and arthropoda. When such an animal is injured, there is an accumulation of these cells at the injured spot, just as in the inflamed area in a warm-blooded animal. A similar accumulation occurs if an inert foreign body, such as a piece of glass or a little pigment, is introduced into the tissue of the animal. When the foreign body is a living agent, there is evidenced the struggle between the host and the parasite or infective agent, and one example of this, which was well worked out by Metchnikoff, was that occurring in the water flea (*Daphnia magna*), which was found infested in a pond with a kind of yeast called *Monospora bicuspidata*. It was found that, at certain periods, an epidemic of this disease would kill off nearly all the daphniæ in the pond, whereas, at other periods, the animal would survive, although it might contain a few parasites. The ripe spores of the fungus are eaten by the animal, and pass through the intestinal wall into the body cavity. The germinating spores here become surrounded by the leucocytes, and one of two events may happen: the spores may rapidly develop, and the parasite increase

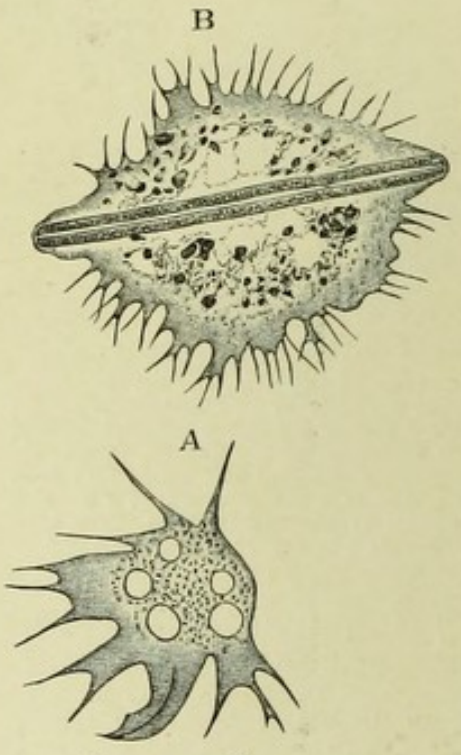


FIG. 21.—Phagocytes.

B shows a plasmode or giant cell, which has been formed by fusion of phagocytes in the body cavity of a worm, around a foreign substance. A shows a single phagocyte vacuolated in parts, and with numerous projections or pseudopods. (Metchnikoff.)

so as to fill the body cavity and eventually destroy the life of the animal, or, becoming surrounded by leucocytes, they become degenerated and die, the animal gaining the upper hand.

If the non-vascular fin of young tadpoles of the lower amphibia (*urodeles*) be slightly injured, the amœboid cells collect at the injured spot, the fixed cells of the tissue taking no part in the process. In older tadpoles, when the blood vessels have developed, there is still this accumulation of leucocytes at the injured spot; but, in addition, there are the

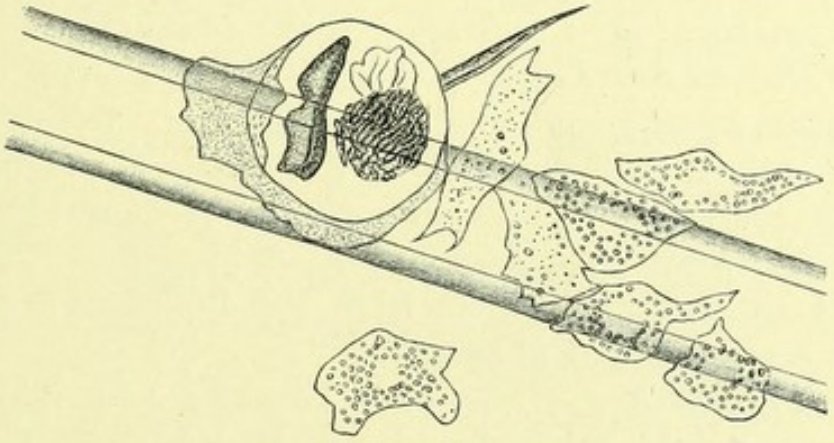


FIG. 22.—Phagocytosis.

This figure shows the effect of passing a spicule of glass into the body of a sponge (spongilla). The wandering cells of the body cavity are attracted by the foreign body, which is seen at one part to be becoming surrounded by the cells. The figure illustrates the point that inert matter attracts the phagocytes. (Metchnikoff.)

phenomena of inflammation, such as the acceleration of the blood stream and the other changes which are observed in the higher animals.

As Metchnikoff points out, the attraction of leucocytes to the injured spot must, in the process of the evolution of inflammation, be considered the primary; the vascular changes being, so to speak, added.

In the higher animals phagocytosis is a part of inflammatory and of infective processes. Inasmuch as nearly all the inflammatory processes are part of infection, phagocytosis is really mainly associated with the invasion of the body by micro-organisms. The cells which act as phagocytes in the

higher animals are chiefly the wandering mesoderm cells (the leucocytes), and some of the elements of the splenic pulp. The endothelial cells of the blood vessels also act as phagocytes. In leprosy, they frequently contain the bacillus: tubercle bacilli, injected into the circulation, are taken up by the endothelial cells of the vessels, and a similar result has been observed with the bacillus of swine erysipelas.

Varieties of Phagocytic Leucocytes. — There are four chief varieties of leucocytes found in the blood, and two other smaller varieties: only two are actively phagocytic.

The Mononuclear Leucocyte (Fig. 94) is also called the large lymphocyte, hyaline cell, and macrophage or macrophagocyte. It forms only 2 to 8 per cent. of the leucocytes of the blood. It has a single round or kidney-shaped nucleus, and a large amount of hyaline protoplasm without granules. The protoplasm stains well. It differs from the lymphocyte by being actively amœboid and phagocytic.

Polymorphonuclear Neutrophile Leucocyte (Fig. 94)—(finely granular oxyphile, microphage). This leucocyte forms the largest proportion of those in the blood, from 60 to 70 per cent.: in children the proportion is lower, 18 to 40 per cent. They are absent from cœlomic fluid, and are the usual form of pus cell. They, indeed, are the chief leucocytes which emigrate from the blood vessels in inflammation. When stained by aniline dyes their appearance is very characteristic. When deeply stained with eosin and methylene blue or with Ehrlich-Biondi, the nucleus is branched, the protoplasm itself fairly abundant, showing numerous small granules, which stain feebly with acid dyes (eosin and fuchsin). These leucocytes are the chief phagocytes, and are actively amœboid.

The consideration of the other leucocytes will be reserved for the discussion of the blood (Chapter XI.). For the present purpose, it may be noted that the chief phagocyte is the polymorphonuclear neutrophile, and the other phagocyte is the hyaline cell or the large lymphocyte.

The phenomenon of phagocytosis is frequently observed in infective processes occurring in disease, in the localities in which the infective agent grows. The leucocytes are observed to contain bacteria within their substance, but these are also present, and are growing, in between the cells. In some cases there is abundant phagocytosis; in others but little. In some instances the bacteria reside chiefly in the cells. This is true of the leprosy bacillus and of the gonococcus, the former of which is an example of a very chronic infection, the latter of an acute. In pus infection, phagocytosis may or may not be abundant, but in some other infections phagocytosis is practically absent, such, for example, as the infection by virulent anthrax and other rapidly acting micro-organisms.

From what has previously been said regarding the reaction between living cells and foreign bodies or infective agents brought into contact with them, the degree of phagocytosis in any particular lesion cannot be considered a haphazard occurrence. Experiment has shown that foreign substances in some cases attract the living cells, in other cases repel them. This action is referred to as chemiotaxis or trophotropism; positive when the leucocytes are attracted, negative when they are repelled.

A good example of this action is seen in one of the lower fungi (*Œthalium septicum*), one of the myxomycetes, a gelatinous mass which grows in tanning vats. This fungus was found to be attracted by oak infusion, and repelled by a solution of glucose.

Of substances which induce *positive chemiotaxis*, the following may be enumerated:—

Most bacteria living or dead, also substances extracted from the bodies of bacteria and called proteins (Buchner), papain, leucin and copper and mercury compounds.

Of substances which induce a *negative chemiotaxis*, the following are the chief:—

Virulent bacteria, alcohol, chloroform, glycerine, bile, quinine, abrus, strong solutions of sodium and potassium salts and salts of gold, silver and iron.

The attraction and repulsion of the living cell no doubt depends on the nutritive relation, mainly chemical, between the foreign substances and the cell, an idea which will be further developed in the consideration of the subject of immunity (Chapter VI.).

CHAPTER II

CHANGES IN THE BODY TEMPERATURE IN DISEASE; PYREXIA

The Normal Body Temperature and its Maintenance.—In health, the temperature of the body shows diurnal variations between certain limits, which are not exceeded, whatever the exercise or food taken. The highest temperature of the mouth during the day is a little under 99° F.; the lowest temperature occurs at midnight, or soon after, and varies between 96° and 97° F. This type is reversed if sleep is taken during the day, and the individual works at night. A temperature above 99.5° F. in the mouth is an abnormal condition; that is, it is a febrile state.

The axillary temperature is about 0.5° F. less than that of the mouth, and the rectal temperature varies in the day from 98.2° to 100.4° F.

Under the age of twenty-five years the daily variation of the temperature is about 2° F.; over the age of forty the daily excursion is about 1° F.; and in old age, the daily excursion may be greater than this and more variable. The daily excursion is greater when manual labour is performed.

The normal type of temperature may therefore be described as follows (Fig. 23):—

Starting at twelve midnight, when the temperature is lowest, namely, 96° to 97° F., there is a gradual rise in the early hours of morning until after breakfast. A cold bath in

the morning before breakfast causes, in some cases, a rise in the mouth temperature. From the morning meal till midday, or later, the temperature is maintained between 98° and 99° F. There is then a gradual fall till midnight, if no further heavy meal is taken. If, however, a large meal is taken in the evening, the temperature again rises somewhat, and tends to fall to the lowest normal after midnight.

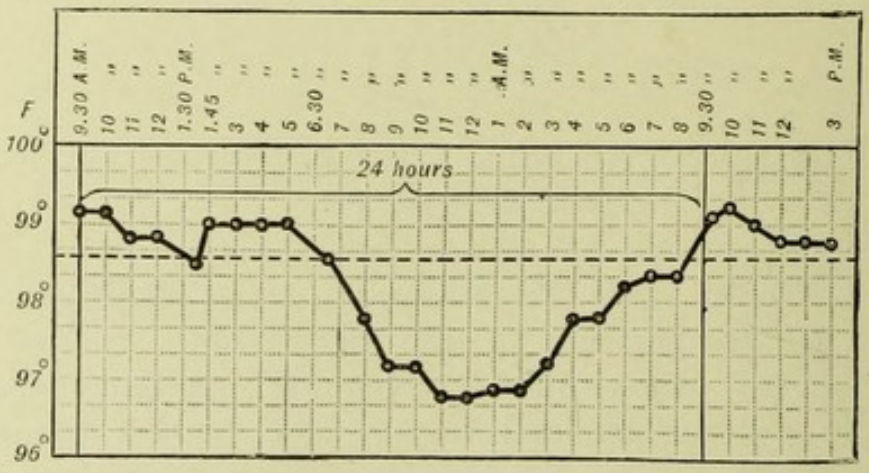


FIG. 23.—Chart of the mouth temperature taken hourly of a healthy lad aged twelve years (Ringer).

The body temperature between the normal limits is maintained by a balance between heat production in the body (thermogenesis) and heat loss from the body (thermolysis), a balance which is regulated by the nervous mechanism (thermotaxis). There is a constant and varying production of heat in the body by the activity of the cells of the tissues, the sources of energy and heat being mainly the carbohydrates and fats taken in with the food, and utilised by the protoplasm of the cells. Muscular activity leads to great production of heat, the muscles forming one half of the body; but even during rest, heat is provided by muscular metabolism. Gland activity also produces heat, the greatest source of heat from this cause being the liver. The hepatic blood is the hottest in the body, being 104° F. The blood in the aorta is 102° F., the mean temperature of the blood being 102.2° F. (39° C).

There is a constant loss of heat from the body by way

of the skin, the lungs and the kidneys: from the skin by means of radiation of heat and the evaporation of the sweat; from the lungs by means of the warming of the inspired air and the evaporation of the water in the expired air. In the kidneys the loss is due to the passage of the warm urine.

In health extra exertion does not lead to a rise of body temperature, nor does excessive loss of heat lead to a fall. The reason for this is that heat production, and, to a greater extent, heat loss, are regulated by a nervous mechanism, which is essentially a reflex one.

The central heat centres are closely connected with the vaso-motor, secretory, sensory and thermic nerve fibres in the skin. "Heat" centres have been described in several parts of the cerebral hemispheres. Thus, in the motor area of the cortex, destruction on one side causes an increased temperature in the extremities of the opposite side lasting for a considerable time after the injury. Stimulation of the centres causes a slight temporary cooling. Basal "heat" centres have also been described; on the median side of the corpus striatum, between the corpus striatum and optic thalamus, and at the anterior end of the optic thalamus; destruction of these parts by means of a needle causes a rise of body temperature. The rise of temperature in injuries to the human brain confirms the existence of the influence of the central nervous system on the body temperature. The reflex nervous mechanism is chiefly stimulated by cold and heat.

Variations of the Body Temperature in Disease.—Pyrexia.—Variations in the normal daily excursion of the temperature occur in two different directions. The temperature may be continuously subnormal, as in the first period after the fall of the temperature in certain infective diseases, and in certain chronic diseases associated with profound changes in metabolism (diabetes, renal disease, neurasthenia). A temperature of 98.4° F. is artificially taken as the normal. A temperature of 99.5° F. is considered as the limit at which pyrexia begins, and the following table shows the

terms in common use for differentiating the degree of body temperature :—

95° F.	Collapse.
96.8° F. to 97.7° F.	Subnormal.
98.4° F.	Normal.
99.5° F. to 101.5° F.	Slight pyrexia.
102.2° F. to 103° F.	Moderate pyrexia.
104° F. to 105° F.	High pyrexia.
105.8° F. and above	Hyperpyrexia.

Types of Pyrexia.—These are usually divided into *continuous and remittent, intermittent and hectic.*

The continuous type (Fig. 24) is when, during the course, the temperature in its remissions never falls to the normal but is regulated to a higher normal, the daily fluctuations being 1° to 2° F. In the remittent type, the daily fluctuations are more than 2° F., and may be 4° or 5° F., but the temperature never falls to the normal. In the intermittent and hectic type (Fig. 25) the temperature falls to the normal or subnormal each day, and this may either be in the morning, as is usual ; or at night, giving, in the latter case, what is called the *typus inversus.* The daily fluctuations may be 6° or more.

These types of pyrexia must be distinguished from the pyrexia of a disease. Some diseases show, in their course, a regular type, others an irregular (Fig. 26). The pyrexia of a disease may end suddenly, as by *crisis*, the temperature falling to the normal, or below, within five to twenty-four or thirty-six hours (Fig. 27) ; or slowly, as by *lysis*, the temperature showing a gradual or "step-ladder" fall to the normal or below, this fall occupying a period of three or more days (Fig. 24).

In *hyperpyrexia* (Fig. 28), which occurs in typhoid fever, rheumatic fever, diphtheria, the exanthemata and in some cases of disease and injury of the central nervous system, the rise of temperature is sometimes sudden and sometimes gradual.

Symptoms and Pathological Changes in the Pyrexial State.—The circulation is affected as shown by an increased frequency of the cardiac beat ; the respiration shows an increase in

the number of respirations per minute; and there is a diminution in the secretion of saliva, gastric juice, pancreatic juice, urine, sweat and bile. Nutrition is impaired; and the effect on the nervous system is well marked, as shown by the rigor, headache, muscular weakness, and, in acute pyrexial diseases, by a state of excitation which may proceed to delirium and end in coma.

The symptoms show great variations in individual pyrexial diseases. In some there is no greatly increased frequency of the cardiac beat, nor is the respiration markedly affected. In others, the dry skin is not observed, and profuse sweating occurs, while the symptoms associated with the nervous system show considerable variation. It is difficult, if not impossible, to say how far these symptoms are due to the state of pyrexia, and how far to the action of the specific poisons which are circulating in the body in infective disease.

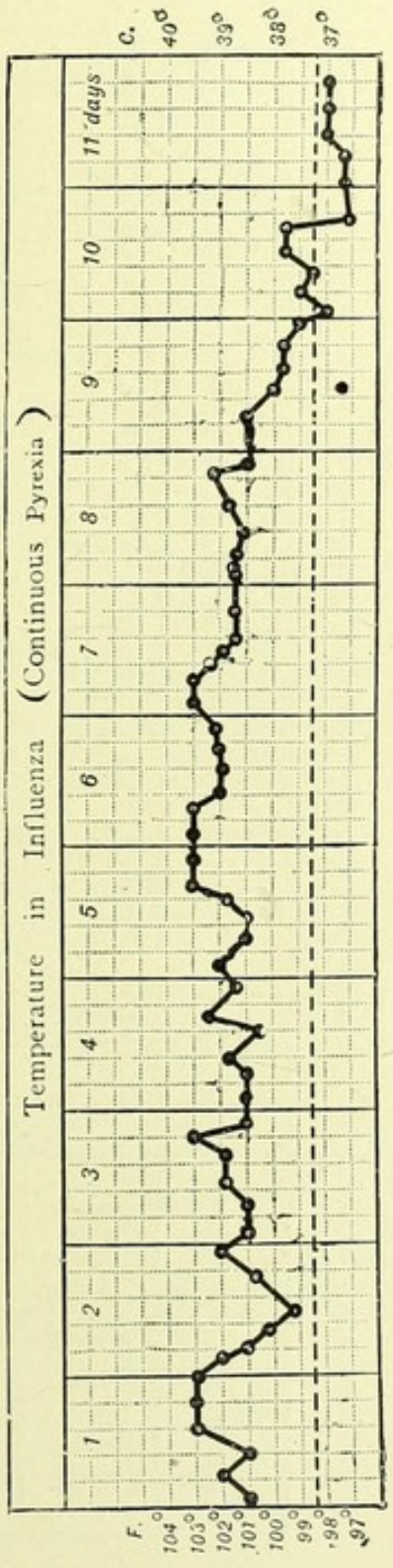


FIG. 24.—Type of a continuous pyrexia of moderate degree ending by lysis: the temperature (axillary) taken every four hours.

In the pyrexial state, there is evidence of increased metabolism, as shown by the increased discharge of carbonic acid (CO_2), and increased excretion of urea.

1. *Respiratory Exchange.* — There is an increased activity leading to an increased intake of oxygen. The respiratory quotient is the proportion between the output of carbonic acid and the intake of oxygen

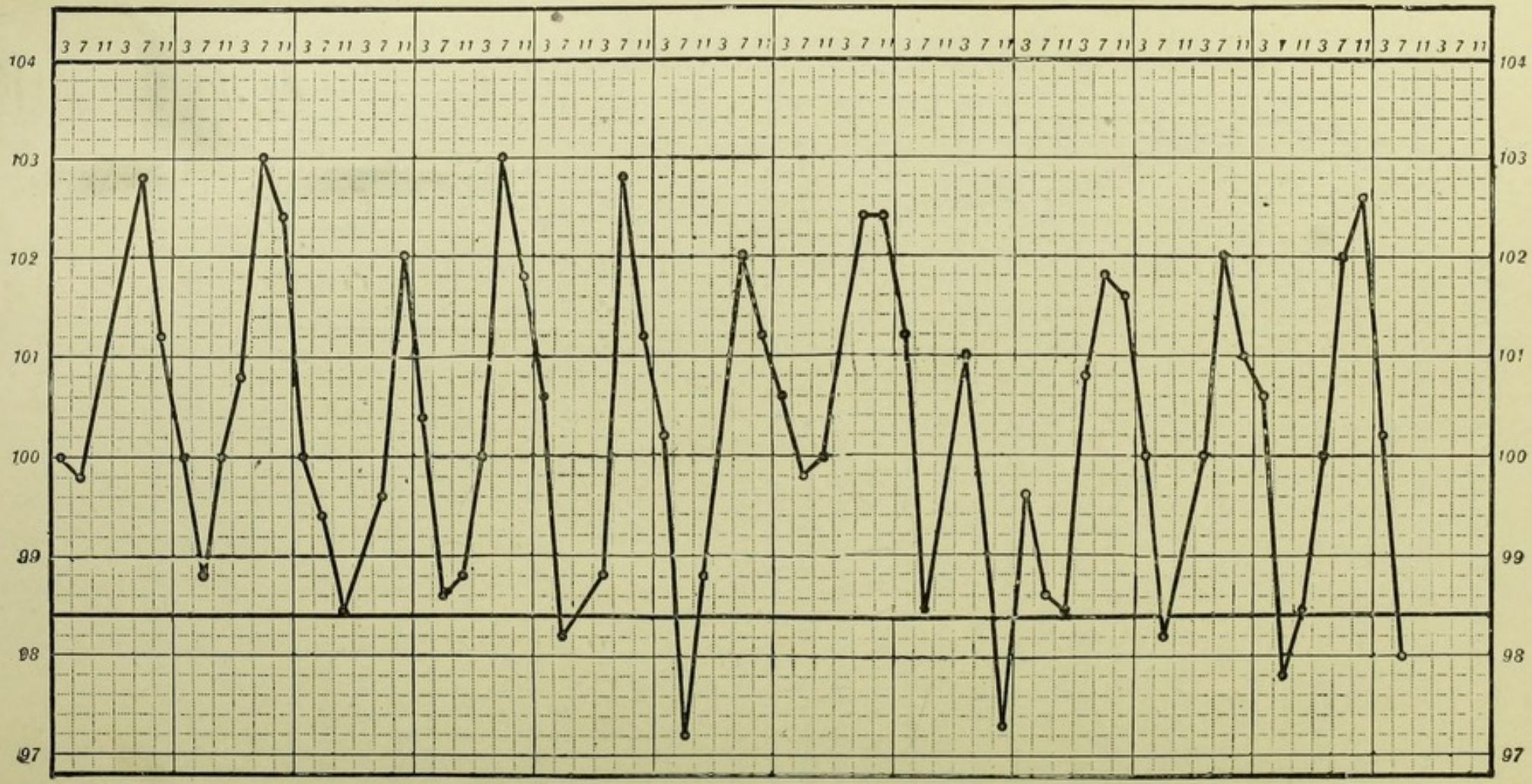


FIG. 25.—Type of intermittent pyrexia ("hectic" fever) in a case of pulmonary tuberculosis: the temperature taken in the mouth every four hours. There is a nocturnal rise to a varying height, succeeded by a morning fall to normal or subnormal.

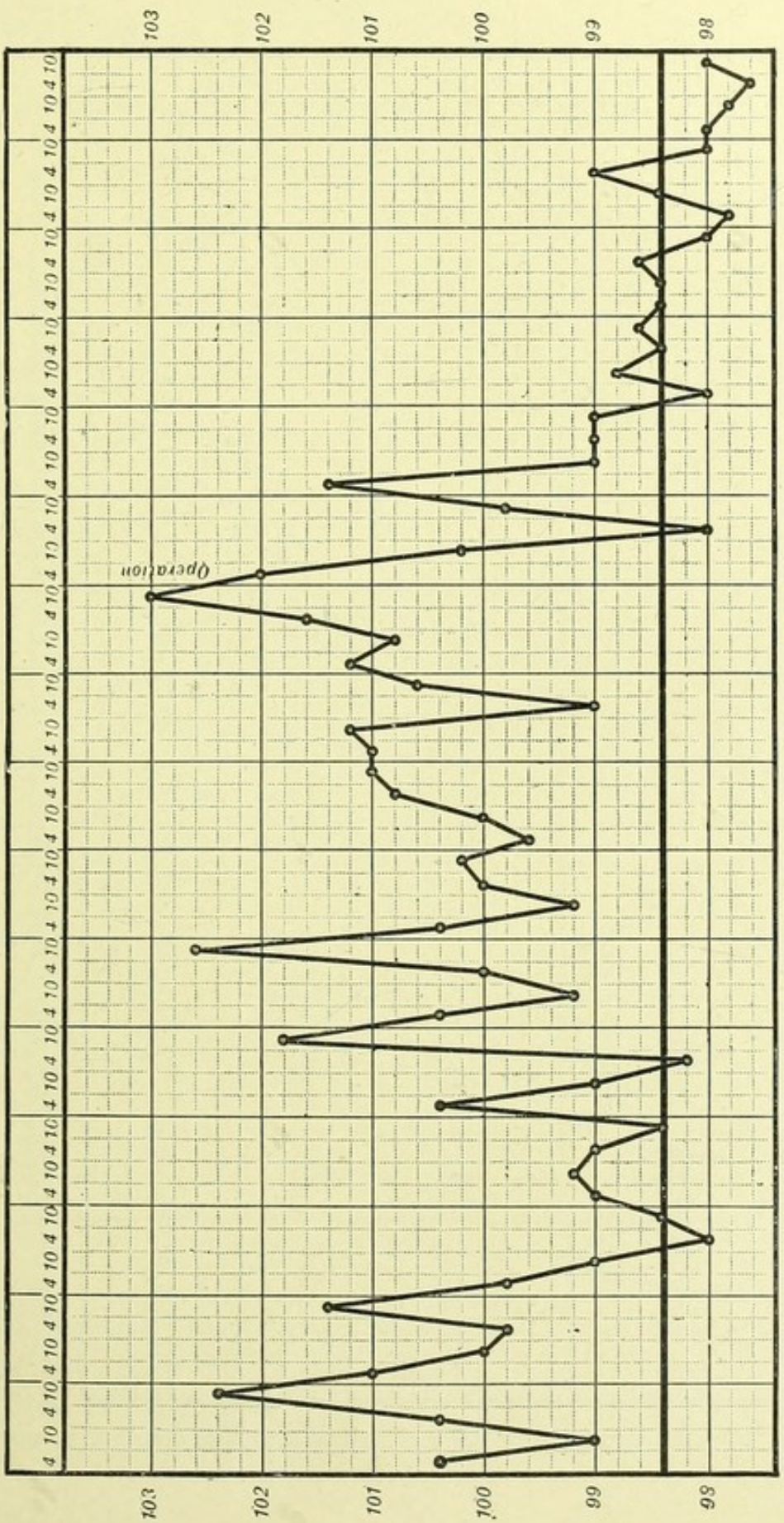


FIG. 26.—Type of irregular pyrexia occurring in pus infection (empyema). A fall of temperature to the normal followed the evacuation of the pus.

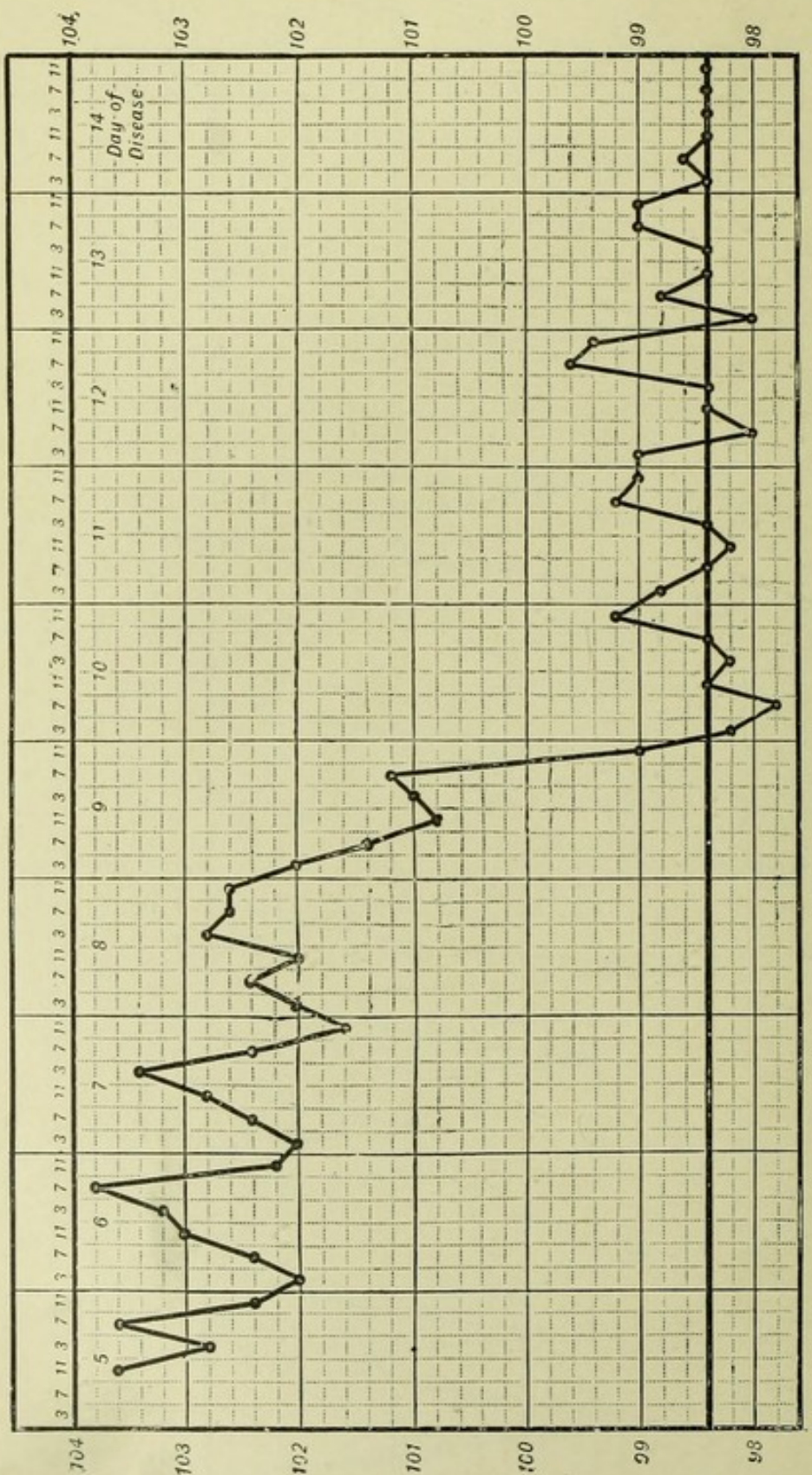


FIG. 27.—Continuous pyrexia of moderate degree, ending by crisis, in a case of primary unilateral pneumonia.

$\frac{(CO_2)}{O}$. The respiratory quotient in fever may be unaltered or diminished; it has been found very variable in the different

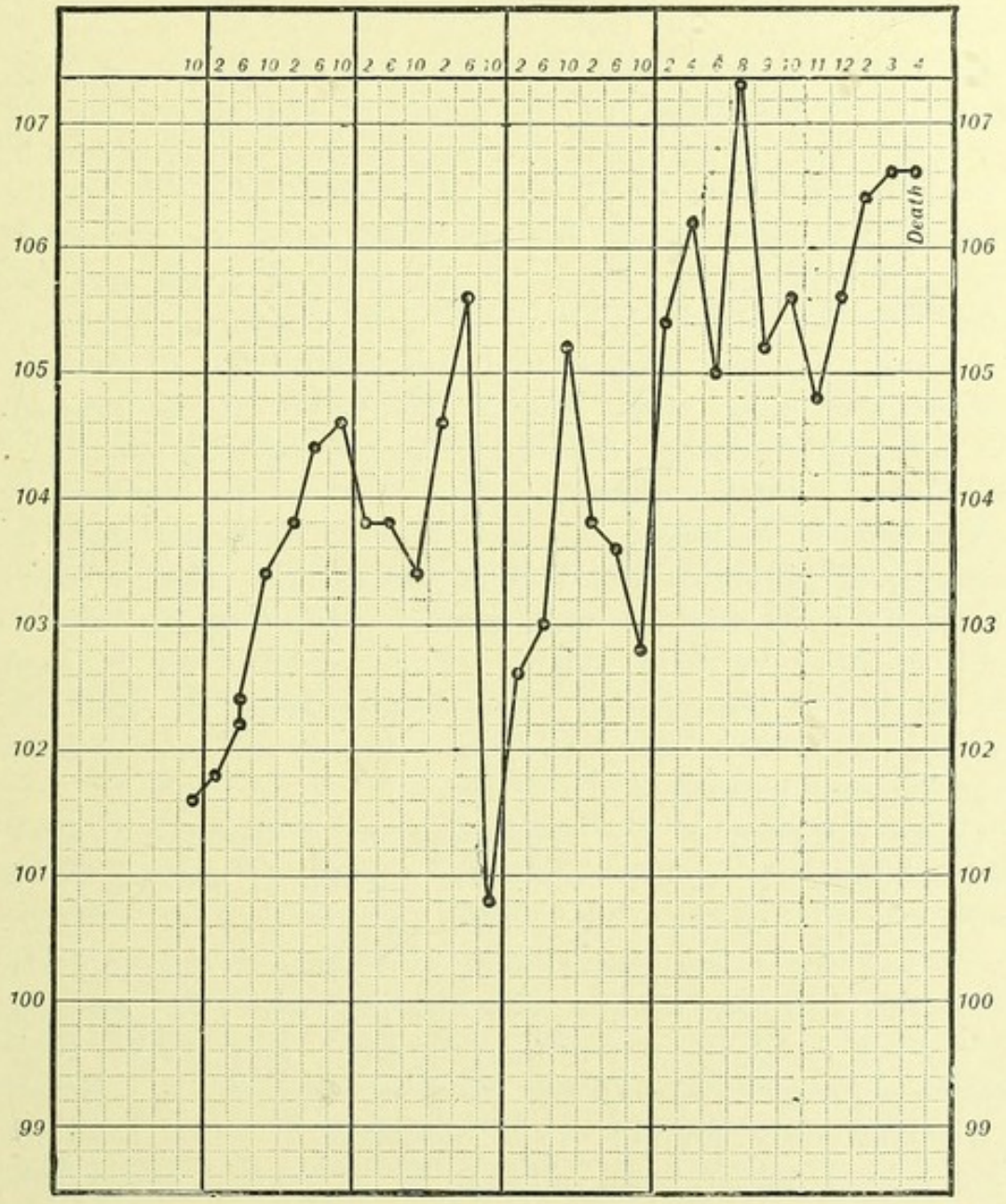


FIG. 28.—Hyperpyrexia in a case of typhoid fever.

experiments performed. Liebermeister found the respiratory exchange doubled or trebled, two or three times the normal amount of CO_2 being discharged. In his experiments, Reynaud found that the increased intake of oxygen was more than the

output of carbonic acid, thus diminishing the respiratory quotient.

2. *Nitrogenous Metabolism: Discharge of Nitrogen.*—There is an increased discharge of urea, which was described by Traube in 1855. In 1859 Ringer investigated a case of malaria, and showed that the increased discharge of urea began before the onset of the rigor; it diminished rapidly after the onset of the pyrexia. This is due to the retention of urea in the body; since, with the crisis, there is a greatly increased discharge, which is sometimes called the *epicritical increase*, and is simply caused by the removal of the retained urea. The increased excretion of urea means an increased destruction of tissue proteid, and this destruction in pyrexia is sometimes more than doubled compared to the normal. The nitrogen discharge diminishes as the pyrexia continues and shows diurnal variations. Not only is the amount of urea discharge increased, but also that of ammonia salts, of creatinin, of hippuric acid and of uric acid. The pyrexial patient lives on his fat and proteid, owing to the diminished quantity of food taken. The available fat is soon exhausted, and the proteid then disintegrates. In lean but muscular men with high pyrexia there is at first a very great increase in the urea discharge.

Other evidence of the disintegration of tissue proteid is obtained from the urine. Thus the amount of *acetone*, which normally only exists in the urine to the amount of 0.01 gramme in the twenty-four hours, is increased ten to forty times, the increase usually disappearing with the pyrexia. Two other bodies not normally present may make their appearance, *aceto-acetic acid* and *β-oxybutyric acid*. The former is not constantly found; it is observed in some cases of chronic lung tuberculosis, as well as in certain non-febrile diseases, such as inanition, diabetes, cancer, poisoning and gastro-enteritis (Chapter XVIII.). The latter acid is found mainly in scarlet fever, measles and typhoid fever. In pyrexia volatile fatty acids (formic, acetic, butyric, and propionic), are sometimes found in the urine: occasionally lactic acid is present.

It has been shown that the administration of sugar in

the febrile state diminishes the amount of urea discharged. The subject, however, cannot be considered simply from the point of view of metabolism. Thus, the increased disintegration of proteids is shown by the increased discharge of urea, and is not explained completely by the exhaustion of the fat, as it still occurs when a large amount of fat is present in the body. Part of the disintegration of proteids is due to the direct action of the circulating infective poisons on the tissues.

3. In the febrile state the liver loses its glycogen and sugar.

4. There is sometimes concentration of the blood, owing to sweating. The alkalinity of the blood is diminished owing to the presence of the organic acids already mentioned as excreted in the urine.

5. The urine shows distinct changes. "Febrile" urine is diminished in quantity, dark in colour, and deposits urates on standing and cooling. The specific gravity is increased. These characters may, however, be absent if much water is drunk, or if pyrexia occurs in diseases associated with polyuria, such as diabetes and granular contracted kidney.

There is a diminished excretion of chlorides in the urine, except in rheumatic fever, typhoid fever and malaria. This diminution does not as a rule last more than three days: only 2.2 grammes sodium chloride may be found in the daily urine as compared with the normal 16.5 grammes. There is an increased excretion of phosphates and potassium. The sulphates vary with the amount of nitrogen in the urine. The urine also contains pathological urobilin and reduced normal urobilin, which arise from the bile or blood pigment.

6. Albuminuria may be present: "febrile" or "toxic" albuminuria (Chapter XVI.). Serum albumin and globulin are found, as well as casts, mainly hyaline. Albuminuria is most common in pneumonia, erysipelas, scarlet fever, diphtheria, smallpox, and typhoid fever; it also occurs in pus infection. Albumosuria may be found (Chapter XVI.).

7. The urine sometimes gives the diazo-reaction, which is an orange-red to cherry-red colour, developed on the addition to the urine of sulphanilic acid, sodium nitrite and ammonia. The reaction is obtained most frequently in

typhoid fever, advanced pulmonary tuberculosis, miliary tuberculosis and measles. It is not common in pneumonia, scarlet fever and diphtheria; and is very rare in rheumatic fever, meningitis and erysipelas. The chemical substance which gives the reaction is unknown.

The metabolic changes observed in different cases of pyrexia show, not adaptation to a new condition, but a disorganisation. In fever, the power of keeping the normal temperature is lost, owing to the action of the febrile agent. The disorganisation which occurs is due to the action of the febrile agent on the heat nerve centres, which are closely associated with the vaso-motor centre. In fever, therefore, thermotaxis, or the regulation of temperature, is disordered. That the vaso-motor centre is affected in pyrexia is shown by many observations. When the temperature is rising, and, during the rigor, the skin is anæmic and dry; in a falling temperature, it becomes moist and hyperæmic. During the early part of the pyrexia and the rigor, the volume of a limb is diminished, as shown by actual measurement; during the fall of temperature, the volume is increased. These changes in the volume of the limb are due to the quantity of blood present, and account for the fall of the surface temperature of the skin during the rigor, and its rise during the defervescence of the pyrexia. A fall of surface temperature corresponds with an increase of internal temperature, and *vice versâ*. Antipyrin and similar antipyretic drugs act by increasing the surface loss. Other evidence of the abnormal condition of the skin is shown in the production of *taches cérébrales* in pyrexia, as well as by the fact that reflex stimulation of the vaso-motor centre does not cause dilatation of the cutaneous vessels.

Causes of Pyrexia.—Pyrexia is one of the conditions accompanying inflammation. It may exist, however, in non-inflammatory conditions. Acute inflammation is associated with fever. In chronic inflammation there may be no febrile rise, but there may be either an irregularity in the diurnal variation of the temperature, or slight pyrexia.

Though pyrexia is described as usually accompanying inflammation, it is more correctly considered as the result of infection, of which, indeed, inflammation is a manifestation.

Pyrexia may be considered as divisible into four classes :—

1. Pyrexia of nervous origin.

2. Pyrexia of unexplained origin ; traumatic fever ; urethral, etc.

3. Pyrexia due to autointoxication, or to degenerative processes.

4. Infective, bacterial, or inflammatory pyrexia. By far the largest number of cases belong to this group.

This classification, which is not completely satisfactory, attempts to divide pyrexia as to its cause.

1. *Pyrexia due to Injury or Disease of the Central Nervous System (Non-inflammatory).—Brain.*—In cerebral hæmorrhage a rise of body temperature occurs. There is an initial fall of the internal temperature, which, in some fatal cases, is not followed by a subsequent rise. In non-fatal cases, the initial fall of a few degrees is succeeded by a moderate rise, 101° to 103° F. In other cases, the rise goes on to hyperpyrexia, and is continuous till death. Hæmorrhage into the pons is the commonest cause of this variation of temperature, but it is also observed when the basal ganglia are affected. Febrile rise of temperature is also observed in tumours of the pons. It is doubtful whether the rises of temperature in disseminated sclerosis are due to the injury to the nervous system, or to auto-intoxication.

Tumours in the region of the cervical cord, or injuries to this part, lead to a rise of body temperature and sometimes to hyperpyrexia. In these conditions, where there is direct injury to the central nervous system, the rise of temperature must be ascribed to the direct damage to the centres or to the nerve fibres.

2. *Pyrexia of Unexplained Origin.—Traumatic Fever* is used in two senses, according as there is, or is not, obvious infection and septic absorption. In cases where there is no obvious septic absorption from the injury, it must be remembered that a severe injury may lead to intoxication from the

intestines, so that cases of traumatic fever may really come under the heading of *infective fever*.

The causation of urethral fever, where not obviously septic, is also unexplained, as well as the rise of temperature that occurs in certain functional nervous conditions. It must be remembered that the disintegration of proteids in the body may give rise to substances which are poisonous, and some of these may be fever-producing. Fever is produced by the injection of lamb's blood into man. Some such explanation may be hazarded as the cause of the fever in pernicious anæmia, leukæmia and lymphadenoma, where there is no obvious infection. Not sufficient, however, is known of these conditions to enable any discussion to be made of the cause of the pyrexia, nor of that which occurs in cirrhosis of the liver, and some cases of jaundice and sarcoma.

3 and 4. *Infective Fever, Zymotic Fever, Toxic Fever.*—The chief agents producing fever are the products of infective agents. In 1865, Otto Weber and Billroth showed that the injection of septic material into animals caused a febrile rise of temperature. In 1875 Burdon Sanderson separated from putrefying material a substance he called *pyrogen*, the injection of which into animals caused fever. Later, it was found that Schmidt's fibrin ferment caused fever; and the idea arose that the febrile agent was of the nature of a ferment.

The products of bacteria and their action are discussed elsewhere (Chapter IV.). It may be repeated here that the excretory products of bacteria are, in many instances, fever-producing. Attention may be drawn to the fact that some of these will, in one case, quickly reduce the temperature, and, in another case, cause a febrile rise. Thus, in rabbits, the typhoid toxine causes a great fall of temperature, whilst in man it produces a febrile rise.

The products of the digestive action of bacteria do not act alike. The albumoses are fever-producing, whether given in single or multiple doses. In multiple doses, they tend to produce a continued rise of temperature. The albumoses of ordinary peptic digestion are also fever-producing agents.

When the proteids are split up beyond the stage of albumoses, in only rare instances are the products fever-producing. The anthrax base does not produce fever.

Of alkaloids that produce a slight rise of temperature, strychnine, atropine and cocaine may be mentioned, as well as mydaleine, which is one of the products of putrefaction.

The fever-producing products of bacterial action, have a special action on the central nervous system, and, no doubt, it is partly to this action that they owe their property of disorganising the heat centres.

CHAPTER III

INFECTION

I. *The Infective Agent*

INFECTION may be defined as the invasion of the body by living agents, which multiply in various parts of the body and produce symptoms by forming toxic substances. Infection may be considered as a part of the subject of parasitism, which includes both animal and vegetable agents which develop in the body.

Animal parasites produce their effects either by causing hæmorrhage from a mucous membrane, by blocking vessels, or, when growing in the tissues, by destroying the proper elements of the organ. Their effects are mainly local. The disease caused by the echinococcus is not an infection, but a purely local growth, and no poisons are produced which cause symptoms. The presence of a tapeworm in the intestinal tract produces no symptoms by poisoning, and the same may be said of all the larger animal parasites. On the other hand, some forms of animal parasitism approach the conditions of infection. Excluding the consideration of the parasite of malaria, trichiniasis may be considered as partly an infection, inasmuch as the symptoms produced are those usually associated with the infective process, such as fever and wasting, and œdematous swelling of the muscles: and a form of trypanosoma has been described as causing disease with symptoms of infection. The filarial parasites are not known to produce symptoms when found in the blood, but are sometimes associated with definite symptoms, as in the sleeping sickness of the West Coast of Africa. The tsetse-fly disease is also associated with definite symptoms. These, however, may be mainly due, as in filaria,

to the mechanical action of the parasite in the blood, and they have as yet not been shown to produce chemical poisons.

Parasites may be divided into infective and non-infective.*

1. *Infective Parasites.* — Micro-organisms, amœba, some protozoa, some animal parasites (?).

2. *Non-infective Parasites.* — Animal parasites generally, some micro-organisms (moulds).

The present article will deal solely with infective parasites, of which the micro-organisms form by far the largest number.

Micro-organisms may be divided into three classes: (1) *Hyphomycetes*, or moulds; (2) *Blastomycetes*, or sprouting fungi; (3) *Schizomycetes*, or cleft fungi.

1. *Hyphomycetes.* — These fungi consist of long filaments,

* Parasites are distinguished from saprophytes, the point of distinction being that parasites exist in, and live on, only living tissues, while saprophytes live on dead animal or vegetable tissue. Examples occur of parasites which are obligatory, that is, can only exist in all their stages as parasites, whether these stages occur only in one animal, or in more than one animal.

On the other hand, parasites may be facultative saprophytes; that is, usually existing as parasites, they are yet capable of living on dead animal or vegetable tissue.

Saprophytes may be obligatory, examples of which do not usually occur in disease.

They may also be facultative parasites, that is, although usually saprophytes, they may become parasites.

The following examples may be given as illustrations :—

1. *Obligatory Parasites.*—Infective agents of erysipelas, gonorrhœa, rabies, variola, scarlet fever, measles, glanders.

2. *Facultative Parasites.*—Infective agents of tuberculosis, actinomycosis, pus infection, diphtheria.

3. *Facultative Saprophytes.*—Infective agents of anthrax, tetanus, typhoid fever, cholera.

These terms, which include both animal and vegetable parasites, are only used in the relation of the parasite to the diseased condition it produces in the living body. They do not refer to any possible cultivation of the infective agent, which must necessarily be on artificial media, but it may be said generally that the more obligatory a parasite is, the less, likely is it to be capable of cultivation in an artificial medium. Many of the micro-organisms which might be considered obligatory parasites can be artificially cultivated, although they may not pass any vegetative existence outside the living body.

which are interlaced into a mycelium. They are reproduced by means of spores attached to specially developed hyphæ. Some of these fungi produce a purely local effect, on the skin, the hair, and the mucous membrane of the mouth. These are trichophyton megalosporon ectothrix, T. megalosporon endothrix and microsporon Audouini which are the cause of ringworm; achorion Schönleinii, the cause of favus; monilia candida, which produces thrush; microsporon furfur, which causes pityriasis versicolor, and some species of mucor, which are found in the auditory meatus in association with ear disease. The disease which these fungi produce is purely local, and does not become generalised in the internal organs of the body.

Some of the hyphous fungi ferment carbohydrates, changing starch into sugar. These are penicillium glaucum, which is non-pathogenic, monilia candida, mucor, aspergillus niger and aspergillus fumigatus. Another genus, oïdium lactis, is non-pathogenic, and is the cause of the souring of milk.

Some hyphous fungi are capable of existing in living tissues, and of producing disease which may cause death. These are aspergillus, actinomyces and streptothrix.

Aspergillus has been found in the lung, being the cause of pneumonomycosis, but it has also been found in pus from the middle ear and antrum, and in tuberculous cavities in the lung. One of the two species of aspergillus (A. niger) has also been found in skin lesions, in the cornea, in the intestine and in the spine, causing Potts's disease. A. niger has been found by most observers as possessing very slight pathogenic properties. A. fumigatus will grow well in the living body, and will produce death when injected into animals.

Actinomyces is the cause of the disease actinomycosis, which occurs in man, horses, cattle and pigs. It is a hyphous, or rayed, fungus, and in some forms resembles a coccus. It was first discovered in 1876 in cattle, by Bollinger, and in 1877 by Israel. In 1879 Ponfick found the fungus in lesions in both cattle and man. It is a disease of temperate climates, and the fungus produces granulation tissue containing giant cells and epitheloid cells, with formation of pus. Thick connective tissue surrounds the lesions, which are slow in

formation. The infection is carried from the awn of barley and other cereals to both cattle and man, but there is also direct infection from cattle to man. The infection takes place through wounds or excoriations of the mucous membrane and skin, through carious teeth, by inhalation, or by means of the alimentary tract. The parts affected in man are: face and neck and lower jaw in about 52 per cent. of the cases; the alimentary tract in about 23 per cent. (cæcum and appendix); respiratory organs in about 13 per cent., producing purulent bronchitis, and in other cases masses in the lung spreading to the pleura and pericardium. The tongue is affected in rather more than 3 per cent. of cases; the skin in about 3 per cent., and other parts, such as the spine, in a much smaller proportion.

Granules which consist of the fungus occur in the pus from the lesions of actinomycosis. These granules are from 2 to 6 millimetres in diameter, or from $\frac{1}{50}$ to $\frac{1}{10}$ of an inch, by $\frac{1}{500}$ to $\frac{1}{300}$ of an inch. The fungus may be cultivated from the pus on artificial media, and either from this cultivation or directly from the lesion the disease may be conveyed to animals, or it may be inoculated from man to the rabbit, or from cattle to cattle. The disease spreads by gradual invasion and destruction of an important part of the tissues, and causes death, partly in this manner, but also in part by a chronic intoxication, as shown by irregular pyrexia and wasting. Metastasis of the lesion is not common.

Mycetoma, or *Madura-foot*, is a disease pathologically resembling actinomycosis. It is due to the growth of a fungus called streptothrix maduræ, resulting in the formation of nodules and a thin pus.

Other forms of streptothrix have been found in lesions both in man and animals. All these conditions have the characteristic of being local formations.

2. *Blastomycetes.*—These are ovoid cells, which multiply by budding, or by the formation of endogenous spores. Saccharomyces induce alcoholic fermentation. The torulæ do not form spores: they act as ferments. Mycoderma have but little action. Yeasts are found in the human body; in some

cases in the urine and fæces, and in the dilated stomach. The variety which is found in these cases is the one common in the air (saccharomyces ellipsoideus).

A form of blastomyces has been described in carcinoma, existing within the cells, and capable of being cultivated in some instances and of producing lesions when inoculated into animals. They also appear to produce some forms of local dermatitis (blastomycosis) but according to our present knowledge, blastomycetes play but an insignificant *rôle* in the production of disease.

3. *Schizomycetes*, or *Bacteria*.—Most of the infective agents which produce disease belong to this class, and are composed of small cells, with no chlorophyll and no visible nucleus. The protoplasm in some forms is not uniformly distributed within the cell wall, and shows breaks; a condition referred to as plasmolysis. The varieties of bacteria are coccus, bacillus and spirillum.

Coccus. — Cocci receive different names, according to the grouping of the individual elements, which are usually spherical in shape, and vary in size considerably in different forms. The diplococcus is arranged in pairs, the streptococcus in chains, the tetracoccus in fours, the sarcina in masses of eight or more, and the staphylococcus either singly, or in groups of numerous elements. Some of the group forms are encapsuled. Though it is convenient to divide the cocci into these different groups, the division is not of as much importance as the action of the individual micro-organism. Whereas sarcina may be inert, streptococcus and diplococcus may induce infection in a varying but virulent degree. The individual grouping of the coccus is also not constant, and the grouping of one particular form may pass into another form, under cultivation. This variation of form, however, does not mean identity of all the forms.

Bacillus. — Bacilli are rods varying in shape and size, and may, in some instances, form threads almost like a mycelium. Some are immobile; others are motile, owing to the presence of cilia or flagella.

Spirillum.—Spirilla are curved forms, the best pathogenic example of which is the cholera vibrio.

CHARACTERS OF THE BACTERIA CAUSING SPECIFIC DISEASES.

Micro-Organism.	Growth on Culture Media.					Staining Reactions.	Disease.
	Gelatine.	Agar.	Potato.	Serum.	Milk.		
Pyococci—							
(α) Streptococcus Erysipelatis.	Not liquefied.	Like drops of dew and in ribbons.	No growth.	Grows.	Grows.	Stained by Gram.	Erysipelas.
(β) Streptococcus Pyogenes.	Not liquefied.	Like drops of dew and in ribbons.	No growth.	Grows.	Grows.	Stained by Gram.	Acute Abscess; Infective Endocarditis; Septicæmia; Pyæmia.
(γ) Staphylococcus Pyogenes Aureus.	Liquefied.	Grows.	Grows.	Grows.	Coagulated.	Stained by Gram.	Carbuncles.
S. P. Albus .	,,	,,	,,	,,	,,	...	
S. P. Citreus .	Liquefied slowly.	,,	,,	,,	,,	...	
(δ) Diplococcus Lanceolatus Pneumoniæ; Pneumococcus. Lance-shaped, non-motile; not capsuled under culture, only in body.	Not liquefied.	Thin transparent growth.	Grows.	Thin, slimy.	Not coagulated.	Stained by Gram.	Pneumonia.
Gonococcus . . . In pairs; no capsule.	No growth.	No growth.	No growth.	Grows with difficulty; lives only a short time.	No growth.	Decolorised by Gram.	Gonorrhœa.

CHARACTERS OF THE BACTERIA CAUSING SPECIFIC DISEASES—*Continued.*

Micro-Organism.	Growth on Culture Media.					Staining Reactions.	Disease.
	Gelatine.	Agar.	Potato.	Serum.	Milk.		
Diplococcus Intracellularis Meningitidis (Weichselbaum's Diplococcus).	Does not liquefy.	Grows best; dies rapidly.	No growth.	Grows.	Grows.	Decolorised by Gram.	Cerebro-Spinal Meningitis.
Micrococcus Melitensis Small coccus.	Not liquefied.	Grows rapidly.	Very slight growth.	Grows.	Grows.	Decolorised by Gram.	Malta Fever; Mediterranean Fever; Rock Fever; Neapolitan Fever.
Bacillus Anthracis . Non-motile rods; forms spores, but not in body.	Liquefies.	Grows well.	Grows well.	Grows well.	Grows well.	Stained by Gram.	Anthrax; Splenic Fever (Charbon: milzbrand).
Bacillus Tuberculosis. Rods; no spores.	No growth.	No growth unless glycerine present.	Grows with difficulty.	Grows.	Grows.	Stained by Gram, also by fuchsin, not decolorised by mineral acid.	Tuberculosis.
Bacillus Lepræ . . Not yet cultivated.	...	...	...	...	...	Like B. tuberculosis.	Leprosy.
Bacillus Diphtheriæ . Rods, curved, straight, or clavate; non-motile.	Not liquefied.	Grows.	Grows.	Grows.	Grows.	Stained by Gram; easily decolorised.	Diphtheria.
Bacillus Typhosus . Rods and threads; ciliated; motile; no spores.	Not liquefied.	Grows.	Grows; colourless.	Grows.	Not coagulated.	Decolorised by Gram.	Typhoid or Enteric Fever.

CHARACTERS OF THE BACTERIA CAUSING SPECIFIC DISEASES—*Continued.*

Micro-Organism.	Growth on Culture Media.					Staining Reactions.	Disease.
	Gelatine.	Agar.	Potato.	Serum.	Milk.		
Bacillus Influenzæ . Very minute rods, straight, not motile; no spores.	No growth.	Grows on blood agar; dies quickly.	No growth.	Grows.	No growth.	Decolorised by Gram.	Influenza.
Bacillus Pestis . . Small oval rods; growing in chains; no spores; forms stalactites in broth cultures containing fat.	White growth.	Grows; circular disks; shows involution forms.	Grows.	Circular disks on blood serum.	Grows.	Decolorised by Gram.	Oriental Plague; Bubonic Pest.
Bacillus Mallei . . Slender rods; non-motile.	Very scanty.	Grows on glycerine agar.	Yellow growth; becoming darker	Yellowish.	Coagulated slowly.	Decolorised by Gram.	Glanders; Farcy.
Bacillus Tetani . . Motile; rods and pear-shaped forms; spores; anaërobic.	Grows on glucose gelatine.	Grows on glucose agar.	...	Grows.	Grows.	Stained by Gram.	Tetanus.
Bacillus Œdematis Maligni. Motile; flagellated; spores; large; anaërobic.	Liquefies; forms gas.	Network; forms gas.	Network.	Liquefied.	Coagulated.	Decolorised by Gram.	Malignant Œdema.
Vibrio Choleræ Asiaticæ. Spirillum; motile; no spores; forms nitrites.	Liquefies.	White growth.	Like B. mallei.	Liquefied.	Coagulated.	Decolorised by Gram.	Asiatic Cholera.
Spirillum Obermeieri. Spirals; very slender; motile; no spores. Not yet cultivated.	...	...	...	...	...	...	Relapsing Fever.

CHARACTERS OF IMPORTANT PATHOGENIC BACTERIA.

(Other than those included in the First List.)

Micro-Organism.	General Characters.	Where Found.	Pathogenic Action.
Micrococcus Tetragenus	A coccus arranged in fours.	In the mouth; in phthisical cavities.	Produces a rapid septicæmia in white mice, white rats and in guinea-pigs. In rabbits, it causes a localised abscess.
Bacillus Pyocyaneus .	A motile bacillus, producing active poisons.	In the mouth, intestine, and on the skin; also in "blue" pus.	Is slightly pathogenic.
Organisms allied to the Typhoid Bacillus—			
1. Bacillus Coli Communis.	Like the typhoid bacillus in its growth, except that it forms gas from glucose, coagulates milk, and forms indol.	In the intestinal contents normally.	Causes septicæmia in guinea-pigs from intraperitoneal injection: an abscess when injected subcutaneously. Is found in man in the intestinal contents, frequently in the spleen in typhoid fever, in abscesses around the intestine, and in infection of the gall-bladder and pancreas.
2. Bacillus Enteritidis (Gärtner).	Like the typhoid bacillus in its growth, except that it forms gas from glucose.	Has been found in "tainted" meat.	Acts like the B. coli communis. Has been found in some cases of meat poisoning.
3. Bacillus Dysenteriæ .	Grows like the typhoid bacillus.	In the stools and tissues of some cases of tropical dysentery, p. 144.	Described as the cause of one form of dysentery.

CHARACTERS OF IMPORTANT PATHOGENIC BACTERIA—*Continued.*

Micro-Organism.	General Characters.	Where Found.	Pathogenic Action.
Resembling the Cholera Vibrio—			
1. Vibrio Metchnikovi (Gamaleia).	Grows like the cholera vibrio, but does not give Pfeiffer's specific reaction (Chapter VI.).	...	The cause of an epidemic in fowls; associated with diarrhœa, stupor and death in forty-eight hours. Produces by inoculation a septicæmia in pigeons, and in guinea-pigs hæmorrhagic œdema, ending in septicæmia.
2. Vibrio Finkler-Prior 3. Vibrio Deneke .	These two vibrios resemble that of cholera in cultivation. The vibrio Deneke is but slightly pathogenic.	...	They do not produce any known diseased condition in man or animals.
Bacillus Botulinus . .	4 μ to 9 μ long by 0.9 μ to 1.2 μ thick; motile, with 4 to 8 flagella. Anaërobic; no spores. Grows best at 20° to 30° C. Rapidly liquefies gelatin. Forms a powerful toxin, nearly as poisonous as the diphtheria and tetanus toxins.	Found in a specimen of ham.	The cause of poisoning in an epidemic from eating ham: the symptoms being mainly nervous, such as ocular palsy, dysphagia and general weakness, with an affection of the heart and respiration. No fever is produced. The toxin has a special action on the nervous system, especially the cells of the medulla and the spinal cord.
Bacillus Enteritidis Sporogenes (Klein).	Anaërobic; growing on all media, and producing a large amount of gas from sugar.	In milk, soil and sewage.	The cause of an outbreak of diarrhœa from milk.

Mode of Growth of Bacteria.—The mode of growth of bacteria must be considered from the point of view of growth in artificial media, and of that of growth in the body.

In artificial media the growth and vitality depend on the temperature, the presence or absence of oxygen, on exposure to sunlight and on the chemical composition of the nutrient medium. Most pathogenic bacteria grow best at a temperature of from 37° to 38° C. A higher temperature is not beneficial to them, and many will not grow below a temperature of from 20° to 22° C. Some, for example the glanders bacillus, lose their virulence when exposed to a temperature below 37° C. This relation to temperature is intensified in the so-called thermophilic bacteria, which are usually non-pathogenic, and which do not grow except at a temperature of 50° C.

The necessity for a certain degree of temperature (37° C.) for the active development of pathogenic bacteria is of great importance, inasmuch as it is at this temperature that they develop in the body. Some of the less specialised forms of bacteria, for example the typhoid bacillus and the colon bacillus, will withstand exposure to very low temperatures, but no living bacillus will withstand a temperature of 60° C., if applied in a liquid medium for some minutes. Spores, however, are not killed at this temperature, and require a higher temperature (100° C.) and a longer exposure.

Relation to Oxygen.—The relation of the growth of bacteria to the amount of oxygen present in the medium in which they grow, is of great importance. Most pathogenic bacteria grow in the presence of oxygen, and so are called aërobic. Others grow in the absence of oxygen (anaërobic), this being excluded by substituting an atmosphere of hydrogen, carbon dioxide, or nitrogen.

For the active growth of some micro-organisms oxygen is essential, and so they are called obligatory aërobes. The best example of this is the bacillus subtilis, which is non-pathogenic; many other examples occur among non-pathogenic bacteria. Most pathogenic bacteria, although aërobic, are

capable of growing in the absence of oxygen, and so are called facultative anaërobes. Examples of these are pus cocci, pneumococcus, bacillus anthracis, the typhoid bacillus, the colon bacillus and the vibrio of Asiatic cholera. A few pathogenic bacteria grow only when oxygen is excluded, and so are called obligatory anaërobes. Examples of these are the tetanus bacillus, the bacillus of malignant œdema, the bacillus of quarter evil and the bacillus enteritidis sporogenes (Klein).

The condition of growth in the body for pathogenic bacteria is, of course, dependent to some extent on the amount of oxygen present. The tissues of the body contain oxygen in more or less firm combination, the red blood corpuscles containing it in the largest proportion. The amount of oxygen which is present in the tissues is relatively small, so that the bacteria of the body are not exposed to the same amount of oxygen as they are in a culture medium, which itself contains free oxygen and is, moreover, exposed to the air.

In this connection it is interesting to note that, although most pathogenic bacteria are aërobes, they are also facultative anaërobes. The amount of oxygen in the tissues does not necessarily prevent the spread in the body of obligatory anaërobes. Thus, although the tetanus bacillus grows only in the region in which it is inoculated, and this want of further spread may be partly due to the small amount of oxygen present in the tissues, yet the bacillus of malignant œdema, which is a similar organism in its relation to oxygen, spreads to the subcutaneous and neighbouring tissues. The main factor in limiting the growth of bacteria in the body is not the presence or absence of oxygen.

The Effect of Sunlight.—Direct or diffused sunlight, destroys bacteria, especially the blue and violet rays. Even spores may be destroyed. The tubercle bacillus is destroyed in a few minutes to one hour by exposure to direct sunlight, and in five to seven days by exposure to diffused sunlight (Koch). The typhoid bacillus, the colon bacillus, the bacillus pyocyaneus, the vibrio of Asiatic cholera are destroyed by

four to seven hours exposure to direct sunlight. If the spores of anthrax be inoculated into a gelatine plate, and part of the surface exposed to direct sunlight or to an electric arc light for two to six hours, they are killed, inasmuch as when cultivated, the plate remains sterile over the exposed area (Marshall Ward).

The times which have been given for the killing of the bacteria by exposure to sunlight are not correct when the bacilli are mixed with organic matter, as, for example, when the tubercle bacillus is in the sputum, or the typhoid bacillus and cholera vibrio are in the motions or urine. The time required for the killing of the bacteria under these conditions is much prolonged, and death of the bacteria may not occur before the organic matter is nearly dry.

Effect of Nutrient Medium.—With those pathogenic micro-organisms which are capable of being cultivated, besides the question of oxygen, which has already been considered, the culture medium must be of a certain composition to ensure good growth. It must contain proteid substances, such as peptone, albumoses, albumen, or fibrin; it must be slightly alkaline or neutral (although some bacteria can grow in a slightly acid medium), and must contain a certain proportion of mineral salts, chlorides of sodium and potassium, calcium and magnesium phosphates. As regards the salts requisite, sodium chloride and calcium phosphate are a necessity for the vitality of protoplasm. Without sodium chloride, a living cell cannot exist, and calcium phosphate bears a peculiar and essential relation to certain transformations of proteids such as the clotting of milk and blood, as well as to the growth of tissues. The proportion in which the salts must be present is practically that in which they exist in the blood, namely, about 0.8 gramme per cent., but an excess of phosphates does not, as a rule, interfere with the growth of bacteria.

The reaction of the medium is of great importance. It is usually made slightly alkaline or neutral to litmus. Some pathogenic bacteria are very sensitive to the reaction of the medium. The anthrax bacillus will grow in neutral solution,

or even one moderately alkaline; the diphtheria bacillus will grow in a slightly acid, neutral, or moderately alkaline solution; whereas, for the tetanus bacillus, the medium must be made as nearly neutral as possible. On the other hand, the typhoid bacillus and the colon bacillus, although growing best in a slightly alkaline medium, will develop in a medium of which the acidity is due to hydrochloric acid, the colon bacillus being more resistant than the typhoid.

The presence of nitrogenous substances, usually in the form of proteids, is necessary for the development of pathogenic bacteria. The substances usually used are commercial peptone (which consists chiefly of albumoses), the serum proteids and gelatine. In some cases the addition of glycerine to the medium stimulates the growth of bacteria; in other cases sugar acts as a stimulant. A small proportion of fat is also present, so that, in some instances, the bacteria appear to require for their proper growth the same three food stuffs, proteids, fats and carbohydrates, which are necessary for the vitality of the animal cell. This is in contrast to the conditions of existence of most non-pathogenic bacteria. Many of these, especially those present in the air, will flourish in liquids containing only mineral salts, with some tartrate, as in Pasteur's fluid. Others, again, such as the putrefactive bacteria, require proteid substances for their proper growth, and with certain specialised bacteria, such as the nitrifying organisms, a culture fluid of sulphate of ammonium, phosphate of potassium and magnesium sulphate, is necessary, with or without silicic acid.

What effect a pathogenic bacterium has on the medium in which it grows is more properly discussed under the heading of Bacterial Products (Chapter IV.). It may here be said that they do not have any appreciable effect on the peptone. Many, however, digest albumen and gelatine.

Bacteria outside the Body.—Pathogenic bacteria may, as a rule, be considered highly specialised forms, the life of which has been altered by the conditions in which they exist in disease. Originally they must have arisen from forms similar to the non-pathogenic bacteria now known. Most pathogenic

bacteria which produce a definite disease may be said to pass all their active existence in the animal body, and in the course of the disease itself. Most do not live for any length of time in the dead body, although in this respect some are more sensitive than others. Some even may disappear from the living body before death occurs, as in some cases of diphtheria and tetanus. Others, again, such as the pus cocci, have a great vitality. The same may be said of the anthrax and tetanus bacilli, owing to the spores they produce outside the body, of the typhoid bacillus and of the colon bacillus.

Very few of the pathogenic bacteria have a prolonged existence outside the body, that is, that they do not have a saprophytic existence under natural conditions. This is probably because the conditions of food and light are unfavourable. The best example to the contrary is the tetanus bacillus, which is found in some kinds of soil. The pus cocci (staphylococcus) also exist in the air, chiefly in towns and buildings, and, as sources of infection, come from dust and previously existing abscesses. The tuberculosis bacillus has, as far as is known, a very short existence outside the body. The same is true of the glanders bacillus and the diphtheria bacillus, but in none of these cases is there any evidence that the bacillus can grow outside the body, except in specially prepared culture media. This is not to be wondered at in the case of the tuberculosis bacillus, which requires specially prepared culture media (serum or glycerine agar), nor of the glanders bacillus, which soon becomes non-virulent when removed from a temperature of 37° C.

The colon bacillus and allied forms appear to have a separate existence in nature, as they are found in contaminated water and in sewage; but many of the forms which have been described are not the same as the one found in the intestinal tract; and the true pathogenic colon bacillus lives only a short time in sewage and soil. The typhoid bacillus is also resistant to external conditions. It will not live for any length of time in water nor in soil, in the latter case being beaten out by the other bacteria present;

but if the bacteria are few, the bacillus may retain its vitality for a considerable time, as in damp rags and linen and in an ordinary broth culture it will live for many months exposed to daylight and at the temperature of the laboratory.

Variability in Virulence of Bacteria.—Cultures of bacteria obtained from disease exhibit very varying degrees of virulence when injected into animals, and this variability is shown in different ways. A pathogenic bacterium, even if it forms spores, may, by being kept in culture, soon lose its virulence, so that it will not be fatal when injected into animals. This degeneration of the culture may be ascribed partly to the medium in which it is grown, and partly to exposure to air and light, inasmuch as if the bacteria are given their natural culture medium, that is, the animal body, their virulence may be recovered. All the forms of bacteria show this degeneration in artificial culture, and the decrease of virulence is sometimes accompanied by a change of form, the so-called involution forms being observed. This is noticeable in the diphtheria bacillus, in which the clavate forms become enlarged and attenuated in parts; with the tetanus bacillus, in which a similar change occurs; with the tuberculosis bacillus, in which the bacilli may grow into long threads of but little virulence; and with the plague bacillus.

The virulence of bacteria depends on their power of producing their characteristic poisons, and they do this much more efficiently in the animal body than in artificial culture media, however suitable these may be for their vegetative growth. The pneumococcus and streptococcus are examples of micro-organisms which rapidly lose their virulence when grown in artificial culture media. This they do in one or two days.

Artificially, the virulence of a bacterium may be *attenuated* or *increased.* The methods of attenuation used are heat or certain antiseptic substances, which partially inhibit the growth. Pasteur, for example, attenuated the anthrax bacillus by growing it at a temperature of 42° C. for over three weeks, and so produced his *premier vaccin*, in which no spores were

formed. The diphtheria bacillus and the tetanus bacillus have been attenuated by exposing the culture to the action of tri-chloride of iodine or of phenol. Methods of attenuation are now mainly of historical interest, but were adopted as a means of producing immunity in animals, the injection of the attenuated virus producing a slight disease which protected the animal against the severe disease (Chapter VI.). The products of the attenuated micro-organism and of the virulent are practically the same. What the method of attenuation apparently does is to lessen the vitality of the bacterium, so that it produces a smaller amount of poison.

Methods of increasing the virulence of bacteria are of more importance. The chief method is one of passage through a series of animals. This may be done either by using the culture of the bacterium, injecting a large dose into one animal, and, on the death of the animal, injecting the exudation produced by the bacterium into a second animal, and so on. Thus the cholera vibrio may be intensified in virulence by injecting a fresh broth culture into the peritoneal cavity of a guinea pig. On the death of the animal, the peritoneal exudation produced is injected into a second animal, or, if sufficient exudation is not present, it may be inoculated into broth, allowed to grow for a few hours, and then injected into a second animal, and so on. In this way, after a series of animals, perhaps twenty or thirty, have been done, it is found that an infinitesimal dose of the culture or exudation will cause death, usually in from sixteen to eighteen hours; the virulence being increased twenty or thirty times. This death is more rapid than that usually produced by an infective agent, and the explanation seems to be that, with the living bacteria, is injected a fatal dose of the chemical poison. The virulence of the pneumococcus and streptococcus have also been increased in this manner by subcutaneous injection, and most of the other bacteria may be intensified in virulence by this method.

Another method is to aid the action of the bacterium by injecting at the same time the chemical products of another bacterium. Thus, in the case of the typhoid bacillus, its

virulence may be intensified by injecting intraperitoneally a small quantity of the broth culture of the bacillus, and subcutaneously a sterilised broth culture of the streptococcus pyogenes or the bacillus prodigiosus. The subsequent procedure is the same as in the other passage experiment. The animal dies, the typhoid bacillus is recovered from the peritoneal exudation, and is injected into a second animal, a subcutaneous injection of the products of the streptococcus being also made. After a certain number of animals have been used, it is found that a smaller and smaller quantity of the products of the streptococcus and of the culture of the typhoid bacillus have to be used, and eventually the typhoid bacillus may be injected by itself, and will produce death. A further increase of virulence may be obtained by continuing the series of animals with the bacillus alone. The degree of virulence to which the bacteria can be raised is astonishing. A fraction of a cubic centimetre of a broth culture, or a single platinum loopful of a solid culture, will be found to cause death in from sixteen to eighteen hours. It may again be said that the rapid death in these cases is due, in part, to the chemical poison which is injected in addition to the living bacillus.

From the lesions produced by bacteria in the animal body cultures are obtained which vary considerably in virulence. Thus, from an abscess, a streptococcus may in one case be obtained which is very virulent, being rapidly fatal to animals when injected; in another case, a culture may be obtained which is only fatal to animals after the virulence has been intensified. The same may be said of the diphtheria bacillus, but the variations in virulence are not so marked as in the case of the streptococcus. In typhoid fever, cultures of the bacillus obtained from the spleen immediately after death, and injected into animals, show great variations in virulence. In some cases the micro-organism produces rapid death; in others it will only do this after intensification. This variation in virulence is not due to any manipulation outside the body, inasmuch as it is only a question of a few hours after removal from the body before the material is used for experiment.

The variability in virulence which is found in actual disease may be dependent on different conditions, either on the fact that the virus which produced the disease was not virulent, or that the virus had become attenuated in the body by the resistance to its growth, or by the degeneration of bacteria which occurs in long-standing lesions, such, for example, as abscesses and some tuberculous lesions.

CHAPTER IV

INFECTION—*continued*

II. *The Chemical Products of Bacteria and their Action*

BACTERIA produce their effect in disease by means of the chemical poisons which they form. Some of the poisons produced are of a highly complex nature, and are closely related to certain poisons produced by animal cells and by plants, such as snake venom, abrin, ricin and robin.

In addition to the formation of these highly complex poisons, the process of putrefaction must be considered, and some simpler transformations, both of carbohydrates and of certain nitrogenous substances, such as urea and ammonia. Many of the processes may be accurately described as fermentation, the process by which the secretion of a cell produces a rapid chemical change in the substances on which it acts. In fermentation it may be considered that the process is one in which a complex body is broken up into simpler chemical forms, but in some cases in which bacteria form very active poisons, the evidence of fermentation is not at present forthcoming.

Simple Bacterial Fermentation.—The simpler forms of bacterial fermentation are instanced by the alcoholic, lactic acid, butyric acid and acetic acid fermentations, as well as the fermentation of urea. In the alcoholic fermentation, yeast transforms cane sugar into dextrose and levulose, and breaks up dextrose into alcohol and various by-products, which are chiefly organic acids. From yeast can be separated the active agent which transforms cane sugar into dextrose and levulose. The breaking up of the dextrose into alcohol and other pro-

ducts is a property of t ıe yeast cell itself: but by expression, a ferment (zymase) h: s been obtained from the yeast-cell, which has this property (Buchner). The transformation takes place according to the following formula:—

$$\underset{\text{Glucose}}{C_6H_{12}O_6} = \underset{\text{Alcohol}}{2\,C_2H_6O} + \underset{\text{Carbon dioxide.}}{2\,CO_2}$$

Glycerine, succinic acid and fusel oils are formed at the same time.

The lactic acid fermentation, which occurs in the production of sour milk, is caused by the bacillus acidi lactici. Lactose is transformed into lactic acid and by-products. Glucose is also transformed into lactic acid. The formulæ usually given for this transformation are as follows:—

$$\underset{\text{Lactose}}{C_{12}H_{22}O_{11}} + \underset{\text{Water}}{H_2O} = \underset{\text{Lactic acid.}}{4\,C_3H_6O_3}.$$

$$\underset{\text{Glucose}}{C_6H_{12}O_6} = \underset{\text{Lactic acid.}}{2\,C_3H_6O_3}.$$

These formulæ, however, do not represent the complete transformation, inasmuch as some of the by-products, such as CO_2 and H_2, are not allowed for.

The butyric acid fermentation is produced by the bacillus butyricus. In the ordinary course of events in milk it follows the lactic acid fermentation, and lactic acid is transformed into butyric acid, with the production of carbonic acid and hydrogen as by-products.

The formula for the transformation is as follows:—

$$\underset{\text{Lactic acid}}{2\,C_3H_6O_3} = \underset{\text{Butyric acid}}{C_4H_8O_2} + \underset{\text{Carbon dioxide}}{2\,CO_2} + \underset{\text{Hydrogen.}}{2\,H_2}$$

The acetic acid fermentation is produced by the mycoderma aceti, which breaks up alcohol into acetic acid and other products.

The lactic and butyric acid fermentations play some part in disease, inasmuch as they occur in the stomach contents in cases of obstruction of the pylorus, and also in the small intestine in some cases of indigestion of food.

Another simple fermentation which is produced by a

bacterium (micrococcus ureæ) is the transformation of urea into ammonium carbonate, according to the following formula :—

$$CO(NH_2)_2 + 2H_2O = (NH_4)_2CO_3$$
Urea + Water = Ammonium carbonate.

The ammonium carbonate is further split up into ammonia and carbonic acid, probably, however, not by the micrococcus. This change occurs in the ammoniacal decomposition of urine, and is really due to a ferment which is excreted by the micrococcus. This ferment may be precipitated by alcohol, and is thus separated from the bacterium. It has been found to produce the same effect as the bacterium itself.

There are several examples in the vegetable kingdom of non-living ferments producing a chemical change in substances. Thus, the ferment known as emulsin splits up amygdalin in the presence of water into oil of bitter almonds and prussic acid.

Nitrification.—Some bacteria have a special action on ammonia and nitrates. The most common action is the oxidation of ammonia, with the production of nitrites and nitrates. The following bacteria produce nitrites :—

B. prodigiosus, Deneke's spirillum, Finkler Prior's spirillum, the B. anthracis and staphylococcus pyogenes.

Some bacteria, *e.g.* vibrio choleræ asiaticæ and vibrio metchnikovi reduce nitrates to nitrites.

Nitrification, however, is a special property of certain bacteria in the soil, and when grown in special media (p. 63). These have been called nitrosomonas (producing nitrites) and nitrobacter (producing nitrates). An important effect is observed in the production of the nitrates of the soil from the ammonia of decaying animal matter.

Putrefaction.—There are a large number of bacteria which cause putrefaction with the formation of a foul decomposing mass. Putrefaction affects proteid substances, but not carbohydrates or fats. It cannot take place without the action of bacteria, for although there are some slight changes in chemical properties observed in solutions of proteids kept for a long time, these are but slight in comparison with the great

changes which occur rapidly in putrefaction and result in the formation of numerous bodies from the proteid molecule.

Putrefactive bacteria are both aërobic and anaërobic, and in a particular putrefying mixture it is not infrequently observed that the aërobic bacteria develop first, and, having exhausted the oxygen in the liquid and formed a scum on the surface, they lead to the development of the anaërobic forms. As the proteid matter becomes exhausted, the bacteria diminish, and when all the food is finished, bacterial development ceases to a great extent, sometimes completely. The main putrefying micro-organisms are:—

The various forms of proteus: P. vulgaris, P. Zenkeri, and P. mirabilis; as well as B. pyogenes fetidus, B. saprogenes, micrococcus fetidus. These are only a few of the putrefactive bacteria, and a large number have not yet been exhaustively studied.

Putrefaction is a rapid process, and, inasmuch as it affects the complex molecule of proteids, it is to be expected that a great variety of chemical products would be formed.

Proteids consist of C.H.N.O.S. and sometimes P., and the products of putrefaction may be divided into two classes—the nitrogenous and non-nitrogenous. The non-nitrogenous consist of gases, such as carbonic acid, hydrogen, sulphuretted hydrogen (H_2S) and marsh gas (CH_4); and of organic acids, such as formic acid (CH_2O_2), butyric ($C_4H_8O_2$) and valerianic acids ($C_5H_{10}O_2$), of the fatty series; as well as lactic ($C_3H_6O_3$), succinic ($C_4H_6O_4$), glutaminic ($C_5H_7(NH_2)O_4$) and aspartic ($C_4H_7NO_4$, amido-succinic) acids. Glutaminic and aspartic acids, it will be noted, are nitrogenous (amido) compounds, and may be produced artificially by boiling proteids with sulphuric acid.

The other nitrogenous products fall into different groups. Free nitrogen is produced, as well as free ammonia. Bodies of the aromatic series, some of which are foul-smelling (such as indol and skatol) and tyrosin, form another group. The third group would include bodies which have been called ptomaïnes or cadaveric alkaloids, many of which are compound ammonias. The fourth group contains the early products of the digestion of proteids, namely, albumoses.

Ptomaïnes.—A large number of these bodies have been described, and at one time they were supposed to play a great part in the production of the symptoms in infective disease due to bacteria. Although this has been proved not to be the case, the ptomaïnes are of some importance in disease, although many of them possess no poisonous action.

Neuridine is very commonly found in putrefying mixtures, but is not poisonous. It is isomeric with cadaverine, which has been found in cholera cultures and in the urine in cases of pernicious anæmia.

Choline ($C_5H_{15}NO_2$) is also frequently found, and is one of the most important of these bodies. It has been found in cholera cultures, and there is evidence that it is present in the cerebro-spinal fluid in cases of general paralysis of the insane (Chapter XIX.). It is obtained from the bile, and is widely distributed in the animal body in lecithin, a compound of choline with glycero-phosphoric and other acids.

Another substance, neurine ($C_5H_{13}NO$) has a similar action to choline, although not so powerful. It is formed by the decomposition of choline, and choline is related to muscarine, which may be considered as oxycholine ($C_2H_3(OH)_2, N(CH_3)_3, OH$), and is formed by oxidising choline with nitric acid. In frogs choline causes paralysis, and atropine antagonises its action. Its general action in higher animals is that of producing diarrhœa, and of affecting the secretions, causing salivation, lacrimation and sweating. The respiration is affected; there is a fall in blood pressure with cardiac failure, while an effect on the nervous system is shown in the production of clonic spasms.

Methylamine, dimethylamine, trimethylamine, as well as saprine and putrescine, are practically non-poisonous.

Methylguanidine ($C_2H_7N_3$) is said to have been found in cholera cultures, and it occurs in some putrefying mixtures. It is a poisonous substance, which causes dilatation of the pupil, increased frequency of respiration, paralysis and convulsions. Mydalein causes a rise of body temperature, as well as dilatation of the pupil, paralysis and convulsions, its main action being similar to that of methylguanidine.

From infected cheese and cream a substance has been isolated called tyrotoxicon, which produces vertigo, nausea, and vomiting, with numbness, rigors, and prostration. Mytilotoxine was isolated from the sea mussel (mytilus edulis), which caused an outbreak of poisoning in Bremerhaven. It acts like curare in poisoning the nerve endings of muscle.

Peptotoxine, supposed to be formed by pepsin; typhotoxine, supposed to be produced by the typhoid bacillus; tetanin and tetanotoxin, supposed to be produced by the tetanus bacillus have not been isolated.

Although but few of the substances named have a definite physiological action, there are no doubt others not yet isolated which produce the symptoms observed in putrefactive poisoning, these symptoms being mainly referable to the gastro-intestinal tract and to the nervous system.

Products of Pathogenic Bacteria: Toxines of Disease.—The chief poisons which produce the symptoms in bacterial disease do not belong to any of the classes previously described. They are not organic acids, nor are they alkaloidal in nature. The poisons may be divided into two classes:—

(1) Intracellular and extracellular poisons (toxines).

(2) Products of the digestion by the bacterium of proteid substances: viz., albumoses and certain by-products.

Some of these poisons may perhaps be correctly described as ferments, but they have not the same properties as the digestive ferments. The chemical nature of a ferment can only be expressed by the character of the work that it performs. It may act in infinitesimal quantities, and it causes a transformation in the substances on which it acts. In the case of the digestive ferments, the result is to make the substances more soluble. Thus both pepsin and trypsin digest proteids with the formation of albumoses and peptone; in the case of trypsin, a further breaking up taking place into leucin and tyrosin. In the case of the diastatic ferments, insoluble starch is transformed into different kinds of dextrin, and into maltose.

This, however, is not the only manner in which proteids

and carbohydrates may be affected by ferments. Albumoses, during their absorption into the blood stream, are retransformed into the proteids of the body. Maltose, in the process of its absorption, is transformed into dextrose, and although these changes are associated with cell action, yet it is probable that the actual change is brought about by ferment action.

Other ferments exist which transform the physical condition of a body, possibly its chemical constitution as well. Thus rennin causes the coagulation of milk; that is, precipitates the caseinogen of milk in the form of casein. Myosin is, in a similar way, formed in dead muscle from myosinogen. Fibrin is formed from the blood proteids partly by ferment action. Besides, therefore, the digestive ferments, the existence of coagulating ferments must be recognised, and both of these are the excretory products of cell activity.

Digestive ferments are sensitive to the action of temperature and moisture. They do not act unless water is present. They act best at a temperature of about 37° C. The vitality of most is affected by a rise of temperature, and the activity of most is destroyed at a temperature of 60° C., or slightly over, although, in this respect, they show a varying resistance.

Ferment action going on in a glass vessel ceases after a time, even though active ferment is still present, and there are still substances to be acted upon. This effect is usually ascribed to the action of the ferment being checked by the accumulation of their products of digestion. This may not be the whole explanation, but it is a fact that more complete digestion occurs if the products are removed during the process by dialysis.

One feature of ferments, which is of importance, is their sensitiveness to manipulation. They keep best in a dry condition, but, after keeping, their activity is found diminished. If kept in solution the deterioration is much more marked; as also when exposed for long to the action of strong alcohol or other precipitating agents.

This sensitiveness to external conditions is also possessed by some of the bacterial toxines. Others, again, are very resistant. In some of their properties bacterial toxines

resemble ferments, but, in the present stage of knowledge, the term ferment is not correctly applied to most of the poisons to be considered. Digestive ferments, both diastatic and proteolytic, have been obtained from bacteria. These have been found to possess the same general properties as other similar ferments. The diastatic action of pathogenic bacteria is but of slight importance in disease; the proteolytic action is of more importance.

The action of bacteria, however, causes a greater breaking-up of the proteid molecule than the digestive ferments. Thus, pepsin does not transform proteids beyond the stage of peptone. Trypsin produces only a small amount of leucin and tyrosin, which may be considered the final stage in the digestion. With the proteolytic digestion by bacteria, not only are albumoses formed, but, in some cases, organic acids, gases (carbonic acid and hydrogen), aromatic bodies, such as indol and skatol, while a few produce complex nitrogenous, but non-proteid, substances.

The chief poisons of bacteria are the intracellular and extracellular poisons, which do not belong to the digestive group of ferments, and to which the term *toxine* is most conveniently limited. In some instances these toxines alone are produced by a micro-organism; in others the bacterium produces this poison as well as the digestive poisons; while, in still others, the digestive poisons are the chief ones formed. There are, besides, other substances produced by bacteria, which are only slightly toxic, but which are important in relation to the formation of antitoxin in the animal body.

There are therefore five chief groups of bacterial products:—

(1) *Poisons produced by the digestive or the destructive action of bacteria on proteids.*

Typical examples of these are the poisons of the bacillus anthracis and of the pus cocci, with the exception of the streptococcus.

(2) *Poisons which are the result of the digestive or destructive action of bacteria on proteids, formed in the same medium as an excretion (the toxine) of the bacterium.*

The bacillus diphtheriæ is the best example of this. A

similar combination of poisons is found in snake venom, in abrin and ricin.

(3) *Poisons which are only excretions*, such as those produced by the tetanus bacillus.

(4) *Poisons which are typically intracellular, but are also excretory.*

Such are the poisons produced by the typhoid bacillus, the bacillus coli communis, the bacillus enteritidis (Gaertner), and the cholera vibrio.

(5) *Non-toxic, or slightly toxic elements, which are important in the formation of antitoxin.*

Products of Individual Pathogenic Bacteria.

Bacillus anthracis.—If the anthrax bacillus be grown in ordinary peptone broth, and removed after several weeks' incubation by filtration, the broth is found to possess practically no toxicity. If, on the other hand, it is grown in broth which does not contain peptones, but contains a proteid, such as alkali-albumin or serum, capable of being digested, after removal of the bacteria, the filtrate is found to contain poisonous substances. These are of two kinds: first, the albumoses, and secondly, nitrogenous bodies, non-proteid in nature and of a resinous consistency. The albumoses give the chemical reactions of the similar bodies produced in peptic and pancreatic digestion. The nitrogenous body is alkaline, and contains carbon, hydrogen, nitrogen, and sulphur, and forms a very loose combination with acids. A gold or platinum salt is not formed. Both the albumoses and the nitrogenous body (which I have elsewhere called provisionally an "alkaloid") have a toxic action, that of the latter being more powerful than that of the albumoses. Injection of the albumoses into animals causes a rise of body temperature and death, the rapidity of which is proportional to the dose (Figs. 29 and 30). It also produces in rodents diminished coagulability of the blood, which is well marked. This is one of the features of the action of peptic albumoses in dogs, but not in rodents. The nitrogenous body is an intense local irritant when injected under the skin, producing a great amount of œdema, but no obvious

necrosis. It does not produce fever, but causes coma and rapid death.

There are no specific symptoms in anthrax; no special affection of the nervous system or other part. The poison is found to cause no degeneration of the central nervous system or the nerves, but the albumoses produce a fatty degeneration of the cardiac muscle, which is a common feature of

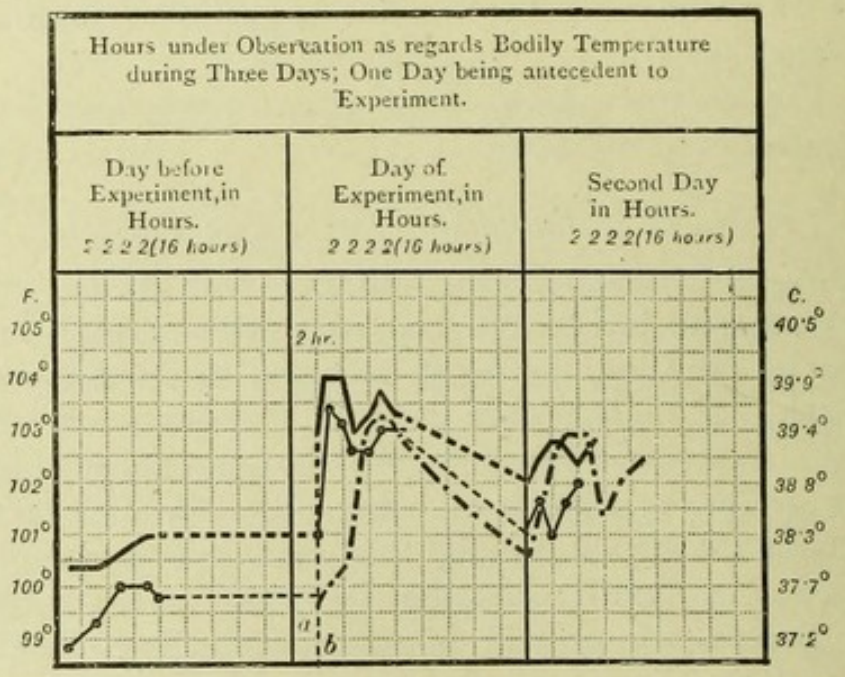


FIG. 29.—Chart showing the effect on the body temperature of the guinea-pig by the subcutaneous injection of anthrax albumoses and of peptic albumoses—*a*, time of injection of anthrax albumoses; *b*, time of injection of peptic albumoses.

Upper Thick Line.—Temperature of a guinea-pig weighing 430 grammes, injected subcutaneously with 0·09 gramme *anthrax albumoses, unheated*. Dose per kilo. of body-weight, 0·2 gramme.

Middle Thin Line.—Temperature of a guinea-pig weighing 440 grammes, injected with 0·09 gramme *anthrax albumoses, boiled* in solution for thirty seconds. Dose per kilo. of body weight, 0·2 gramme.

Lower Broken Line.—Temperature of a guinea-pig weighing 460 grammes, injected with 0·09 gramme *peptic albumoses, unheated*. Dose per kilo. of body-weight, 0·195 gramme.

No local œdema; no general symptoms, except fever, in any of the guinea-pigs.

the prolonged action of the poisons produced by bacterial digestion.

The same poisons formed artificially in, and separated from, the bacterial culture, are found in the blood and spleen of animals (guinea-pigs and sheep), as well as of man, dead of the disease. The results of the analysis of the tissues in a full-grown sheep dead of anthrax are given in the following table:—

Sheep inoculated subcutaneously with a virulent Anthrax Culture.	Albumoses.	Alkaloid.
From Local Lesion . . .	0.167	0.1346
From Spleen	0.191	1.2080
From Blood	(Chiefly deutero-albumose) 0.455	0.6430
	grm. 0.813	grm. 1.9856

There is no evidence of any amount of toxic excretion of the bacillus. Darmier, by using a large quantity of the bacilli, separated a toxine, which appears to be one of the intracellular poisons. Small doses produce wasting and death, and immunity may be produced by the toxine. The fact remains, however, that the amount of this toxine present is in great contrast to the other cases, such as diphtheria and tetanus, where there is a large amount of a similar poison excreted. The symptoms in anthrax are mainly to be ascribed to the products of the breaking-up of the proteid molecule by the digestive action of the bacillus.

Bacillus diphtheriæ.—If the diphtheria bacillus is grown in broth, unlike the anthrax bacillus, a powerful toxine is found in the liquid after the organisms are removed by filtration. This poison is referred to as the diphtheria toxine, or sometimes as the broth toxine. In addition to this, however, the diphtheria bacillus digests proteids, as, when grown in a solution containing alkali-albumin or serum, it is found that a large quantity of albumoses is formed, together with an acid body; the solution, in addition to these, containing some of the toxine formed in broth.

Attempts have been made to isolate the toxine from the broth. Roux, in his first experiments, precipitated it by means of calcium phosphate, using Brücke's method for the separation of pepsin. He obtained a precipitate which was free of peptone, and which consisted chiefly of calcium phosphate. It was, however, highly toxic, acting in infinitesimal doses.

The action of the broth toxine is very characteristic. It is highly poisonous, and even less than 0.01 c.c. injected sub-

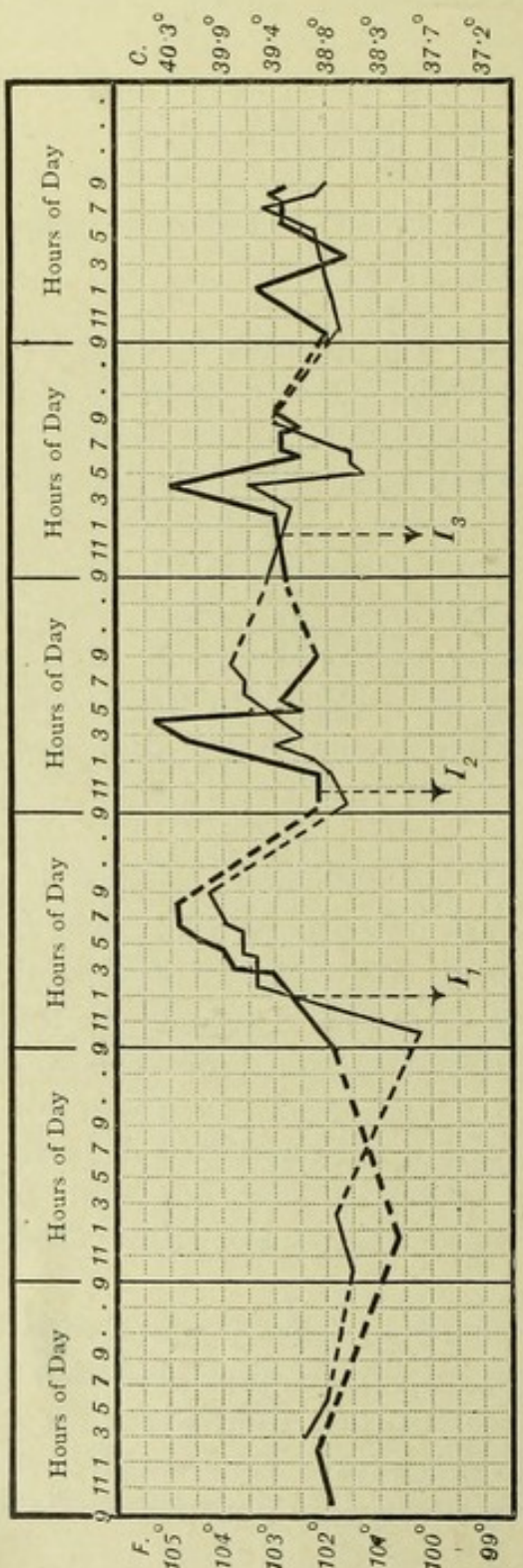


FIG. 30.—Chart showing the effect on the body temperature of the repeated injection intravenously of the albumoses of anthrax and of infective endocarditis.

I_1 I_2 I_3. Occasions of injection of anthrax albumoses.

Thick Line.—Temperature following injection of three doses of anthrax albumoses (each 0·04 gramme per kilo. of body-weight) on three successive days. Total dose per kilo. 0·12 gramme.

Thin Line.—Temperature following injection of three doses of albumoses from infective endocarditis (each 0·051 per kilo.) on three successive days. Total dose per kilo. 0·153 gramme.

The injections were made intravenously in rabbits.

cutaneously will kill a guinea-pig weighing 200 grammes. The albumoses are less toxic than the toxine. The effect of the toxine can be removed from the solution containing the albumoses, either by precipitating by means of alcohol, and keeping the precipitate under alcohol for a long time, or by keeping the mixture at a temperature of 60° C. for a few minutes. The toxine is not a proteolytic ferment, as it will not digest proteid substances exposed to its action. It is, therefore, probably not the agent in the formation of the albumoses, which may be looked upon as due to the direct action of the micro-organism.

In the actual disease, as it occurs in man, the toxine is found mainly in the false membrane, but it is also present in the spleen and blood. Albumoses are practically absent from the membrane, or exist in only very small quantity. They are found in the blood and most abundantly in the spleen, nearly 1 gramme of the dried and purified product having been obtained from the spleen in some cases, as shown in the following table:—

No. of Case.	Seat of Disease.	Albumoses in Grammes.			Alcoholic Extract.
		Blood and Spleen.	Blood only.	Spleen only.	Blood and Spleen.
1	Larynx.	0.974	...	...	0.271
3	Tonsils.	0.5955	...	...	...
4	Pharynx and larynx.	...	0.149	...	0.107 (Blood only)
5	Pharynx and larynx.	0.805	0.450	0.355	0.455
6	Nose and pharynx.	...	Trace.	0.715	...

Physiological Action.—The toxine and the albumoses have a similar action, although that of the albumoses is much weaker than that of the toxine. They affect the body temperature, the weight, the respiration, the heart and both the central and peripheral nervous systems.

The results obtained by an injection of a mixture of albumoses and toxine imitate the combined action of the poisons as they exist in the body. In the following table are shown the results of injection of the mixed toxine obtained from the tissues of patients dead of diphtheria.

INTRAVENOUS INJECTION IN RABBITS OF MIXED DIPHTHERIA ALBUMOSES AND TOXINE OBTAINED FROM CASES IN MAN.—MULTIPLE DOSES.

Weight of Rabbit in Grammes.	No. of Doses.	Total Dose per kilo. of Body Weight in Grammes.	Death in	Paralysis in
1100	2	0.136	7 Days.	2 Days.
1970	2	0.153	11 ,,	6 ,,
970	3	0.157	10 ,,	7 ,,
1565	2	0.100	Killed in 24 days.	20 ,,
1200	2	0.083	Recovery in 54 days.	8 ,,

TABLE OF LOSS OF WEIGHT.

Original Weight in Grammes.	Weight at Death.	Proportional Loss of Weight.	Death in	Fever Period.	Dose of Albumoses per kilo. of Body Weight.
1100	970	$\frac{1}{8}$	7 Days.	7 Days.	0.136
1970	1520	$\frac{1}{4}$	11 ,,	1 Day.	0.153
970	530	$\frac{1}{2}$	10 ,,	6 Days.	0.157

The *effect on temperature* is more marked with the albumoses than it is with the toxine, and repeated intravenous injections of the albumoses in rabbits frequently produce a rise of temperature lasting several days after the injections are stopped. The toxine also produces a rise of temperature, which, however, is very irregular in its course.

In one experiment 2 c.c. of artificially prepared broth toxine was injected into the marginal vein of the ear of the rabbit.

This was followed by some rise of temperature on the same day, and a rapid fall to about 96° F. on the following day, ending in death (Fig. 31). When 5 c.c. of the same mixture was given, there was a great rise of temperature, followed by the death of the animal in a shorter time than in the first experiment (Fig. 31).

The diphtheria poisons, besides producing rise of temperature, may cause a fall of body temperature. In one experiment

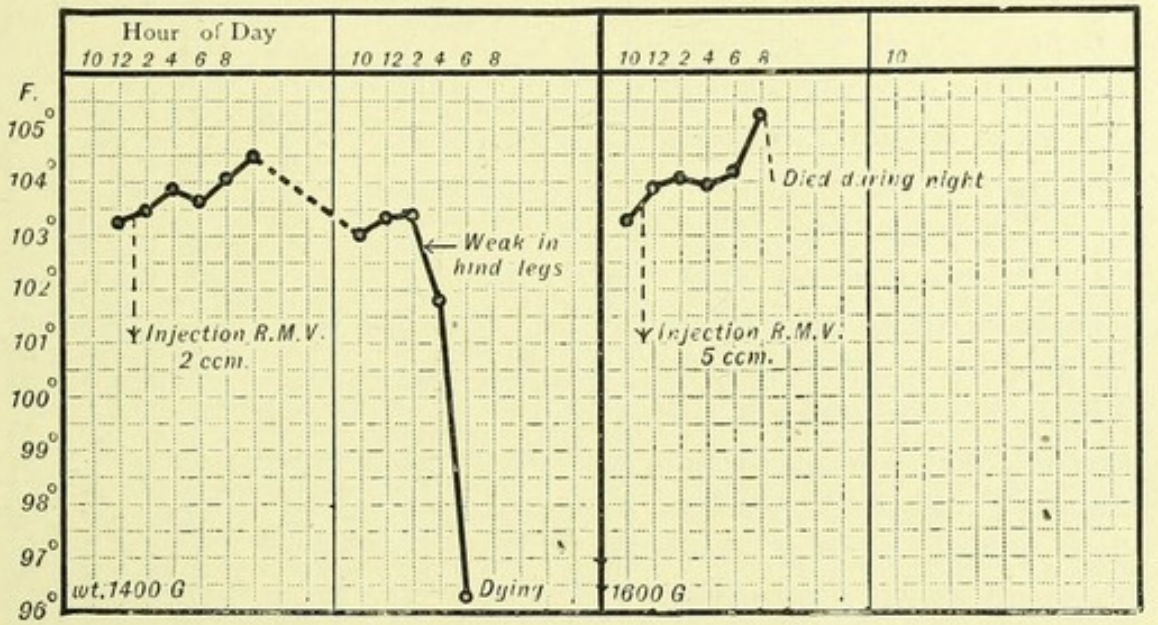


FIG. 31.—Two curves showing the effect on the body temperature in the rabbit from the intravenous injection of diphtheria toxine and albumose, prepared by growing the bacillus in a solution of alkali-albumin in broth (without peptone) for 27 days at 37° C. The left curve shows the effect of the injection of 2 c.c. The temperature rose slightly on the day of injection but dropped suddenly on the following day at the onset of paralysis. The curve on the right shows the effect of 5 c.c. of the same liquid. The temperature rose gradually and the animal died during the night.

0.2 gramme of a dried mixture of the two poisons was injected into the marginal vein of the ear of a rabbit. There was scarcely any rise of body temperature, but the next morning the temperature had fallen 3° C., and the second injection of a small dose still further increased the depression of temperature, the animal dying in twenty-four hours.

Heating the mixture of diphtheria toxine almost constantly causes a fall of body temperature when injected. Five c.c. of broth toxine, which had been kept at 60° C. for one hour, produced a fall of temperature, which was followed by

a rise to the normal, and recovery. In another experiment, the same dose of the same toxine was heated for ten minutes at 60° C., and, after injection, produced a continuous, but gradual, fall of temperature up to the time of death on the fifth day of experiment (Fig. 32). A similar dose of the same toxine, unheated, produced a rise of temperature, not a fall (Fig. 32).

The *effect on the body-weight* of these poisons is to produce a gradual loss, which is very great if the animal lives a week or ten days (Table, p. 82). The loss of body-weight is not solely due to the diminished quantity of food taken, but to some change in nutrition produced by the poison. It is more marked in the case of the diphtheria poison than in that of most of the other bacterial poisons, but a similar loss of weight accompanies the slow action of snake venom and of abrin (p. 89).

The *effect on respiration* is well marked, both in rodents and in the monkey. A rabbit injected with the diphtheria poison shows,

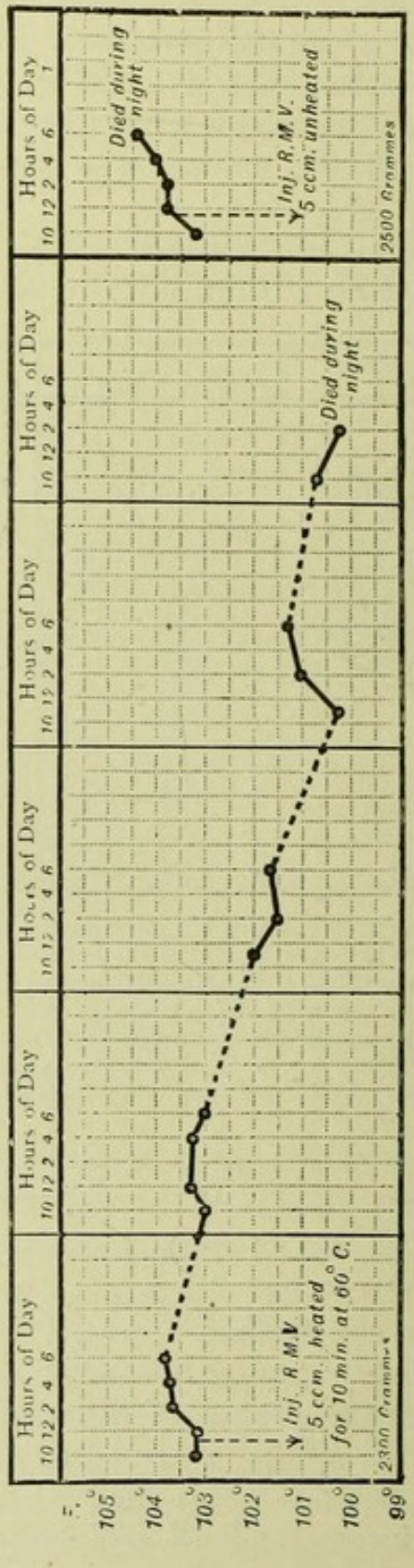


FIG. 32.—Two curves comparing the effect of the intravenous injection in rabbits of heated and unheated mixtures of diphtheria toxin and albumose, prepared by growing the bacillus for 38 days in a solution of alkali-albumin in broth (without peptone). The left curve shows the effect of the toxic mixture heated for 10 minutes at 60° C. There is a gradual fall of body temperature till the time of death on the fifth day. The curve on the right shows the effect of the same dose of unheated toxic mixture. There ensued a rise of temperature with death in less than 24 hours.

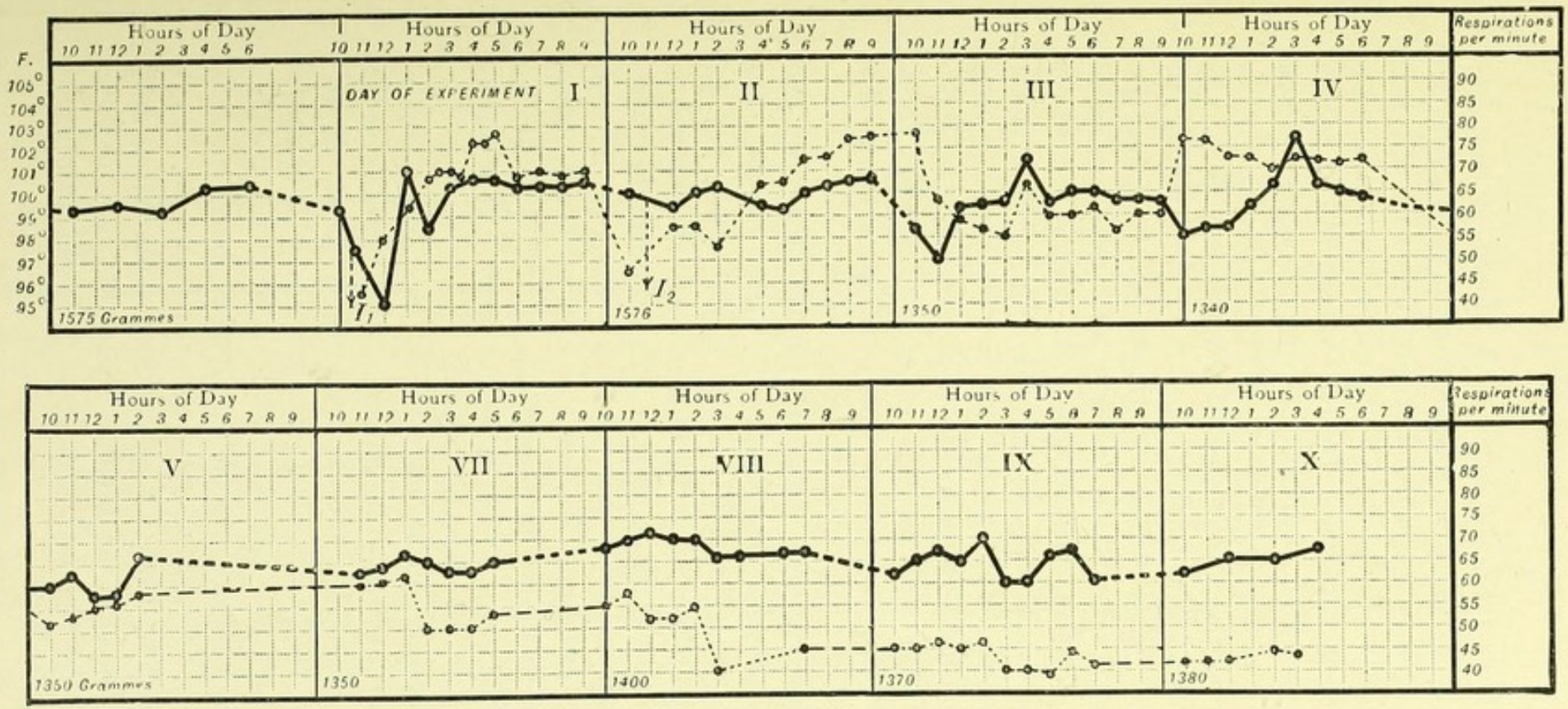


FIG. 33.—Chart showing the effect of the intravenous injection of diphtheria albumoses (from a human spleen) in a monkey.

Plain Line.—Temperature curve. *Dotted Line.*—Curve of respiration. Weight of Animal.—1575 grammes.

Dose I —Injection of first dose of 0·3 gramme albumoses into R. brachial vein.

Dose I_2.—Injection of second dose of 0·3 gramme albumoses into L. brachial vein.

Result of Experiment:—1. *On the Temperature.*—This was not raised to any great extent, but was irregular as shown by the curve. Temperature taken in the rectum.

2. *On the Respiration.*—The respirations were greatly quickened after each dose, and remained frequent until the seventh day of experiment.

3. *On the Weight.*—After the second dose the animal lost in weight about 226 grammes, regaining somewhat afterwards.

4. *General Symptoms produced.*—After the first dose there were no general symptoms. But in three hours after the second dose the animal became progressively weaker, so that in seven hours after the injection it could not sit upright or move the arms and legs. There was therefore complete motor palsy of the limb and trunk muscles; but no respiratory paralysis and no palsy of the facial muscles, as the animal lying on one side with food within reach of its mouth ate vigorously and swallowed perfectly. No knee-jerks were obtainable, and no reflex on pinching the limbs. Without loss of consciousness therefore the albumoses produced complete motor and sensory palsy of the limbs and trunk, excluding the respiratory muscles. This condition lasted for over 24 hours after the second injection; in 26 hours the animal could sit up. There were still no knee-jerks. The animal gradually and completely recovered, and remained quite normal for several months; when it was killed. The knee-jerks reappeared on the second day following the injection, and recovery from the motor and sensory palsy was complete on about the same day.

towards the end of its action, attacks of dyspnœa of irregular onset, lasting but a short time, and followed by very rapid shallow breathing. These respiratory attacks occur usually just before death. In the monkey the effect on respiration is seen chiefly in an increased rapidity. In an experiment in which two doses of 0.3 gramme of diphtheria albumoses were injected intravenously into a monkey, there was some irregularity in the temperature until the ninth day of experiment (Fig. 33). The change in the body temperature was not nearly so marked as that of the respirations. With the first injection the respirations rose to nearly 80 a minute, and this increased rapidity, though not so marked, lasted until about the ninth day. Three hours after the second injection, motor palsy appeared, and in seven hours there was complete motor and sensory palsy of the limbs and trunk, with loss of knee-jerks and skin reflex. There was no loss of consciousness. This condition lasted twenty-four hours, the knee-jerks being the last to be recovered.

The *effect on the nervous system* is partly shown in the experiment just quoted. Although, in the rabbit, the diphtherial poison has no effect on the spinal cord, yet, in the monkey, it can produce complete motor and sensory paralysis by affecting this part; and, in man, diphtheria palsy is sometimes associated with degenerative changes in the cells of the spinal cord; and in some cases, of death from acute diphtheria, an excessive pigmentation of the cells of the anterior horn is observed. There is no evidence of affection of the brain in any animal by the poison.

The chief effect of the poison, however, in man and animals, is on the peripheral nerves. In experimental diphtheria in rodents, paralysis, slight in extent, sometimes local, sometimes shown only by a general weakness, is constantly observed (Fig. 34), and this paralysis is dependent on a widespread but varying degeneration of the nerves, both sensory and motor. The degeneration is seen to be at first a breaking-up of the myelin sheath, with its subsequent attenuation and disappearance. It may go no further than this, but usually the axis cylinder becomes attenuated, and finally ruptured,

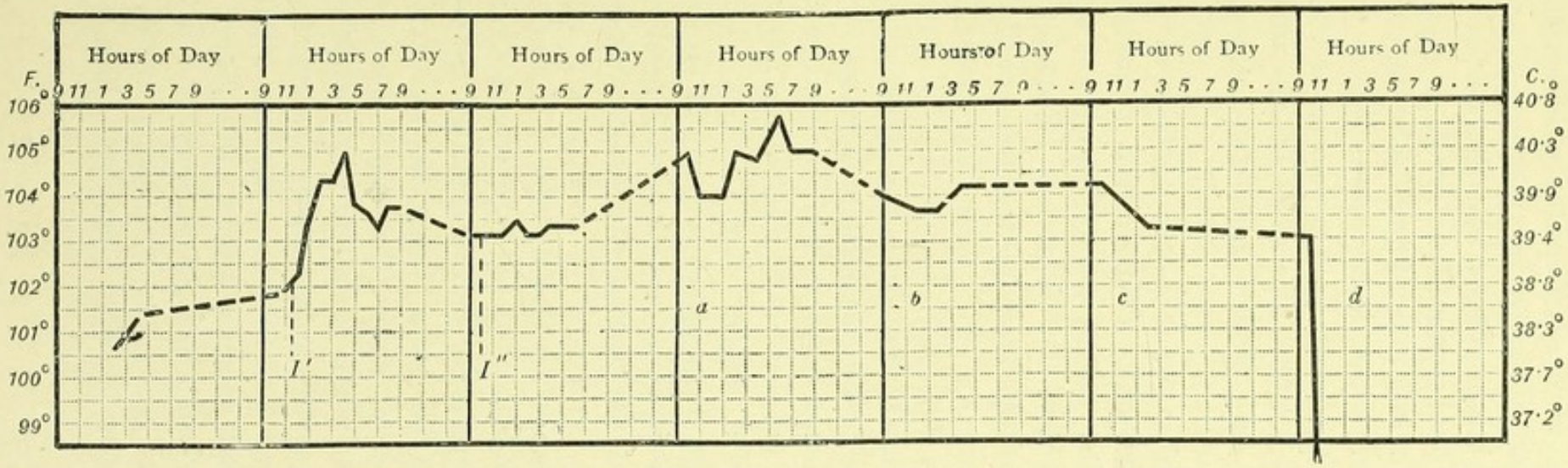


FIG. 34.—Showing the effect on a rabbit, weighing 1100 grammes, subjected on successive days to intravenous injection (into marginal vein left ear) of 0.076 gramme of diphtheria albumoses from blood and spleen of a patient dead of the disease. Total dose = 0.136 gramme per kilo. body-weight of experimental animal. Death on the seventh day.

I′. Occasion of first injection; body-weight of animal at this date, 1100 grammes.
I″. Occasion of second injection.

a. On this day paresis of left hind leg noted.
b. On this the above paresis more marked; weight of animal reduced to 930 grammes.
c. On this slight paresis of right hind leg, which was increasing next day.
d. On this paresis of all limbs, especially those of left side. Died; temperature at death 86·45° F.; weight, 970 grammes.

in which case the nerve fibre degenerates to the periphery. The nerves most frequently affected are, not the large trunks, but the small intramuscular branches, and the small branches of the sensory nerves. The sympathetic nerve fibres may be affected, but the vagus was in no case found to be degenerated.

The *effect on the heart*, which is so prominent a symptom in human diphtheria, is shown in experimental diphtheria by degeneration of the muscle fibres, which, in the early stage, become granular, and, in the later stage, fatty, losing their striation and nuclei.

The *effect on the kidney* varies considerably in different animals. In man, in the acute disease, and always in very severe cases, there may be suppression of the renal secretion, the exact causation of which is not known. Occasionally, in man, fatty degeneration of the renal cortex follows diphtheria. In the rabbit and guinea-pig this does not occur, but it occurs, in some cases, in the cat.

In the rabbit the diphtheria poison may produce *fatty degeneration of the liver;* in the guinea-pig this does not occur, but one of the characteristic actions of the bacillus in the guinea-pig is the production of double pleural effusion, which does not contain the bacilli.

The other effects of the diphtherial poison will be discussed when antitoxines are considered, as well as the nature of the poison, in so far as it can be discussed (Chapter VI.).

Snake Venom; Abrin, Ricin, Robin.—It is necessary here to consider certain poisons allied to the bacterial toxines, which are produced in one case by the activity of an animal cell (snake venom); in the other cases by the activity of the cells of growing plants, as in the seeds of the abrus precatorius, or prayer-bead; the seeds of the castor-oil plant (ricinus communis), and of the robinia pseudacacia.

Investigation of these poisons has thrown great light on the nature of bacterial poisons, and, in the main, it may be said that they show two kinds of poisons, one belonging to the class of digestive products; the other an excretory product, which corresponds to what has been called above

the bacterial toxine. Thus, chemically, snake venom contains proteids of the nature of globulin and albumose. The poison of the viperine snakes contains two proteid bodies, the globulin and the albumose, both of which are poisonous, and each of which appears to have a distinctive action—the globulin acting more particularly on the blood, and the albumose on the nervous system. If the globulin be precipitated from its solution by heating it to its temperature of coagulation, its activity is destroyed, but the toxic properties of the albumose are still present, although somewhat impaired. Cobra venom does not contain so much globulin as that of the viperine snakes, so that heating its solution to the temperature at which the globulin is coagulated does not greatly diminish the toxicity of the venom, and it requires the solution to be boiled for a short time before the poisonous action is destroyed.

Abrin.—The seeds of the abrus contain two proteid substances, globulin and albumose, both of which are poisonous, and both of which produce similar symptoms. The product which has been obtained from the seeds and called abrin is a mixture of these two substances in varying proportion. The physiological effect of this substance is, first, that of a great local irritant, producing intense conjunctivitis when applied to the eye, and causing œdema and necrosis of tissue when injected subcutaneously. Its general effect is that of lowering the body temperature; in pigeons, which have naturally a high temperature, the fall of temperature may be more than 12° C. (Fig. 35). It also produces a fall of temperature in the cat and the rabbit (Fig. 36). The number of respirations is increased in some cases; in others is diminished. Subcutaneously injected, abrin produces diarrhœa, which is commonly bloody, and is associated with the signs of a hæmorrhagic gastro-enteritis, there being great inflammation of the mucous membrane of the intestine, and especially of the adenoid patches. The symptoms do not arise until some time after the injection; that is, there is a period of incubation.

The abrus poisons are very sensitive to heat, the action

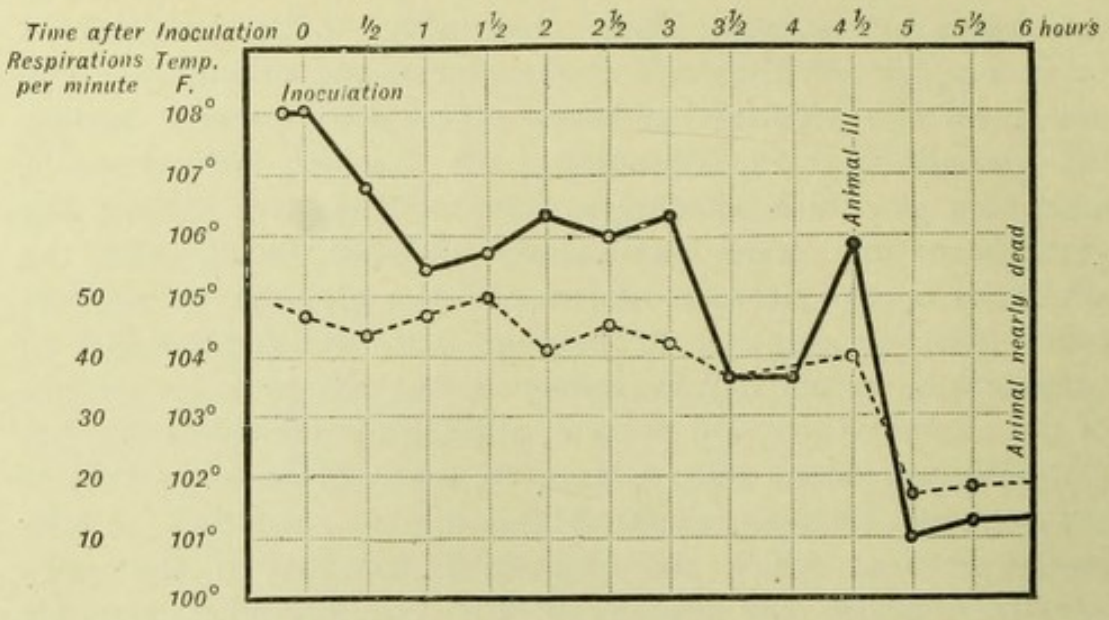


FIG. 35.—Showing effect of abrus-albumose on temperature and respirations of the pigeon. Temperature taken in rectum every half-hour. Dotted line, respiration; thick line, temperature.

A pigeon, weighing 335 grammes, was given hypodermically a dose of 20 mgms. albumose, equal to 60 mgms. per kilo. of body-weight. In 4½ hours, the animal began to show symptoms of poisoning, and died in about 6 hours or rather longer. The temperature began to fall from the first, and with a few rises continued to fall until the animal was nearly dead, when the observations were ceased. The curve of the number of respirations per minute follows very closely the temperature curve.

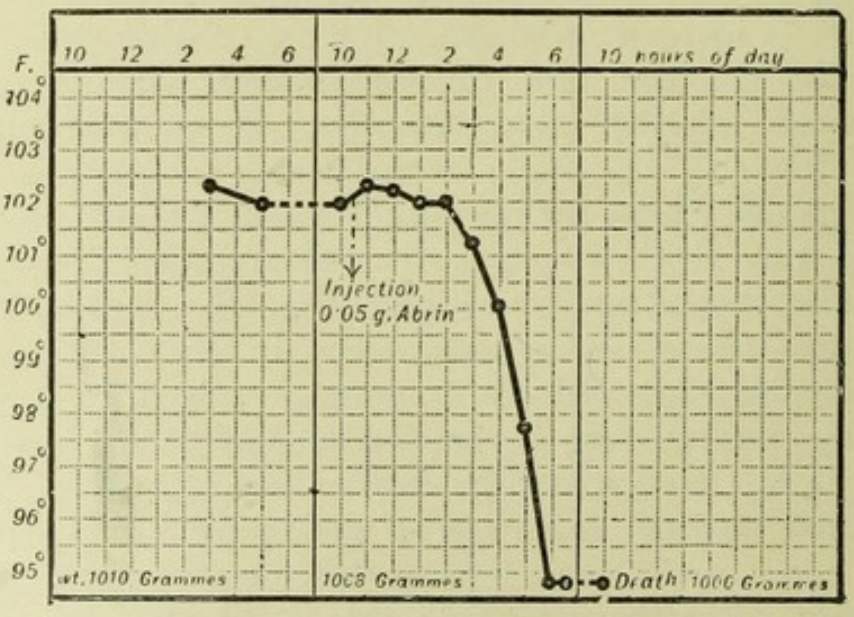


FIG. 36.—Showing the effect of the intravenous injection in the rabbit of 50 mgms. of abrin. Soon after the injection there was a rapid and continuous fall of temperature till death.

of the globulin being completely destroyed by the momentary raising of the temperature of its solution to 75° or 80° C.; that of the albumose is destroyed at a rather higher temperature, 85° C.

Not only by its general effects, that is, by its period of incubation and by the definite symptoms produced, does the abrus poison reproduce the features of an infective disease; but, like some of the bacterial poisons, as will be seen, it produces an antitoxine which is specific in its action (Chapter VI.).

Ricin.—In its general action ricin resembles abrin, but it is a more powerful poison. By intravenous injection, 0.03 mgm. per kilo. of body weight is fatal to rabbits (Kobert). When given by the alimentary tract it may also be fatal, but about a hundred times the intravenous dose is requisite, and Kobert calculated that, by the digestive tract, 0.18 gramme would be fatal to an adult man. Guinea-pigs are very susceptible to the poison, white mice less so; and Ehrlich calculated that 1 gramme of ricin would kill a million and a half guinea-pigs, so that the toxicity of the substance, although not so high as that of the poison of some snakes and the diphtheria toxine, is still very considerable (p. 108). Subcutaneously injected, ricin produces, like abrin, diarrhœa and general prostration, and it also gives rise, in the animal body, to an antitoxine, which is specific, but differs from anti-abrin. The activity of ricin is as sensitive to heat as abrin. Robin is a poison similar to ricin and abrin.

There are other poisons in the animal kingdom which are closely related to those which have been just discussed. The poison of some spiders has been shown by Kobert to be proteid in nature, their activity being destroyed by heat. The blood of murænidæ (murena, eel, conger) was shown by Mosso to be poisonous. Lupin seeds also contain a poison of a similar nature.

Bacillus tetani.—The tetanus bacillus, when grown in broth, neutral or slightly alkaline, in the absence of oxygen and in the presence of a small percentage of sugar, forms a

powerful toxine, which has a characteristic action. Guinea-pigs are highly susceptible to the poison; mice less so, and rabbits still less. When injected subcutaneously it produces symptoms, after a period of incubation of greater or less duration. The symptoms are mainly confined to the production of tetanic spasms, which are first observed in the muscles at the site of inoculation, and subsequently spread all over the body. The spasms are both tonic and clonic, and are readily excited by external influences, such as pinching the skin. During one of these attacks of spasms the animal dies. A rise of body temperature, or an irregularity in the body temperature, is also a result of the injection of the toxine.

This poison, which, in its general chemical characteristics resembles the diphtheria toxine, is readily affected by heat It is destroyed by keeping the solution at 65° C. for a few minutes, and at 60° C. for twenty minutes, while, at lower temperatures, it requires a longer exposure to affect its vitality. Drying preserves the activity of the toxine. It is very susceptible to the action of light and of oxygen, and a solution of toxine from these causes soon loses its power, and may become practically inert.

The poison directly combines with the cell elements of the central nervous system, and, mainly, with the motor cells of the spinal cord, and, to a less extent, of the brain. It appears to have no direct action on the peripheral nerves or their endings. There is no free poison in the central nervous system, but, in some cases, there is evidence of its presence in the blood and organs.

The tetanus bacillus has some digestive action, as is seen in its slow liquefaction of gelatine, but this slight digestion appears to have no relation to the formation of toxine, and is much less marked than is the case with the diphtheria bacillus.

From the organs of persons dead of tetanus no poisonous substances may be obtained. From the central nervous system no free poison can be extracted, owing, doubtless, to the fact that the toxine combines with the cell elements.

But with the heart blood, in one case, Kitasato found that injection of the serum gave rise to the characteristic spasms of tetanus. In an extended examination of the spleen and blood in several cases of tetanus, no poison corresponding to the toxine was found, possibly because the prolonged manipulation with alcohol and exposure to light may have destroyed it, but two classes of products were separated. Albumoses were present in the spleen and blood, and gave rise, on injection, to fever but not to tetanic spasms. On the other hand, certain non-proteid bodies were extracted, some soluble in alcohol and some in ether, and, in two experiments, the injection of the latter gave rise to definite tetanic spasms, with rapid death in one case and recovery in the other. In these cases spasms came on in a few minutes, and there was no period of incubation, such as is seen in the action of the toxine. It may be that these non-proteid bodies are the immediate agents in producing the spasms, the chief poison being the toxine which is formed in peptone broth, or in solutions containing no proteid matter. The toxicity of the poison is very great: one-twentieth of a milligramme is fatal to a mouse.

Contrasting the chemical products of the diphtheria bacillus and the tetanus bacillus, it is seen that in both there is a toxine formed, which is the chief agent in producing the symptoms of the disease; that in both there is evidence of a digestive action of the bacillus, and of the formation of certain end products; but whereas, in the case of diphtheria, the albumoses produce fever, with paralysis and some degree of nerve degeneration, in the case of tetanus they appear to have no special action except that of producing fever. One of the end products in the case of the diphtheria bacillus is an organic acid, which produces a slight degeneration of the nerves. There is evidence in the case of tetanus that some, at least, of the end products are capable of giving rise to tetanic spasms.

Bacillus typhosus, Bacillus coli communis and Bacillus enteritidis (Gaertner).—These three bacilli may be grouped

together in the consideration of their poisons, as not only are they closely related morphologically, but the poisons they produce are of a similar nature.

They have a very slight digestive action, the typhoid bacillus least of all, and the poisons they form are, to some extent, excreted, but are mainly found in the bodies of the bacilli.

If a virulent typhoid bacillus be grown in broth, and, after a period of two or three weeks or longer, the bacillus be removed by filtration, the filtrate is found to have a definite, but slight, toxicity. If, after growing even a shorter time, say for seven days, the bacillus be not filtered off, but be killed by chloroform, it is found that the toxicity of the liquid, when injected, is much greater than if the bacillus be removed. It is still more increased by breaking up the bodies of the bacilli by prolonged exposure to a temperature of 60° C., by drying the broth, and grinding the residue to a powder, or by separating the bacilli by centrifugalisation, drying them and grinding to a powder. The bodies of the bacilli are, therefore, necessary in order to obtain a highly toxic product from artificial cultures, and the dead bacilli may be boiled for five minutes, not only without destroying the toxicity of the poison, but with the result of actually bringing out its effects. This effect of heat on the typhoid toxine is in great contrast to the effect of even moderate temperatures on the toxines of diphtheria and tetanus, and the poison is also contrasted with these by the fact that, in any artificial culture, it exists mainly in the bodies of the bacilli, and is excreted into the liquid only to a slight extent.

The digestive action of the typhoid bacillus, when it is grown in a liquid medium containing alkali-albumin or serum, is very slight. Some albumoses are formed, but in very small quantity, even after thirty-two days' culture. This is again in great contrast to the digestive action of anthrax and of diphtheria.

The physiological effects produced by the typhoid toxine are well marked. They consist, in rabbits, of a great lowering of the body temperature and in the production of profuse

mucous diarrhœa, in whatever way the toxine is introduced into the body, except by the mouth. If the poison is given in a small dose intravenously, it may produce an initial fall of temperature, but no diarrhœa, and the chief symptom observed is wasting, which steadily progresses until death. In these cases, there is no obvious gross change in any of the organs after death, but, on staining with osmic acid, the

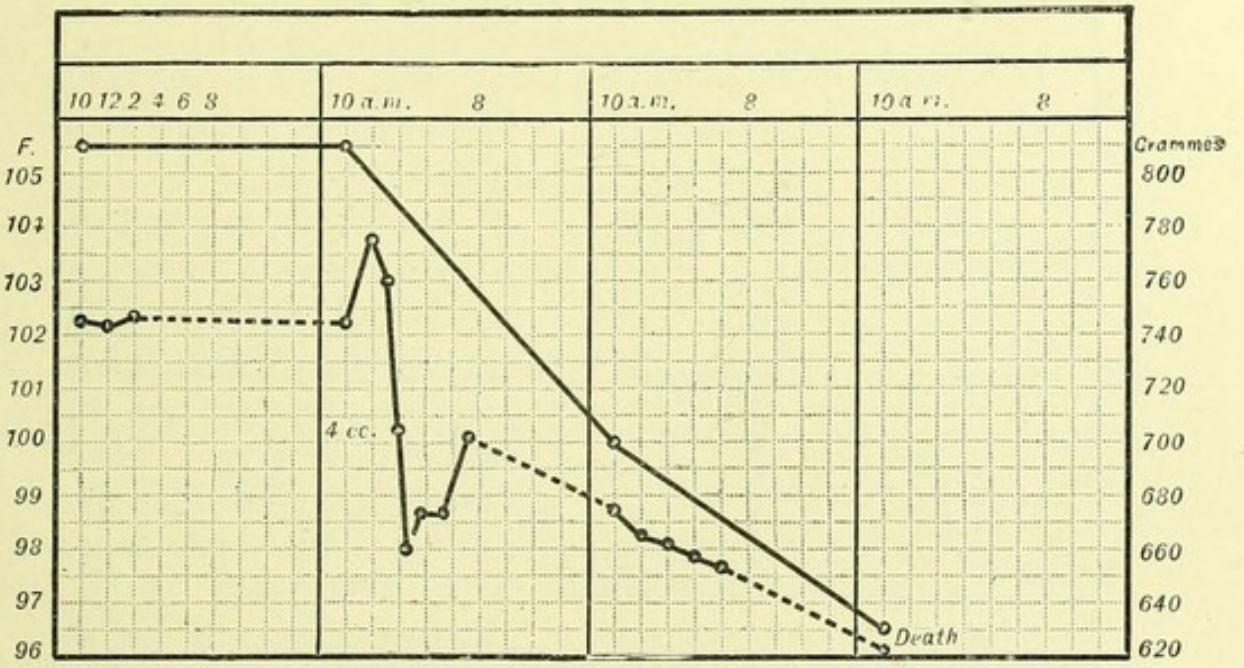


FIG. 37.—The effect of the typhoid toxine on the temperature and weight of the rabbit. The liquid injected was a 13 days' old culture of the virulent bacillus in peptone broth. The bacilli were then killed by chloroform, the latter evaporated off in vacuo and the mixture of broth and bodies of the bacillus injected intravenously. The result is shown as a lowering of the body temperature, at first suddenly, afterwards gradually till death. There was also a progressive loss of weight. The upper line represents the weight, the lower line the temperature.

heart muscle shows well-marked fatty degeneration of its fibres.

A depression of the body temperature is one of the most marked features in the action of the typhoid toxine in rabbits, and this depression may continue until death occurs. It is seen when a large dose of the poison is injected (Figs. 37 and 38). In other cases, where the amount of poison injected is less, there is an initial fall of temperature, followed by a rise above the normal, lasting, perhaps, two or three days (Fig. 39). With a very small dose of the poison, a

slight rise of temperature only may be noted. In man, the typhoid poison, as obtained from artificial cultures, produces a rise of temperature, and not a fall. It has been used extensively in antityphoid inoculation, the liquid employed being simply the dead bodies of the bacillus from an agar culture, or from broth. After injection there is a local swelling, with pain, and more or less œdema, and, after a few hours, there is a rise of temperature to 102° C., or above, which lasts from eighteen to twenty-four hours (Fig. 40).

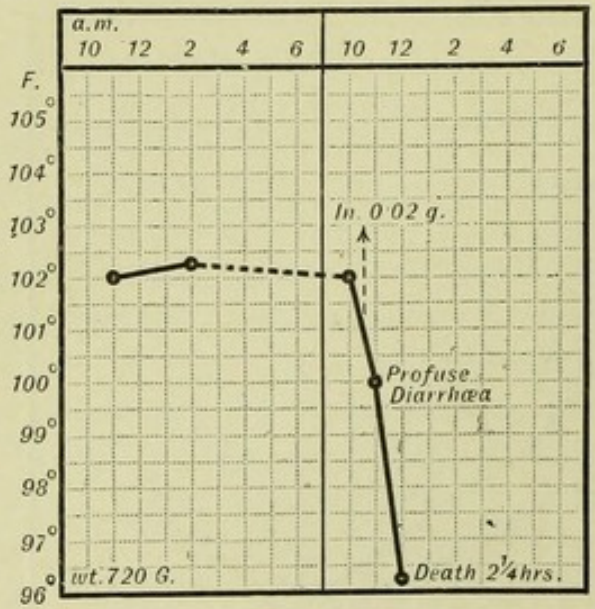


FIG. 38.—The effect of the dried typhoid toxine (intracellular poison). The bacilli were killed by heating the culture fluid twice for 10 minutes to 60° C. They were then separated by centrifugalising, washed with distilled water, and dried over sulphuric acid. The dried bodies (0.02 gramme) were ground up with a little water and injected intravenously. There resulted a sudden fall of temperature, diarrhœa and death in 2¼ hours.

Sanarelli described definite changes in the Peyer's patches of the intestine as the result of the subcutaneous injection of the typhoid toxine. These changes were swelling, congestion and even superficial ulceration of the patches. It will be remembered that a subcutaneous injection of abrin produced this effect on the intestine, but all observers have not found this change in the intestine with the typhoid toxine.

From the spleen of persons dead of typhoid fever, albumoses in fair quantity may be obtained. Thus, in three different cases, 0.369 gramme, 0.37 gramme, .0.652 gramme were obtained, which gave the chemical reactions characteristic of the bodies. Beyond, however, producing a slight rise of temperature, the albumoses were found to have but little physiological action. The alcoholic extract of the spleen was also without effect. The toxine may, however, be extracted from the spleen when the splenic pulp is rubbed

through wire gauze and filtered, after being treated with an excess of normal salt solution. The injection of the

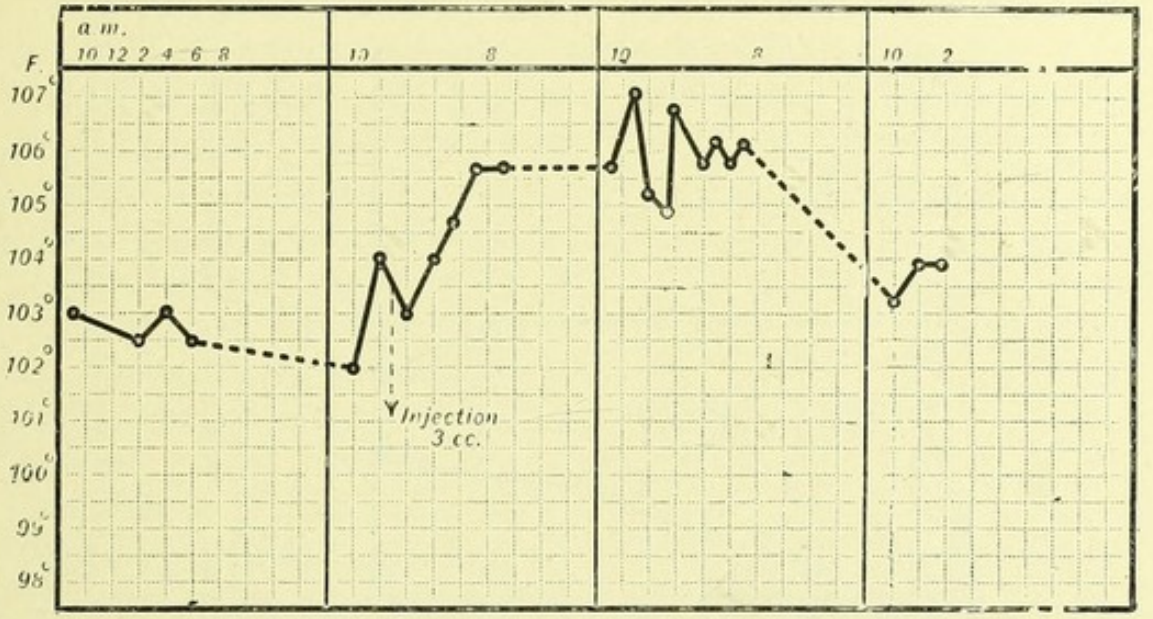


FIG. 39.—The effect of the typhoid toxine on the temperature of the rabbit. The liquid was a 7 days' culture of the bacillus in peptone broth; the bacilli were treated as described under Fig. 37 and the mixture of dead bacilli and broth injected intravenously. Following the injection there is a steady rise of temperature, highest on the following day (107° F.): the animal subsequently recovered. The experiment shows a weaker action of the toxin than that in Figs. 37 and 38.

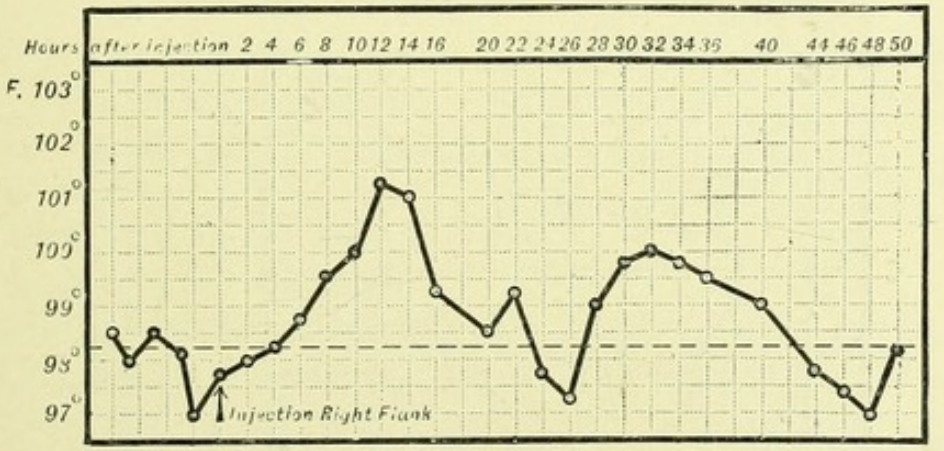


FIG. 40.—Temperature reaction following the subcutaneous injection of typhoid vaccine (1.5 cc.m.) in a healthy male æt. 18. The pyrexia produced lasted with a slight intermission for 48 hours. The vaccine is a mixture of broth and bodies of the bacillus and the result may be compared with the mild action of the toxine in rabbits shown in Fig. 39.

filtrate into rabbits was found, after a period of incubation, to cause a great fall of temperature, with collapse and profuse

mucoid diarrhœa, effects which are precisely similar to those produced by the toxine of the typhoid bacillus obtained from artificial cultivation.

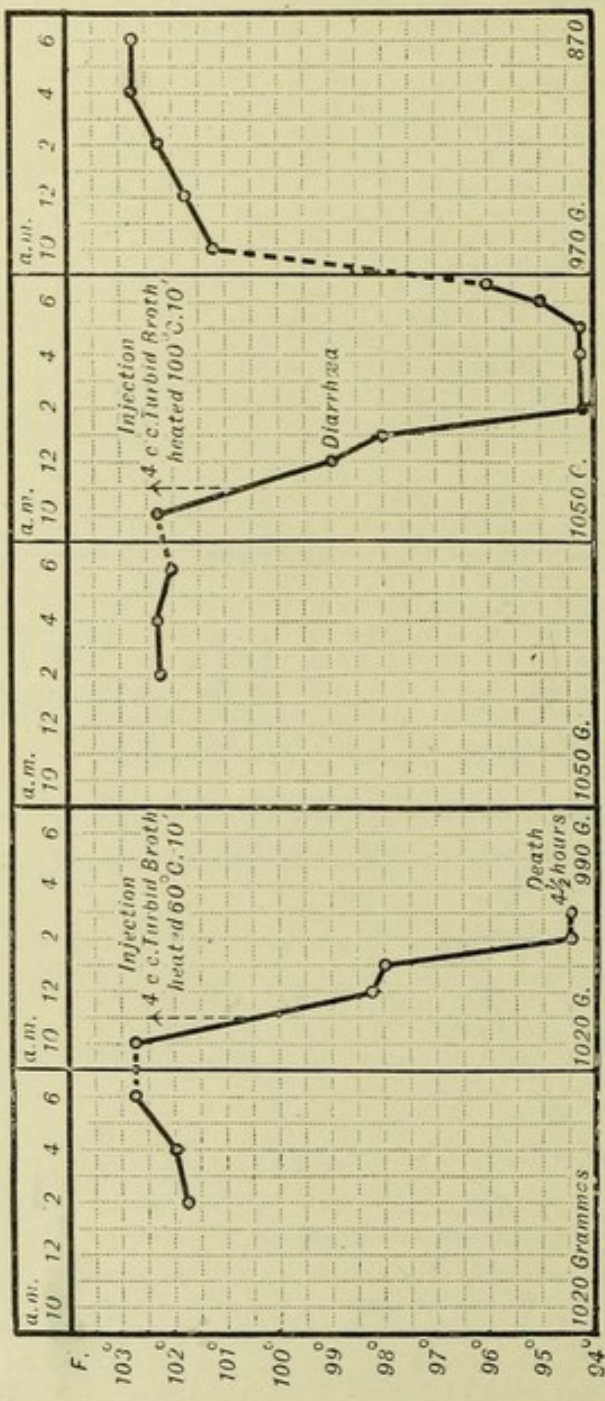


FIG. 41.—The effect of the intravenous injection of the intracellular toxine of bacillus enteritidis Gaertner in rabbits. The liquid used was a mixture of the bodies of the bacilli in broth, 22 days' culture. The left curve shows the effect after heating the injection liquid to 60° C. for 10 minutes. There was a rapid fall of temperature till death. The right curve shows the effect of the same dose heated to 100° C. for 10 minutes. The temperature fell 8° F., but rose again to the normal, and the animal survived. Compare with Figs. 35, 36, 38, and 42.

Gaertner's bacillus closely resembles the typhoid bacillus, and differs chiefly, in culture, by the fact that it forms gas in glucose-gelatine. The character of the poison which it

produces is similar to that of the typhoid toxine, namely, that it produces a great depression of temperature, with loss of weight and diarrhœa (Fig. 41).

It is slightly more active than the typhoid bacillus in its digestive effect on proteids, but, unlike the typhoid bacillus, when grown in Marmorek's fluid (broth, two parts; serum, one part), it sometimes produces a partial precipitation of the proteid solution in the form of a gelatinous clot.

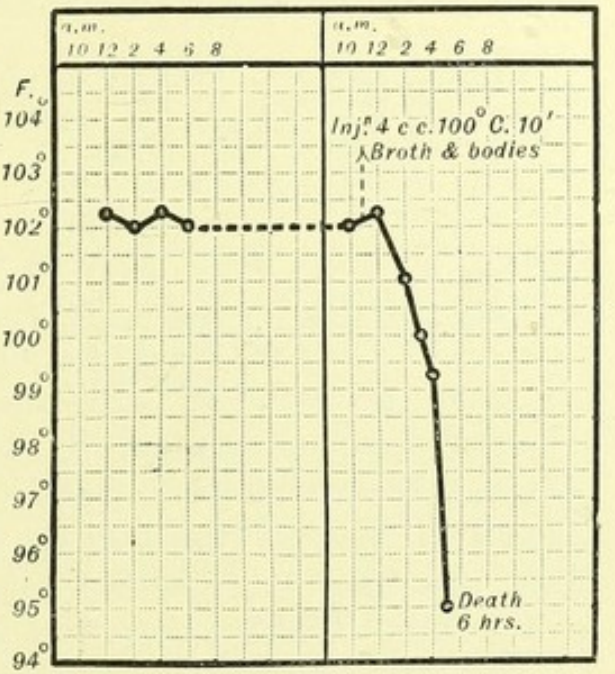


FIG. 42.—The effect of the intravenous injection of the intracellular toxine of the bacillus coli communis in a rabbit. The liquid injected was an 18 days' culture of the virulent bacillus in peptone broth, heated to 100° for 10 minutes. The toxine caused a rapid fall of temperature and death in 6 hours.

Bacillus coli communis.—The type of action of the poison of the bacillus coli communis is the same as that of the two other bacilli, in some cases producing a great fall of temperature (Fig. 42), and, in others, a rise of temperature, with a loss of body weight, and, in some cases, the production of diarrhœa.

To a much greater extent than the two other bacilli, bacillus coli communis digests proteids, but this effect is still far behind the digestive activity of the anthrax or the diphtheria bacillus. When grown in the presence of coagulable proteids, such as diluted serum or Marmorek's fluid, the bacillus coli communis causes the precipitation of the proteid in the form of a gelatinous clot. This clotting of the proteid solution is of interest in connection with the experiments of Stillmark, who found that ricin also produces a clotting in proteid solutions, especially serum. Stillmark used it as an argument in favour of the ferment nature of ricin.

Heating the dead bodies of the bacillus, suspended in the broth culture fluid, increases the toxicity of the solution, as

with the typhoid bacillus and Gaertner's bacillus, but, in the case of the bacillus coli communis, it requires a temperature of the boiling point of water to effect this.

Altogether, the mode of action of the toxine of the bacillus coli communis is more irregular than that of the poisons of the other bacilli, not only as regards the lethal dose, but also as regards the irregular kind of fever and after-fever produced.

Vibrio choleræ asiaticæ.—The products of the cholera vibrio may be divided into the two classes already described, namely, the toxine and the products of proteid digestion. The toxine is a most powerful poison, and is chiefly intracellular, although it is also excreted from the body of the bacillus. Pfeiffer thought the main poison intracellular; intraperitoneal injections causing collapse and a great lowering of the body temperature, and sometimes clonic spasms. The excreted poison, examined by Metchnikoff and Roux, had a physiological action like Pfeiffer's toxine. The latter, however, found that most of the toxicity was destroyed at 60° C., but other observers have shown that the cholera toxine is not, in the main, destroyed, even at 100° C.

The action of the cholera toxine in producing collapse and a fall of body temperature brings it into close relation, in its effects, with the intracellular toxines of the three bacilli last considered, namely, the typhoid bacillus, bacillus coli communis and Gaertner's bacillus.

The cholera vibrio also digests proteids, and the albumoses, in the condition in which they are separated, possess toxic properties, sometimes to a marked extent (Scholl). The digestive action of the cholera vibrio is, as a rule, much greater than that of the three bacilli last mentioned. The intracellular toxine must, however, be considered, according to present knowledge, as the most important poison produced by the cholera vibrio. A large dose produces very rapid death, and 0.4 c.c. of the filtrate of a broth culture of a virulent vibrio will kill a guinea-pig weighing 200 grammes.

Bacillus tuberculosis. — The exact nature of the chemical

products of the bacillus tuberculosis is not known, but the following facts are not without interest. Koch prepared a substance which he called *tuberculin*, which consisted of a glycerine broth culture of the bacterium, in which the bacilli had been killed by heat. This liquid is toxic to healthy animals. Injected into a healthy calf, or, in smaller doses, into a healthy man, it causes malaise and a moderate degree of fever, the symptoms soon passing off. If, however, a much smaller dose be injected into a man or animal, the subject of tuberculosis, what is called the *tuberculin reaction* ensues (Fig. 43). Sometimes there is well-marked œdema at the site of inoculation, but the prominent symptom is a rise of temperature of 3° C. or more, which ensues in a few hours, and is followed by a fall. Besides this rise of temperature, there is an effect on the tuberculous lesion, round which inflammation occurs, the lesion itself undergoing necrosis, and being, in some instances, destroyed. The effect in tuberculous guinea-pigs and in tuberculous human beings, is very irregular, the most marked results being seen in lupus.

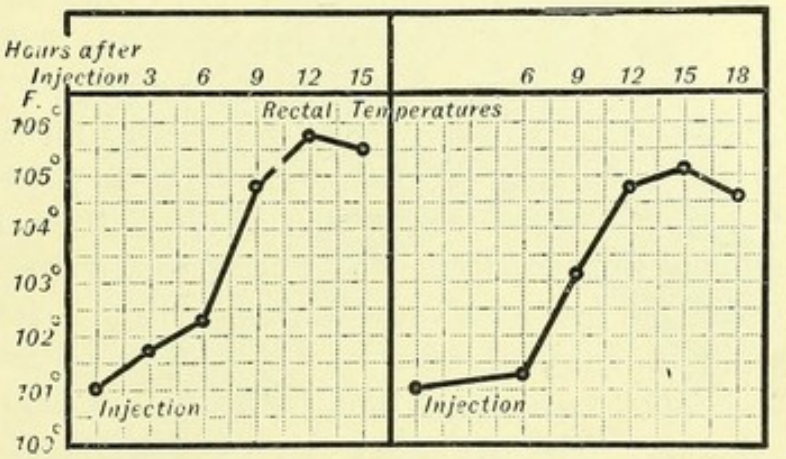


FIG. 43.—Charts of the tuberculin and of the mallein reaction. The left curve shows the effect of the injection of tuberculin in a tuberculous cow; the right curve that of mallein in a horse suffering from glanders. (Prof. J. McFadyean.)

Koch has described a tuberculin "R." and "O." The latter is prepared by grinding up virulent cultures of the bacillus, after drying, and treating them with distilled water. The first extract is the tuberculin "O." Successive extracts of the residue, when more dissolved, were mixed together, and called tuberculin "R." Tuberculin "O" resembles the original tuberculin; "R," in repeated small doses, is said to produce immunity against tuberculin, and against living

tubercle bacilli. At present this statement must be received with some caution. It is quite clear, however, that from the bodies of the tubercle bacillus can be extracted a substance, which has a specific action on a tuberculous lesion, although this cannot be considered, in the majority of instances, a beneficial action from the point of view of treatment.

Tuberculin contains albumoses and non-proteid extractives. It is, however, not accurate to describe these albumoses as products of the tubercle bacillus, inasmuch as they are present in the original broth, and although, when separated by the only methods known, which are somewhat crude, the albumoses give the tuberculin reaction, yet tuberculin can be prepared free from albumoses, as when tubercle bacilli are grown in a medium containing a nitrogenous non-proteid substance, such as asparagin, instead of peptone.

It has been considered doubtful whether the tuberculin reaction is specific, that is, whether it is the only substance which can produce the effect, for it has been found that ordinary peptic albumoses, ricin, lactic acid, and even milk, give a similar reaction in tuberculous guinea-pigs; and Buchner stated that the bodies he called proteins gave the reaction. On the other hand, it has been stated that tuberculin reacts in cases other than tuberculosis, such as cancer and syphilis. But it is doubtful whether it reacts, in such cases, in the small doses which are effectual in cases of tuberculous disease.

There is no evidence, as yet forthcoming, that the tubercle bacillus possesses any digestive properties, but other substances have been described as due to its activity, which may be classed under the heading of nucleo-proteids. Of this nature is probably the poison separated by De Giaxa. When injected into the veins in large doses, it causes thrombosis in the right heart and the pulmonary artery and its branches, the animal dying in asphyxia. Small doses cause capillary thrombosis, especially in the liver and lung; in the lung, catarrh and pneumonia may be found instead of infarction, and both the liver and the kidney may be found fatty. Subcutaneously injected, similar results are observed,

although the effect is much slighter. A local lesion produced by these injections consists chiefly of leucocytes, which undergo caseation and not uncommonly fibrosis. Intratracheal injection of the poison causes catarrh and pneumonia and even nodules, which resemble true tubercles (Boccardi). De Giaxa states that rabbits, goats and horses, treated with the poison, give the reaction of tuberculin.

Bacillus mallei.—A substance called *mallein* has been prepared from this bacillus, which resembles tuberculin in its action. The bacillus is grown in glycerine broth for three or four weeks, and, after destroying the bacillus by heat, the liquid is filtered and is called mallein. One c.c. of this liquid, injected into a horse suffering from glanders, causes a large and painful local swelling within twenty-four hours and a rise of temperature of over 2° C. (Figs. 43 and 44). Mallein is used for the diagnosis of glanders in animals, and is of great value in this respect.

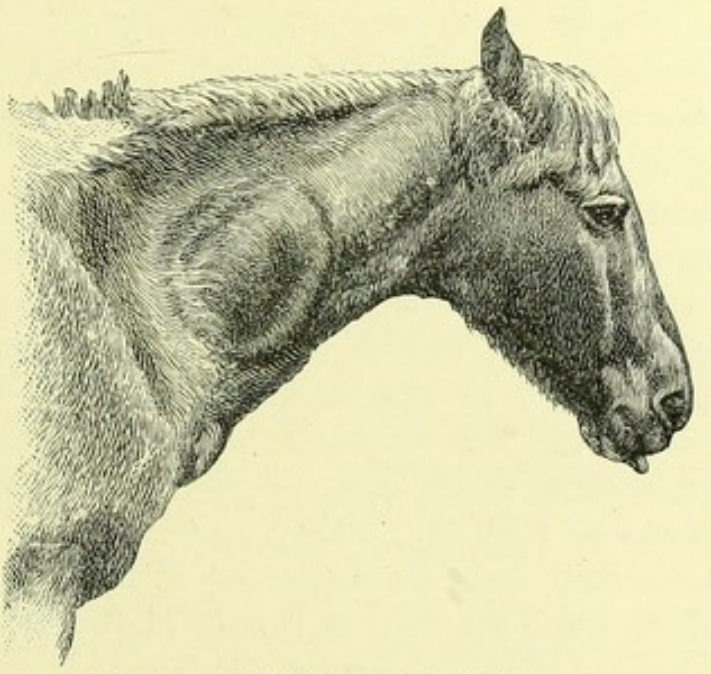


FIG. 44.—Mallein swelling in horse.
The figure shows the large swelling in the neck of a horse suffering from glanders, which follows the subcutaneous injection of a dose of mallein. At the same time as the swelling there is a temperature reaction (Fig. 43). (Prof. J. McFadyean.)

Buchner extracted from the bodies of certain bacilli, namely, those of anthrax and glanders, and the bacillus prodigiosus, certain albuminous bodies which he called *proteins*. These contain nitrogen, and give the general reactions of proteids, but are not sufficiently defined to be classed with any of the known groups of these substances. Probably they correspond to some of the intracellular toxines which have been discussed, and it appears hardly necessary to retain the name.

General Action of Bacterial Poisons.—Although our knowledge of the poisons produced by bacteria is, at present, very imperfect, yet it is clear that it is by their means that pathogenic micro-organisms are capable of producing the effects of infective disease. It is by their formation, more or less rapid according to the activity and growth of the micro-organism in the body, that an infective disease, lasting days, weeks, or months, is possible. Any mechanical action due to a large increase in number of bacteria blocking the vessels, is fortuitous, and is not a special feature of the process of infection in any disease.

None of these poisons can, as yet, be defined chemically; in none of them is there indication of their chemical constitution, and of some, referred to as the "toxines," an ultimate analysis has not been made, as is the case also with pepsin, diastase, or other ferments. Speaking generally, the poisons can only be defined as regards the effect of external conditions on them (such as heat, light, oxygen), and as regards their physiological action in the animal body. In the preceding pages, two groups of these poisons have been made; one containing the products of the digestion of proteids by the bacterium, which may be called the digestive group of bacterial poisons, and the other, in which the poison is either intra-bacterial, or is an excretion of the bacterium. This group is more toxic than the members of the first group, and resembles, in some of its properties, the bodies known as ferments.

The association of the poisons of both groups with bodies of a proteid nature is an important fact, and the association is, in most instances, so close that the proteid cannot be separated from the toxine.

General Action.—After injection there is no immediate effect of the poison. This is because there is a period of incubation which is followed by the symptoms peculiar to the action of the poison.

The body temperature may be affected in two ways: either in the production of a febrile rise, or of a great depression of temperature.

The poisons produce degeneration of tissues, and a special

action on the nervous system and the heart. This selective affinity of toxines for special organs and parts is a very characteristic action, and is also observed with non-bacterial poisons. Blood-destruction, or hæmolysis, is another effect of the bacterial poisons.

(1) The products of the first group, the digestive products of bacteria, are chiefly the albumoses, which are constantly found in the body after death from infective disease, and are excreted in the urine. Their mode of formation and relation to normal proteolytic digestion are shown in the following table :—

Primary Agent, or Primary Infective Agent.	Secondary Agent, or Ferment.	Digestive Products.
Living cell . .	Pepsin . . .	Proteid { Syntonin. Hetero-albumose. Proto-albumose. Deutero-albumose. Peptone.
Living cell . .	Trypsin . . .	Proteid { Globulin-like body. Tryptone (Peptone). Proteid product { Leucin, tyrosin. A bitter body.
Bacillus anthracis .	Anthrax digestion .	Proteid { Hetero-albumose. Proto-albumose. Deutero-albumose. Peptone. Proteid product { Alkaloid (base). Leucin, tyrosin.
Bacillus diphtheriæ .	Diphtheria toxine . (Roux and Yersin's poison) in membrane.	Proteid. { Hetero-albumose. Proto-albumose. Deutero-albumose. } In membrane. Proteid product. { Organic acid. } In body.

In some diseases the toxic albumoses appear to play an important rôle, such as anthrax, diphtheria and pus infection; and similar albumoses, although with a different action, are found in abrus seeds and in snake venom. Albumoses, no doubt, differ considerably in their toxicity, and, probably, in their chemical constitution. The albumoses formed in gastric digestion are poisonous when injected into the veins of an animal. In the dog they produce great fluidity of the blood, and a fall of blood pressure. They also produce in other animals a considerable rise of body temperature and may cause death. This effect of peptic albumoses cannot be ascribed to the ferment pepsin which may be present associated with them. Pepsin may be more or less completely destroyed by heat, and the albumoses still retain their toxic power, although this is diminished.

In the case of anthrax it is quite clear, from the facts which have been brought forward, that the albumoses play an important part in the disease, and that their action is not due to the association of any toxine which may be separated by heat. In other instances, however, there is great difficulty in deciding how far the toxicity of the albumoses is due to the presence, in association with them, of a toxine or excreted product. Thus, in diphtheria, both toxine and albumoses are present in quantity. By heat or by alcohol the activity of the toxine may be fairly readily destroyed, and the albumoses are then found to have a definite action, which is like that of the toxine, only weaker, except that it is a more certain fever-producer than the toxine. The albumose, separated from toxine, has also been found to cause the production of antitoxine in the blood of the horse.

In the case of abrin, a poisonous globulin and albumose are present, and both are very sensitive to heat. No toxine has been separated from these bodies, although it is possible to assume that one is associated with the proteids. Snake venom, in which there are also a poisonous globulin and albumose, is in the same position as abrin. In many instances, however, the bacterium does not appear to have any great

digestive power, and the chief toxines in the disease appear to be the excretion of the micro-organism.

2. The poisons of the second group are essentially of a different nature to those of the first group or class of digestive proteids. Several considerations are against the conclusion that all these poisons are of a proteid nature. Diphtheria poison is as toxic as cobra venom, or as the venom of the Australian tiger snake (hoplocephalus curtus). Roux and Yersin obtained the diphtheria toxine from the broth culture in such a form that it acted in imponderable doses. Brieger and Cohn, by means of precipitation by zinc salts and the subsequent decomposition of the zinc salts with carbonic acid, obtained a toxic product from diphtheria, causing all the characteristic symptoms; but this product did not give any proteid reactions, neither the xantho-proteic nor the biuret reaction, so that it may be considered that the diphtheria poison is not necessarily associated with a distinct proteid.

It may be that this poison, together with the poison of tetanus and the intracellular poisons previously discussed, is of a ferment nature. The arguments which may be used in this respect are:—

(1) That they act in infinitesimal doses.

(2) That they act after a period of incubation, and slowly; and may produce death after many days by profoundly affecting the general nutrition.

(3) That they are sensitive to the action of heat.

This sensitiveness to the action of heat is, however, not universal. On the one hand the toxines of diphtheria and tetanus are more sensitive to heat than the digestive ferments; but the toxines of the typhoid bacillus, of the B. coli communis, of Gaertner's bacillus, and of the cholera vibrio resist for a time a temperature of 100° C. If these poisons are of a ferment nature, their physiological action is unlike that of any of the other known ferments. They are not digestive ferments, in the ordinary sense of the word. Experiments made to test the digestive action on ordinary proteids of the diphtheria and tetanus toxines have not shown the slightest

indication of digestion. But digestive ferments are not the only substances of the kind which are known, and although bacterial toxines may themselves have no digestive action, yet they may, when combined with the particular tissue they affect, produce poisons which are formed in the splitting up of bodies contained in the cell. There is some evidence that, in the case of tetanus, such a poison, which is not the toxine, is present in the body.

The toxines produced by micro-organisms, though they may be related to each other, are not identical. The difference is sometimes shown in the special tissues which they select for their action, and in the symptoms produced, but the most definite test for the toxines is what may be called their *toxic reaction* in the body, which results in the formation of substances antagonistic to their action (antitoxines). In the case of abrin and ricin, the physiological actions are closely similar, ricin acting rather more powerfully than abrin: so that, as far as their physiological action goes, if these alone were investigated, they might be considered as identical substances. But an animal which has been made immune to abrin is not immune to ricin, and *vice versâ* (Ehrlich), so that the poisons, although they may be related, yet are essentially different. Further discussion of this subject will be made under the heading of "Immunity" (Chapter VI.).

The following table shows the comparative toxicity of some of the substances which have been discussed. The figures represent the number of grammes of body weight of a rabbit or guinea-pig, which will be killed by 1 gramme of dried poison:—

Hoplocephalus curtus	4,000,000
Diphtheria toxine	4,000,000
Ricin	1,500,000
Pseudechis (viper)	80,000 to 2,000,000
Pelias berus (adder)	250,000
Anthrax albumoses	3,000
Cholera albumoses	3,000

CHAPTER V

INFECTION—*continued*

III. *The Infective Process*

IN previous chapters the characters of the infective agent, and of the chemical products of its life processes have been considered. The character of the infective process, as it affects mainly the human being in individual diseases, will now be considered.

Proof of an Infective Agent being the Cause of Disease.— In order to prove that an infective agent is the cause of an individual disease, it is necessary to determine the following facts, which may be stated as postulates :—

1. The infective agent must be constantly found in the disease.

2. It must be obtained from the lesions of the disease or from the blood and tissues in pure culture.

3. It must reproduce the disease in susceptible animals.

4. It must be obtained from these animals in pure culture.

5. The chemical products with an identical physiological action must be obtained from artificial cultures of the infective agent and from the tissues of man or animals dead of the disease.

6. A specific serum reaction (antitoxic, antimicrobic) is to be obtained with the infective agent.

It is not necessary, in order to demonstrate that a particular micro-organism is the cause of a disease, to prove all these propositions. In the case of most diseases due to bacteria the first four propositions are, as a rule, readily shown, with

the exception that, in some instances, it is impossible to find an animal susceptible to the disease. The fifth proposition applies mainly to those instances where the chemical products of an infective agent have a specific action which is readily investigated, such as is the case with the bacillus of diphtheria and of tetanus. The specific serum reaction, when obtained both from the blood of patients suffering from the disease, and from the blood of animals rendered immune by treatment with the infective agent or its products, is an additional and conclusive proof of the specificity of the infective agent.

As illustrations, the following examples may be quoted.

The proof of *pus cocci* being the cause of suppuration rests on the fact that they are constantly found in abscesses, from which they may be separated in pure culture. This pure culture can reproduce abscesses in animals or a condition of septicæmia, and the cocci can be obtained from these animals in pure culture.

In other instances, evidence of the micro-organism being the cause of the disease rests on the same experimental data. This is the case with the pneumococcus and pneumonia; with the bacillus anthracis and anthrax; the bacillus mallei and glanders; with the bacillus pestis and plague; with the bacilli of diphtheria and tetanus and the corresponding diseases; with actinomyces and actinomycosis.

In the case of diphtheria and tetanus, however, there is another proof, embodied in the fifth proposition stated above. The chemical products present in the bodies of patients dead of diphtheria produce a palsy due to nerve degeneration, similar to that caused by the products of the bacillus of diphtheria which are formed outside the body in culture media. In tetanus, the products of the tetanus bacillus produce the characteristic tetanic spasms, although it is not possible to obtain from persons dead of the disease, in the majority of instances, any poison producing these spasms.

It is not necessary that the disease produced in animals should reproduce the lesions characteristic of the disease in man, in order to prove that the micro-organism is the specific infective agent. In some instances, such as is the case with

the pus cocci, tuberculosis, actinomycosis, tetanus and anthrax, the lesions of the disease produced in animals are practically identical with those occurring in man. In the case of diphtheria, it is not always easy to reproduce in animals the membrane characteristic of the disease in the human being, although this has been done, but the lesion produced by the subcutaneous injection of the bacillus is pathologically identical with the false membrane, inasmuch as it shows the characteristic fibrin exudation and necrosis of the tissues.

In the case of some diseases, such as *cholera and typhoid fever*, no animals naturally susceptible to the disease are known. Both the typhoid bacillus and the cholera vibrio are, as has been seen, pathogenic to animals when introduced intraperitoneally or subcutaneously. By using alkalies to neutralise the acidity of the stomach contents, and opium to quiet peristalsis, Koch succeeded in reproducing in pigs the symptoms of cholera, ending fatally, by introducing the vibrio into the alimentary tract. In previous experiments, choleraic symptoms were produced by injecting the organisms directly into the duodenum of pigs and rabbits (Nikati and Rietsch). Subsequent experiments have shown that an intestinal infection occurs in the marmot by feeding with the vibrio, and, similarly, very young rabbits become infected when the vibrio is added to the milk given as food. The symptoms produced are great prostration, subnormal temperature, sometimes anuria and cramps, with diarrhœa.

Other micro-organisms, such as the spirilla of Finkler-Prior, of Deneke and of Miller, will produce these symptoms. But the fact remains that the vibrio, which is found constantly associated with cholera, is capable of producing in animals an intestinal infection, with the symptoms of the disease. Experiments have been performed by workers on themselves. Both Emmerich and Pettenkofer swallowed the vibrio, with the production of diarrhœa, the motions containing the vibrio; serious illness ensued in one case. A worker with the vibrio in Hamburg contracted fatal cholera from a cultivation at a time when there was no cholera in Germany. That the vibrio is the cause of the disease is shown by the results of preventive

inoculation against cholera (p. 170), in which the vibrio is used subcutaneously as a prophylactic, and which has resulted in the reduction of the mortality; by the facts already stated; as well as by the specific serum reaction (p. 187).

The case of *typhoid fever* is somewhat similar to that of cholera, inasmuch as no animal is naturally susceptible to the disease, nor, in most animals, is it possible to reproduce the intestinal lesions of the disease. Remlinger has produced in some rabbits a definite infection of the intestine by giving them virulent cultures with their food. Some of the rabbits were not infected; after a period of fever, diarrhœa and bodily depression, with loss of weight, undergoing complete recovery. Others, however, succumbed with the same symptoms, and there was found great congestion of the small intestine, the contents of which were liquid. Peyer's glands were enlarged, and there was some ulceration at the level of the cæcum. The spleen was greatly enlarged, and the bacillus was obtained in pure culture from the organs. In one experiment, the animal was fed for five days with the typhoid bacillus. On the eighth day fever was observed, and there ensued the train of symptoms previously mentioned up to the seventeenth day, when the animal died. In another experiment, seven days after feeding the fever began, and the symptoms progressed for twenty days, ending in death. Similar results were obtained in rats. The blood serum of the infected animals gave the specific typhoid reaction (p. 188). Intestinal infection by the typhoid bacillus has also been successfully carried out by the method used by Koch for the cholera vibrio. The chimpanzee has also been successfully infected through the intestines, ulceration being produced. Besides these facts, however, the occurrence of the typhoid serum reaction with the blood of animals rendered immune to the bacillus, as well as in the blood of patients suffering from disease, is a proof of the bacillus being the cause of the disease in man, inasmuch as this reaction is specific.

In some cases of disease, the infective agent has not yet been cultivated. This is the case, *e.g.*, with *leprosy*, *relapsing fever* and *malaria*.

The *leprosy bacillus* shows the characteristic staining reaction of the B. tuberculosis, which is possessed, to a less extent, by the smegma bacillus, by the Timothy grass bacillus and Rabinowitch butter bacillus, *i.e.*, the red colour of the fuchsin taken up by the bacillus is not discharged by mineral acids (acid-fast bacilli). The leprosy bacillus, however, has not been cultivated, and the inoculation experiments in human beings, which must necessarily be scanty, are quite inconclusive. The leprosy bacillus is, however, not the same as the bacillus tuberculosis: tuberculosis may occur in lepers. There is some evidence to show that the disease may be contracted by living in a leper community.

In *malaria*, the proof of the plasmodium being the cause of the disease, rests on the following facts:—

1. Its constant presence in the red blood corpuscles during the acute disease.

2. Its definite development in association with the symptoms of the disease and with the recurrence of the attacks.

3. Although not directly infective from man to man, it has been reproduced in a healthy man by mosquitoes, which have been artificially fed with the tertian parasite (p. 149).

Sources of Infection.—In only a few instances, the infective agent has a separate existence for a greater or less length of time outside the body (p. 63); the main source of infection is the disease itself.

Infection may occur during the life of the infected man or animal by the discharges (from the local lesion, from the mouth, lungs, intestine, or urine) passing from the body; or, after the death of the infected individual, by the contamination of the air, soil, water, or food with the infective agent. The source of infection must be looked for in pre-existing disease, aided, to some extent, by external conditions. On the whole, however, external conditions of light, heat and moisture, are hostile to the preservation of specific infective micro-organisms. In some instances, they live a short time in water, but in other external media they are destroyed, probably by putrefactive bacteria.

The following examples will illustrate these points:—

The pus cocci, as sources of infection, are derived chiefly from pre-existing abcesses, and are not found in garden soil, or water, to the extent which is sometimes stated.

Staphylococci are found in the mouth, on the skin, in the vagina and cervix uteri, and are present in the dust or the air of badly ventilated rooms containing the sick. The streptococcus of pus and of erysipelas does not have any length of existence outside the body. It rapidly dies, even when most carefully cultivated. Some forms of streptococcus are found in the mouth and nasal passages. The pneumococcus and Friedländer's pneumobacillus are also found in the mouth. The infective cocci are, therefore, closely associated with man and animals, although they may not produce any lesion in a healthy individual.

In the intestinal tract micro-organisms are normally found which are capable of infecting the body. The chief of these is the bacillus coli communis, which is passed out in the motions. This bacillus, obtained from the motions of a healthy individual, is pathogenic, and it is doubtful whether it is identical with the many forms obtained from water and soil which have been described as closely allied to it in artificial culture.

In diphtheria, the source of infection is the discharges from the diseased mucous membrane in cases of the disease; these may infect food products, especially milk, and so lead to the spread of the disease; otherwise, the diphtheria bacillus is not known to have a separate existence outside the body. This is also the case with tuberculosis, where the sources of infection are the sputum, the milk of cows suffering from tuberculosis of the udder, and the lesions of man and animals dead of the disease.

In typhoid fever and in cholera, the source of infection is a previously existing case of the disease, which may infect by its discharges, or the discharges may contaminate water, milk and other foods.

Modes of Infection.—The infective agent must enter the

tissues from without. The main channels by which it enters are as follows:—

1. By the mucous membrane of the mouth, of the pharynx, and of the gastro-intestinal tract. Sometimes, it enters where there is no defect in the defensive mechanism; in other cases, where there is some slight abrasion of the mucous membrane or some previous lesion, such as ulceration, which has left a weak spot. From the nose, infection may pass to the frontal sinus or to the brain through the cribriform plate of the ethmoid bone. From the mouth or pharynx, infection may pass to the ear, to the salivary glands, or to the lymphatic glands below the jaw. From the duodenum infection may pass to the pancreas or gall bladder, and from the cæcum to the appendix.

In this same group is the infection which occurs from the vagina to the uterus in the female, where there is some damage to the uterine mucous membrane, as after childbirth, or where the mucous membrane is intact, as in some cases of infection of the tubes and ovaries. Infection may also pass from the urethra or bladder to the vesiculæ seminales and the testicles.

2. By means of the bronchial mucous membrane. The infection may occur in the mucous membrane itself, in the alveoli of the lungs, or may pass through the mucous membrane without apparent damage, and affect the bronchial glands or pleura.

3. By inoculation. Infection by inoculation occurs in disease, frequently through an abrasion of the skin or mucous membrane of the mouth. It may also occur, however, by a puncture, either by a foreign body, or by an intermediate host, as in the case of filarial disease and malaria, and by the bite of an infected animal, as in the case of rabies, transmitted by the bite of the dog, wolf, or other infected animal.

In individual cases it is not always possible to discover the site of entry of the infective agent into the body, and this is so because the site of entrance may be healed before the symptoms of the disease become pronounced; and, in the

case of mucous membranes, infective agents may pass through into the tissues of the body without producing any local lesion, as is the case, for example, in some cases of septicæmia, infective endocarditis and tuberculosis.

Course of Infection.—In infective processes there are two chief conditions to be considered:—

1. A generalised infection, in which the body is invaded by the living agent, which may become more or less generally distributed in the tissues.

2. A local infection and intoxication, in which the living agent forms a local lesion or focus, from which poisons enter the circulation and produce symptoms of the disease.

An example of true infection would be anthrax, in which there is at first a local lesion, and subsequently a diffusion of micro-organisms throughout the tissues—the connective tissue as well as the organs. Anthrax is, indeed, one of the best examples of general infection by a micro-organism. In some cases of infection the distribution is not so general as in anthrax. Thus, in tuberculosis, the lesion may be for a long time only local, and then the disease becomes generalised. This takes place by the formation of foci in different parts in which the infective agent grows. A similar example occurs in some forms of pus infection.

Examples of local infection and intoxication are found in tuberculosis, where symptoms are produced by the absorption of poisons from one local lesion; in pus formation, where there is a single abscess, and in such diseases as diphtheria and tetanus, which are the best examples of intoxication occurring from a local lesion.

It is evident that, although infective processes may be divided into these two classes, yet the division is not sharply defined. In both cases there is a chemical poisoning of the body by the products of the infective agent. In one case, that of intoxication, there is only a local growth of micro-organisms; in the other, that of infection, the growth is more generally distributed.

With regard to intoxication, it is not a matter of in-

difference in the production of symptoms where the local lesion is. If the lesion is situated in the connective tissue or in a non-vital organ, the symptoms are those only of the poisons produced by the infective agent. If, on the other hand, the local lesion leads to a greater or less destruction of a vital organ, such as the liver, kidney, suprarenal capsules, the thyroid or the brain, special symptoms are produced, which may indeed mask the symptoms due to the infective process.

After the infective agent has entered the body, two different events may happen. At the site of entry there may be a local lesion, and this may be followed by: (*a*) Intoxication of the body; or (*b*) Infection of the body.

In many instances there is no local lesion produced, or, at any rate, so slight a one as to escape observation. This may occur in the skin, as in the inoculation diseases, or in the mucous membrane, in some cases of disease in which there is usually a local lesion. A local lesion varies, not only in extent, but in the result produced in the body. In some instances it is the only part of the body in which the bacteria grow, and it is by the manufacture of their poisons in the local lesion that an intoxication of the body results. This occurs, for example, in most cases of diphtheria; in all cases of tetanus; in many cases of pus infection; in tuberculosis, and most cases of pneumonia.

In all these instances, whatever effect is produced in the body, the site of the local lesion, whether it be the mucous membrane, skin, lung or other part, is the only place where bacteria grow, and where the toxines are manufactured.

On the other hand, a local lesion may be followed by infection of the body, and the results of this infection are not, as a rule, the distribution of the bacteria in all the tissues of the body, but the production of a greater or less number of lesions in other parts of the body, due to the same cause as the local lesion.

In anthrax, from the malignant pustule of the skin, or the lesion in a mucous membrane, bacilli enter the blood stream and the lymphatic stream, and are distributed to practi-

cally every tissue of the body, especially towards the end of life; in some places producing a local lesion, if the bacilli have grown there for any length of time.

The diseases previously mentioned as usually showing a local lesion, followed by intoxication of the body, may also show infection of the tissues. Thus, in some severe and fatal cases of diphtheria, bacilli may be found, not only in the local lesion, but also in the lung, in the spleen, and even in the blood.

The local lesion of pus infection, that is, the abscess, may lead to other similar local lesions in the tissues, the result of infection from the focus of suppuration.

Similarly, tuberculosis, although it may remain localised for a long period, shows frequently a general infection of the body, characterised by the development of similar lesions in other parts of the body.

Croupous pneumonia, which, in the majority of instances, forms only a local lesion, may, in other cases, show general infection, as when it is followed by meningitis, peritonitis, otitis media and infective endocarditis.

Typhoid fever is characterised by a definite local lesion, from which infection of the body occurs. Cholera, on the other hand, develops practically no local lesion in the intestinal tract, nor a general infection, but leads to profound and rapid intoxication of the body.

Mixed Infections; Concurrent Infections; Infections in Sequence.—The remarks last made apply solely to the specific effect of a single infective agent, but in cases of disease, instances commonly occur of infection by two or more infective agents, that is, a mixed or concurrent infection, or a different infection immediately following a first infection which predisposes to its development. There may be concurrent or mixed infections, as well as a secondary infection, from the site of the primary lesion, and different from the primary infection; or a secondary infection, not through the site of the primary lesion, but in some other part of the body, and due, primarily, to the effect of the first disease in lowering the resistance of the body.

The subject now under consideration is by no means as yet fully worked out, but certain facts in connection with it are of importance. There are but few infective diseases which are antagonistic to each other; more frequently they aid one another. One of the commonest examples of mixed infections, or infections in sequence, is pus infection, which may graft itself on numerous diseases of the mucous membranes of the orifices of the body and upper respiratory tract. The subject is best illustrated by considering these infections mainly as regards the locality in which they arise.

Primary Place of Infection, the Throat and Upper Air Passages.—Diphtheria, in which the local lesion is in the throat or upper air passages, is frequently complicated by a pus infection of the glands below the jaw, and may also be complicated by empyema, the source of infection of which is also from the throat. Gangrene or putrefactive changes may occur in the throat. Similar results may be observed in scarlet fever. The broncho-pneumonia of laryngeal cases of diphtheria is due to the action of the bacillus itself, but croupous pneumonia may occur, due to the pneumococcus.

Primary Place of Infection, the Intestines.—Examples of secondary infection not infrequently occur in typhoid fever, The ulceration of the intestine is due to the bacillus itself. but a streptococcus infection may occur subsequently, leading to suppuration of the mesenteric glands and other parts; or an infection by the bacillus coli communis, without perforation of the wall of the gut. The mode of entry of these infections is through the mucous membrane of the intestine. Pneumonia, pleurisy and meningitis, are also observed in typhoid fever, and these may be due to the pneumococcus.

The occurrence of tuberculous infection in association with enteric fever is a possibility, and it has been observed that a tuberculous process sometimes appears to begin after an attack of typhoid fever. It may be, however, that the acute disease only lights up a chronic tuberculous lesion.

Primary Site of Infection, the Respiratory Tract.—Pneumonia, due to the pneumococcus, may lead to bronchiectasis, and the bronchiectatic cavity may be subsequently infected

by pus cocci, or may serve as a cavity for the growth of putrefactive bacteria. Chronic tuberculous cavities may become infected by the streptococcus or the micrococcus tetragenus, and an infection of the lung by these micro-organisms may occur in such cases as a secondary effect. Infection by the influenza bacillus occurs in tuberculosis of the lungs; in which also may occur infection by the pneumococcus and the streptococcus.

The relation of the infections of scarlet fever and diphtheria is very important. The most common occurrence is an infection in sequence; scarlet fever being followed by diphtheria. The order may, however, be reversed, and the two infections may progress concurrently. These two infections, indeed, appear to predispose to one another in a more marked way than in the case of any other infective disease. Scarlet fever may also be followed by other diseases, of which the most important are chicken-pox, measles and hooping-cough. In other cases a definite attack of erysipelas follows it. On the other hand, scarlet fever infection does not appear to predispose to that of the typhoid bacillus.

Influenza and varicella may run concurrently, or in sequence; the latter being shown by its characteristic rash, and the former by its general symptoms.

Hooping-cough and measles predispose to infection by pus cocci, the pneumococcus and the bacillus tuberculosis.

That certain toxic conditions of the body bear a relation to the supervention of infection is discussed elsewhere (p. 164). It may be stated here that chronic alcoholism leads more particularly to infection by pus cocci, by the pneumococcus and by the bacillus tuberculosis. Cirrhosis of the liver is also associated with these infections, which may run a rapid course. Chronic Bright's disease, in which there is evidence of a chronic intoxication, predisposes to the invasion of the body by the pneumococcus and by the bacillus tuberculosis: as also does diabetes.

Examples of antagonism between infective diseases are not common. It appears, however, that pus cocci are, to some extent, antagonistic to the plague bacillus; and the bacillus pyocyaneus is antagonistic to the anthrax bacillus.

Sequelæ of Infection and Intoxication.—Recovery may take place from both these conditions—in some cases without leaving any trace of damage, in others with evidence of damage more or less permanent. One infective focus may lead to a permanent effect, although the process of infection ceases, as, for example, where an abscess damages a large portion of the liver, or where vegetations on the valves of the heart lead to their irregularity and contraction, and so to a permanent defect of the circulation. The after-effect of the process of intoxication may be as important. Not only is there a general poisoning of the cells of the organs, but there is a specific effect of the poisons on particular organs. The cloudy swelling of the liver and myocardium may lead to fatty degeneration. The intoxication of the nerve cells may lead to their permanent damage, while the peripheral nerves may be specifically affected. In some instances, too, the kidney substance suffers more than that of the other organs.

The Infective Process as it occurs in Disease in Man.

1. *Anthrax.*—In the human being, anthrax is inoculated in the skin or mucous membrane of the mouth, and appears as a malignant pustule or carbuncle. Infection almost invariably comes from the undressed hides of animals (sheep, cattle, horses) dead of the disease. The pustule rapidly extends, producing a large brawny swelling. This contains the anthrax bacilli, chiefly between the cell elements, in the lymphatics and in the blood vessels. Intoxication and infection of the body follow. In the well-established disease, which ends fatally, bacilli are found in the neighbouring lymphatic glands, in all the organs of the body, and, in some of these, may produce a local inflammatory lesion, if the patient has lived sufficiently long. The blood does not contain the bacilli until near death, or after death. No spores are at any time found in the bacilli in the body during life, but they may be found in the cadaver some hours after death.

In animals, the disease takes three forms: either as a local lesion in the skin, as a gastro-intestinal, or as a respira-

tory infection. In all cases a general infection of the body ensues, as in man. Both in man and animals the spleen is greatly enlarged: hence one of the names of the disease —splenic fever (*milzbrand*).

Anthrax is, in animals and man, most commonly a pure infection. Experimental inoculation of the bacillus subcutaneously in susceptible animals leads to inflammation at the site of injection, followed by an infection of the body, causing rapid death; and, in such cases, after death, the bacilli are found in all parts of the body.

2. *Pus Infection.*—The commonest agents in the production of pus are the pus cocci, the various forms of staphylococcus pyogenes and streptococcus pyogenes. But other forms of cocci may produce pus, such as the micrococcus tetragenus, the pneumococcus, the diplococcus intracellularis meningitidis and the gonococcus. In certain conditions the bacillus coli communis and the typhoid bacillus produce pus, as well as the glanders bacillus, the tuberculosis bacillus, actinomyces and putrefactive bacteria.

The form of pus infection to be here considered is that produced by the staphylococcus and the streptococcus, and both of these may lead to two different forms of infection. (1) In one there is local suppuration, with or without formation of abscesses in different parts of the body: as, for example, in local abscesses and pustules; carbuncles, furuncles, and acute suppurative periostitis; in acute catarrhs, and in ulcerative endocarditis. (2) In the other form of infection there is septicæmia, or a general infection and poisoning of the body; sometimes without any definite local lesion at the site of entrance of the coccus.

The action of the streptococcus must be distinguished from that of the staphylococcus. It is, as a rule, more virulent, and tends more commonly to produce a general infection of the body than the staphylococcus. It thus leads to a spreading inflammation, or suppuration. It is the cause of spreading erysipelas, and it may be the cause in the throat of a fibrinous or croupous inflammation, with the production of a false membrane. It is, in all probability, the commonest

cause of puerperal peritonitis and septicæmia: a streptococcus enteritis is also recognised.

2. *Abscesses and Pyæmia.*—(*a*) *Local Formation of Abscess.*—The formation of an abscess may be purely local, and while producing intoxication of the body, may remain localised, no general infection occurring.

(*b*) *Spread of Pus Infection locally.*—Another result which may happen is that, from the abscess, infection occurs along (*a*) the lymphatics to the nearest lymphatic glands, which then become infected, and may suppurate, and the disease may spread no farther than this; or (*b*) along the veins as far as a solid organ: as in pylephlebitis and in phlebitis of the superficial veins.

(*c*) *Spread by General Infection.*—In other cases again, a general infection of the body occurs (septicæmia, pyæmia), and this results from the cocci being taken up by the lymphatics, and so carried into the blood stream, or thrombosis of the veins occurring round the focus of suppuration; the thrombus disintegrating by the action of the cocci, and so being carried along the vessel to the heart. In both cases, the infective matter is carried to the right side of the heart, and distributed to the lungs, in which numerous foci of embolic suppuration may occur. This results in one form of pyæmia, in which, besides the local lesion, or a secondary lesion directly connected with it, bacterial embolism occurs in the pulmonary circulation. This is observed from spreading abscesses in all parts of the body; in the pelvis, or from skin and gland abscesses.

In other cases, *embolic suppuration* occurs in the course of the general systemic circulation, abscesses resulting in the brain, spleen, kidneys, joints and sometimes the liver. It may be that, in some cases, the minute cocci are carried through the blood vessels of the lungs, or by means of a patent foramen ovale (crossed embolism, Chapter XIII.), and so enter the left ventricle; thence they are carried through the aorta to the organs of the body. This must be the explanation, for example, of the occurrence of abscess of the brain in

some cases of empyema. But, besides this, there may be an infection of the valves of the heart, resulting in *infective endocarditis*, and, when this occurs in the mitral or aortic valves, the results are widespread septic embolism of the organs connected directly with the general systemic circulation.

The local lesions produced in these conditions contain the infective agent: cocci are found in the pus, sometimes within the cells, but more commonly in the liquid. Streptococci are not infrequently found degenerated. As a rule, however, they preserve their typical form. The parts of the body not affected by the suppurative lesions do not, as a rule, contain the cocci; these are, practically, absent from the blood.

The sequelæ of these forms of pus infection are practically nil. When recovery takes place, it is complete, especially, in those cases in which the lesions have been in an indifferent tissue, such as the connective tissue. If, however, the lesions have been present in an important organ, such as the liver, heart, or brain, impairment of function may be subsequently observed.

(*d*) *Infective Endocarditis* (Fig. 45).—One form of infective endocarditis has been mentioned above as occurring as a secondary infection in pyæmia. It also occurs when there is no evident primary local lesion, and may be produced, not only by the staphylococcus and streptococcus, but also by the pneumococcus, the gonococcus (very rarely), the bacillus coli communis, and some other forms of bacteria at present but little studied. Experimentally, infective endocarditis has been produced by injecting cocci after a lesion of the valves has been made. Besides the conditions already mentioned, infective endocarditis may be associated with pneumonia, influenza, dysentery, scarlet fever, chorea and biliary infection associated with gall-stones. The infection most frequently follows damage to the valves by rheumatism or scarlet fever.

The results of infection of the valves of the heart depend, as indicated above, on the side of the heart affected (Fig. 101).

Thus, if the valves of the right side be the seat of the lesion, the secondary lesions are found in the lungs — pulmonary infective embolism. If the valves of the left side be affected, the secondary lesions are found in the brain, the liver, spleen, kidneys, intestines and other abdominal organs —systemic infective embolism. Medium sized arteries may

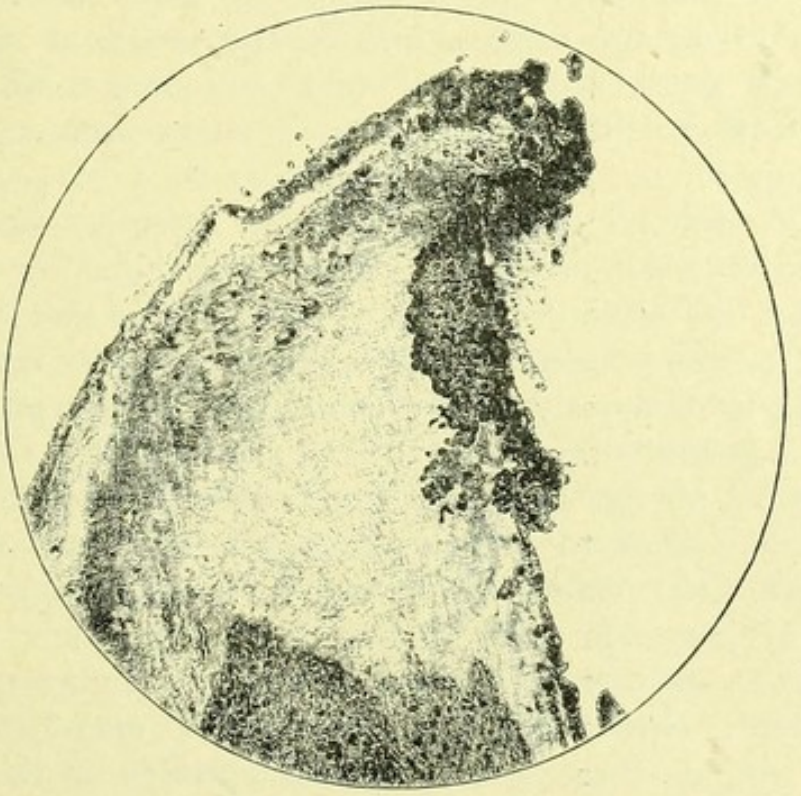


FIG. 45.—Infective endocarditis.

The figure represents a vertical section of a vegetation of the mitral valve in a case of infective endocarditis. Below, a portion of the valve is seen (shown dark in the figure), which is invaded by leucocytes. Most of the figure shows above this the fibrinous cap of the valve, composing the vegetation. The fibrils of fibrin are seen, and the dark masses at the edge of the fibrin are masses of bacteria, which are seen invading the fibrin and disintegrating it, as well as growing in the substance of the fibrin. The particular organism in this case was a staphylococcus.

be blocked, and those of the limbs or intestines, leading to thrombosis, infective arteritis, or infective aneurism.

The localities in which the micro-organisms are found at death, are the lesions in the valves of the heart and the secondary lesions. They are not found generally distributed in the blood or tissues.

(*e*) *Septicæmia.*—The term *septicæmia* is applied to those

cases in which a general infection of the body occurs, with or without any definite local lesion being produced. Examples which occur in man are not so well defined as those which can be produced by micro-organisms in animals. Thus, in the mouse, a typical septicæmia is produced by the bacillus muri-septicus. The injection of this into an animal causes a general infection of the body, the bacilli being found at the site of injection, in all the organs, and in the blood at death. In the rabbit there are several micro-organisms which have the same effect; the subcutaneous or intravenous injection of the pneumococcus, leads, for example, to a form of septicæmia. A general distribution of the bacteria, without any special local lesion, may also follow the injection into the peritoneum of virulent cultures of the bacillus coli communis and the typhoid bacillus. If similar virulent cultures be injected subcutaneously in the rabbit, an abscess only results, without a general infection.

Injection of the pyogenic cocci into the circulation of animals may lead to a septicæmia, or, if they are mixed with some inert material, making them clog together, may produce abscesses in different organs.

In man, septicæmia is seen in cases of infected wounds, in puerperal septicæmia and in infective endocarditis. In infected wounds there is an enormous growth of the bacteria (usually pyogenic cocci), and one result of this may be that previously stated, an intoxication of the body without infection. A similar condition may occur in the puerperal state, not only in putrefactive decomposition of portions of retained placenta, but in cases of distinct infection of the placental site, which is practically an open wound. But infection of the body may occur from the infected wound, leading, as stated above, in some cases to a pyæmia, with or without infective endocarditis. In other cases, however, there is no definite local lesion produced in the body, but the micro-organisms are found in the internal organs, and in some cases in the blood.

Again, cases of infective endocarditis which are primary may, in some instances, be followed by embolic abscesses—

pyæmia—but in other instances no definite local lesions are found, and the condition is practically comparable to the septicæmia following an infected wound; in these cases the damaged valve, with its growth of micro-organisms, representing the wound. Indeed, all these conditions show an infinite variety between typical embolic pyæmia and typical septicæmia.

In some cases of septicæmia no local lesion can be found, and the site of entry of the micro-organisms may be a small punctured wound, or some slightly damaged part of a mucous membrane.

The lesions which are found in man in cases of septicæmia are chiefly those which result from acute bacterial poisoning. Thus, the blood will be dark and fluid; there is post-mortem staining of the endocardium and of the vessels; there is frequently rapid decomposition of the body; the heart muscle, liver and kidneys show cell degeneration, chiefly in the form of cloudy swelling, passing on to a fatty degeneration. The spleen is usually enlarged, soft and diffluent, dark or chocolate red. Thrombosis of one of the peripheral veins may be found, with œdema of the limb. There may be no local lesion present, or the wound through which the infection occurred may have healed, or it may obviously be an infected wound.

Micro-organisms which produce these conditions may be observed microscopically, or obtained in culture from the different organs—the heart's blood, brain, kidneys, spleen, liver. They are found in the capillary blood vessels, between the cells, and sometimes in the cells. They are not usually found in the blood of the larger arteries or veins. A coccus of one or other form may be obtained, or, in other cases, the bacillus coli communis and the typhoid bacillus.

3. *Tuberculosis.*—Tuberculosis may be local or generalised. The local lesion may be at the site of entry of the bacillus into the body, or, as in the case of bones, joints and some other parts, the local lesion may be produced in a part remote from the site of entry, at which there is no discoverable lesion.

Generalised tuberculosis results from an acute infection of the disease, or as an acute dissemination from a chronic local lesion, but the bacillus is not generalised, as in cases of septicæmia; generalisation simply meaning the formation of more or less numerous local lesions in different parts of the body. The disease spreads after the bacillus has entered the body:—

1. By direct extension in the organ affected, either in the tissue of the organ or by open tubes—*e.g.*, the bronchial tubes in the lung, and the intestine.

2. Outside the part affected, by means of the lymphatics, to the nearest lymphatic glands.

3. By means of the circulation; the vessel walls becoming affected, and the tuberculosis lesion discharging its contents into the blood stream. This is the mode of origin of remote tuberculosis, which must thus be considered as embolic in origin.

The means of entrance of the bacillus into the body are mainly three:—

1. By inoculation.
2. By inhalation.
3. By the alimentary tract.

Inoculation is accidental, as a rule, and occurs in the skin. It may also occur, however, in surgical operations on tuberculous parts, and may be followed by general infection of the body. The origin of disease by inhalation may be through the tonsils or the bronchial tubes, and the results may, in each case, be of two characters. There may be a local lesion of the tonsil—although this is not common—with a subsequent infection of the lymphatic glands below the jaw; or there may be no obvious lesion of the tonsil, and the glands below the jaw and neck become tuberculous (scrofulous adenitis), or an affection of the middle ear through the Eustachian tube may result. Similarly, in the bronchial tubes the invasion of the tubercle bacillus may produce a local lesion in the bronchial mucous membrane, followed by an infection of the lung, and this is said to be a common result of infection in pulmonary tuberculosis (Birsch-Hirschfeld). But

in some cases there is no obvious lesion of the bronchial mucous membrane or of the lung, and the bronchial glands become infected, as in the primary bronchial gland tuberculosis in children and in cattle; or the pleura, as in primary tuberculous pleurisy.

In the alimentary tract below the mouth, tuberculosis of the œsophagus or stomach is extremely rare, even in the later stages of general tuberculosis. Below the stomach, however, both in the small and large intestine, primary tuberculosis is observed. Infection of the mucous membrane of the intestine occurs only when the bacillus is taken into the alimentary canal. Infection of the mucous membrane does not occur as a result of the generalised disease, although the mesenteric glands may in a few experimental cases become affected. As in the case of the mouth and the lung, there may be a local lesion, which is shown in the deposit of tubercle in the lymphoid tissue, followed by ulceration, with a subsequent infection of the mesenteric glands; or there may be no local lesion at the site of entrance, but an infection of the mesenteric glands alone (tabes mesenterica). In the human subject, both with or without a local lesion of the mucous membrane, tuberculous peritonitis may occur.

Whether or not a local lesion occurs at the site of entry of the tubercle bacillus into the body, appears to depend on the dose of the poison. With a large dose a local lesion appears invariably to be produced; with a small dose no local lesion is observed. There are, however, intermediate cases in which a very small local lesion is produced, for example, in the intestine, and the resulting generalised disease is out of all proportion to the size of the lesion. These results have been proved experimentally by the feeding of animals with tuberculous material.

A small dose of the poison tends also to limitation of the disease. If a large dose be inoculated into a rabbit or guinea-pig, within three or four weeks there is dissemination of the disease to nearly every organ of the body, but, with very small doses, only a local tuberculosis may result at the

site of inoculation, the disease practically not spreading even in a hundred and twenty days.

Distribution of the Lesions in Man. — (*a*) *Pulmonary Tuberculosis.* — Tuberculosis may be primary or secondary, and the two commonest seats of primary tuberculosis are the lungs and the abdominal organs.

The invasion of the disease in the lungs occurs in the manner already described, and the locality first affected is usually one or both apices (Fig. 46). A tuberculous lesion is here formed, which spreads by direct continuity, as well as by means of the bronchial tubes and of the blood vessels. The inhalation of the infective material by the bronchial tubes leads to a tuberculous broncho-pneumonia, patches of which, more or less well defined in shape, are to be found in parts of the lung remote from the primary lesion. Spread by the blood vessels occurs by the ulceration of a tuberculous nodule into the lumen of the artery (Fig. 47); an infected embolus is then carried to another part of the lung,

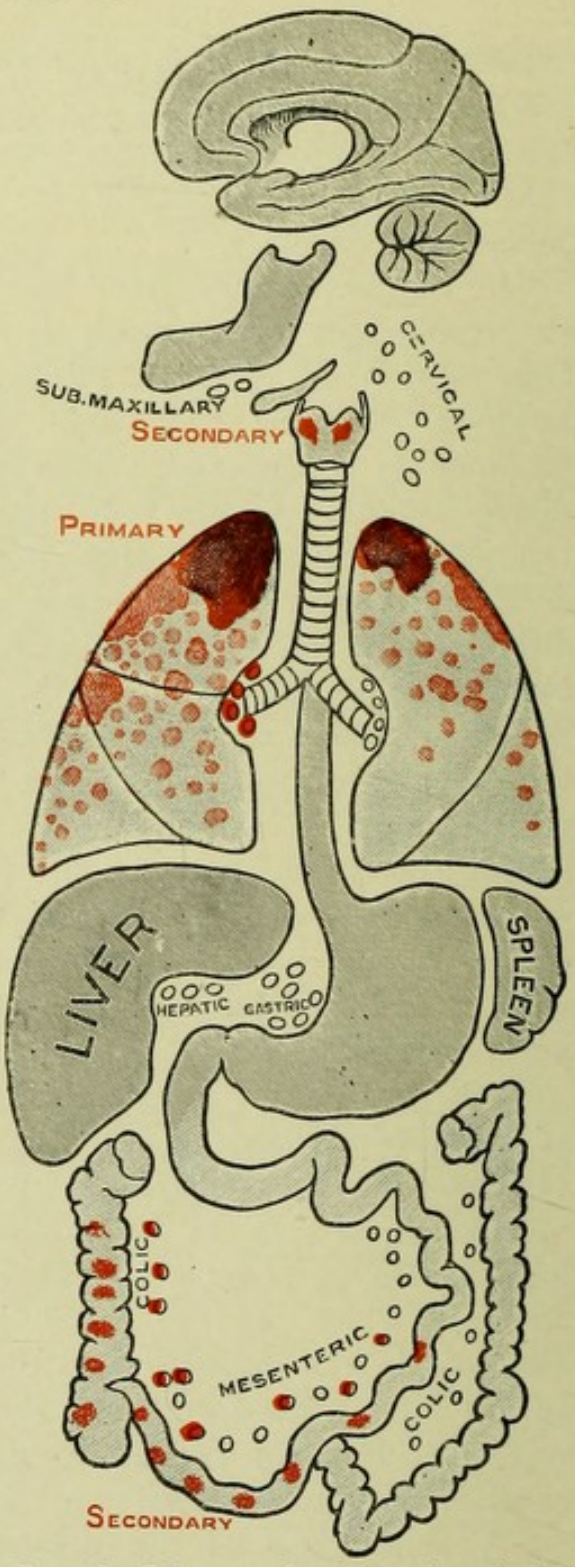


FIG. 46.—Primary pulmonary tuberculosis.

The diagram illustrates the lesions observed in primary lung tuberculosis. In the lungs themselves, as seen at death, there is a cavity at the apex and more recent scattered lesions below, while the bronchial glands are affected from the lung. Other common secondary lesions occur in the larynx and intestines by means of the sputum which is coughed up and swallowed. Tuberculous lesions in the other abdominal organs and in the brain are in this form of tuberculosis rare.

where it gives rise to a tuberculous lesion, or most commonly a general miliary tuberculosis. The most usual appearance, at death, of the lungs in a case of chronic pulmonary tuberculosis is the presence, at the apex of one lung, of a cavity, with thick walls, irregular sides, and traversed by the remains of bronchial tubes and vessels. Round the cavity, the bronchial

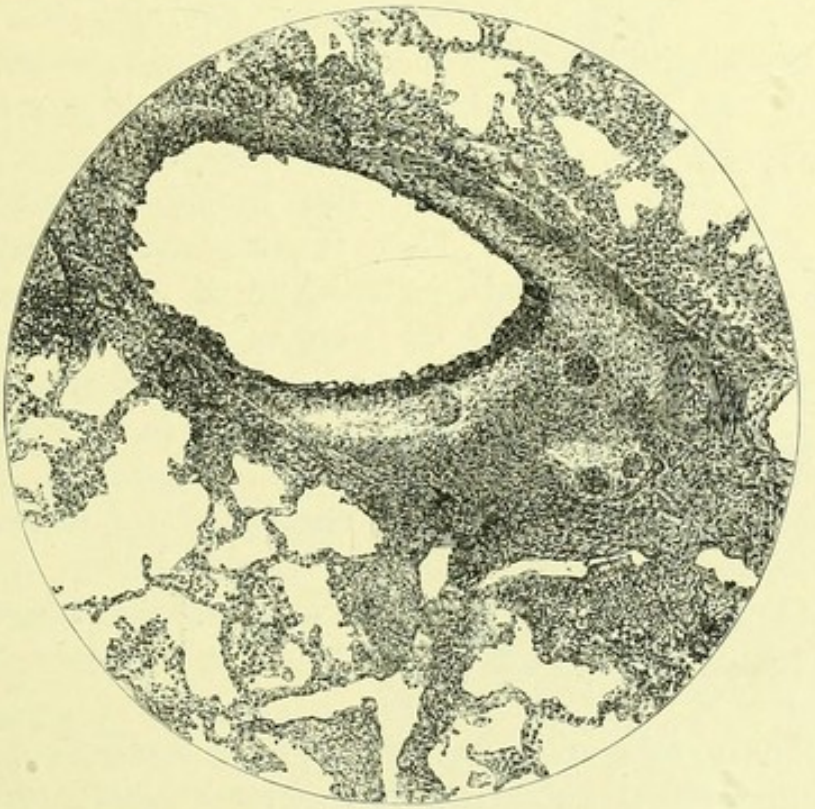


FIG. 47.—Tuberculosis in an artery of the lung.

The figure shows a section of lung, some of the alveoli being seen, as well as a transverse section of a small branch of the pulmonary artery. At one side the arterial wall is greatly thickened, due to the formation of the tubercle, caseating in parts, and containing three or four giant cells. The figure shows that the tubercle in its development has separated the muscular coat from the internal coat. By the rupture of this caseating mass into the blood stream arterial tuberculous embolism occurs in the lung. If the wall of a vein is affected and the rupture occurs into the lumen, the infective material is carried to the left side of the heart, and so through the systemic circulation to the various organs of the body.

tubes are dilated; below the cavity, the tuberculous lesions are more recent, being less fibroid, and recent cavities may be observed. At the base of the lung the lesion is still more recent, and this is also observed in the other lung. There may be no other tuberculous lesion in the body, and, in such a case as this, one lung becomes infected from the other, mainly by means of the expectoration from the primarily

diseased lung, which is inhaled into the healthy lung; or, in some cases, infection may occur by means of the bronchial glands, through which the lymphatics from both lungs pass.

Primary tuberculosis of the pleura may also be a localised disease; it may, however, be associated with or followed by infection of the lung tissue and of the bronchial glands.

Secondary Deposits in Pulmonary Tuberculosis.—Primary lung tuberculosis, when it becomes chronic, is not usually associated with generalisation of the disease in the organs of the body, and the parts commonly affected secondarily are those which are exposed to the action of the infective sputum from the lungs. This is the explanation of the occurrence of laryngeal tuberculosis and of tuberculous lesions in the pharynx and fauces, as well as of the more common intestinal infection. In a few cases isolated tubercles may be found in the liver and spleen; a few in the peritoneum or in the pelvic organs, and in these cases a secondary infection has taken place from the lungs by means of the general systemic circulation, the bacilli being carried by the pulmonary veins to the left side of the heart and so distributed. Such a mode of infection, however, is quite accidental.

Pulmonary tuberculosis may itself be secondary, either to primary abdominal tuberculosis, to gland tuberculosis in the neck, or to cases of remote tuberculosis, such as those that occur in the joints, bones, generative organs and kidneys. In such cases, however, the lesions produced are usually those characteristic of the acute, and not of the chronic, form.

(*b*) *Primary Bronchial Gland Tuberculosis* (Fig. 48).—This is observed almost solely in children, and occurs in the manner already explained. It may result in a secondary tuberculosis in the lungs, in the glands above the root of the lung; and by the lymphatics along the carotid artery the infection may be carried to the base of the brain, leading to tuberculous meningitis. In some cases an acute general tuberculosis supervenes, by which not only the organs in the chest, but those in the abdomen, are affected.

(*c*) *Tuberculosis of the Glands of the Neck* (Fig. 49). —This common form of the disease frequently remains localised. Its mode of origin has been already described. In some cases, however, spread of the disease occurs from the local lesion. This is usually downwards through the glands of the neck to the lungs, which become affected, and the association of tuberculous glands of the neck with tuberculosis of the lungs is by no means uncommon. Sometimes an acute or chronic tuberculosis follows.

(*a*) *Abdominal Tuberculosis* (Fig. 50). — This is not infrequently a primary disease, almost solely in children. It may exist in three different forms :—

1. With ulceration of the intestine, disease of mesenteric glands, and tuberculous peritonitis.

2. With disease of mesenteric glands with or without ulceration of intestine.

3. With disease of mesenteric glands and tuberculous peritonitis.

Primary intestinal tuberculosis, with peritonitis, may be followed by a general

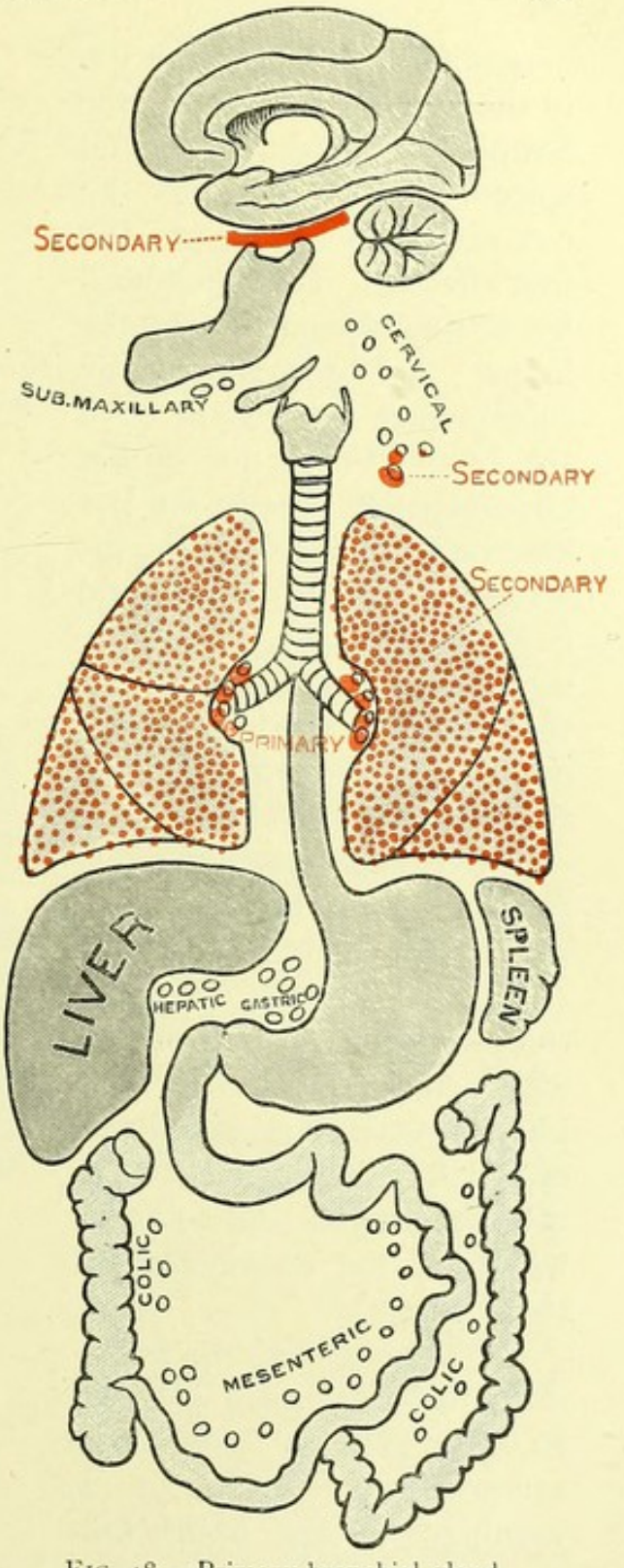


FIG. 48.—Primary bronchial gland tuberculosis.

This diagram illustrates a not uncommon form of tuberculosis in children and in cattle. The primary seat of infection is the bronchial glands, the course being through the air passages. The lungs are secondarily affected from these glands, and it may be the lower cervical glands, while meningitis is common. General tuberculosis may result.

dissemination of the disease in the abdominal organs; the lymphatic glands, liver and spleen, with sometimes the ovaries and kidneys, are the first affected. This is followed by acute tuberculosis of the lungs, and sometimes by tuberculous meningitis. All the lymphatic glands of the abdomen and thorax are not necessarily affected. In the abdomen, the lumbar and cœliac glands frequently escape, and, in the thorax, the anterior and posterior mediastinal, sometimes even the bronchial. When tuberculous peritonitis exists, dissemination of the disease to other parts is not so common, owing to the fact that the thickening of the peritoneum which ensues blocks the lymphatics of the membrane itself, especially that attached to the diaphragm, and so tends to check the conveyance of the virus.

(*e*) *Remote Tuberculosis.*—This includes cases in which so-called primary tuberculosis arises in the bones, joints, meninges of the brain, kidneys, testicles and ovaries. In many cases, the site of entrance of the bacillus cannot be discovered at the time

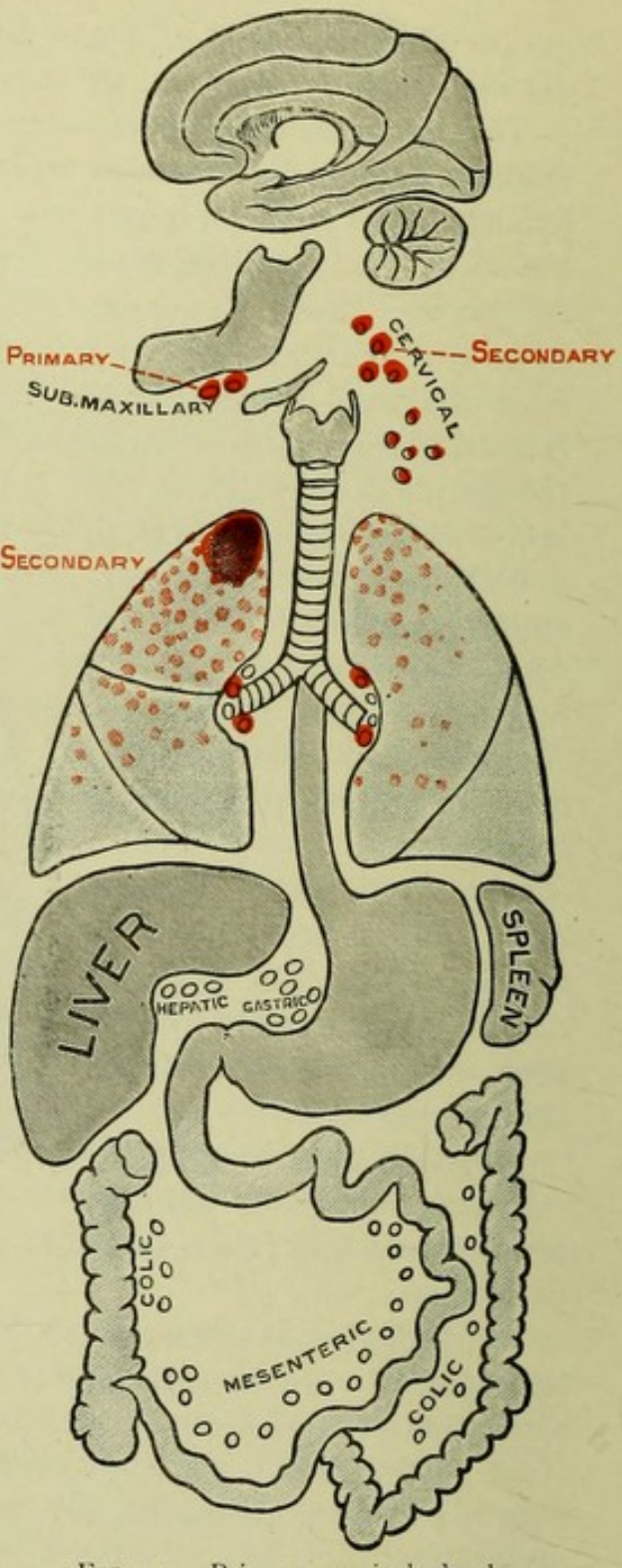


FIG. 49.—Primary cervical gland tuberculosis.

In this case the glands below the jaw or in the upper cervical region are first affected, and the lesion may remain stationary in this position, or a secondary lesion, as shown in the diagram, may occur in the lungs and bronchial glands.

of death. In others, however, there is found an old tuberculous focus, which may be very small in size, either at the apex of one or other lung, in the glands below the jaw, in the bronchial glands, or in the mesenteric glands.

Tuberculosis in Animals.—The occurrence of natural tuberculosis in animals is mentioned elsewhere (p. 160). The modes of infection are not different from those already discussed with the human being.

Experimental tuberculosis has thrown great light on the pathology of the disease, mainly on the occurrence of the disease after inoculation, feeding, or inhalation of material containing tubercle bacilli, and on the spread of the disease according to the virulence and dose of the tuberculous virus.

Inoculation Experiments.—In guinea-pigs (Fig. 51), after inoculation subcutaneously in one or other groin with virulent tuberculous material, a local lesion is produced in from seven to ten days; the inguinal glands become tuberculous in from seven to fourteen days, and in about the third week the dis-

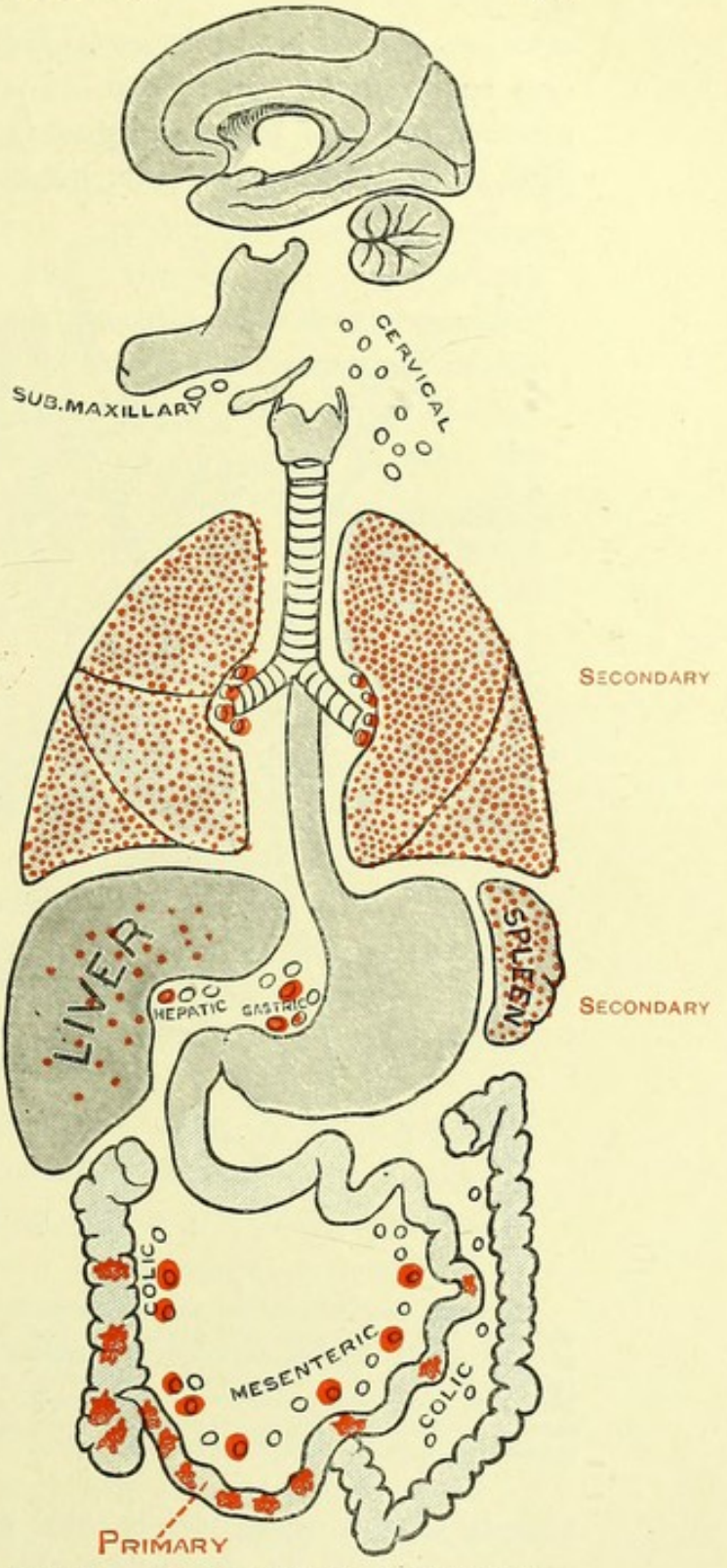


FIG. 50.—Primary abdominal tuberculosis.

The channel of infection is here the intestine, and the local lesions resulting may be (1) intestinal ulceration and tuberculosis of the mesenteric glands, as shown in the diagram, or (2) no intestinal lesion, but tuberculosis of the mesenteric glands (tabes mesenterica), or (3) with or without lesions described in (1) and (2), a tuberculous peritonitis. Secondary lesions occur in the gastric glands, in the glands in the hilum of the liver, in the liver and spleen, and in the lungs.

ease has spread to the internal lymphatic glands in the abdomen, and to the liver and spleen. In the fourth week the posterior mediastinal and bronchial glands are affected, and in about the fifth week the lungs. The disease may then spread into the

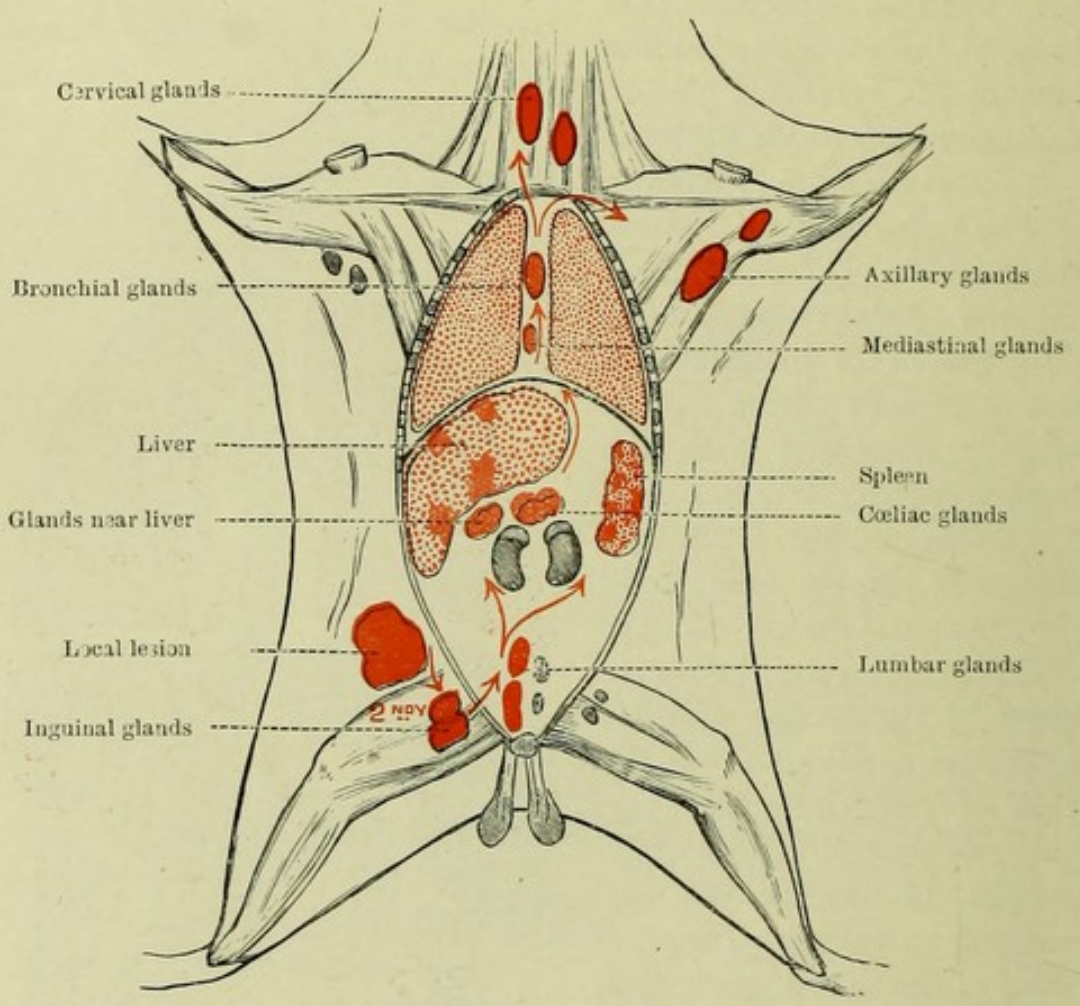


FIG. 51.—Tuberculosis in a guinea-pig following inoculation.

The lesions are coloured red, and the course of infection is marked by arrows. The inoculation was in the right groin, and produced a local lesion which affected first the inguinal glands, next the right lumbar glands, and then the glands near the stomach and liver and the liver and spleen. Subsequently the posterior mediastinal and bronchial glands were affected, and the lungs. In advanced cases both the axillary and cervical glands may be affected as well as the anterior mediastinal. The progress of the disease, therefore, following inoculation in the guinea-pig, is mainly by means of the lymphatic channels.

glands of the neck and to the meninges of the brain. The mesenteric glands are affected only in very advanced tuberculosis following inoculation: the suprarenal bodies and the kidneys are not affected. The fact of the mesenteric glands being affected after inoculation shows that the tuberculous

infection inside the body can take place against the current of the lymph stream, a fact which is also shown in affection of the lungs following tuberculosis of the bronchial glands.

Intraperitoneal inoculation of virulent tuberculous material produces an intense tuberculous peritonitis, with a great thickening of the omentum, and the deposit of miliary tubercles in both the parietal and visceral peritoneum. This occurs in about ten to fourteen days, at which period of the disease the lumbar, cœliac, anterior and posterior mediastinal lymphatic glands may be tuberculous. The liver and the spleen, and even the lungs, may be affected at this time. In twenty-one days nearly every organ is diseased, except the gastro-intestinal tract, and, in the guinea-pig, the suprarenal capsule and kidney.

Inoculation into the anterior chamber of the eye produces, in seven to ten days, a local tuberculosis, which spreads to the neighbouring lymphatic glands, and finally to the lungs and other organs of the body.

The facts shown by such experiments are the slow development of the disease, and the spread by means of the lymphatic channels. These results are the same, whether the inoculation material be obtained from the cow, or from the human being, as, for example, sputum, or whether a pure culture of the tubercle bacillus is used.

If a small dose of the tuberculous virus is used for subcutaneous inoculation, the generalised disease is not produced, but an affection of the neighbouring glands, to which the disease tends to become limited.

Feeding Experiments.—If guinea-pigs be fed with a single dose of virulent tuberculous material obtained from the cow or man, a local lesion is produced in the small intestine and cæcum, which is visible to the naked eye in from eighteen to twenty-one days. From this lesion the disease spreads, in about twenty-eight days, to the mesenteric and cæcal glands, and then to the cœliac glands, the liver, spleen, posterior mediastinal and bronchial glands and lungs, in this order.

If pigs are fed with virulent tuberculous material, the course of infection is practically the same as in the guinea-

pig, but, in this animal, the tonsil, as well as the intestine, is liable to be affected by a local lesion. There may, however, be only a small ulcer in the intestine, showing the site of entrance of the tubercle bacillus, and the internal glands and organs of the body may be extensively affected by the disease.

If the material used for feeding pigs and calves is non-virulent, the result is somewhat different, and the main results may be stated as follows. (1) No local lesion is produced at the seat of invasion. (2) The lymphatic glands in connection with one or other part of the alimentary tract become affected by the disease; either the mesenteric, cœliac, posterior mediastinal glands, or the glands below the jaw. (3) From this focus in the glands, the disease may become generalised; quite distant parts may be affected through the blood stream, namely, the lungs or the epididymis.

Calcification of the tuberculous lesion is frequently observed in experimental tuberculosis in the larger animals, both in the lesions of the intestines, glands and lungs, as it occurs in the natural disease in man and animals. The presence of calcification does not exclude the presence of living tubercle bacilli: some of the calcareo-caseous nodules are infective.

Distribution of the Tubercle Bacillus in the Body.—The bacillus is present only in the lesions produced by the disease. It is seen in the earliest lesion, the miliary tubercle, in the caseous tubercle, chiefly in the periphery of the caseous matter, and, most abundantly of all, in the semi-liquid purulent contents of recent cavities; in these, as well as in old cavities, it is probable that the bacilli actually increase in numbers. Some die, some are expectorated, and all the bacilli found in the sputum are not living.

In the calcareous masses bacilli are present, if any caseous matter still exists; but, in the completely calcareous nodule, no bacilli are discoverable. In some of the old calcareo-caseous masses the bacilli are very few in number, and stain badly, and are, no doubt, dying or dead.

Tubercle bacilli are discharged from the body, not only

in the sputum, but in cases of tuberculous disease of the skin and upper air passages; in tuberculosis of the intestines and of the genito-urinary tract. The bacilli are not present in the healed lesions of tuberculosis, neither in a completely calcified nodule, nor in the lesions of the disease which have become completely fibroid. They are not found in the healthy organs, nor, except in rare instances, in the blood.

Secondary Infection in Tuberculosis.—A tuberculous lesion, especially if ulcerated and communicating with the external air or with the alimentary tract, may become infected by other micro-organisms. Thus, from the alimentary tract putrefactive bacteria may develop in the lesion, and cause intoxication of the body. This may be observed, not only in intestinal tuberculosis, but also in the cases where a bronchial gland becomes adherent to the œsophagus, and discharges its contents into it. The more common invasion of the tuberculous lesion is by the pus cocci; either the staphylococcus, the streptococcus, or the micrococcus tetragenus. This is likely to happen in tuberculosis of the nasal cavities, in tuberculous disease of the middle ear and in pulmonary tuberculosis, more particularly where there is cavity formation. A pyæmia or septicæmia may result from this secondary pus infection in one of the manners previously described. A great rôle has been ascribed to the secondary infection of the streptococcus in pulmonary tuberculosis in the advanced stage in producing the symptoms and lesions observed. To this infection has been ascribed the high and continuous fever which is seen in such cases, as well as the non-tuberculous broncho-pneumonia observed in the lungs. Some of these effects may be due to the streptococcus infection, but it is noteworthy that, not infrequently in such cases, the infection appears limited to the lungs. Too much stress has been laid on this secondary infection, but a streptococcus infection may occur and lead to empyema, or to abscesses in the brain.

A pneumococcus infection may occur in tuberculosis, more especially tuberculosis of the lungs, and may result in the production either of pneumonia or of an empyema. Individuals

the subject of tuberculosis are not resistant to the invasion of any infective disorder, and, in them, influenza runs a rapid course, the influenza bacillus being found with the tubercle bacillus in the expectoration.

4. *Syphilis.*—Syphilis is an acquired disease, and results from inoculation of the virus which produces a local lesion, or hard chancre, followed by a general infection and intoxication. Infection from the primary sore occurs first by way of the lymphatics, the nearest glands, such as the inguinal, being affected. Subsequent to this there is a general infection which results in lesions in the throat, in skin eruptions and in loss of hair, as well as lesions in the bones. This is the so-called secondary stage of the disease. This secondary infection occurs by means of the blood stream. In a later stage the internal organs are affected.

The lesions produced by the disease are, besides the primary sore and the secondary manifestations—(1) The occurrence of gummata, which are large, caseous masses developing in one or other part of the body; (2) The arterial disease which is described later (Chapter VIII.). These are the tertiary lesions which are produced by the infection of syphilis.

Other lesions, however, are produced which result from the intoxication of the disease. These are albuminoid degeneration of the various organs (Chapter VII.) and certain forms of nerve degeneration, more particularly tabes dorsalis and general paralysis of the insane (Chapter XIX.).

The gummata occur in the muscles, in the periosteum of bones, in the internal organs, such as the liver, spleen, kidney, lungs and brain. The arterial disease is observed in and near gummata and other syphilitic lesions, but may be observed apart from these lesions, more particularly in the aorta and in the arteries of the brain.

The process of infection in syphilis may be compared to that in tuberculosis. The first part of infection, as in tuberculosis, is by means of the lymphatics. The subsequent course, however, of the infection differs from that of tuberculosis in the fact that it is mainly through the vascular system. Unlike tuberculosis, syphilis may be transmitted to

the offspring, producing what is called congenital syphilis. In some cases the lesions manifested in the infant are like the secondary manifestations in the acquired form, as regards the production of eruptions and of ulceration. Gummata are also observed. In addition, however, there are special lesions of the permanent teeth, more particularly of the incisors and canines, which become peg-shaped and notched, as well as of the cornea, which shows interstitial keratitis. Both acquired and congenital syphilis may lead to nerve degeneration.

5. *Intestinal Infections and Intoxications.*—(α) Some of the intestinal infections are definite diseases, such as typhoid fever, cholera, dysentery and ulcerative colitis. (β) In other cases, there is a definite train of results referable to the intestinal tract produced by different micro-organisms, and mainly as a result of food poisoning. Three of these micro-organisms are Gaertner's bacillus, B. botulinus and B. enteritidis sporogenes (Table, p. 59). Infection may also take place by the bacillus coli communis, the natural habitant of the intestinal tract. (γ) A third class of cases is where putrefaction occurs in the intestinal contents, and intoxication of the body ensues, and this kind of intoxication may occur simultaneously with one or other of the infections. (δ) Acute infective enteritis may be due to one of the micro-organisms of food poisoning mentioned, or, in some cases, it may be due to a streptococcus. (ϵ) Collateral infection may occur from the intestine, viz., of the appendix, of the bile-ducts or gall-bladder, and of the pancreatic duct and pancreas.

A. *Typhoid Fever.*—In typhoid fever the infection is by way of the intestines. The cases may be divided into two groups, in one of which, by far the more common, there is the characteristic ulceration of the Peyer's patches of the small intestine, and the solitary glands of the large intestine. In the second case there is no ulceration in the intestine, but there results the so-called typhoid septicæmia.

The typhoid bacillus has the peculiarity of being distributed with difficulty in the tissues, even though it may cause death. Thus, in experiments with the typhoid bacillus, even if virulent, the subcutaneous injection of a culture leads

only to the formation of an abscess, from which the bacillus may be obtained in pure culture, the organism not being found in the blood, or the internal organs of the body. The peritoneal injection of the virulent bacillus leads to the distribution of the micro-organisms in the blood and organs of the body, but in some cases, especially if the bacillus is not very virulent, the distribution is irregular; they are usually found in the spleen, but may be absent from the blood and other organs.

In cases of typhoid fever in man, the organism can always be obtained from the mesenteric glands and the spleen: it is also present in the intestinal lesion. In the blood its presence is very irregular, and large quantities of blood have to be used for the diagnosis. It has been found in the blood of the heart, in venous blood, and in the blood of the skin eruption. In some cases it has been found in the kidneys, the liver and in the bile. It is found, in a certain proportion of cases, in the urine, but in the stools it is not frequently discovered, except in cases where there is profuse diarrhœa without putrefactive decomposition of the fæces. The presence of the bacilli in these different parts does not necessarily lead to the formation of any local lesion, but many of the "inflammatory" complications of typhoid fever are due to the bacillus. It can itself produce pus, as is seen from experiments in rabbits. In some cases of abscess formation in typhoid fever, the bacillus is found in the pus, sometimes with the staphylococcus and the streptococcus pyogenes. The secondary lesions which may be produced are purulent cerebro-spinal meningitis, abscesses of the lungs and kidneys, cystitis, and acute inflammation sometimes leading to pus formation in the joints, bones, skin, testicle, lymph glands, parotid and thyroid glands. In the pus of these purulent complications, pus cocci alone may be found, as well as the bacillus coli communis.

Other cases of mixed infection occur in typhoid fever. The mesenteric glands may undergo gangrenous inflammation, and the bacillus coli communis is frequently present in these glands, as well as in the spleen, at death, and may be the cause of cystitis.

In the very rare cases of typhoid septicæmia, the micro-organism is found constantly in the spleen and lymph glands, and sometimes in the other parts already mentioned. Any gross lesion of the tissues may be absent.

Cholera.—In cholera, the process of infection resembles, to some extent, that obtaining in typhoid fever. There is no gross local lesion in the intestinal tract, only the shedding of the epithelium, and many cases of cholera are good instances of the growth of a specific bacterium in the intestinal tract, and a subsequent intoxication of the body, resulting in death.

The vibrio is frequently found in pure culture in the rice-water stools. It disappears within a fortnight. In most cases it is not found in the blood or internal organs. It has, however, been found in the lungs, liver, kidneys and spleen; very rarely in the blood. The explanation of this appears to be given by the results of experiment. With very virulent cultures of the vibrio, an intraperitoneal injection leads to the distribution of the micro-organism in the internal organs, as in the case of the typhoid bacillus. If the vibrio is, however, less virulent, its development tends to be limited to the peritoneal cavity, even though it may produce the death of the animal.

The gross effects of the intoxication of the vibrio of cholera are shown chiefly on the side of the circulation; there being deep congestion of the liver and kidneys, with cloudy swelling and sometimes fatty degeneration of the cells of the tubules. Hæmorrhagic spots may be present in different parts of the body. The right side of the heart is distended with dark blood.

Dysentery.—The infective agency in dysentery has not yet been completely worked out, but there is some evidence to show that one form is due to an amœba, and another is due to a bacterium.

Amœbic Dysentery.—The *amœba dysenteriæ* was described by Lösch of St Petersburg in 1875. It is found in the stools and in the liver abscess. It is spherical and of a greenish tint, and relatively large, being from 12 μ to 26 μ in diameter. Its protoplasm is divided into two parts, granular and dark internally, homogeneous externally (ectoplasm). It contains a nucleus, as well as red blood cells and bacteria, which it has taken in from

the intestinal contents. It moves by means of pseudopodia, and becomes immobile at 75° F. It is plentifully abundant in the stools at the acute stage of the disease, and is the cause of the liver abscess which sometimes follows, being found in the abscess walls, as well as in the pus. It frequently shows degenerative changes. It has not been cultivated, but the disease has been transmitted to cats by means of rectal injections; when given by the mouth it produces no effect.

The amœba is not, however, the cause of all cases of dysentery, and endemic dysentery is possibly due to a bacterium which has been isolated by Shiga. This bacillus closely resembles, in its morphological characters, the bacillus coli communis and the typhoid bacillus. It forms an intracellular poison. A specific serum reaction is given by the blood of convalescents from this form of tropical dysentery.

Ulcerative colitis is an infection of the large intestine, the cause of which is unknown. A similar anatomical change is observed in "Asylum" dysentery.

B. *Food Poisoning.*—Cases of food poisoning are usually divided into two classes, in one of which the effects are ascribed to chemical substances present in the food when eaten—that is, the chemical products of bacteria which have developed in food and been killed by cooking. In the second class of cases, the bacterium, when taken in the food, is still living, so that an intestinal infection occurs.

In both cases the food is spoken of as *tainted food;* but food which may cause poisoning, and even death, does not necessarily give any putrefactive odour. It may be doubted whether, in the absence of living bacteria, food can give rise to any serious poisonous effects. The amount of chemical poison swallowed in the absence of living bacteria must be very small. More and more evidence is forthcoming that food poisoning is due to the agency of specific pathogenic bacteria present in the food. The result is the growth of the bacterium, usually in the small intestine: an intoxication of the body follows, or an infection of the organs of the body, sometimes with the production of remote lesions.

Gaertner's bacillus has been shown to be the cause of some

outbreaks of food poisoning. It is a bacillus closely allied to the typhoid bacillus, both in its mode of growth and in its poisonous chemical products (p. 93). It produces not only an intestinal intoxication, but also an infection of the body, and has been found in the liver and other organs of man in certain epidemics of food poisoning.

The B. enteritidis sporogenes has been shown to be the cause of some cases of poisoning by milk. It is an anaërobic micro-organism, and produces its effect mainly by an intoxication from the alimentary canal.

To the B. coli communis must be ascribed some rôle in certain conditions of intestinal poisoning. It is a natural habitant of the large intestine, being found in the motions soon after birth and afterwards, and in the fæces of all large animals. It is a pathogenic bacillus, closely allied to the typhoid bacillus and to Gaertner's bacillus. As obtained from normal fæcal matter, it may not possess any great degree of virulence, but its virulence may be enormously increased artificially, and is increased in certain intestinal infections. Thus, in typhoid fever, it has been shown to increase greatly in number and in virulence in some instances, and this may be the case also in other conditions in which there is no putrefactive decomposition of the intestinal contents.

C. *Putrefactive Processes in the Intestine.*—Putrefaction of the intestinal contents, with a subsequent intoxication of the body, occurs in three different conditions:—

1. It accompanies certain intestinal infections—for example, those of typhoid fever, dysentery, tropical diarrhœa and tuberculous enteritis.

2. It occurs in organic disease of the intestine, chiefly of the cæcum, appendix and large intestine.

3. It may occur without the two previous conditions being present, and is then to be ascribed to a derangement of gastro-intestinal digestion permitting the overgrowth of putrefactive bacteria.

The bacteria which produce putrefaction in the intestine are no doubt of many different forms, proteus vulgaris, P. Zenkeri and bacillus saprogenes being the chief. The con-

ditions which favour putrefaction are:—partaking of decomposing food imperfectly cooked; stagnation of the intestinal contents, whether due to weakness of the muscular wall or to actual obstruction in the gut; and imperfection in the digestive processes in the stomach and small intestine, not only in the quality of the secretions, but in the deficient action of these on the proteids, and in a deficient absorption of the digestive products.

The results of putrefaction in the intestine are, not only an intoxication of the body by the chemical products (p. 71), but a local irritative effect on the intestine, causing congestion, an excessive secretion of mucus, sometimes slight hæmorrhage, and usually the exudation of a quantity of liquid. Erosion or ulceration of the mucous membrane may follow, more particularly in cases where there is obstruction to the passage of the intestinal contents.

D. *Acute Infective Enteritis* (*Infantile Diarrhœa, Cholera Nostras*).—These conditions, although grouped together, are probably not due to one infection, and future research may show several different bacteria which may produce the results seen in infective enteritis. In such conditions the micro-organism is taken in with the food, or it is an infection starting with a bacterial growth in the mouth, and passing on to the intestinal tract. The association of this bacterial growth on the tongue, gums, cheeks and fauces of children with acute infantile diarrhœa is frequent. In infantile diarrhœa putrefactive bacteria are found in the motions, especially the proteus vulgaris. In some cases the condition is found to be due to a streptococcus, so that a streptococcus enteritis must be recognised. The same may be said of the B. enteritidis sporogenes.

The lesions found after death in such cases may be very slight, and not visible to the naked eye. Some congestion of the small intestine may be present, with some superficial loss of epithelium: gross lesions here, or in other parts of the body, may be absent.

Some of these cases are examples of the growth of specific bacteria in the intestinal tract, with subsequent

intoxication of the body. In other cases erosion and ulceration of the lymphoid patches in the large and small intestine have been found, with or without some enlargement of the spleen. These are cases of intestinal infection in which the bacteria invade the tissues of the body.

6. *Malaria.* — Malaria is due to a protozoon, which was discovered by Laveran in 1880. It is found in the blood, inhabiting the red corpuscle, in which it undergoes its phases of transformation. It does not invade the tissues. Its action results in a disintegration of the red blood corpuscle, the colouring matter of which is set free as insoluble pigment (melanin).

Three kinds of parasites are described according to the differences in their intracorpuscular phases of development, namely, the parasite of tertian, of quartan and of æstivo-autumnal or irregular fever. Malarial fever has been previously classified as quotidian, tertian and quartan, according as to whether the attacks occur each day, every second day, or every third day, but it was found that there was no special parasite in quotidian fever, and that, in cases of a daily attack of the fever, this was due to the development either of two groups of tertian parasites, or of three groups of the quartan parasite, maturing on successive days.

The *tertian parasite* (Plasmodium vivax, Fig. 52) is the least virulent of the three forms. In its early stage, in the red corpuscle, it is seen as an oval body, which undergoes amœboid movement, and becomes pigmented. The phases of development of the parasite (schizogony) take forty-eight hours; segmentation takes place and the paroxysm occurs. The segments form the rosette, and the rosette disintegrates, setting free the pigment and the young parasites (merozoites), which then undergo the same process of intracorpuscular development.

The *quartan parasite* (Plasmodium malariæ, Fig. 53) undergoes similar changes, but the chief difference is that the period of development (schizogony) takes from sixty-four to seventy-two hours. The pigment granules are larger and blacker than those in the tertian form, and, during segmentation, the pigment tends to form rays between the segments.

The segments ultimately set free are from six to ten or twelve, being fewer in number than in the case of the tertian parasite.

The *æstivo-autumnal parasite* (Laverania malariæ or Plasmodium immaculatum, Fig. 54) is more variable than the two already mentioned. It may form a hyaline body inside the red corpuscle, is more ring-like than the other two forms, and



FIG. 52.—Malaria. Diagram of the intracorpuscular changes of the tertian parasite.

(1) Shows the early stage of the merozoite within the red corpuscle; (2) to (2c) show the various forms the parasite assumes during its growth and pigmentation (amœboid forms); (3) is the formation of the sphere; (4) and (4a) the division of the parasite into segments or merozoites; while (5) shows the merozoites freed from the corpuscle. Phases (1) to (3) are those which occur in the prepyrexial stage of malaria, and take forty-eight hours to develop.

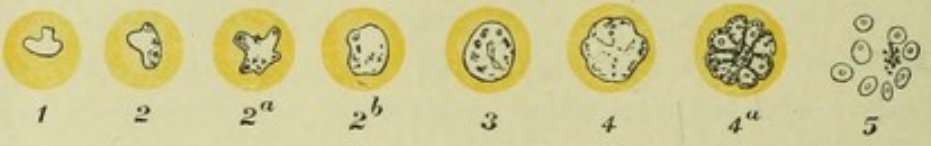


FIG. 53.—Malaria. Intracorpuscular changes of the quartan parasite.

The main features in the phases of this parasite are the same as in the tertian. The differences are that the pigment is blacker, that the segments, or merozoites, are fewer in number, and that the prepyrexial phases take seventy-two hours for their development.



FIG. 54.—Malaria. Intracorpuscular changes of the parasite of æstivo-autumnal malaria. (See also Fig. 56.)

The main features of the development are the same as in the tertian and quartan parasite. The differences are that the parasite is much smaller and less pigmented, and frequently assumes a ring-like form. Two parasites may be in one corpuscle as shown in (2). The merozoites are smaller and more numerous than in the case of the quartan parasite.

has a shaded central part, with a smaller amount of pigment. Schizogony occurs in the spleen, bone-marrow and liver, and at irregular intervals.

Other forms of the malarial parasite are observed, and are mainly related to the sexual development of the parasite in the mosquito. These are the flagellate body, which is developed from the intracorpuscular organism, and is freely movable when set free. The flagella are long compared to the body,

which contains granules of black pigment. They are most numerous in the irregular forms of malaria. The crescent form of Laveran is also frequently observed, and it may form a flagellate body. Ovoid forms are also seen (Fig. 56).

The development of the parasite leads to the disintegration of the red corpuscle, with the result, in prolonged cases, of producing anæmia and pigmentation of the internal organs, the liver, spleen and brain. The effects of the parasite, however, are not limited to this disintegration of the red corpuscle. It must also form a powerful poison, which causes the rise of temperature and other effects observed in malaria. More particularly in the quartan and irregular forms of malarial fever these effects are to be found: not only is there high fever, but there is a profound nervous disturbance, as well as the production of hæmorrhages. The blood is hydræmic, and there may be a condition of hæmoglobinæmia, the liberated hæmoglobin dissolving in the plasma. In chronic malaria, there is melanæmia with deposit of pigment in the liver, spleen and bone-marrow.

The *pernicious* malarial fevers may show either profuse hæmorrhage (mostly from the kidneys), or jaundice, or a profound effect on the gastro-intestinal tract or on the brain, with the production of delirium, ending in coma.

Malaria has been conveyed from man to man by experimental inoculation, the period of incubation in the regular fevers being eleven or twelve days, in the irregular, from two to five days.

The entrance of the parasite into the human being is not by means of the mucous membranes, but by means of the mosquito, one genus of which, *anopheles*, or the *speckled wing mosquito* (Fig. 55), has been shown to be capable of harbouring the parasite after being fed with malarial blood, and the anopheles so infested has been shown, by direct experiment, to be capable of giving the disease to the human being. Anopheles is a genus widely distributed in the world, and is found both in malarious and non-malarious districts. In other genera of mosquito the parasite has been found not to live. The anopheles lives chiefly in swampy districts, containing

almost stagnant pools. Its larvæ will not develop in running water.

It has been shown that healthy men can live in a badly malarious district, if, from sunset to sunrise, they live in mosquito-proof huts. The adult black races living in malarious districts are more or less immune to the disease, sometimes completely so. This immunity may be partly hereditary, but it has been shown that the children of these black races contain the parasite in their blood, so that the immunity of

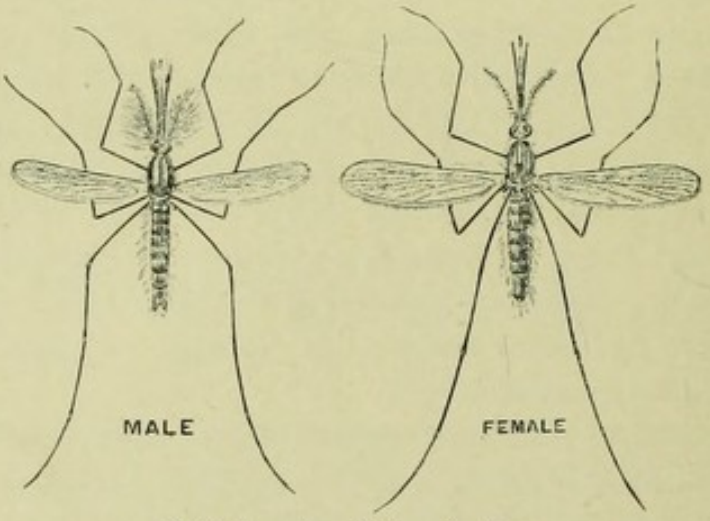


FIG. 55.—Anopheles claviger.

This is one of the species of mosquito in which the malarial parasite undergoes a sexual generation (Fig. 56), and which conveys the infection to man by the introduction, beneath the skin, of the parasite from the salivary gland.

the adult may be due partly to heredity, but partly to an acquired faculty.

The phases the malarial protozoon undergoes in the red corpuscle of man are only one part of its life history. Another phase of development takes place in the anopheles. The intracorpuscular development is called schizogony, and is asexual; the development in the mosquito is called sporogony, and is sexual (Fig. 56). The female mosquito when it sucks the blood of a malarial patient takes into its stomach the protozoon in all the phases of its intracorpuscular development. All die except the male and female gametocyte, which are presumably derived from the merozoites. The male gametocyte becomes a flagellated body, and the flagella unite with the

female gametocyte or macrogamete. The resulting conjugation is a zygote, an oval-shaped body with pointed ends, and it is this zygote which undergoes further development in the

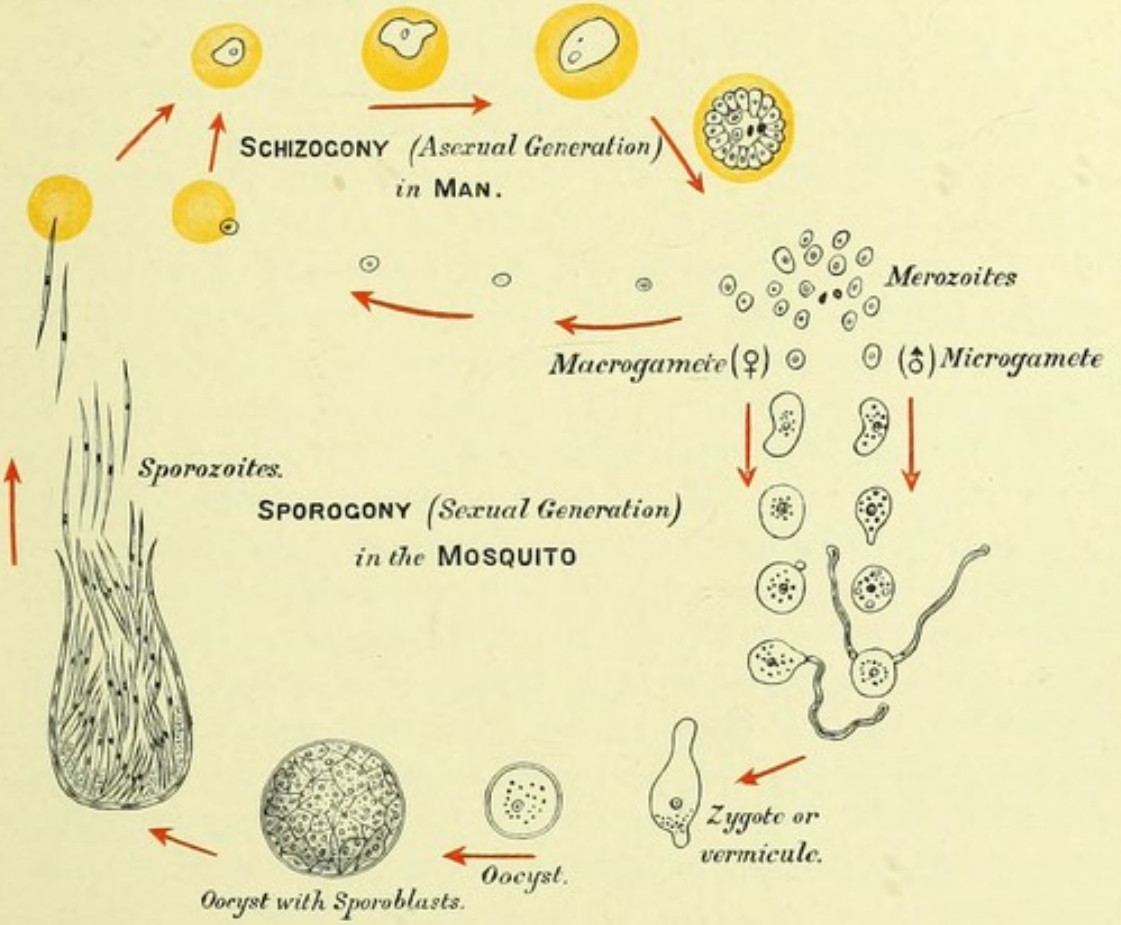


FIG. 56.—Malaria. Diagram of the phases undergone by the parasite of æstivo-autumnal fever in the red corpuscles of man and in the mosquito.

The upper circle represents the process of *schizogony*, or asexual generation occurring in man. The parasite develops in the red corpuscle, divides into segments or merozoites, which, set free in the blood, enter other red corpuscles, and so reproduce the disease without fresh infection by the mosquito. *Sporogony*, or sexual generation, which is shown in the lower circle, occurs only in the mosquito. There is a male and female element, *microgamete* and *macrogamete*, which are the crescents. The changes of shape these undergo are shown in the diagram, the female being distinguished by the pigment surrounding the nucleus; while in the male this is distributed throughout the protoplasm. The male develops into the flagellated body: one of the flagella conjugates with the macrogamete, and the result is a *zygote* or vermicule, which becomes a spherical *oocyst*. This subsequently divides into numerous multiple cells, or sporoblasts, and these again into curved needle-shaped bodies, or *sporozoites*. These are the bodies which, when the mosquito stings, enter the blood and so into a red corpuscle.

stomach of the mosquito, and finally projects from the stomach wall into the body cavity. Becoming spherical, the zygote divides, while still encapsuled, into sub-divisions called blastophores, and these blastophores subsequently develop into elongated bodies called sporozoites. The capsule enclosing

the sporozoite then ruptures, and the sporozoites are carried through the poison or veneno-salivary gland of the mosquito, from which they are inserted into the human being by the sting. Entering the red corpuscle, they undergo the phases which have been already described. These phases of development of the malarial protozoon do not stand alone in nature. Similar phases are shown by the coccidia, for example coccidium Schubergi, which is parasitic in the intestinal epithelium of a centipede, lithobius forficatus; and by other Protozoa more closely allied to the malarial parasite. The malarial parasite belongs to the order Hæmosporidia of the Protozoa: other members of the order are like it amœboid, and show an alternation of hosts, schizogony occurring in a warm-blooded animal (mammal or bird), sporogony taking place in an invertebrate host. Many common birds are thus infected with hæmoproteus (proteosoma) danilewskyi and halteridium danilewskyi; these live in the red corpuscle, but the intermediate host is not known. Piroplasma (apiosoma) bigeminum is the cause of Texas fever in cattle. The disease, which is transmitted by the bites of ticks, is characterised by high pyrexia, loss of appetite, jaundice, emaciation and frequently hæmoglobinuria—hence the name "red-water" fever. A similar disease in dogs, called "malignant jaundice," is caused by piroplasma canis.

Concurrent Infections with Malaria.—Dysentery, pneumonia, and typhoid fever, are the chief infective diseases which may co-exist with malaria, each due to their own infective agent. There is no necessity for the term *typho-malarial fever*, as in this case there is an infection by two distinct infective agents.

Hæmoglobinuric fever, which is also called black-water fever, bilious remittent fever, and West African fever, is a febrile disease, the most prominent feature of which, besides the rise of body temperature, is the occurrence of hæmoglobin and its derivatives in the urine. The attacks are paroxysmal. At present its cause is not known, there being no direct evidence that the malarial parasite is responsible for its occurrence.

7. *Malignant New Growths.*—Although the mode of origin

of malignant new growths is not yet known, they may be conveniently considered in this chapter, in order to contrast and compare their characters with the processes of infection which have been discussed.

Malignant new growths are of two kinds: cancer or carcinoma, which arises from epithelial tissues, either epiblastic or hypoblastic, and sarcoma, which arises from mesoblastic tissues.

Cancer is at first a local disease arising either in epithelial tissue, or in one or other organ of the body.

1. A primary tumour occurs and infiltrates the surrounding parts, its spread not being limited by the periphery of the organ or part. In its growth it shows degeneration to a greater or less degree, frequently becoming adherent to the surface and ulcerating.

2. It invades, by means of the lymphatic channels, the neighbouring lymph glands, in which is reproduced a secondary growth resembling the primary.

3. Subsequently secondary growths occur in other parts, and these are initiated by particles conveyed by the blood stream from the main growth. These secondary growths are called metastases.

4. The growth is apt to be invaded at the surface by micro-organisms, producing putrefactive decomposition, and sometimes an intoxication of the body.

As illustrations of the spread of cancer in the body, the following examples may be taken. In cancer of the mamma the earliest part infiltrated is the axillary glands, followed by an affection of the glands above the clavicle. Infiltration occurs in the pleura and lung, while metastases may occur in the liver and spine. In epithelioma of the lip and tongue infiltration of the primary growth is seen, and invasion of the glands below the jaw. As a rule, metastasis does not occur. In cancer of the stomach, and of the colon and rectum, the neighbouring lymphatic glands are affected, and metastasis occurs in the liver, the peritoneum being affected by direct invasion.

The resemblance to infection, more particularly to that of tuberculosis and syphilis, which the mode of spread of cancer

shows, is evident from the following considerations: 1. Cancer occurs near the surface and at places exposed to the influence of agents from outside, such as the mamma, tongue, lips, œsophagus, stomach, colon and rectum, vagina and uterus. In the gastro-intestinal tract it is noticeable that the most frequent seats of growth are the flexures or narrowings of the canal; as at the pylorus, in the cæcum, at the hepatic and splenic flexures of the colon, at the sigmoid flexure, at the anus and in the rectum near it. It might therefore, *primâ facie*, be considered that cancer is due to some agent entering the body from without.

2. From the primary growth spread takes place by means of the lymphatics to the nearest lymphatic glands. Some instances may be quoted, although rare, where the glands are invaded without there being a primary lesion, as occurs in some cases of tuberculosis (p. 129). This occurs in chimney-sweeps' cancer, where the inguinal glands may be affected without a skin lesion.

3. The occurrence of metastases, mainly through the circulation, is another point of resemblance to the mode of infection in tuberculosis and syphilis; but, whereas in these two instances the local lesion produced is the result of irritation of the tissue, in cancer the cells of the primary growth are actually carried by the lymphatic or blood stream, giving rise to the idea that the infective agent, if present, resides in the cells of the new growth.

In the secondary growth there is a multiplication of the epithelial cells. This, when it occurs in a lymphatic gland, cannot be ascribed to the transformation of the cells of the lymphatic gland into epithelial cells, as this does not occur.

4. After a primary growth has been removed—apparently completely—recurrence takes place. This might well be explained by the fact that the removal, although complete to the naked eye, was not really complete. But not infrequently recurrence occurs in the scar of the operation, and at some distance from the periphery of the primary growth, as if indeed during the operation the cut tissue had become infected.

5. Attempts have been made to discover the infective

agent, but they have hitherto been unsuccessful. Microscopical examination of the cancerous tumour has shown the presence of ovoid "nucleated" bodies in the epithelial cells, which by some are considered parasitic and by others as degenerated nuclei. Attempts to cultivate an infective agent have not hitherto been successful. Cultures have been obtained from some specimens of cancer of certain blastomycetes or yeast-like organisms, but although these have proved pathogenic to certain animals, their injection has not yet succeeded in producing a carcinomatous tumour. It may be that the animals used were not susceptible to the infection, and so the characteristic new growth was not produced. Attempts to inoculate fresh cancerous tumours into various animals, both domesticated and in monkeys, have uniformly resulted in failure, whether the inoculations were made by grafting, by the injection of an emulsion of the growth subcutaneously, intravenously, or intraperitoneally; or whether the growth was used for inoculation after being kept for a long period in different kinds of earth, so as to enable the possible infective agent to develop extra-corporeally. It may be that the only animal susceptible to human carcinoma is man. Growths with a similar structure also occur in domesticated animals, and inoculation of the tumour from one animal into another of the same species has been successful.

Sarcoma is, as has been said, of mesoblastic origin. It arises primarily more particularly in the lymphatic glands and in the bones and periosteum, but it may also arise in the organs of the body. Its mode of spread is from gland to gland, or by infiltration. Metastasis occurs by the blood stream and not by the lymphatics, the lungs being commonly affected, as well as other organs.

The Effects of Malignant New Growths.—Malignant new growths—whether carcinoma or sarcoma—unless removed, invariably lead to death. After removal there may be no recurrence for some years. Subsequently, however, recurrence usually takes place, not necessarily at the seat of the primary growth, but elsewhere in the body. Malignant growths cause death in different ways. They are associated with wasting and

anæmia which are parts of the cancerous "cachexia." Death may be caused :—

1. By infiltration and destruction of important organs and tissues, such as the liver, kidney, lungs, heart, blood and brain.

2. By interference with the passage of the food, or with its digestion and absorption. Interference with the passage of the food occurs, for example, in cancer of the œsophagus, pylorus and colon; with the digestion of the food in obstruction at the pylorus, which is followed by bacterial decomposition of the stomach contents; or by cancer of the pancreas, which destroys the organ supplying one of the main digestive juices.

3. Part of the fatal result is sometimes due to the invasion of the tumour by micro-organisms, which may invade the tissue, causing gangrene, as in rupture of carcinoma of a hollow viscus. Putrefactive decomposition of the intestinal contents may also occur.

It may be said that the evidences of an intoxication in cancer are but slight, inasmuch as the profoundest effects on the body are observed in cases where an important organ, such as the liver, is destroyed, or where the cancer occurs in the alimentary tract. Pyrexia does not occur in carcinoma, but is observed in some cases of generalised sarcoma.

Malignant disease, more particularly of the abdomen, is associated with fatty degeneration of the heart, liver and kidneys, which perhaps may be due to a cancerous intoxication, but is also to be ascribed to the malnutrition of the patient, owing to the deficient amount of food assimilated.

CHAPTER VI

INFECTION—*continued*

IV. *Immunity*

Two facts are of importance in commencing the study of immunity:—

1. Specific bacteria are not infective to every class of animal.

2. Recovery takes place in infective disease.

That specific bacteria are not infective to every class of animal shows that there is a condition of the body which prevents their growth and the formation of their toxines. That, in a large number of cases of infective disease, recovery takes place, shows that after a time the body becomes resistant to the further growth of the bacterium. Moreover, in cases of the same infection in different individuals, there is a varying degree of severity of infection, that is, a varying degree in the growth of the bacteria. An animal or man may therefore show *susceptibility* to an infective disease, or *refractoriness;* and both these qualities may be possessed, to a varying extent, not only by different animals, but also by different individuals of the human race.

Immunity may be defined as a condition of the body, natural or acquired, rendering it resistant to the invasion of one or more infective disorders.

In natural immunity the disease is not acquired under the ordinary conditions of existence, but in some cases the specific germ, when inoculated, may produce a disease, which develops in a modified or an acute form. In other cases, even the inoculation of the specific virus is without result, so

that, besides natural immunity, there is a special immunity and an inoculation immunity of animals and man to disease. It is evident that inoculation is a much more severe test of immunity than the observations of natural immunity.

Natural Immunity.—There are certain infective diseases which are observed naturally in man only; others in animals only; and a third group of diseases which are present in both man and animals.

Infective Diseases occurring in Man only.

1.

Typhoid Fever.	Malta Fever.
Cholera.	Leprosy.
Diphtheria.	Gonorrhœa.

2.

Amœbic Dysentery.	Sleeping Sickness.
Malaria.	

3.

Scarlet Fever.	Typhus.
Measles.	Dengue.
Hooping-Cough.	Yellow Fever.
Variola.	Beri-Beri.
Syphilis.	Delhi Boil.
Mumps.	Frambœsia.

Diseases occurring in Animals only.

Swine Plague (Pigs).	Horse Sickness (Horses).
Contagious Pleuro-pneumonia (Cattle).	Black Leg (Sheep).
Distemper (Dogs).	Nagana, Tsetse Fly Disease (Herbivora chiefly).
Diseases allied to Malaria.	

Infective Diseases occurring in Man and Animals.

Tuberculosis.	Tetanus.
Anthrax.	Foot and Mouth Disease.
Glanders and Farcy.	Plague.
Pyæmia.	Actinomycosis.

Such a classification of disease as regards its distribution in the animal kingdom, is provisional, inasmuch as the

infective agent is not known in all the diseases named, and further investigation may limit the number of diseases to which man alone and domestic animals alone are subject. Although disease may be observed in man alone, yet the bacterium may produce disease and death in some of the lower animals when injected into the body.

Taking the first group of diseases observed in man only, typhoid fever and cholera have not been observed in any animal in the form in which the disease occurs in man, although the infective agent in each case is fatal to certain animals when injected either subcutaneously or intraperitoneally, and in both diseases, under certain conditions, infection may take place by means of the alimentary tract, the usual mode by which the disease is conveyed in man.

Diphtheria may possibly, in future, be shown to be a natural disease in certain animals—for example, cats (Klein) and horses (Cobbett); but, for the most part, it may be considered as a disease peculiar to man, although the bacillus is highly infective to rodents, cats, horses and cows. The Malta fever coccus is infective to monkeys, but rodents, guinea-pigs and mice are non-susceptible, unless the bacillus is injected into the brain beneath the dura mater (Durham). Leprosy, as far as is known, is a disease peculiar to man, and cannot be inoculated into animals. Relapsing fever is observed chiefly in man, but can be inoculated into monkeys.

With regard to the other diseases mentioned in group 3 of the first class, the infective agent is unknown, or, at any rate, extremely doubtful. No animals are known to suffer from scarlet fever, measles, syphilis, or from the other diseases mentioned. The infective agent is, moreover, unknown, and injection of the morbid secretions has not produced any diseased condition in the lower animals.

The second class of diseases, namely, those peculiar tc animals, includes some, like pleuro-pneumonia, distemper and horse-sickness, in which the infective agent is unknown; but such diseases do not occur in the human being, nor does swine plague or black leg.

The tsetse fly disease, which affects herbivora and carnivora

in certain parts of Africa, is not transmissible to man; the infective agent (trypanosoma Brucei) does not flourish in the human body.

The class of diseases occurring in both man and animals is gradually extending, and investigation has brought to light many curious facts in the natural immunity of animals to certain diseases, as distinguished from inoculation immunity.

Tuberculosis is a natural disease in man, cattle and pigs; it is a rare disease in goats, sheep, horses and dogs. Both goats and dogs are capable of being infected by the tuberculous virus, but, in the case of the latter animal, large doses have to be given. It is unknown as a natural disease in wild animals; yet most of them can be infected by it. Metchniknoff has recorded an extraordinary resistance of an Algerian rat (meriones) to the disease after inoculation. Guinea-pigs and rodents are very susceptible to the disease on inoculation, although they do not suffer naturally from it.

In the case of anthrax, man, cattle, sheep, pigs, goats and horses develop the disease naturally. Algerian sheep are refractory; adult white rats, dogs and pigeons are very refractory to the disease on inoculation.

Diphtheria may be inoculated with success into rabbits, guinea-pigs, dogs, cats, monkeys and cows, the inoculation resulting in a fatal infection. White rats and mice are very refractory to inoculation, and mice are also not susceptible to the toxine of diphtheria.

To inoculation by the pneumococcus, rabbits and mice are susceptible; guinea-pigs and fowls are refractory, especially fowls.

However interesting these facts are, their discussion does not lead to any clear idea on the subject of immunity. From the facts which have been given, it is clear that natural immunity is purely a relative term: that whereas, for example, the disease may be peculiar to man or an animal in the sense that it does not occur naturally, yet neither man nor animals may have an inoculation immunity against the disease.

Examples of extreme refractoriness of animals to disease

occurring in man are of great importance, especially in those cases, such as typhoid fever and cholera, where the infective agent is known. Until, however, the infective agent in all these diseases has been separated and studied, but little progress can be made in the determination of the causes of natural immunity. In some instances, so-called natural immunity appears to depend mainly on absence of infection. In others, however, there is a natural defence in the body against the invasion of the infective agent.

The Natural Defence of the Body against the Invasion of Micro-organisms.—Bacteria are not present in any of the tissues of the healthy body. They exist in the mouth and throat in greater or smaller number. They are taken in with the food, but do not develop in the stomach. They begin to develop in the small intestine, especially towards the lower end, and are present in large numbers in the contents of the large intestine. In the upper part of the nasal cavity they are not present, and in the normal bronchial tube they are, as a rule, absent. They are present in the vagina, but not in the urethra. Where bacteria exist normally in the body, they may be considered as practically outside the tissues. Most of the bacteria found in the localities mentioned are non-infective, but some are capable of producing disease; as with the pneumococcus, which may be present in the mouth; micrococcus tetragenus, which is also present in the mouth secretion, and bacillus coli communis, which is found, with other bacteria (chiefly putrefactive) in the intestine. There is some evidence, also, that pathogenic bacteria may be present in the mouth and intestine without giving rise to disease, as in the cases in which the diphtheria bacillus is found in the throat, and no lesion is present.

The natural defences of the body against the invasion of bacteria are three in number:—

1. An unabraded and healthy mucous membrane.

2. The hydrochloric acid of the gastric juice, which is secreted on the entrance of food into the stomach, at a time when the bacteria are also present.

3. The natural antagonistic action of certain substances present in the liquids and cells of the body. This action is sometimes referred to as the "bactericidal action" of serum, or as due to the presence of defensive proteids or alexins. These terms, however, are too narrow to express this antagonistic action, which will be more fully discussed when the question of artificially-produced immunity is considered.

With regard to the defence of the mucous membrane against the invasion of micro-organisms; this exists partly in the epithelium (whether stratified, columnar, or ciliated), but is, no doubt, partly due to the active phagocytosis which occurs in the mucous membrane, especially in the tonsils and those parts of the intestine which contain lymphoid tissue.

The hydrochloric acid of the gastric juice inhibits the growth of bacteria, or actually kills them. Normal gastric juice will, for a long time, remain undecomposed. In the ordinary healthy person, bacteria taken with the food do not develop in the stomach. Most of them, however, are simply inhibited in their growth, which takes place in the small and large intestine. To some pathogenic bacteria the gastric juice is destructive, for example, those of cholera and tubercle; but this is not the case with the typhoid bacillus, as it can grow in a liquid containing a small quantity of hydrochloric acid. A diminished inhibition of the bacteria in the stomach occurs in cases where there is a diminution in the secretion of hydrochloric acid, so that, in such cases, pathogenic and other bacteria can pass through the stomach unharmed.

The factors in immunity and in infection are three in number:—

1. The degree of virulence of the infective agent.
2. The dose of poison.
3. The degree of resistance of the body to the invasion.

The virulence of the infective agent has already been discussed (p. 65).

Within certain limits, the dose of the poison is important. A smaller amount of weak virus may not infect, while a large

amount will, and the amount of virus which will cause infection depends, to some extent, on the mode in which it is introduced into the body. Infection directly through the circulation requires the smallest dose, and is as a rule the most certain. Infection beneath the skin, and into the peritoneal cavity, also requires a small dose to be effective; but infection through ingestion, that is, by way of the alimentary tract, is the most uncertain of all, owing to the exposure of the bacteria to the resistant mucous membrane, to the action of the gastric juice, and to the action of the bacteria (acid-forming and putrefactive) of the intestinal contents.

The degree of resistance of the body is difficult, if not impossible, to define in natural immunity; but, in artificial immunity, there is evidence to show that this resistance is, in the main, due to antagonistic substances in the tissues of the body.

The natural resistance of the body may be increased by the production of artificial immunity, and it may be diminished by various means. The factors that are usually considered under the heading Etiology of Disease are those which, to some extent, are concerned with the resistance to infective disease. Such factors are the influence of age, sex, climate, surroundings, food and heredity. But these factors are, in the main, indefinite, and their detailed discussion would not serve any useful purpose in a work on Pathology.

Hereditary predisposition to infective disease may be dependent, not only on the special character of the surroundings, but also on the vigour of the individual, and on the nature of the infection. The absence of vigour of the individual may depend on deficient development or nutrition of certain parts, or on the weakness of some of the natural defences against the invasion of infective disease. Tuberculosis, for example, is but rarely directly inherited, although, doubtless, hereditary predisposition to the infection exists in certain cases. Syphilis is the best example of hereditary disease, and, in this case, there may be germinal infection. In the case both of tubercle and of anthrax, infection may be passed to the offspring by means of a placental infection.

The influence of a previous condition of the body, as predisposing to infection, cannot be disregarded. These conditions may be divided into two classes, both of which may be considered under the heading of the Influence of Injury.

The Influence of a Previous Injury as affecting Infection.— 1. The injury may be mechanical, as in the blow on the chest which precedes the development of pulmonary tuberculosis in some cases. A chronic lesion of the skin may also lead to infection, and the blow which sometimes precedes cancer of the breast may also be placed in the same class.

2. But the most important previous injury which predisposes to infection is one in which the body has been exposed to the action of the poisons of a previous infective disease, or to the continued action of a poison, such as alcohol. Thus infection by tuberculosis follows hooping-cough and measles; or pneumonia may follow these. Pus infection follows that of diphtheria, scarlet fever and other conditions. Syphilis and alcoholism predispose to tuberculosis; alcoholism also to the invasion of the pneumococcus and of pus cocci. In chronic Bright's disease, the infection of tuberculosis or of the pneumococcus is frequently observed.

Many attempts have been made experimentally to diminish the resistance of the body to an infective disease. Thus, as regards the anthrax bacillus, to which pigeons are naturally resistant, invasion of the body was aided by previous starvation of the animals. White rats, however, were not affected in this way, but might be rendered susceptible to the bacillus by giving them hard work to do on an unsuitable diet. In frogs, the anthrax bacillus does not develop, but, if the animal is kept at a temperature of 25° to 35° C., development of the bacilli is observed. In these experiments, the chief agents used were the alteration of the surroundings of the animal or of its food.

Attempts have been made to prove experimentally that both the spleen and the pancreas are necessary for the continuance of either natural or acquired immunity. Thus it is stated that the removal of the spleen removed the artificially produced immunity of rabbits to tetanus, and that

the removal of the pancreas destroyed the natural immunity of pigeons to anthrax. These statements, however, are not correct, and more particularly with regard to the spleen. It has been shown that the presence of this organ is not necessary for the continuance of immunity.

The resistance of the body, however, may be diminished by means of chemical substances which are injected into the body at the same time as the bacillus. Part of this subject has already been considered, as it is one of the means by which the virulence of bacteria is increased (p. 67). But other facts in this connection are that sugar injected with the staphylococcus pyogenes aureus increases the suppuration caused by this micro-organism, and chloroform narcosis removes the natural immunity of frogs and rats to the anthrax bacillus.

On what resistance to disease actually depends, these experiments, however, shed no light. More help has been gained by the study of the means and results of producing *artificial immunity* in animals; that is, increasing the resistance of the body to infective disease.

Artificial immunity may be produced in three different ways:—

1. By the injection of an attenuated living virus.
2. By the injection of the chemical products of the virus.
3. By injecting the blood serum of animals made immune by one or other of the first two methods.

The first two methods are practically the same, inasmuch as the bacterium acts by means of its chemical products, but the action of the living virus cannot be controlled so well as that of the chemical poison. The production of immunity by the injection of the living virus is frequently referred to as *active immunity or preventive inoculation*, and this may be extended to include the method when the chemical poison alone is used. *Passive immunity* is produced by the third method mentioned.

Illustrations of the Production of Artificial Immunity.

(A) *By the Attenuated Virus.* — 1. *Vaccinia* (Jenner). — The process of vaccination confers immunity against subsequent

vaccination, and a relative immunity to smallpox. After the insertion of the lymph into the skin, a dry papule appears, which becomes a vesicle, and subsequently a pustule; a scab then forms and falls (Figs. 57 and 58).

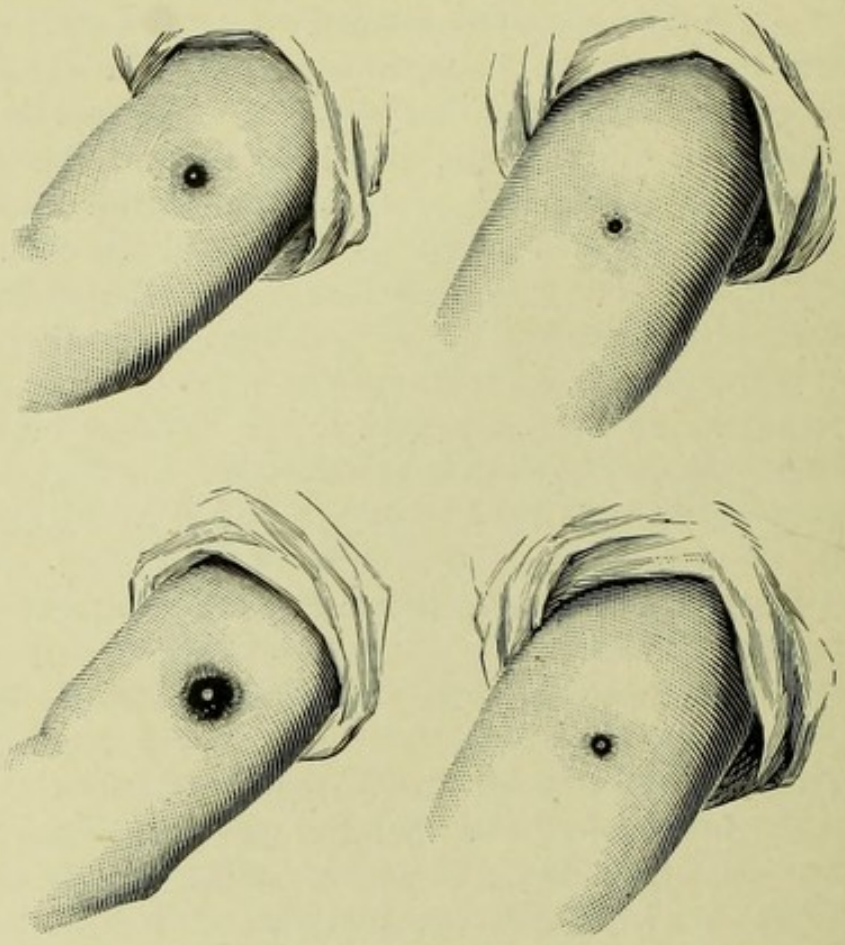


FIG. 57.—Smallpox and vaccinia.

Figs. 57 and 58 show the appearances resulting from vaccination and smallpox inoculation in the arm.

In Fig. 57 the appearances on the fourth and fifth days are shown, that resulting from smallpox on the left and from vaccinia on the right. The differences are the greater size of the smallpox vesicle and the more intense areola round it (G. Kirtland).

The duration of the different stages is as follows:—

First to fourth day	Dry papule.
Fifth to tenth day	Vesicle (umbilicated).
Eleventh day	Pustule.
Fourteenth to twentieth day . . .	Scab forms and falls.

The general symptoms which are associated with this infective disease are a rise of temperature, slight in extent,

which begins at about the third day and may last until the eighth day. There may be malaise, headache and the other symptoms associated with a slight infection; rashes may appear on the body, erythema, roseola, urticaria. Vaccinia

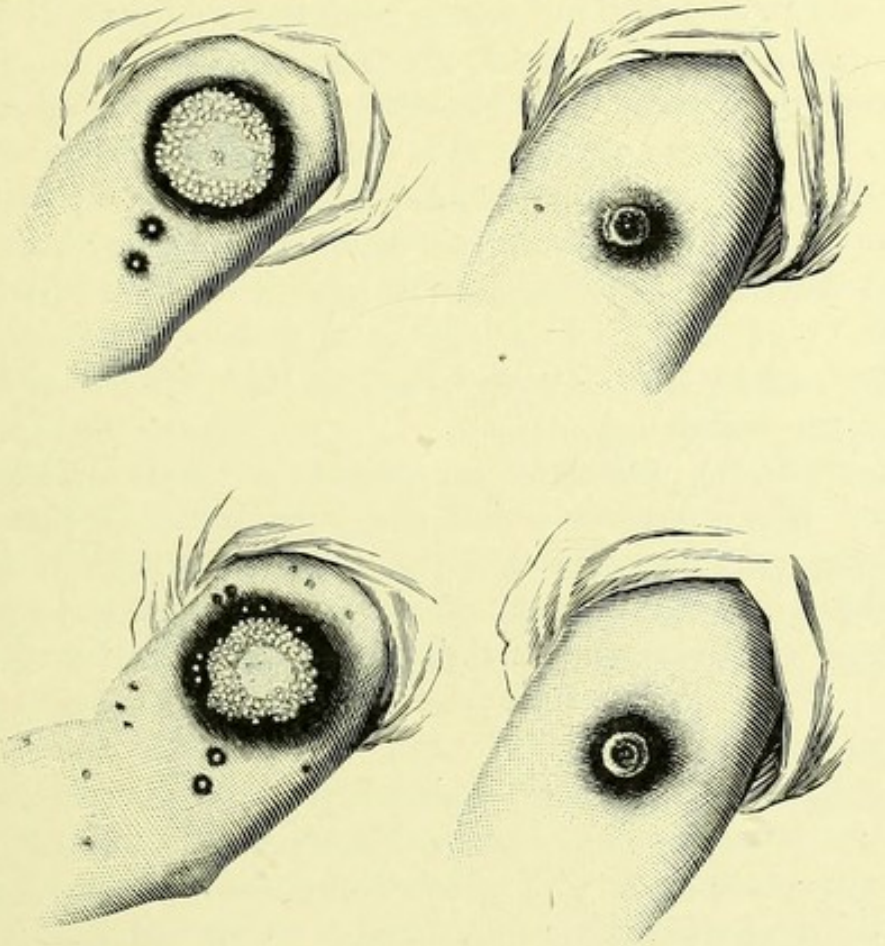


FIG. 58.—Smallpox and vaccinia.

This figure shows the same arm as in Fig. 57, but on the tenth and eleventh days. The differences in the appearance are still more marked. The site of inoculation of smallpox shows a large crop of vesicles surrounded by a dark areola, and also vesicles lying outside the areola.

The vaccinia arms, on the other hand, show on the same day a well-marked vesicle and areola, with a tendency to drying up of the vesicle on the eleventh day (G. Kirtland).

may be purely localised to the seat of inoculation, but it sometimes gives rise to a general eruption, which is preceded by the formation of supernumerary vesicles round the point of inoculation. Sometimes the vaccinated individual inoculates other parts of the skin by scratching the seat of inoculation, and so conveying the poison. In the blood of the vaccinated some leucocytosis is observed at about the third day, but it disappears early in the second week.

The result of the inoculation with the smallpox virus in the human being is very similar to that of vaccination, but both the local process and the general symptoms are more intense. Secondary vesicles are very numerous, and the secondary eruption more common. Inoculation may result in an attack of smallpox, proving fatal.

Immunity Produced.—The receptivity to successive vaccination diminishes during the second week, at about the ninth day, and is extinct before the fourth week ; that is, at this period immunity to vaccination is established, and subsequent vaccination produces no result, within a certain variable number of years. As in all other cases the immunity gradually diminishes, and is finally lost, so that re-vaccination can now be successful.

Whether the immunity so produced is an immunity to smallpox is a question which has been much discussed. It is probable that several different kinds of lymph have been used since the introduction of vaccination, and it is possible that some of these lymphs did not contain the true infective agent. The original idea was that cowpox was smallpox modified by being passed through the cow. Recent additions to our knowledge on the subject may be summarised as follows: Monkeys are susceptible to both smallpox inoculation and vaccination, and inoculation runs a course as in man. Inoculation of variola and vaccinia gives rise to a specific inflammation, and from these areas are obtained different kinds of lymph, such as *variolous lymph* and *vaccine lymph.* When the calf is used, it is called *calf lymph*, and that from the human subject is referred to as *humanised lymph.* It has been found that, in many cases, inoculation with vaccine lymph protects against the subsequent inoculation of variolous lymph, and *vice versâ.* This is an important fact, as showing that variola and vaccinia are closely allied diseases, and that they are probably due to the same infective agent. Immunity is specific, and such immunity as has been described could not be produced if the two diseases were essentially different.

There is a large amount of evidence to show that, in man,

vaccination protects against smallpox, the protection in some instances being absolute, in others relative; that is, although the vaccinated individual may develop smallpox, it runs its course in a modified form, and the mortality is much less than in unvaccinated individuals.

The micro-organisms which have been found in vaccine lymph, and not variolous lymph, are mainly staphylococci, such as occur in the skin. Another organism has also been found, which is a small bacillus, best stained by carbol-methylene blue. It is very slow in growing, and has been cultivated in the hen's egg. Whether it is the true infective agent or not is as yet unproved.

2. Vaccination was the precursor of the modern methods of preventive inoculation. In the modern instances, however, the infective agent is known, and so the process has been more fruitfully studied than that in vaccination. In this method the infective agent has to be attenuated to prepare the animal for the strong dose of poison which is subsequently injected. The subject of attenuation has been already discussed (p. 65)

Anthrax.—Pasteur attenuated the anthrax bacillus, by growing it at a temperature of 42° C. in broth. He thus obtained his *premier vaccin*, which was injected into a sheep, as a preparation for a dose of the stronger poison. In this method of attenuation the bacilli, in less than a month, lose their virulence, so that they are no longer fatal to rodents, and they do not produce spores. The *deuxième vaccin* was made by the same method, but the bacilli were allowed to grow only twelve days, so that they were much more virulent than those of the *premier vaccin.*

Sheep were first treated subcutaneously with five drops of the *premier vaccin*, and, twelve days later, with the *deuxième vaccin.* Fourteen days later it was found that immunity had been established, inasmuch as a virulent culture of the bacillus produced no symptoms. Injection of this virulent culture increases the immunity already produced. The immunity lasts in sheep about nine or ten months. It has not been

found very effective against intestinal anthrax infection, but it has undoubtedly led, in France, to a great reduction in mortality from anthrax. Immunity may also be produced by the chemical products of anthrax (p. 174).

Fowl-cholera, etc.—Pasteur also showed that immunity could be produced against fowl-cholera by the same method as with anthrax.

Other instances of producing immunity by means of the living virus are chiefly of historical interest, as, in the main, the chemical products of the bacteria are now used, and not the living bacterium. The tetanus bacillus and the diphtheria bacillus, which have become attenuated by age, have been said not to act as a vaccine, but the tetanus bacillus, when treated with trichloride of iodine, an antiseptic which diminishes its activity, was found to produce a moderate degree of immunity. So, also, the injection, at first, of very small doses, of the tetanus bacillus into dogs, which are refractory to its action, produced immunity, which was increased by continued treatment with the bacillus, in gradually increasing doses (Tizzoni).

The diphtheria bacillus was attenuated by growing it with trichloride of iodine, and was found to produce immunity; also by heating a week-old culture to 60° to 70° C. In the latter case it was found that immunity was not produced until about fourteen days after the injection of the vaccine.

Cholera (Haffkine).—In this case cultures of two degrees of virulence are used: the weaker first, followed by the *virus exalté*. Ordinary cultures of the vibrio are not fatal to animals by subcutaneous injection. Large doses, however, of young cultures, injected into the peritoneal cavity of a guinea-pig, are fatal in twenty-four hours.

To obtain the *virus exalté*, the peritoneal fluid is removed from such an animal, and incubated at 37° C. in broth. This is then injected into the peritoneum of another guinea-pig, and so on, until an exalted virus is obtained, capable of killing a guinea-pig in very small doses (p. 65). Before injection, the exalted virus is grown on agar, and an emulsion is made of

one culture, in broth, the organisms being sometimes killed by the addition of 0.5 per cent. of carbolic acid. The weak virus is obtained by growing the vibrio with a current of air passing over it. It is found that, in guinea-pigs treated first with the weak virus, and then with the exalted, the animals are protected against many times the fatal dose of the virulent living vibrio, injected intraperitoneally.

In man, the symptoms produced by the subcutaneous inoculation of the virus are those of general malaise, with some swelling at the site of inoculation and some fever. From statistics obtained from India, in which preventive inoculation against cholera has been extensively used in epidemics, it would appear that it is in some degree successful, not so much in preventing the incidence of the disease, as in diminishing the mortality. The immunity produced is relative, and not absolute.

(B) *Immunity produced by the Chemical Products of the Infective Agent.*—1. *Plague* (Haffkine). — The plague prophylactic is obtained by growing the bacillus in a liquid medium for five or six weeks, at the end of which time the bacilli are greatly degenerated. The bacilli are then killed by heating the liquid to 65° to 70° C. for one hour. It loses its toxic properties, but it was found to confer immunity in rabbits (which are naturally resistant to plague), whereby they could resist the injection of ten or fifteen times the lethal dose of virulent plague bacilli.

The dose given in man is 3 c.c. This causes fever, with headache, nausea and malaise, and some swelling and pain at the site of inoculation. Comparing the results as regards the mortality in the inoculated and uninoculated, it appears that this is less in those who have been inoculated, although the incidence of the disease was not appreciably diminished. What immunity is produced lasts only a short time, possibly six months.

2. *Typhoid Fever* (Wright).—The method of antityphoid vaccination is practically the same as that of cholera and plague. The bacillus is grown in broth for three to four weeks, the culture being then sterilised, so that the liquid injected con-

tains chiefly the bodies of the bacillus, with the intracellular poison previously described (p. 95).

The dose given is ½ to 1½ c.c. for the first vaccination. The strength of this is ⅔ of the lethal dose for a guinea-pig weighing 250 grammes. In the second vaccination, which must not be done within ten days or a fortnight after the first, one and a half to twice the original dose may be injected subcutaneously. The symptoms produced in man by the poison come on in one to six hours, usually about the third hour, and are shown first by malaise and some tendency to faintness. Fever ensues, the temperature rising to 101° to 103° F., and usually persists for eighteen or twenty-four hours (Fig. 40). The degree of bodily depression is sometimes considerable, but no serious results have supervened. At the site of inoculation there is tenderness, redness and swelling. The swelling may be considerable, but it passes off, as a rule, in forty-eight hours.

Experiments on animals have shown that this vaccine increases the resisting power against the living bacilli, and the blood of the inoculated patients gives the typhoid serum reaction. At first, however, there is an increased susceptibility to infection, and it is only later that there is a marked increase in the bactericidal action of the serum. Small doses of the vaccine act better than large doses.

Although the results of preventive inoculation cannot be, as yet, accurately gauged, it would appear that, in some instances, it has diminished the mortality from typhoid fever, although it has not appreciably diminished the incidence of the disease.

3. *Hydrophobia* (Pasteur).—The infective agent of hydrophobia has not yet been isolated, but the toxine which has been found has many characteristics in common with those produced by some bacteria. The infective agent has been described variously; as one of the blastomycetes, as a bacillus, and as a protozoön, but none of these has been proved to be the real cause of infection.

The virus itself is very sensitive to external conditions; it is destroyed by one hour's exposure to 50° C., and is killed by

putrefaction. Drying also diminishes its virulence. Pasteur obtained a constant strength of the virus by passing the virus of the dog through a series of rabbits or guinea-pigs, and he produced immunity in dogs by subcutaneous injection of a weak virus, followed by that of a stronger. The most effective way of introducing the virus into the body is beneath the dura mater.

Pasteur attenuated the virus by drying the spinal cord of rabbits dead of the disease in a sterile jar of air containing potash solution. The virus diminishes in strength up to the fourteenth day, when it dies. The weak virus, in different stages of the drying, is used in the early stages of producing immunity against the strong poison. More than this, it was found that, after infection had actually occurred, and before symptoms had developed, treatment of the dog or of man by graduated doses of the virus produced an immunity against the disease.

The treatment in man extends about twelve days, and is begun by using 2 c.c. of emulsion of dried cord twelve to fourteen days old. Every day, or every second day, emulsion of cords containing a stronger amount of poison is given, until, at the end of the treatment, emulsion of cord only one day old may be given without harmful effect. In severe bites treatment is somewhat more rapid than this. The results obtained show a remarkable diminution in the mortality following bites by rabid animals.

The principle underlying the process is that, after infection has occurred, provided the period of incubation is sufficiently long, the symptoms of disease and a fatal result may be obviated by producing a rapid immunity, and this principle has been extended to the treatment of other infective diseases, notably diphtheria and tetanus.

An antirabies serum has been prepared from the blood of animals which have been immunised by the injection of the hydrophobia virus attenuated by digesting it with pepsin. This serum has the power, not only of producing immunity in animals, but of preventing the development of symptoms after the virus has been injected (Tizzoni).

It has previously been said that the process of immunisation which takes place when an animal is treated with the living infective agent is practically the same as the production of immunity by means of the chemical products of the infective agent, but, in the latter case, the dose of the poison can be more accurately regulated. In most instances the object is to obtain the most virulent toxine possible, the dose of which can be determined after dilution.

4. *Anthrax.*—Toussaint and Chauveau showed, some years ago, that a culture of the bacillus of anthrax, killed by heat, was a vaccine against the bacillus. Hankin separated an albumose from cultures of the bacillus, and found that it afforded partial protection against the subsequent injection of the bacillus, and that for this purpose only very small doses of the albumose were required.

These results are interesting from a historical point of view, as following Wooldridge's researches on chemical vaccination against anthrax. His work must be considered as the earliest which indicated the more recent discoveries in the production of immunity by chemical products. He found that the injection of the substance which he called *tissue fibrinogen*, which is really a nucleo-albumen (Chapter XIII.), partially protected rabbits against the infection of the bacillus of anthrax, and that a better effect was produced if the bacillus were grown in solution for a short time before it was injected. Only a partial protection was obtained.

5. *Bacillus Pyocyaneus.*—This bacillus is pathogenic for rabbits and guinea-pigs, and produces both œdema and abscess. Subcutaneously injected, it produces an abscess, and, if the animal recovers, immunity is produced.

Sterilised cultures of the bacillus are also found to produce immunity, as well as the filtered urine of rabbits which have been inoculated with a virulent culture of the bacillus. The serum of animals immunised against the bacillus, if inoculated with the bacillus, causes the micro-organisms to agglomerate and sink to the bottom of the tube (*Agglutination*, p. 186), whereas, grown in ordinary serum, they become diffused through the liquid.

These results with the bacillus pyocyaneus show, not only that the chemical products do produce immunity, but that the serum and urine contain substances in which the immunising properties exist, and that these substances may be formed during the occurrence of the infection. Moreover, these substances have a special effect on the bacillus itself, causing it to agglutinate.

In connection with this part of the subject, Metchnikoff showed that the blood of rabbits killed by the bacillus of hog cholera acted as a vaccine when heated between 54° and 58° C.

6. *Diphtheria.* — In diphtheria there is the best example of the production of immunity by means of the chemical products of the bacillus. A toxine of a high degree of virulence is obtained by growing the bacillus in broth distinctly alkaline, and sometimes with a current of air passing over the surface. The virulence of the toxine has already been considered (p. 79).

When gradually increasing doses of this toxine are injected into a refractory animal, such as the horse, each dose produces a local reaction, with some degree of fever and illness, all of which diminish as the treatment is continued. At the end of a varying time the serum of the blood removed from the animal is found to possess highly immunising properties. Injected into an animal, it will prevent any results following the subsequent injection of a fatal dose either of the bacillus or of the toxine; injected with the toxine in certain proportions of each, it completely prevents the development of any symptoms; injected, in certain conditions, after the toxine or the bacillus has been injected, it will also prevent any symptoms or fatal results occurring (Fig. 59). The substances in the blood, therefore, are not only *antimicrobic*, but are *antitoxic*. They, moreover, antagonise the toxine, and can counteract the action of the toxine even if subsequently injected; this allows of their being used for the treatment of the disease. The exact nature of the reaction between the toxine and antitoxine is discussed on p. 179.

The antitoxic properties of the serum of the treated horse

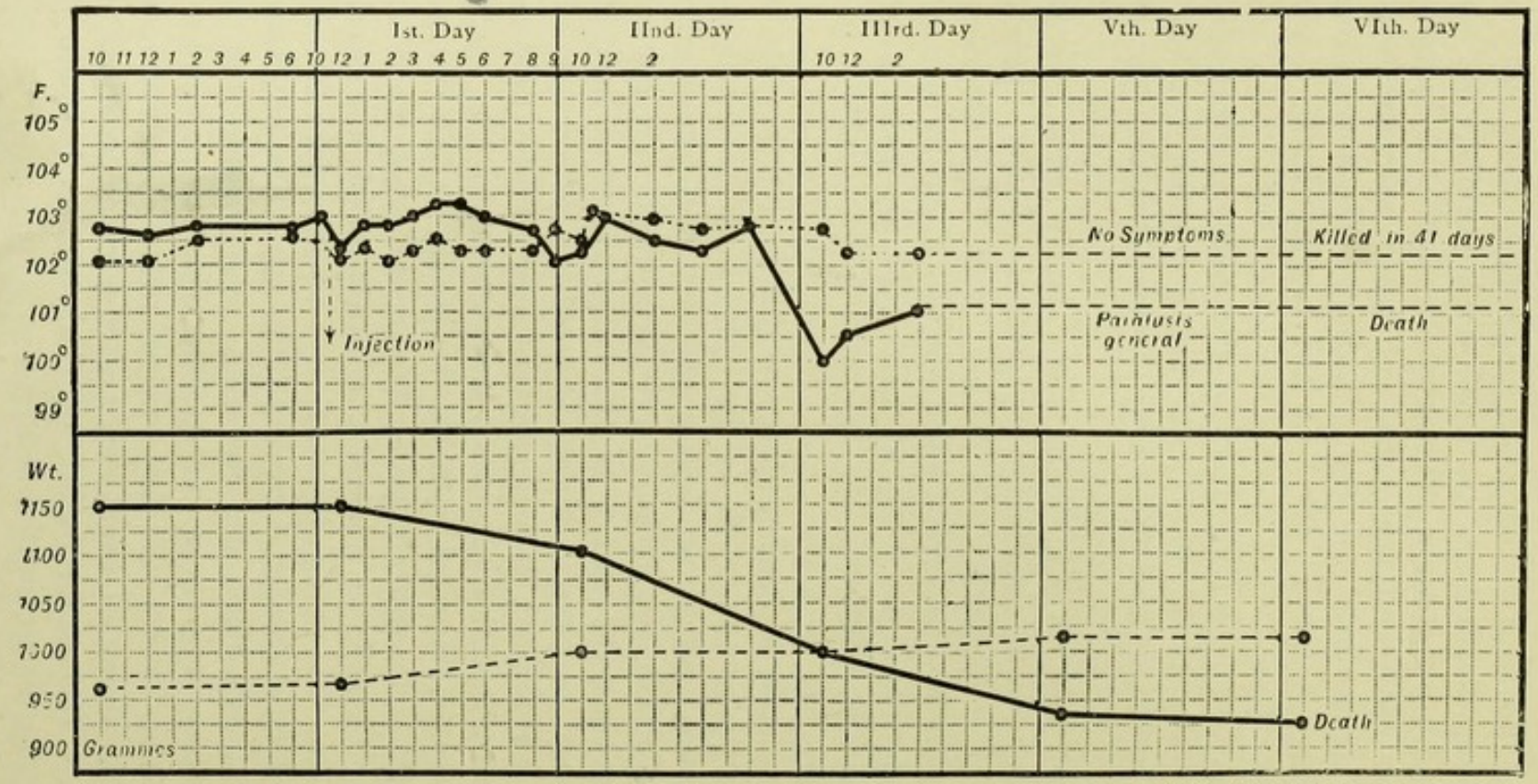


FIG. 59.—Chart showing the counteraction by the diphtheria antitoxin of the effects of the diphtheria toxine in rabbits. The upper chart represents the body temperature ; the thick line showing the curve of a rabbit which received intravenously 0.5 c.c. of broth diphtheria toxine ; the dotted line showing the curve of a rabbit which received 0.5 c.c. toxine mixed with 0.3 c.c. diphtheria antitoxin. The latter animal showed no symptoms ; the former showed a fall of temperature on the third day followed by paralysis and death on the sixth day. The lower chart shows the effect on the body-weight in the two animals.

last many months, and can be kept up by repeated injections of the toxine. Instead of using the toxine in the initial stages, the so-called *serum toxine* may be used, which is obtained by growing the bacillus in a mixture of broth and serum (p. 79), whereby not only the toxine, but also the albumoses, are used for injection. By preparing the horse with this serum toxine, more rapid immunisation is said to be produced (Cartwright Wood).

7. *Tetanus.* — By a method similar to that used in diphtheria, a tetanus antitoxine has been prepared from the horse, which has the same properties as the diphtheria antitoxine. It is antimicrobic and antitoxic, and can be used for the treatment of the disease. The treatment, however, has not yet been so successful as in the case of diphtheria, owing, possibly, to the firm combination which takes place between the tetanus toxine and the nerve cells (p. 185).

8. *Ricin and Abrin, and Snake-Venom.* — It is important to compare these results with the experiments which have been performed with the allied vegetable poisons, abrin and ricin, and with snake-venom. With abrin and ricin immunity has been produced by the repeated injection of very small doses, or, better, by gradually increasing doses or by feeding the animals with the poison. In the animals that are made immune in this way, the poisons do not cause conjunctivitis when applied to the eye, nor do they produce any symptoms or lesions when subcutaneously injected, so that the immunity is complete. A very high degree of immunity may be obtained. It develops slowly, and in the first few days of experiment is not very obvious. The blood-serum of the immunised animals contains a substance which is antagonistic to the action of the poisons. There is both an antiabrin and an antiricin, each specific for its own poison, but not for the other.

These results show that, even with a non-bacterial poison, the tissues of the body are capable of reacting against it; producing substances which antagonise its action.

The same has been found with regard to snake-venom (Calmette, Fraser). Repeated and minute doses of cobra-venom injected into the horse produce, in time, an immunity

against the fatal dose of the poison, which, for the horse, is 15 mgm. of dried cobra-venom. Five mgm. of this poison is fatal to a dog, and about 31 mgm. to a man, mice and rats being still more susceptible to the poison.

It was found that 5 c.c. of the serum of the immunised horse protected against a fatal dose of the venom in a rabbit, and that this serum was also curative, being capable of saving several animals after a fatal dose of the poison had been injected. This curative effect has been proved to occur in actual snake-bites in man, the dose given being from 25 c.c. to 30 c.c. The venom, therefore, not only produces in the body a substance antagonistic to itself, but this substance can produce immunity after the poison has been injected. The antivenene of cobra-venom will not protect against the daboia venom. It is possible, however, that a partial protection is obtained with the cobra antivenene in the case of the poison of most venomous snakes. It is now the practice to prepare the serum by injecting horses with a mixture of cobra and viperine venom.

The Blood and Tissues in Immunity.

The researches of recent years into the changes which occur, more especially in the blood, in immunity, have revealed the fact that the injection of certain substances (poisons, ferments and some proteids) into the body, leads to the formation of substances which are antagonistic to the action of the poison or substance injected. These antagonists are grouped under the heading of *anti-bodies*. They are sometimes referred to as *anti-sera*, inasmuch as they are chiefly found in the serum of the drawn blood. The formation of these substances takes place not only when bacterial poisons and others allied to them are injected, but even when a ferment, such as rennin, is injected, or when proteids foreign to the body or animal cells are used for injection.

These anti-bodies may be grouped as follows:—

Anti-Bodies. — 1. Antitoxines and antiferments; 2. Ag-

glutinines; 3. Coagulines and precipitines; 4. Cytotoxines (hæmolysines, bacteriolysines, spermatoxine, etc.).

1. *Antitoxines and Antiferments.—Antiferments* are produced when certain ferments are injected into the animal body. These antiferments prevent the action of the original ferments. The best known of these is antirennin, which is produced in goats by the repeated injection of rennin. The serum added to a certain quantity to milk prevents its coagulation by means of rennet. An antiemulsine has also been prepared, an antitrypsine and an antifibrin-ferment. The *antitoxines* are substances which completely counteract the effect of the toxines. Examples of these may be instanced in the diphtheria and tetanus antitoxines, in the antitoxine of the bacillus pyocyaneus, and in antivenene, antiabrin and antiricin.

The most extensive researches have been done with the diphtheria and tetanus antitoxines, and with antivenene, and the following remarks apply chiefly to these.

(*a*) *Relation of Antitoxine and Toxine.*—If a toxine and antitoxine be mixed together outside the body before being injected, it is found that no symptoms are produced on injection, if they are present in certain proportions, and this is true in whatever part of the body the injection is made—under the skin, into the peritoneal cavity, or into a vein.

For the purpose of estimating the strength of both, the diphtheria toxine and antitoxine artificial units have been established (Ehrlich). The *toxic unit*, or simple lethal dose, is the amount of toxic broth which is fatal in four days to a guinea-pig weighing 250 grammes. The *antitoxine immunity unit* is the amount of serum which will completely neutralise the effect of 100 simple lethal doses of toxine for a guinea-pig of the weight mentioned; that is, this amount of serum mixed with toxic broth containing 100 lethal doses, injected into the guinea-pig, causes no symptoms. For reasons presently to be stated, Ehrlich found it was preferable to have a standard antitoxic serum, and, in the actual testing, to determine the strength of each sample of manufactured toxic broth against this standard antitoxine.

There is a difference between the physiological action of toxic broth which is just made, and that which has been kept for some time. On keeping, it is found that the broth loses most of its toxic properties: this old toxine Ehrlich calls *toxoid*. It is not quite without physiological action, inasmuch as, subcutaneously injected, it produces a local lesion and wasting of the body. Ehrlich considers that the toxoid is a different body from the toxine which produces the acute symptoms of diphtheria poisoning, and that the toxoid is, at any rate, one, if not the chief, of the active agents producing the antitoxine.

This change in the fresh diphtheria toxine may be illustrated as follows:—

Using only one manufacture of toxic broth for all the experiments, it may be found that, when fresh, one immunity unit of serum would neutralise, say α c.c. of toxic broth containing β toxic units. If the toxic broth be old, one immunity unit will still be neutralised by α c.c. of the broth, but the number of toxic units in this broth will be found to be not β, but $\beta - x$: that is, although the same quantity of antitoxine is required to neutralise both the fresh and the old broth, yet the old broth contains a diminished number of toxic units.

Ehrlich therefore considers that the toxine consists of two groups—the *toxophore* (toxine-bearing) group, and the *haptophore* (binding) group (Fig. 60); that the toxophore group somewhat rapidly degenerates, and leaves eventually only the haptophore group, which would be equal to the toxoid. In the action of the toxine it is the haptophore group which unites with the elements of the cell with which it has affinity: hence the name *haptophore* (ἅπτειν, to bind).

If the amount of antitoxic serum injected with the toxine is not sufficient to neutralise it, the animal suffers from symptoms which are proportional to the amount of toxine not neutralised, and which may end in death; and this result is observed, even though an additional amount of antitoxine be immediately injected subcutaneously. If, in rabbits, the toxine be injected intravenously, and immedi-

ately afterwards a certain amount of antitoxine is also injected intravenously, the animal may be saved; but if an interval of seven or eight minutes is allowed to elapse between the injections, the animal dies unless a very large dose of antitoxine is given. After a longer period, the injection of antitoxine does not counteract the poison.

These results have been confirmed by many observers, and show that, for a time, the toxine is free in the blood, and capable of being neutralised by the antitoxine; that after a short period it becomes combined with the elements of the body, and is thus with difficulty neutralised. After a still longer period, it has produced its effect on the body, and no neutralisation by antitoxine is possible.

These facts demonstrate the rationale of the treatment by antitoxine of diphtheria as it occurs in man. Large doses have to be given, and it is only because, in the natural disease, toxines are formed slowly, that it is possible in the early stages of the disease to inject sufficient antitoxine to counteract the effects of the disease. When sufficient toxine has combined with the tissues to produce a fatal result, this cannot be prevented by the injection of even large doses of antitoxine, although this will prevent the action of any more toxine, or its formation by the bacillus.

The question whether this neutralisation is a purely chemical one, or whether it requires the medium of the cells of the body, has been much discussed.

The neutralisation of the toxine by antitoxine does not need the medium of the body in order to take place.

Calmette, in his experiments with cobra poison, showed that although this was not apparently affected by an exposure to 68° C. for ten minutes, the antitoxine was completely destroyed by the same treatment. In this way the effect of antitoxine could be removed in a mixture with toxine, in the case of there being no chemical neutralisation of the two substances. Calmette found that mixtures of cobra poison and antitoxine, which produced no symptoms when injected into a rabbit, were fatal if they were previously heated for ten minutes at the temperature mentioned. It

will be noted, however, that Calmette allowed the antitoxine to act on the toxine for only ten minutes before subjecting the mixture to heat. The time was, perhaps, too short for a complete chemical union between two bodies of such complex molecular construction as the toxine and antitoxine.

The poison of the bacillus pyocyaneus is not destroyed by boiling, but its antitoxine is. A heated mixture of the two substances causes death when injected; a similar mixture unheated producing no symptoms (Wassermann).

Similar experiments have been done with the antitoxine of diphtheria, and with the same results. The separation of the toxine and antitoxine was made by heat, the toxine being destroyed at a temperature of 60° C., whereas the antitoxine is not destroyed by heating to 70° C., although it loses its power if heated to higher temperatures.

On the other hand, Kanthack showed that cobra antitoxine counteracted the influence of cobra poison in preventing the coagulation of *shed* blood, and the hæmolytic action of cobra poison upon blood is also prevented by antitoxine *in vitro* (Stephens and Meyers). Ehrlich also showed that antiricin prevented the precipitation of the corpuscles in defibrinated blood, one of the characteristic actions of ricin. As C. J. Martin and Cherry have pointed out, in these experiments in which neutralisation of the toxine by antitoxine outside the body has not occurred, the element of time has not been sufficiently taken into account. These observers utilised the method depending on the different behaviour of the toxine and antitoxine in passing through a porcelain filter, coated with a film of gelatine. The toxine passes through, while the antitoxine does not. In a mixture, therefore, they could be separated by means of this filter, provided they had not chemically combined.

In the case of diphtheria toxine and antitoxine, when the mixture was kept for two hours at 30° C. and then filtered, it was found that the filtrate had no toxic action, showing that the toxine had remained behind; whereas when not so kept, the filtrate was toxic. Experimenting with snake-venom and

antivenene, it was found that, if sufficient time were allowed for the toxine and antitoxine to react upon each other, the same results were obtained as in the case of the diphtheria products.

These results conclusively show that the neutralisation of the toxine by antitoxine, although slow, is essentially a chemical process, and explains some of the facts previously mentioned with regard to the interaction of these two bodies. Thus it was seen that the small amount of antitoxine requisite to neutralise a large amount of toxine when these were mixed before injection into the body, was quite inadequate to prevent death if the toxine and antitoxine were injected subcutaneously in different spots. In this latter case, the toxine is absorbed, combines with the tissues on which it acts, and produces its poisonous effects before it is neutralised by the antitoxine. Although some of the toxine is neutralised, yet sufficient is left to produce a fatal result.

The amount of antitoxine requisite to neutralise the toxine, when these are injected subcutaneously at different spots, is from twenty to a hundred times larger than the amount of antitoxine required when the two substances are mixed together before injection.

(*b*) *Theory of Antitoxine Formation and Action.*—Ehrlich supposes that the protoplasm of the cell has different elements possessing affinity, not only for toxines of various kinds, but also for the elements of food. These parts of the cell he refers to as *side-chains*, and represents diagrammatically as projections from the cell of varying shapes, as in the accompanying figures (Figs. 60 and 61). The toxine unites itself to a side-chain by means of its haptophore group, and then, mainly by its toxophore group, affects the vitality of the cell. The toxine may kill the cell or produce alterations in the structure, but it also leads, under certain conditions, to the formation of numerous other side-chains, which are antagonistic to it. These side-chains express the reaction of the cell to the action of the toxine, and eventually become liberated in the blood as antitoxine. In Ehrlich's words—"Antitoxines represent nothing more than side-chains reproduced in excess during regeneration, and there-

fore pushed off from the protoplasm, and so coming to exist in a free state."

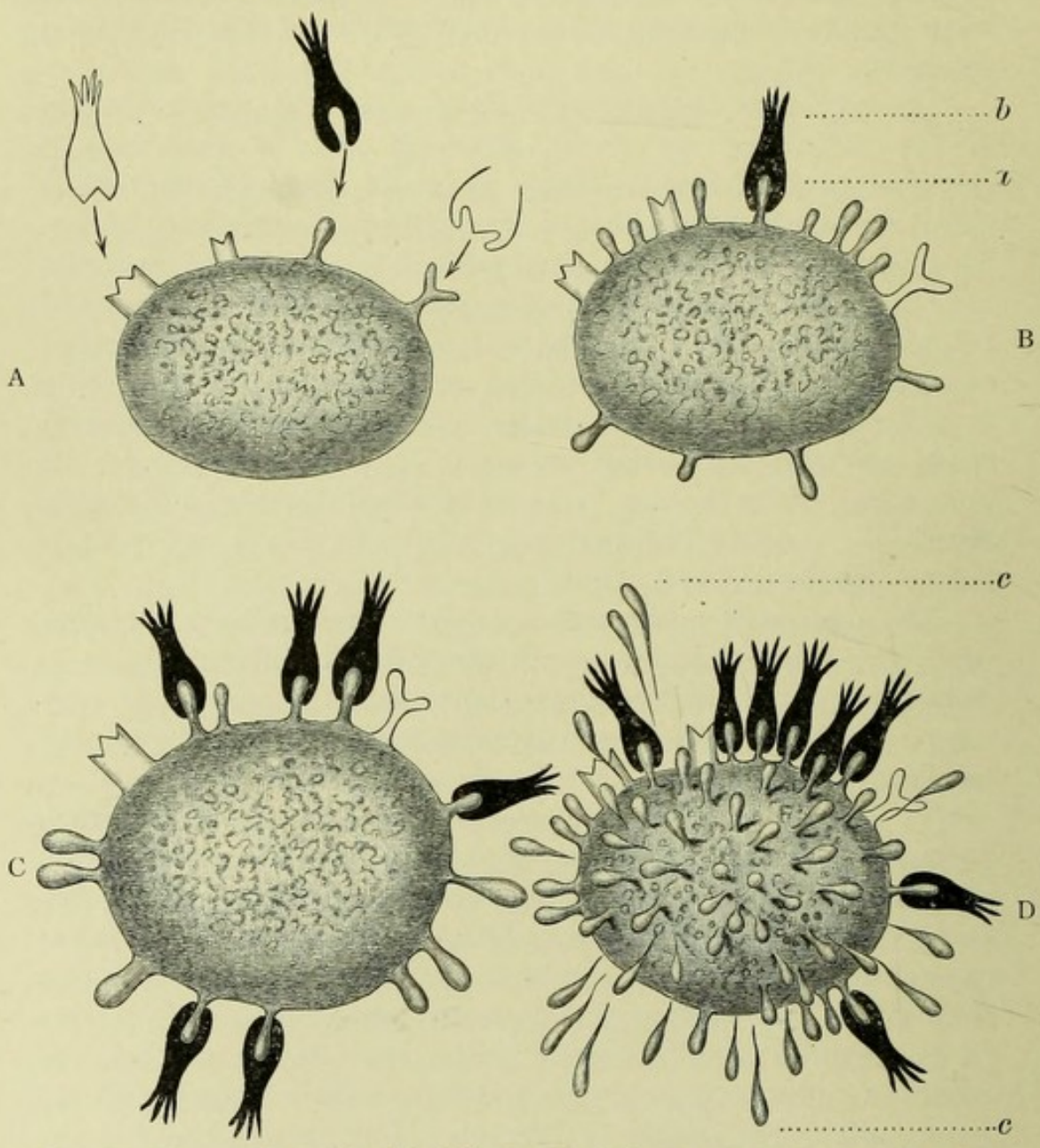


FIG. 60.—Diagram illustrating Ehrlich's theory of side-chains of cells combining with toxine molecules, and the formation of anti-bodies (Ehrlich).

A is the diagram of a cell with side-chains projecting from its surface of various shapes, each adapted to combine with a particular toxine molecule or food element.

B is an animal cell, in which one of the side-chains has combined with a toxine molecule composed of haptophore (*a*) and toxophore (*b*) parts. The side-chain is commonly called a "receptor."

C represents the diagram of a cell, with the receptors of which numerous toxine molecules have combined.

D is the diagram of a cell in which, following the combination of the toxine molecules with the receptors, there is the formation of new side-chains (*c*), which, set free in the blood, constitute the antitoxine.

As regards the combination of the toxine with the protoplasm of the cell, there is much evidence of this in the selective affinity of toxines for certain tissues. The action of strychnine, for example, in producing convulsions, is due to the direct effect upon, and, no doubt, combination of the alkaloid with the motor cells of the spinal cord. In the guinea-pig and, probably, in man, there is evidence that the toxine of tetanus is almost solely contained in the central nervous system combined with the *tetanophile atom groups*, whereas, in rabbits, it is contained in the other organs as well.

In the case of toxines, such as those of anthrax, typhoid, cholera, in which there is not any evidence of any special action on tissues, it must be supposed that the general effect is due to a more or less universal combination of the toxine with the elements of the body.

The formation of antitoxine is not so readily discussed. The antitoxine is, probably, not a new formation, or, at any rate, not a body widely separated, chemically, from the elements of the body. It is, like the toxine, closely associated with the proteids, and may, indeed, be itself a proteid body.

There is evidence that, in some cases, the antitoxine exists normally in the blood. Thus, the serum of some normal horses contains a small quantity of an antitoxine which counteracts the diphtheria poison, and proteid substances have been obtained from different parts of the body, notably the spleen, which, to some extent, counteracted the action of anthrax (Hankin). That the formation of antitoxine "is not a purposeful, intelligently directed process," is shown by the remarkable results observed in the reaction of the blood against the injection of certain non-poisonous substances.

Thus, rennin (the rennet ferment), when injected into the horse, leads to the formation of a large quantity of antirennin, the action of which, outside the body, is to stop the activity of the ferment, and this formation takes place in proportion to the amount of ferment injected. The blood serum of the normal horse contains a small quantity of this antirennin (Morgenroth).

Moreover, Bordet has shown that in animals injected with

milk, the blood serum acquires the property of coagulating the milk of the animal from which the milk was obtained. Thus, if goats' milk were used, goats' milk alone would be coagulated, and not human or cows' milk. A similar reaction in the blood is obtained by injecting the serum of different animals or the white of egg. A reaction takes place, leading to the formation of substances (coagulines), which precipitate only the form of albumen which has been injected.

These results are extremely important in explaining the formation of antitoxine, which must be considered as a substance not new to the body, but as little removed from the proteid substances of the body, or, at any rate, as closely connected with the processes of nutrition in the cell protoplasm.

2. *Agglutinines and Bacteriolysines (Antimicrobic Substances).*—The properties of an antimicrobic serum are different from those of an antitoxic serum. An antimicrobic serum protects an animal against the invasion of the particular micro-organism used in its preparation, but will not protect against the action of the toxine of the micro-organism, or, at any rate, only to a very slight extent, so that it would appear that, in some instances, the antitoxic property and the antimicrobic property are produced by different actions of the micro-organism and its toxine; whereas, in some instances, as in those just considered, the toxine of the micro-organism produces, by its reaction, a serum which is both antitoxic and antimicrobic.

The subject has been, as yet, only touched upon in regard to this investigation, and inasmuch as different animals react differently to the same micro-organism, it may be found that, in these cases, it is partly a question of one animal forming an antimicrobic serum, and another forming an antitoxic serum.

The chief antimicrobic sera which have been prepared, are the antityphoid, anticholera, antiplague, antipneumococcic, and antistreptococcic (Marmorek's serum). A true antitoxic cholera serum has, however, been prepared, as well as, it is said, for plague and for tuberculosis.

The preparation of "antimicrobic" serum is illustrated by Pfeiffer's experiments with cholera and typhoid.

Pfeiffer's Specific Serum Reaction for Cholera and Typhoid Fever.—The diluted blood serum of guinea-pigs highly immunised against the cholera vibrio, when inserted with a virulent vibrio into the peritoneal cavity of another guinea-pig, kills the vibrio, causing the vibrios to clump together (agglutination), and finally disintegrating them (bacteriolysis).

Guinea-pigs were made highly immune by treating them at first with a subcutaneous injection of a culture of the vibrio, killed with chloroform. After ten to fourteen days, the animal received very small and increasing doses into the peritoneal cavity of an agar culture of a virulent vibrio, twenty hours old. The symptoms were allowed to abate before a fresh injection was made. After this treatment, the serum was obtained from the blood, and preserved by adding 0.5 per cent. phenol. If 10 to 30 mgm. of this serum, mixed with one loopful of an agar culture of the vibrio in 1 c.c. of broth, were placed in the peritoneal cavity of a guinea-pig weighing 200 grammes, the vibrio would become immotile in twenty minutes, and finally disintegrate.

This is a specific reaction occurring between the cholera vibrio and anticholera serum, and has been found to be given by all varieties of cholera vibrio, obtained from many sources. A similar reaction occurs with the typhoid bacillus and anti-typhoid serum prepared in the same way.

Gruber and Durham utilised a simpler method of immunising guinea-pigs, and found that the reaction could be obtained outside the body in tubes, and could be watched occurring under the microscope. This is known as the serum reaction of cholera and typhoid fever.

Thus, if 2 to 4 mgm. of an agar culture are mixed in 0.5 c.c. of broth, and 10 mgm. of immunised serum dissolved in 0.5 c.c. of broth, and the two liquids mixed and placed in the incubater at 37° C., it is observed that the micro-organisms first begin to clump together; they then cease movement, and, in some instances, undergo disintegration. If the reaction is done in a tube, the micro-organisms sink to the bottom. The clumping and cessation of movement occupy ten to fifteen minutes, and the micro-

organisms sink in about one hour's sedimentation, although this may take longer.

Pfeiffer found that the serum of convalescent cholera patients contained the same substances as the serum of the immunised guinea-pigs, and in typhoid fever the serum possesses antimicrobic properties, both during the occurrence of the disease and for some time afterwards. The reaction in typhoid fever is sometimes referred to as Widal's reaction. It is used for the purposes of diagnosis of the disease, and is specific.

Typhoid Serum Reaction.—This may be performed in two ways, either under the microscope or in small tubes. The serum is obtained from the patient by receiving the blood into capillary pipettes, which are then sealed at each end. After the blood is coagulated, the ends of the tube are broken off, and the small column of clot and serum blown into a sterilised tube. It is then diluted, and mixed with a twenty-four-hour-old broth culture of the typhoid bacillus in varying dilutions—1 in 30, 1 in 50, and 1 in 100 or less. If a portion of the liquid is placed under the microscope in a hanging drop, within thirty minutes to an hour, or less, all the bacilli are clumped together (agglutination), and are motionless. This is a positive and complete reaction. A partial reaction, however, is frequently obtained, where there is more or less complete clumping, and a partial immotility. The reaction is specific, and occurs only between the typhoid serum and the typhoid bacillus.

Durham has shown that the reactions of other allied micro-organisms, the bacillus coli communis and Gärtner's bacillus, overlap the reaction of the typhoid bacillus. Thus it may be found that the serum from an individual case will give the reaction with all dilutions up to 1 in 200 with the typhoid bacillus; a reaction up to dilutions of 1 in 100 with Gärtner's bacillus; and a reaction with the bacillus coli communis in solutions not so dilute. These results express the close relation which exists between these three micro-organisms, but they do not vitiate the diagnostic value of the typhoid serum reaction as applied clinically; and as

an aid to the diagnosis of typhoid fever, it is, as a rule, sufficient to observe the effects in dilutions of 1 in 30 or 1 in 50, and 1 in 100.

Agglutination is not observed solely in the instances which have been mentioned: it has been observed in Malta fever and in glanders as well.

The reactions which have been discussed are not so simple as it would appear at first. Pfeiffer thought that the antimicrobic substance in the serum became bactericidal only

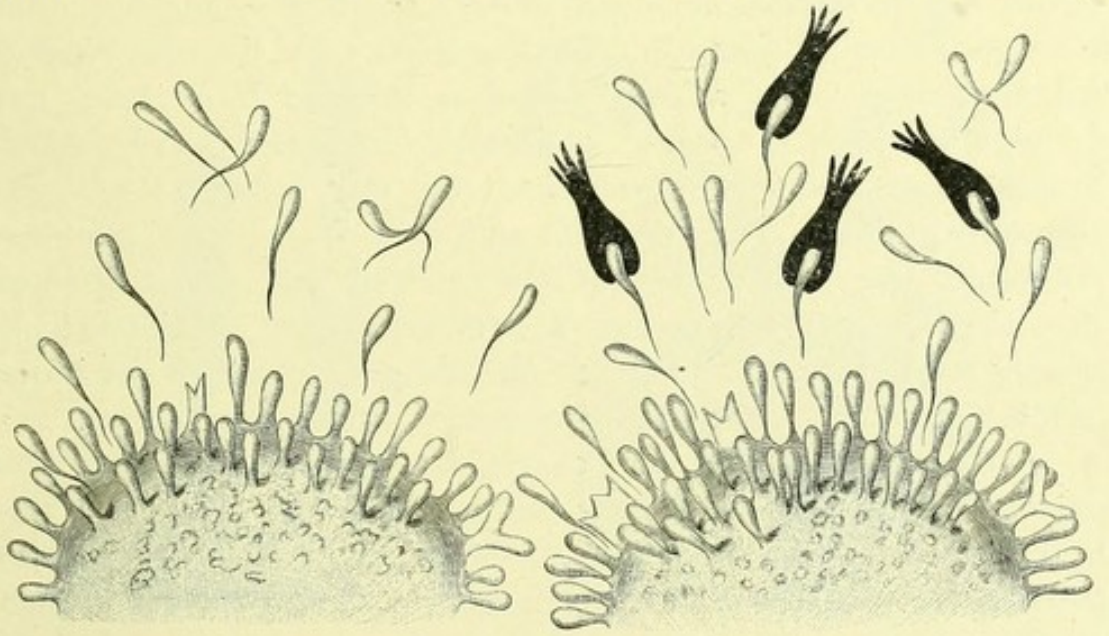


FIG. 61.—Diagram showing antitoxine formation (Ehrlich).

E represents a portion of the cell with numerous side-chains, some of which are being set free in the blood. This represents the continuous formation of antitoxine when no more toxine is present to be combined with the cell.

F is a diagram showing what occurs when toxine is injected into an animal in whose blood there is free antitoxine. The toxine molecules never reach the cell, but combine in the blood stream with the free antitoxine.

in the presence of living protoplasm. But it has been shown that, not only the peritoneal fluid, but normal serum, can take the place of the living cell; that is, that the specific serum reaction for cholera is observed outside the body, when a culture of the vibrio, anticholera serum and fresh serum from a normal guinea-pig, are mixed together.

For this reaction to occur, there is necessary the body in the anticholera serum, and another body which is present in the normal serum. The former Ehrlich calls the *connecting link* or *immune body;* the latter he calls the *complement* or

addiment, and his notion of the process is illustrated in the figure (Fig. 62).

3. *Coagulines and Precipitines.*—These are substances which are formed in the animal body when solutions or mixtures of proteids are injected. Thus the injection of milk leads to the presence in the serum of a substance which produces coagulation in the kind of milk used, and the reaction for the different kinds of milk (human, goat's and cow's) is specific. There are also specific coagulines and precipitines for serum, when the serum of one animal is injected into another. This does not hold good for all animals. Thus guinea-pigs do not yield a specific serum when rabbits' blood is injected into them, nor do pigeons yield a specific coaguline for fowls' blood. Anti-bodies have also been produced by the injection of egg-albumin, globulin from sheep's and ox's blood and peptone. Although the subject is not yet worked out, yet it appears that the specific anti-bodies are allied when obtained from closely related races. Thus the specific precipitine of the blood of the higher apes reacts to some extent with human serum.

4. *Cytotoxines.*—Cytotoxines are anti-bodies which are produced by the injection into the animal body of cells. The best known of these are the hæmolysines, which are specific substances dissolving the hæmoglobin from the blood corpuscles; but to the same group belongs the bacteriolysines, which dissolve bacteria and are bactericidal substances, and certain cytotoxines produced by the injection of spermatozoa (spermatoxine), of ciliated epithelium (trichotoxine), of leucocytes (leucotoxine or leucocidin), of kidney substance (nephrotoxine), of liver substance (hepatotoxine); and similar substances produced by the injection of pancreas and of the suprarenal bodies.

Injection of spermatozoa into the peritoneal cavity confers on the serum of the animal used the property of causing cessation of movement in, and ultimately destroying, the variety of spermatozoa used, whether those of the bull, the rabbit, or of man. The property depends on two substances, as in the case of hæmolysines, namely, of an immune body (*fixateur*), and of a complement or alexine (*cytase*). Rabbits

or ducks treated by injections of dogs' liver yield a serum which, injected into healthy dogs, kills them with the appearances and symptoms of acute yellow atrophy of the liver. A similar effect has been observed in the kidney tubules from the injection of nephrotoxine.

Hæmolysines are discussed in Chapter XII.

Summary.—The facts which have been brought forward in

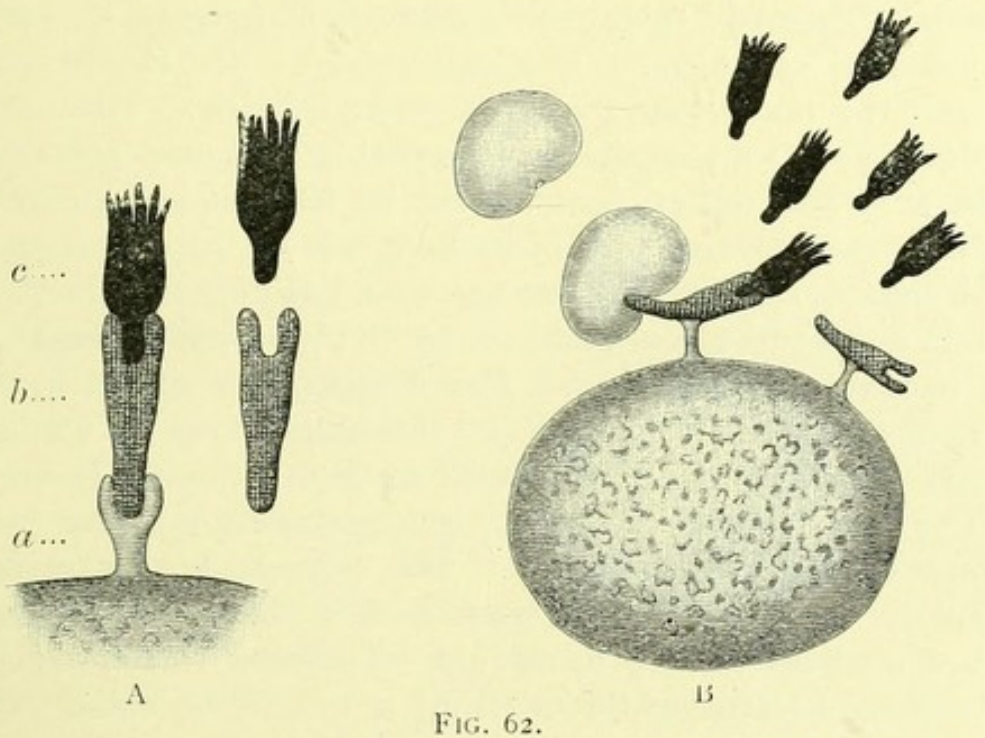


FIG. 62.

A represents the periphery of an animal cell with a single receptor, which has combined with a complement coloured black by means of a connecting link or immune body. Without this immune body the complement cannot become attached to the cell.

B represents an animal cell in which the same has occurred, that is the receptor is joined to the immune body, which is connected with a "ferment toxic group" and a complement.

the preceding chapters to some extent aid in the explanation of both natural and acquired immunity. Two phenomena stand out as the result of the investigation of these subjects; the occurrence of phagocytosis and the presence in the blood and tissues in artificially produced immunity of substances which are antagonistic to the invading micro-organisms. Pathogenic bacteria, when they enter the immune animal, are not passed out by the mucous membranes or excretory organs, but are destroyed in the body, and it is the mechanism of their

destruction — an essentially vital act—which is the main problem in the question of immunity. The phagocytes are divided by Metchnikoff into macrophages and microphages (p. 32). Each of these contains a specific cytase or ferment, macrocytase and microcytase, the former of which acts specially on elements derived from animals, the latter chiefly on bacteria. The macrophages are those which take up red corpuscles and spermatozoa, but they may also take up the bacteria of leprosy, tuberculosis and actinomycosis, as well as the malarial organism. The microphages are almost solely occupied in taking up the pathogenic bacteria. The cytases are destroyed at a temperature of 55° to 56° C., and correspond to the substance called complement by Ehrlich, and alexine by Buchner. According to Metchnikoff, it is by the disintegration or plasmolysis of the phagocytes that the cytases which they contain are set free, and these confer on the serum its hæmolytic and bactericidal properties. The microphages digest bacteria by means of the microcytase, and this action may go on in the plasma when the microphages set free their contained ferment.

The properties of the serum of a naturally immune animal do not explain its immunity. The pigeon, for example, is refractory to the influenza bacillus, but its blood is a good culture medium for the bacterium. The dog is refractory to the anthrax bacillus, while its serum is not bactericidal. Other examples might be given showing that the effect of the serum of a naturally immune animal does not explain its immunity. This immunity is due, according to Metchnikoff, to the action of the phagocytes, by themselves for the most part in natural immunity, and with the aid of immune bodies or anti-bodies (fixateurs) in artificial immunity. The origin of the immune bodies is still a matter of discussion. Metchnikoff, on the one hand, believes that their main source of origin is the phagocytes themselves; while Ehrlich believes that the cell most affected by the toxine produces the antitoxine.

CHAPTER VII

ON THE DEGENERATION AND REGENERATION OF CELLS AND TISSUES

THE degeneration of cells and tissues is a frequent occurrence in disease, both acute and chronic. It is due to both local and general causes. Of the local causes may be mentioned—(1) The local action of a poison, such as occurs in an infective focus (inflammatory area); (2) A diminution in the supply of nutriment; and (3) The influence of disease of the nervous system.

The most potent cause of cell and tissue degeneration is the circulation of a poison in the body, and such poisons may produce a widespread degeneration. Tissue degeneration may also follow what may be called nutritional changes, more particularly the diminished supply of food through defects of the digestive organs or of the local blood supply. The nutrition of the cell is a very delicate process, and one which is readily disorganised by the character of the food supplied to it; and, in the case of solid and secretory organs, by the varying influence of the nervous system on its activity. As regards the food supplied to the cell, two factors must be borne in mind: the character of the food brought to the cell may be unsuitable, or the blood vessels supplying the cell may be so altered by disease as to bring insufficient nourishment, even of a suitable character.

The influence of the nervous system on the vitality of the cell is difficult to gauge, but may be evidenced in two different ways. Thus the nerve supply of an excretory organ being disorganised or abolished, the cells of the organ are not brought into activity as they normally are by reflex influence. The cell therefore becomes disorganised, and tends

to degenerate. Again, the nerve supply to a voluntary muscle may be diseased, and so lead to inactivity of the muscle fibre, thus leading to degeneration.

The cell is capable of certain changes in health, such as the absorption of nutrient material, the assimilation of such material, the discharge of products of activity of the cell, and the reproductive changes which are evidenced in division of the cell. In disease similar changes occur but are modified. The assimilation of nutrient material diminishes with degeneration of the cell, and in the early stages the products of cell activity show an exaggeration of the normal secretion. As degeneration proceeds, however, secretion diminishes and finally ceases. The structure of the cell is altered, and finally is completely lost.

The *normal cell* (Fig. 63) consists of a cytoplasm which shows a reticulum of plastin; the nucleus also contains a reticulum, which undergoes various changes in the degeneration of the cell. The composition of a normal cell is as follows: it contains proteid substances, such as nucleo-albumin, of which the plastin consists, and globulins. The amount of albumin present is small, and albumoses, which are the products of digestion in the alimentary tract, are absent from the normal cell. The vacuoles of the cell contain a watery fluid which changes in reaction from alkaline to acid during the activity of the cell. The nucleus consists of chromatin (plastin) and achromatin, while the nuclear matrix is rich in proteids. From the cells of healthy organs the proteid substances above mentioned can be extracted. The most characteristic proteid of the cell must be considered as the nucleo-albumin, inasmuch as this does not exist in solution in any fluid of the body.

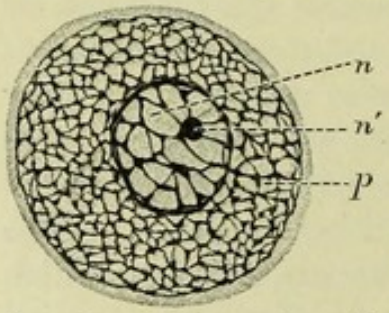


FIG. 63.—Diagram of a cell, the protoplasm of which is composed of spongioplasm and hyaloplasm.

p, Protoplasm; *n*, nucleus; *n'*, nucleolus. (Quain's Anatomy.)

The *secretion of cells* and the substances discharged from them vary considerably according to the specialisation of the cell, but the substances discharged are not the same as those forming the nutriment of the cell. Ferments are discharged

from cells—chiefly of the glands concerned with digestion —and are manufactured by the cell. Thus there is the ptyalin of the saliva, the pepsin of the gastric juice, and the trypsin of the pancreatic juice. This secretion of ferments by the cell is, however, only an emphasised property of all cells. It is probable that the cell digests its nutriment by means of ferments, and it is true that an amylolytic ferment can be extracted from most tissues, and a proteolytic from many.

The proteid substances which are brought as nutriment to the cell are probably in health always of the same kind; from whatever source they are derived, animal or vegetable, they are digested in the alimentary tract, and are transformed into the proteids of the body by the mucous membrane of the intestine. What is called a proteid is, however, neither chemically nor physiologically a single substance. Albumins and globulins are no doubt of infinite variety, although their general chemical reactions and their percentage composition may be the same. The cells of the body are adapted to receive only one or other form of proteid substance, and it has been shown that some forms injected into the body do not serve as nutriment to the cell, but produce substances foreign to the normal metabolism of the body (p. 190). In some instances proteid substances different from those already mentioned as constituting part of the cell are formed by the cell, and sometimes secreted from it. Thus *gelatin* is obtained by treating with boiling water a substance called collagen existing in the white fibres of connective tissue, in bone and cartilage. Gelatin is soluble in hot, and insoluble in cold, water, and contains no sulphur, unlike ordinary proteids. It is digestible by gastric juice, forming substances like albumoses and peptone. The proteid substance in cartilage is called *chondrogen;* it is a mixture of collagen and mucinoid substance, and by boiling yields chondrin which contains gelatin. *Mucin* is a glucoside compound of a proteid with animal gum found in the secretion of mucous membranes, in synovia and saliva, and in bile. It is a viscid, slimy tenacious substance, soluble in dilute alkali, and precipitated from solution by acetic acid, the precipitate being insoluble

in excess of the acid. *Colloid substance* occurs normally in the thyroid gland, and resembles mucin, except that acetic acid does not precipitate it. It is found also in tumours of the thyroid gland and in ovarian cysts. Other transformed proteids resembling mucin are called *spermatin*, from semen; and *elastin*, from elastic tissue.

Speaking generally, it may be said that the nature of the activity of the diseased cell does not alter in disease as regards the substances which it forms. Thus the formation of mucin and of colloid substances is frequently observed. This generalisation, however, is not correct as far as present knowledge goes, inasmuch as one substance is formed in disease which is not known to be formed by the normal cell. This is *lardacein*, which is formed in albuminoid degeneration. It is a substance coloured mahogany brown by iodine, and so reacts like glycogen, but it is nitrogenous, and has the percentage composition of a proteid. It is insoluble in water, alcohol and ether, dilute acids and alkalies. Strong alkalies dissolve it, and so after a long time does the gastric juice.

The following forms of degeneration of cells and tissues will be considered:—1. Cloudy Swelling; 2. Fatty Degeneration; 3. Albuminoid Degeneration, Zenker's Degeneration; 4. Mucinoid Degeneration; 5. Colloid Degeneration; 6. Dropsical Degeneration; 7. Atrophy; 8. Necrosis; 9. Fibrosis.

1. *Cloudy Swelling* (Fig. 64).—This is a change seen in the heart muscle and the cells of the kidneys and liver. The muscle fibres or the cells become enlarged, do not stain readily with dyes, and show in the protoplasm numerous small granules which are stained brown, but not black, by osmic acid, and are in the fresh condition of the cell soluble in acetic acid and insoluble in alcohol and ether. In addition to these changes the muscle fibre of the heart shows a longitudinal fibrillation, which is most marked after treating with osmic acid. Cloudy swelling is observed in infective diseases, such as rheumatic fever, typhoid fever, pneumonia, scarlet fever and diphtheria. It has been ascribed to the prolonged high temperature which exists in some of these cases. Without denying that the prolonged high

temperature of the body may inflict a damage on the cells of organs, and so lead to degeneration, it may be said that cloudy swelling occurs in cases in which a high temperature does not exist for any length of time, as, for example, in cases of diphtheria, where the temperature may be low or not raised for long at all above the normal, and yet toxæmia persists and cloudy swelling is found after death. Cloudy swelling is closely related

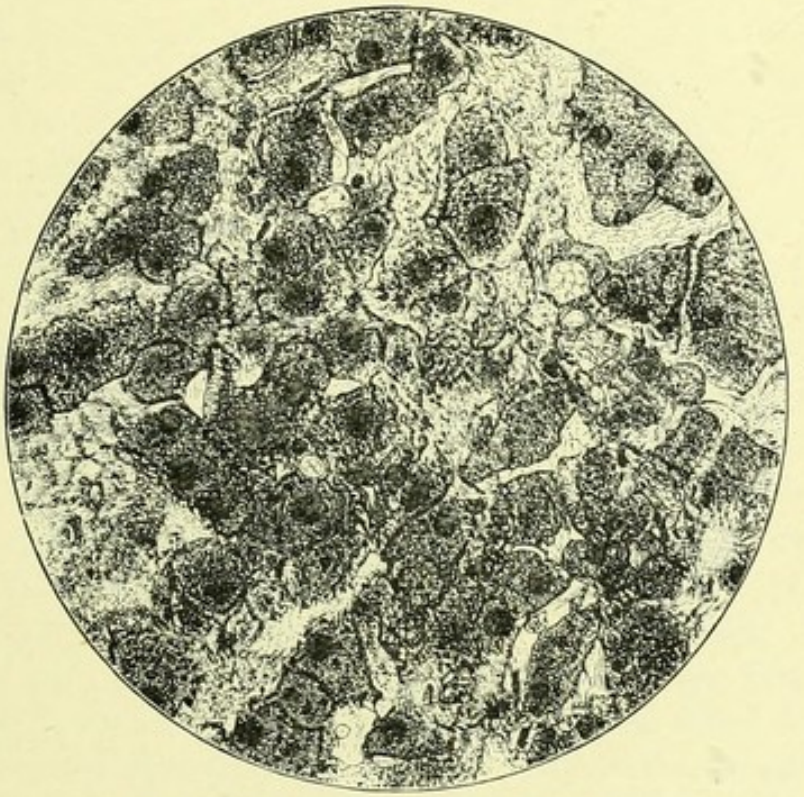


FIG. 64.—Cloudy swelling of the liver.

The liver cells are seen enlarged and studded throughout with fine granules of a uniform size: the nuclei are distinct. These granules are not fat, as they are not soluble in ether. They dissolve, however, or become transparent in acetic acid.

to fatty degeneration, and in the same cell are to be seen the granules which are characteristic of cloudy swelling, and others, soluble in ether and stained black with osmic acid, which are fat granules. Both cloudy swelling and this form of fatty degeneration are toxic in origin, being due to the direct effect of a poison on the cell.

2. *Fatty Degeneration.*—The fatty changes which occur in the body are divided into two classes. In *fatty infiltration* or

lipomatosis (obesity, adiposis), there is an increase in the normal fat in the localities in which it exists, both beneath the skin, in the abdomen and round the heart (Fig. 65). This change is pathologically related to fatty infiltration of the liver, which normally contains some fat. This is increased in certain conditions—for example, in animals that are suckling and in fishes after spawning.

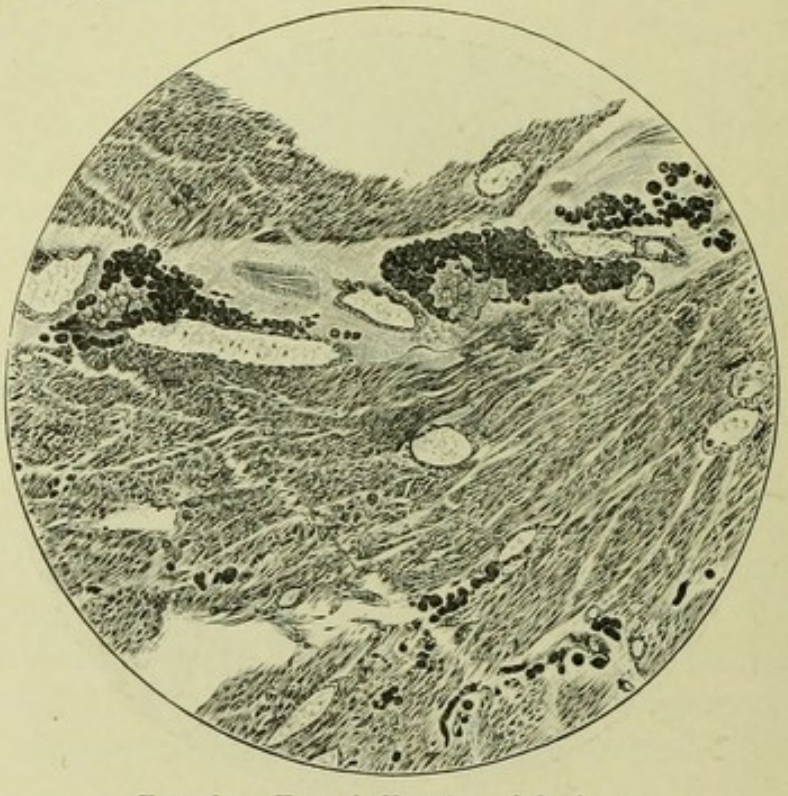


FIG. 65.—Fatty infiltration of the heart.

A section of the cardiac muscle under a low power, stained with osmic acid.
The muscle fibres are seen cut, mainly longitudinally, showing here and there blood-vessels. The chief characters of the specimen are the masses of fat cells, which are stained black by osmic acid. In the upper part of the figure these cells are in large groups in a strand of connective tissue.
In the lower part of the figure the fat cells are seen penetrating the bundles of fibres.

Fatty degeneration is the change to be discussed here. It differs from fatty infiltration pathologically in the fact that the globules of fat are formed by the protoplasm of the cell, and not brought to it as nutriment. It is the most common of all the degenerations occurring in the cells of the body. All the cells of the body utilise fat in their metabolism. When fat accumulates in the cell it is due either to the fact that the fat brought to it is not utilised after absorption, or that the fat

manufactured by the cell is not discharged. From this point of view fatty degeneration may in its pathological processes come into line with fatty infiltration, in which the main feature is that the fat brought to the cell is stored in it without being used for the needs of the body.

The changes observed in the cells in fatty degeneration are characteristic. In the *heart muscle* (Fig. 66) minute globules are seen which are stained black by osmic acid, and which run longitudinally in the fibre, commonly in lines. The faint transverse striation of the fibre is lost as the granules increase in number. The nucleus degenerates and disappears, and in the advanced stage no structure of the fibre is observed, but only a collection of fat granules. In the cells of the *liver* (Fig. 67) a similar change occurs, the globules of fat being, however, of varying size, but their accumulation leads, as in the muscle fibre, to the eventual destruction of the cell. In the *kidney* (Fig. 68) the epithelium of the convoluted tubes is mainly affected, and here similar changes are seen to those occurring in the liver cell. The cells of the glands of the body and of the nervous system undergo the same changes, which need not be further described.

The fat of the body consists of tri-palmitin, tri-stearin and tri-olein, and shows the same composition whether obtained from normal subcutaneous fat, from the fat of lipomatosis or fatty infiltration, or from the fat in fatty degeneration. The organism manufactures fat from proteid substances and by the agency of cells. Dead proteids cannot of themselves be transformed into fat, although the contrary has been stated to be the case. The transformation under certain conditions of dead bodies into adipocere, which is a kind of fat, is at first sight an instance of the transformation of proteids into fat by a chemical process. It is, however, probable that the transformation occurs by means of living organisms present in water in which the body lies, and not by any cell-transformation of the proteids into fat. Again, portions of recently removed organs implanted in the abdomen of a living animal undergo fatty degeneration, but this fatty degeneration does not affect the cells of the implanted organ, but is seen in the leucocytes which invade the organ in great numbers.

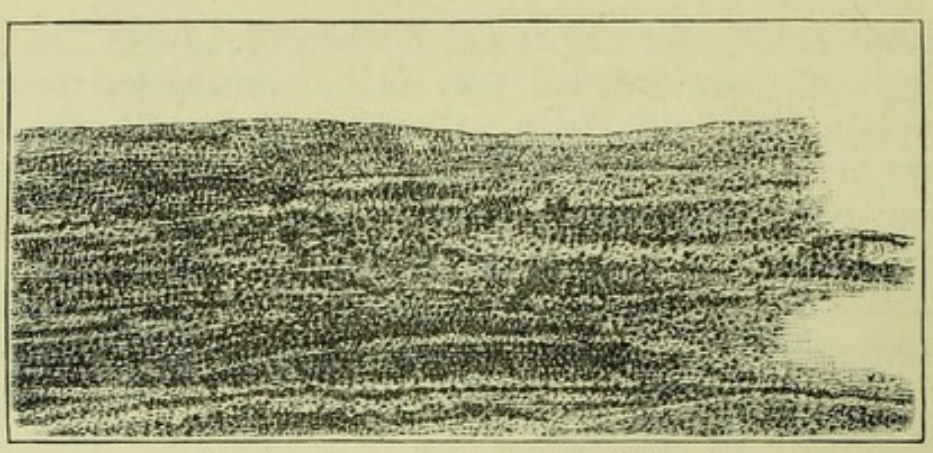


FIG. 66.—Fatty degeneration of the heart.

The muscle fibres are stained by osmic acid. The fibres show longitudinal striation, and occupying most of the fibres are globules stained black by osmic acid. These are particles of fat. The nuclei are not shown, as the specimen was not counter-stained.

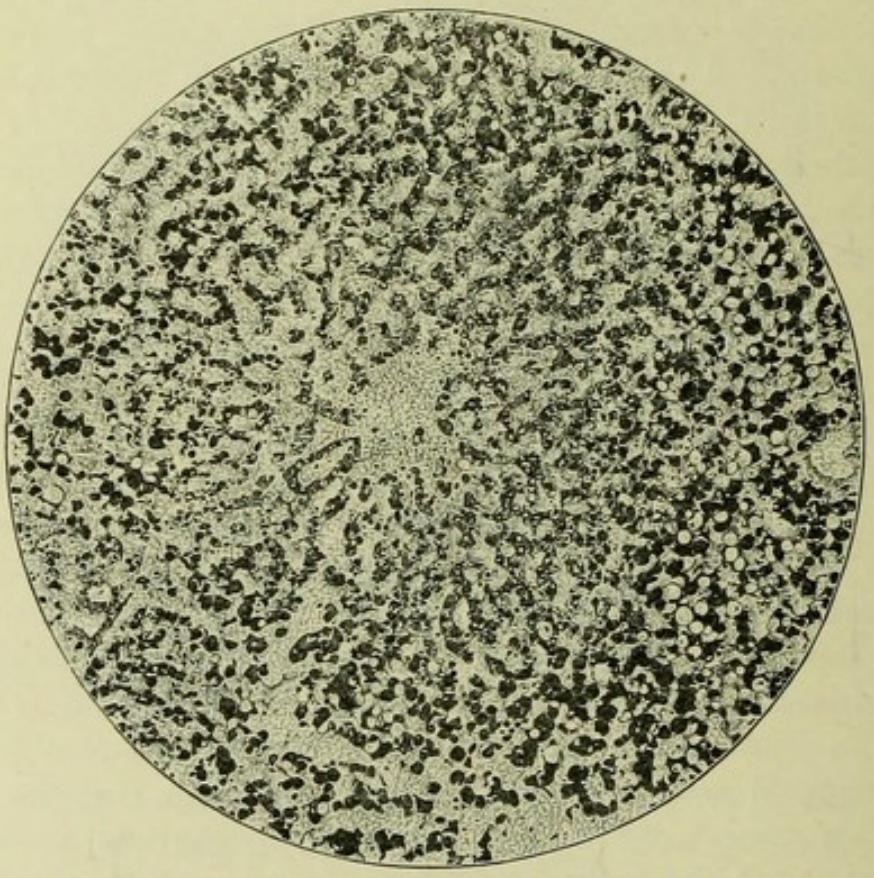


FIG. 67.—Fatty degeneration of the liver under a low power, stained by osmic acid.

A transverse section of a lobule is shown with the central vein distended with blood, and connected with the distended hepatic capillaries. There is, therefore, some venous congestion.

The main characteristic of the specimen is, however, the presence in the cells, more particularly at the periphery of the lobule, of globules of fat, which in most instances show as black masses; in some, however, where the fat has fallen out and disappeared, round spaces only are seen.

Towards the centre of the lobule the fat particles are less numerous.

Fatty degeneration is the result of a damage to the functional activity of the cell, provided that the damage is not sufficiently great to kill the cell outright. This damage to the cell ending in fatty degeneration may arise from three causes :—

1. A deficient supply of nutriment to the cell, due either to a defect in the blood supply of the part or to a diminution



FIG. 68.—Fatty degeneration of the kidney.

A section of the kidney is shown stained by osmic acid, and not counter-stained. The tubules shown are chiefly straight tubules, and the cells are stained almost black by the acid, owing to the extreme fatty degeneration of the protoplasm. From a case of acute infective disease, in which the liver and heart also showed advanced fatty degeneration.

in the total amount of oxygen taken into the body or supplied to the part.

2. There may be a defect in the nerve supply to the tissue, as is seen in the fatty degeneration occurring in peripheral neuritis and in paralysis due to disease of the central nervous system. Of like nature is the fatty degeneration occurring in disused muscles. The removal of nervous influence is probably also responsible for the degeneration occurring in certain

glands in the body, more particularly in those that have a secretion.

3. One of the most potent causes of fatty degeneration is the action of poisons. In some instances these causes act together, a defect in the circulation or in the nerve supply acting with a toxic cause.

1. *Fatty Degeneration due to a Defective Supply of Nutriment to the Cell.*—In this case there are two conditions to be considered. In one the arterial supply to the part is diminished by disease of the vessel, whereby the supply not only of liquid nourishment, but of oxygen, varies greatly from the normal. In the other there is no arterial disease, but the supply of oxygen is deficient. The following examples may be given of fatty degeneration due mainly to a diminished supply of arterial blood. In disease of the coronary arteries of the heart, the muscle fibres show in many instances fatty degeneration, which is frequently very irregularly distributed. The kidney cortex, in cases of arterio-sclerosis, shows a similar change. In advanced albuminoid disease of the liver and kidneys, areas of fatty degeneration are frequently observed, and the change is no doubt directly to be ascribed to a diminished supply of blood, due to the great narrowing of the vessels of the organ. The fatty areas which occur in cirrhosis of the liver and in granular contracted kidney are to be ascribed to the same main cause, the diminished blood supply in this case being due to the contracting bands of fibrous tissue. After parturition, and during involution of the uterus, many of the muscle fibres undergo fatty degeneration, disappearing as the organ regains its normal size. This change is to be ascribed to the diminished blood supply to the organ, which occurs immediately after the contraction of the uterus following parturition. New growths, in which the blood supply is deficient, as in scirrhus and other forms of carcinoma, frequently show areas of fatty degeneration of the cells.

To the diminution in the amount of oxygen supplied to the tissue has been ascribed a large rôle in the production of fatty degeneration. This appears to be the explanation of

the fatty changes which are observed in the heart, arteries, liver, kidneys and other organs in the profound anæmias, more particularly pernicious anæmia. To a much less extent similar changes are found in chlorosis, secondary anæmias and in leukæmia. In all these conditions the amount of hæmoglobin in the blood is diminished, and so a deficient quantity of oxygen is carried to the tissues. There is thus a diminished metabolic activity in the organs and tissues, and it is to this, as well as to the diminished amount of oxygen, that the fatty changes are ascribed. The same explanation has been offered regarding the fatty changes which occur in old age in the lens, the cornea (arcus senilis), cartilage, epithelial tissues and the genital organs, as well as that occurring in cachectic states, as in malignant disease; but in such cases, besides the diminished functional activity of the cell and the diminished amount of oxygen supplied to the tissue, the action of a circulating poison cannot be eliminated. The fatty degeneration which occurs in the liver and kidneys in cases of venous stagnation (prolonged passive hyperæmia) has been ascribed to the diminished arterial blood pressure and the diminished amount of oxygen. Thus fatty degeneration is observed in "nutmeg" liver, the cells of the periphery of the lobule undergoing fatty degeneration, while those in the centre of the lobule undergo atrophy from pressure by the distended capillaries (Fig. 73). In the fatty changes in the kidney which are observed in cases of morbus cordis, a similar explanation has been made. Fatty degeneration of the liver is observed in cases of pulmonary tuberculosis, and the change has been ascribed to the diminished intake of oxygen. In emphysema and chronic bronchitis fatty degeneration of the liver does not occur. In this case also the disease of the lungs tends to cause a diminished intake of oxygen, but owing to the fact that the muscles are more vigorous than in cases of pulmonary tuberculosis, the respiratory efforts are more energetic, and so sufficient oxygen is taken into the body; hence fatty degeneration of the liver does not occur. This, however, is only an explanation in part, as in pulmonary tuberculosis another factor obtains, namely, the circulation of a poison in the body.

2. *Fatty Degeneration due to Disease of the Nervous System.*—It is possible that the removal or disorder of the nervous influence which is exerted on the secretory glands may lead to the degeneration of their cells. But little, however, is known of this subject. The instances of fatty degeneration occurring in this class are illustrated by the degenerative changes taking place in the central nervous system as the result of the destruction or disease of the higher nerve centre, or of the fibres proceeding from it; and secondly, the similar changes which occur in the fibres from disease of the lower nerve centre, as well as the changes observed in the muscles supplied by the nerve fibres (Chapter XIX.).

Destruction of the cortical nerve centres of the motor area, or destruction of the white fibres that run through the internal capsule, leads to fatty degeneration of the fibres passing through the base of the brain and the spinal cord; this extends downwards as far as the lower nerve centre. Destruction or disease of the spinal cord at one spot leads to fatty degeneration in certain tracts, both upwards and downwards. The chemical change which occurs in the degenerated fibres affects chiefly the lecithin of the white matter. The change is shown by the fact that the degenerated fibres are stained black by a mixture of osmic acid and Müller's fluid (Marchi), whereas the normal nerve fibres of the spinal cord are not stained black by this fluid. Lecithin is a complex body composed of glycero-phosphoric acid, stearic acid and neurin or choline. It is not known into what bodies lecithin is decomposed during the process of degeneration of the fibre, but it has been shown that the lecithin is much diminished in the degenerated tracts of the spinal cord as compared with the healthy tracts (Mott).

Destruction of the lower centre leads to degeneration of the motor fibres attached to it as far as to the muscle. Section of the motor nerve below the centre leads to degeneration of the fibres as far as the muscle. There is some evidence that disease of the lower centre, stopping short of destruction of the cell, may also lead to degeneration of the nerve fibres below, but this degeneration is not complete and occurs irregularly. Similarly, disease may cause

degeneration of bundles of fibres in the nerve without the whole nerve being affected. In this case only the fibres affected show degeneration as far as the muscle. When degeneration occurs in the fibre from the centre to the muscle or from a part of the nerve downwards to the muscle, it is spoken of as Wallerian degeneration. The essential feature of this is that the axis cylinder of the nerve

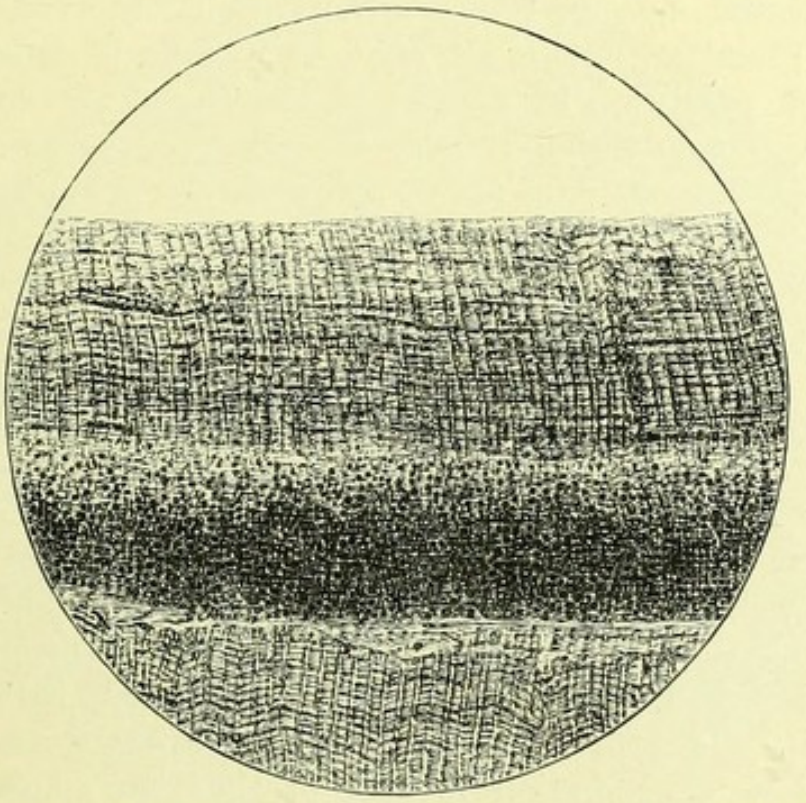


FIG. 69.—Fatty degeneration of voluntary muscle. Stained with osmic acid.

Portions of three voluntary muscle fibres are shown longitudinally. The upper and lower are practically normal, while in the centre fibre the transverse striation is practically lost, and the fibre is occupied by numerous small and uniform particles of fat, staining black with osmic acid.
(From a case of degeneration of voluntary muscle in diphtheritic paralysis.)

fibre is degenerated, and fatty degeneration occurs in the muscle fibre attached.

Fatty degeneration of voluntary muscle (Fig. 69) occurs in two stages, in the first of which the muscle fibre shows a tendency to longitudinal fibrillation after staining with osmic acid, and to the formation of granules in parts which do not stain black with osmic acid. In this stage transverse striation is less evident, but is not completely lost. In the second stage

the transverse striation is lost; numerous small fat granules staining deeply with osmic acid appear in the substance of the fibre, and eventually the nuclei disappear.

Fatty degeneration occurs in the voluntary muscles: (1) when these fall into disuse; and (2) when they are directly affected by disease of the lower nerve centres and of the peripheral nerves.

In disused muscles fatty degeneration is observed, as in the muscles round an ankylosed joint, as well as in muscles that have been paralysed by disease of the higher nerve centres. This fatty degeneration is very irregular in distribution, and is associated with marked atrophy of the majority of the fibres. When there is actual disease of the lower nerve centre or of the peripheral nerves the fatty degeneration of the fibre is dependent on the number of nerve fibres which undergo Wallerian degeneration. This is seen very obviously in experimental diphtheritic palsy, where degeneration of the nerves results from the injection of the diphtheria toxine (Chapter XIX.). The nerve degeneration is patchy, some of the fibres show only a breaking-up of the myelin sheath, others show as well degeneration and rupture of the axis cylinder, with a subsequent Wallerian degeneration downwards. The muscle attached to this partially degenerated nerve shows partial fatty degeneration, many fibres being normal while others show degeneration in one of the two stages already described (Fig. 69). Excessive fatty degeneration of the voluntary muscle is only seen where the centre is extensively destroyed, or in some severe cases of peripheral neuritis.

On what the fatty degeneration of the voluntary muscles depends is not quite clear. There are evidently several factors which might be supposed to take part in the process. The removal of the nervous influence prevents contraction of the fibre, and so causes diminution of its metabolic activity. This may be the only explanation of the so-called trophic influence of the nerve centre over the fibre, but, in addition, the influence of the circulation must be considered; damage to the vaso-motor nerves producing a disordered circulation, and so a diminished or irregular supply of nourishment and

oxygen to the muscle fibre. This leads to accumulation of the products of the metabolism of the muscle.

3. *Fatty Degeneration due to the Action of Poisons.—Toxic Fatty Degeneration.*—The poisons which when introduced into the body lead to fatty degeneration are divided into two classes. (1) One class includes chemical substances, such as

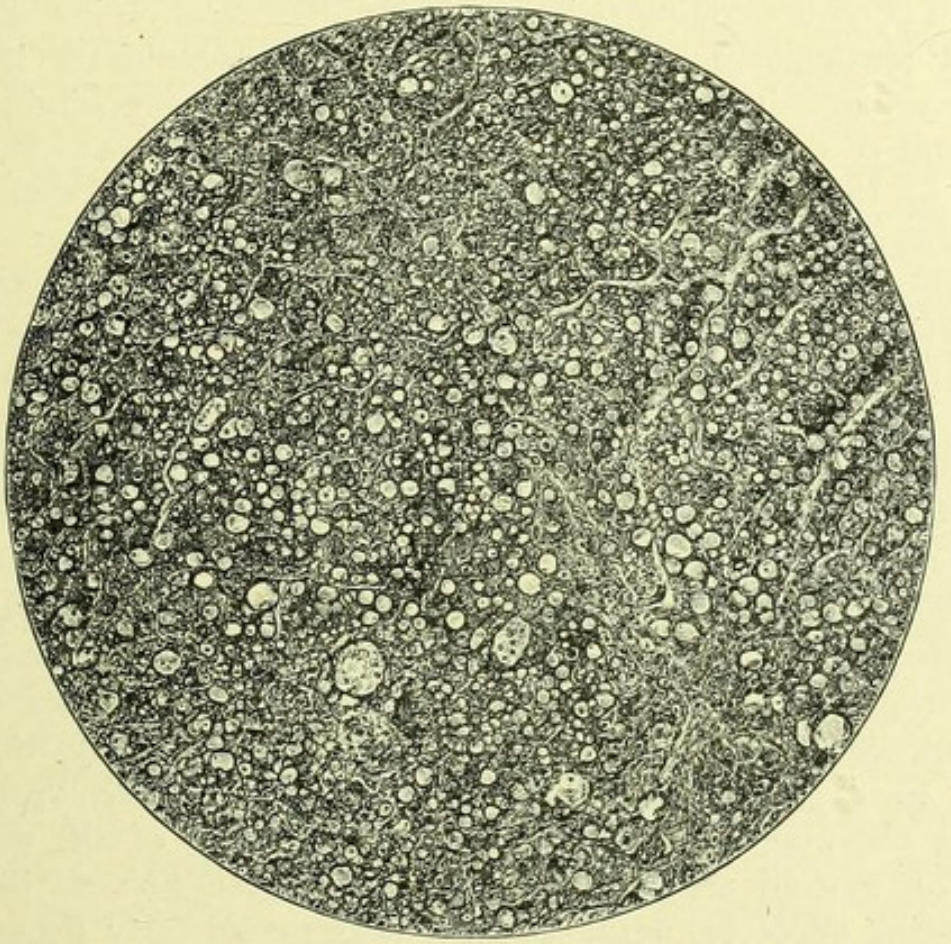


FIG. 70.—Acute yellow atrophy of the liver. (Stained with hæmatoxylin.)

The lobular structure of the organ is lost, only faint indications of the lobules being shown by strands of connective tissue. The liver cells are completely degenerated: in parts they are granular, and over the whole of the area they show globules of fat, represented in the figure by clear spaces.

phosphorus, antimony, arsenic, mercury; chlorate of potassium, pyrogallic acid, chloroform, ether, iodoform: (2) the other, bacterial poisons and the poisons of infective disease.

To the action of poisons is to be ascribed the widespread fatty degeneration which is not uncommonly observed. In poisoning by phosphorus, for example, not only is there well marked fatty degeneration of the liver (Fig. 70), kidneys and

heart, but also of the glands secreting the digestive juices and of the voluntary muscles. It has been said that this widespread fatty degeneration is due to the diminished amount of oxygen which is taken in in phosphorus poisoning. This is probably not the sole explanation, and a more potent factor appears to be the direct action of the poison on the cell.

In chronic alcoholic poisoning, fatty degeneration is observed more particularly in the heart and liver, sometimes in the kidneys, and although this has been ascribed to the diminished amount of oxygen supplied to the tissues, yet it may well be due to the direct action of the poison on the cell and protoplasm.

The second class of cases, namely, the fatty degeneration occurring in infective disease more closely concerns the subject. In most of these cases the fatty degeneration occurring in the liver, kidneys, spleen, heart and nervous system is preceded by cloudy swelling. The change is not due to a high body temperature, but to the circulation of a poison which directly affects the functional activity of the cell.

With bacterial poisoning and the poisons of infective disease, the fatty degeneration may be general or localised. When general, the heart, liver, kidney cortex and, to some extent, the spleen are found affected, the voluntary muscles and, to a great extent, the glands secreting the digestive juices escaping. In some instances the cells of the central nervous system are affected, mainly by those poisons having a specific effect on nerve tissue. Widespread fatty degeneration affecting the internal organs may be found in prolonged illness from rheumatic fever, enteric fever, pneumonia, tuberculosis, diphtheria and scarlet fever. In some instances, however, the fatty changes are localised, affecting more particularly one organ, such as the heart, the liver, or the kidneys. This may be illustrated by the results of the experimental injection of bacterial poisons. In the rabbit the injection of the diphtheria toxine produces fatty degeneration of the heart and, to a less extent, of the liver. In some cases the liver is not affected, nor are the kidneys. The voluntary muscles show fatty degeneration, but only in proportion to the degree

of nerve degeneration. In the cat, besides the nerve degeneration, a well marked fatty degeneration of the kidney cortex may be produced. The injection of anthrax poison as well as of some other bacterial poisons produces a well-marked fatty degeneration of the heart, but of no other organ or tissue. This local fatty degeneration must therefore be explained, not by any general change taking place in the body, such as a diminution in the amount of oxygen, but by a specific effect of the circulating poison on the tissue for which it has a chemical affinity. This, no doubt, is the explanation of the fatty changes occurring in the kidney cortex in scarlet fever and in some other infective diseases, and these changes may be associated, or not, with the phenomena of inflammation.

In inflammatory or infective foci fatty degeneration is observed, affecting not only the leucocytes present in the foci, but also the cells of the tissue. This fatty degeneration frequently ends in death of the cell, so that the process is referred to as *necrosis* (p. 214). There is apparently a wide difference between such an infective focus as a whitlow or abscess and a caseous tubercle. From the present point of view, however, fatty degeneration of the cells is a feature of both, and ends in complete destruction of the cell. (See Caseation, p. 219).

3. *Albuminoid Degeneration.—Zenker's Degeneration.*—Both these are examples of toxic degeneration. Albuminoid (amyloid) degeneration (Fig. 71) occurs in chronic suppuration, especially of bones or joints, in chronic empyema, pulmonary tuberculosis and in syphilis. It has also been found in cases of leukæmia, malaria and cancer. It is a degeneration affecting the smaller blood vessels and the connective tissue, and is observed mainly in the liver, spleen and kidney. It is also seen in the lymph glands, in the mucous membrane of the stomach and intestine, the suprarenal bodies and the heart. How the insoluble proteid body called lardacein is produced is not known. Lardacein (p. 196) consists of hydrogen, oxygen, nitrogen, carbon and sulphur, and has been described as a compound of chondragen, sulphuric acid and a proteid. It is a degeneration product which is very

characteristic, and apparently has no relation to the amyloid bodies which are found in the prostate and in the nervous system in certain conditions. The frequency and extent of albuminoid degeneration has diminished owing to the improved treatment of suppurating areas and of syphilis. Organs are very variously affected by the degeneration. In individual



FIG. 71.—Albuminoid disease of the kidney.

A section of the cortex is shown, in which all the normal structure is lost. The clear spaces are tubules from which the epithelium has dropped out; in some of these spaces remains of the epithelium are to be seen. Between the tubules there is a great deal of fibrous tissue.

Four Malpighian corpuscles are shown, in all of which there is a translucent area of albuminoid degeneration, with some indications of the nuclei of the capillaries which are destroyed.

instances the liver, spleen, or kidney may alone be affected, most frequently, perhaps, the spleen, while the affection of the other organs, such as the heart, mucous membranes and suprarenal bodies, is only observed in advanced cases.

Zenker's degeneration (Fig. 72) is a hyaline change occurring in the voluntary muscles in enteric fever. It is most commonly found in the rectus abdominis, and but little is known of the nature of the substance formed.

4. *Mucinoid Degeneration.*—The physiological production of mucin by cells occurs in the epithelial cells of the mucous membranes of the body and of the cells of the glands which open on the surface of the mucous membranes. This mucin formation is a special property of certain cells of the epithelial lining. As the result of catarrh or inflammation due to an

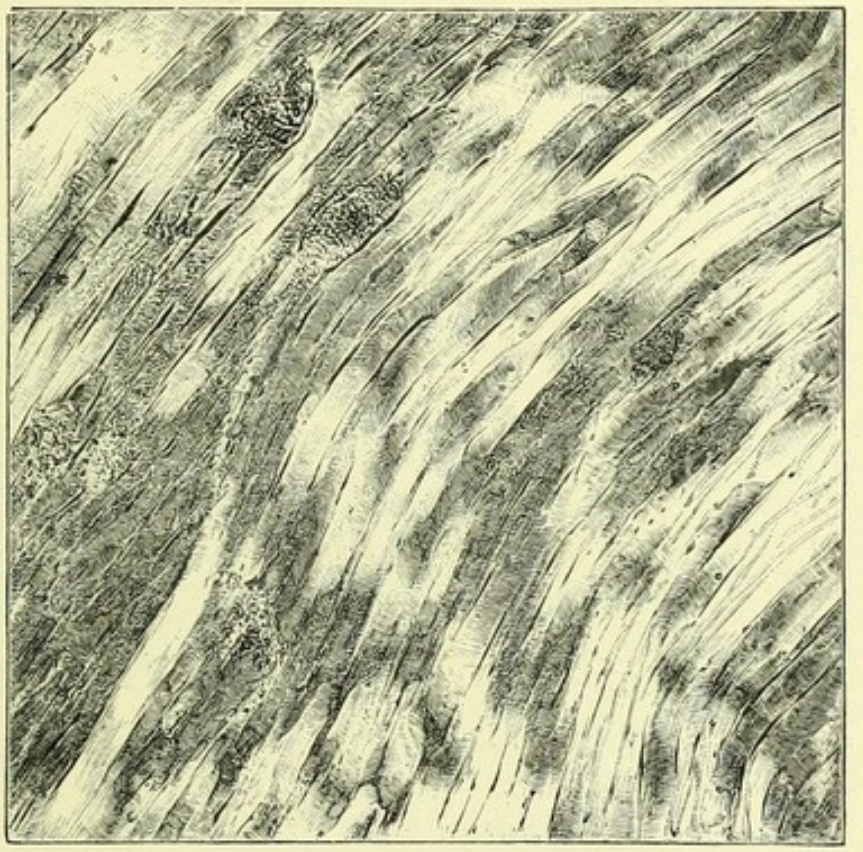


FIG. 72.—Zenker's degeneration of voluntary muscle.

A longitudinal section of muscle is shown in which in parts the fibres show their normal transverse striation, while in other parts there is no structure in the fibre to be detected, with the exception that the sarcolemma is intact.
(From the rectus abdominis in a case of enteric fever.)

irritant, the mucin formation greatly increases, so that all the epithelial cells become mucin-bearing cells. All mucous membranes may be affected in this manner. Mucin is, however, widely distributed in the body, and is present in small quantities in connective tissue. The quantity in connective tissue is increased in myxœdema and in the myxomatous stroma of new growths. In the cells of new growths undergoing degeneration, some of the globules observed consist of

mucin, and this is another example of the irregular metabolic activity of diseased cells. The tenacious substance present in ovarian cysts is not mucin, but is closely allied to it (p. 196).

5. *Colloid Degeneration.*—Colloid degeneration is observed mainly in certain forms of carcinoma, where the cells are transformed into a translucent and glistening material. The substance formed in colloid carcinoma is supposed to be similar to that found in the thyroid gland, but that it is the same is not proved. In new growths in the thyroid and in goitre, the colloid material is increased in quantity, but this is not the same pathological change as the colloid degeneration of the cells of carcinoma.

6. *Dropsical Degeneration.*—This is really an infiltration of the cells by fluid and is observed in inflammatory areas, in nerve cells and more particularly in soft neoplasms. The droplets of fluid are seen in the nucleus as well as in the protoplasm of the cell, the cell eventually being destroyed.

7. *Atrophy.*—By atrophy is meant the diminution of the cells of the part without gross signs of degeneration. It appears as the result of old age, of the disuse of parts and of circulatory defects. In old age the diminution and disappearance of the elastic tissue of the skin and bronchial mucous membrane is a well-known phenomenon. The fat in many instances also disappears, although this may be due to a change in the amount of nutriment taken. The atrophy which occurs in the internal organs in old age may be ascribed to a diminished functional activity. The atrophy of the thymus gland in childhood is as yet unexplained, but that of the genital organs at the menopause may be ascribed to a cessation of function. The main cause of atrophy appears to be the diminution or cessation of functional activity, provided that no irritant acts on the tissue, and that no infection takes place. The following examples will illustrate this point. Atrophy occurs in a voluntary muscle as the result of cessation of function, whether this be due to ankylosis of the joint

of a limb or to the removal of nervous influence. This atrophy is frequently associated, as has been stated, with fatty degeneration. Atrophy of the intestine occurs on the distal side, when an artificial opening joins the gut to the surface of the body,

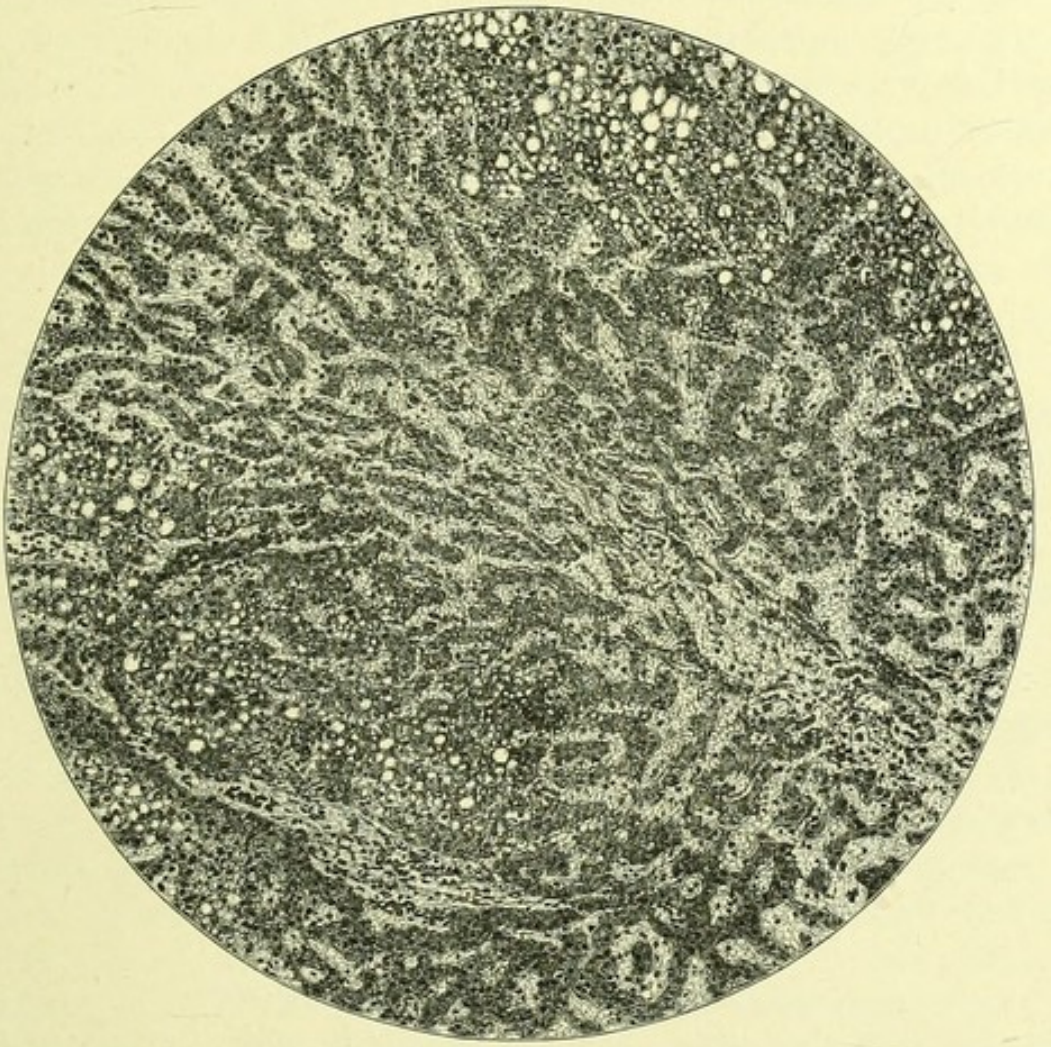


FIG. 73.—Mechanical congestion of the liver; "nutmeg" liver.

A longitudinal section of a lobule is seen with a dilated central vein, which is shown in the middle of the figure. Passing from this are the dilated hepatic capillaries, widely separating the groups of hepatic cells, those of the latter nearest to the central vein being atrophied from pressure. At the periphery of the lobule the hepatic cells have undergone fatty degeneration, as shown by the clear spaces in the figure.

thus preventing the contents from passing into the lower part of the gut. All the coats of the intestine suffer equally Atrophy of the heart cannot be ascribed to any particular cause. It is referred to as *brown atrophy*, owing to the increase of the pigment round the nucleus of the fibre. Brown atrophy is found in cachectic conditions and in advanced old

age, and is never found by itself, other organs of the body being also degenerated. It is possible that it is due to a deficient amount of nutriment carried to the heart, though it is not associated necessarily with disease of the coronary arteries. Atrophy from pressure occurs in cases where the pressure is continuously applied for long periods. This is observed in the skin and in the liver cells from the pressure of the distended capillaries in mechanical congestion (Fig. 73), and in the heart, liver and kidney, from the pressure of contracting fibroid tissue. Intermittent pressure leads to hypertrophy of the epithelium of the skin.

8. *Necrosis.*—Necrosis is a term applied to the condition in which death of the tissues occurs; gangrene is a term synonymous with necrosis. Necrobiosis has been used to denote the death of individual cells, but the term is unnecessary.

Necrosis is either infective or non-infective, and may be classified as follows:—

(1) Necrosis due to stoppage of the circulation.

(2) Necrosis due mainly to disease of the central nervous system.

(3) Necrosis produced by mechanical causes (heat, cold, electricity), by chemical poisons, or by pressure.

(4) Infective necrosis, which may also be called inflammatory or bacterial necrosis.

1. *Necrosis due to Stoppage of the Circulation.*—The circulation through the main artery of the limb, and of that supplying the toes and fingers, may be stopped by aneurism or by thrombosis resulting from disease of the arterial wall, such as atheroma; pressure on the artery will produce the same result. Stoppage of the circulation by spasm of the artery has been supposed to occur in Raynaud's disease and in ergotism, but in the former of these conditions it has been shown that in some cases there is a definite arterial disease. In some cases of disease, in addition to the arterial changes there is disease of the walls of the veins, and subsequent thrombosis leading to complete stoppage of the circulation.

This has been observed in cases of gangrene of the lower extremities.

Death of the part or gangrene, is observed in the toes and feet, and in the intestine following embolism of the superior mesenteric artery. In Raynaud's disease the toes, fingers and ears may be affected, and in diabetic gangrene the lower extremities. Two varieties of the condition are described —dry and moist gangrene; they only differ according to the amount of fluid the part contains. Dry gangrene is observed usually as the result of embolism or thrombosis of the peripheral arteries. Ergotism also leads to dry gangrene as well as Raynaud's disease. Dry gangrene, produced by freezing, may be due to thrombosis. Dry gangrene tends to the formation of a slough which may include the extremity in the whole of its thickness, the separation of the necrosed and healthy parts being by a line of demarcation. In moist gangrene, venous thrombosis usually plays a part, thus leading to the accumulation of fluid in the necrosed area. It must be said, however, that the majority of cases of moist gangrene belong to the infective class.

Coagulation Necrosis.—This is a form of necrosis which occurs as the result of stoppage of the circulation in certain organs, such as the kidney or spleen; it results in the death of the cell, which takes place by means of a process probably allied to *rigor mortis*. It is seen in its typical form in the formation of the white infarct of the spleen and kidney (Chapter XIII.). In some cases, owing to the stoppage of the circulation through the main renal vessels, the whole kidney cortex may be in a state of coagulation necrosis. No recovery is possible from this condition. In this description coagulation necrosis is considered as a non-infective process. Frequently, however, the term is applied to certain changes produced by infective processes in tissues, such as the formation of fibrin in inflammatory areas and the subsequent death of the cells. This, however, is not the same process, and the term coagulation necrosis ought to be limited to the condition described, namely, to the death of the cell owing to the sudden stoppage of the circulation to the part. Fatty

degeneration subsequently occurs in the areas affected by coagulation necrosis.

2. *Necrosis due to Disease of the Nervous System* (Chapter XIX.).—Under this heading are described the formation of acute bed-sores and the occurrence of cystitis in acute disease and injury to the spinal cord, the so-called trophic changes which occur in the eye in paralysis of the fifth nerve, and the joint changes which occur in tabes dorsalis and some other chronic spinal affections. It has to be considered, however, how far these conditions are due to the disease of the nervous system, and how far to an infection readily occurring in a tissue in which the functional activity is diminished. Thus the cystitis of disease of the spinal cord is not due to the nerve disease directly, but is an infection of the bladder occurring in a damaged tissue. This is not a necrotic process. The same remarks apply to the eye changes occurring in paralysis of the fifth nerve. Acute bed-sores, on the other hand, appear to be directly related to the disease of the nervous system, and are not, at any rate in the first instance, apparently infective in origin. The exciting cause is in some instances pressure on the part when lying in bed.

Charcot's disease of the joints appears to be mainly a necrotic process, non-infective and dependent on the disease of the spinal cord.

3. *Necrosis produced by Mechanical Causes* (heat, cold, electricity) *and by Chemical Poisons or Pressure.*—Pressure necrosis is sometimes observed in the body from calculi and exostoses. This necrosis depends partly on pressure on the cells of a solid organ, or pressure on the organ driving out the blood or causing thrombosis. Pressure necrosis, therefore, comes really under the heading of necrosis due to a circulatory disturbance.

Heat and cold, which may both produce necrosis, cause this result by killing the cells directly, heat leading to moist necrosis, cold leading as a rule to dry necrosis. The effect of these agents in producing necrosis is, in the main, but little dependent on their effect on the local circulation.

Chemical agents, such as mineral acids and caustic alkalies

and the corrosive salts of the metals, also act directly on the cells of the part, destroying them. Ricin and abrin (p. 89) also produce necrosis of the cells by a direct action as do, also, many of the bacterial poisons.

4. *Infective Necrosis.*—Many bacterial poisons are powerful agents in producing the death of the cell or tissue. When injected under the skin of an animal they produce a

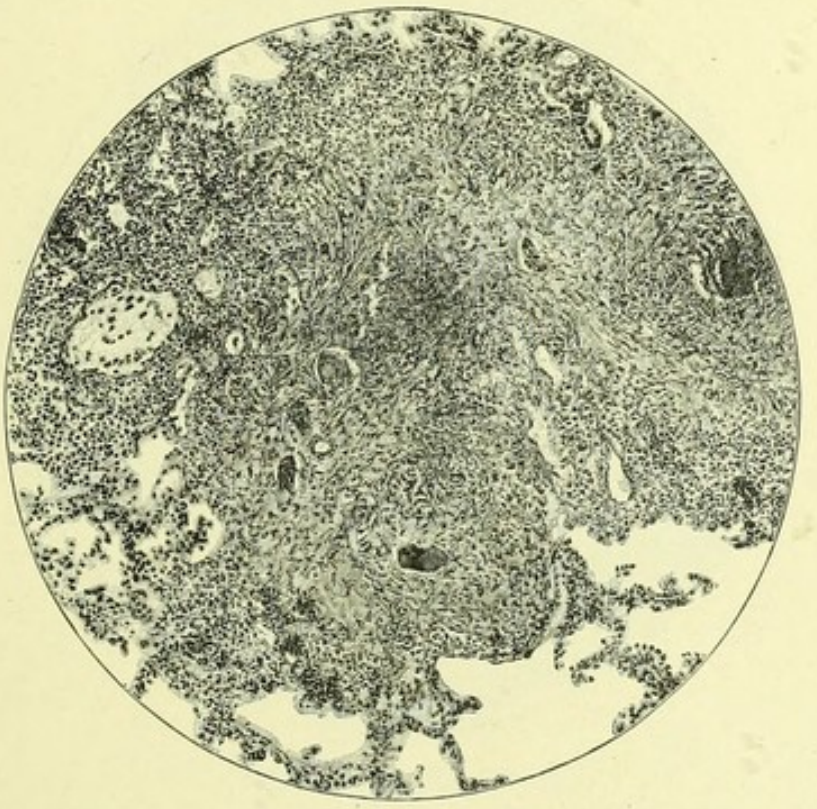


FIG. 74.—Caseous tuberculosis of the lung.

Part of the alveolar structure of the lung is seen, but the greater part of the figure is occupied by a tubercle, which contains four giant cells, and which shows in parts a collection of round cells, and in other parts an amorphous caseous mass.

result varying partly according to the dose administered and partly according to their nature. If in a small dose or not highly toxic, they produce the phenomena of inflammation, in redness and swelling with œdema. If in larger amount, or highly toxic, the ordinary phenomena of inflammation may be absent, and necrosis of the tissue follows. Necrosis of some of the cells of a part occurs as the result of any action of the bacteria, and a similar necrosis, which may be called inflammatory necrosis, occurs in local infections. Thus in a

diffuse infection (inflammation), which subsequently becomes localised, besides the phenomena of inflammation and the fatty degeneration of exuded leucocytes, there is a damage not only to the cells but to the connective tissue of the part which ends in necrosis, and this necrosis may be aided by thrombosis of the surrounding vessels. Although

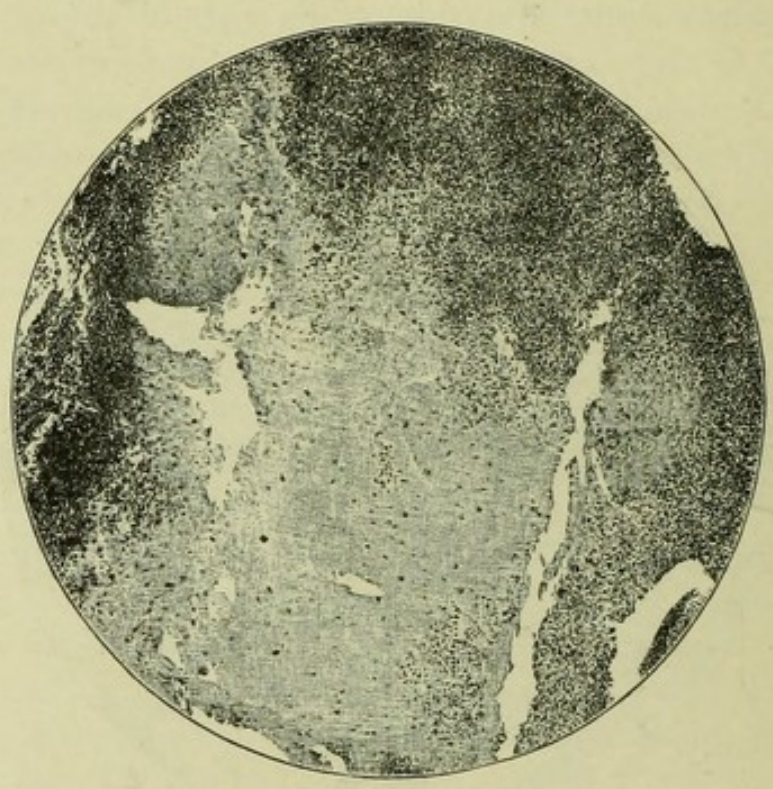


FIG. 75.—Bacterial necrosis.

The figure was taken from a section of a nodule of bacterial necrosis (non-tuberculous) in the pharyngeal mucous membrane of the pig.

A central clear area of necrosed cells is seen, with few nuclei, and these degenerating; surrounding this area is a peripheral zone of round cells (leucocytes). The nodule was sharply marked off from the surrounding healthy mucous membrane.

Under a higher power the necrosed area was seen to consist mainly of amorphous matter, with a few cells and very numerous cocci, mostly arranged in chains. No other bacteria were present, including tubercle bacilli.

the circulatory disturbance in an infective area may aid necrosis, the chief agent in its causation is the action of the bacterial poisons. This necrosis may be seen in varying degrees in infective areas, from that observed in the formation of a whitlow to the severe condition known as spreading gangrene. In this latter condition, from an inoculation, usually of an extremity, rapid infection of the limb ensues, with great

brawny swelling and the destruction of all the tissues of the limb. Spreading gangrene is always of the infective variety. Another variety is spoken of as colliquative gangrene. This usually occurs in connective tissue or in loose tissue like the lung, and the name is given to denote the large amount of liquid containing fragments of necrosed tissue present in the gangrenous area.

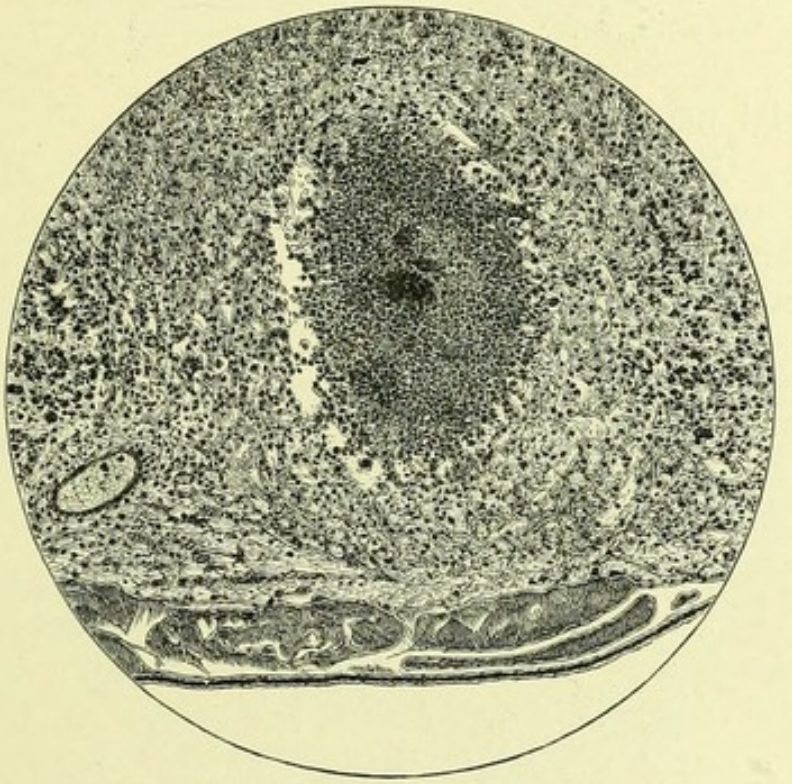


FIG. 76.—Bacterial necrosis.

The figure shows the lower part of a Peyer's patch of the intestine of a guinea-pig, with the muscular and peritoneal coats attached.

In the lower part of the patch is a nodule separated from the surrounding normal lymphatic tissue, and composed of round cells undergoing degeneration (necrosis). In the nodule are two or three dark areas, which under a higher power are seen to be groups of bacilli.

No tubercle bacilli were present, and the animal was not tuberculous.

In the rest of the Peyer's patch were two or three similar necrotic areas.

Other forms of infective necrosis may be described as caseous and bacterial necrosis.

Caseation (Fig. 74) is observed as a result of the action of certain infective agents, such as those of tubercle and syphilis. It may also be observed, however, in non-infective infarcts (Chapter XIII.). It is a constant part of the changes in the lesions produced by syphilis and tubercle wherever they are

formed. In the lesions of both diseases the main element is cellular, and is not supplied with blood vessels. No doubt the absence of blood vessels as well as, in a syphilitic lesion, the surrounding endarteritis is partly the cause of the subsequent necrosis which commences in the central parts of the nodule, but probably a greater part is due to the action of the poisons of the infective agent on the cells of the nodule. The process is a chronic one, and has no relation to coagulation necrosis.

Bacterial necrosis (Figs. 75 and 76) is closely related to caseation. It is frequently observed in the liver, the spleen and other organs of guinea-pigs and rabbits, as well as in the large herbivora. Whitish areas are observed, in which there is complete necrosis of the cells: numerous micro-organisms are present, which are not tubercle bacilli. The bacteria may be found in the vessels surrounding the necrosed area, but the process is evidently not due to stoppage of the circulation, but to a direct effect of the bacteria on the cells.

9. *Fibrosis.*—This when it affects certain organs, such as the liver and kidney, is called *cirrhosis.* When it affects the nervous system it is called *sclerosis.* The terms *fibroid degeneration* and *fibroid substitution* are also used, the former more particularly when the change affects organs, such as the heart and kidney, and is primary; the latter when the fibrosis is secondary to a previous diseased condition of the part. Both these terms are, however, unsuitable, and in discussing the pathological processes involved in fibrosis, the main condition to be considered is that the process is essentially one of a new formation of fibrous tissue. It is not therefore, strictly speaking, a degeneration, but is limited to certain changes which occur in fibrous tissue in disease, whether this exists as connective tissue or as a modified connective tissue, such as bone and cartilage.

In the discussion of the various examples of fibrosis in disease, it will be evident (1) that an increase of fibrous tissue constituting fibrosis can only occur by changes occurring in the elements of previously existing connective tissue;

and (2) that this change is dependent on an injury whereby there is irritation of the connective tissue elements.

The increase of fibrous tissue which is observed in fibrosis can only result, as has been said, from previously existing connective tissue (Fig. 77). In connective tissue, as is seen in the subcutaneous tissue and in the submucosa of mucous membranes, there are bundles of white connective tissue fibres,

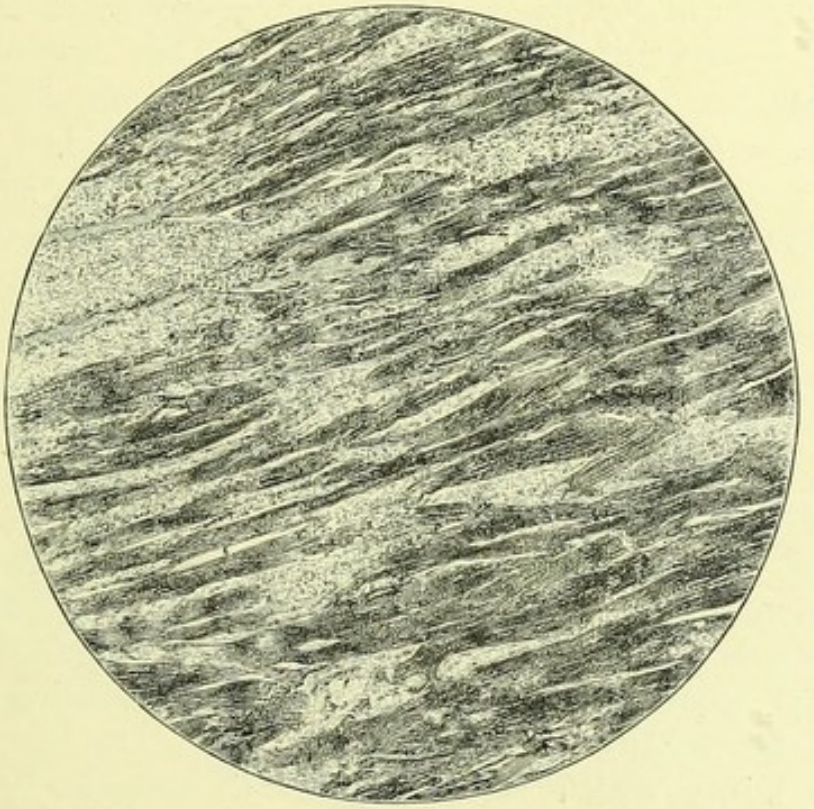


FIG. 77.—Chronic interstitial myositis.

The early stage of this was shown in Fig. 6.
The above figure shows the voluntary muscle fibres separated in parts—sometimes widely—by strands of connective tissue. The fibres themselves have undergone atrophy.

and also elastic fibres, with the proper connective tissue cells; the tissue containing liquid, blood vessels and lymphatics. Into this tissue, when it is affected by an injury or poison, the leucocytes of the blood immigrate. The connective tissue corpuscles undergo division, and when connective tissue is formed with the resulting fibrosis, the main elements in its formation are formoblasts — oval, pear-shaped, or spindle-shaped cells, with large nuclei; they elongate and not only

form the cell elements of the new connective tissue, but also the white fibres. Elastic fibres are never formed in the new connective tissue of fibrosis. It has been discussed as to whether formoblasts are derived from the leucocytes or from the connective tissue corpuscles. There is no evidence as to their derivation from leucocytes, and judging by analogy, it must be concluded that the main—perhaps the sole—source of origin of the formoblasts is a previously existing connective tissue corpuscle. The new connective tissue has new vessels formed in it by the apposition of cells in lines, a channel being subsequently formed. The new vessels are produced from the capillaries of the surrounding part. The white fibrous tissue of fibrosis frequently undergoes degeneration, especially when in large strands, the fibres becoming hyaline and staining but feebly with reagents. The process of fibrosis above described is modified in some regions by the character of the connective tissue present, as, for example, in the central nervous system the connective tissue is represented by neuroglia, which is composed of very fine branching fibres with sparsely-scattered cell elements. There is no reason to suppose that the process of fibrosis in the central nervous system is essentially different from that occurring elsewhere; the main part being taken by the glia cell elements present.

The injury which results in fibrosis may be of different kinds.

1. Fibrosis is part of the repair of wounds in which there is a solution of continuity and a destruction of some of the proper cell elements of the part. The amount of fibrous tissue formed in a wound when healing or healed depends, however, not solely on the degree of initial injury, but on the continued presence of an irritant in the wound, such as a foreign body, or, in infective wounds, bacteria and their products.

2. The irritation of a non-infective foreign body in the tissues leads to fibrosis. This may occur when a foreign body not containing bacteria is embedded in the subcutaneous tissues or other parts. It is also observed round necrosed

areas in the tissues, such, for example, as the fibrosis occurring round non-infective infarcts, where the area of dead tissue acts as a foreign body in producing irritation and fibrosis.

3. In infective foci (inflammatory foci) fibrosis occurs (Figs. 78 and 79); it is observed round the focus when the extension of the bacterial growth ceases, so that the infective focus may become completely surrounded by a fibrous capsule. It also

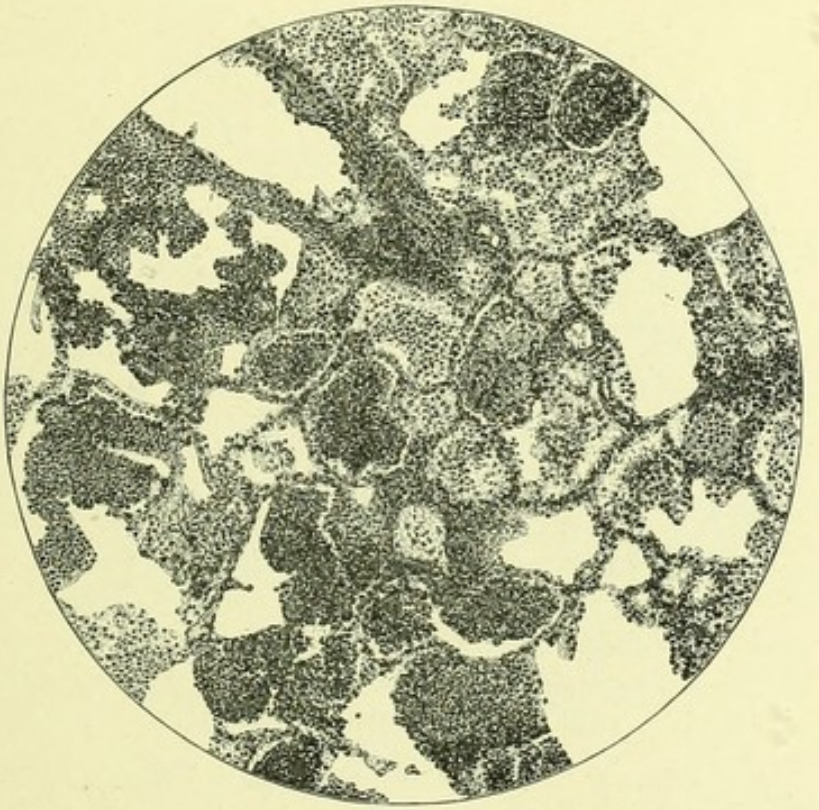


FIG. 78.—Broncho-pneumonia (early stage) in Chronic Pulmonary Tuberculosis.

The alveoli of the lung are seen packed with round cells, which are mainly leucocytes, but are in part derived from the alveolar epithelium. No fibrin was present.

occurs in the infective focus itself, provided that complete destruction of the tissue does not occur, and is observed during the process of healing. The amount of fibrosis left by an infective focus after infection has ceased, depends on the degree of destruction of tissue and the prolongation of the irritation. The greatest amount of fibrosis is observed in chronic infective foci, as, for example, in chronic tuberculosis.

4. Fibrosis of the internal organs, either local or general,

may result from the circulation in the body of toxic agents, both chemical and bacterial. Thus, in chronic alcoholism, extensive fibrosis of the liver is observed (cirrhosis of the liver, "gin-drinker's" liver), and the peripheral nerves may also show an interstitial fibrosis.

With regard to the poisons of infective disease, but little

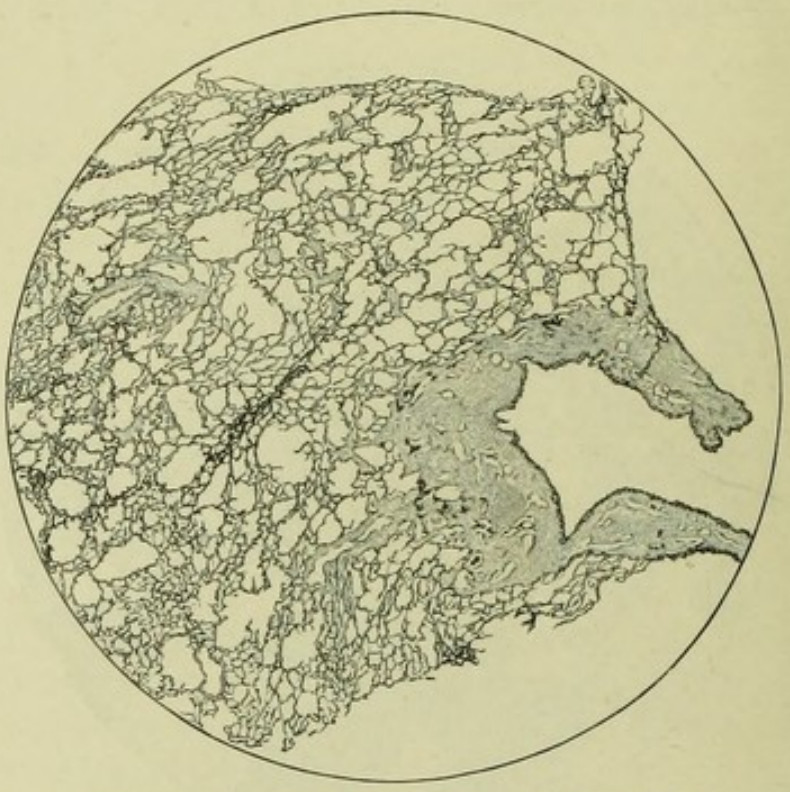


FIG. 79.—Bronchiectasis, the result of infection.

The figure shows a section of lung tissue under a low power. The alveolar tissue of the lung is seen, in many parts normal, but in other parts the alveolar wall is ruptured, producing an emphysematous condition.

The bronchial tube is shown on the right side of the figure, with epithelium proliferated and muscle intact, but with a dilated lumen and with great thickening of the walls, which are composed almost solely of connective tissue.

The spaces seen in the wall of the bronchus are partly blood vessels, and partly the remains of the alveolar tissue of the lung.

(From a case of bronchiectasis following broncho-pneumonia in a child.)

can definitely be stated. It appears, however, to be a fact that after infective diseases fibrosis of one or other organ may occur, more particularly of the liver, kidneys and heart.

Fibrosis of Special Parts.—Fibrosis of the heart muscle (Fig. 80) is observed as the result of pericarditis, where the cause is obviously inflammatory, and occurs in hypertrophy of the left

ventricle, such as is observed in chronic renal disease. In the latter case the causation is not very obvious, but it may possibly be due to the circulation of a poison in the blood. Fibrosis of the lungs is observed usually after an infection such as that of tuberculosis, more rarely of pneumonia and of actinomycosis. It may also result from the inhalation of solid particles from the air. Fibrosis of the liver occurs in various forms.

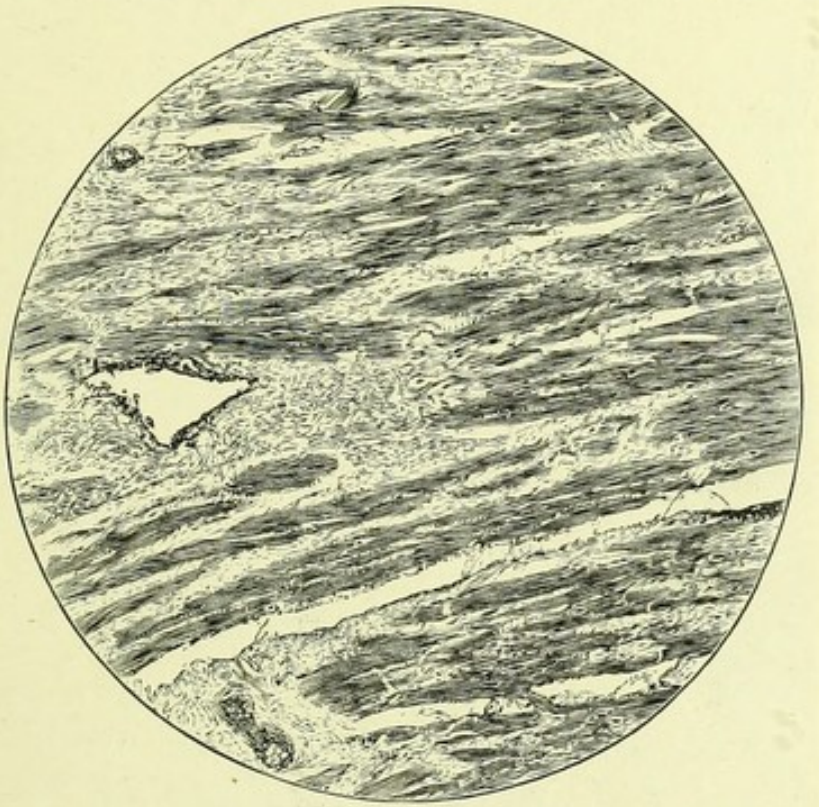


FIG. 80.—Fibroid heart.

A section of the muscle substance of the heart is shown in which the muscle fibres are depicted, for the most part cut longitudinally. The fibres themselves show the nuclei, but are widely separated by strands of connective tissue, containing blood vessels, and in parts are atrophied by pressure of this connective tissue.

In atrophic cirrhosis the irritant is alcohol, and the result is a multilobular cirrhosis (Fig. 81). In hypertrophic cirrhosis (Fig. 82) the irritant is unknown in some instances. In some cases it may be alcohol, in others the poison of an infective disease. In syphilitic cirrhosis the irritant is the syphilitic poison residing in the gummata. In cirrhosis secondary to chronic peritonitis the neighbouring inflammation accounts for the condition. Fibrosis of the spleen is a rare condition unless

it is associated with some form of infection, such as syphilis or malaria, with leukæmia or with a degenerative change such as albuminoid disease. In some cases of prolonged mechanical

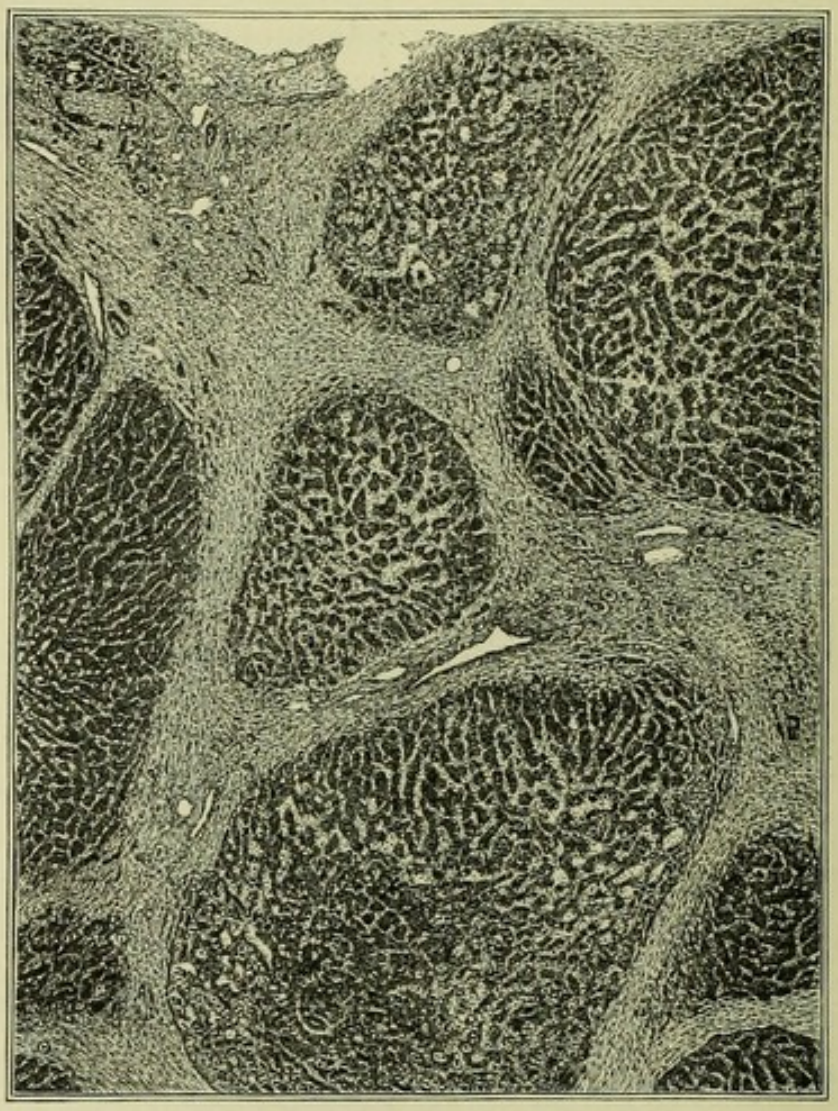


FIG. 81.—Multilobular cirrhosis of the liver under a low power.

The normal lobular structure of the liver is lost, and the substance of the organ is broken up by thick strands of connective tissue into masses varying in size, each of which consists of several lobules of the liver. The liver cells are undergoing atrophy, partly by pressure and partly by the cutting off of their blood supply. In the upper part, for example, there is a mass of liver cells which have almost completely degenerated, while in some parts, in the rest of the figure, the liver cells are practically normal in appearance.

congestion of the spleen, the trabeculæ of the organ are thickened; the fibrosis that occurs is but slight in extent. Fibrosis of the kidneys is observed mainly in the chronic forms of renal disease; some of these are obviously the

result of a previous inflammation; in other cases, such as that referred to as senile contracted kidney and the gouty kidney, the cause is not so obvious, although the condition is possibly due to the passage through the kidneys of irritant substances. In the nervous system, fibrosis is in some cases due to one or other form of infection, though the actual mode of produc-

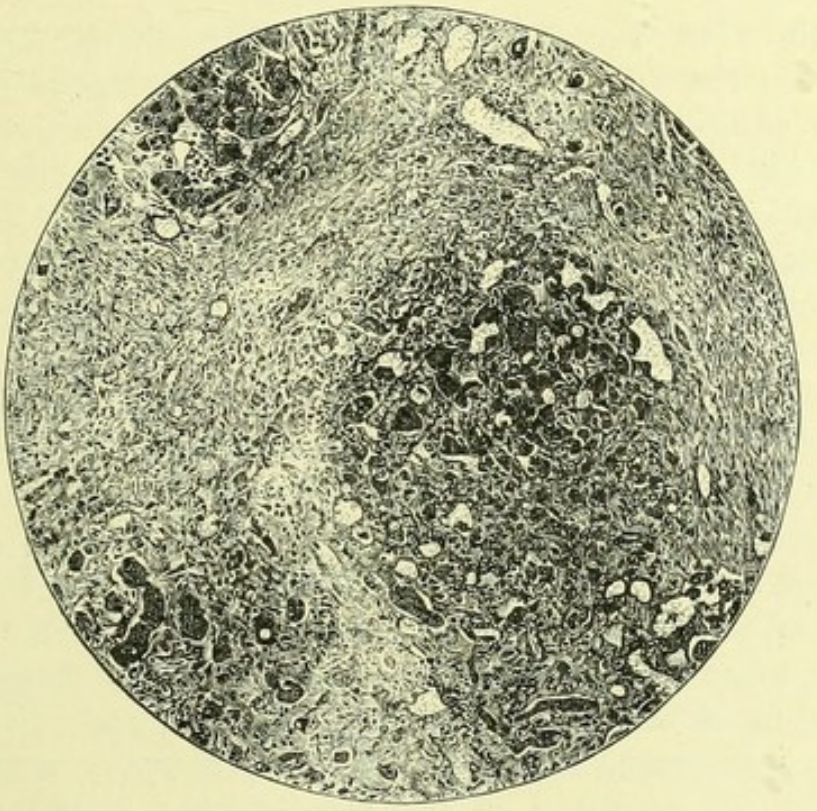


FIG. 82.—Unilobular or hypertrophic cirrhosis of the liver.

The normal lobular structure of the liver is lost, and the substance of the organ is, as in multilobular cirrhosis, broken up into masses by thick strands of connective tissue. The masses, however, are smaller than in the multilobular variety, and may consist of only one lobule. There is advanced degeneration of the liver cells, and in the strands of connective tissue elongated tracts can be seen lined by cells. These are considered by some as small bile-ducts, and by others as the remains of liver cells.

tion and the process of infection are at present but little understood.

The Regeneration of Tissues.—This term refers to the process by which, after a portion of an organ has been destroyed, regeneration takes place, supplying the loss. The process, however, is comparatively limited. Any great destruction of a part is not regenerated, and the place of the

part destroyed is occupied by fibrous tissue, by a cavity, or by an open wound. The individual tissues of the body vary considerably regarding their powers of regeneration, and it may be said generally that the more highly the tissue is specialised, the less power does it possess of regenerating. Thus with regard to nerve cells there is probably no regeneration; degeneration of a cell of the central nervous system means the loss of a cell. It is otherwise, however, with the peripheral nerves. With these nerves regeneration takes place in cases of solution of continuity, or of disease destroying the axis cylinder, when the healthy part of the nerve is in apposition to the diseased or severed part. For the process of regeneration to occur, the new fibres formed must grow down in the track of the nerve, and probably in the primitive sheaths of the damaged nerve fibres.

The question of regeneration of muscular tissue is of some interest, as the muscles, both voluntary and involuntary, undergo both in health and disease great variations in bulk and in activity. Thus hypertrophy occurs, and in hypertrophy of both kinds of muscle not only is there an increase in bulk of each fibre, but an increase in the number of fibres. This is more particularly the case with the heart muscle and the involuntary muscle of hollow viscera. If, however, damage be done to a small part of a voluntary muscle or of the heart, regeneration of the muscle fibre in the part does not occur. The place of the damaged and dead fibre is taken by connective tissue and a scar results.

The regeneration of connective tissue readily occurs from the surrounding healthy tissue, and by the same process which has been described in the repair of wounds. In connective tissue containing fat, the fat may also reappear, but the process is a slow one. With the modified connective tissues, such as cartilage and bone, regeneration takes place to a greater or less extent. Thus after destruction of a portion of cartilage the cells of the cartilage subdivide and form part of the new tissue, but this is for the most part composed of fibrous tissue, so that the regeneration is only partial and a scar results. A similar process takes place in the case of

bone. The new bone is formed by the cells of the periosteum, but not in so regular a manner as in the original bone, and in many cases the change is associated with great increase of fibrous tissue.

Epithelial cells, more particularly those of the skin, are readily regenerated. Destruction of the cells over an area is followed by the reproduction of cells at the periphery of the destroyed area, which gradually spread as a thin layer over the exposed subcutaneous tissue. The cells themselves have a considerable degree of independent vitality, inasmuch as they may be removed from a portion of skin and grafted on to the surface of an open wound, thus forming the centre for a new growth of epithelium. The epithelium of mucous membranes is also readily regenerated, the best example of which perhaps occurs in the healing of the ulcers of enteric fever. Subsequently to their healing but little evidence is obtained in the mucous membrane of previous ulceration. The epithelium of both the skin and mucous membranes is extravascular, and on this perhaps depends the great power of regeneration.

The question of the regeneration of the cells of solid organs, such as the liver and kidney, and of the glands of mucous membranes, is not easily decided. With regard to the liver the cells are capable of subdivision, and it might be considered probable that in an irregular destruction of cells of the liver neighbouring cells might divide and take the place of the destroyed cells. There is, however, but little direct evidence that this occurs. The cells of the liver are affected in cloudy swelling, from which recovery is possible without destruction of the cell. When the cell, however, undergoes fatty degeneration, some of the cells are destroyed, and regeneration may occur from the surrounding cells. Indeed, in prolonged illness from infective disease, it is probable that some of the cells of the liver undergo fatty degeneration, and yet complete recovery of bodily health may ensue.

The regeneration of the cells of glands, tubular or acinous, and of the kidney tubules, must be considered as doubtful, unless one or more cells remain comparatively normal. If

all the cells of an acinus or tubule are destroyed, it must be considered extremely doubtful whether regeneration can occur from the cells of the duct of the tubule or gland. Indeed it is frequently observed that in such cases the acinus or tubule forms a cyst, in which the cells show complete degeneration or are absent, their place being taken by fluid.

Hypertrophy of muscular tissue has already been referred to (p. 228). There remains for consideration the so-called hypertrophy of organs. Hypertrophy of a part is not synonymous with enlargement, which may be due to many different conditions—inflammatory and otherwise. The term must be limited to the enlargement of an organ to compensate for the loss of tissue in another part of the organ. If one lobe of a lung is congenitally small, the other lobe is greatly enlarged so as to compensate for the diminished size of the smaller lobe. If one kidney is congenitally atrophied the other kidney is much larger than normal. These examples of enlargement, however, occur during the process of intra-uterine and early extra-uterine development, and cannot be considered as in the same class as the question as to whether destruction of a portion of lung during life leads to a compensatory hypertrophy of another part of a lung, or whether destruction of a portion of one kidney or of the whole of one kidney leads to hypertrophy of the other. It may be said with regard to the kidney that there is no evidence that a true hypertrophy or an increase of the proper renal tissue occurs to compensate for the loss of substance by disease. In the case of a lung, when the air-breathing capacity of one part is diminished or destroyed, the rest of the lung may enlarge, and this is called *compensatory emphysema*. In this case also there is no evidence of the formation of new alveoli, but only of the dilatation of pre-existing alveoli and so of an increased air containing capacity.

CHAPTER VIII

CHANGES IN THE CIRCULATION IN DISEASE

BEFORE proceeding to discuss in what manner the circulation may be affected in disease, it is necessary to discuss some of the facts regarding the circulation of the blood in health.

The Heart and Vessels.—The central organ of the circulation is a force pump, which is sufficiently powerful for the complete circulation of the blood. Its activity depends on the integrity of the muscular substance and of the valves, as well as on the condition of the nervous system. The muscular substance has an independent rhythm of its own, which is well observed in the excised hearts of cold-blooded vertebrates. It is also seen in the excised mammalian heart, if means be taken to supply nutriment to the tissue. The contraction of the heart muscle is, no doubt, propagated along the fibres by direct continuity, so that division of the fibres proves a great hindrance to the propagation of contraction. The condition of the healthy vessels is of great importance in the maintenance of the normal circulation. The arteries possess elasticity and contractility, dependent on the elastic tissue and the muscular layers.

The circulation of the blood takes place in a closed system of tubes, the arteries contrasting with the veins in being over full. On the elasticity of the arteries, as well as on the great resistance offered to the circulation in the capillaries, depends the fact that the intermittent flow of the blood from the heart is converted into a continuous flow in the small arteries, the capillaries, and the veins. The venous

tension in the systemic circulation is much less than the arterial, and the flow of blood in the veins is somewhat more rapid as the larger vessels and heart are reached, owing to the suction action of the heart, as well as to the fact that the flow is from branched smaller vessels into large trunks.

The pulmonary circulation differs from the systemic circulation in the fact that there is no great difference between the arterial and venous blood pressure.

The Effect of the Nervous System on the Circulation is of the highest importance. The heart contains intrinsic ganglia, and is connected with the cardio-inhibitory centre in the medulla by the vagus and sympathetic fibres. The rhythmic contraction of the heart is due partly to an independent muscular rhythm, as has already been mentioned, and partly to the presence of the intrinsic ganglia. In the mammalian heart, more than in the hearts of cold-blooded animals, this inherent property of rhythmic contraction is closely dependent on the supply of nutriment to the muscle fibre, and on the pressure of the blood in the cavities of the heart. The vagus and sympathetic fibres of the heart are the channels by which the organ is affected reflexly through the cardio-inhibitory centre. Through the vagus, inhibitory impulses are transmitted to the heart, whereby the beat becomes less frequent, diminished in size, or ceases altogether. Through the sympathetic fibres, augmentor impulses are transmitted, whereby the heart beat is increased in force and in frequency. Section of the vagus nerves leads to augmentation; section of the sympathetic fibres does not, in all cases, lead to slowing of the heart, although such has been stated to be the case.

The influence of the nervous system on the arteries is by means of the vaso-motor nerves connected with the vaso-motor centre in the medulla; this centre is mainly excited reflexly. The main vaso-motor nerves are the constrictors, stimulation of which leads to contraction of the artery, and section of which leads to dilatation. Active vaso-dilatation may also occur.

In health, the arteries of a part or organ vary in size, and so allow more or less blood to pass to the part. More

blood passes when the organ is active than when it is in a resting state, and this mechanism which comes into action reflexly through the vaso-motor centre, plays, as is obvious, a great economic rôle in the circulation of the blood. The dilatation of the arteries of a small area produces no appreciable effect on the circulation of the blood or on the general arterial tension, but if a large area of arteries is affected, then there is a general lowering of blood pressure. This, for example, occurs when the arteries of the abdominal area supplied by the splanchnic nerves are dilated, leading to fulness of the abdominal veins.

The pulmonary arteries have been shown to possess vaso-motor nerves, but their effect is much less than on the systemic arteries. Thus, similiarly, with the arteries of the brain; nervous fibres are found in the pia mater, but the circulation in the brain is not directly affected by innervation from the vaso-motor centre, and the blood pressure follows that of the general systemic circulation.

Circulation of the Blood in Disease.

The circulation of the blood in disease is affected by—(1) The condition of the heart; (2) the condition of the blood vessels; (3) the condition of the central nervous system, as affecting the heart and vessels.

The ways in which the circulation may be affected are manifold, and comprise:—

1. *The effect of general disease*, which may act either by affecting the supply of nutriment to the tissues under consideration, as, for example, by impoverishment of the blood (diminution of oxygen, increase of carbonic acid, diminution of proteids), or by the circulation of poisons which may have a specific effect on the heart itself, sometimes on the blood vessels, and frequently on the nerve centres connected with the vascular system.

2. *By local disease of the heart or vessels.*

A. Effect on the Circulation of Disease of the Heart.—This

will be discussed under the headings—1. The Effect of Diseases of the Pericardium; 2. The Effect of Changes in the Muscular Substance, and the Effect of Disease of the Coronary Arteries; 3. Disease of the Valves and the Effect of Malformations.

I. *Effect of Diseases of the Pericardium.*—The pericardial sac is of great value in the normal action of the heart, as it allows the contractions of the organ to take place without embarrassment by the surrounding organs. It is affected in many different ways by disease: by inflammation, which may cause a rapid effusion into the sac or subsequent adhesions; by a slow and passive effusion, as in general dropsy; by new growths passing in from without; or by hæmorrhage into the sac. Of these conditions, however, the most important from the present point of view are the occurrence of inflammatory effusion and the occurrence of general adhesions. The effect of inflammation without these conditions is on the muscular substance, and will be discussed under that heading.

Effect of Pericardial Effusion.—The effect on the circulation of the blood of fluid in the pericardial sac does not necessarily depend on the amount of liquid present. Large quantities of fluid may be present in the sac without producing any obvious effect on the circulation. This occurs in cases of passive effusion, where the liquid is slowly thrown out, and the sac accommodates itself to its increased contents. It is in active effusion, where the liquid is rapidly thrown out, that effects are observed. The main factor in producing an effect on the circulation is the degree of tension of the liquid in the pericardium. Normally, the sac shows a negative pressure of 3 to 5 mm. of mercury, and it is when this pressure becomes positive and is rapidly increased, that effects are observed. The main results are a small, compressible pulse, varying greatly in frequency, though usually above the normal; muffled cardiac sounds, with an increase of distinctness of the second pulmonary sound; a diminished arterial tension, and an increased venous tension, which is sometimes evidenced by cyanosis and turgescence of the veins of the upper part of the body.

There is experimental evidence to show that the effects of pericardial effusion on the circulation are due to the degree of tension of the fluid in the sac (Cohnheim).

In testing the effect of pericardial effusion, the sac was filled with varying quantities of warm oil by a tube which was connected with a manometer. Not only is the tension in the pericardium thus measured, but, by injecting more and more oil, it can be increased. At the same time tracings were taken of the blood pressure in the femoral artery, the jugular vein and in the pulmonary arteries and veins. If the oil is slowly injected until the pericardial pressure rises to 30 or 40 mm., there is but little effect, but if the tension is increased to double this, two results are observed: in the first place, the arterial pressure falls 20 or 30 mm. of Hg, and the venous pressure rises 60 mm. of soda. This is in the systemic circulation, and the same results are observed if the pericardial pressure be even further increased. Thus, when it rises as high as 100 to 120 mm., the pressure in the femoral artery falls one half, the respiratory and systolic elevations and the blood pressure being diminished. The venous pressure rises still higher than before, up to 100 mm. of soda. The removal of the pericardial pressure causes a return to the normal condition. Still greater pressure in the pericardial sac causes a still greater increase of the venous pressure, while the arterial pressure diminishes until the systolic elevations are no longer observed in the curve, and the animal is pulseless. Recovery is still possible if the pericardial pressure be rapidly removed; otherwise death ensues.

The pulmonary circulation does not behave in quite the same manner as the systemic. There is normally but little difference between the pressure in the pulmonary artery and vein, contrasting strongly with the great difference of pressure in the aorta and the large systemic veins near the heart. In the over-filled pericardium, the pulmonary arterial pressure falls, but the venous pressure also falls, unlike what occurs in the systemic veins.

The pressure of the blood within the arteries depends on—(1) The resistance offered to its passage through the small

arteries and the capillary network; (2) On the power of the left ventricle; and (3) On the amount of blood discharged at each ventricular contraction.

In the experiments under consideration, conditions (1) and (2) are unchanged, so that the fall of blood pressure is not dependent on any change in the peripheral resistance or in the power of the left ventricle. The diminution of blood pressure depends on the third factor, that is, on the diminution in the amount of blood discharged at each ventricular contraction. This diminished output is a sequence of the diminished flow of blood into the heart during diastole. A rise of venous pressure does not necessarily follow a fall of arterial, as, after section of the cervical cord, it does not rise, although there is a great fall of arterial pressure.

The cause of the rise of venous pressure in over-filled pericardium is the diminished flow of blood into the heart, whereby the venous system becomes over full.

Venous Pulse in Pericardial Effusion.—According to some, the venous stream into the auricle and ventricle is, normally, practically continuous, being but little affected by the auricular systole. In over-filled pericardium, the venous blood may enter only during the diastole; the contraction of the auricle as well as the increased tension in the pericardium, preventing its entrance during the systole of the auricle. A pulsation in the veins of the neck ensues. This pulsation is pre-systolic, preceding the ventricular systole, and it may be called the *pre-systolic venous pulse.* The auricular systole, with the increased tension in the pericardium, momentarily prevents the entrance of blood from the over-filled veins. The pulsation in these veins thus ensues during the contraction of the auricle. This venous pulse may be compared with the systolic venous pulse, which occurs in tricuspid regurgitation. This is produced by the contraction of the right ventricle, imparting an impulse through the incompetent tricuspid valve into the dilated veins which enter the auricle.

II. *The Effect of Disease of the Heart Muscle on the Circulation.*—The continued action of the heart muscle in health

depends on the integrity of the fibres and their continuity, on the integrity of the nerves and cardio-inhibitory centre in the medulla, and on the supply of oxygenated blood through the coronary arteries. These arteries arise near the commencement of the aorta, and at each systole of the left ventricle blood enters them.

1. *Disorder of the Coronary Circulation.* — The heart of cold-blooded animals will continue beating for some hours in the absence of a continuous supply of nourishment, but with the mammalian heart this does not occur, unless steps be taken to supply a continuous flow of nutrient fluid. If this is done, at a proper temperature, the heart continues to beat for some time. If, in the rabbit, the coronary circulation be suddenly stopped, the heart ceases to beat; both sides simultaneously, or the right last. In the dog important results follow the ligature of one of the large branches. After about ninety seconds, irregularity and infrequency of the cardiac beat is observed, followed by sudden stoppage in diastole. This is an important result, and may be explained by the fact that the contraction of the layers of fibres of the heart is due in part to their continuity; a solution of continuity of the fibres prevents the proper propagation of the contraction. Thus, when fibres in the frog's heart are divided, perhaps only one impulse in three will pass over the gap made. The right and left coronary arteries supply different regions, and their anastomosing branches are but few in number. Ligature of a large branch would therefore seriously and suddenly interfere with the nutrition of a large area of muscle fibres, and thus the continuity of propagation of impulse would be interfered with. The ventricle beating imperfectly tends to dilate, from the accumulation of blood constantly pouring into it, and eventually the accumulation is sufficient to make the heart stop in diastole.

The coronary arteries are frequently found diseased in middle and old age. Atheromatous patches are observed along their extent, but, more important than this, the orifices of one or both arteries may be stenosed, sometimes very considerably. In some cases of sudden death, this stenosis of

the coronaries is the only lesion found to account for the fatal result, and it is evident that, if extreme, it is adequate to do so, inasmuch as the heart muscle receives much less blood than normal, and, if called upon to make a certain effort, as in unwonted exercise, may fail to respond, and so cease to beat; in the same manner as when, in the dog, one of the large branches of the artery is ligatured. Disease and occlusion of the coronary arteries lead to changes in the heart muscle; more particularly, to fatty degeneration of the muscle fibre (frequently patchy), and to the occurrence of fibroid patches, which are sometimes roughly triangular in shape, and may pass through the whole extent of one or other ventricle, more particularly the left. These fibroid patches, which are sometimes met with in the hypertrophied left ventricle in renal disease, have been ascribed to embolism of the coronary artery, leading to necrosis, and subsequent fibrosis. Disease of the coronary arteries may have some relation to the causation of angina pectoris, but the exact connection is at present impossible to define.

2. *Disease of the Heart Muscle itself.*—The muscle fibres may be damaged in many different ways, which may be summarised as follows:—

(*a*) An interstitial inflammation may occur, in association with pericarditis, and lead subsequently to a diffuse fibrosis of the heart, whereby the muscle bundles are more or less widely separated. Similar diffuse fibrosis is met with in certain cases of hypertrophy of the left ventricle associated with chronic renal disease (Fig. 80).

(*b*) Fibroid patches, as stated above, may occur, causing a solution of continuity in the muscle layers.

(*c*) Degeneration of the muscular substance itself may occur. Cloudy swelling of the fibre occurs in acute infective disease, and may be followed by degeneration of the fibre. Fatty degeneration (Fig. 66) also follows certain intoxications, such as by alcohol, arsenic and phosphorus. It occurs in profound anæmias, and in malignant disease, and is associated with adherent pericardium.

(*d*) Loss of muscle substance occurs in fatty infiltration of

the heart, which affects, at first, mainly the apex of both ventricles and the substance of the right ventricle. In this case, the increase of surface fat, as well as the spread of fatty tissue in between the muscle fibres, not only diminishes the actual amount of muscle, but causes a solution of continuity in the muscle fibres (Fig. 65).

(*e*) Pigmentary degeneration of the fibre or brown atrophy of the heart, is undoubtedly a sign of a damaged heart, but it is difficult to define exactly how much damage it means. The muscle fibre is atrophied as well as pigmented. The pigment visible is simply an increase of the normal pigment of the muscle fibre.

The lesions which have been mentioned may affect the contraction of the muscle fibre, and so the heart activity, in two different ways:—

1. The muscle fibre itself may be greatly weakened, as in the case, more particularly, of cloudy swelling and of fatty degeneration, but also of the other conditions mentioned.

2. The propagation of the impulse of contraction may be greatly hindered by the separation of fibres, as in the case of diffuse fibrosis and of fatty infiltration; or continuity may be actually destroyed, as in the case of fibroid patches.

With all these conditions leading to diminished heart power, there is a tendency to accumulation of blood in the heart, and so to dilatation of the organ.

Dilatation and Hypertrophy of the Heart.—As has previously been stated, the regular beat of the heart depends upon more than one factor, namely, on the power of the heart muscle, on the degree of resistance in the peripheral arteries and the capillaries, and on the action of the nervous system on the heart itself.

During health the mean arterial pressure remains fairly equable. In the early period of prolonged muscular exercise it is somewhat increased, owing, no doubt, to the sudden strain on the heart. The general tendency of muscular exercise is, however, to lessen blood pressure. On the other hand, it is said that sedentary occupations tend to increase the

mean arterial pressure. Although the beat of the heart does vary somewhat in health, it is within very small limits. In disease, however, the activity is greatly modified by:—

1. Structural alterations in the valves of the heart or the cardiac muscle.

2. Structural alterations in the arteries.

3. Increase of peripheral resistance in the arterioles.

4. The influence of the nervous system on the heart itself.

One of the results of these changes is dilatation of the cavities, with or without hypertrophy. Dilatation is associated with hypertrophy, the latter being the natural mode of overcoming the former, or producing *compensation*, as it is called. Dilatation may affect all the cavities of the heart or it may be partial. In dilatation the cavities are over-filled, and this over-filling is an exaggeration in the ventricles of the normal condition, as these cavities probably never completely empty themselves, even at the height of the ventricular systols.

General dilatation of the heart results fro n three chief causes:—

1. One or other of the conditions weakening the muscular structure already discussed (p. 238).

2. As the final result of a valvular lesion. This first leads to partial dilatation, but subsequently, owing to an increase of the lesion, the circulation of the blood through the heart may be so embarrassed that general dilatation occurs.

3. As the result of an increased peripheral resistance, lasting for a considerable time (months or years).

Whether hypertrophy accompanies dilatation or not depends on many factors. The heart muscle, like other muscles, has a reserve power, that is, it does not contract to its full strength. This is shown by the fact that stimulation of the augmentor fibres of the sympathetic nerves causes great increase in the strength of the contractions of a normal heart, as well as by the fact that a moderate degree of pressure exerted on the heart, as in the experiments with over-filled pericardium (p. 234), leads to no alteration in the

blood pressure; a similar result occurs when a moderate degree of obstruction is experimentally applied to the exit of blood from the heart by the aorta and pulmonary artery.

In both these instances, the blood pressure does not vary because the heart contracts more forcibly. Within certain limits, the amount of blood in a cavity of the heart acts as a direct stimulus to its contraction. If, in disease, more blood enters the cavities of the heart, there is a greater effort on the part of the organ to expel its contents, and this effort continued for long periods (months or years) leads, under certain conditions, to hypertrophy of the muscle.

The conditions under which increased action and hypertrophy occur are (1) the degree of stress which is laid on the heart, and (2) the power of the heart muscle to undergo hypertrophy. Thus, if the resistance to be overcome is too great, as in some instances of dilatation and in some cases of increase of peripheral resistance, hypertrophy may not occur, even in the absence of obvious disease of the muscle fibre.

The main cause preventing hypertrophy is disease or malnutrition of the muscle fibre of the heart.

The conditions in which hypertrophy of the heart occurs may be summarised as follows:—

1. In some cases of prolonged overwork, as in young labourers and soldiers. In some prolonged cases of exophthalmic goître there is hypertrophy of the heart, in which, no doubt, the main factor is the continued rapid action, with a healthy muscle substance.

2. In valvular lesions hypertrophy results from the overfilling of one or more cavities.

3. In adherent pericardium there is the same explanation.

4. In renal disease hypertrophy of the left ventricle occurs as the result of an increase of peripheral resistance, due to fibrosis and contraction of the arterioles. In emphysema the right ventricle hypertrophies, owing to the increased resistance in the pulmonary arterioles.

For hypertrophy to occur the muscle substance must be healthy, so that it is chiefly observed in young adults.

The hypertrophy which is produced as a result of disease may

be sufficient to overcome the embarrassment of the circulation; in other words, the occurrence of hypertrophy may compensate for the lesion which has produced the defect in the circulation. But in many cases it is not sufficient. The muscle has hypertrophied to its full extent, which is not sufficient to carry on the circulation properly. When compensation is completely compensatory, the normal mean arterial pressure may be maintained, as in cases of slight valvular lesion, but when hypertrophy is not sufficient, the circulation is carried on with a diminished arterial pressure, so that there is a tendency to venous stagnation.

In cases where hypertrophy is due to increased peripheral resistance, as in cases of chronic renal disease, the circulation is carried on at a heightened mean arterial pressure, which may, of itself, lead to serious results (p. 256).

III. *The Effect of Valvular Lesions on the Circulation.*—The closure of the auriculo-ventricular orifices is for the purpose of preventing the blood passing back into the auricles when the ventricles contract, in order that it should go into the large arteries. Closure of the semilunar valves of aorta and pulmonary artery, not only prevents regurgitation of blood into the ventricles, but is a great aid in maintaining the pressure in the arteries. These elastic tubes are over full and are part of a closed system, which begins at the semilunar valves and ends at the auriculo-ventricular valves.

In all valvular lesions part of the blood stream is diverted from its natural direction, so that there is a diminished normal stream; there is less blood sent into the aorta, and so there is a diminished arterial pressure. This is the case in the chronic lesions of the valves usually met with in disease.

Stenosis of the Aortic and Pulmonary Orifices.—In both these cases there is obstruction to the exit of blood from the heart. Whether this occurs solely from disease of the valves, as in the case of the aorta, or from congenital malformation of

the pulmonary valves associated with some contraction of the artery itself, the obstruction tends to cause accumulation of blood in one or other ventricle, which thus has to contract more forcibly to expel its contents.

It has been found experimentally that there are two periods of events, according to the degree of obstruction. Thus, if the obstruction is only moderate in degree, no change is observed in the femoral arterial pressure curve, or in the venous pressure curve taken from the jugular vein; that is, there is no alteration in either the arterial or venous pressure. If, however, the obstruction be very great, there is a steep and sudden descent of the arterial pressure. The absence of any change in blood pressure in moderate obstruction is due to the fact that the ventricle acts much more forcibly, there being an increased intraventricular pressure, and that this increased contraction is sufficient to drive the blood past the obstruction. With extreme stenosis this does not occur. In aortic obstruction, with diminished arterial pressure is associated an increased venous pressure. The cardiac beat is augmented, the pulse is infrequent and shows in a tracing a high rise with a flattened top.

The main point shown by the experiment quoted is that, with a certain degree of obstruction produced by valvular disease, the heart is capable of maintaining the circulation, hypertrophy occurring to enable it to do this for months or even years. If, however, the obstruction is great, hypertrophy is insufficient and dilatation results. In the compensated cases, there is a tendency to dilatation, and it may be said that dilatation only becomes of pathological importance, when the systolic contraction is unable to empty the cavity.

Incompetence of the Aortic Orifice.—This, which is usually referred to as *Aortic Regurgitation*, occurs when the valves are not accurately apposed to each other, because the cusps are partly destroyed, distorted, or adherent. Various degrees occur, allowing a greater or less amount of the blood sent from the left ventricle to regurgitate after the ventricular systole. Dilatation therefore occurs succeeded by hypertrophy, but

the dilatation which occurs in well-marked cases of regurgitation is not explained by the small amount of blood which regurgitates immediately after the ventricular systole. In aortic incompetence the arterial system is no longer closed in the sense in which the word is used above (p. 242). The lesion of the valves tends to make the left ventricle part of the arterial system, so that the tension of the blood in the arteries is continuously being exerted on the walls of the ventricle during its diastole, and this continuous pressure is one factor in producing dilatation in such cases. There is thus never a negative pressure in the ventricle.

Stenosis and Incompetence of the Mitral Orifice.—Disease of the mitral valve ends in producing rigidity and distortion of the valve, and shortening and adhesion of its chordæ tendineæ. The effect on the orifice is to produce constriction, resulting in obstruction and incompetence. The final effect on the orifice varies considerably. Thus, obstruction to the passage of the blood from the left auricle into the ventricle may be the chief defect present, as in the case of the so-called *button-hole mitral.* In other cases, with some obstruction, the valve is permanently open by a narrow orifice, so that there is not only difficulty in the passage of the blood from the auricle to the ventricle, but during the ventricular systole part of the blood is diverted from the aortic stream back into the auricle. In still other cases, the valve, although stiff, is widely open, being held in this position by the shortened and adherent chordæ.

Incompetence of the valve may also be produced by dilatation of the left ventricle, as occurs in some cases of aortic valvular disease, in dilatation of the heart due to degeneration of the muscle substance, and in adherent pericardium.

It is evident that the circulation would be embarrassed in different ways, according to the degree of stenosis or incompetence of the orifice. In extreme stenosis, without regurgitation, the left auricle becomes over full, while the left ventricle is natural in size or even smaller than normal.

The increase of pressure in the left auricle obstructs the flow of blood in the pulmonary system, and the right ventricle tends to become over full and so to dilate. Hypertrophy of the left auricle may occur, although, when such hearts are examined after death, there is usually no evidence of hypertrophy. The chief means of overcoming embarrassment of the pulmonary circulation is hypertrophy of the right ventricle, and if the stenosis of the orifice be not extreme, this hypertrophy may be sufficient to carry on the pulmonary circulation efficiently for many years, although at an increased pressure. If, however, stenosis be extreme or the right ventricle be unable to hypertrophy sufficiently, either from pericardial adhesions, from fatty infiltration, or from degeneration of the muscular substance, dilatation of the whole right side of the heart occurs, resulting in tricuspid regurgitation and an embarrassment of the systemic venous circulation. In some of these cases, which have lasted many years, a thickening of the tricuspid valve, leading to stenosis of the orifice, is observed. Such an occurrence must be attributed to the long-continued increase of pressure on the right side of the heart.

In cases where the incompetence of the mitral valve is greatly in excess of the stenosis, the results on the circulation are not the same as when stenosis is the only or predominant lesion present. There is, in such a condition, a free entry of blood from the pulmonary veins into the auricle and into the ventricle, but at the ventricular systole, a greater or less quantity of blood is sent back into the auricle through the incompetent valve. This tends to dilatation of the left auricle. This quantity of blood passes back again into the ventricle during diastole, as well as the further supply of blood from the pulmonary veins. The whole of the left side of the heart, therefore, obtains more blood than normal, and so tends to dilate, the dilatation being followed, in the case of the left ventricle, by well-marked hypertrophy. This hypertrophy is merely secondary to the increased pressure, due to the increased amount of blood in the left ventricle. It is a question how far it is beneficial in remedying the

defective circulation caused by the mitral incompetence. If this is not great, it is evident that a more powerful contraction of the ventricle will send a larger amount of blood into the aorta, as well as a larger amount back into the left auricle, but the more blood sent into the aorta, the greater is the relief to the pulmonary circulation, even though the valve lesion remains the same; so that, in slight degrees of incompetence, the hypertrophy of the ventricle must be considered as beneficial.

In great degrees of incompetence, however, the extra amount of blood sent by the hypertrophied ventricle into the auricle, as well as into the aorta, tends greatly to increase the embarrassment of the pulmonary circulation. In mitral incompetence, as will now be seen, for the hypertrophy of the left ventricle to be beneficial in carrying on the circulation, there must be, in addition, hypertrophy of the right ventricle. The regurgitation of blood into the auricle at each ventricular systole tends to embarrass the pulmonary circulation. This embarrassment, accompanied as it is by an increase of pressure, throws increased work on the right ventricle at its systole, and its hypertrophy tends to relieve the embarrassment, even at the expense of increase in the pressure in the pulmonary area.

It is now readily seen how hypertrophy of the right ventricle, associated with hypertrophy of the left, may compensate for the hindrance to the circulation caused by incompetence of the mitral valve. Thus, although the hypertrophied left ventricle tends to drive more blood into the aorta, as well as back into the left auricle, the hypertrophied right ventricle, acting more vigorously and increasing the pressure in the pulmonary system, contracting at the same time as the left ventricle, tends to diminish the quantity of blood sent into the left auricle by the left ventricle, so that this increase of pulmonary pressure leads to an increased quantity of blood being sent into the aorta. It is true that however much the right ventricle may hypertrophy, the pressure in the pulmonary area cannot even approximate that in the aorta, but the increase of pressure in the pulmonary area

with the hypertrophy of the left ventricle, may be sufficient to carry on the circulation, with but few signs of embarrassment.

In conditions where there is great mitral incompetence, and great dilatation and hypertrophy of the left ventricle, complete compensation is not possible, inasmuch as the increase of pulmonary pressure produced by the contraction of the hypertrophied right ventricle is insufficient to diminish appreciably the large quantity of blood sent back into the left auricle by the hypertrophied left ventricle. The continued dilatation of the left ventricle, in such cases, leads to further embarrassment of the circulation through the heart.

Hypertrophy of the right ventricle necessarily occurs in cases of compensation in mitral incompetence. When compensation fails or is incomplete, owing to the great regurgitation of blood, or to the inability of the right ventricle to hypertrophy, tricuspid incompetence ensues, and so a great embarrassment of the general systemic venous circulation.

Associated Valvular Lesions.—Lesions of the aortic valve or mitral valve may exist alone, but in some cases they are associated. The three main conditions to be discussed are:—

1. Where there are well-marked lesions of both valves.

2. Where there is a slight lesion of one valve, and a well-marked one of the other, either aortic or mitral.

3. Where the mitral valve is affected secondarily to well-marked aortic valvular disease.

1 and 2. In the condition where both sets of valves show well-marked lesions, the embarrassment of the circulation through the heart is extreme, whether the aortic valve show mainly obstruction or incompetence, or the mitral valve show mainly stenosis or incompetence. Thus, the great hypertrophy produced by aortic obstruction leads if mitral regurgitation be present as well, to very great embarrassment of the pulmonary circulation, an embarrassment which cannot be overcome by any hypertrophy the right ventricle is capable of undergoing. The same remarks apply to the association of aortic regurgitation with mitral regurgitation. The

association of stenosis of the mitral valve with disease of the aortic valves is not uncommon. In this condition, although the left ventricle gets less blood from the left auricle, it is yet over full, owing either to the obstruction, or to the regurgitation of blood at the aortic orifice. It is evident, however, that if the disease be not excessive, great hypertrophy of the left ventricle would not lead at its systole to any increase of pulmonary pressure, and it might be great enough to drive a sufficiency of blood into the aorta, while the hypertrophy of the right ventricle might be sufficient to overcome a moderate obstruction at the mitral orifice. With a certain degree of mitral stenosis, therefore, associated with a slight degree of aortic valvular disease, the circulation of the blood may be maintained sufficiently for the needs of the economy. If the aortic valvular disease is, however, well marked, great dilatation of the left ventricle ensues and life is impossible, owing to the left ventricle being incapable of emptying itself.

3. In cases of aortic valvular disease, sometimes when there is obstruction but more often when there is regurgitation, mitral regurgitation occurs without disease of the valve, owing to the dilatation of the left ventricle, and this secondary mitral incompetence may lead to the results of embarrassment of the pulmonary circulation previously described. This functional dilatation of the mitral valve results from dilatation of the ventricle, which is caused either by a great degree of aortic valvular disease—so great that hypertrophy is unable to compensate for it; by extra strain put on the heart, as in the following of a laborious occupation; by weakness of the muscular wall, due either to fatty infiltration or degeneration, or by pericardial adhesions.

B. Changes in Cardiac Force and Rate in Disease.—The cardiac rate in health varies within somewhat wide limits, but the variation is, as a rule, only momentary. It is called out by some special need of the organism. Age, sex, exercise, food and sleep affect the rate. In the female the rate is somewhat greater than in the male. In infancy and

childhood the rate is more frequent than in adult life and old age, as is shown in the following table (Kirke's *Physiology*).

	The Average Rate per Minute is
Before birth	150
Just after birth	140 to 130
During the first year	130 „ 115
During the second year	115 „ 100
During the third year	100 „ 90
About the seventh year	90 „ 85
About the fourteenth year	85 „ 80
In adult age	80 „ 70
In old age	70 „ 60
In decrepitude	75 „ 65

Exercise increases, for a time, the cardiac rate as well as the force of the contraction of the heart. A heavy meal also increases the rate of the beat; while, in sleep, the rate is diminished. Section of both vagi increases the cardiac rate, the inhibitory influence, reflected from the cardio-inhibitory centre along the vagus, being thus removed. Stimulation of the peripheral end of the cut vagus at first diminishes the size of the beat, and, if the stimulus be great, stops the heart in diastole. Stimulation of the sympathetic fibres causes not only an increase in the cardiac rate, but also an increased force in contraction. The fibres conveying this stimulus are called *augmentor fibres*. The rate may also be affected reflexly. Peripheral irritation of a sensory nerve, or of a serous membrane, acts reflexly and slows the heart.

In disease, the cardiac rate and force are, in many instances, affected by way of the nervous system, but other factors occur which also have a profound influence. These are abnormal conditions of the heart muscle and of the valves of the heart, and changes in the peripheral resistance.

In health the force of the cardiac beat shows variations only as far as the reserve muscular power of the heart will allow. Some of these variations are dependent on alterations in the peripheral resistance, but variations due to this cause are only momentary. Any prolonged increase or

diminution of the peripheral resistance is an abnormal, and so a diseased, condition.

The heart rate is slowed:—

1. By the action of drugs, such as digitalis, muscarin and others.

2. In hypertrophy of the heart, more particularly following aortic valvular disease; and in increase of the peripheral resistance.

3. In many cases of weakness of the muscular wall, as, for example, in fatty degeneration.

4. As a result of disease of the brain, either of the meninges or of the cerebral substance.

5. In certain unexplained, mainly toxic, but possibly functional, conditions, referred to as *bradycardia*. Examples of this occur in the convalescence of acute fevers, such as typhoid fever, in jaundice and myxœdema.

The cardiac rate is increased:—

1. By the action of certain drugs, such as digitalis in large doses, atropine and others.

2. In cases of cardiac disease, in which, owing to disease of the valves (uncompensated), there is a hindrance to the normal passage of the blood from the heart.

3. In cardiac failure, whether due to want of compensation of a valvular lesion, to disease of the muscle of the heart, to an increased peripheral resistance, or to toxæmia, such as that occurring in pyrexia and in exophthalmic goitre.

4. By an effect on the central nervous system, the cardio-inhibitory centre being affected by functional or organic disease of the other parts of the brain, or reflexly from the organs of the body.

The cardiac rate becomes irregular:—

1. In valvular lesions, such as those of the mitral valve in which the wave of contraction is interfered with.

2. In weakness or disease of the muscular wall.

3. As the result of a profound toxæmia.

4. As the direct effect of disease of the brain.

An explanation of the changes of the cardiac rate in disease is, as is evident, by no means simple. Thus, *slowing*

of the heart occurs in some instances in association with an altered condition of the muscular substance. It is observed in hypertrophy of the left ventricle following aortic obstruction, and, in this case, a slow action is associated with the increased strength necessary to drive the blood from the left ventricle into the aorta. But a slow rate may also be associated with fatty degeneration of the muscular tissue, and the explanation is, in this case, that it is due to the fact that the muscle is weak and takes a long time to expel the blood from the heart. Slowing due to the action of drugs may be caused by an action either on the muscular substance or on the intrinsic ganglia of the heart. The chief examples of slowing of the rate occur as a result of direct or indirect excitation of the vagus centre. Owing to excitation of this centre, slowing occurs in asphyxial conditions, carbonic acid being the irritant. Reflex slowing is the explanation of the diminished cardiac rate in cerebral affections. In those instances of bradycardia occurring after infective disease, the explanation appears to be twofold, the diminished rate being due to an effect of the poison either on the muscular substance or on the vagus centre itself. The latter explanation is more probably the correct one.

Acceleration of the cardiac beat also does not admit of a simple explanation. It may be due to an affection of the nerve centre, to an altered condition of the muscle of the heart, or to a hindrance to the normal circulation of the blood through the heart, and all these conditions may end in so-called cardiac failure, in which there is a gradually increased frequence of the cardiac beat, with a fall of blood pressure. Increase of the cardiac rate, due to an affection of the nerve centre, is observed in pyrexia, in which it must be ascribed to a paralysis of the vagus centre. It is sometimes said that this paralysis is caused by the circulation of the hot blood. This explanation, however, does not appear to be adequate. The increase of cardiac rate varies considerably in pyrexia (p. 39), not only in different individuals, but in different febrile diseases, and although, in so-called acute

fevers, the average rate of increase is about ten beats per minute for 1° F. rise of temperature, yet this proportion of increase does not hold good, even for many cases of high or even moderate pyrexia. Moreover, in some of these conditions the increased cardiac rate not only persists, but may actually first manifest itself, after the pyrexia has ceased. It appears more rational to ascribe the increased cardiac rate to an effect of the poison of the infective disease in paralysing the vagus centre. Similar paralysis of the vagus centre is observed in the later stages of some cerebral affections, meningitis or cerebral tumour.

In functional conditions of the central nervous system, grouped together as neurasthenia, an accelerated cardiac rate is observed, as well as in exophthalmic goître, and, in both these cases, acceleration may be ascribed to paralysis of the vagus centre.

Acceleration may be due to weakness of the muscular substance, as in fatty degeneration, in fatty infiltration, and in infective disease, when the muscle fibre undergoes degeneration. In the first two cases, the acceleration is due to the ineffectual efforts of the heart to empty itself, and is, no doubt, increased by a reflex effect on the cardiac centre in the medulla. In the case of an infective disease, the acceleration is due to the effect on the muscle fibre, as well as to the direct effect on the vagus centre already considered.

In valvular disease acceleration is noted when there is want of compensation, and more particularly in cases of mitral disease. The prime cause of acceleration is the disturbance of the circulation of blood through the heart, and, no doubt, in mitral disease, to the disturbance of the circulation in the left auricle, and subsequently in the right heart. Reflex stimulation, starting from the auricle, affects the heart centre and increases the cardiac rate, which must be considered as, in part, an attempt of the heart to force on the blood by rapid contractions.

Irregularity of the cardiac beat, either in force or rhythm, arises either from conditions in the centre in the medulla,

or in the heart itself. The irregularity that is so commonly associated with disease of the mitral valve, either stenosis or incompetence, is a sign of want of compensation of the valvular lesion.

The regular rhythm of the heart is dependent partly on the contractions initiated in the auricles and passed on to the ventricles, and the degree of contraction of a cavity is dependent on the amount of work to be done, *i.e.*, the tension of the blood in the cavity. In mitral disease, the work of the left auricle is increased by its containing too much blood and by the obstruction at the mitral orifice. When compensation is adequate, the contraction of the left auricle, aided by the increased force of the hypertrophied right ventricle, may be sufficient to initiate regular contractions of the heart. When compensation is inadequate, the contraction may at one time be more powerful than at another, and so alterations in the force of contraction of the heart result. Irregularity in rhythm may be explained in the same way, some of the initiating contractions of the auricle not being sufficiently powerful to cause a general contraction of the ventricles.

In many instances where compensation is adequate during quietude of body, irregularity is induced by muscular exertion. In normal conditions, more stress being thrown on the heart by exertion, it would beat more rapidly and powerfully, and the blood would pass more quickly through it. The embarrassment of the circulation of the blood in the left auricle in mitral disease would be increased by the greater flow of blood to the heart, and by the attempts to beat more rapidly. That this interference with the initiating impulse of the auricle is one of the chief causes of the irregularity observed in disease of the mitral valve, is shown by the fact that irregularity of the heart is not nearly so common a symptom in aortic valvular disease, and when it does occur, it is due to another cause, namely, a weak action of the muscular substance, associated with degeneration of the muscular fibres.

Weakness or disease of the muscular wall may be the cause of irregularity in the action of the heart, as in fatty degenera-

tion, fatty infiltration and the degeneration of the muscular substance observed in infective disease. The main cause of the irregularity in these instances is the weak contraction of the muscular fibres. Their power is inadequate with every contraction to empty the heart; that is, the work to be done is more than the muscle can perform. This would necessarily lead to irregularity in the contraction of a normal regularly contracting muscle. The heart, having lost its reserve power of contractility, might, for a certain number of beats in the minute, contract sufficiently forcibly, but after this effort, it becomes exhausted and drops one or two beats. Irregularity is therefore observed in cases of cardiac failure.

The regularity of the heart may also be affected through the cardio-inhibitory centre in the medulla. An irregular beat is not infrequently observed in affections of the brain, either tumour or meningitis, and this is to be explained by a reflex effect on the medullary centre or by a direct effect, owing to the increased intra-cranial pressure. It also results from the direct action of poisons on the centre, as in excessive tobacco-smoking. Irregularity may also be caused by an effect on the centre through the sensory nerves of the periphery, as is observed in cases of severe pain or vomiting, and, more particularly, when there is a slight lesion of the mitral valve, or some degeneration of the muscle substance. Whether the cardio-inhibitory centre can initiate impulses to the heart or not is not decided, but it is clear that, in certain conditions of the centre itself, it may, as a result of reflex stimulation, send to the heart, during a certain short period of time, impulses varying in intensity, either inhibitory, along the vagus nerve, or augmentor, along the sympathetic fibres. This would lead to irregularity both in force and rhythm of the cardiac beat. It is more likely to occur in a damaged centre, and this is observed, not infrequently, in moribund conditions, in which the vagus centre, as well as other parts of the nervous system, is affected.

C. Effect of Arterial Disease on the Circulation of the Blood.—The main factors in maintaining the normal circulation of

the blood have already been discussed, as well as the manner in which the circulation may be affected by the altered conditions of the heart in disease. Disease of the arteries may also affect the circulation, and in two ways—local disease affects the circulation of a particular part or organ; while general disease of the arteries has an effect on the main arterial blood-pressure, and so on the activity of the heart.

1. *Effects of Local Arterial Disease.*—The local diseases here under consideration are:—*Atheroma* (Fig. 83), which may be either local or general; *syphilitic arteritis* (Fig. 84); *tuberculous arteritis* (Fig. 47); and the *periarteritis* of the small vessels of the brain, which leads to the formation of miliary aneurisms. Disease leads, in the case of atheroma, to a loss of contractility and elasticity of the arterial wall, and to an enlargement of the lumen of the vessel. In the case of syphilitic arteritis, the disease is more local and leads to narrowing of the vessel. Normally the supply of blood to a tissue varies according to its activity, and the amount is regulated by the action of the vaso-motor nerves. During activity the vessels are dilated, and more blood passes to the part. During rest this physiological congestion disappears. If the artery has lost its elasticity and contractility, this physiological effect is not observed during activity, and an insufficient supply of blood thus results, when most needed by the tissues; disorders of nutrition therefore occur (Chapter XVIII.).

The arterial area affected by the disease is of importance. Thus, when atheroma affects the peripheral arteries, great defects of nutrition may occur in the muscles; but when it affects the vessels at the base of the brain only, no nutrition defects may be observed if the heart is normal and the mean arterial blood-pressure is maintained, inasmuch as the circulation of the blood through the brain is dependent on the general arterial blood-pressure.

In syphilitic arteritis of the arteries of the base of the brain, however, the circulation is affected, inasmuch as the lumen of the vessels is diminished, so that, the general circulation not being affected, there is a deficient supply of the blood to some parts of the brain leading to defects in nutrition.

Local disease of the arteries leads to thrombosis (Chapter XIII.) and to aneurism. An aneurism of the peripheral arteries has no effect on the general circulation; the circulatory defect is local, and dependent on the amount of blood which is allowed to pass through the aneurism. With aneurism of the aorta, the local dilatation of the vessel no doubt hinders, to some extent, the proper circulation of the blood, inasmuch as the vessel has lost its elasticity and contractility; but there is no increased resistance to the circulation of the blood, and so there is no hypertrophy of the left ventricle.

2. *Effect of Widespread Disease of the Arteries.*—The arteries throughout the body may be affected by a condition described as *angeio-sclerosis* (arterio-sclerosis) (Thoma). This includes two different conditions: atheroma and arterio-capillary fibrosis (Figs. 83, 85 and 86). Both these changes may be observed in the same individual. The effect of widespread disease depends on the nature of the disease and on the part affected. Thus, atheroma, which may affect in some instances the peripheral arteries of the body throughout the greater part of their extent, leads to dilatation and elongation of the vessel, which subsequently becomes tortuous, as well as to a loss of contractility and elasticity of the arterial wall. The arterioles, that is, the arteries just before they break up into capillaries, are usually not affected by the disease. On the other hand, it is the arterioles and smaller arteries which are affected in arterio-capillary fibrosis. Arterio-capillary fibrosis leads to diminution of the calibre of the artery and to a loss of elasticity; but, in the early stages, there may be hyper-

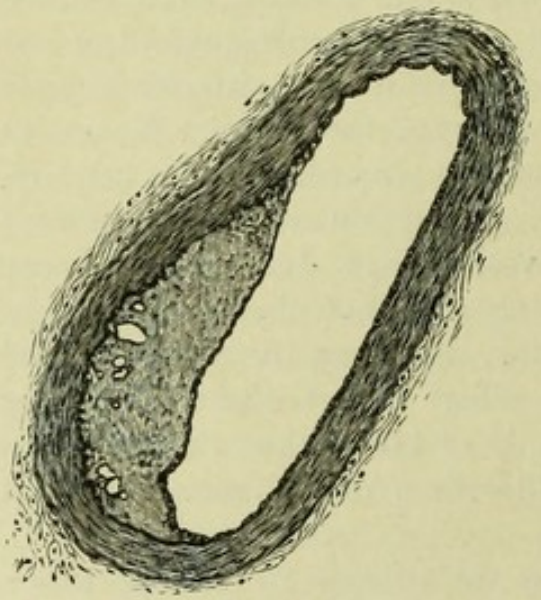


FIG. 83.—Atheroma.

Transverse section of a small artery, in which the external and middle coats are practically normal, but the internal coat in one part is greatly thickened by the formation of almost hyaline connective tissue. In the part of this connective tissue, near the elastic laminæ, are clear spaces.

trophy of the muscular coat and so an increased contractility. In any case, the condition leads to a great increase in the peripheral resistance to the circulation, so that it is difficult for the blood to pass from the arterioles into the capillaries. In widespread atheroma of the arteries, without disease of the arterioles, there is no increase of the peripheral resistance, and there is no difficulty in the passage

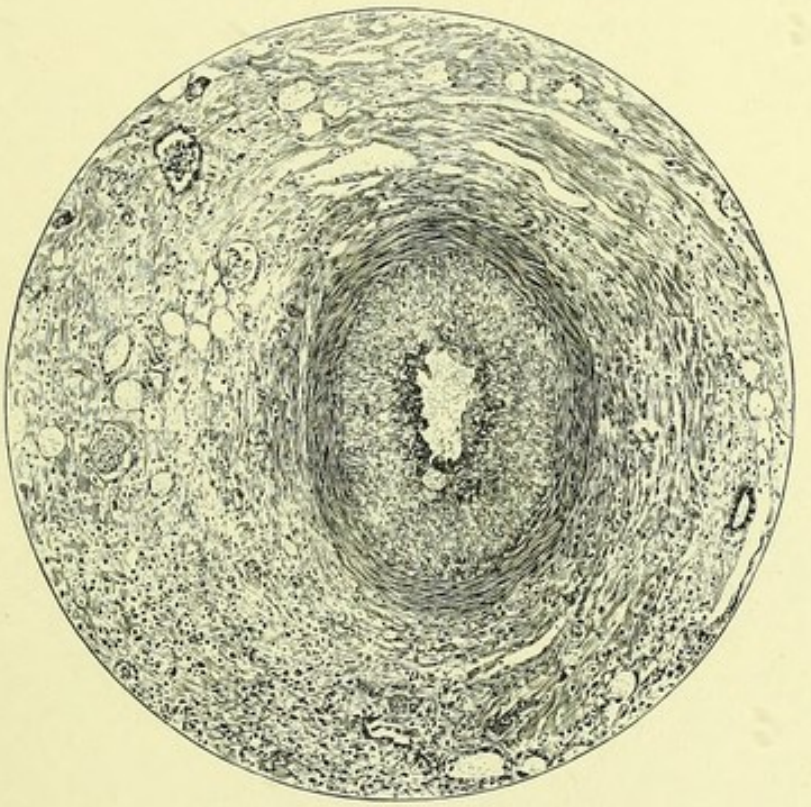


FIG. 84.—Syphilitic arteritis.

A transverse section of an artery is shown, in which the lumen is greatly narrowed and distorted. All the coats of the artery are thickened, the most marked thickening being in the internal and external coats.
(From a section near a local syphilitic lesion.)

of the blood from the arteries into the capillaries and veins. The loss of elasticity and contractility leads to a diminished mean arterial blood-pressure, so that there is a tendency to stagnation of the blood in the veins, or rather to a diminished venous blood-pressure. In arterio-capillary fibrosis, on the other hand, the mean arterial blood-pressure must be increased for the circulation to be maintained.

The maintenance of the arterial blood-pressure depends,

not only on the condition of the arteries, but also on the condition of the heart; so that the cardiac force and cardiac capabilities must be taken into account in considering the observed effects of peripheral disease of the arteries on the circulation. Arterio-capillary fibrosis is associated with an increase of the mean arterial blood-pressure, more particularly in cases of chronic renal disease. Owing to the increased

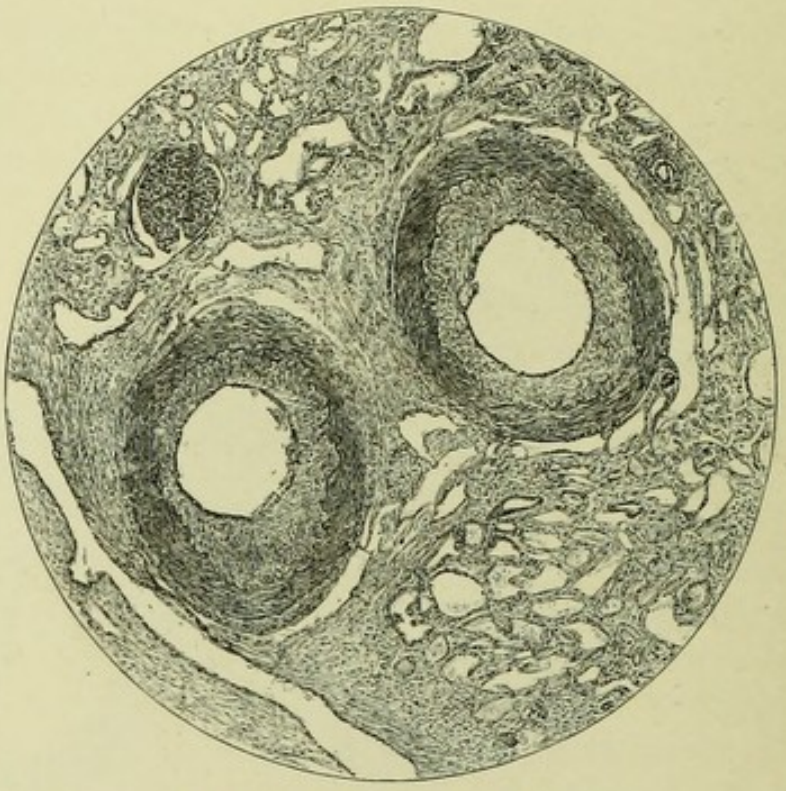


FIG. 85.—Arterio-capillary fibrosis.

A transverse section of two small arteries of the kidney is shown, with some of the renal substance, which was extensively fibroid.

The vessels show some thickening of all the coats, but mainly a fibroid thickening of the intima, diminishing the lumen of the vessel.

resistance in the arterioles, the heart has to act more forcibly in driving the blood into the capillaries. This leads—in the course of months and years—to hypertrophy of the left ventricle, the right being unaffected. This hypertrophy is a necessity for the maintenance of the circulation in this condition, and is indeed compensatory to the disease of the arterioles. Atheroma of the peripheral arteries may be associated with this condition; but, provided that the heart

is hypertrophied, and still capable of powerful contraction, the mean arterial blood-pressure is still high. The heart muscle, however, from one or other of the causes previously discussed (p. 238), may not be capable of powerfully contracting or of undergoing hypertrophy. In this case, then, there is a weakly-acting heart, as well as an increased peripheral resistance, and the left ventricle dilates. Conditions varying

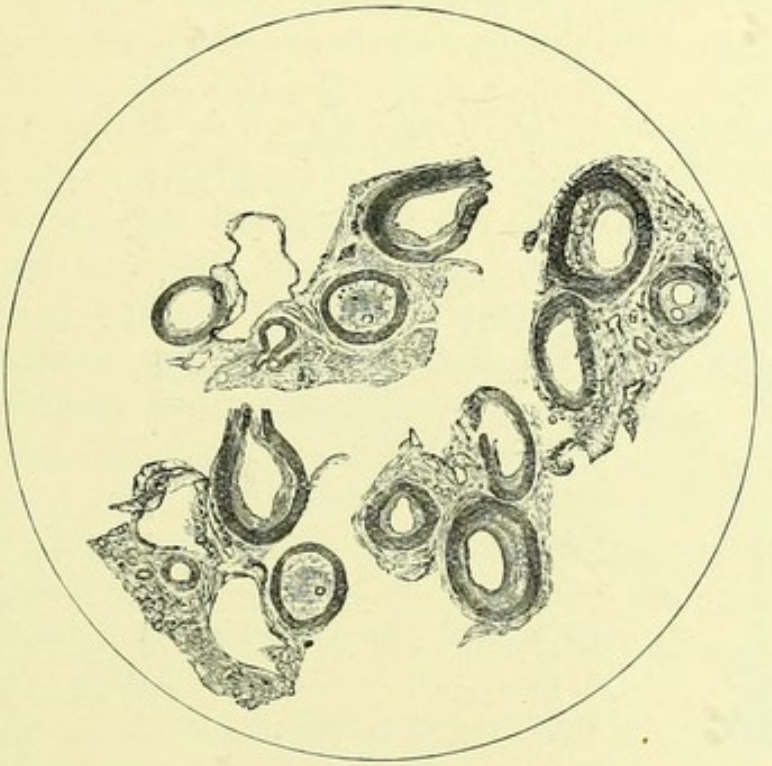


FIG. 86.—Arterio-capillary fibrosis.

The figure shows a transverse section of several small renal arteries. The lumen is contracted irregularly in the different vessels, due to an irregular thickening of the coats. In some the intima is chiefly affected, while in others the muscular coat is the chief one thickened. (F. W. Mott.)

between the two extreme cases described are frequently observed. A weakly-acting heart, when made to contract more powerfully, as by the administration of strychnine or digitalis, is observed to increase the mean arterial blood-pressure; so that, in an individual with chronic renal disease and a low arterial blood-pressure, this may become obviously increased by the administration of these drugs. Again, the high arterial blood-pressure in chronic renal disease may be increased by certain conditions, such as constipation or bronchitis,

or may be diminished by purgation, and by the administration of certain drugs, such as amyl nitrite and erythral nitrate. The action of these drugs in reducing the arterial blood-pressure has been ascribed to an effect on the arterioles, which are thereby dilated, and from this it may be concluded that a portion, at any rate, of the increased peripheral resistance is due to a muscular contraction of the arterioles. But it is possible also that part of the effect is due to an action on the heart, whereby its activity is diminished.

Measurements of the Blood-Pressure in Man.—The increase or diminution of the arterial blood-pressure is commonly gauged by means of the finger; and the "tension of the pulse," as it is said, estimated by the degree of pressure which is required to obliterate it. This, however, is not an accurate method, and, practically, determines only the extremes of arterial blood-pressure. A more accurate means of determining the arterial blood-pressure is by a sphygmometer (Hill & Barnard). This consists of a vertical glass tube, expanded above into a small bulb, closed by a glass cap, as in the figure (Fig. 87). A tube is attached below to a small india-rubber bag, which is filled with coloured fluid. The tube is graduated from zero to 200°, representing millimetres of mercury. To take an observation the tap is opened, the clamp attached to the wrist, and the bag placed over the artery. Gentle pressure on the bag brings the liquid up to zero, when the tap is closed. The bag is still further pressed down by means of the clamp on to the artery, causing the red liquid to rise in the tube, and the liquid exhibits pulsations corresponding to those of the artery. The maximum pulsation is the reading of the mean arterial pressure. In healthy young adults the normal blood-pressure in the radial artery is from 110 to 120 mm. Hg., and is constant. When lying down, the pressure is slightly less. During muscular

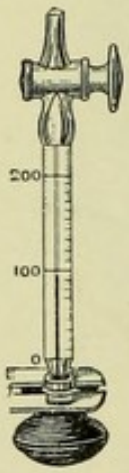


FIG. 87.—Hill & Barnard's sphygmometer. (*For description, see the text.*)

exertion, the pressure is increased, but afterwards becomes subnormal. The pressure is lowered during rest and sleep, but raised during mental exertion.

By means of a hæmodynamometer (Oliver) the arterial pressure can also be measured, the record being made on a dial. This is also used for observing venous pressure.

On the Causes of Arterial Degeneration.—The occurrence of tuberculous or syphilitic arteritis is simply explained as an infection of the arterial wall by the specific infective agent. The explanation of the occurrence of arterio-capillary fibrosis, and of atheroma, the other form of angeio-sclerosis, is not so easy. Arterio-capillary fibrosis is associated with chronic renal disease, and has not been observed in any other condition. The muscular hypertrophy and fibroid thickening of the arterioles are probably to be ascribed to the irritant effect of some poison, although this has not been discovered. Atheroma is a degenerative process. It is difficult to see how it can be a compensatory process, as considered by some. The affection of the intima of the artery, and subsequently of the middle coat, would be due either to an effect on the inner wall of the vessel, or to an effect on the arterial blood supply of the wall of the artery.

As predisposing or leading causes in the production of atheroma, old age, strain, alcohol, lead, syphilis, and gout, have been instanced. Strain might act by increasing, within long periods, the tension inside the artery; gout and alcohol by producing deficient nutrition of the tissues. Syphilis, again, may act by producing disease of the vasa vasorum.

The effect of continued increase of blood-pressure in producing atheroma is seen in its occurrence in cases of granular contracted kidney. Many cases of atheroma occur without granular contracted kidney, and in these cases the disease may be localised. Thus, in individual cases, the first part of the aorta may be alone affected, or the whole of the aortic trunk, the peripheral arteries alone, or the arteries at the base of the brain. In such cases, in the absence of any high arterial pressure, there must be some other element

besides strain in the production of the arterial degeneration. How far syphilis may be a cause is not yet determined. In any case, it can only be considered a predisposing cause, as atheroma itself is not a syphilitic lesion.

The influence of increased pressure is observed in atheroma of the pulmonary artery and its branches, which occurs in long-standing cases of mitral stenosis, where a high pulmonary arterial pressure has been maintained for a long period.

CHAPTER IX

CHANGES IN THE CIRCULATION

Œdema and Dropsy.

ŒDEMA and dropsy may be defined as a collection of fluid in the connective tissues and cavities of the body, and in certain of the organs, such as the lungs, brain and intestines; it is not observed in the liver, kidney, or spleen substance, or in the spinal cord. It may be either local, affecting a limb, part of the lungs or brain, or one body cavity—such as the abdomen; or it may be general, in which case it either affects the subcutaneous tissues chiefly (anasarca), or the cavities of the body chiefly, as well as the subcutaneous tissues.

Local œdema is observed in pressure on veins, in thrombosis and in inflammatory areas. General œdema is observed in morbus cordis, in anæmia, in cachexia and in Bright's disease.

Œdema of the pericardium is called hydropericardium; of the pleura, hydrothorax; and of the peritoneum, ascites. The pericardium normally contains a small amount of fluid, and small quantities are present in the pleura and peritoneum. Connective tissues contain lymph, a fluid derived from the capillaries and the tissues, but this does not collect normally in the tissues, and is reabsorbed partly by the lymphatics and partly by the venous capillaries.

Chemical Composition of the Lymph and other Similar Fluids.—The composition of lymph may be contrasted with that of plasma in the following table, in which the composition of

human lymph, of lymph from the thoracic duct of the dog, and of blood plasma, is given :—

	Blood Plasma.	Human Lymph.	Lymph from Thoracic Duct (Dog).
	Grammes per cent.		
Total Solids . . .	9.71	1.366	3.7 to 5.5
Proteids	...	...	3.4 to 4.1
Fibrin	0.405	0.107	...
Other Proteids . .	7.884	0.230	...
Extractives . . .	0.566	0.131	...
Sugar	0.1 to 0.15	0.1	0.1
Urea	0.009	0.016 (dog)	...
Inorganic Salts . . .	0.855	0.878	0.8 to 0.9

It is important to note that the composition of lymph varies considerably, according to the part of the body from which it is obtained, and this more particularly affects the percentage of proteids present. Thus, from the limbs the lymph contains 2 to 3 grammes per cent. of proteids; from the intestines, 4 to 6 per cent.; and from the liver 6 to 8 per cent. Like blood plasma, lymph coagulates spontaneously — sometimes slowly, sometimes rapidly. It contains cell elements and leucocytes. The composition of chyle differs from that of lymph mainly in the presence of a larger amount of total solids, and the larger proportion of proteids and of fat. (See Table, p. 266.)

Composition of Œdema and Dropsical Fluids.—These are all alkaline, and yellowish or yellowish-green, from the presence of a lipochrome. The specific gravity varies between 1010 and 1015; and in long-standing cases—more particularly of ascites — the specific gravity may be much lower. These figures contrast with the specific gravity of blood, which is

1060; of blood plasma, which is between 1026 and 1029; and of inflammatory exudations, which is 1018 or over.

Dropsical fluids do not coagulate spontaneously, unless serum or blood be added. They contain a few cell elements, or these may be entirely absent. In their want of coagulation and the absence of the cell elements, they contrast with the normal lymph.

The substances which are present in the dropsical fluids are the same as those which exist in lymph, but in different proportion: thus, of proteids, fibrinogen, serum globulin and serum albumin are found; of extractives, cholesterin and sugar; while the salts are like those of the blood and in about the same proportion. The composition differs from that of lymph and blood plasma chiefly in the proportion of the total proteids present. Thus, blood serum contains from 5 to 6 per cent. of total proteids; the fluid in hydrothorax, from 0.8 to 2 per cent.; ascitic fluid, from 0.03 to 0.8 per cent. (or an average of about 0.4 per cent.); the fluid of subcutaneous œdema, 0.2-0.6 per cent.; hydrocele fluid, 0.5 per cent. (p. 9). Although, in all instances, the total proportion of proteid present in dropsical fluids is less than in lymph, the actual amount found in the fluids from one region in different cases varies considerably, and nowhere more than in the case of ascitic fluid, in which, sometimes, only traces of proteid are found, while, at other times, there is a considerable quantity.

In considering the lower proportion of proteid in dropsical fluid as compared with lymph, the composition of the blood in the particular case of disease must be taken into account, as well as other factors to be presently discussed.

In Chylous Dropsical Effusions, such as chylous ascites and chylous hydrothorax, the composition of the fluid differs from those just considered, owing to the large proportion of fat present. In clear dropsical effusions only a small proportion can be obtained, about 0.034 per cent.; whereas, in chylous effusions, the amount of fat varies between 0.9 and nearly 2 per cent. This is shown in the following table, in which the percentage composition of chylous effusions is compared

with that of chyle and of a specimen of ascitic fluid, comparatively rich in proteids :—

	Human Chyle.	Chyle of Dog.	Serum of Dog.	Chylous Ascites.	Ascitic Fluid.
Specific Gravity .	...	...	...	1012 to 1022	1010 to 1015
Total Solids . .	4.1 to 5.6	9.623	6.399	5.2 to 7	1.55
Proteids . .	1.1 to 1.3	2.216	4.524	1.9 to 4.46	0.617
Fat, Cholesterin, and Lecithin .	...	...	...	0.93 to 1.993	...
Other Organic Substances .	...	0.234	0.291	...	0.024
Salts . . .	0.625	0.792	0.876	0.48 to 0.7	0.846

The amount of sugar both in chyle and chylous fluid varies considerably.

The comparison of chylous ascites with ascitic fluid shows that it bears the same relation in composition as chyle does to serum, inasmuch as it contains a much larger proportion of proteids and a much larger proportion of fats. This is due to the direct mixture of chyle with ascitic fluid. The fluid of chylous hydrothorax is practically of similar composition to that of chylous ascites.

The Normal Formation of Lymph and its Functions.—Lymph is a part of the fluid portion of the blood which is passed out of the capillaries, and so has become extravascular. It is collected, no doubt, in the main, in the lymph spaces of the tissues, and soon passes into the lymphatic system, and through the thoracic duct into the venous system. Part of it is also collected by the venous capillaries and so enters the venous system directly. The lymph in the lower part of the body mixes, in the thoracic duct, with the lymph from the liver and from the intestinal tract; and, as has already been stated, the lymph from the limbs contains less proteid than that coming from the liver.

It has been much debated whether the formation of

lymph is due to a process of filtration and osmosis from the blood capillaries (Ludwig); or whether it is a secretion of the endothelial cells of the capillaries (Heidenhain). In the first case, the formation of lymph would be, in great part, dependent on the intravascular pressure, more particularly the blood pressure in the capillaries. The greater the increase of intracapillary pressure, the greater the amount of lymph which would leave the vessels. In the second case, the formation of lymph would be dependent not so much on the intracapillary pressure as on the secretory activity of the endothelial cells of the capillaries. The conclusion that the lymph was probably a secretion rested on experiments which were directed to show, not only that an increased formation of lymph was independent of the intracapillary pressure, but that the injection of certain substances (lymphagogues) into the body caused an increased flow of lymph in the thoracic duct, varying in composition according to the substances used. Thus it was found that, associated with the great fall of arterial blood-pressure in the vessels below complete obstruction of the thoracic aorta, there was, practically, no alteration in the flow of lymph from the thoracic duct. Obstruction of the inferior vena cava above the diaphragm causes a general fall of blood-pressure, with a greatly increased flow of lymph from the thoracic duct; whereas, obstruction of the portal vein causes an increased flow of less concentrated lymph.

Lymphagogues are divided into two classes. In the first, the injection of such substances as commercial peptone and leech or crayfish extract, causes an increased flow of concentrated lymph through the thoracic duct. Although the action of these substances is also to produce a fall of arterial blood-pressure, yet the increased flow of lymph occurs even if the pressure is not lowered. In the second class, the injection of sodium chloride, sugar, and potassium iodide in concentrated solution causes an increase of thin lymph, without any appreciable rise in the arterial pressure. These results, which at first appear to be in favour of the secretion hypothesis, are, however, better explained by the idea that the process is one

of filtration (Starling). It has been shown that the increased flow of lymph on the ligature of the portal vein is due directly to the increased pressure in the capillaries of the portal system, the pressure being so great that, not only large hæmorrhages occur in the mucous membrane of the intestine, but red corpuscles are present in the lymph. In obstruction of the vena cava just above the diaphragm, the increased flow of lymph in the thoracic duct, with an increased percentage of solids in the lymph, is due to increased lymph production from the highly permeable capillaries of the liver; the lymph does not come from the intestines. This case, again, is an instance of increased capillary pressure, which produces a greater effect in the liver than it does in the intestines. Again, in cases in which the aorta is obstructed, although there is a great fall of arterial pressure, which would influence considerably the capillary pressure in the intestines, there is but little alteration in the pressure in the hepatic capillaries; and that the increased flow of lymph is due to the changes in the liver is shown by the fact that ligature of the hepatic lymphatics stops the flow of lymph in the thoracic duct when the thoracic aorta is obstructed.

With regard to the action of the so-called lymphagogues, it may be said that the injection of the saline lymphagogues into the circulation causes an increase in the volume of the blood, owing to osmosis, the water of the tissues being attracted into the blood stream. This plethora leads to an increase in the capillary pressure, and to this is most probably to be ascribed the increased flow of lymph, inasmuch as bleeding carried out previous to the injection of the lymphagogue prevents the increased flow of lymph, the water which dextrose or salt attracts from the tissues into the blood being just sufficient to bring up the volume of the blood to the normal.

The action of Heidenhain's first class of lymphagogues is not so readily explained. The increased flow of lymph following the injection of leech extract does not appear to be dependent on a rise of capillary pressure; for, although this rise of capillary pressure does occur, especially in the portal

system, it is only temporary, while the increased lymph flow lasts about three times longer. These substances are poisons, which, injected into the circulation, may damage the endothelial cells, and it does not appear necessary to conclude that they stimulate secretion. They may, by damaging the endothelial cells, cause an increased permeability of the capillary wall.

In discussing the causes of œdema and dropsy in disease, it appears more reasonable to consider that the factors in the production of these conditions are an increased capillary pressure, an increased permeability of the capillary wall, and a condition of hydræmic plethora, all of which are factors which would lead to an increased transudation of lymph. But in œdema, an increased transudation is not the only point. There may be diminished absorption of the lymph which is transuded, and this, theoretically, would have the same effect in the production of œdema as an increased transudation. In œdema and dropsy, however, an increased transudation of lymph from the capillaries is the main factor, diminished absorption of lymph from the tissues playing a subsidiary part.

For the purpose of discussion these facts may be set forth in the following table (Starling):—

Increased Transudation of Lymph is produced by—(*a*) An increased capillary pressure, which may be produced by: (1) venous obstruction; (2) vaso-dilatation; (3) plethora.

(*b*) Increased permeability of the capillary wall which may be produced by: (1) local injury, as in inflammation; (2) malnutrition, as in wasting diseases and anæmias; (3) by poisons.

(*c*) Hydræmia, or a watery condition of the blood.

Diminished Absorption of Lymph occurs: (*a*) through the lymphatics, as in paralysis of the limbs and obstructions of the large lymphatic trunks; (*b*) through the veins, as in venous obstruction, hydræmia, and in concentrated transudations.

It is necessary to consider some of these points in detail.

Venous Obstruction.—The obstruction to the flow of blood

in the veins is a common factor in the production of œdema and dropsy. Thus, it follows thrombosis of certain veins, for example, the femoral, and pressure on the large venous trunks, and occurs in stagnation of the blood in the right side of the heart from whatever cause. If the femoral vein of a normal animal be tied, no œdema of the leg is produced. This is probably because the venous obstruction is not sufficient. If the vena cava inferior be tied, œdema of both legs occurs, and a similar result follows the injection of plaster of Paris into the veins, as in Cohnheim's experiments. This accords very well with what is known of œdema of the leg, following thrombosis of the femoral vein in disease. The thrombosis which occurs is not limited to the femoral vein, but is usually present in the smaller veins of the leg, so that the condition is comparable to the experiment of injecting plaster of Paris. An attempt was made to show that the production of œdema of a limb with venous obstruction was in part dependent on the action of the vaso-motor nerves. Thus, as has been stated, ligature of the femoral vein causes no œdema of the limb, but this ensues if the sciatic nerve be cut, or the vaso-motor nerves of the limb before they join the sciatic nerve (Ranvier). This, however, does not show that there is any special influence of the nervous system in the production of œdema. The section of the sciatic nerve causes arterial dilatation, and so an increase in the capillary pressure, which has already been augmented by the tying of the vein. In the conditions of disease, in which venous obstruction is the main or sole cause of the œdema, besides the increased transudation of lymph, there is also a diminished absorption, and this is brought about partly by the obstruction to the main venous trunk. Absorption by the lymphatics is also impeded, for the movement of the lymph in the limbs is dependent, partly on the suction power of the venous blood at the entrance of the thoracic duct into the jugular vein, but mainly on the movements of the limb; that is, the muscles by their contraction press on the lymphatics in the fascia, so aiding the onward movement of the lymph. The obstruction to the vein and the impeded movements of the

lymph, owing to the quiescence of the limb, are the chief reasons why the increased amount of fluid in the tissues is not removed.

Lymphatic Obstruction. — Obstruction of the lymphatic trunks, causing a diminished absorption of lymph, is not a common factor in the production of œdema. This is mainly owing to the fact that the lymphatics freely anastomose, and, in the limb, it requires very extensive thrombosis of the lymphatics to produce œdema, such as, in all probability, occurs in white leg. On the other hand, obstruction, thrombosis, or pressure on the thoracic duct, may aid in the production of œdema, though such obstruction is not infrequently followed by rupture.

Increased Permeability of the Capillary Wall.—This must be considered one of the important factors in the causation of increased transudation of lymph. The capillary wall is composed of endothelial cells, closely apposed to each other, and, though flattened, they are living and show some degree of contractility. There are no openings between the cells, and there is no evidence that, in disease, such openings or stomata are formed. The living capillary wall thus offers a considerable resistance to the passage of the albuminous plasma through it. There is some evidence that the permeability of the capillary wall is not the same in all parts of the healthy body. Increased permeability of the wall is shown not only in the larger amount of liquid which is transuded, but in the larger proportion of albuminous substances that this liquid contains. The lymph from the limbs contains from 2 to 3 per cent. of proteids; that from the intestine from 4 to 6 per cent.; whilst that from the liver contains from 6 to 8 per cent. These facts may be taken as indicating that the liver capillaries are more permeable than the intestinal, and the intestinal capillaries than those of the limbs.

In disease, increased permeability of the capillary wall is conceivably produced by direct injury—either mechanical or toxic—or by the malnutrition of the endothelial cells, which

is due to defective nutritive properties in the blood, such as a watery condition (hydræmia), or anæmia. Thus, œdema of the rabbit's ear follows an artificial anæmia, produced by bandaging the ear. After the bandage is removed, the part becomes œdematous, and, more particularly, if, in addition, the vein at the root of the ear is tied, so as to increase the capillary pressure. The increased transudation in inflammation was ascribed to injury of the vessel wall by the poisons present in the inflamed area (p. 9); and this indeed seems to be the only explanation, the effect of the poisons on the capillary wall leading to an increased permeability.

Hydræmia and Hydræmic Plethora.—Hydræmia is a term applied to the condition of the blood in which there is a deficiency of the solid constituents, both dissolved and floating. The total volume of blood is not increased. In hydræmic plethora the volume of blood is greater than normal, while the watery condition of the blood is still present. A condition of hydræmia alone might be supposed to aid the exudation of lymph by diminishing the proportion of proteids dissolved in the blood, and so aiding their passage through the capillary wall. This may be so, and instances of the occurrence of œdema are recorded following the removal of blood, such as was frequently resorted to as a part of medical treatment in the early part of the last century. This empirical observation does not decide the part which hydræmia plays in the production of œdema, inasmuch as no accurate account was taken of the diseased condition for which venesection was performed. Bleeding a healthy animal leads to only a slight increase in the lymph flow and to no œdema. If, however, a condition of hydræmic plethora is produced, the lymph flow is enormously increased, and, with a very great degree of plethora, there is some œdema of the internal organs, although not of the extremities. Hydræmic plethora may be produced artificially by the intravenous injections of large quantities of normal saline fluid. The lymph flow is thereby increased over thirty times in a few minutes, but this effect is prevented if, previous to the injection of the saline fluid, the animal is bled

to the same amount. In hydræmic plethora, however, it is not so much the condition of the blood which leads to the increased flow of lymph, as the increased capillary pressure which it causes.

Œdema and Dropsy in Diseased Conditions.—In disease, œdema and dropsy may be either local or general. Examples of *local œdema* and dropsy are: (1) Inflammatory œdema; (2) Hydrocephalus; (3) Obstruction of the venous circulation, where this occurs as a result of blocking of, or pressure on, large veins, or as the result of embarrassment of the circulation in the right side of the heart; (4) Œdema of the lungs, resulting from embarrassment of the pulmonary circulation. If the embarrassment at the heart is great, the œdema may become general. (5) Local dropsy is also observed in anæmia (chlorosis) and pernicious anæmia, and in chronic diseases, with or without cachexia, and towards the end of the disease. It is observed in diabetes, and in the advanced stages of tuberculosis, malignant disease and disease of the central nervous system. In these conditions the œdema is almost solely confined to the lower extremities; (6) Angeio-neurotic œdema is a local condition occurring mainly in neuritis and neuralgia.

General Dropsy is observed: (1) In embarrassment of the circulation on the right side of the heart, whether this occurs from disease of the mitral valve, or in the advanced stages of emphysema and bronchitis; and (2) in Bright's disease. In general dropsy, due to cardiac embarrassment, the subcutaneous tissues of the lower extremities are first affected; then those of the abdominal wall. This is followed by ascites, hydrothorax and hydropericardium. In the majority of instances, the upper extremities and the head and neck are not affected. In Bright's disease the œdema due to the renal disease is general, and it first affects mainly the subcutaneous tissues of the limbs, trunk, head and neck. In the later stages of chronic Bright's disease, the general dropsy of the subcutaneous tissues and body cavities which occurs, is mainly cardiac in origin.

In considering these examples of œdema and dropsy from the point of view of their causation, it is obvious from what has been said that it is impossible to give any concise and accurate classification of the different conditions. In the causation of œdema in a particular disease several of the factors which have been discussed operate. Two classes, however, stand out as distinct: *Inflammatory or Toxic Œdema*, and *Obstructive Œdema*. A third class has been suggested, of *Hydræmic Dropsy*, or œdema associated chiefly with an altered condition of the blood. But, as has been shown, hydræmia is not of itself a potent cause of œdema, and, in including the œdema of anæmia, cachexia and Bright's disease, under the head of hydræmic dropsy, it is evident that there must be some other cause than the hydræmia to account for the condition.

Venous obstruction dropsy is clear in its explanation. Thus, in the obstruction of a vein, the main cause of the œdema is the increased capillary pressure, with the diminished absorption previously discussed. In diseases of the heart, œdema is observed in disease of the mitral valve, which causes embarrassment of the circulation on the right side of the heart; and, in other conditions of dilatation of the right heart, whether the result of long-continued emphysema and bronchitis, of aortic valvular disease (in the later stages), of adherent pericardium, or of a general dilatation of the heart due to disease of the myocardium. In all these conditions there is obstruction to the flow of venous blood through the heart, and, from this point of view, the causation of the œdema may be said to be the same as in venous obstruction. Subsidiary causes, however, are to be noted. In prolonged disease, there is hydræmia; there is also injury to the vessel wall, due to malnutrition, and there is the passage of a diminished quantity of urine.

In anæmia, the œdema occurs round the ankles, and is rarely extensive. The changes in the blood may be said to predispose to œdema by diminishing the nutrition of the endothelial cells, but the main cause is an increased capillary pressure in the legs, induced by the upright position. Thus,

the œdema is observed at the end of the day, and disappears during the night, or with rest. In the profound anæmias, such as pernicious anæmia, similar observations are made, but the œdema is here frequently associated with a failing power of the heart. In cachectic conditions, besides a weakly-acting heart, there is malnutrition of the vessel wall, caused by the changes in the blood, and leading to an increased permeability. In Bright's disease, the explanation of the œdema is not quite clear. Œdema is observed in many cases of acute Bright's disease, and in chronic Bright's disease, in which there is a parenchymatous change in the kidneys. It is not observed, as a rule, in the granular contracted kidney associated with high arterial pressure and hypertrophied heart, nor in the early stages of the lardaceous kidney. There is some relation between the occurrence of œdema and the amount of urine passed. Thus, in the acute disease and in chronic parenchymatous nephritis, the amount of urine is greatly diminished, and œdema is present. In the granular contracted kidney, with hypertrophied heart, and in the early stages of the lardaceous kidney, a large amount of urine is passed, and there is, as a rule, no œdema. Although there is some relation between the amount of urine and the presence of œdema, yet the œdema of Bright's disease cannot be ascribed to diminution in the amount of urine. When there is complete suppression of urine, as in the blocking of both ureters by calculi or in the experimental ligature of both ureters, there is no œdema. Again, in acute Bright's disease, œdema is not always present, although the urine may be greatly diminished and contain a large amount of albumin. The loss of albumin in the urine leads to a condition of hydræmia, and the diminished amount of urine to a condition of hydræmic plethora; that is, to the retention of water in the blood. But this fact does not appear to offer a complete explanation of the œdema of acute Bright's disease, and it is possible that the œdema is associated with the circulation of poisons in the blood, and that it may be of the same nature as the inflammatory or toxic œdema which is observed sometimes in infective disease.

In chronic parenchymatous nephritis, the conditions of anæmia and of hydræmic plethora are important factors in the production of œdema. In the granular contracted kidney, no œdema is observed, while the left ventricle remains hypertrophied and there is high arterial pressure. In this stage, a large quantity of urine is passed. When, however, from one cause or another, the diseased kidney becomes acutely or subacutely inflamed, œdema is observed, and the urine diminishes. The cause of this œdema is possibly the same as that of acute Bright's disease. Extensive œdema occurring in chronic parenchymatous nephritis, and in the late stages of granular contracted kidney, is due to failure of the heart, producing the results previously described.

CHAPTER X

CHANGES IN RESPIRATION IN DISEASE

Normal Respiration is carried out by means of the respiratory apparatus, consisting of an impervious and elastic chest wall containing a cavity which is made larger by means of the muscles. Inside the cavity are the lungs, which are separated from the chest wall by the two layers of pleura. Expansion of the chest wall takes place by means of the contraction of the external intercostal muscles, and of the part of the internal intercostal which is between the cartilages. This expansion is permissible owing to the curve of the ribs, their downward slope, and their attachment by flexible cartilage to the sternum in front. The greatest degree of expansion is seen in the lower ribs. The muscles which aid expansion of the ribs are the scaleni, the levatores costarum and the serratus posticus superior. An increase of the vertical diameter of the chest takes place by means of the contraction of the diaphragm, which flattens, and so increases the vertical diameter, mainly at the sides. The central tendon moves downwards a little. In man the respiration is more abdominal than costal; in woman the reverse is the case, and in them expansion of the upper part of the chest is more marked than of the lower. When the chest is enlarged in the manner described, the air remaining in the lungs (residual air) is rarefied, and so air enters the respiratory passages from outside, and expansion of the lungs takes place. Expiration is, unlike inspiration, not usually an active process. Both the chest and lungs return to their resting position by their elasticity. Expiration may, however, become an active process, as in speaking,

singing, sneezing, coughing. The abdominal muscles are the chief ones contracting in forced expiration. They are aided by the interosseous part of the internal intercostals, and by the other muscles which depress the ribs.

The number of respirations per minute varies somewhat in health between fourteen and eighteen; in infancy they are more frequent. Inspiration is somewhat longer than expiration. The term *tidal air* is given to the quantity of air which is changed in each respiration. In adults it is about 300 c.c. (20 cubic inches). The *complemental air* is the quantity above the tidal air which can be drawn into the lungs with the deepest inspiration: it is about 1600 c.c. (100 cubic inches). The *supplemental air* is the quantity of air above the tidal air which can be expelled by a forcible expiration. This is about the same in amount as the complemental air. The *residual air* is also about 1600 c.c. (100 cubic inches), and is the air which always remains in the lungs after forced expiration. The sum of the complemental, tidal, and supplemental air is sometimes referred to as the *vital* or *respiratory capacity*. It is from 3500 to 4000 c.c. (225 to 250 cubic inches).

The muscles concerned in respiration are voluntary muscles, and both the external intercostals and diaphragm can be contracted at will, although the normal expiration is involuntary. The regular movements of the muscles in respiration are controlled by the respiratory centre (nœud vitale) in the medulla. This centre is partly automatic but is mainly brought into action reflexly. Thus, in respiration, afferent impulses pass from the lungs by the vagus; efferent impulses pass from the centre through the spinal cord to the muscles concerned in respiration. It is also affected by the higher centres of the brain, and reflexly through the sensory nerves of the body, not only those supplied to the respiratory tract, but those of the skin and of the internal organs. The respiratory centre is directly stimulated during life by the condition of the blood passing through it, the chief conditions of the blood being its temperature and the quantity of oxygen and carbonic acid contained in it. In normal conditions the

object of respiration is to obtain a sufficiency of oxygen with which to supply the tissues, and the intake of oxygen is proportionate to the needs (*i.e.*, the activity) of the tissues. At rest and during sleep the respirations are less frequent and not so deep as when awake or when exertion is taken.

From this short account of normal respiration it is evident that in disease the respiratory act may be altered in many different ways, not only by an affection of the respiratory apparatus, but also by an affection of the respiratory centre and its nerve connections in one way or another.

Disordered Respiration.—In disease, respiration may be increased in frequency or diminished. It may be irregular and shallow, or laboured. The term *dyspnœa* is used to indicate a condition of laboured breathing, or increased frequency of respirations. From a pathological point of view it would be better to limit the term to conditions in which there is a difficulty in the passage of air in and out of the lungs—inspiratory dyspnœa being limited to a condition in which there is a difficulty of the entrance of air into the lungs; expiratory, where there is difficulty of the exit of air from the lungs. From this point of view the term *dyspnœa* would be practically limited to conditions in which there is some mechanical obstruction to respiration. The term, however, is not limited to these conditions, and it is more useful to consider it as including difficulty or increased frequency of respiration, with or without mechanical obstruction.

The respiratory act is affected in disease:—

1. By changes in the respiratory muscles and in the chest wall; by changes in the air passages and in the alveoli; and by changes in the chest outside the lungs, as in the pleura and mediastinum.

2. By changes in the pulmonary circulation.

3. By changes in the systemic circulation.

4. By variations in the composition of the blood, such as a diminution of hæmoglobin from whatever cause.

5. By changes in the nervous mechanism of respiration.

These conditions are the primary cause of changes in the respiratory act. They lead to certain effects which are the direct cause of the changes in respiration. These direct causes are as follows:—

1. *Deficiency of oxygen-containing air entering the lungs, and of oxygen in the blood.* This must be considered the main direct cause of disorders of respiration. Whether the air contains less oxygen, or whether from one or other cause less air enters the lungs, the final result is the same, namely, a diminished quantity of oxygen in the blood, and so a diminished quantity in the tissues. The same result is brought about, not by a diminished entrance of oxygen-containing air into the lungs, but by a diminished amount of hæmoglobin in the blood. In this case, although oxygen is present, the hæmoglobin is not in sufficient quantity to supply the tissues with a proper amount of oxygen. The changes observed in respiration as the result of these causes must be considered as directed to obtain more oxygen, for they are such as increased frequency of respiration and increased strength of respiration. In this class of cases therefore, the changes observed in the respiratory act are directed to a beneficial end.

2. A second class of direct causes of changes in respiration is an *effect, reflex or direct, on the nervous centre, whereby this is either stimulated, paralysed, or disordered.* The result is either an increased frequency of respiration, a diminished frequency, or irregularity. The direct effect on the respiratory centre is due in one class of conditions to the action of poisons on the centre, as in uræmia, diphtheria and other infective disorders, and such cases of poisoning as by snake-venom. A direct effect is also observed in disease of the brain; whether of the meninges, as in meningitis, or of the brain substance, as in cerebral tumour and the various forms of sclerosis.

The changes in the respiratory act observed as the result of these direct causes are due to changes in the respiratory centre, which is stimulated by a deficiency of oxygen, or an increased amount of carbonic acid in the blood circulating

through it, by the circulation of poisons through it and by the direct effect of disease of the brain.

Reflex irritation of the respiratory centre also occurs: mainly through the vagus from the lungs and stomach, but also through the sensory nerves of the skin. The reflex effects are seen either in increased respiratory effort or in inhibition.

I. *Conditions of the Respiratory Apparatus Leading to Disordered Respiration.*—The conditions here to be discussed are mainly due to organic changes in one or other part of the respiratory apparatus, either the upper air passages, the trachea, the bronchi, the alveoli, the pleura and mediastinum, or the chest walls. These conditions have some changes in common. These are (1) the deficient entrance of air into the alveoli—that is, inspiratory dyspnœa with, in some cases, expiratory dyspnœa. (2) The continuance of long periods of inspiratory dyspnœa leads to deficient oxygenation of the blood, and so to deficient vitality of the tissues. (3) The effect of deficient entrance of air into the alveoli results in dyspnœa or increased respiratory movements. This must be considered as an effort to obtain more oxygen, and so as part of the mechanism of compensation. Compensation may be complete in some instances, but is usually partial.

A. *Direct Obstruction to the Entrance of Air into the Lungs.*—(*a*) This occurs in naso-pharyngeal and laryngeal obstruction, and in stenosis of the trachea. The commonest example of naso-pharyngeal obstruction is seen in adenoid vegetations. The result of these is to produce an inspiratory dyspnœa or laboured inspiration. If long continued without treatment, the inspiratory dyspnœa leads, with the soft chest walls of a child, either to a flattened chest or to a contraction of the base of the chest partly due to the more powerful action of the diaphragm in its endeavours to expand the chest properly. Naso-pharyngeal obstruction may to some extent act reflexly on respiration by acting as an exciting cause of attacks of asthma in predisposed subjects. Laryngeal obstruction, whether due to a spasm of the glottis

to a pedunculated polypus, to diphtheria, or to œdema of the glottis, causes inspiratory dyspnœa. There is a prolonged inspiration, frequently accompanied by a harsh noise or stridor, and an easy expiration. The prolonged inspiration is simply due to the fact that there is difficulty of entrance of air through the obstructed part. Bilateral paralysis of the openers of the glottis, the posterior crico-arytænoid muscles, produces the same result as spasm of the glottis. (*b*) In stenosis of the trachea produced by disease, there is both inspiratory and expiratory dyspnœa; the number of respirations per minute is reduced, while the depth is increased, and stridor is frequently present. In experimental occlusion of the trachea it is found that no dyspnœa is present with a certain degree of stenosis, owing to the fact that the more powerful contraction of the respiratory muscles supplies the lungs with a sufficiency of air. This fact explains the absence of dyspnœa in many cases of goître, where the trachea is partly pressed upon. Severe dyspnœa from stenosis of the trachea occurs in compression from both sides by a goître, producing the so-called "sword sheath" form of compression. With this there is softening of the cartilages. Diphtheria, stenosis from tertiary syphilis, and compression by an aneurism, also lead to severe dyspnœa.

Obstruction of the air passages inside the lung is a frequent occurrence, and leads to both inspiratory and expiratory dyspnœa. Sudden obstruction of a large bronchus experimentally produced may lead to pneumothorax, or to death from overstretching of the pulmonary capillaries. In disease, obstruction of a large bronchus is rarely complete. It leads to a diminished entrance of air into the part of the lung which it supplies, and apart from the infection of the bronchial tube which results and which is not at present under discussion, it leads to partial or complete atelectasis (collapse)—that is, the air disappears from that part of the lung. This is due to absorption by the blood of the gases in the alveoli, the oxygen being absorbed first, the carbonic acid next, and the nitrogen last. Obstruction of a large bronchus is produced by inhaled foreign bodies, by the

pressure of new growths or aneurism, and by syphilitic stenosis. The degree of dyspnœa which results from obstruction to a large bronchus depends on the power of compensation. Compensation occurs by dilatation of the unaffected alveoli, and by the increased activity of the respiratory muscles. In cases, however, where the chest wall is rigid, no dilatation of the alveoli is possible, and with the weakened respiratory muscles increased attempts at contraction produce but little effect. Compensation, therefore, is never complete. Laboured respiration is present when the patient is at rest in cases where there is no compensation; while in cases of partial compensation there is no difficulty of respiration during rest, but only on exertion. Obstruction of the small tubes produces an effect on respiration only when they are more or less universally affected. This commonly occurs with the bronchitis of childhood and in some cases in adults. Atelectasis or collapse, following obstruction of the small tubes is constantly seen. The broncho-pneumonia observed with it is a part of the infection, and not due simply to the obstruction of the tubes.

Severe dyspnœa due to obstruction of the small tubes is observed in asthma, a disease characterised by recurrent attacks of severe dyspnœa without, for long periods, any sign of organic disease of the lungs. In the attacks of asthma the dyspnœa is inspiratory, and to a less extent expiratory. Over the parts affected the respiratory murmur is absent, a fact strongly in favour of the condition being associated with a narrowing of the bronchioles due to a contraction of their muscular coats. As the attack passes off the respiratory murmur reappears.

B. *Obstruction to the Entrance of Air in the Spongy Lung Tissue* may be due to consolidation or destruction of the lung, to œdema, to new growths, or to pressure on the lung by fluid in the pleura, or a tumour in the mediastinum. The effect on respiration of these conditions depends on two factors. The first is the extent to which the alveolar tissue is destroyed, and the second is the rapidity of the diseased process. Thus an acute consolidation of the lung, such as

occurs in pneumonia, acute œdema and a rapid effusion of fluid or air into the pleura, leads to great dyspnœa which is chiefly inspiratory. On the other hand, a tumour of the lung may destroy a large part of the spongy tissue without causing marked difficulty of respiration, and so with cases of chronic tuberculosis of the lung and very slowly forming effusion in the pleura. The effect, therefore, is proportional to the rapidity of the disease as well as to the degree of destruction of the alveolar tissue and the capacity of compensation. The absence of marked difficulty of respiration in many cases of chronic tuberculosis of the lung where the air-breathing capacity is diminished to a greater extent than in many cases of pneumonia with severe dyspnœa, is due to several factors. The first is the dilatation of the alveoli in the more healthy parts of the lung (compensatory emphysema), and the second is the diminished needs of the tissues for oxygen. Metabolism of the tissues in these prolonged cases is diminished, and so less oxygen is required. Dyspnœa, however, frequently appears on exertion, and it may be sudden and severe in onset, as when pneumothorax or pleural effusion occurs on the side of the chest least affected by the tuberculosis.

C. *The Condition of the Chest-wall and Muscles* has an important effect on the modification of respiration in disease. An affection of the diaphragm or external intercostal muscles produces an inspiratory dyspnœa, resulting in the presence in the lungs of too large a quantity of residual air. The muscles not acting sufficiently, the accessory muscles of respiration come into play, but this does not lead to the entrance of a sufficient quantity of air, and there is consequently a similar diminution in the amount of air expired. The tidal air being diminished, the residual air is increased. The movements of the diaphragm are more frequently affected in disease than those of the external intercostal muscles. The diaphragm may be imperfect, as in some cases of diaphragmatic hernia, or in rare cases it may be absent. A diminished contractility is observed in infective disease and in fatty degeneration, which

occurs in prolonged cases of emphysema and bronchitis, in morbus cordis, in pernicious anæmia, in chronic nerve disease, such as general paralysis of the insane (Cohnheim), and in wasting diseases. Its action may also be hampered by the invasion of new growths, or by the *trichina spiralis*, and it may be paralysed by pressure on the phrenic nerves and in diphtheria, lead-poisoning and hysteria. In great abdominal distension, whether from tumours or fluid, or in tympanites, the action of the diaphragm is greatly impeded; as well as in adhesions to the lungs or the abdominal organs.

As has been said, inefficient action or paralysis of the diaphragm leads to inspiratory dyspnœa. This, however, may not be present if the external intercostal muscles are vigorous, for costal respiration, replacing the abdominal, compensates for the loss of the action of the diaphragm. Even if the external intercostal muscles be intact, their power of compensating for the loss of the diaphragm depends on the presence or absence of rigidity of the chest. In ossification of the cartilages, the action of the external intercostals in expanding the chest is very limited. The external intercostal muscles themselves are not commonly affected in disease. In rare cases of peripheral neuritis they may be paralysed, and in wasting diseases they are diminished like the rest of the muscles of the body. They are also atrophied in chronic disease of the lungs and pleura.

Rigidity of the chest wall with the loss of elasticity in the lung tissue which occurs in emphysema leads to expiratory dyspnœa, and so to a larger quantity of residual air. The result is an imperfect interchange of gases in the lungs, and, on exertion, dyspnœa, both inspiratory and expiratory, is produced.

II. *Influence of the Pulmonary Circulation on Respiration.*—This must be considered separately from the condition of the bronchial tubes or lung tissue, inasmuch as normal respiration depends on the regular exchange of gases between the air and the circulating blood in the lungs. If, therefore, sufficient blood is not brought to the lungs to be aërated, or

if there is a relative stagnation of the blood in the lungs, the aëration of the systemic blood is deficient. The result is increased respiratory movements, owing to stimulation of the respiratory centre.

(1) The amount of blood brought to the lungs may be deficient, either as a whole, as in pressure on the pulmonary artery, or in part, as in local disease of the lungs. This partial deficiency occurs in cirrhosis of the lung, in embolism of a large branch of the pulmonary artery, in chronic tuberculosis and in emphysema, in both of which cases the vessels of the lung may be destroyed, and it is also seen in pressure on the lung, as by gas or fluid in the pleura, or by tumours. The pulmonary circulation is also affected in completely adherent pleura, in extensive collapse of the lung tissue, and in chronic bronchitis. The direct cause of the dyspnœa in these conditions is the deficiency of oxygenated blood in the respiratory centre. The increased movements of respiration which occur are beneficial in so far as they tend to introduce more air into the lungs, and so produce a more rapid interchange of gases.

(2) Embarrassment of the pulmonary circulation due to morbus cordis leads to disordered respiration. In failure of compensation, more particularly in mitral disease, there is a diminished contraction of the right ventricle; and in stenosis of the mitral valve there is in addition an increased resistance to the entrance of the blood into the left ventricle. This leads to an increased arterial pressure in the pulmonary circulation; the relative stagnation of blood diminishes the interchange of gases, and the direct cause of the increased respiratory movements is, as in the first class of cases discussed, a deficiency of oxygenated blood in the respiratory centre. The dyspnœa occurring in morbus cordis from embarrassment of the pulmonary circulation is not so evidently beneficial as in the first class of cases considered. By some it is considered of little use, inasmuch as the respiratory exchange is not increased by the increased movements of respiration, mainly owing to the slow blood current through the lungs. The respiratory movements may, however, be considered to

have one useful effect, namely, in causing the blood to flow more rapidly from the systemic veins into the chest.

Compensation for disordered respiration due to defects in the pulmonary circulation takes place by means of hypertrophy of the right ventricle of the heart.

III. *Influence of the Composition of the Blood and the Presence of Poisons on the Respiration.*—(1) *Influence of Composition of the Blood.*—A diminution in the proteid and other soluble elements of the blood would affect the vitality of the respiratory centre, rendering it, perhaps, in the early stage, more irritable to stimulation, and, in the later stage, less irritable; but the condition of the blood which is more closely concerned with disordered respiration is the presence of a diminished quantity of hæmoglobin. In this case, although the respiratory apparatus and nervous mechanism may be normal, there is an insufficiency of oxygen in the blood and in the tissues, owing to the fact that there is not sufficient hæmoglobin to combine with the oxygen. Thus the respiratory centre is stimulated to action by deficiency in the amount of oxygen carried to it, and dyspnœa results. The increased respiratory movements have no marked effect in remedying the condition, as, although the oxygen in the lungs is sufficient in quantity, the hæmoglobin in the blood is deficient (see Chapter XVII.). In moderate degrees of anæmia, such as is observed in chlorosis and in some forms of secondary anæmia, the dyspnœa is not observed when the body is at rest, only on exertion. In profound anæmia, such as is seen in pernicious anæmia and in severe secondary anæmias, the difficulty of respiration (*besoin de respirer*) exists with the body at rest. This is a "deficiency of oxygen" dyspnœa.

(2) *The Circulation of Poisons in the Blood* may lead to disordered respiration and dyspnœa by a direct effect on the respiratory centre. Some poisons lead to dyspnœa by causing stagnation of the pulmonary circulation, but this effect is not observed in those under consideration. Uræmic dyspnœa (renal asthma) may be quoted as an example of this form of disordered respiration, although the question of a uræmic

poison is not yet settled. This form of dyspnœa is not associated with embarrassment of the pulmonary circulation. It may be associated with an increased systemic arterial pressure, but its most important association from the present point of view is that with definite nerve symptoms, such as headache, twitchings, convulsions and coma; a series of symptoms which indicates the action of some agent or agents on the brain. The dyspnœa may be continuous or intermittent, occurring in definite attacks, like those of asthma, but without the cyanosis or other signs accompanying that condition. It is relieved in some cases by the removal of blood, or by the administration of nitrites which dilate the peripheral vessels, or by purgation.

Some of the poisons of infective disease act directly on the respiratory centre. To such an action must be ascribed the attacks of dyspnœa which occur in diphtheritic paralysis and in the later stages of acute diphtheria. Snake-venom and abrin also apparently have a direct effect on the respiratory and other centres in the medulla.

IV. *Influence of the Nervous System on Respiration in Disease.*—The physiological relations of the respiratory centre have already been discussed (p. 278). Its activity is diminished normally when the blood circulating through it contains a diminished quantity of oxygen or an increased quantity of carbonic acid. After birth it is the stimulation of the centre by the diminished quantity of oxygen which causes at first independent respiratory movements of the newly born child. In disordered respiration the influence of the quality of blood is of great importance, and has been previously discussed. The respiratory centre may in disease, however, be affected by conditions other than that of the quality of the blood supplied to it, and it may show the results either of abnormal stimulation or of a diminished excitability.

Abnormal stimulation and excitability of the respiratory centre is observed in hysterical dyspnœa, in neurotic asthma, in uræmia, in ligature of the vessels supplying the brain, and when blood at an abnormally high temperature passes

through it. It is evident that the two first conditions are separable pathologically from the three last, inasmuch as in both hysterical dyspnœa and neurotic asthma there is a functional disturbance of the respiratory centre not associated, as far as is known, with any abnormal condition of the blood supplied to it. In both these functional conditions there is some evidence that the actual dyspnœic attack results from the stimulation of the centre by a peripheral irritation, some local condition in the respiratory tract or internal organs.

A diminished excitability of the respiratory centre is observed in disease of the brain, such as tumours, hæmorrhage (especially when affecting the medulla) and meningitis, also in long-continued febrile disease or chronic diseases of the respiratory organs. In this class, as in the first, the affection of the respiratory centre by brain disease is not directly associated with any change in the quality of the blood supplied to the centre, though this is probably the case with long-continued pyrexia, or with hyperpyrexia, and with chronic diseases of the respiratory tract.

Cheyne-Stokes Breathing (Fig. 88).—*Periodic Respiration.*—This is a peculiar form of breathing which is best described as

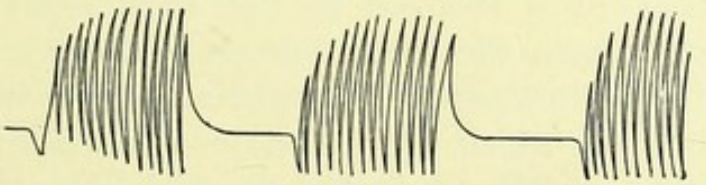


FIG. 88.—Tracing of Cheyne-Stokes' respiration. (Pembrey.)

The tracing shows the periodic character of the respiration. The respiratory acts are grouped, and the groups are separated by a period of absence of movement. When respiration begins again, the first is short, and the movements gradually acquire a maximum, after which they fall, and another period of rest ensues (Kirke's Physiology).

periodic respiration. It consists of a series of inspirations increasing to a maximum (dyspnœa), then declining until the respirations cease; a pause (apnœa) preceding the recurrence of the phenomenon. Four or five periods of respirations with pauses may occur in the course of one minute. In some cases a pause lasts thirty or forty seconds, the respirations

lasting about the same period. Periodic respiration is observed physiologically in hybernating animals, and respirations with pauses are observed in some children during sleep. It is also seen in disease: in disease of the brain, such as tumours, hæmorrhage, meningitis and anæmia; and in disease of the heart, such as fatty heart, sclerosis of the coronary arteries and stenosis of the aortic valves. It is always associated with severe illness, and usually appears before its fatal termination. Experimentally, it may be produced by the injection of morphine into the veins of rabbits and dogs, by the injection of magnesium sulphate into dogs, or by ligature of the vessels supplying the brain.

The explanation of the phenomenon is not easy, but the chief pathological condition seems to be one of diminished irritability of the respiratory centre. The centre appears to be in a dying condition. The increase of respirations leading to dyspnœa appears to be brought about by a diminished arterial blood supply to the centre, the deficiency of oxygen stimulating the centre to increased activity for a time. It soon, however, gets exhausted, hence the decline of the respirations and their final cessation. After a certain period of rest the centre regains its activity for a time, and the phenomenon is repeated. Cheyne-Stokes breathing experimentally produced is relieved by the administration of amyl nitrite, which dilates the blood vessels (Filehne).

A similar phenomenon in the circulatory system is observed in Traube's curves, which are undulations in the arterial blood-pressure curve which gradually diminish in size until the heart ceases beating. Traube's curves are ascribed to exhaustion of the vaso-motor centre in the medulla.

Means of Compensation in Disorders of Respiration.—As has been shown in the previous pages, disordered respiration may be due to several factors which include defects of the respiratory apparatus, defects of the pulmonary circulation as well as changes in the composition of the blood and in the condition of the central nervous system. It has also been pointed out that several factors may be present in each individual case,

and it is important to determine the presence of these factors in order to judge how far compensation is possible. In some instances of disordered respiration the increased respiratory movements are directed to the removal of the condition producing the dyspnœa, while in other conditions — chiefly nervous and toxic in origin—the disordered respiration is purposeless in character.

Compensation takes place mainly when the disordered respiration is due to a defect in the respiratory apparatus and in the pulmonary circulation.

1. *Compensation in Defects of the Respiratory Apparatus.*— When there are any of the defects in the respiratory apparatus previously discussed (p. 281), compensation takes place by means of the enlargement of the lungs either generally or, more commonly, locally. This is referred to as *compensatory emphysema*, and consists in the dilatation of the healthy alveoli, whereby they contain more air. It has been doubted whether in some cases the filling of the alveoli with more air means an increased respiratory exchange. It may, however, possibly mean this, as its occurrence in cases of chronic pulmonary tuberculosis must be considered as beneficial. It is said that a true hypertrophy of the lung is possible. It is difficult, however, to see how there can be a formation of new alveoli.

The second means of compensation is the action of the accessory muscles of respiration, such as the sterno-mastoids, the scaleni, the serrati and the muscles passing from the chest to the upper limb. These by more firmly fixing the upper part of the chest facilitate the expansion of the middle and lower part of the thorax by the external intercostal muscles. This action of the accessory muscles is, however, of but little avail if they have been weakened by disease, or if the chest be rigid, as in old age.

Hypertrophy of the respiratory muscles occurs as an aid in compensation. Dyspnœa or laboured respiration, must be considered itself a compensatory process; inspiratory dyspnœa in order to get more air into the lungs; expiratory dyspnœa to expel more air. With laboured inspiration not only is

more oxygen taken into the lungs but the pulmonary circulation is increased owing to the inspiratory action of the chest.

2. *Compensation in Defects of the Pulmonary Circulation.*—In cases where there is retardation of the blood in the lungs, or where (as in emphysema) there is difficulty in the passage of blood through the lungs, compensation for the disordered respiration produced occurs by means of hypertrophy of the right side of the heart. This, by increasing the force of circulation through the lungs, tends to relieve the disordered respiration by increasing the respiratory exchange.

3. A third method of compensation occurs in certain chronic diseases of the respiratory apparatus. Thus, in chronic cases of pulmonary tuberculosis, where the air-breathing capacity of part of a lung is destroyed, there may be no dyspnœa. This may occur also in extensive pleural adhesions, in slowly advancing pleural effusion, and in tumours of the lung, as well as in emphysema and in bronchiectasis. In these conditions there may be no dyspnœa when the patient is at rest, although the air-breathing capacity of the lungs is diminished. Dyspnœa, however, supervenes on exertion, or if a complication be present, such as disease of the mitral valve and pneumo-thorax or pleuritic effusion compressing the more healthy part of the lung. Such conditions last for many months or years, and the organism adapts itself to a diminished oxygen supply. The total metabolism of the body is diminished owing to the diminished quantity of oxygen present in the blood, but a disordered respiration is not seen, inasmuch as the tissues receive sufficient oxygen, when the body is at rest, to carry on their functions. Continued deficiency of oxygen, however, leads to tissue degeneration, such as fatty degeneration (p. 202).

Cyanosis.—The result of want of compensation in disordered respiration is cyanosis, in which there is blueness of the extremities, and of the face, ears and nose. In cyanosis the blood in the capillaries parts more completely than normal with the oxygen and takes up more carbonic acid. Receiving a diminished quantity of oxygen from the air in the lungs, the

oxygen contents of the blood are not renewed. Marked cyanosis is prevented by a general anæmia, as in chronic tuberculosis of the lungs. It is seen, however, in acute tuberculosis.

Asphyxia or *Suffocation.*—Asphyxia occurs either from some sudden stoppage of the entrance of air into the lungs, or stoppage of the pulmonary circulation, or is the final result of one or other of the chronic respiratory defects previously described. Rapid asphyxia occurs in œdema of the lungs, in hæmorrhage into the bronchi, in embolism of the pulmonary artery, in spasm and œdema of the glottis, and in double pneumothorax, as well as in the sudden compression of the trachea by a goitre.

In acute asphyxia two stages are recognised. In the first, there is a rise of blood pressure accompanied by laboured breathing, restlessness and clonic convulsions. In the second there is a fall of blood pressure, and this is accompanied by a cessation of respiration and ends in death, the heart beat being continued for a short time after the breathing has ceased. The effect in acute asphyxia is due to the cutting off of the supply of oxygen.

Slow suffocation is observed as the termination of the respiratory defects previously discussed and ends in death. There is laboured breathing with restlessness, and usually a fall of blood pressure; clonic convulsions are usually absent, but towards the end of life, when the respiration is becoming shallow and rapid, twitchings of the muscles may be observed.

Failure of compensation in chronic respiratory defects may be due to an extension of the original disease, such as occurs in chronic pulmonary tuberculosis, to weakness of the muscles of respiration, either from exhaustion or fatty degeneration, or to the invasion of an infective disease causing pyrexia, which weakens the muscles and diminishes the activity of the respiratory centre, as well as to a progressive anæmia.

Modified Respiratory Acts.—Cough, Sneezing, Hiccough.—Cough.—An active cough is preceded by a deep inspiration and

accompanied by a sudden expiration due to the spasmodic contraction of the abdominal muscles. During this explosive expiration the glottis, previously closed, is forced open by the rush of air due to the sudden compression of the lungs. Cough is a reflex act, and the afferent impulses to the respiratory centre are carried by branches of the vagus—chiefly by the superior laryngeal nerve to the larynx, and by other branches to the bronchial mucous membrane, to the alveolar tissue of the lung, to the pleura, and to the external auditory meatus. Cough may also be excited through the sensory nerves of the skin, as by the application of cold. The parts most sensitive to peripheral irritation in inducing cough are the larynx, the bifurcation of the trachea and the bronchial tubes. The chief irritant exciting cough is the presence of excessive mucus or other secretion, or a foreign body, on the laryngeal or bronchial mucous membrane.

Peripheral stimulation carried by the afferent nerves in the branches of the vagus supplied to the abdominal viscera (stomach and liver) does not excite cough, and there is no evidence of the existence of a "stomach" cough, that is, a cough excited by irritation of the branches of the vagus supplied to the stomach. When cough exists in stomach conditions it is usually due to the irritation of acid or other liquids and of gases irritating the larynx and the fauces.

It is evident that in diseased conditions, intensity of cough depends on three conditions: (1) The amount of peripheral irritation, which is equivalent to the amount and character of foreign matter to be expelled; (2) To the part of the respiratory tract which is irritated; and (3) To the degree of irritability of the respiratory centre. Thus a large amount of secretion present in the larynx or bronchial tubes will lead to excessive cough, more particularly if the secretion is of a tenacious character and with difficulty expelled. Excessive irritability of the respiratory centre, which in common with that of other centres occurs in prolonged anæmia and in wasting diseases, leads also to excessive cough, even a slight degree of peripheral irritation, causing an excessive response from the respiratory centre. Excessive cough is observed in

laryngitis and bronchitis when the secretion of the inflamed mucous membrane is tenacious. The cough diminishes when the secretion becomes more liquid, and thus more easily expelled. In bronchitis, when the secretion is not tenacious, the cough is not excessive unless the secretion is so copious as to collect in the smaller tubes, and so leads to great difficulty of expectoration. This may occur during the day, but more particularly occurs at night during the period of sleep, thus leading to excessive cough in the morning on waking.

The alveolar tissue of the lung when affected by disease is less productive of cough than the laryngeal or bronchial mucous membranes. Thus a large portion of the alveolar tissue of one lung may be consolidated without producing as much cough as a mild inflammation of the bronchial mucous membrane; a short dry cough is produced, not excessive and infrequent. A similar degree of cough is excited by inflammation of the pleura, but the pleura may be extensively diseased by a chronic condition without the production of any noticeable cough. An affection of the diaphragm itself does not lead to cough, except as regards the affection of the pleura accompanying it.

Excessive cough which in some cases leads to a temporary cyanosis, to exhaustion and to vomiting, occurs more particularly in irritative laryngeal conditions, in chronic bronchitis, and in tuberculosis of the lungs. In chronic bronchitis the excessive cough has been already partly explained as due to the accumulation of secretion in the bronchial tubes during the night, and to an excessive secretion during the day, as well as in other cases to the tenacious character of the secretion and the difficulty of expelling it. There is another factor, however, which occurs as a sequence of the repeated paroxysms of cough in chronic bronchitis, and that is the irritability of the respiratory centre, induced by an irregularity of the blood supply. Thus the paroxysms of cough lead to a temporary diminution in the respiratory exchange of the lungs, and so to a passing cyanosis in which the respiratory centre is affected like the other parts of the body. The temporary cyanosis is followed by a dyspnœic condition, and

this irregular action of the respiratory centre leads eventually to its disorganisation, so that its irritability is increased.

In chronic tuberculosis the centre is also affected, its irritability being increased, but this is brought about in another manner. The anæmia produced by the wasting disease leads to an impoverished blood supply to the centre, and so to an increased irritability. Excessive cough, therefore, in chronic tuberculosis of the lungs is in the majority of instances due more to the irritability of the centre than to accumulation of secretion in the bronchial tubes.

Although it is stated above that there is probably no such condition as a "stomach" cough, yet cough may be excited by the presence of food in the stomach. Thus, in cases of chronic bronchitis and chronic tuberculosis of the lungs with cough, the occurrence of paroxysms of coughing after the ingestion of a large meal is a frequent occurrence. One possible explanation of this is that the presence of a large meal in the stomach leads to a diminution in the respiratory movements, and so to an accumulation of secretion in the lungs. But this is not the sole explanation, and it is possible that there is an afferent impulse from the stomach to the centre in the medulla whereby the cough is induced. Vomiting not infrequently follows a paroxysm of coughing induced by a large meal, but the vomiting is in the majority of cases a mechanical act, the excessive action of the abdominal muscles during the respiratory act pressing on the stomach, and so leading to the vomiting.

Sneezing.—Sneezing is the same kind of reflex act as in coughing, there being an explosive expiratory effort during which a current of air is directed through the nose, and not through the mouth, as in coughing. It is excited mainly by irritation of the nasal mucous membrane either by a foreign body or by excessive secretion. It is in some instances excited reflexly through the eyes, as when a bright light causes sneezing. As in coughing, the degree of sneezing depends on the severity of the peripheral irritation as well as on the irritability of the respiratory centre. Thus a simple act of sneezing occurring in the course of a common cold

may be contrasted with the excessive degree of sneezing which occurs in individuals subject to "hay fever," and in this case the peripheral irritation of the nose leads not only to the special act (that is sneezing) with which the nasal mucous membrane is associated, but to dyspnœa, producing "hay asthma."

Hiccough.—Hiccough is due to a violent inspiratory contraction of the diaphragm which ceases by a sudden closure of the glottis. It is caused by reflex irritation from the stomach, especially in cases where the organ is irritated by over-eating and drinking. It usually occurs in individuals with excitable nervous systems. It may also be produced from peripheral irritation of the peritoneum, as in peritonitis especially when it affects the diaphragm.

CHAPTER XI

CHANGES IN THE BLOOD IN DISEASE

I. *Changes in the Red and White Corpuscles*

THE changes which occur in the blood in disease are very numerous, and may be grouped under the following headings: 1. Changes in the red and white corpuscles; 2. Changes in the amount and distribution of the hæmoglobin the former contain; 3. Changes in the coagulability of the blood and other chemical variations from the normal; 4. The presence of bacterial and animal parasites in the blood (Chapters III. and VI.).

Chemical variations other than coagulability are discussed under separate headings; they are such as changes in the amount of water, proteid and other normal constituents, changes in the amount of sugar, and the presence of abnormal chemical substances.

Changes in the Corpuscular Element of the Blood.—1. *The Red Corpuscles: Anæmias.—Origin of the Red Corpuscles.*—The red corpuscles are formed from the middle layer of the embryo, like the white discs. They are formed in two ways. Before birth they are intracellular in origin. In the protoplasm of the cell, spherical globules, varying in size, are formed, which eventually become adult corpuscles, the cell itself being developed into a primitive blood vessel. Another mode of origin, which also continues through life, is from the red marrow. The *Erythroblasts* (Fig. 89) which are here formed are nucleated cells varying in shape, some being round, others oval, and some pear-shaped, while others again show a division of the

nucleus. The nucleus disappears as the cell becomes transformed into the adult red corpuscle.



FIG. 89.—Erythroblasts from the bone marrow (Kirke's Physiology).

The figure shows the varying shape of the nucleated and immature red corpuscles as they occur in the bone marrow. They vary in size and in shape, some being pear-shaped, others oval, and some showing division of the nucleus and commencing division of the cell.

Structure of the Red Corpuscles.—When blood is shed, the red corpuscles form into rouleaux, the concave surfaces of the discs being apposed to each other. They frequently become crenated, and under the action of water they swell, losing their biconcave shape and becoming more globular. The average diameter varies between 6.6 μ and 8 μ, or an average of 7.5 μ. The average number of corpuscles is, in adult man, 5,000,000 per cubic millimetre, and in adult woman, 4,500,000. The size, shape, rouleaux formation and number of corpuscles are important points to be considered in diseased conditions of the blood. In addition, there is the relation between the amount of hæmoglobin and the number of corpuscles. This is called the *colour index*, and is the ratio between the percentage of hæmoglobin and the percentage of corpuscles. Thus, if the percentage of hæmoglobin found in a particular instance is 30, and the percentage of red corpuscles is 80, the colour index is $\frac{30}{80} = 0.37$.

2. *Normal Variations in the Red Corpuscles and the Amount of Hæmoglobin.*—The average number of corpuscles in adult life is fairly constant, and, as a rule, the amount of hæmoglobin varies with the number of corpuscles. In the newly born, the red corpuscles are between 7,000,000 and 8,000,000 per cubic millimetre. Their number, however, diminishes within seven to ten days after birth. In healthy young men the normal number may be increased to 6,000,000 per cubic millimetre. In old age the red discs are sometimes, but not always, diminished. An increased number of corpuscles, up to 8,000,000, has been found in those living at high altitudes, and this increase appears to

be proportional to the height above the sea level. In this case, the hæmoglobin, although increased, is not proportionately so to the increase of the corpuscles. A diminution in number takes place on returning to life at a lower level.

After a meal, the red corpuscles are slightly diminished. Excessive fatigue causes a diminution ; it may be of 500,000 per cubic millimetre. The drinking of large quantities of liquid diminishes the corpuscular count. This is, on the other hand, increased by sweating and fasting, both of which lead to concentration of the blood. Menstruation, childbirth and lactation diminish the number of corpuscles.

Increase of the Corpuscles in Disease.—In cyanosis, whether local or general, an apparent increase in the number of corpuscles (polycythæmia) occurs, owing to the relative stagnation in the peripheral blood. A high corpuscular count may also be found in conditions in which the blood becomes concentrated. These conditions are usually temporary, and are such as profuse watery diarrhœa, profuse sweating, persistent vomiting, starvation of liquids and large serous effusions. There is, however, no real increase in the number of corpuscles in these cases, the increased number counted being due to the concentration of the blood. A true polycythæmia is said to occur in phosphorus poisoning, in which the red corpuscles have been found to be over 8,000,000 per cubic millimetre, and in carbonic oxide poisoning in which a record of over 6,500,000 has been made.

3. *Changes in Shape and Structure of the Red Corpuscles in Disease.*—The red corpuscles show great variations in shape in the anæmias, more particularly in profound secondary anæmias and in pernicious anæmia. Changes in shape are called *poikilocytosis* (Figs. 90 and 91) ; the corpuscles becoming elongated or oval, pear-shaped, or with irregular edges. Changes in size also occur, very small corpuscles being met with (microcytes), and others larger than normal (macrocytes). Vacuolation of the corpuscles also occurs ; in dried and stained specimens the vacuoles appear as clear, unstained and sharply defined round or oval spaces. In fresh blood these vacuoles change their shape, and are, no doubt, present in the corpuscles in

the blood. A granular degeneration of the corpuscles is seen in some cases. Deformed corpuscles sometimes show irregular movements, which are described as amœboid. They do not, however, possess the definite characteristics of the amœboid movements of the leucocyte. The changes which have been described are taken as indicating necrobiosis or degeneration of the corpuscles, and no doubt this may be taken as, in the main, correct. Whether, however, the degeneration occurs in

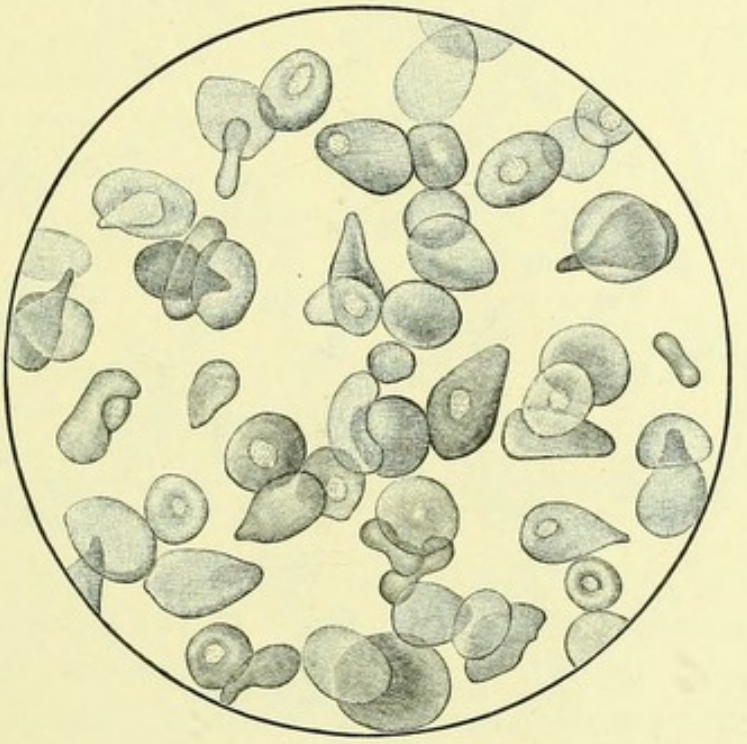


FIG. 90.—Blood in pernicious anæmia.

The drawing shows the characteristic shapes of the red corpuscles in advanced pernicious anæmia. Some are pear-shaped, some oval, and some kidney-shaped—poikilocytosis. Some of the corpuscles are large—macrocytes; others are small—microcytes; some are vacuolated.

the blood itself, or whether it takes place in the red marrow, is not known. Another change which may be described as a form of degeneration is an irregularity in the staining properties of the corpuscle. Thus, the red corpuscles normally have an affinity for acid stains, such as eosin and aurantia. By the Ehrlich-Biondi stain, which contains orange G, acid fuchsin and methyl green, the corpuscles are normally stained dark lemon colour, and the nuclei greenish. The diseased corpuscles will take up the methyl green, as well as the

orange, giving a reddish-purple result. Such cells, which are nearly always deformed, are referred to as *polychromatophilic.*

Nucleated red corpuscles (Fig. 92) are normally absent from the blood, although they are present in the bone marrow. They occur in the blood in many cases of disease, and are of various forms. The *normoblast* is precisely similar to the erythroblast of the bone marrow. It is an immature red

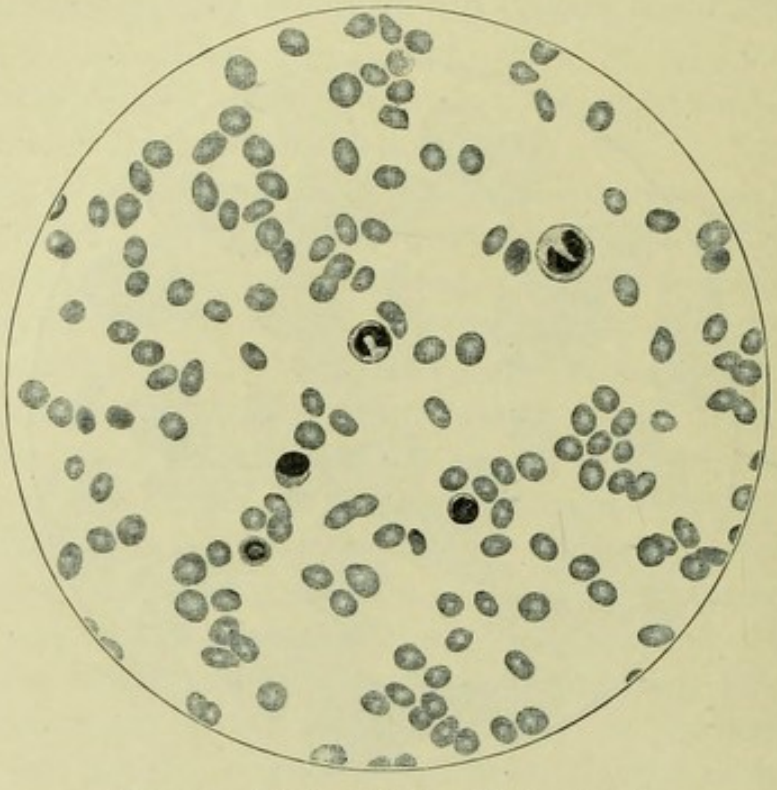


FIG. 91.—A blood film in splenic anæmia.

This figure represents the varying shape and size of the red corpuscles in the blood in splenic anæmia. The tendency to the oval form of the red corpuscle is well shown. One nucleated red is seen, and the leucocytes are few in number.

corpuscle which has entered the blood stream before its time. The nucleus is frequently irregularly situated, as, indeed, it is in the erythroblast. It may be central or peripheral, or even projecting from the surface. The term *microblast* is given to the small nucleated red corpuscle; the term *megaloblast* to the nucleated red corpuscle larger than normal. The megaloblast is a degenerated cell with a very large nucleus, surrounded by a pale corpuscular body. The cell shows an irregular staining and is polychromatophilic. Irregular

nucleated red corpuscles are not infrequently observed in profound anæmias. Thus, a very small degenerate nucleus may be seen in a large cell. The nucleus may show karyokinesis, and the bifid nucleus may also undergo degeneration. Different significance has been given to the presence of the varieties of nucleated cells in the blood; the megaloblast, for example, being considered as of the most serious import. It may be said, however, that the normoblast is practically an undegenerated erythroblast, and the microblast is an immature erythroblast, and that the megaloblasts are erythroblasts showing more or less extensive degeneration in the nucleus, as well as in the body of the corpuscle. In so far, therefore, as the megaloblast shows more advanced degeneration, its import is more serious than that of the normoblast.



FIG. 92.—Nucleated red corpuscles.

The figure shows the varying shape of nucleated red corpuscles (normoblasts, microblasts, megaloblasts) which are seen in the blood in pernicious anæmia, leukæmia, and some cases of advanced secondary anæmia.

The Condition of the Blood in Anæmia.—The condition of anæmia or bloodlessness, is usually divided into two classes, primary and secondary. To the first belong chlorosis and pernicious anæmia; to the second belong those anæmias which follow, or are associated with, some disease, toxæmia, or disordered nutrition. It is, however, probable that no anæmia is really primary; that, for example, the profound destruction of red corpuscles which occurs in *pernicious anæmia* is secondary to some toxic or other condition, which profoundly interferes with blood formation or directly destroys the corpuscles in the blood. There is indeed strong evidence that many cases of pernicious anæmia are associated with, if not directly due to, a process of intoxication, more particularly from bacterial growth in the mouth and the intestinal tract. *Chlorosis* is secondary to some defective formation of the body, or some irregularity in the uterine functions, aided by external non-hygienic conditions. No accurate explanation is, however,

forthcoming of the causation of the blood change in chlorosis. It is a disease of young females under the age of twenty-four years, and most commonly arises at or near puberty. In many instances it runs in families. The blood condition does not show destructive changes, as in pernicious anæmia. *Splenic anæmia* is a name given to certain anæmic conditions occurring more particularly in children, in which, in addition to the blood changes, the spleen is enlarged. The blood changes may at one time be of the chlorotic type, and later, of the pernicious anæmia type. As in the other severe anæmias, there are periods of pyrexia during the course of the disease. *A secondary or symptomatic anæmia* may be associated with very different conditions, and may be of varying degrees. Four degrees of secondary anæmia have been described (Cabot).

First Degree.—In this there is a diminished amount of hæmoglobin, and a lowered specific gravity of the blood, without any diminution in the number of corpuscles.

Second Degree.—There is a diminished amount of hæmoglobin, but no appreciable diminution in the number of red cells, which show, however, some degenerative changes. Thus rouleaux formation is lost, and the cells vary in size, microcytes and macrocytes being present, while poikilocytes are observed, as well as vacuolation and irregular staining with the Ehrlich triple stain.

Third Degree.—There is a diminution in the amount of hæmoglobin, and in the number of corpuscles ; and, in addition, normoblasts may be observed.

Fourth Degree.—In addition to the changes seen in the third degree, microblasts and megaloblasts are present, the latter more commonly than the former.

The conditions associated with secondary anæmia are very various, and are such as—infective disease, malignant disease, chronic suppuration, chronic dysentery, renal disease, cirrhosis of the liver, bad hygienic conditions, rapid child-bearing and prolonged lactation, intestinal parasites, and poisons, such as lead and arsenic.

The First Degree of Secondary Anæmia may be observed in

such conditions as—bad hygienic surroundings, multiple pregnancies, prolonged lactation, and following some infective diseases.

The Second Degree is more common than the first, and is observed in cases of malignant disease, cirrhosis of the liver, leukæmia, lead-poisoning, and in such infective conditions as typhoid fever, erysipelas, tuberculosis, pyæmia, measles and scarlet fever. The changes in the blood in these conditions may resemble those present in some cases of pernicious anæmia. Frequently, however, the necrobiotic changes are not so marked as in the latter condition.

The Third Degree of anæmia, frequently without the presence of normoblasts, is observed in the anæmias of infancy and early childhood, soon after the occurrence of large hæmorrhages, in malaria, and in acute septicæmia.

It is evident that the causes which may, in these conditions, be supposed to affect the structure of the blood, are various.

1. Thus, in some there is the presence in the body of poisonous substances which, by their long-continued action, may exercise a profound effect on blood formation and on the vitality of the red corpuscle. This would occur in infective disease, including chronic suppuration and chronic dysentery. The action of lead and arsenic in producing changes in the blood may be ascribed to the same cause, that is, a chronic toxic condition.

2. In other conditions there is actual loss or destruction of the red corpuscles. Such loss occurs after large hæmorrhages. Obvious and great destruction occurs in malaria, more particularly the chronic form.

3. The main cause in the production of some forms of secondary anæmia must be ascribed to the interference with the functions of an important organ, or with the assimilation of food. This would occur in cirrhosis of the liver, in renal disease and in malignant disease of an important organ.

Primary Anæmia: Chlorosis, Pernicious Anæmia.—The best examples of primary anæmia are chlorosis and pernicious

anæmia, but although they may provisionally be classed together as primary, the blood changes are in great contrast.

In *chlorosis* (Fig. 93), the blood, when drawn, is pale and watery, coagulating readily. The specific gravity is 1030, or slightly more. The red cells average a little over 4,000,000 to the cubic millimetre; it is not common to find them much

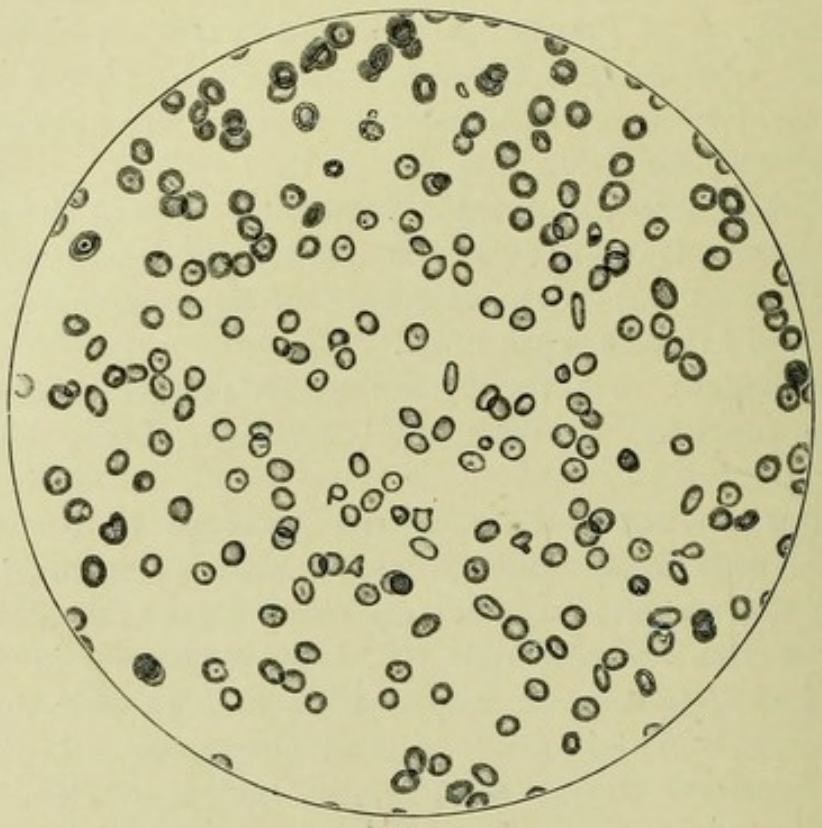


FIG. 93.—Blood in chlorosis.

The figure shows a film of the blood corpuscles in chlorosis. Many of the red corpuscles are normal in shape, but a few are oval, and some are pear-shaped. Some are smaller than normal, but there are no macrocytes.

below 2,000,000. The hæmoglobin averages 41 per cent., while the colour index is low—on an average about 0.5. The red cells are pale, and somewhat diminished in size. Macrocytes are very rare, while microcytes are fairly common; poikilocytosis is frequently observed to a slight degree, but it is very rarely well-marked. The presence of nucleated corpuscles has been observed, but their occurrence is extremely rare. Leucocytosis is, as a rule, absent, though an increase of the lympho-

cytes may be present. Myelocytes are very rarely observed, and the blood plates are increased.

In *pernicious anæmia* (Fig. 88) the blood, when drawn, is pale and watery; it is very fluid, and very slow in coagulating. The red corpuscles show no rouleaux formation; their average number per cubic millimetre, when the individual first comes under medical observation, is a little over 1,000,000 (1,200,000). In the later stages the number drops to 500,000, and may even be as low as 143,000 (Quincke). The hæmoglobin varies from 18 to 40 per cent., the average being about 35 per cent. The colour index is usually over 1. Microscopically, the red cells show great variations in size (macrocytes and microcytes), as well as in shape (marked poikilocytosis). Polychromatophilic cells are frequently met with, as well as nucleated red cells, megaloblasts being more common than normoblasts. The white corpuscles are diminished, even to 500 per cubic millimetre.

The contrast between the blood in chlorosis and that in pernicious anæmia is therefore well marked. In the former the chief change is in the diminution in the amount of hæmoglobin, and to this diminution is to be ascribed the low specific gravity of the blood. The specific gravity of the plasma is not diminished, and may be increased. The change in shape of the corpuscles is but slight, and there is no diminution in the number of leucocytes. There is in chlorosis, therefore, no evidence of blood destruction, which is the main feature of the blood in pernicious anæmia. The great diminution in the number of corpuscles in this disease, with their marked degeneration, shows that they are the chief element affected. The plasma and white corpuscles are also affected, as shown by the diminished coagulability of the blood, and the diminution in the number of leucocytes.

The tissue changes which occur in profound anæmias are—(1) a deposit of hæmosiderin in the liver or spleen (Chapter XIV.), or pigmentation; (2) fatty changes in the heart, liver, and kidneys (p. 203); (3) hæmorrhages (Chapter XIV.); (4) changes in metabolism (Chapter XVIII.), and in the central nervous system (Chapter XIX.).

2. *The White Corpuscles (Leucocytes): Blood Platelets.*—The

average number of leucocytes per cubic millimetre is about 7500, but this number varies considerably, not only in different individuals, but in different conditions of the same individual. The number of blood plates has been reckoned to be between 200,000 and 300,000 per cubic millimetre. The following are the varieties of leucocytes normally present in the blood (Fig. 94):—

The Lymphocyte is a small cell of an average diameter of

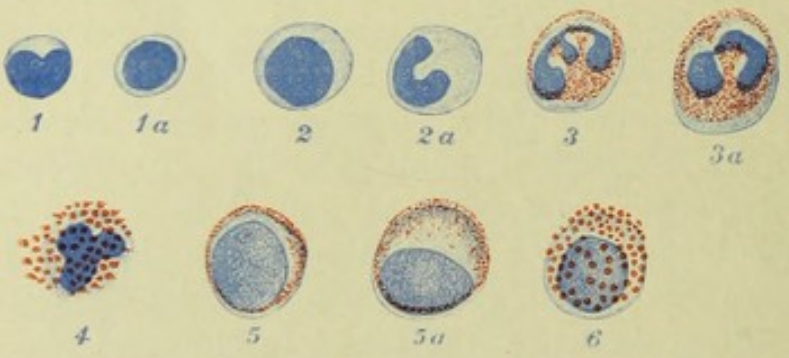


FIG. 94.—Varieties of leucocytes (as stained by eosin and methylene blue).

1 and 1*a*. The lymphocyte is a small cell with a large nucleus and but little protoplasm, which does not contain granules staining red with eosin.

2 and 2*a*. The mononuclear leucocyte (macrophagocyte) is larger than the lymphocyte, while it contains more protoplasm. No granules staining red with eosin.

3 and 3*a*. The polymorphonuclear leucocyte (microphage) is characterised by a multilobed nucleus, surrounded by protoplasm, which contains numerous fine granules staining red with eosin.

4. The eosinophile leucocyte has a multilobed nucleus, and is characterised by the large granules, which stain red with eosin.

5 and 5*a*. The myelocyte has a large oval nucleus staining poorly with methylene blue, and the protoplasm also does not stain well, and has fine granules staining red with eosin.

6. The eosinophile myelocyte is like the myelocyte, but has large eosinophile granules, like the eosinophile leucocyte.

10 μ, and has a round nucleus, staining deeply with aniline dyes, and a small amount of protoplasm, which stains lightly. It forms from 20 to 30 per cent. of the leucocytes of human blood, is increased in number after food, and closely resembles the small cells of lymphoid tissue. In children the percentage of lymphocytes may be from 40 to 60. It is not amœboid, and does not act as a phagocyte.

The large Mononuclear Leucocyte forms 4 to 8 per cent. of the leucocytes, and is of an average diameter of 13 μ (p. 32).

Polymorphonuclear Neutrophile Leucocyte forms 62 to 70

per cent. of the leucocytes, and is of an average diameter of 13.5 μ (p. 32).

The Eosinophile Leucocyte, or coarsely granular oxyphile, forms only a small proportion of the leucocytes of the blood ($\frac{1}{2}$ to 4 per cent.), and is of an average diameter of 12 μ. It is found abundantly, like the next form, in cœlomic fluid, in serous cavities, connective tissue and in bone marrow. Unlike the hyaline cell, its protoplasm, which is abundant, contains relatively large granules which stain with acid dyes, such as eosin, and not with alkaline dyes, such as methylene blue and basic fuchsin.* The nucleus is lobed liked that of the preceding form. The eosinophile leucocyte is amœboid, and is non-phagocytic. Two other forms of leucocytes, neither of which is phagocytic, but both of which are basophile cells, are described.

Coarsely Granular Basophile Leucocytes are present in cœlomic fluid, but are absent from human blood in health. They are present in leukæmia. They have a round nucleus, and the granules of the protoplasm, which are large, stain with basic dyes.

Finely Granular Basophile Leucocytes (mast cells) are very small cells, with a trilobe nucleus, the protoplasm containing very small granules staining with basic dyes. They form $\frac{1}{4\,0}$ to $\frac{1}{2}$ per cent of the leucocytes, and are increased after meals.

In disease, other forms of leucocytes make their appearance in the blood. These are:—*The Myelocytes*, or mononuclear cells, with neutrophile granulation; the *Eosinophile Myelocyte*, or mononuclear eosinophile cells, and the small *Neutrophile Pseudo-Lymphocytes.*

1. *The Myelocyte* is a large cell, 15.75 μ in diameter, with a large oval or reniform nucleus, staining faintly, and situated

* The term acid and basic dyes does not necessarily mean that the substances are acid or alkaline to test paper, the dyes being a compound of acid and base used in their technical senses. In the acid dyes there is an excess of the acid moiety; in the basic dyes an excess of the basic. Eosin is thus an acid dye, methylene blue a basic. Ehrlich's "neutral" stain acts really as an acid dye.

either centrally or at the periphery of the cell. The protoplasm shows neutrophile granulation, thus differing from the large mononuclear cells. The myelocytes vary in size; and, unlike the polymorphonuclear neutrophile leucocyte, they show no amœboid movement. In disease, the myelocytes are found mainly in splenic myelogenous leukæmia, but they have also been found in sarcoma of the bone marrow; in severe post-hæmorrhagic anæmia; in severe mercurial poisoning; in *anæmia pseudo-leukæmica infantum*, and in some infective diseases, such as diphtheria.

2. *The Eosinophile Myelocyte* shows the large oxyphile granulations characteristic of the eosinophile cell, and is found mainly in splenic myelogenous leukæmia and in *anæmia pseudo-leukæmica infantum.*

3. *The Neutrophile Pseudo-Lymphocytes* are about the same size as the lymphocytes, but show neutrophile granulation of the protoplasm. They have been found in hæmorrhagic small-pox and in recent pleuritic effusion, but their exact significance or origin is unknown.

Alterations in the Number and Character of the Leucocytes in Disease.—The number of leucocytes may be diminished—a condition called *leucopenia*—or they may be increased in number. The increase may be one affecting only the normal leucocytes of the blood—a condition called *leucocytosis;* or one particular variety of normal leucocyte may be increased—as when the lymphocytes are increased, *lymphocytosis*, or the eosinophile cells are increased, *eosinophilia.* On the other hand, there may be a large addition made to the number of leucocytes in the blood by the presence of myelocytes, as in *splenic myelogenous leukæmia*, and a very large increase of lymphocytes, which occurs in *lymphatic leukæmia*, as distinguished from the moderate increase which occurs in lymphocytosis.

By some, two classes of leucocytosis are made: *Active Leucocytosis*, in which the leucocytes which are increased are those showing amœboid movement; namely, the polymorphonuclear neutrophile, the eosinophile and the mononuclear leucocytes;

and *Passive Leucocytosis*, in which the increase is of non-amœboid leucocytes, such as the lymphocyte and the myelocyte (Ehrlich and Lazarus). This classification is a useful one, as it contrasts the kinds of leucocytes which are increased.

Active Leucocytosis.—This is divided into (*a*) Polymorphonuclear Leucocytosis, with the subdivisions: (I.) Polymorphonuclear neutrophile leucocytosis; and (II.) Polymorphonuclear eosinophile leucocytosis; and (*b*) Mixed Leucocytosis, in which, in addition to the above, the mononuclear elements are affected.

I. *Polymorphonuclear Neutrophile Leucocytosis* is the ordinary form of leucocytosis. These leucocytes are not derived from the lymph glands, as Virchow supposed, but by an emigration from the bone marrow (Ehrlich). The eosinophile cells are diminished sometimes considerably. This form of leucocytosis occurs both in physiological and pathological conditions.

1. *Physiological Leucocytosis* is observed:—

(*a*) *In the newly born*, in which, up to the fourth day, the leucocyte count may be as high as from 17,000 to 30,000 per cubic millimetre.

(*b*) *During digestion.*—Starvation greatly diminishes the number of leucocytes, sometimes to 1000 per cubic millimetre. In one to five hours after a meal, rich in proteids, leucocytosis is observed, the increase being sometimes 33 per cent. The change is more marked in children than in adults.

(*c*) *In pregnancy*, in the later months, there is leucocytosis, which may be as high as 13,000 per cubic millimetre. This is more marked in primiparæ. The leucocytes are also increased after parturition.

(*d*) *Bodily exercise and cold baths* also increase the leucocyte count.

2. *Pathological Leucocytosis.*

(*a*) *In acute and chronic anæmic conditions*, leucocytosis occurs, especially after profuse or long-continued hæmorrhages.

(*b*) *Inflammatory leucocytosis* (Fig. 95) is the most frequent

form of polymorphonuclear neutrophile leucocytosis. It occurs in infective diseases, during their continuance; such as in local infections or abscesses, in septicæmia, pneumonia, erysipelas, diphtheria and scarlet fever; while in typhoid fever, measles,

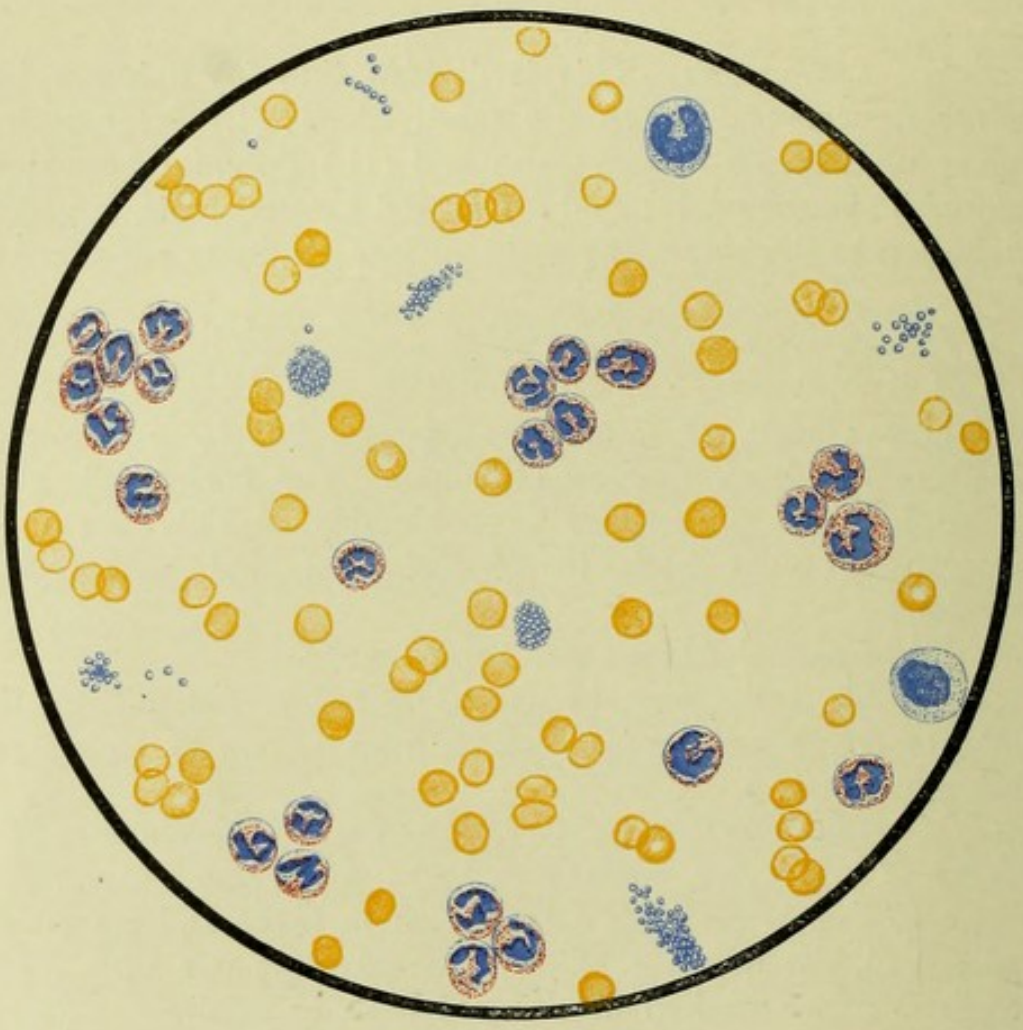


FIG. 95.—Blood film in leucocytosis.

The figure shows the large increase in the blood of the polymorphonuclear leucocyte—inflammatory or infective leucocytosis. The blood platelets are also greatly increased. The red corpuscles are normal. From a case of mouth infection ending in gangrene.

malaria, influenza, rötheln, mumps, cystitis and tuberculosis, polymorphonuclear leucocytosis is absent. In typhoid fever and measles, there may be leucopenia.

3. *Toxic Leucocytosis* occurs in poisoning by illuminating gas and quinine; it follows the administration of salicylates and is also observed as the result of etherisation. It is seen following

injections of tuberculin and thyroid extract. To a toxic action may perhaps be ascribed the polymorphonuclear leucocytosis which occurs in chronic renal disease, in acute yellow atrophy of the liver, in some cases of cirrhosis of the liver and in cases of gout.

A large number of substances have been tested as regards their effect in producing an increase of leucocytes. Thus, the administration of camphor and some of the essential oils by the mouth causes an increase of leucocytes ; the subcutaneous injection of albumoses, pepsin, nuclein, extract of leech and curare lead to the same result ; while, in the case of irritants subcutaneously injected, such as turpentine, croton oil and salts of mercury, great leucocytosis was produced, which appeared to be out of proportion to the amount of local reaction produced. The action of bacterial poisons in producing polymorphonuclear leucocytosis is partly considered with the subjects of Phagocytosis and Chemiotaxis (p. 27). From experiments which have been performed, it appears that the degree of leucocytosis depends on the age of the animal and the dose of the poison, and on the resistance or degree of immunity, of the animal. Thus, young animals show greater leucocytosis than older ones. A very large dose of toxine causes a reduction in the number of leucocytes, and a non-fatal dose produces leucocytosis ; a slowly fatal dose causes a varying effect ; while in immune animals, there is but little, or no, leucocytosis. These results are to be explained by the facts which have already been discussed under the heading of *Immunity* (Chapter VI.). Leucocytosis, as the result of bacterial poisoning, appears to be dependent on the slow action of the poison. This action is absent in immune animals ; therefore but little leucocytosis results.

4. *Mononuclear Leucoc tosis* is observed in malignant tumours.

II. *Polymorphonuclear Eosinophile Leucocytosis.*—The eosinophile cells are increased in certain diseased conditions—sometimes relatively and sometimes absolutely ; that is, instead of constituting $\frac{1}{2}$ to 4 per cent. of all the leucocytes, they may form 10, 20, or 30 per cent., or even above this. The average normal number of eosinophile cells to the cubic millimetre is

between 100 and 200. This may be increased in disease to over 4000, and as many as even 29,000. An increased number of the polymorphonuclear eosinophile cells is observed in healthy infants, but not in adults. Leukæmia is sometimes associated with polymorphonuclear eosinophile leucocytosis, but the conditions in which it has been more particularly observed are as follows:--

(*a*) In *bronchial asthma* an increase has been observed up to 10 or 20 per cent. In the sputum of infants and adults suffering from the disease eosinophile cells are found, in addition to Charcot-Leyden crystals. The leucocytosis is well-marked at the time of the attacks, and is directly connected with the attacks.

(*b*) *In certain skin diseases* eosinophilia is observed, more particularly in pemphigus, prurigo and psoriasis, and the degree of leucocytosis appears to be connected with the extent of skin involved.

(*c*) In *helminthiasis.*—Eosinophilia has been observed in ankylostomiasis more particularly, but also in other cases of parasitism of the intestine, as in oxyuris, ascaris and tænia mediocanellata, and in trichiniasis.

(*d*) Eosinophilia is also observed during convalescence from certain infective diseases; for example, pneumonia, rheumatism and malaria; and has occurred as the result of the injections of tuberculin.

(*e*) A slight increase in the eosinophile cells has been observed in the cachexia associated with malignant tumours.

Passive Leucocytosis.—I. *Lymphocytosis* is a relative increase in the lymphocytes of the blood. There may, or may not, be an actual increase of the total leucocytes, and, with an increase of the total leucocytes, the appearances of the blood are similar to those of lymphatic leukæmia. Relative lymphocytosis is observed in the blood of the healthy infant, as well as in some diseases of infancy, such as the various forms of gastro-intestinal disturbance and infection. Other causes are congenital syphilis and scurvy. In adults, it is observed in chlorosis, pernicious anæmia and the secondary

anæmia of syphilis; as well as, somewhat irregularly, in certain infective diseases, such as typhoid fever, tuberculosis, smallpox and chronic malaria. Usually it is observed towards the end of an infective disorder. Absolute lymphocytosis is a rare condition.

II. *Leukæmia.*—Leukæmia may be divided into two groups of cases:—

1. *Myelocytæmia*, or splenic myelogenous leukæmia, in which there is an enlarged spleen, with changes in the bone marrow, but not in the lymphoid tissues generally. The disease runs a chronic course, lasting from two to five years.

2. *Lymphæmia*, or lymphatic leukæmia, which exists both in the acute and chronic form. The acute lasts six or seven weeks, and the chronic from two to four years or more. In this disease the lymphatic glands are enlarged, and the spleen may also be greatly enlarged.

1. *Splenic Myelogenous Leukæmia* (Fig. 96).—The blood, when shed, is opaque and flows sluggishly; coagulation is slow. The red corpuscles, in the early stage, show no diminution in number, or in the amount of hæmoglobin. In the advanced disease, the average number of red cells is about 3,000,000 per cubic millimetre, and the colour index averages about 0.6. There is poikilocytosis to a greater or less extent, but the most characteristic microscopic feature of the red corpuscles is the presence of very numerous nucleated red cells, which are as numerous as in the worst forms of pernicious anæmia. The nucleated cells are usually normoblasts, megaloblasts being somewhat uncommon. The white corpuscles show the main change in the blood. The number of white corpuscles is enormously increased, and the average proportion of the white cells to the red is about one to seven, the figures varying in individual cases. The highest is one white to two red, and the lowest is one white to thirty-seven red; some cases are, however, recorded in which the white equal or even exceed the red in number. The average number of leucocytes per cubic millimetre is about 450,000, while the variations in

individual cases are between 98,000 and over 1,000,000. The characteristic feature of the blood condition and of the disease is the presence of a large number of myelocytes (mononuclear neutrophile cells). The presence of these characteristic cells

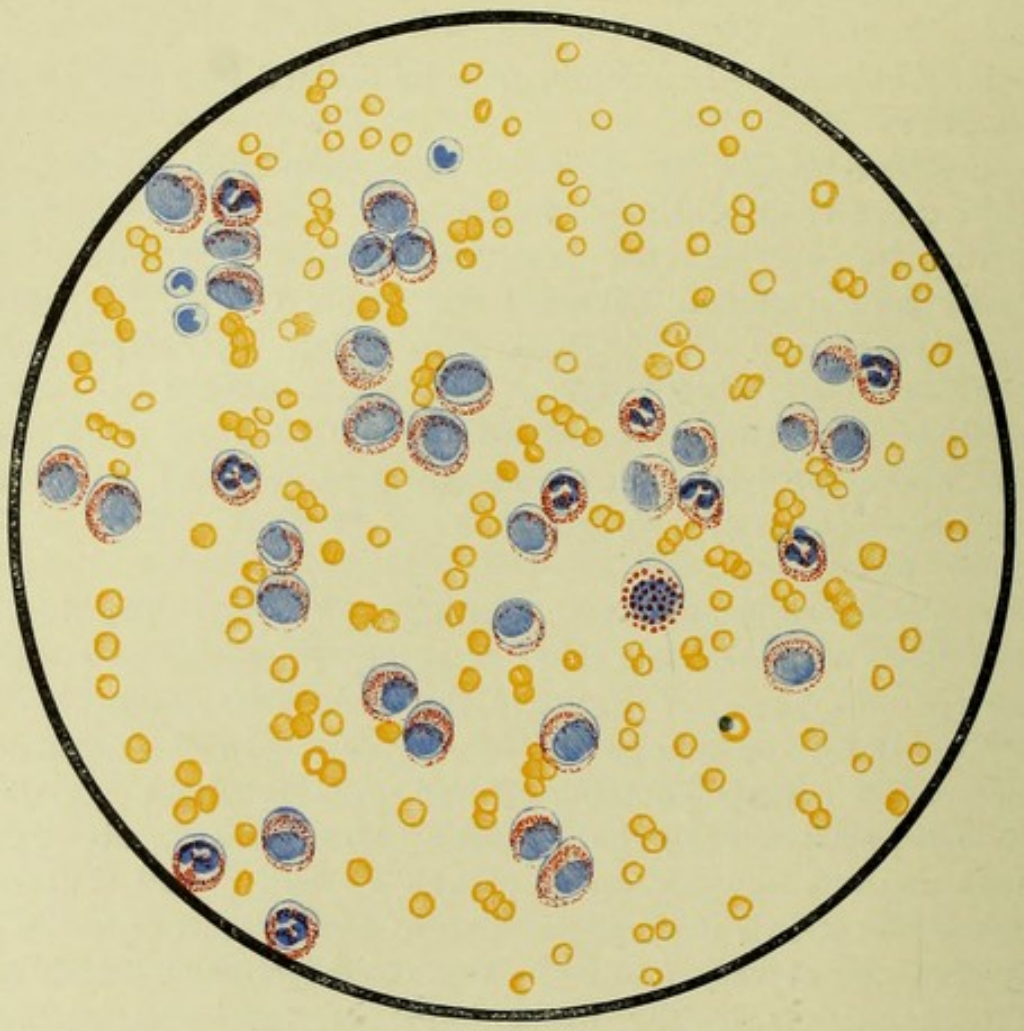


FIG. 96.—Blood film in leukæmia.

There is an enormous number of myelocytes (see Fig. 94) in the blood: absolutely and relatively to the normal leucocytes. A few polymorphonuclear and mononuclear leucocytes are seen, as well as lymphocytes. A few red corpuscles are nucleated (normoblasts).

gives a picture in the blood preparation in marked contrast to that present in leucocytosis. The myelocytes form an average of 30 per cent. of the total leucocytes in splenic myelogenous leukæmia; but their actual number per cubic millimetre varies enormously, being from 50,000 to 150,000. The last figure may be taken as representing the usual number in the later stages of

the disease. The eosinophile myelocyte, or mononuclear eosinophile cell, is present in leukæmia, but not in such large numbers as the myelocyte. Of the normal leucocytes of the blood, the eosinophile cells are absolutely increased. The average normal number of eosinophile cells per cubic millimetre is between 100 and 200. In splenic myelogenous leukæmia the number is very greatly increased, sometimes to as much as fifty, or more, times than the normal; and this increase continues with the progressive increase of leucocytes during the course of the disease. In some cases of leukæmia the eosinophile cells are diminished, and this is observed when infection occurs. From numerous observations, it appears that absolute increase of the eosinophile cells is an integral part of the changes in the blood in splenic myelogenous leukæmia. The polymorphonuclear neutrophile cells are absolutely increased in comparison with the normal blood, but relatively diminished in proportion to the other leucocytes present. When the leukæmic individual, however, suffers from an infective febrile disease, the polymorphonuclear neutrophile cells show an enormous increase, and may largely preponderate over the other leucocytes. This means that, as the result of infection, polymorphonuclear neutrophile leucocytosis is added to the typical changes of the blood in leukæmia. The lymphocytes are affected in the same way, but are relatively diminished. Coarsely granular basophile cells may be observed. The finely granular basophile leucocytes are absolutely increased, and the increase may be considerable. Irregular forms of leucocytes are not unfrequently observed, those smaller in size than normal, or cells with the nucleus undergoing division.

During the remissions which sometimes occur in the disease, the spleen is diminished in size and the total number of leucocytes is decreased. The proportion of myelocytes remains, however, about the same.

2. *Lymphæmia*, or lymphatic leukæmia (Fig. 97).—The red corpuscles in this condition present much the same appearances as in splenic myelogenous leukæmia, with the exception that normoblasts are rather less common. The white cells

show an increase, the proportion of white to red being, on an average, about two to fifty, the average number per cubic millimetre being about 100,000. The great increase in the white corpuscles is due solely to the increase in the lympho-

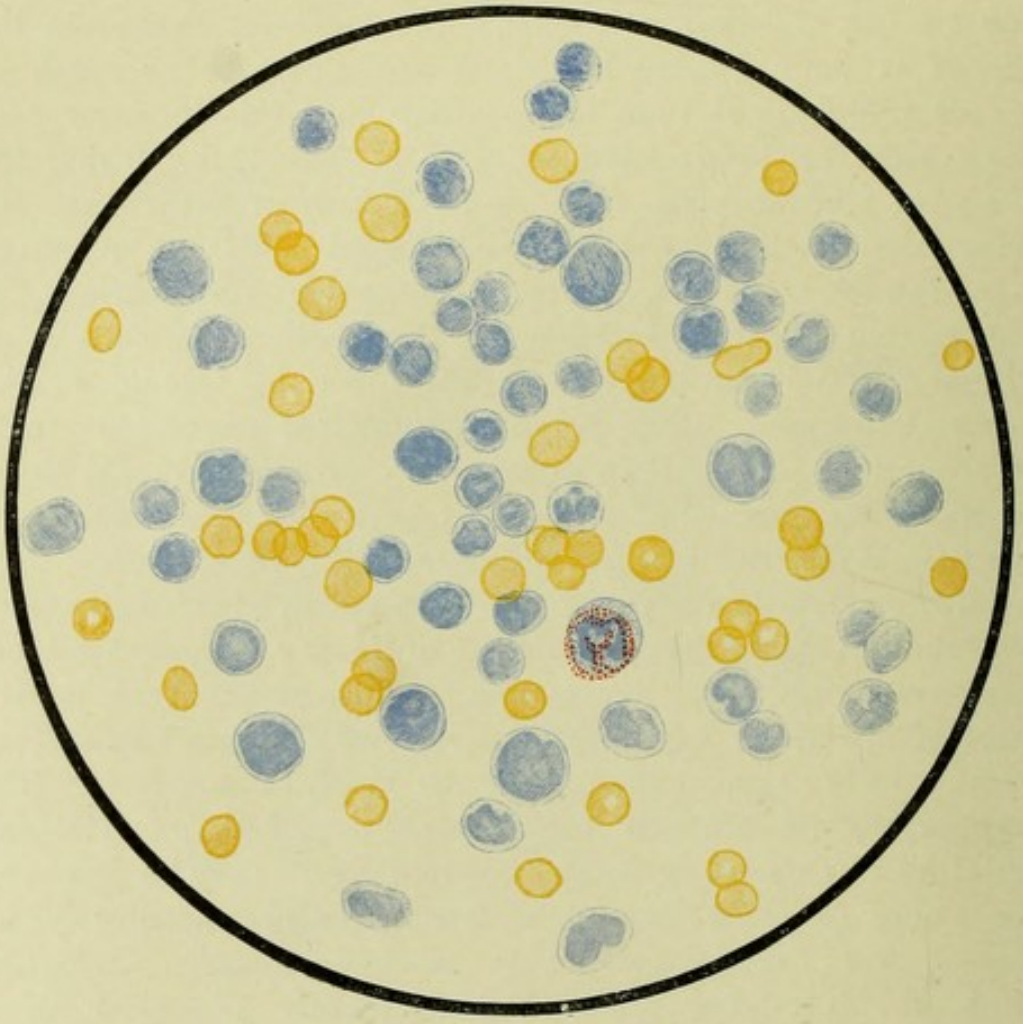


FIG. 97.—Blood film in lymphæmia.

There is an enormous increase in the number of lymphocytes, which almost completely fill the field. There are no myelocytes, and the polymorphonuclear leucocytes are not increased. From a case of acute lymphæmia (lymphatic leukæmia).

cytes—small and large—which may form 90 per cent. or more of the leucocytes present. The lymphocytes often show degeneration. The other leucocytes of the blood are diminished—both the polymorphonuclear neutrophile and the eosinophile cells; myelocytes are rarely found. In acute leukæmia the large lymphocytes predominate, and there is great diminu-

tion in the number of the red corpuscles. The blood condition in lymphæmia is affected, as in splenic myelogenous leukæmia, by intercurrent disease. In one case septicæmia, complicating lymphatic leukæmia, caused a great increase in the white cells, due to polymorphonuclear leucocytosis. In the majority of observed cases, however, intercurrent disease, such as carcinoma, tuberculosis, pneumonia, influenza, erysipelas and abscess of the kidney, decreases the number of leucocytes. The condition of the blood in lymphæmia may be contrasted with that in Hodgkin's disease or lymphadenoma. In this disease the blood count may be normal, or there may be a moderate degree of anæmia; and an increase of the leucocytes, when present, is due to polymorphonuclear neutrophile leucocytosis.

Origin of the White Corpuscles.—The place of origin of the different forms of leucocyte is of importance in disease. The subject has given rise to much controversy, but the main facts in relation to it are as follows:—There are three places of origin: the lymphatic glands and lymphoid tissue throughout the body, the bone-marrow and the spleen.

Production of Leucocytes in the Spleen.—After removal of the spleen, a general enlargement of the lymphatic glands of the body occurs, with occasional changes in the thyroid. Experimenting in animals—for example, the guinea-pig—removal of the spleen is followed by enlargement of the lymph glands during the first year, and this enlargement is accompanied by an increase in the number of lymphocytes in the blood, or lymphocytosis. In a longer period after splenectomy, there is, in the guinea-pig, a great increase of the eosinophile cells. At no time are the cells which correspond to the polymorphonuclear neutrophile leucocytes of man increased. Cases of splenectomy in man have not been examined, as regards the blood condition, with sufficient persistence to allow any correct deductions to be drawn; but, at any rate in some cases, splenectomy is followed by lymphocytosis, and this again by eosinophilia. The lymphocytosis which is observed, is to be ascribed to an increased activity on the part of the lymphoid tissue in the

body; and, on the hypothesis that the eosinophile cells are formed in the bone-marrow (Ehrlich), the subsequent eosinophilia is to be ascribed to the increased activity of the bone-marrow. It must be admitted, however, that the function of the spleen in the production of the leucocytes of the blood must be very slight, and it is chiefly concerned with producing changes in the dying red and white corpuscles in the blood stream.

Production of Leucocytes in the Lymphoid Tissue.—The lymphocytes of the blood are the same cells as those which are found in the lymphatic glands and in the lymphoid tissue which exists in many parts of the body; for example, in the gastro-intestinal tract, in the spleen, and in the lungs. The lymphocytes, which normally form about 25 per cent. of the leucocytes, are diminished in the blood in cases of extensive disease causing destruction of the lymph glands; as, for example, in cases of lympho-sarcoma, where they have been found to be diminished to 0.6 per cent. In the disease called malignant lymphoma, which is characterised by a rapid swelling in the lymph glands, the lymphocytes are increased, possibly as the result of irritation of the glands. The other conditions, however, in which the lymphocytes are increased, do not add much to our knowledge of their origin. Lymphocytes are cells without amœboid movement; they do not pass out of the vessel, and so are not found in inflammatory effusions. In gastro-intestinal diseases of infants they are increased in the blood, presumably coming from the lymphoid tissue in the intestinal tract. Whooping-cough is accompanied by an increase in the number of lymphocytes, but the cause of this is unknown. It is stated that the injection of pilocarpine increases the lymphocytes, but, as a rule, the effect of poisons is not to increase the lymphocytes, but to increase the polymorphonuclear neutrophile leucocyte, the leucocyte of inflammation and infection. Even in cases of disease, such as lymphatic leukæmia, in which the number of lymphocytes in the blood is enormously increased, the leucocyte which exudes in inflammatory areas is the polymorphonuclear neutrophile, and not the lymphocyte.

Origin of the Leucocytes in the Red Bone Marrow.—Bone marrow contains cells, which are shown to have specific granules when properly stained (Ehrlich). These granules are (1) neutrophile, (2) eosinophile, and (3) basophile. Most of the cells found in the bone marrow contain granules; a few are free from granules, and to these belong the cells in a state of division which are there observed. There is but little doubt that the most abundant leucocyte in the blood—the polymorphonuclear neutrophile leucocyte—originates in the red bone marrow. Transitional forms are to be observed, from the mononuclear cells to the polymorphonuclear, the latter being an advanced stage of the former and the only ones found in the blood. A similar process takes place with regard to the polymorphonuclear eosinophile leucocytes. The mononuclear neutrophile cell, which develops into the polymorphonuclear neutrophile leucocyte, is the myelocyte. It does not enter the blood in normal conditions, and, practically, only in one disease—splenic myelogenous leukæmia.

The establishment of the fact that the commonest leucocyte in the blood — the polymorphonuclear neutrophile — has its origin in the bone marrow, is very important, inasmuch as leucocytosis, or the increase of the total leucocytes of the blood, is shown by an increase of this polymorphonuclear neutrophile leucocyte, and, indeed, it has been said that leucocytosis is a function of the red bone marrow (Ehrlich).

Disease of the red bone marrow has a varying effect on the leucocytes of the blood. It is not often that the bone marrow is so extensively diseased as to leave no normal marrow to continue the functions. In some cases, however, of tumour of the bone, the bone marrow is replaced by growth, and a severe anæmia may result, with a moderate leucocytosis. In other cases, however, besides the anæmia and the occurrence of nucleated red corpuscles, there is a great increase in the leucocytes, mainly due to the presence of myelocytes; this, however, is a rare condition. In acute lymphæmia the bone marrow is replaced by lymphoid tissue, and the change is so extensive that a great alteration in the leucocytes of the blood takes place, there being a great diminution in the poly-

morphonuclear neutrophile leucocyte. In the marrow itself the neutrophile cells are, however, scanty. In some of the blood diseases which have been described, the yellow bone marrow becomes red like "currant jelly," and takes on blood-forming functions.

CHAPTER XII

CHANGES IN THE BLOOD IN DISEASE—*continued*

II. *Changes in the Hæmoglobin: Hæmolysis, Hæmoglobinæmia*

HÆMOGLOBIN, the colouring matter of the blood, is found only in the red corpuscles, and not dissolved in the plasma. The plasma has its own yellow colouring matter, which is called lutein. In the corpuscles hæmoglobin exists in the form of reduced hæmoglobin and oxyhæmoglobin. Reduced hæmoglobin gives a characteristic spectrum of a broad absorption band between the lines D and E (Fig. 98). Oxyhæmoglobin gives two bands, a narrow one close to D and a broader one nearer E. *Methæmoglobin* is a derivative of hæmoglobin, and may be prepared from it artificially by the action of oxidising agents, such as potassium permanganate and nitrite of amyl. It is a dark chocolate colour, and contains oxygen probably in firmer combination than in oxyhæmoglobin. It may be obtained in a crystalline form, and shows three absorption bands in the spectrum, one in the red between C and D and two between D and E, differing somewhat from the similar lines of oxyhæmoglobin. Methæmoglobin may be transformed into oxyhæmoglobin, and then to reduced hæmoglobin by means of ammonium sulphide or sodium hyposulphite. *Hæmatin* is a product of decomposition of hæmoglobin, which is produced by the action of strong alkalies or acids. It exists in an alkaline or acid form, and combines with hydrochloric acid to form hydrochloride of hæmatin or crystals of hæmin. Both acid and alkaline hæmatin give spectra differing from that of hæmoglobin.

Hæmatin contains iron, but has certain derivatives which are iron-free. These are chiefly hæmatoporphyrin and hæmatoidin. Hæmatoidin is considered elsewhere (Chapter XIV.). Hæmatoporphyrin occurs in certain combinations in urine.

Part of the subject now under consideration concerns the presence in the circulating blood of hæmoglobin, set free by the solution of the red corpuscles. Methæmoglobin in these conditions may be found in the urine, but has not been observed in the circulating blood. The hæmoglobin which is set free is passed out of the body in the urine, either as hæmoglobin or methæmoglobin. In some instances this condition is associated with jaundice (Chapter XV.), but in most cases this association is not observed. The solution of red corpuscles in the blood is due to many different causes, some of which are clear, such as those due to poisons, while others are still obscure. Hæmoglobin is a cell derivative; that is, it is originally formed in cells, and in the healthy body it is contained solely within formed elements, the red corpuscles. There is, however, more or less continuous destruction of certain of the red corpuscles occurring in the liver and spleen, and the hæmoglobin goes to the formation of the colouring matter of the bile.

With the doubtful exception of the spleen, hæmoglobin is nowhere in solution in the liquids of the body. When the corpuscles are removed from the body, the colouring matter is readily dissolved by the addition of distilled water to them, and this solution is prevented by the addition of salts to the water. The solution of hæmoglobin by distilled water, and its prevention by the addition of salts, may simply mean that distilled water kills the cell, and so dissolves its readily soluble contents. The discovery, however, of certain substances which, added to the blood outside the body, readily dissolve the colouring matter from the corpuscles, or, as it is said, produce hæmolysis, is an important fact in the explanation of the solution of the hæmoglobin from the red corpuscles in disease. These substances are certain bacterial poisons and the sera of certain animals.

The conditions of disease in which the red corpuscles are

destroyed inside the vessels, producing hæmoglobinæmia and causing the appearance of the colouring matter in the urine, hæmoglobinuria, are as follows:—

1. *Toxic Conditions.*—In poisoning by chlorate of potash, pyrogallic acid, arseniuretted and phosphoretted hydrogen, by quinine, and in severe cases of mineral acid poisoning, hæmoglobinæmia and hæmoglobinuria are observed.

Also as the result of the action of snake-venom and certain vegetable poisons, such as ricin, abrin and crotin.

2. *In sunstroke, frost-bite, and severe burns.*

3. *As the result of the injection of the blood of one animal into another.*

4. *In Infective disease*, such as septicæmia, pyæmia, typhoid fever and scarlet fever.

5. *In other conditions*, of which the cause is unknown, such as the conditions referred to as paroxysmal hæmoglobinuria, Raynaud's disease and infantile hæmoglobinuria.

After the destruction of the red corpuscles, the colouring matter is discharged in the urine, either as hæmoglobin or as methæmoglobin. In both cases it is usually in solution, but it may be partly precipitated as a brownish sediment. A few red corpuscles may also be observed. In the same case the colouring matter may at one time be discharged as hæmoglobin, and at another time as methæmoglobin, and it is probable that the change into methæmoglobin takes place in the urine itself.

1. *Toxic Hæmoglobinæmia.*—The occurrence of hæmoglobinuria as a sequence of poisoning by chlorate of potassium or pyrogallic acid is simply explained by the drug destroying a certain number of corpuscles, liberating the hæmoglobin, which is then discharged in the urine. With its occurrence there is an increase in the amount of urea excreted. Quinine is said to produce this effect, when given in certain cases of chronic malaria.

2. The cause of the destruction of the red corpuscles in sunstroke, frost-bite and severe burns is not yet determined. It is at present not explained by the mere effect of heat or cold on the part of the body affected, although, if this were extensive

and led to the destruction of a large number of red corpuscles, the occurrence of hæmoglobinæmia is conceivable. It is possible, however, that, in these conditions, an element of infection may be present. With severe burns, indeed, this is usually the case.

3. Hæmolysis, following the injection of the blood of one animal into another, has already been mentioned in connection with *Immunity* (p. 190). The results obtained have an important bearing on the destruction of the red corpuscles in disease. The serum of some animals containing, as it is said, a *hæmolysin*, dissolves the blood corpuscles of others. Thus, the normal serum of the dog dissolves the red corpuscles of the guinea-pig, rabbit, rat, goat and sheep. The property is lost if the serum is warmed to 55°-60° C., but is restored by adding the normal serum of the guinea-pig or other animal. It is thus seen that the hæmolysin consists of two parts, one of which is not sensitive to heat, and the other of which is destroyed by heat and exists in the blood of the animal whose corpuscles are dissolved.

The above may be taken as an example of hæmolysin normally occurring in the blood of an animal. Hæmolysins may be manufactured by the injection of the blood of one animal into another. The serum of normal rabbits has no effect on the blood of the ox, that is, it causes no solution of red corpuscles; but if rabbits be treated by repeated intraperitoneal injections of ox blood (20-30 c.c.) it is found that, after a time, the serum of the rabbit "lakes" fresh ox blood, that is, acts as a hæmolytic. Thus it is found that as little as 0.1 c.c. of the serum will "lake" 2.5 c.c. of a 5 per cent. suspension of ox blood in isotonic salt solution. A new body has therefore been formed by the injection in the rabbit of the ox blood. This body is called the *Immune Body* (Fig. 62). It requires, for its hæmolytic action, another substance or *complement*, which exists normally in the guinea-pig's or rabbit's blood. The immune body is found resistant to heat and even to putrefaction, while the complement is readily destroyed by heat. In the sera from different animals the immune body and the complement may be obtained, which, in conjunction, will cause hæmolysis of the blood of another animal.

The blood corpuscles of rabbits injected into the horse, cause the serum of this animal to be poisonous to rabbits, a few c.c. being fatal, whereas even 60 c.c. of normal horse serum intravenously injected has no serious effect on the rabbit (Bellfanti and Corbone). Bordet showed that, in this case, there was a specific hæmolysin or immune body, present in the serum of the horse, and that this hæmolytic property of the serum was lost by heating it for half an hour at 55° C., but the property was regained by adding normal serum to the warmed serum. The following additional examples of this may be given:— The blood of guinea-pigs, mixed with warmed dog's serum (containing immune body), is hæmolysed by fresh guinea-pigs' blood serum (containing complement); guinea-pigs' blood with warmed calf serum is hæmolysed by guinea-pig serum; sheep's blood with warmed rabbit serum added is dissolved by calf serum; goat's blood with warmed rabbit serum is dissolved by goat serum; and guinea-pigs' blood with warmed sheep serum is dissolved by guinea-pig serum.

The effect of the injection of the blood of one animal into another results not only in the production of hæmolysins, but of other anti-bodies. Thus, the serum of one animal treated by the injection of the blood of another animal yields an anti-hæmatic serum, which may contain three kinds of anti-bodies:—

1. Agglutinin, which causes the red corpuscles to adhere together;

2. Hæmolysin, which dissolves the colouring matter of the red corpuscles; and

3. Precipitin, which precipitates the proteids of the serum.

The agglutinin and hæmolysin are formed when the red corpuscles alone are used for injection; the precipitin when the serum alone is so used.

The substances which are described as hæmolysins, and the other anti-bodies, belong to the same group as the antitoxic and other similar bodies previously discussed in the consideration of Immunity. Their chemical nature is not yet understood. They are not, however, chemical salts in the ordinary acceptation of the term, but are closely related

to the nitrogenous proteid substances concerned in the nutrition of the cell.

The agglutinin, which causes the red corpuscles to adhere together, is not necessarily associated with the hæmolysin. Thus, although it is found that guinea-pigs repeatedly injected with defibrinated rabbit's blood yields a serum which possesses both hæmolytic and agglutinating action, yet the latter is not destroyed by exposure to 55° C. for half an hour, as is the case with the hæmolytic. Moreover, goats treated for a long time with the corpuscles of the sheep yield a serum which has a hæmolytic, but not an agglutinating action. It has been stated that the serum from anæmic subjects (in chlorosis, secondary anæmias, and leukæmia) possesses, in some instances, an agglutinating action on the blood of the patient or of healthy persons. The subject, however, requires further investigation.

The hæmolysin, as already stated, consists of two parts (Fig. 62), the immune body and the complement, the complement being sensitive to heat and external conditions, the immune body being more resistant. The substances called by Buchner *Alexines* (cytases, Metchnikoff) are anti-bodies existing normally in the blood and tissues, or manufactured by the different methods already discussed (p. 178). The alexines (complement) are sensitive to heat, losing their properties by exposure to a temperature of 55° C. Some experiments, however, seem to show that the immune body combines with the red corpuscles, even in the absence of the complement. Thus, goat serum obtained from an animal treated during a long period with the blood corpuscles of a sheep, has a pure hæmolytic action on the sheep's blood. This property is destroyed by heat, but is restored by adding normal goat serum. If this heated serum is mixed with sheep's blood, no hæmolysis occurs. The mixture is then centrifugalised, and the sediment of corpuscles removed from the supernatant clear liquid. To this liquid more blood corpuscles are added, as well as normal goat serum. No hæmolysis occurs, showing that a part of the hæmolysin is separated with the corpuscles. If to the separated corpuscles normal goat serum is added, hæmolysis occurs. By this method it may be considered that

the immune body, being united to the red corpuscles, is separated from the complement, which is destroyed by heat.

Similarly, normal goat serum dissolves the blood of the guinea-pig and rabbit, the activity being destroyed at 55° C. Horse serum, which of itself has no action on guinea-pigs' or rabbits' blood, restores the activity of the heated goat serum when added to it, and a repetition of the experiment, which has just been described, gives the same results.

It has already been stated that hæmolysins may occur naturally in the blood, or they may be manufactured by injecting one animal with the blood of another species.

Hæmolysins may, however, be divided into two classes, in one of which, *heterolysin*, a specific hæmolysin is produced by the injection of the blood of another species of animal; as, for example, when rabbits are injected with ox-blood. But hæmolysins are also produced by the injection of the blood of the same species as when goat's blood is injected into another goat, this hæmolysin acting on the blood of the allied animals, but not on the blood of the species used. These hæmolysins are called *Isolysins*. When a hæmolysin is injected into a normal animal of the same species from which it was obtained, an *anti-hæmolysin* is formed which counteracts its effects.

These observations have opened up a new field in the pathology of the blood. They indicate the formation in the body of toxic substances, that is, of substances having a specific physiological action, which are not produced by an infective agent, but are the result of a disordered metabolism of the cell.

4. The occurrence of hæmoglobinæmia and hæmoglobinuria in infective disease is to be explained by the specific action of the bacterial poisons circulating in the blood. The rapid post-mortem staining due to the diffusion of the hæmoglobin and occurring in cases of septicæmia is an instance of bacterial action. *Bacterial hæmolysins* are formed by several pathogenic micro-organisms—*e.g.*, by the streptococcus, the staphylococcus, B. tetani, B. pyocyaneus, typhoid bacillus, B. dysenteriæ, and the micrococcus tetragenus.

5. The similar changes occurring in paroxysmal hæmoglobinuria, in Raynaud's disease and in infantile hæmoglobinuria, are, however, not yet explained. Paroxysmal hæmoglobinuria and the similar phenomenon which occurs in some cases of Raynaud's disease, is observed chiefly in men, and is supposed to be related to a previous infection by syphilis, malaria, or gout. The determination of the attack is, apparently, exposure to cold. Cold undoubtedly initiates the attack, during which there is a rapid diminution in the number of red corpuscles in the blood, and the plasma becomes coloured by the escaped hæmoglobin. The attack is accompanied by an initial fall of temperature, succeeded by a reactionary rise.

Bearing these facts in mind, it is impossible to avoid coming to the conclusion that the condition is really a toxic one, which is quite unlike the effects of any ordinary effect of exposure to cold, particularly as the condition may be brought about in the summer, as well as in the cold weather. Observations have been made tending to show that the exposure of animals to cold for a certain length of time leads to destruction of the red corpuscles and to hæmoglobinæmia, but the experiments are far from conclusive. What toxic condition is present in paroxysmal hæmoglobinuria it is impossible to say.

Infantile hæmoglobinuria occurs soon after birth, and is a febrile illness, frequently fatal, the chief symptom of which is the presence of hæmoglobin and methæmoglobin in the urine. It is not improbable that this condition is due to an infective process.

CHAPTER XIII

CHANGES IN THE BLOOD IN DISEASE—*continued*

III. *Coagulability of the Blood in Disease—Thrombosis—Embolism*

1. *Chemistry of Coagulation.*—The coagulation of the blood is due to the formation of fibrin, an insoluble proteid body, which slowly shrinks, entangling the red, and to some extent the white, corpuscles. The precursor of fibrin, fibrinogen, is dissolved in the plasma, and, when acted upon by the fibrin ferment (*thrombin*), is split into a small quantity of globulin and a larger quantity of fibrin. The fibrin ferment originates in the white corpuscles and blood platelets. These, when they disintegrate, liberate a nucleo-proteid (*pro-thrombin*), which combines with the calcium salts, forming the fibrin ferment or thrombin.

The modern theory of the coagulation of the blood thus includes the interaction of three substances, the fibrinogen of the plasma, the nucleo-proteid of the white corpuscle and the lime salts. The combination of the two last forms the fibrin ferment. *Nucleo-proteids* are compounds of proteids with nuclein, and are found both in the nuclei and protoplasm of cells. They are obtained from the various solid organs of the body, as well as from the lymph glands and the thymus. Some contain iron and are called hæmatogens. They may be extracted from tissues by means of the prolonged action of water, and are precipitated from solution by acetic acid; or they may be separated by grinding up the organ with sodium chloride, and pouring the sticky mass into distilled water, the nucleo-proteid rising to the surface.

In discussing the coagulation of the blood in disease, the important points to remember are that the fibrinogen and lime salts are present in the blood plasma, whereas the nucleo-proteid is present only in the cell elements, and is liberated by the disintegration of the cell.

2. *Intravascular Coagulation — Experimental.*—The intravenous injection of Schmidt's fibrin-ferment causes coagulation or thrombosis in the venæ cavæ, in the right side of the heart and in the pulmonary artery. Similar results are obtained by injecting the extracts of various organs. The body on which this intravascular coagulation depends is the nucleo-proteid, which was called by Wooldridge "tissue fibrinogen." Two phases are observed as the result of the injection of solutions of nucleo-proteids; a *negative phase*, when the injection is made slowly or only a small dose is given, the negative phase being shown in diminished coagulability, that is, in increased fluidity of the blood; and a *positive phase*, or intravascular clotting, when a large amount of nucleo-proteid is injected into the veins. Coagulation first takes place in the portal system, then in the general venous system, pulmonary artery, and the right side of the heart; and lastly, in the general arterial system. Very rarely is thrombosis of the pulmonary veins observed. The formation of clot is assisted by an increase in the quantity of carbon dioxide (CO_2) in the blood. Albino rabbits are not affected. Similar results are obtained by the injection of solutions of nucleo-proteid from various sources. The substances called artificial colloids produce the same result. These substances, artificially prepared, resemble, in some of their physical and chemical properties, the proteids, but they are not nucleo-proteids. The intravenous injection of the venom of the Australian black snake also gives two phases, very small doses producing a permanent negative phase or an increased fluidity of the blood; moderate and large doses giving a positive phase, that is, an instantaneous intravascular clotting. It is noteworthy that, in animals in which intravascular clotting has occurred, the blood which is not coagulated remains fluid outside the body; so that both positive and negative phases are shown in the same animal.

It is legitimate to conclude from the experiments that the injection of nucleo-proteid into the blood supplies the substance which is necessary for the formation of fibrin but which is not normally present in the plasma. Certain substances, such as ether, tannin, arsenic, glycerine and toluylene-diamine, when injected in large doses, cause intravascular clotting. This probably results from the setting free of nucleo-proteids by the disintegration of the white corpuscles. The disintegration of the white corpuscles is one of the factors in intravascular clotting in disease.

3. *Diminished Coagulability of the Blood.*—The diminished coagulability of the blood, as mentioned in the last paragraph, is present in the negative phase following the injection of nucleo-proteids and other substances; it is also produced by the injection of certain bodies, the action of which is unexplained. Thus, the intravenous injection of albumoses, such as exist in commercial peptone, and of extract of leech, have a pronounced effect in this way. After the injection of albumoses in the dog, in a dose of about 0.3 gramme per kilo. of body weight, the fluid blood may be removed and centrifugalised, leaving a clear "peptone" plasma. Although this plasma does not for a long time spontaneously coagulate, coagulation may be brought about in it immediately by the addition of lymph cells, of nucleo-proteids and of calcium chloride. Dilution with water or sodium chloride solution, neutralisation with acetic acid, or the passage through the plasma of a stream of carbonic acid (CO_2), also produces coagulation in it. The effect on the blood of the injection of the albumoses passes off, and a second dose is now found not to have any effect in diminishing the coagulability of the blood. The dog is therefore immune to the albumoses, and the blood of this "peptonised" dog confers immunity on a normal dog. This fact brings the subject into line with what has already been discussed under "Immunity" (Chapter V.), as the reaction of the body against toxic substances. The negative phase, resulting from the injection of nucleo-proteids, has by some been ascribed to the formation from these substances of peptone in the blood; but this is not proved.

There is some evidence to show that the lungs and liver have an effect on the coagulability of the blood, the lungs tending to diminish the coagulability, while the liver tends to increase it. Thus, if the blood be allowed to circulate through the heart and lungs alone, also if the thoracic aorta be occluded, the blood gradually loses its power of coagulation. The functional activity of the liver appears to be necessary for the specific action on the blood of albumoses. Thus, after forming an Eck's fistula (that is, making a communication between the portal vein and the vena cava inferior), and removing the liver, the injection of albumoses does not produce the characteristic blood change.

The following synopsis may be given of the conditions in which coagulation is prevented or hastened, inside or outside the body.

Coagulation is prevented outside the body by the application of cold, and by the addition of neutral salts to the blood—more particularly of sodium oxalate, which combines with the calcium, and so prevents its taking any part in coagulation. *Inside the body*, it is prevented by the injection of albumoses and certain other substances, such as abrin, snake-venom and nucleo-proteid in certain doses: also in certain infective diseases.

Coagulation is hastened outside the body by the application of warmth; by contact of the blood with solid bodies; and by the addition of calcium salts. *Inside the body*, it is hastened: (1) *when the vessels are healthy;* in infective diseases, and in certain cachectic states, or by the intravascular injection of the substances which have already been considered, such as nucleo-proteid, snake-venom, fibrin ferment, laky blood and foreign particles. (2) *In diseased vessels* it occurs when there is solution of continuity of the endothelium or a roughening of the surface, and in dilatation of the vessels from disease.

Thrombosis.

Thrombosis is the term applied to the formation of a thrombus or clot in the heart or living vessels: artery, vein,

capillary, or lymphatic. The formation of a clot in the vessels in disease is, as a rule, a local phenomenon. It has no relation to any increase in the amount of fibrin in the blood—a hypothetical condition, which was formerly called hyperinosis. It is a local condition, which may be obviously associated with some disease of the vessel or of the surrounding part, or with some altered character of the blood.

The following conditions may be said to lead to the formation of a thrombus, either singly or conjointly: (1) A slowed blood stream; (2) The presence of foreign bodies in the vessels, such as an embolus; (3) Discontinuity of the endothelium and roughening of the intima from disease: (4) An altered character of the blood, leading to disintegration of the white corpuscles or to an increase of blood plates, and in many cases due to the circulation of toxic substances or bacteria.

The Structure and Development of Thrombi.—Thrombi are red, white, or mixed, the red being formed in stagnating blood, the white and mixed in the moving blood stream. The recent red thrombus is composed of fibrin entangling red and white corpuscles. It is noteworthy that, if the end of the clot be exposed to the moving blood stream, it becomes covered with a white layer, resembling in structure the white thrombus. Thrombi formed in the moving blood stream are either white or mixed. Although the white thrombus may contain a few red corpuscles, it is mainly composed of blood platelets, leucocytes and fibrin, the leucocytes being the polymorphonuclear neutrophile cells. The granular matter, which is seen in sections of the thrombus, is, presumably, composed of disintegration granules of the blood platelets: some may be due, however, to the disintegration of the white corpuscles. Fibrin is seen in anastomosing fibrils, which enclose white corpuscles and a few red. The leucocytes are more numerous than are found in post-mortem clots. Mixed thrombi are frequently stratified, there being layers of white thrombus, separated by fewer layers of red thrombus. It is probable that the red layers are formed by the blood forcing its way into the white thrombus, stagnating

and clotting, while the white layers are formed like the ordinary white thrombus. Hyaline thrombi are found mainly in the capillaries, which are distended with a homogeneous slightly yellow substance, giving Weigert's fibrin stain.

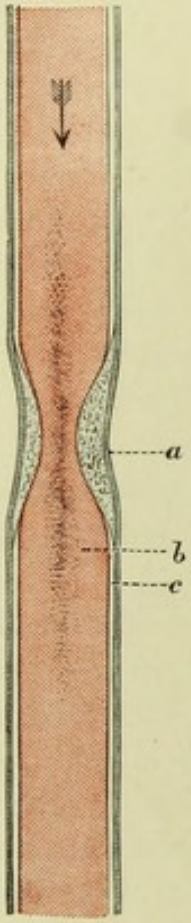


FIG. 99.—Diagram showing the effect on the blood stream of slight injury to the wall of a small artery.

(*b*) is the red axial stream; (*c*) the narrow plasma zone; at (*a*) the vessel has been scratched with a needle.

Beneath the injury the vessel wall is contracted, the axial stream is diminished in size, and between the axial stream and the vessel wall there is a blood plate thrombus. Within half an hour of the injury the thrombus had diminished in size, and in two hours showed only a remnant; while the contraction at the site of injury was still visible. (Eberth and Schimmelbusch.)

There does not appear to be any difficulty in the explanation of the formation of the red thrombus. The blood coagulates *en masse* and gives the characteristic red clot seen in shed blood. The mode of formation of the white thrombus, on the other hand, as well as that of the hyaline thrombi, has given rise to a great amount of discussion. Occurring, as it does, in the moving blood stream, there is no coagulation of the blood *en masse*, and the initiation of the clot has been ascribed to the blood platelets, or the leucocytes, or to both. The older view was that the clot was mainly due to the accumulation of leucocytes at one spot; their subsequent disintegration leading to the formation of fibrin, which does not, in a moving blood stream, entangle many of the red corpuscles. Subsequent experiments, however, showed that the initiation of the white thrombus is due, more particularly, to the accumulation of blood platelets, followed by the accumulation of leucocytes: a process called *conglutination* (Figs. 99 and 100) (Eberth and Schimmelbusch). Afterwards fibrin is formed from the plasma round the platelets and leucocytes. More particularly is this observed at the margin of the platelets. In connection with this, the question as to whether the blood platelets exist in normal blood, has been raised, and their origin has been ascribed to the disintegration both of

white and of red corpuscles. The origin of the hyaline thrombi of the capillaries is not clear. They have been found in the lungs, in the liver and kidneys, and are a feature of the action of the hog cholera bacillus (Welch). Some consider the hyaline material to be composed of non-fibrillated fibrin; others, again, regard it as formed by the coalescence of red

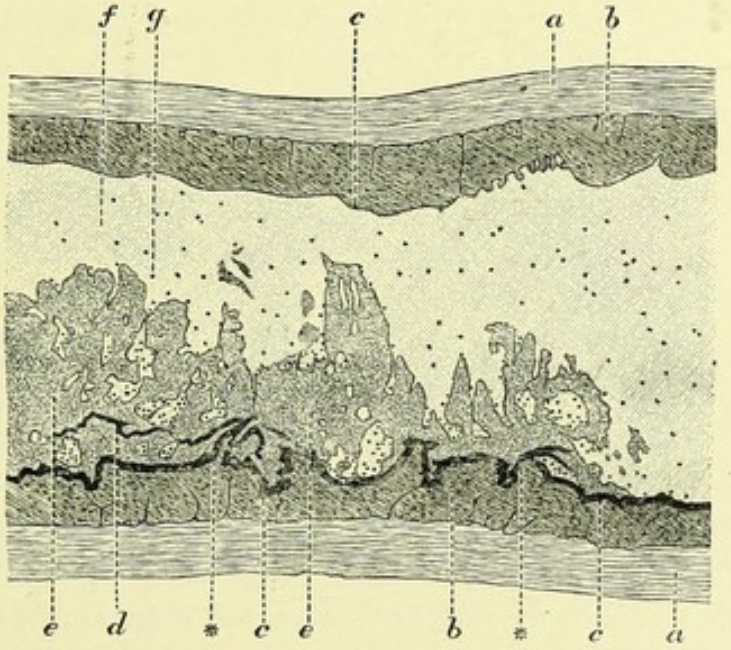


FIG. 100.—Drawing showing the results of moderately severe injury to the wall of a vein.

The transverse section of a dog's jugular vein, through the length of the wall of which a thin thread has been drawn. Excision after thirty minutes.

(*a*) Adventitia; (*b*) media; (*c*) intima; (*d* and *) portion of the thread used in the experiment; (*e*) heaped up mass of blood; (*f*) fibrils of fibrin; (*g*) blood plate thrombus.

The result of the injury to the vessel wall is the formation of a clot of blood plates. In this clot scattered leucocytes are seen, as shown by black dots in the figure. The red corpuscular element of the blood is almost solely present near the seat of injury. (Eberth and Schimmelbusch.)

corpuscles; while some have even considered it to be derived from the leucocytes.

Changes occurring in Thrombi.—Small thrombi, especially those situated in the walls of veins and arteries, may be absorbed, some thickening of the intima being left. The *absorption of the clot*, no doubt, is mainly due to a phagocytic action of the leucocytes: either those present in the clot itself, or those entering the clot from the blood stream. Complete

absorption occurs in some instances, leaving, perhaps, some slight fibroid thickening of the vessel wall. The clot may also soften at the centre, and the blood stream be restored through the channel formed; this is called tunnelling of the clot. Partial absorption of the clot may occur, followed by deposition of calcium salts. It is more common in veins than in other parts, and is the mode of formation of phleboliths. In large clots, portions may be softened, even though no invasion of micro-organisms has taken place. This occurs in some clots in aneurisms, and in those occurring in the auricles of the heart. The softening is here ascribed to the action of a proteolytic ferment, possibly pepsin, in the clot.

Organisation of the clot may occur. The mass of fibrin, leucocytes and blood platelets, takes no part in the formation of the fibrous tissue which constitutes the organised clot. The endothelium of the vessel proliferates and invests the clot. The clot is invaded by leucocytes in the blood, which act as phagocytes, and by the new tissue which starts from the wall of the vessel. This new tissue is cellular and is composed of round or spherical cells and of elongated cells or fibroblasts. These are transformed into connective tissue. New vessels are formed in the clot by budding from the vasa vasorum; these become lined by endothelium. Organisation of the clot may result in complete or partial occlusion of the vessel.

Invasion of the clot by micro-organisms frequently occurs. In some cases this leads to no naked-eye change in the clot, but, in others, softening of the clot occurs, so that it may be completely disintegrated. This more particularly is seen when the clot is infected by pus-forming organisms.

Occurrence of Thrombosis in Disease.—Thrombi are observed in the heart, arteries, veins, capillaries and lymphatics, most commonly in the heart and veins.

1. *Thrombosis in the Heart.*—Thrombi are found in the cavities of the heart in cases of stagnation of blood in the heart, whether due to valvular disease or to dilatation secondary to disease of the muscular substance; and to inter-

ference with the circulation through the heart, which occurs in lung disease, in arterial disease and in renal disease. Not infrequently after death the right ventricle, and sometimes the left, is occupied by a partially contracted, non-adherent clot, which extends through the auriculo-ventricular orifice into the auricle, and so into the veins; this is more common on the right side than on the left. The clot is partly decolorised, partly red. It has been suggested that it is formed during the process of dying, and this may be so in some cases. As a rule it must, however, be considered as a post-mortem phenomenon. It presents quite a different appearance to the thrombi which are formed in the heart during life. These are situated usually in the auricular appendices, and are white and globular and adherent to the columnæ carneæ. Similar clots, varying in shape, are also to be found adherent to the muscular substance between the columnæ carneæ in the ventricles. Globular clots, unattached to the heart wall, and called *ball thrombi*, have been found loose in the left auricle in some cases of mitral stenosis. They are not common, and are no doubt detached globular clots. Thrombi in the auricles are most frequently met with in valvular disease of the heart; more particularly mitral disease, but they are also met with in cachectic states (tuberculosis, cancer and anæmia) towards the end of life, and are found also in certain infective diseases, such as enteric fever, although rarely.

Fibrin is deposited in other cardiac conditions, such as on vegetations of the valves, rheumatic or infective, and over patches of atheroma in the aortic or mitral valve, or sometimes over tumours projecting into the heart. This deposit of fibrin is not so much dependent on the stagnation of blood in the heart as it is on the roughening of the surface of the endocardium.

2. *Thrombosis in the Arteries.* — Thrombosis in arteries usually occurs round an embolus (p. 345). It is rarely caused by pressure on the vessel, and is most commonly associated with disease of the arterial wall. This disease is either chronic arterial disease, such as arterio-sclerosis, aneurism,

and syphilitic disease; or the arterial disease is acute, as in acute infective arteritis. It is probable that cases of thrombosis in arteries rarely, if ever, occur in the absence of disease of the wall, and this may be either an irregularity of the intima, a general thickening of the vessel causing a diminution of the lumen, or an invasion of the vascular wall by micro-organisms. The arteries which may be affected are those of the brain, coronary arteries of the heart and the peripheral arteries—chiefly of the lower limbs. Arterial thrombosis in the brain and heart is usually associated with chronic disease, either syphilitic or atheromatous. The same may be said of the thrombosis which occurs in the arteries of the leg. In some instances, however, as when arterial thrombosis occurs in typhoid fever, in influenza, and in some other infective diseases, there is no chronic arterial disease, and it is not possible in all cases to determine that the wall of the artery is invaded by micro-organisms. This is, however, sometimes the case, micro-organisms being found not only in the clot but in the vessel wall, and they may thus be considered as the determining cause of the thrombosis.

Thrombosis of the pulmonary arterial system is usually the result of embolism, but it may occur independently of embolism, in cases where there is disease of the lung: either chronic as in tuberculosis, or acute as in pneumonia and gangrene.

3. *Thrombosis in Veins.*—This is the commonest form of thrombosis observed in disease. Two classes may be described. In one the thrombus begins in the venous radicles, starting from a diseased focus, which is usually a focus of infection (such as suppuration or ulceration). The thrombus increases towards the heart, and may extend as far as the large venous trunks, but it rarely reaches the large trunk veins. In the second class of case the thrombus arises in a large venous trunk, usually of a limb, and passes towards the heart; in this way the venæ cavæ may become affected. In both classes of case the thrombus may be infective or non-infective. Examples of the first class may be quoted in the thrombosis starting in the uterine veins after parturition; in the veins

round the appendix in appendicitis; in the radicles of the portal vein, when there is ulceration or some other intestinal infection; and in the thrombosis in the pulmonary vein, which occurs in some cases of tuberculosis of the lungs. Examples of the second class may be quoted in the thrombosis of the femoral vein, which occurs in certain infective diseases and in cachectic states. In the latter case the clot is usually referred to as a *marantic thrombus.* In the two classes of cases just mentioned there may be no obvious disease of the vessel wall, although, in some cases, the walls of the vein are invaded by micro-organisms and so damaged. This is obviously the case in well-marked bacterial phlebitis, and in certain other cases of phlebitis which occur in gout. Thrombosis occurs in the larger veins, when no obvious disease of the vessel wall has been observed—*e.g.*, in the femoral veins—more particularly on the left side, in the cerebral sinuses, in the veins of the arm, and in the pulmonary and superior mesenteric veins. The veins of the upper extremity are much less frequently affected than those of the lower: in the proportion, it is said, of 1 to 50. Of the infective conditions with which this kind of thrombosis is associated, the following are the most important:—Enteric fever, influenza, septicæmia, chronic tuberculosis, chronic suppuration, chronic dysentery and syphilis. It is observed in other infective conditions, but not so commonly as in those enumerated. A similar thrombosis is also met with in certain chronic diseased conditions not evidently due to infection, such as cancer, chronic diarrhœa. dilatation of the stomach, profound anæmia, chlorosis, and renal disease.

4. *Thrombosis in Capillaries.*—Hyaline thrombi found in capillaries have previously been mentioned (p. 337). They are found chiefly in infective diseases, in the capillaries of the lungs, liver and kidneys. They have been observed in pneumonia and in hæmorrhagic infarcts of the lung, and are extensively produced in experimental infection by the hog cholera bacillus (Welch)

Causes of Thrombosis in Disease.—The formation of fibrin,

as has been already stated, is due to the action of the fibrin ferment which originates in the white corpuscles and blood platelets upon the fibrinogen dissolved in the plasma of the blood. It is necessary to consider how far this theory of coagulation explains the occurrence of thrombosis in disease. It is evident that the liberation of the fibrin ferment is the main factor in the formation of fibrin, inasmuch as the fibrinogen is always present in the plasma.

The factors which are considered to lead to thrombosis are four in number: (1) A slowed blood stream; (2) the presence of a foreign body in the blood current; (3) disease of the vessel wall; (4) an altered condition of the blood, due to a toxæmia.

1. A mere slowing of the blood stream cannot be considered, in the majority of instances, as the sole cause of thrombosis. It is, however, an important factor, as is seen in its occurrence in the auricular appendices and in the frequency of thrombosis in the veins. Complete stagnation of the blood stream is not commonly observed, but it may be seen where there is pressure on a vein, and this complete stagnation would lead to thrombosis. That thrombosis is more common in the veins than in the other parts of the vascular system is due in part to the slower blood flow. The thrombus, indeed, more commonly than not, starts from the pockets of the valves, where the blood stream is slowest, and the veins, more particularly of the larger trunks, with their thin walls and lower blood pressure, are more readily affected by the contraction of the muscles, which renders the fasciæ tense, and by their frequently passing beneath the hard-walled arteries. In this way it has been explained why the left femoral is more frequently thrombosed than the right, since it is a long vein, passing obliquely beneath the right common iliac artery, and possibly exposed to pressure by the sigmoid flexure.

In the heart cavities the action of the slowed blood stream is obvious. Thus thrombosis most commonly occurs in the auricular appendices and in the depressions between the columnæ carneæ. Thrombosis is also more common in the

right ventricle than in the left, and usually occurs in either cavity when it is dilated, and there is great embarrassment of the circulation.

2. The effect of foreign bodies in producing thrombosis is seen most obviously when an embolus lodges in an artery or vein. This is practically a foreign body, and round it a thrombus is rapidly formed, if the patient lives long enough. Similar thrombosis is observed round fragments of tumour, the cells of an organ, or parasites which accidentally enter the circulation. The thrombosis which occurs in these cases is, no doubt, initiated by an attraction of the leucocytes to the foreign body, leading to the formation of fibrin.

3. In the case of damage to the vessel wall the conditions of thrombosis cannot be stated in a general manner. It may be inferred that, in a normal vessel, the vitality of the endothelium is an important factor in preventing the coagulation of the blood. Disease of the intima of a vessel interferes with its vitality, but it does not necessarily lead to thrombosis: another factor is important, namely, the slowing or stagnation of the blood stream. Thus, the deposition of fibrin is not commonly observed over the raised and circumscribed patches of atheroma observed in the aorta, even in cases where the patch is calcareous and the endothelium is completely destroyed. If, however, the aortic disease leads to the formation of an aneurism, the stagnation of the blood in the sac is an additional factor leading to thrombosis. In these cases the stratified clot is due to the repeated formation of a white thrombus, the red part of the clot being due to the coagulation *en masse* of the blood which has oozed in between the layers of clot (p. 335).

Thrombosis occurring in the peripheral arteries and veins is not so obviously explained. In thrombosis occurring in the arteries of the leg and leading to gangrene, such as is observed in senile gangrene and in diabetes, and certain other cases which come under neither of these headings, the disease of the arterial wall may be extensive. The lumen is diminished irregularly, the artery has lost its elasticity and contractility; and this, with a weakly acting heart, and thus a slowed

circulation, may be sufficient to lead to thrombosis. In some of these cases the venæ comites are also diseased, the walls being thickened, and this additional embarrassment of the circulation is an added factor favouring the thrombosis. It is possible, indeed, to consider a very atheromatous small artery as foreign a body to the blood as a glass tube. Thrombosis in syphilitic arteritis is due, not only to the damage to the vessel wall, but to the slowed blood stream through the greatly narrowed artery.

In varices of the leg thrombosis frequently occurs, as also in hæmorrhoids. Here the factors in producing thrombosis are the slowed blood stream and the thickening of the vessel wall; and, in addition, mechanical injury, such as blows on the leg in varices, or the passage of the motions causing inflammatory thickening of the venous walls in hæmorrhoids. In varicocele, thrombosis is not so common.

Another class of injury to the vessel wall must be considered. In anæmias (chlorosis and the profound anæmias) degeneration of the endothelium has been observed; and thrombosis, which may occur in these conditions, has been supposed to be associated with this damage to the endothelium. It is very doubtful, however, whether this damage can of itself lead to thrombosis. It is probable, in these conditions, that there is an additional factor which is the main one, namely some chemical and structural change in the blood. In thrombosis occurring in infective disease the vessel wall is in many instances apparently normal. In other cases, however, it has been found infiltrated with micro-organisms and the clot to be invaded by these, so that some are inclined to ascribe such thrombosis to the direct and local action of the bacteria on the blood.

4. An altered character of the blood is no doubt, in many instances, an important factor, in conjunction with those enumerated, in the production of thrombosis. The main alteration which would lead to this result is the liberation of fibrin ferment by the disintegration of the white corpuscles and of the blood platelets. It is considered by some that the blood platelets do not exist in normal blood, but that

they are derived either from the white corpuscles or from the red. This point is undecided, yet there is but little doubt that they play an important part in the initiation of thrombosis. A profound effect on the white corpuscles is observed in many infective diseases, either in the way of increase of particular kinds, or in their disintegration or diminution, but how far this effect initiates the thrombosis in such diseases as enteric fever and influenza, it is impossible to say. It is, however, clear that toxic substances which disintegrate white corpuscles lead to intra-vascular coagulation (p. 333). Increase of blood platelets is observed in some diseases, for example, chlorosis, in which thrombosis may occur; but, although blood platelets are said to be relatively increased in chlorosis, in leukæmia and in many cases of profound anæmia in which thrombosis may occur, their number is very variable, and they may be greatly diminished in many infective diseases more commonly associated with thrombosis than the anæmias. The exact relation of the number of blood platelets to the occurrence of thrombosis cannot be at present determined. The general trend of opinion and observation is to consider the occurrence of thrombosis, when there is no disease of the vessel wall and no slowing of the blood stream, as due to the circulation in the blood of a toxic substance, which causes disintegration of the white corpuscles.

Embolism.

Emboli are bodies which are either formed in some part of the circulatory system, and are carried to another part, or enter the circulation from without, as when portions of tumour, masses of bacteria, fat, or air, get into the circulating blood. Emboli are either infective or non-infective; or, as is sometimes said, septic or simple. As a rule, emboli are formed in the circulatory apparatus, and are derived from the following sources:—

Emboli from the Heart (Fig. 101).—Non-infective emboli in the heart are usually derived from thrombi in the auricular appendices, sometimes in the ventricles. From the right side

of the heart the emboli are carried to the lungs, and from the left side into the systemic circulation; the emboli so derived

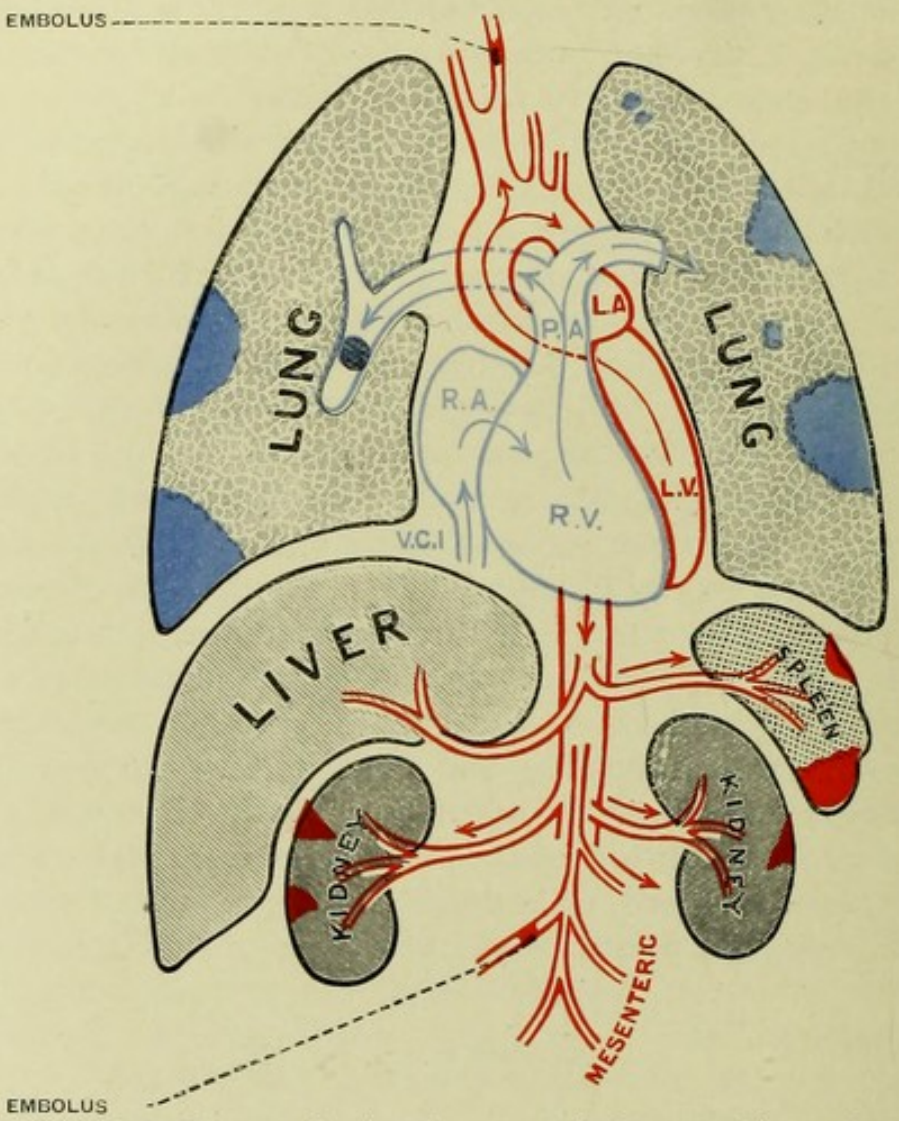


FIG. 101.—Diagram showing the course of pulmonary (blue) and systemic (red) embolism.

In pulmonary embolism the embolus may come through the inferior vena cava or from the right heart itself, and pass into the pulmonary artery. If large, it blocks a large branch, as shown in the right lung of the figure. If smaller, it produces infarctions varying in size.

In systemic embolism, in which the embolus comes mainly from the left side of the heart, the embolus may lodge in one of the large branches of the aorta or pass to the brain. It may lodge in the splenic artery, or, if smaller, produce infarctions in the spleen. Infarctions in the kidney also occur; as well as in the intestine, from an embolus in one of the mesenteric arteries. The liver is not affected, owing to the free anastomosis of its vessels.

are usually large. Infective emboli are derived from the vegetations in infective (ulcerative) endocarditis, occurring either on the mitral, aortic, or pulmonary valves. Embolism of the

systemic circulation occurs when the valves of the left side are affected, and of the lungs when the pulmonary valves are affected. Large fragments may be detached in such cases, but small emboli are not infrequently detached.

From the Arteries.—Embolism does not commonly result from changes in the arteries. A disintegrated atheromatous patch may give rise to a fine embolism in rare cases, or a portion of clot lying at the mouth of an aneurism may be detached and carried into the circulation, blocking the aorta or a large vessel. Septic embolism sometimes arises in the aorta in ulcerative endocarditis, the emboli being carried along the systemic circulation.

From the Veins.—The heart and the veins are the sources of the larger emboli. In the veins the emboli are portions of thrombus, which are detached either by mechanical injury, which occurs in the veins of the leg, or after softening by the action of bacteria. The emboli may thus be either infective or non-infective. Emboli from the veins are carried to the right side of the heart, and not infrequently lodge in the pulmonary artery. Small fragments of septic venous emboli are carried into the smaller branches and even capillaries of the lungs, there lodging; and bacteria may even pass through the capillaries of the lungs from this source. Although emboli from the veins usually lodge in the pulmonary artery and lungs, yet they may pass to the general arterial system without passing through the pulmonary system. This occurs when there is a patent *foramen ovale*, and is called *crossed embolism*. It is not common, but it has been observed, not only in thrombi from the veins, but in certain cases of irregular deposition of secondary malignant tumours. The term *retrograde embolism* has been applied to the condition when the embolism is found on the distal side of the thrombus in a vessel; that is, away from the heart. This has been observed both in venous thrombi and in tumours, more particularly the latter. It has been ascribed to a certain backward pressure of blood from the right side of the heart itself, but is more probably associated with some obstruction of the flow in the veins or lymphatics, leading to increase of pressure on the thrombus or portion of tumour, and so to the detachment of the fragment on the distal side.

In the majority of instances, however, the emboli follow the blood stream. If arising on the left side of the heart, they enter the systemic circulation. When large, they are stopped in one of the main branches, sometimes at a bifurcation, a portion of the embolus entering each branch. This is sometimes called a *riding embolus*. When smaller and softened, as in septic emboli, they pass into the smaller arteries of an organ, and then into the capillaries. Large emboli may be either non-infective or infective; small emboli are usually infective.

Certain arteries are more frequently blocked by emboli than others, though perhaps no great stress is to be laid on this order of frequency. Whether the embolus lodges or not in a particular artery appears to depend on the size, consistence and shape of the embolus. Emboli are more frequently found in the renal, splenic and cerebral arteries; next in order of frequency come the arteries of the lower and upper limbs, the cœliac axis, the central artery of the retina, the superior and inferior mesenteric arteries, the abdominal aorta and the coronary arteries.

Embolism from the venous circulation and from the right side of the heart affects the pulmonary artery and lungs almost exclusively, except in the case of crossed embolism. Large emboli become blocked in the large branches of the pulmonary artery; small emboli are lodged in the smaller vessels. The emboli may be either infective or non-infective.

Results of Thrombosis and Embolism. — The occurrence of thrombosis in the heart is a sign of embarrassment of the circulation of blood in the organ, but does not, of itself, produce any definite effect, unless a clot be detached and become impacted in the mitral orifice, an event of very rare occurrence which leads to sudden death. The effect of complete stoppage of an artery, either by a thrombus or by an embolus with subsequent thrombosis, depends on the position and anastomoses of the vessel. If, as in certain localities, there is free anastomosis between the different arterial branches, no particular disturbance of the circulation in the part results. This is observed in the skin, in bone and in such organs as the thyroid and

uterus. Sudden stoppage of the circulation through the abdominal aorta is incompatible with life. It leads to rapid necrosis and desquamation of the epithelium of the intestinal tract, as well as to paralysis of the lower limbs. When the chief artery of a limb is completely blocked, the result and effect depend on the completeness of the collateral supply. Thus, circulation through the brachial artery may be stopped by aneurism of the aorta, and no great nutritional effect be noted in the limb, owing to the completeness of the supply through the circumflex and other arteries. This, however, only occurs if the stoppage be gradual; and, in a sudden stoppage, in which the collateral supply has not had sufficient time to compensate, death of the part may ensue.

In all cases of plugging of arteries, with the exception of such a large trunk as the main trunk of the aorta, completeness of the collateral circulation, to a great extent, determines the result; for if a small artery be plugged, and sufficient blood can enter the tissue through the collateral vessels, no damage to the tissue may result. If, however, the blood supply is not sufficient through the collateral circulation, the cells of the tissue are affected, and become atrophied, or undergo fatty degeneration; or, as in the more sudden forms of stoppage of the circulation, undergo coagulation necrosis. In addition, the tissue may become suffused with blood, owing to the diapedesis of the red corpuscles through the vessel wall.

The sensitiveness of tissues to the stoppage of the blood supply varies considerably. Nervous tissue is perhaps the most sensitive (Chapter XIX.), and renal tissue comes next. Blockage of one carotid by an embolus will lead to well-marked degeneration of the cerebral hemisphere on the same side, as the circle of Willis does not ensure a supply to the part by means of the other carotid and the two vertebral arteries. The renal epithelium dies in from one and a half to two hours after the blood supply is cut off (Litten).

Infarction.—In the acute forms of arterial obstruction, such as occurs in embolism and thrombosis, the result is frequently the production of an *infarct* in the affected tissue. Infarcts occur in the lung, spleen, kidneys and intestines, rarely, if

ever, in the liver, owing to the free anastomosis of the vessels. They are either red (hæmorrhagic) or white (anæmic); infective or non-infective.

Dealing now only with the non-infective infarcts, the mode of formation of the hæmorrhagic infarct of the lung, spleen and intestines, and of the white or anæmic infarcts of the kidney and spleen has to be considered. Infarcts are usually wedge-shaped, coming to the surface of the organ, from which, when recent, they project slightly; their wedge shape corresponding to the area of supply of the artery which is blocked. Hæmorrhagic infarcts of the lung and spleen occur in mitral stenosis more particularly, and plugging of the artery may occur either by an embolus or thrombus. Cohnheim explained the formation of the hæmorrhagic infarct by saying that after the blocking of an end artery (that is, an artery not joined by collaterals) there was a reflux from the veins which had no valves, leading to congestion of the affected area, and to a subsequent diapedesis of the red corpuscles which crowded the tissue (Fig. 102). It has, however, been shown that such a venous reflux is not necessary for the explanation of the occurrence of an infarction. Thus, an infarction may be produced experimentally in the intestine of the dog, the veins of which have valves. Also if the artery is strictly terminal no hæmorrhagic infarction occurs, even if the vein has no valves; and the vein may be ligatured and an infarction experimentally produced. Thus, with regard to the kidney, infarction was produced after ligature of the right vein and artery, but it was prevented if the capsule were stripped, even though the vein remained pervious. The congestion in this case is produced by an afflux of blood from the capsule. If the access of blood is good, circulation is restored; if not, infarction occurs (Litten).

These experiments emphasise the statement made previously, that the permanent effect on a tissue or part of the stoppage of the blood supply, depends on whether the area affected can get a sufficiency of blood from the surrounding parts or not. In experimental infarction of the intestine, two or three hours after complete closure of the superior mesenteric artery, there is bloodlessness of the intestine, which is increased by its tonic

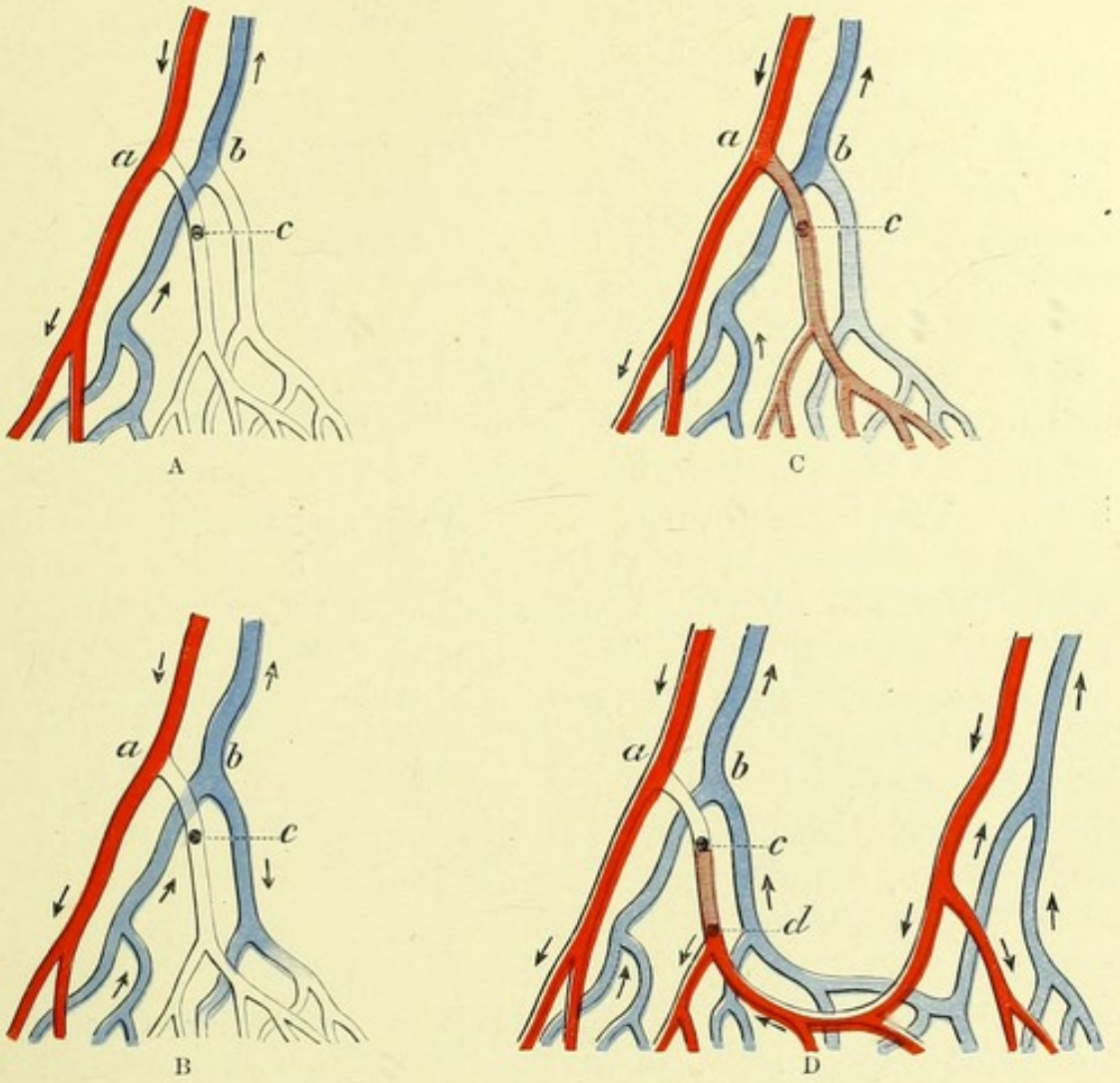


FIG. 102.—Diagrams of the effect of embolism on the circulation. (Cohnheim.)

The arrows represent the direction of the blood stream:—(*a*) The nearest collateral arterial branch; (*b*) the nearest collateral venous branch; (*c*) is the embolus itself.

The diagrams represent the experiments which were performed with small emboli of wax on the vessels of the tongue of the frog.

A is a diagram showing the changes in the circulation when the embolism is produced slowly. In this case there is no sudden stoppage of the circulation, but the irregular embolus entering the arterial branch at first does not completely block it, so that there is a slight blood stream round its edges. There is obstruction to the circulation, and what happens is that the red corpuscular element of the blood is gradually removed by the collateral arterial and venous streams, leaving only a clear plasma in the vessels with obstructed circulation. This is shown in the figure by the vessels being left white.

B represents a further change in the slowly produced embolism. There is a reflux of venous blood, as shown in the figure, into the parts containing the obstructed vessels, leading to an infarction.

C represents the effects of a sudden embolism. In this case the blood stagnates in both artery and vein on the distal side of the embolus, and, finally, coagulation occurs, the red corpuscles not being removed, as in the slowly produced embolism.

D represents the effects of an embolism when the obstructed vessel anastomoses with the neighbouring vessels. It is seen that there is a clear plasma zone between the embolism and the main vessel. On the distal side of the embolus, as far as the collateral artery (*d*), the blood stagnates and coagulates, while the circulation of the part is but little affected, owing to the free anastomosis.

contraction. Sudden and complete stoppage of the arterial supply to a loop of intestine is followed by infarction, as shown by hæmorrhage and necrosis. The blood which is the source of the hæmorrhage comes from the anastomosing arteries; and not by reflux from the veins, and the hæmorrhage by diapedesis is the result of the stasis of the circulation (Welch and Miall). The hæmorrhage which occurs in an infarct, although a prominent, is yet only a secondary change. The chief result of the complete and sudden blockage of the arterial supply to a part is necrosis, or death of the tissue (p. 214). This is seen in the further changes which take place in the hæmorrhagic infarct. It becomes encapsuled with fibrous tissue, as if it were foreign matter. The colouring matter is absorbed, after disintegration of the red corpuscles, and the affected area becomes fatty, and, if small, is not infrequently absorbed, leaving a scar. In the lungs, these changes are not commonly observed, inasmuch as the infarcts are multiple, frequently very large, and occur at a stage of the disease when the patient does not survive. In the spleen and kidneys, however, these changes are seen.

In the white or anæmic infarct hæmorrhage is absent, and necrosis is a prominent feature. These are observed mainly in the kidney, and the result of suddenly cutting off the blood supply is death of the cells of the tubules, which undergo coagulation necrosis (p. 215). The change is due to the coagulation of the protoplasm of the cell itself, and not to that of any surrounding liquid, as is sometimes stated.

In the brain, as the result of embolism, a similar necrosis is observed. It, however, does not consist in coagulation of the protoplasm, but is a slower process and results in softening of the affected area.

Infective Embolism.—The embolus invaded with micro-organisms may be either large or small. It may come from a thrombus in a large vein, or from a clot in a small vein leading from an infective focus. It may also come from the vegetations of the heart in ulcerative endocarditis, and bacterial emboli not infrequently arise from an infected area opening into an artery or vein. The large infective emboli

will, in the first instance, produce the same lesion as a non-infective; that is, an infarction in one or other organ; and frequently, at death, it is impossible to distinguish the two varieties of infarction by a mere naked-eye inspection. If, however, the individual has survived sufficiently long, the infective infarcts undergo softening, either suppurating or showing a colliquative necrosis. With the smaller infective emboli, and with emboli composed of bacteria, definite infarction may not be observed, but, round the area where they lodge, inflammation occurs, ending in suppuration or in softening (p. 123).

Air Embolism.—The presence of air in the circulating blood results during the course of operations on the head and neck, in which the external air is sucked into the veins and sinuses. The air, if in large quantity, is carried to the right side of the heart and to the lungs. As a rule, it does not pass through the lung capillaries. If in large quantity, it causes paralysis of the right side of the heart, owing, it is said, to the air and blood being churned. It blocks the capillaries of the lungs, and death may result from paralysis of the right side of the heart, and from ensuing cerebral anæmia. The results of air embolism appear to be due, not so much to the quantity of air introduced as to the suddenness of its introduction. Thus, in large animals, such as horses and dogs, large quantities of air have been experimentally introduced into the circulation, and have caused no appreciable change if the introduction is slow. Air embolism has been supposed to result from intra-uterine injections after parturition, but this is doubtful.

The presence of bubbles of gas in the blood and organs at death does not necessarily show the presence of air. In "caisson" disease, in which sudden death occurs in divers who are exposed in the apparatus to a heightened atmospheric pressure, the result has been ascribed to liberation of bubbles of nitrogen in the circulating blood, owing to the sudden relief of pressure. Bubbles of gas may be found in the blood of the heart and veins after death, and in some of

these cases, when death has been ascribed to air embolism, the gas has been shown to be produced by a micro-organism, the bacillus aërogenes capsulatus (Welch). It is evident, therefore, that bacteriological examination is necessary before the source of bubbles of gas in the blood at death can be determined.

Fat and other Forms of Embolism.—Fat embolism is not infrequently observed, and may or may not produce appreciable effects. It results from the entrance of liquid fat into ruptured blood vessels, usually veins, and is in the majority of instances caused by injury. Thus, it occurs from fracture of long bones, in diseases of the bone marrow, in softening of the brain and in fatty liver. A condition of lipæmia or excess of fat in the blood is observed in diabetes, as well as in other conditions, such as Bright's disease, but no obvious effects are to be attributed to the presence of this fat in the blood. In fat embolism the liquid fat usually enters the venous circulation, and is carried to the right side of the heart, whence it is sent to the lungs, which retain most of it in the small arteries and capillaries. Some, however, passes through the capillaries of the lungs, and is distributed mainly to the brain, heart and kidneys. The fat being itself non-infective, the effects of the embolism are mainly mechanical. If the fat is very large in amount, the result in the lungs and brain is œdema and numerous ecchymoses. In the heart and kidney cortex fatty degeneration results, owing to the interference with the local blood supply.

Other and rarer forms of embolism occur when the cells of an organ or tissue enter the circulating blood. Thus, in some cases of injury of bone or of disease, such as leukæmia, bone marrow cells may be found in the capillaries as well as liver cells in degeneration of the liver, and cells of the spleen may be found in the liver in cases of malaria. Cells of tumours may be also carried in the circulation to distant parts. As a rule, this form of embolism produces no result. It is only small in amount, and the cells undergo atrophy. In some cases, however, a thrombus is formed round the embolic cells, and may even produce an infarction.

CHAPTER XIV

HÆMORRHAGE AND PIGMENTATION

Hæmorrhage.—Cases of hæmorrhage may be divided into two classes. In one there is a solution of continuity in the wall of the vessel. This is hæmorrhage *per rhexin*, and the whole blood escapes, the corpuscles as well as the plasma. In the other form of hæmorrhage there is no observed lesion of the wall of the vessel, but there is diapedesis of red corpuscles through the vessel wall, with a certain amount of plasma; this is hæmorrhage *per diapedesin*. Hæmorrhage per rhexin may occur in arteries, capillaries, or veins. Hæmorrhage per diapedesin can only occur in the smallest vessels (arteries or veins) or capillaries.

A. The causes of hæmorrhage may be usefully tabulated as follows:—

Causes of Hæmorrhage.—1. External causes, or those arising outside the tissues. (*a*) Traumatism, whether due to mechanical injury, the passage of a urinary calculus, or the bites of insects and worms, such as the *anchylostoma duodenalis*, which causes intestinal hæmorrhage and *bilharzia hæmatobia*, which causes hæmaturia. (*b*) Ulcers of the skin and stomach or intestinal tract and malignant growths, which invade the vessel wall.

2. Spontaneous hæmorrhage, resembling those of the first class, but arising in the tissues. (*a*) Hæmorrhage from aneurism of the systemic or pulmonary arteries; or from miliary aneurism. (*b*) Hæmorrhage from the lungs (hæmoptysis) in early tuberculosis and other lung affections and in cardiac disease. (*c*) From the heart; in fatty degeneration, abscesses,

and localised myocarditis. (*d*) From diseased veins of the leg (varices), and of the rectum (hæmorrhoids).

3. Hæmorrhage occurs as the result of dry cupping. In the same class may be placed the hæmorrhage which occurs in asphyxia, tetanus, strychnine poisoning, whooping-cough and eclampsia.

4. Toxic hæmorrhages, which occur in certain forms of poisoning and acute infective disease. The mineral poisons leading, by their general action, to hæmorrhage are lead, antimony and mercury (both acute and chronic poisoning), the intestines in the case of the last being chiefly affected. Organic poisons leading to hæmorrhage are:—Some forms of snake-venom, abrus poison, and some bacterial poisons, including putrefactive products; toxæmic diseases of the liver, such as acute yellow atrophy and *icterus gravis;* infective diseases, such as typhus fever, ulcerative endocarditis, yellow fever, septicæmia, congenital syphilis, and the hæmorrhagic forms of variola, scarlet fever, diphtheria and typhoid fever; also the toxic conditions known as purpura and scurvy. Probably in this class come some of the cases of hæmorrhage occurring in newly born children.

5. Profound anæmias, such as pernicious anæmia, advanced secondary anæmias and leukæmia.

6. Hæmophilia, or the hæmorrhagic diathesis.

7. Neuropathic hæmorrhage, such as occurs in the lungs, and from the nose and stomach, in acute nerve conditions (apoplexy, epilepsy).

Hæmorrhage is either arterial, venous, or capillary. It is called parenchymatous when it occurs in the solid tissue of an organ. It may cover a small area, when it is referred to as petechiæ or ecchymoses. It may be suffused through an organ, and is then referred to as hæmorrhagic suffusion. Hæmorrhagic infarction is a local hæmorrhage, following the blocking of an artery (p. 350). Hæmorrhagic focus is also a term used, and the term hæmatoma is applied to a hæmorrhagic focus forming a palpable mass. Blood discharged from the body receives special names, such as the blood of hæmoptysis, from the lungs; hæmatemesis, from the stomach; melæna, from the rectum; hæmaturia, from the urinary tract;

and menorrhagia and metrorrhagia, from the uterus. These terms, however, are of clinical and not pathological significance.

In discussing the causes of hæmorrhage, the distinction of hæmorrhage *per rhexin* from hæmorrhage *per diapedesin* must be borne in mind. Clear examples of hæmorrhage *per rhexin* are those due to traumatism, to the passage of a urinary calculus, or to the other causes mentioned in the first class in the list. In the other classes, examples of both rhexis and diapedesis occur. The occurrence of hæmorrhage has to be studied in connection with the degree of blood pressure—arterial, venous, or capillary—and of disease of the vessel wall. Both these causes frequently act together in inducing hæmorrhage.

The Effect of Blood Pressure: Arterial.—No increase of the arterial blood pressure, within the limits occurring in the living body, will cause rupture of a normal artery. The normal carotid can withstand fourteen times the normal pressure without rupture. Spontaneous hæmorrhage, therefore, resulting from a ruptured artery, depends not only on the blood pressure but on another factor, disease of the vessel wall. In the systemic arteries, spontaneous hæmorrhage occurs with an increase of blood pressure, most commonly in miliary aneurisms of the small arteries of the brain; the rupture of a large aneurism is frequently initiated by a sudden exertion, which momentarily increases the arterial pressure. Permanent increase of arterial pressure, such as is observed in granular contracted kidney in association with hypertrophy of the left ventricle, is constantly associated with hæmorrhage which occurs in the retina, in the brain and from the kidneys, and in all these cases, there is disease of the vascular wall, as well as a high arterial blood pressure.

In the pulmonary arterial system an increase of the arterial pressure is constantly associated with hæmorrhage from the lungs. Thus, in mitral stenosis, spontaneous hæmorrhages occur from rupture of the pulmonary capillaries, and even of the arterioles. In aneurism of the pulmonary arteries in tuberculous cavities of the lung it occurs frequently.

The spontaneous hæmorrhage following the rupture of the vessel is due to a momentary increase of the arterial pressure caused by some sudden exertion, or a fit of coughing.

Venous Pressure.—The jugular vein will rupture only if a hundred times the normal pressure is applied to it. The rupture of a large vein in disease depends on disease of the vessel wall, and on no mere increase of the venous pressure. The hæmorrhage occurring from varices of the leg or from the rectum is associated with disease of the vessel wall, aided by a local increase of the venous pressure, and is determined either by an open ulcer or by traumatism. A general increase of the venous pressure, such as occurs in embarrassment of the circulation of the right side of the heart (as in mitral stenosis) and of the portal circulation (as in cirrhosis of the liver), is a factor in the spontaneous hæmorrhage of hæmorrhoids.

Capillary Pressure.—An increase of capillary pressure, leading to hæmorrhage, *per rhexin* or *per diapedesin*, occurs mainly when there is a retardation of the venous flow from a part.

Disease of the Vessel Wall.—Disease of the vessel wall of an artery or vein, leading to the occurrence of hæmorrhage, is of great importance, in association with an increase of the blood pressure. Atheromatous degeneration of a large or medium-sized artery does not, as a rule, lead to hæmorrhage, unless an aneurism is formed. This is, no doubt, due to the fact that, in many of these instances, the arterial blood pressure is not only not raised, but is actually lowered. In cases, however, of arterio-capillary fibrosis accompanied by high arterial tension, the association of atheromatous degeneration, producing as it does inelastic brittle vessels, is an important factor in the production of hæmorrhage. It is commonly present when a high arterial pressure has existed for some years. With hypertrophy of the left ventricle, arterio-capillary fibrosis and high arterial pressure, numerous miliary aneurisms are found in the substance of the brain. These aneurisms owe their formation primarily to disease of the vessel wall, but also to the fact that the vessels lie in a perivascular space, thus allowing of the formation of a small dilatation. In the spinal cord these

perivascular spaces are absent, so that the aneurisms are not formed. In granular contracted kidney the flame-shaped hæmorrhages which occur in the retina are directly dependent on the degree of arterial pressure. They are associated with disease of the arteries of the retina, but are usually capillary or venous. Liability to their occurrence appears to be due to the fact that the vessels are less supported on one side than on the other. Hæmorrhage from the kidney in granular contracted kidney is associated with the degree of high arterial pressure, but also with the acute and subacute congestions to which the diseased organs are liable. The disease of the arteries of the kidney, the contraction and degeneration of the glomerulus and the coincident degeneration of the kidney tubules explain the liability to hæmorrhage on any sudden increase of arterial pressure, or any suddenly produced congestion.

The importance of an increase of arterial pressure in the production of hæmorrhage when the vascular wall is diseased, is seen in diseases of the arteries other than those described. Thus, in syphilitic arteritis, in which there is localised disease of the vessel wall, there is no tendency to hæmorrhage unless the arterial pressure be increased by some other cause, and the same may be said of atheroma. Disease of the vessel wall may itself, however, lead to hæmorrhage without any increase of arterial pressure, when the wall is rapidly softened, as in embolic aneurism and in infective arteritis.

Degeneration of the pulmonary artery and its branches is observed when the pulmonary pressure is increased over a long period, as in mitral stenosis and other forms of obstruction to the pulmonary circulation. In these cases, however, the arterial disease does not commonly progress beyond the formation of comparatively small fatty atheromatous patches in the intima of the vessels, and these do not appear to have any direct effect in the production of pulmonary hæmorrhage or apoplexy. The hæmorrhages which occur in the lung in prolonged increase of the pulmonary arterial pressure are mainly capillary, and are due to the rupture of these vessels, unsupported as they are by solid tissue.

Disease of the walls of the veins is an important factor in producing hæmorrhage, and this need not be associated with any general or local increase of the venous pressure. Hæmorrhage from a venous trunk is usually produced by a lesion of the walls of the vessel by ulcer or traumatism.

The conditions of hæmorrhage which have just been discussed do not offer any great difficulty in explanation. They comprise the first two classes given in the list.

Asphyxial and Other Petechiæ. — Dry cupping, in which there is a sudden and great reduction of the atmospheric pressure over an area of the skin, leads to the occurrence of petechiæ in the subcutaneous tissues of the area affected. Beneath the cupping glass it is seen that the skin is raised, owing to the reduction of pressure, and becomes dusky. There is thus an afflux of blood to the part, which is not rapidly conveyed away. The occurrence of petechiæ has been ascribed to the sudden rise of arterial pressure in the part, causing an increased intracapillary pressure, and so rupture. This explanation does not appear, however, to be correct, and the petechiæ are probably traumatic in origin, the rupture of the capillaries being produced by their over-distention with blood, which ensues on the sudden reduction of pressure on the surface leading to retardation of the venous flow.

Asphyxial petechiæ are observed in the lungs, pleura and pericardium. Their constant occurrence in these parts points to some change in the thoracic circulation, produced by the asphyxial condition. In asphyxia there is cyanosis, which is due not only to the reduction of the amount of oxygen in the blood and the increase of carbonic acid, but also to venous stasis. The right side of the heart becomes embarrassed, so that all the thoracic organs are in a state of passive hyperæmia. The production of petechiæ is not due simply to the state of congestion, but is the result of the powerful, repeated and spasmodic attempts at respiration. The convulsive action of the diaphragm and the intercostal muscles, and of the accessory muscles of respiration, in their ineffectual efforts to get air into the lungs, converts the thorax into a large cupping glass

(Cohnheim), the suction action leading to rupture of the capillaries, and so to the production of petechiæ.

Asphyxial petechiæ occur elsewhere in the body, as do those which are observed in tetanus, strychnine poisoning, whooping-cough and eclampsia. These occur in the muscles and in tissues of loose texture, such as the loose connective tissue of the conjunctiva. In the muscles the petechiæ are traumatic in origin, and are due to the convulsive contractions of the muscles. In loose connective tissue the hæmorrhage may be in the form of petechiæ or of suffusion, and, in such cases, it is directly due to the condition of cyanosis and temporary increase of venous pressure leading to an increased intracapillary pressure and rupture of the capillary walls.

Toxic Hæmorrhage. — The hæmorrhage which occurs in metallic poisoning, in poisoning by snake-venom, and in certain acute diseases, does not admit of a ready explanation. In the majority of instances, there is no direct evidence of any gross lesion of the vascular wall. In these cases the hæmorrhage occurs by diapedesis. In the hæmorrhage of the intestine which occurs in poisoning by mercuric salts, the result has been ascribed to a fall of blood pressure, leading to increased capillary pressure, and so to hæmorrhage. There is, however, no direct evidence of this, and it is possible that there is a direct effect of the poisonous salt on the vascular wall, leading to an increased permeability. In acute diseases there is, probably, a more profound effect on the walls of arteries, capillaries, and veins than is usually recognised, an effect which may be produced by the invasion of the vessel wall by bacteria, or by the action of the poisons circulating in the blood. In these conditions rupture of the vessel wall may be observed, with the production of petechiæ in the brain, heart, lungs, liver, spleen, kidney and gastro-intestinal tract. More commonly, however, there is no obvious rupture, and the wide distribution of the petechiæ, with the limited distribution of the bacteria, points to the profound effect of the circulating poisons on the vessels. In such cases it is supposed that the vessel wall shows increased permeability, and the hæmorrhage occurs *per diapedesin.*

Large flat hæmorrhages may occur in the subcutaneous

tissue, the loose subperitoneal tissue, in the mediastina and elsewhere in acute diseases, especially in the hæmorrhagic forms of the infective diseases. These are not obviously due to hæmorrhage *per rhexin*, and appear to be induced partly by an effect on the vessel wall of the circulating poison, and partly by a profound change occurring in the composition of the blood, resulting in hæmolysis (p. 329). In some of these cases, although the red corpuscles are present in the hæmorrhagic focus, the hæmoglobin from many of them is liberated, staining the tissue. This liberation results from the destruction of the corpuscles, which occurs in the blood stream itself.

The relation of diminished coagulability of the blood to the occurrence of hæmorrhage is not actually determined. It may, however, be that, in such conditions, blood more readily passes out of unruptured vessels.

In the *profound anæmias*, such as pernicious anæmia, advanced secondary anæmia and the later stages of leukæmia, hæmorrhages occur, usually from mucous surfaces, such as the gums, nose and gastro-intestinal tract. They also occur, though less frequently, in the brain and solid organs, and in the retina. In such conditions there is a profound change in the composition of the blood; there is a deficiency of oxygen and of hæmoglobin, degeneration of the red corpuscles and a diminished coagulability of the blood. The vascular wall is also affected, as shown by the fatty degeneration of the endothelial cells which occurs. The hæmorrhages which occur, in all probability, are mostly *per diapedesin*. In some instances, however, they may be initiated by slight traumatism occurring in the gums near the tartar of the teeth, and in the stomach. It cannot, however, be said that, in most instances, traumatism plays a great part in the production of the hæmorrhages. Obviously, it is absent in the production of the flame-shaped hæmorrhages of the retina in pernicious anæmia.

In hæmophilia the hæmorrhages which occur are initiated by traumatism, and their continuance is due to a deficient coagulability of the blood, in the main apparently dependent either on a deficiency or an irregular combination of the lime salts.

The hæmorrhagic foci which are observed in the lungs in

death from apoplexy, epilepsy, and in some cases of cerebral tumour and meningitis, and which may be referred to as neuropathic hæmorrhage, are difficult of explanation, but are possibly initiated by sudden changes in blood pressure, brought about by a direct effect on the centres of the medulla.

B. *Results of Hæmorrhage.*—1. *Death from Hæmorrhage* may occur: (*a*) From copious and repeated loss of blood, whereby sufficient blood is not left in the body to carry on the vital processes; (*b*) By its effect on vital organs: this occurs when the hæmorrhage takes place into the pericardium, from rupture of the heart or an aneurism, or by traumatism; or when it occurs in the brain, more particularly in the pons and medulla, and also when blood from a hæmorrhagic focus in the cerebral hemispheres finds its way into the ventricles.

2. *The Spontaneous Cure of Hæmorrhage per rhexin* frequently occurs. Coagulation of the blood occurs outside and inside the vessel. At the site of the lesion, if small, a white thrombus is formed, preceded by the adhesion of the blood platelets to the sides of the lesion (Fig. 99). In a larger lesion, and with a copious loss of arterial blood, there is retraction of the arterial wall, followed by a lowering of the arterial pressure with a slowing of the circulation, these events tending to cause a cessation of the hæmorrhage. Experimentally, it has been found also that, towards the end of the bleeding, there is an increased coagulability of the blood, which may perhaps be produced by an increase of platelets, or by a liberation of fibrin ferment from the white corpuscles.

3. *Changes occurring in the Extravasated Blood.*—Blood extravasated in the tissues or from a mucous surface undergoes coagulation; for example, in the brain, in the subcutaneous tissue and from the stomach and other mucous surfaces. It may, however, remain fluid when slowly extravasated into joints and serous cavities. Absorption of the liquid parts occurs, with disintegration and absorption of the fibrin by means of the phagocytic action of the white corpuscles, and, to some extent, of the tissue cells. The white corpuscles, for the most part, die; some become phagocytes (chiefly the mononuclear leucocyte),

taking up the disintegrating red corpuscles and fibrin. The red corpuscles disintegrate, the hæmoglobin diffuses. In blood slowly extravasated into cavities, the oxyhæmoglobin becomes reduced, and, if the medium is acid, as in the stomach and intestine, the colouring matter becomes dark or coffee-ground in appearance, and is precipitated as a chocolate brown amorphous matter.

In the tissues, the hæmoglobin may undergo one of several changes: into hæmatoidin crystals, hæmosiderin, or pigment granules.

Hæmatoidin (Fig. 103) is found in blood clots in the brain and elsewhere, in aneurisms and in *corpora lutea*. It occurs either in brick-red rhombohedral crystals or as amorphous matter. It is insoluble in water, alcohol, ether, acetic acid and dilute mineral acids or alkalies: and is soluble only in concentrated acids and caustic alkalies. It gives a play of colours with strong nitric acid—Gmelin's reaction. It is free from iron, and is chemically identical with bilirubin. It gives no absorption bands in the spectrum.

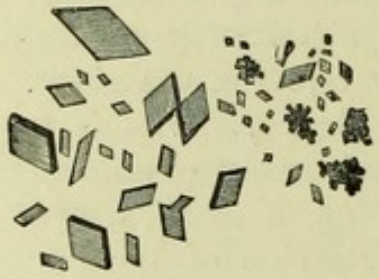


FIG. 103.—Hæmatoidin crystals. (Kirke's *Physiology*).

The rhombohedral crystals of hæmatoidin are seen, varying in size, as well as some amorphous masses, also composed of hæmatoidin.

Hæmosiderin is a derivative of hæmoglobin, containing iron and found not only in extravasations and in thrombi, but in the liver, spleen and kidneys in pernicious anæmia. In the liver (Fig. 104) it occurs chiefly in the outer zone of the lobules, and is demonstrated by treating sections of the organ with a 5 per cent. solution of ferrocyanide of potassium, followed by a 1 per cent. solution of hydrochloric acid. This gives the Prussian blue test for iron.

Pathological urobilin (see Urine, p. 402) is found in the urine after extensive extravasations of blood. The urine passed is dark, like jaundiced urine. The substance is probably identical with normal urobilin. It is soluble in alcohol, acids and acidulated water; it is partly soluble in ether and benzene. In acid solution, the spectrum shows a band close to F.

The formation of brown *pigment granules* and flakes follows,

in some instances, the extravasation of blood, especially if it is small in amount. The pigment is both extracellular and intracellular. The mononuclear leucocytes take up the red corpuscles, and pigment is formed inside the corpuscles, which

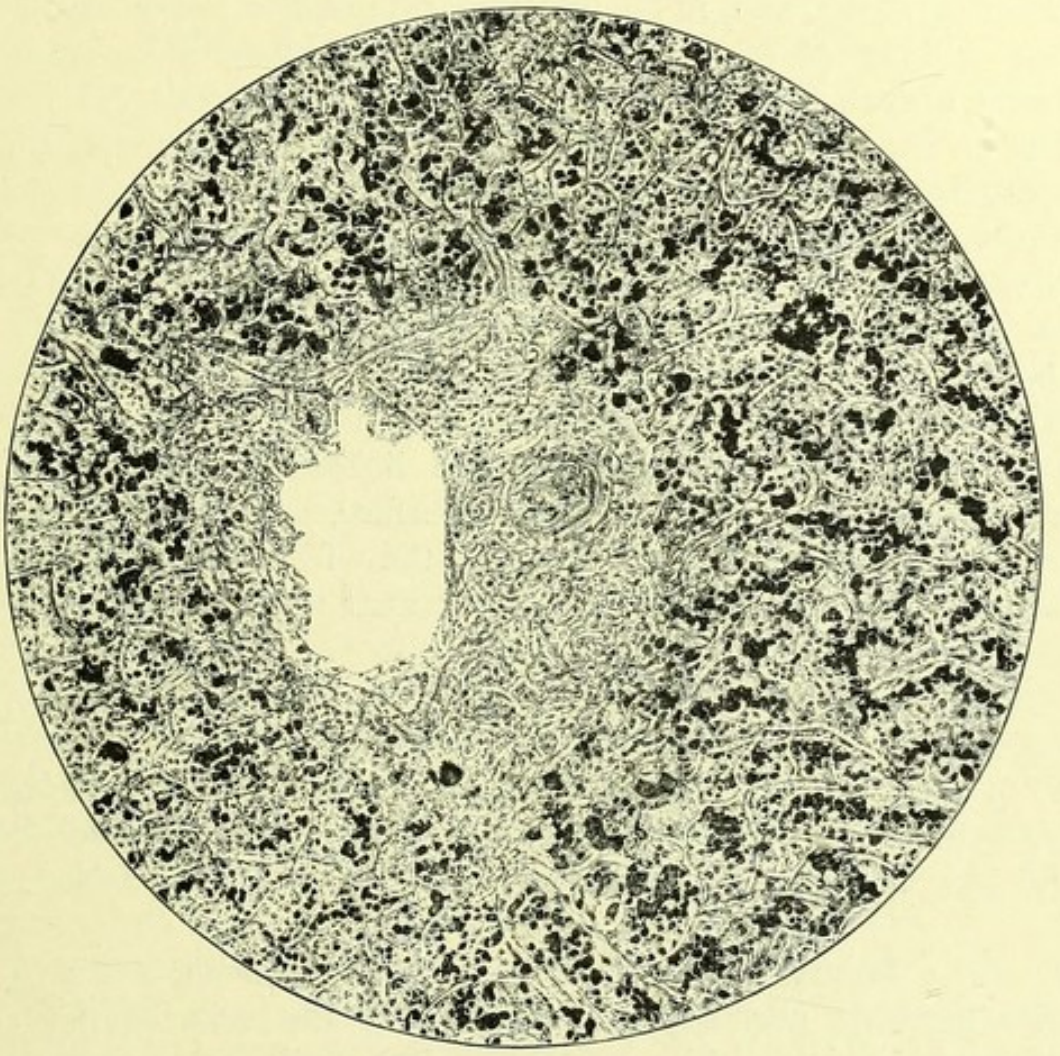


FIG. 104.—Hæmosiderin in the liver in pernicious anæmia.

A transverse section of a liver lobule is shown with the central vein. Surrounding it is a clear area of liver substance unpigmented and unstained. The liver cells outside this area show numerous black granules, which, in the fresh section, are greenish-blue.

The specimen was stained with ferro-cyanide of potassium and hydrochloric acid for free iron.

ultimately disappear, leaving the pigment free. The same process occurs with the tissue cells, and pigment granules may be carried to the nearest lymphatic gland. The formation of pigment granules from the hæmoglobin of the exuded red corpuscles is more commonly observed in inflammatory areas in the intestine, peritoneum, lungs and pleura.

Large hæmorrhages incite, even when non-infective, surrounding inflammation. The hæmorrhagic focus may organise, by granulation tissue passing into it from surrounding healthy tissue. The hæmorrhage may itself destroy the tissue invaded, and, if no infection occurs, the tissue atrophies and a scar is left. In some cases, the hæmorrhagic focus forms a cyst, for example, in the brain (apoplectic cyst). A fibrous capsule is formed round the hæmorrhagic focus, which ultimately softens, the cells degenerating and the hæmoglobin undergoing the changes already described. Invasion of a hæmorrhagic focus by bacteria may occur; either putrefactive or pus micro-organisms. Putrefaction affects the contents of the hæmorrhagic foci, whereas pus is formed in the periphery of the focus, and is discharged into the hæmorrhagic area. Putrefaction and pus formation are liable to occur when the hæmorrhage is near an external surface, such as the mouth, in the lungs or pleura when the focus opens into a bronchus, in or near the vagina, or near the alimentary tract.

Morbid Pigmentation.—Pigmentation, as met with in disease, may be divided into two classes—true and false. True pigmentation results from an increase of the normal pigment in the body or is due to a pigment derived from the blood. Other forms of pigmentation are called false.

True Pigmentation.—1. *Increase of the Normal Pigment.*—The pigment normally is contained in the cells of the *rete Malpighi* of the skin, of the retina, pia mater, choroid, sclerotic and heart muscle. The pigment of the heart muscle is increased in various forms of degeneration and in cachexia. This is sometimes referred to as brown atrophy of the heart (p. 239). The amount of pigment in the skin varies normally within wide limits. It is, however, increased in Addison's disease, more particularly over the parts exposed to pressure, and pigment also appears in the buccal mucous membrane. The skin pigment is increased in certain chronic inflammations of the skin, such as that produced by phtheiriasis; this increase of pigment is due to irritation. In

pregnancy, the skin becomes pigmented, especially about the face, and in exophthalmic goître patchy and varying pigmentation may be observed on the hands, head and neck.

In melanotic sarcoma and carcinoma arising from the skin and retina, the pigment of the primary growth is repeated and reproduced in the secondary growths.

2. *Hæmatogenous Pigmentation, or Pigment derived from the Blood.*—(*a*) This may result from extravasation of blood (p. 364); (*b*) or from the destruction of red corpuscles inside the vessels. The condition of hæmoglobinæmia produced by the liberation of hæmoglobin in the blood is discussed in another chapter (p. 325). This is not the same condition as that which obtains in malaria, in which pigmentation of the spleen, liver, brain and other parts occurs. In this case the malarial parasite forms the pigment (insoluble melanin) during its process of growth, and during the destruction of the red corpuscle. The formation of hæmosiderin in the liver, more particularly in pernicious anæmia, has also been referred to (p. 364). In this case it is probable that the liver is the chief agent in destroying the red corpuscles and causing the deposition of the hæmoglobin derivatives.

3. *False Pigmentation* requires but little explanation. It is such as occurs *post mortem* in the black colour of the liver and intestine, due to the formation of iron sulphide by the sulphuretted hydrogen liberated during decomposition.

Jaundice is also an example of false pigmentation, due to the bile colouring material. The yellow colour of the tissues and skin in cachexia and profound anæmias is due to the excessive formation of the colouring matter of fat (lipochrome). Pigment in other matters introduced into the body also causes false pigmentation, such as tattoo marks, the inhalation of coal dust, iron, and other matters into the lungs, and the prolonged administration of nitrate of silver, which produces a blue discoloration of the skin, a condition known as *argyria*.

CHAPTER XV

THE EFFECTS OF DISEASE OF THE LIVER

I. *Changes in the Biliary Secretion: Jaundice—Variations in the Secretion of the Bile—Gall-stones.*

A. *Jaundice.*—Jaundice is a condition in which the bile colouring matter, bilirubin, is present in the tissues which are stained green, brownish-green, or, in prolonged cases, a blackish-green colour. The tissues which are stained are the skin, conjunctivæ and the connective tissues generally; the mucous membranes are not stained unless they are inflamed, and the colouring matter is not present in the secretions of the digestive juices, or in the tears. The bilirubin is excreted in the urine, which varies in colour from greenish-yellow to black. Bilirubin is also excreted from the skin. If the bile does not enter the intestine at all, the motions are clay coloured and frequently show glistening particles of fat.

The physiological effects of the presence of bile in the tissues in jaundice are but slight. Itching of the skin is sometimes present, and yellow vision and xanthoma have been ascribed to the conditions somewhat doubtfully. To the presence of the bile acids in the circulation, the slowing of the pulse (bradycardia) which is sometimes observed, is ascribed, as well as the slight increase in the arterial blood pressure. It is doubtful whether bilirubin possesses any poisonous action. Intravenous injection in rabbits has been said to produce death with an effect on the kidneys, heart and central nervous system. The method used for preparing the bilirubin was, however, open to objection, all the bile salts not being removed. The bile acids and salts have a distinct physiological action. Injected subcutaneously or intra-

venously, they produce slowing of the heart's action, with convulsions, ending in coma and death. Outside the body they have a hæmolytic action on the red corpuscles; but it is perhaps doubtful whether this action takes place in disease, as in jaundice the bile acids are never in sufficient quantity in the blood or tissues to produce their pronounced physiological action (p. 377).

The severe symptoms which are sometimes associated with jaundice are due, not to the condition itself, but to the disease producing the jaundice. The severest symptoms are observed in malignant jaundice (*icterus gravis*). This term is, however, a misnomer. There is no such thing as malignant jaundice. The cases referred to are those usually of severe infective disease associated with jaundice as one of the symptoms.

In discussing the causes of jaundice, it is necessary to bear in mind certain physiological facts relating to the formation of bilirubin and the bile acids, and to the circulation of the bile. Bile acids and bilirubin are made by the liver, and not by the blood and tissues, a fundamental fact to remember in the discussion of those cases of jaundice which were formerly supposed to be hæmatogenous in origin. Nowhere in the body but in the bile secretion are bilirubin and bile acids found.

Bilirubin ($C_{16}H_{18}N_2O_3$) is a derivative of hæmoglobin, and is of the same composition as hæmatoidin (p. 364), the formation of which is ascribed, not to cell agency, but to a purely chemical change occurring slowly in the hæmoglobin of old blood clots. It is doubtful, however, whether, under these conditions, cells are not the agents in forming the hæmatoidin. At any rate, in the liver the rapid formation of bilirubin must be due to the activity of the liver cells. Bilirubin is a substance insoluble in water, slightly soluble in alcohol and ether, readily soluble in acids and alkalies, chloroform and benzene. It is held in solution in the bile chiefly by the bile salts. It is iron-free, and shows no absorption bands in the spectrum, although the violet end of the spectrum is absorbed. It gives a play of colours with strong nitric acid, due to the formation of different coloured oxidised derivatives (Gmelin's reaction). The green oxidised product is called biliverdin; the yellow, choletelin ($C_{16}H_{18}N_2O_6$).

During the play of colours obtained by the nitric acid, the solution shows absorption bands in the spectrum, between D and F.

The bile acids consist of taurocholate and glycocholate of soda. Taurocholic acid is of the formula $C_{26}H_{45}NO_7S$; glycocholic acid is $C_{26}H_{43}NO_6$. The bile salts are special secretions of the liver. They are not found normally in the blood and tissues; they are present only in small quantity in the fæces and in normal urine.

Bile, the secretion of the liver, is discharged into the intestine, and plays a certain part in the processes of digestion. Some of the bile colouring matter is discharged in the fæces as stercorin. Most of it is reabsorbed, and discharged in the urine as urobilin, some, no doubt, going back to the liver and being excreted again. But little of the bile salts is excreted; they are mostly reabsorbed and passed back to the liver, where they are possibly reconverted. There is, therefore, to some extent, a bile circulation from the liver to the intestines, and back again to the liver by means of the blood vessels.

It is necessary to consider the physiological relations between bilirubin, hæmoglobin and the bile salts. Bilirubin does not exist in the normal blood, or, if present, it is in such small quantities as not to be detected by analysis. It is present, however, in the blood of the horse (Hammarsten). Bilirubin is a derivative of hæmoglobin, and, although the transformation of hæmoglobin into hæmatoidin—which is identical with bilirubin—occurs in old blood clots, yet it must be considered that, normally, the liver is the only organ or tissue capable of manufacturing bilirubin. Frerichs concluded that bile acids were converted into bilirubin in the body, the colouring matter being found in the urine after the injection of bile acids. It was shown, however, that the bile acids liberated hæmoglobin from the blood corpuscles, so it was considered probable that the bilirubin was derived, not from the bile acids, but from this liberated hæmoglobin (Kühne). The injection of hæmoglobin in solution into the circulation of dogs does not cause the appearance of bilirubin in the urine, as had been stated,

but only of hæmoglobin. Subsequent researches confirmed the conclusion that the injection of hæmoglobin or oxyhæmoglobin, into the circulation of healthy animals, did not cause the appearance of bilirubin in the urine; but that it had the effect of increasing the amount of bilirubin in the bile, a similar event happening if bilirubin were injected into the circulation. It has also been shown that the increase of bilirubin in the bile, following the injection of hæmoglobin into the circulation, is not the result of the transformation of the one body into the other in the blood, but that the conversion takes place in the liver itself, the cells of which are observed enclosing the red corpuscles and the hæmoglobin (Naunyn). Moreover, if the liver be extirpated, no bile colouring matter is found in the body (p. 384). It may be concluded that the presence of free hæmoglobin in the blood may lead to hæmoglobinuria or urobilinuria, and leads to an increase in the amount of bilirubin secreted by the liver, but not to the formation of bilirubin in the blood, or to its excretion in the urine.

The results of these experiments have a direct bearing on the causes of jaundice. Jaundice has been divided into two classes—*obstructive* and *non-obstructive*. In the obstructive form, the bile is prevented from entering the intestine; it is therefore reabsorbed by the lymphatics of the liver and carried to the thoracic duct, and so into the venous circulation. The colouring matter stains the tissues in the manner already described, and is excreted in the urine with the bile acids. Obstructive jaundice has also been called hepatogenous.

In non-obstructive or hæmatogenous jaundice, there was considered to be no obstruction. Jaundice is less intense than in the obstructive form, and only the bilirubin, and not the bile acids, were described as excreted in the urine.

This distinction of the two forms of jaundice in these terms is no longer admissible, and it is best to divide jaundice into:—

1. That caused by pressure on, or obstruction of, the ducts outside the liver.

2. Pressure on the ducts inside the liver.

3. Toxæmic jaundice, or that due to poisoning of one form or another.

1. *Affection of the Duct outside the Liver.*—This occurs :—

(*a*) In gall-stones, by inspissated bile, by worms in the duct, and, rarely, by foreign bodies entering the duct from the intestine. Inflammation of the duodenum, and catarrh of the duct causing plugging by mucus, lead to the same result as the first of the causes mentioned. Stricture of the duct is produced by a cicatrised duodenal ulcer, by perihepatitis, or by a cicatrised ulcer of the duct itself, caused by a gall-stone.

(*b*) Tumours at the neck of the gall bladder, passing downwards, or situated at the orifice of the duct, are also causes.

(*c*) Pressure from without is observed in tumours of the liver, stomach, pancreas, kidney, omentum, ovary, uterus (pregnant uterus), aneurism and fæcal accumulation.

2. *Pressure on the Ducts in the Liver* itself is observed mainly in cirrhosis of the organ, and in "nutmeg" liver (passive hyperæmia).

3. *Toxæmic Jaundice* is observed as the result of:—

(*a*) The action of poisons, such as toluylene-diamine, phosphorus, arseniuretted hydrogen, pyrogallic acid and snake-venom ; and follows the injection of large quantities of distilled water into the circulation.

(*b*) It is also observed in infective diseases, such as pyæmia, yellow fever, malaria, relapsing fever, "epidemic" jaundice, Weil's disease (infective jaundice), "malignant" jaundice, and acute yellow atrophy of the liver. It is seen in rare cases of typhoid fever, typhus fever, pneumonia and scarlet fever.

1 and 2. The explanation of the cause of jaundice in the first two classes of cases is simple. The liver, being normal, continues its secretion of bile which, however, is unable owing to the obstruction to reach the intestine. It is therefore reabsorbed, appears in the tissues, and is excreted in the urine. The channel of absorption has been shown to be the lymphatics of the liver and the thoracic duct. Experimentally, after ligature of the common bile duct, jaundice

supervenes, but this does not occur if, at the same time, the thoracic duct be ligatured, or an opening be made into it. The jaundice persists in these cases, and is intense as long as the obstruction lasts. Variations in the intensity of the condition are, however, observed. The motions never become of a normal colour, remaining clay-coloured, but the actual colouring of the skin and the amount of colouring matter observed in the urine varies in prolonged cases to a considerable extent from time to time. This is due to the fact that the amount of bile secreted by the liver in such cases varies considerably, especially if there be pyrexia, or the liver substance be damaged. In some cases of cirrhosis of the liver, there is but little or no jaundice, even though the condition has lasted for some time. This means either that a diminished amount of bile is secreted or that the obstruction is not sufficient to cause the absorption of a large quantity of the secreted bile. In some cases, on the other hand, the jaundice is intense, and lasts for a long period, and, even when absent in well-marked cirrhosis, it usually appears towards the end of the disease.

3. Toxæmic jaundice is the result of the action of poisonous substances, and so, unlike the first two classes of cases, it is accompanied by severe symptoms, due to the physiological effect of the poison on other organs and tissues. Thus, it is accompanied by pyrexia, and by the signs of an action on the nervous system, such as stupor, coma, twitchings and convulsions. In this form of jaundice, there is no obvious obstruction to the flow of bile in the bile ducts.

The earliest theory of the explanation of toxæmic jaundice, due to Morgagni and Boerhaave, ascribed the condition to the fact that the biliary constituents were not eliminated, and so accumulated in the blood. It is quite possible to suppose that a transient jaundice might be due to the accumulation of the bile constituents in the blood, but only in the event of the liver and kidneys being damaged by disease. A subsequent theory was that of Frerichs, who considered that there was a diminished oxidation of the bile constituents which were absorbed into the circulation from the intestine, so that

they accumulated in the body, and that the condition was also associated with an increased secretion of bile, or polycholia. Frerichs' theory was, however, based upon erroneous data, the chief of which was that the bile acids were convertible into bilirubin.

The more modern idea of the causation of toxæmic jaundice is that it is due to a temporary obstruction to the flow of bile in the smaller bile ducts. The bile is secreted normally at a very low pressure, so that any general cause, which obstructs (even temporarily) the flow of bile in the small bile ducts, will cause an absorption of the bile by the lymphatics, and so a slight, and often temporary, jaundice. The jaundice, in these cases, is associated with the action of a poison, and the actions of some of these poisons have been investigated, with the following results. Toluylene-diamine is a poisonous substance, which, injected into dogs, causes both hæmoglobinuria and jaundice. The action on the secretion of bile may be divided into two stages. In the first the bile is increased in quantity, that is, there is polycholia; in the second the bile is diminished, and becomes more like viscid mucus. The secretion then regains its normal character, as the action of the poison diminishes. Jaundice supervenes at the end of the first stage, continues during the second, and disappears in the third. The first stage—that of polycholia—is, no doubt, associated with the destruction of red blood corpuscles. The stage of jaundice is associated with a viscid mucous secretion; this, temporarily leading to an increase of pressure in the bile ducts due to a partial obstruction of the smaller bile ducts, causes the jaundice which passes off in the third stage, as the secretion of bile becomes less viscid and more copious.

The action of arseniuretted hydrogen and of phosphorus in the production of jaundice is explained in the same way (Stadelmann), and it is to be noted that, after extirpation of the liver, arseniuretted hydrogen causes the appearance of hæmoglobin in the urine, and not bilirubin (Minkowski and Naunyn).

It is of interest to note that dogs infected with *piroplasma canis* suffer from jaundice: while cows infected with *piroplasma*

bigeminum show hæmoglobinuria (Texas fever). Both these organisms are parasitic in the red corpuscle, which they destroy (p. 152).

The occurrence of jaundice in the infective diseases already enumerated has probably the same explanation, which is evidently a much simpler one than any other that has been advanced. The sequence of events may be summarised as follows: the toxic substances liberate the hæmoglobin from the red corpuscles; the colouring matter is transformed by the liver, and so there is polycholia, or, at any rate, polychromia, that is, an increase in the colouring matter. This is soon followed, however, by a second stage of viscid bile, which causes an obstruction to the flow, and so leads to jaundice. As would be expected, the jaundice is, as a rule, slight, and markedly diminishes from time to time, even disappearing and returning.

There are some cases of jaundice which cannot, at present, be included in any of the above classes. *Infantile jaundice* occurs soon after birth, and is, in some instances, due to organic disease. In other cases, however, no obvious obstruction is present, and the jaundice has been ascribed to sudden changes in the hepatic circulation, or to a sudden polycholia leading to an absorption of the excess of bile by the lymphatics of the liver. *Nervous jaundice* has been described as following anxiety or sudden excitement. In these cases the jaundice supervenes suddenly after the initial cause, and is, as a rule, temporary. It has been ascribed either to spasm of the ducts, or to the absorption of the bile by the blood capillaries, and not by the lymphatics, the blood capillaries absorbing the bile, owing to a sudden fall of blood pressure in the portal system. It is, however, very doubtful whether the blood pressure in the liver capillaries could fall below the pressure of the bile in the bile ducts.

Influence of Jaundice on Metabolism.—In jaundice, as a rule, a deficient amount of food is taken so that the amount of nitrogen in the urine is less than the normal, but the total output of nitrogen is greater than the intake, there being thus

a loss of nitrogenous material from the tissues. This is shown in the following table (Müller, quoted by Von Noorden):—

	Number of Calories in the Daily Food.	Daily Amount of Nitrogen in Grammes.		The Amount of Nitrogen lost from Tissues.
		Absorbed.	In Urine.	
1. Man greatly emaciated; jaundice due to gall-stones . .	1082	10.19	10.85	0.66
2. Man, jaundice due to gall-stones; cirrhosis of the liver . .	1610	14.11	15.88	1.77
The same . . .	883	17.18	17.14	...

The amount of urea in the urine is not appreciably altered in jaundice.

The absorption of the food products varies in jaundice. The absorption of carbohydrates and of proteids is but little, if at all, affected; the chief effect is on the fat. Careful estimation of the amount of fat taken in with the food, and the amount passing undigested in the fæces, has shown that in jaundice from 40 to 80 per cent. may be unabsorbed as compared with about 7 per cent. in healthy individuals on the same diet. The diet in the experimental cases, both of the jaundiced and healthy, consisted of milk, white bread and butter. The fat which appears in the fæces consists only of a small quantity of normal fat, and a large quantity of fatty acids combined with alkalies. It appears to be the contrary when the pancreatic juice is prevented from entering the intestine. In this case there is little fatty acid in the fæces, the fat appearing chiefly as neutral fat.

The persistence of jaundice has a deleterious effect on the activity of the liver cells, for although bilirubin continues to be secreted for long periods, yet the secretion of the bile acids diminishes. Normally, the bile acids are not destroyed in the blood or intestine, and being re-absorbed, pass again into the bile. In cases of jaundice they are but rarely found

in the urine, and if they were formed in normal quantity it is probable that they would produce toxic symptoms. It is rare, however, for any toxic symptoms as the result of poisoning by bile acids to occur in cases of jaundice. The amount of bile acids present in the bile in long-standing cases of jaundice is diminished. Thus bile obtained from a biliary fistula in such a case was found to contain only 0.055 per cent. of taurocholate of soda and 0.165 per cent. of glycocholate of soda, the normal amount of bile salts being 2 per cent.

In the jaundiced liver, the amount of glycogen is somewhat diminished, but glycosuria is rarely present either in jaundice or in other diseases of the liver. It is very doubtful if sugar appears in the urine even if large quantities of glucose are given daily—100 to 200 grammes—although a positive result has been stated to have been obtained.

B. *Variations in the Secretion of Bile in Disease.*—The bile may undergo either an increase or diminution in quantity, or one constituent, more particularly the bilirubin, may be diminished, so that pale or colourless bile is secreted. In some instances substances not normally present in the bile have been observed. But little is known of the conditions in disease in which polycholia occurs. In most cases of disease of the liver leading to degeneration of the cells, the bile is diminished in quantity or altered in quality. A rise of body temperature leads to the secretion of pale or colourless bile; this has been noted, also, in some cases of fatty degeneration of the liver. Albumin is present in the bile in some cases of Bright's disease, and after the injection of water into the blood. The injection of sugar leads to the presence of sugar in the bile, and this is also observed in diabetes. The bile may contain an excess of urea, as in Bright's disease and in cholera; and in cases of acute yellow atrophy of the liver it contains leucin and tyrosin, as do many other liquids of the body in that disease. Hæmoglobin has been found in the bile (hæmoglobincholia), as the result of the action of the poisons which also cause jaundice. Thus it occurs from the

action of toluylene-diamine, pyrogallic acid, phenylhydrazin, potassium chlorate and aniline compounds (Filehne).

The action of drugs on the secretion of the bile has given rise to much discussion and experiment. For a complete discussion of this subject, works on Pharmacology must be consulted. It may here be stated, however, that the latest researches tend to negative the idea that any of the so-called cholagogues actually stimulate the secretion of bile by the liver, but to show that there is an increased secretion when bile itself is administered.

The Secretion of the Gall Bladder.—The gall bladder is a receptacle for the bile, but its mucous membrane has a secretion of its own, the chief constituent of which is called "mucin," or, more accurately, nucleo-albumin. In dropsy of the gall bladder (hydrops cystidis felleæ), which results from permanent obstruction of the cystic duct, the liquid found is clear and viscid. The discharge, in a case of fistula, gave the following analysis:—Specific gravity, 1009.5; total solids, 15.36; organic matters, chiefly "mucin," 6.72; chlorides (as NaCl), 5.73; sodium carbonate, 2.2; other salts (phosphates and potassium salts), 0.71; (Mayo Robson, quoted by Gamgee). This analysis probably represents the secretion of a diseased gall bladder, and not of a normal one.

C. *Cholelithiasis* (Gall-stones).—Gall-stones are found mainly in the gall bladder, sometimes in the ducts within the liver, and sometimes in the common bile duct. In the latter case they always come from the gall bladder. They vary greatly in size, number and chemical composition. The largest sized calculi may occupy the whole of the gall bladder, or there may be two large calculi. It is more common, however, to find several medium sized calculi, and, although the number present may be in some cases reckoned by thousands, the average number is under twenty.

The chemical composition shows they consist mainly of cholesterin, bilirubin-calcium and calcium carbonate. Other coloured derivatives of bilirubin may be present, such as bilicyanin and choletelin, but gall-stones do not contain

either free bilirubin or the salts of the bile acids. Cholesterin ($C_{26}H_{43}HO$) is present in the bile, and is held in solution by the salts of the bile acids, by soaps and neutral fats. It is found also in many other tissues, such as the white matter of the brain and spinal cord and nerve fibres, and blood corpuscles. The amount present in bile varies considerably, from 0.05 to 0.35 per cent. Cholesterin is very widely distributed in all cellular tissues, both animal and vegetable, and is probably an excretion of the liver. It is insoluble in water or saline solutions, but is readily dissolved by alcohol and ether.

Bilirubin (p. 369) is insoluble in water, but is readily dissolved by dilute solutions of caustic alkalies and ammonia. It is no doubt held in solution in the bile by the alkaline salts present and by the bile salts. The calcium compound which is present in gall-stones may be prepared artificially by precipitating an alkaline solution of bilirubin with calcium chloride. The precipitate is insoluble in water, alcohol, ether and chloroform, and has the formula of $C_{32}H_{34}N_4O_6Ca$.

The varieties of biliary calculi may be classified as follows (Figs. 105 and 106):—

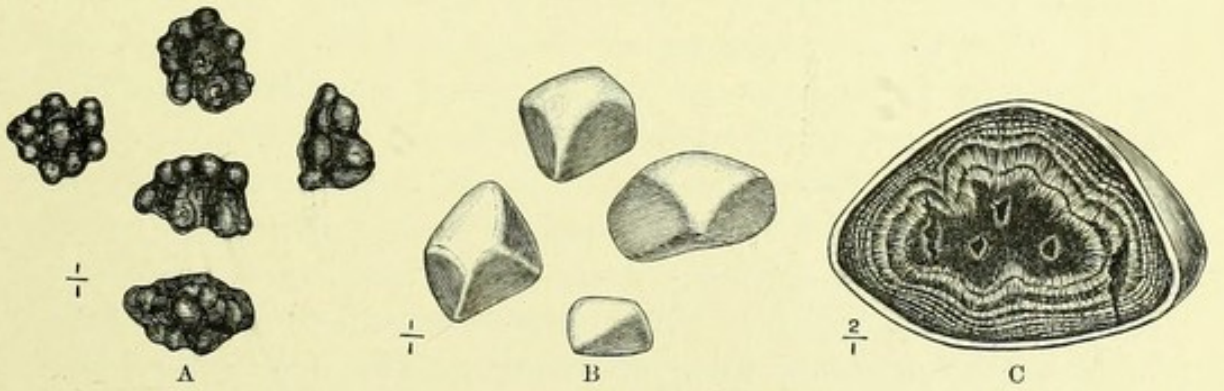


FIG. 105.—Gall-stones.

A shows the soft crenated bilirubin-calcium stones, natural size. These are black when removed from the gall bladder, and are soapy to the touch.

B represents the common facetted biliary calculus, natural size.

C represents a section of one of these calculi, twice the natural size. In the centre is a black mass of bilirubin calcium, with three or four cavities. Radiating from this to the periphery are fine needles of crystals of cholesterin, which are interrupted in parts by concentric dark rings of bilirubin-calcium.

The periphery of the stone is formed by a white hard layer composed of phosphate and carbonate of lime.

1. Pure cholesterin calculi, which are known as biliary sand or pearls, and are usually seen as very light glistening yellowish

globules, without any internal structure, and completely soluble in alcohol and ether.

2. Stratified cholesterin calculi, which may be very large, and which sometimes show a nucleus, from which radiate

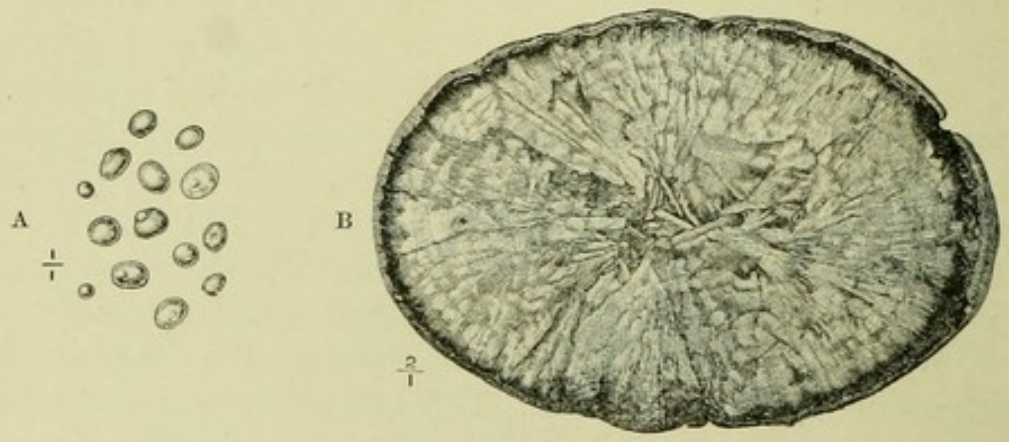


FIG. 106.—Gall-stones.

A represents cholesterin perles, natural size. They are glistening on this surface, and dissolve completely in ether.

B is a section of a pure cholesterin stone twice the natural size (Naunyn). The stone is seen to be composed almost solely of largish crystals of cholesterin, which interlace at the centre of the stone, but radiate mostly to the periphery. At the periphery is a little bile colouring matter, and the surface of the stone is composed mainly of cholesterin, with some lime salts.

closely packed crystals of cholesterin, arranged in layers. This form of calculus may be very large, oval, or globular. Analysis shows that they contain 65 to 98 per cent. of cholesterin, and from 1.5 to 27 per cent. of other organic matters, only a very small proportion of which is bilirubin.

3. The commonest form of biliary calculus is yellow or whitish-brown, and is usually found multiple and facetted ; they may be soft when freshly obtained. On section, they show a central nucleus, which is commonly dark, and composed of the bile pigment in combination of calcium. The nucleus has also been found to be composed of inspissated mucus, degenerated epithelial cells, degenerated blood clot, or rarely a parasite such as a dried round worm (ascaris lumbricoides). The middle zone of the calculus is composed of concentric layers, united by radiating crystals of cholesterin. This layer consists almost solely of cholesterin, but is coloured in some cases with bile pigment. The external layer of the calculus is composed either of a mixture of cholesterin and bile pigment, or of calcium carbonate mixed with pigment.

4. The calculi called mixed bilirubin-calcium stones are composed of bilirubin-calcium and cholesterin in varying proportions. They do not, however, show the structure of the ordinary calculus, although they may possess a nucleus of cholesterin.

5. Pure bilirubin-calcium stones are not uncommon. They are usually small and soft. They consist almost solely of bilirubin-calcium and derivatives of the bile colouring matter, with only minute quantities of cholesterin.

6. Calculi are sometimes found containing only traces of cholesterin and bilirubin, and consisting mainly of calcium carbonate, with a smaller quantity of calcium phosphate.

7. Lastly, casts of hepatic ducts may be found, consisting mainly of inspissated bile.

Mode of Formation of Gall-stones.—Gall-stones are more common in women than in men, in the proportion of three or five to one. The tendency to their formation also increases with age, being most frequent at sixty years and over, and being very uncommon under twenty years of age. The tendency to the formation of gall-stones is not affected, apparently, by heredity, by diet, by the circumstances of life, or by the condition of fatness or spareness. It appears to be purely a local condition, induced by changes occurring in the bile in the gall bladder. The points for consideration are the conditions of precipitation of bilirubin, cholesterin and calcium carbonate from the bile in the gall bladder. It is to be noted that these three substances are held in solution very lightly; bilirubin, by the alkaline salts of the bile, being readily precipitated by calcium; cholesterin being held only lightly in solution by the bile salts; while calcium carbonate is, with difficulty, kept in solution by the carbonic acid present. It has been stated that calcium carbonate is secreted by the mucous membrane of the gall bladder (Frerichs), and it has been supposed that the precipitation of the bilirubin and of the cholesterin is due to the bile becoming acid, owing to an acid fermentation (Frerichs). This acid fermentation can only occur by means of a micro-organism, and, in the majority of cases of gall-stones,

no acid-forming micro-organism is apparently present. It has again been supposed that the cholesterin is secreted by the epithelial cells in the gall bladder and bile ducts. This is increased when the epithelium becomes diseased. This theory of the formation of gall-stones (Naunyn) supposes that damage to the gall bladder is done by micro-organisms which enter by the common bile duct from the intestine, and consist mainly of the bacillus coli communis. It cannot be admitted, however, that it is proved that this condition is the most usual cause of the formation of gall-stones.

The regular and complete emptying of the bladder during health would preclude the formation of gall-stones, so that one of the causes must be considered as a comparative stasis of the bile in the gall bladder, a stasis not necessarily due to any organic obstruction, but possibly due to a diminished contractility of the muscular wall of the bladder. This may be one of the factors explaining the increased formation of gall-stones as age advances, as it has been shown that the muscular fibres of the gall bladder undergo atrophy in old age (Charcot and Pitres).

The occurrence of bilirubin-calcium in gall-stones must be considered as the result of a process of precipitation, and this precipitation might readily be initiated by the antecedent precipitation of calcium carbonate through a diminution in the quantity of carbonic acid, the calcium combining with the bilirubin in the process of precipitation. In all liquids in which organic substances are held in solution very lightly, the precipitation of one substance tends to the precipitation of another, so that the cholesterin might readily be deposited round the bilirubin-calcium nucleus. Precipitation of the cholesterin must, however, be considered a separate process from that of the bilirubin-calcium, and it may possibly be initiated by a diminution in the quantity of solvents, namely, the bile salts and the soaps.

II. *Disordered Functions of the Liver.*—The functions of the normal liver may be given as follows:—

1. The secretion of bile.

2. The storage of glycogen — the glycogenic function of the liver.

3. The proteolytic function of the liver, whereby proteids are transformed or broken up, or non-proteid nitrogenous bodies are changed. Thus, the liver has to deal with the formation of urea and uric acid.

4. The liver has a profound effect on certain poisons, which are absorbed into the system. Not only are certain poisons excreted in the bile, but some are actually destroyed by the liver.

5. The hæmolytic function of the liver. To the liver cells has been ascribed the important function of breaking down the hæmoglobin of the red corpuscles, some of this hæmoglobin going to the formation of bilirubin, the remainder being present in the organ as hæmosiderin (p. 364). The hæmosiderin is in some animals, for example, rabbits, increased by food, and is greatly increased in one disease, namely, pernicious anæmia.

The alterations of some of these functions in disease, namely, urea formation and the glycogenic function, are discussed in the chapter on *Changes in Metabolism* (p. 424). Hæmolysis has already been discussed (p. 323). Here it is necessary to discuss the effect of disease of the liver on the body.

The influence of liver disease on nutrition may in individual instances depend on different causes.

1. There may be partial or complete obstruction to the flow of bile leading to slight or intense jaundice.

2. There may be damage to the liver cells, as in cirrhosis and atrophy.

3. There may be obstruction to the portal circulation, interfering not only with the absorption of the digested food products but also with the functions of the stomach, pancreas and intestine.

4. There may be coincident disease or disorder of the stomach and intestine associated either with a portal obstruction or with the original cause of the liver disease, as in alcoholism.

Extirpation of the liver has been performed in geese after an Eck's fistula has been made, that is, after the portal vein has been joined to the inferior vena cava, so that the portal blood is diverted from the liver into the systemic venous system. The animals lived from six to twenty hours. A great change was observed in the urine, which, instead of containing, as normally, 60 to 70 per cent. of uric acid, was found to contain only from 2 to 3 per cent. The ammonia in combination was found to be increased to 60 per cent., the normal being from 9 to 18 per cent.; and lactic acid appeared in the urine. It is evident, therefore, that removing the liver from the body greatly disturbs proteid metabolism; in geese the normal transformation into uric acid of the products of this metabolism not taking place. In those diseases of the liver in which there is great destruction of the cells—as in cirrhosis and acute yellow atrophy—ammonia and lactic acid are found in the urine.

After extirpation of the liver, it was found that the injection of arseniuretted hydrogen, which in a normal animal causes jaundice, no longer produced this result, but caused hæmoglobinuria.

In dogs, when the liver is thrown out of action, as by the formation of an Eck's fistula, ammonium carbamate acts as a poison when injected into the circulation, owing to the fact that the liver does not transform it into urea. If the hepatic artery is ligatured, there is an increase in the blood of ammonium carbamate. The removal of the liver has also an effect upon the muscle-glycogen, causing a great diminution.

The effect of great destruction of the liver is not seen in any disease except *acute yellow atrophy*, and also, perhaps, in the late stages of advanced cirrhosis. It is difficult to decide to what extent the symptoms of acute yellow atrophy are due to destruction of the liver substance, or to the action of the poison producing the atrophy. The special liver symptoms produced are confined to the appearance of jaundice; the vomiting, the nervous symptoms—such as a tendency to coma and delirium—the pyrexia, may all be ascribed to the action of a toxic agent on the tissues generally, and, for the

present, the subject must be left undecided at this stage. The initial experiments which have been done with hepatotoxin are, however, of interest in this connection (p. 190). In acute yellow atrophy the main change is the profound destruction of the liver cells. The effect on nutrition is due not only to the liver disease but to the greatly diminished quantity of food which is taken. The urea is greatly diminished—in some cases only traces having been found. The amount of nitrogen in the form of ammonia compounds is increased in proportion to the urea. Leucin and tyrosin are sometimes found in the urine, the latter even to the amount of 1.5 gramme daily. The same bodies are found also in the liver substance and other tissues of the body. Their presence has been ascribed to the breaking down of the liver substance, but their formation is more reasonably ascribed to the action of bacteria. The uric acid, both in acute yellow atrophy and in phosphorus poisoning, is not appreciably diminished in quantity, and may be increased. Lactic acid is sometimes found in the urine, as well as albumoses and aromatic oxy-acids (p. 403).

Slow destruction of the liver substance occurs in *cirrhosis* and in carcinoma. In these cases, again, it is difficult to say how far the symptoms observed are due to a destruction of the liver substance, or to the action of some toxic agent. It may be said however, that slowly progressing cirrhosis of the liver has a marked effect on the metabolism of the body, and may, of itself, produce death, even without the production of portal obstruction and ascites. Thus, wasting and bodily weakness ensue, which may be directly ascribed to the liver condition; but whether the hæmorrhages which occur, and sometimes the nervous symptoms, such as delirium and coma, are actually due to the liver disease, it is impossible, at present, to say. Pyrexia is observed in some cases of cirrhosis. The same difficulty in its explanation exists, as with the symptoms just discussed. It is present even when there is no obvious sign of infection, such as tuberculosis. The destruction of the liver, which occurs in cirrhosis, undoubtedly predisposes to bacterial infection of one or other part of the

body, the disease tending to lessen the resistance of the body to infection. The liver being also a destroyer of poisons, the body is more readily affected by powerful drugs than in health. In cirrhosis of the liver there is damage to the liver cells, which are atrophied by pressure, and obstruction to the portal circulation. The effect on nutrition is dependent on these two factors, as well as on the diminished quantity of food and on the occurrence of hæmorrhage and of diarrhœa. There is, as a rule, a diminished excretion of nitrogen which appears to be chiefly due to the condition of partial inanition, although in some cases the nitrogen equilibrium appears to be normal. Moreover, the nitrogen excreted, although for the most part existing in the form of urea, shows an increase in the amount of ammonia compounds which are present in the proportion of 8 to 12 per cent. to the total nitrogen excretion, as compared with 2 to 5 per cent., which is the normal amount. This increased excretion of nitrogen in the form of ammonia is at the expense of the amount of urea, and is no doubt to be ascribed to the inefficient transformation of ammonia compounds into urea by the liver cells, which are in part destroyed. The amount of uric acid is normal. The secretion of uric acid is not affected by liver disease, even the severest form, such as acute yellow atrophy. No leucin or tyrosin is found in the urine, and albumosuria does not occur. There is a considerable quantity of urobilin in the urine.

CHAPTER XVI

THE EFFECTS OF DISEASE OF THE KIDNEYS

A CERTAIN degree of functional activity of the kidneys is essential to life. This is due to the fact that the kidney excretes certain substances which are the products of nitrogenous metabolism (such as urea and uric acid) or are the products of bacterial decomposition occurring in the intestine. The urine is the main channel for the excretion of the final products of nitrogenous metabolism, but these products are not of themselves poisonous, and so it is not simply their retention in the body which leads to death after cessation of kidney function. The salts of potassium which occur in the urine are poisonous when administered in large doses either to the human being or to animals; but besides this, damage to the kidney has been shown to have a profound effect on the metabolism of the body in a manner as yet unexplained.

If the excretion of urine is stopped death ensues, as is seen when double nephrectomy is performed, both ureters are ligatured, or, as in rare cases in man, when coagulation necrosis of the cortex results from thrombosis of both renal arteries. The results observed in complete cessation of the kidney function show a series of symptoms which are fairly characteristic. Experimentally, there is no repeated vomiting, no convulsions, only occasional slight dyspnœa and a fall of temperature, with wasting and muscular weakness. The duration of life is from three to five days in animals. In man, complete cessation of the renal functions is observed in cases of impaction of a calculus in both ureters; in the removal of one kidney or in the impaction of a calculus in the ureter, the other kidney having

been totally destroyed by disease; and in the rare cases already mentioned of coagulation necrosis of the cortex. The duration of life in such cases is from seven to fourteen days, and the symptoms observed are mainly contraction of the pupils, muscular weakness and a subnormal temperature. Sometimes there is severe vomiting, but there is no loss of consciousness, and no convulsions are seen.

The urine itself is poisonous. In rabbits, 25-75 c.c. per kilo. of body weight causes death. The toxicity varies in different diseases (Bouchard). The effects produced are convulsions or coma, with contraction of the pupils and failure of respiration, and have been ascribed to the poisonous action of the salts of the urine and certain unknown substances. The toxicity of the urine is said to be diminished in uræmia.

It is important to consider the effect of the partial loss of the kidney substance on the secretion of urine and on the general metabolism of the body (Bradford). If part of one kidney is removed in a dog the only effect noted is an increase in the amount of water secreted, that is, *polyuria*. If, in addition to the first operation, the other kidney be removed, there is a persistent and great increase in the amount of water excreted, but nothing further is observed if the amount of kidney substance left is equal to one-third of the total kidney weight. The removal of three-quarters of the total kidney weight is fatal, and, besides the polyuria observed in the other experiments, the animal dies greatly wasted, showing a fall of temperature and occasionally diarrhœa. There is a great accumulation of urea in the blood and tissues, and to the excretion of this the polyuria is directly due. Coma, convulsions, dyspnœa or vomiting are not observed, and there is no appreciable increase in the arterial blood-pressure.

The removal, therefore, of the greater proportion of the kidney substance leads to the accumulation of urea in the blood and tissues, and to its increased formation, the loss of kidney substance having a profound effect on the proteid metabolism of the body. It has been suggested that this effect is due to the absence, following destruction of the kidney substance, of some internal secretion. There is, however, no evidence of this, as in the case of the thyroid, pituitary body and the suprarenal

bodies, and the great transformation of proteid into urea which occurs as the result of removal of three-quarters of the kidney substance is as yet unexplained. This removal does not reproduce the symptoms of uræmia, as they are seen as the result of disease of the kidneys in man (p. 393).

Destruction of the Kidney Substance in Disease.—The kidney substance is damaged to a greater or less extent in diseases of various origin.

1. In Bright's disease, which may be divided into the acute; chronic parenchymatous, mixed fatty and fibroid; and the granular contracted kidney, the chief change is inflammatory. Into the various forms and degrees of these conditions it is not necessary here to enter, but to them generally belongs the fact that the stress of the disease falls on the cortex; the Malpighian bodies (the filtering apparatus) and the convoluted tubules (the secretory apparatus) being mainly affected, the blood vessels of the former being obliterated and the cells of the latter undergoing degeneration.

The extent of the damage in Bright's disease varies considerably, and is to be gauged by the extent to which the different parts mentioned are diseased.

2. In lardaceous disease of the kidneys the small vessels of the cortex are mainly affected, more particularly in the Malpighian capsules. The convoluted tubules are secondarily affected, being either fattily degenerated or compressed by fibroid tissue. In the former case the degeneration is secondary partly to the neighbouring lardaceous disease of the vessels, and partly to the disease producing the lardaceous disease, namely, suppuration, tuberculosis, or syphilis.

3. Extensive caseous tuberculosis of both kidneys may occur, and so end life; so with double calculous pyelitis. Tumours are usually unilateral, especially when primary.

In all these instances the pathological question to be considered is a partial damage to the kidney substance, the remainder of the kidney being practically normal and still capable of secreting. The effect of such disease from the point of view of damage to the kidney is to be gauged by

the extent of damage, or rather by the amount of normal kidney substance remaining. In calculous pyelitis and in tuberculosis, in addition to the damage to the kidney there is the process of infection.

4. Double hydronephrosis must be placed in a different category from the last group, inasmuch as in the case of Bright's disease the damage to the kidneys is general. Double hydronephrosis arises from pressure on both ureters in the pelvis or obstruction to the passage of urine from the bladder either by enlargement of the prostate or by stricture of the urethra It also occurs as the result of a new growth obstructing the orifice of both ureters and the bladder. Double hydronephrosis is incompatible with life. The obstruction to the flow of urine, although not complete, leads to dilatation of the pelvis of the kidney, and to the pressure of the fluid on the kidney substance, which becomes anæmic, fibroid and atrophied.

Effects of Bright's Disease on the Kidney Functions.—The effect of Bright's disease on the kidneys is to be discussed (1) as to the effect on the secretion of urine, (2) as to the effect on the circulation, and (3) as to the effect on the general metabolism.

1. The effect on the urine in Bright's disease is observed not only in the amount of water secreted, but in the amount of the nitrogenous substances which are found in it. The amount of water varies considerably, and is to some extent in inverse proportion to the œdema (p. 275). Circumstances, however, which more materially diminish the secretion of water, are the degree of congestion of the kidney substance, especially of the Malpighian capsules and the affection of the convoluted tubules. Thus a diminished amount of water is observed in acute and in chronic parenchymatous nephritis; while in the granular contracted kidney not only is the amount of water not diminished but it is increased, diminishing only in the periods of subacute congestion which occur in this variety of kidney disease. It must be considered, therefore, that one of the chief conditions diminishing the

quantity of water is congestion of the organ, and more particularly of the cortex. Blocking of the tubules by swollen cells acts only slightly in diminishing the urine. If, however, there is swelling of the cells over a large area of the kidney, as in some forms of acute and of chronic parenchymatous nephritis, the kidney becomes anæmic from pressure on the blood vessels, and so less urine is secreted. This swelling of the kidney cells is an important fact in the pathology of the organ.

2. The effect of kidney disease on the circulation, and the effect of the circulation on the secretion of urine, are of great importance. An increase in the quantity of urine is caused by an increase in the general blood pressure, which produces a rise of intracapillary pressure. This is caused by an increase of cardiac action, by contraction of the arterioles, or by the production of hydræmic plethora, as in the drinking of large quantities of water. Relaxation of the renal arterioles also leads to an increased quantity of urine. The opposite conditions to the above lead to a decrease in the quantity. These physiological facts have a bearing on the amount of urine excreted in disease of the kidneys. In acute Bright's disease there may be a condition of increased arterial pressure produced by a contraction of the arterioles. This does not, however, lead to any increase in the amount of urine excreted in that disease, an increase being prevented by the permanent congestion of the organ, and thus the relative stagnation of the blood in it, as well as by the swelling of the cells of the convoluted tubules. The condition is not the same in the granular contracted kidney or in some forms of mixed fibroid and fatty kidney in which there is an increased general arterial pressure with hypertrophy of the left ventricle of the heart, and an increased quantity of urine is excreted. The increased arterial pressure produces an increased flow of urine in this case because the organ is not so uniformly diseased nor swollen as in acute Bright's disease, so that the effect of the increased blood pressure can be exerted on the more or less normal parts of the kidney substance.

An increased flow of urine is also observed, at any rate in the early stages, in lardaceous disease of the kidneys, and

in this case the increased flow is more particularly to be ascribed to an increased permeability of the walls of the capillaries in the Malpighian bodies of the kidney which are affected by the lardaceous degeneration.

The presence of an increased arterial blood pressure, when temporary, as in acute Bright's disease, or permanent, as in granular contracted kidney, whatever its mode of production, must be considered as in part a compensatory effort to repair the damage to the organ. Its occurrence in acute Bright's disease is not yet explained, but inasmuch as it is sometimes temporary and is relieved or removed by bleeding, by purgatives, or by the administration of nitrites, such as amyl nitrite and erythrol nitrate, it is plausibly attributed to a generalised spasm of the arterioles produced perhaps by some poison circulating in the blood.

In chronic granular contracted kidney, on the other hand, the long-continued high arterial pressure is associated with hypertrophy of the left ventricle and with a structural change in the arterioles in the form either of a fibrosis (arterio-capillary fibrosis), or of a spasm of the arterioles with or without hypertrophy of the muscular coat. The degree of arterial pressure in granular contracted kidney varies from time to time, and is reduced by the same means as in acute Bright's disease, though these means have a less effect than in the acute disease. It is probably correct to consider this increase of blood pressure as compensatory, inasmuch as it tends to increase the secretion of the kidney, the damage to which tends to diminish the secretion. As has been stated, in acute Bright's disease this compensatory effort is not very effective in increasing the secretion; whereas, in the granular contracted kidney, the compensatory effort on the part of the circulation produces, at any rate for long periods, an increased secretion.

A certain degree of high arterial pressure is of service, and indeed a necessity, in chronic granular contracted kidney. The degree of arterial pressure varies from time to time. It is increased by an exacerbation in the disease of the kidneys, whether by an increase of the fibrosis or by the attacks of subacute congestion to which such kidneys are liable. It is

also increased by diseased conditions elsewhere in the body, such as the occurrence of a febrile disorder, of bronchitis, of constipation, or any form of intestinal intoxication. It is diminished and sometimes completely abolished mainly by failure of the heart, whether by fibroid or fatty disease of the left ventricle, or degeneration of the muscular substance consequent on an infective disease. It is also diminished by profuse diarrhœa or sweating.

When the high arterial pressure diminishes and becomes subnormal, the amount of urine also diminishes. The amount of urine may also diminish with a continuance of the high arterial pressure, and this occurs when congestion of the organ supervenes, and at the onset of uræmia.

Uræmia.—Uræmia is a common termination of all forms of Bright's disease, whether acute, chronic parenchymatous, or fibroid, as well as of other diseases of the kidneys, in which both organs are affected. It must be distinguished from the results of complete (obstructive) suppression of the urine, which occurs in the human being from the impaction of a calculus in both ureters or from the removal of both kidneys, the results of which have been already described (p. 387). In true uræmia the symptoms observed are referable partly to the digestive system, partly to the respiratory system, and partly to the nervous system, but all the effects are due to an action on the central nervous system. Uræmia may occur with or without the signs of an increased arterial pressure. Persistent nausea, or vomiting, or diarrhœa, are observed with or without dyspnœa, and there are cramps, muscular twitchings or convulsions, with contracted pupils, delirium, maniacal attacks, paralysis, or coma. In individual instances one or other of these effects becomes prominent. Thus, repeated vomiting may be the chief sign in one instance, dyspnœa in another, headache in another, twitchings or convulsions or contraction of the pupils, with rapid passage into delirium and coma in others.

The explanation which has been offered of the occurrence of uræmia is twofold: that it is due either to œdema and anæmia of the brain, or it is an intoxication affecting chiefly the central

nervous system. It is difficult, however, to understand how œdema or anæmia of the brain can produce the prolonged irritative symptoms characteristic of many cases of uræmia, and the condition appears more plausibly explained by the supposition of an intoxication. What poison it is which produces the symptoms is not known. The retention of the urinary constituents in the tissues has been supposed to be the cause; and Bouchard separated "urotoxins," which he stated were retained in the body in uræmia. Urea, or any other of the nitrogenous bodies, does not produce, when injected, the symptoms of uræmia. It has been suggested that these nitrogenous bodies may by decomposition yield others of a more poisonous nature, such as ammonium carbamide. In this case the intoxication may be due to retention of the urinary constituents in the body. It has also been considered that a new poison might be formed which would produce the symptoms, and some have described such a poison in the blood. Experimental evidence as to the cause of uræmia is not as yet forthcoming.

Changes in Metabolism in Kidney Disease.—The changes in nutrition which are observed in Bright's disease vary considerably, not only in individual cases but in the various forms of the disease, and other factors than the disease of the organ have an important bearing on the changes that occur. The disease of the kidneys itself to a greater or less extent interferes with the excretion of the nitrogenous substances, and in some cases with the excretion of the amount of water. The presence of œdema, as in acute Bright's disease and chronic parenchymatous nephritis, leads to other changes in nutrition. The changes in the circulation, either in the direction of increased arterial pressure, as in acute Bright's disease and granular contracted kidney; or of diminished arterial pressure, as in some cases of chronic parenchymatous nephritis and the later stages of all forms, lead to further changes in the general nutrition. Anæmia and loss of body-weight are the effects of the prolonged disease.

Proteid Metabolism in Renal Disease.—A diminished

quantity of food is taken in acute Bright's disease and in some cases of chronic nephritis. The secretion of the gastric juice is not affected in the majority of uncomplicated cases of granular kidney, in which there is general well-being of the individual; but in acute and chronic parenchymatous nephritis there may be a great diminution in the amount of hydrochloric acid secreted by the stomach, leading to a diminished digestion of proteid food. The absorption of the food in the intestine is sometimes markedly affected in acute and chronic Bright's disease. It varies considerably, and may not differ from the normal, but in some cases the amount of nitrogen present in the fæces is considerably greater than in the healthy individual on the same diet.

The metabolism of the nitrogenous constituents of the body varies considerably in individual cases and in the various forms of the disease. Three different classes may be recognised (Von Noorden). In one class the nitrogenous equilibrium is maintained; in a second class the nitrogenous excretion is less than the intake, so that there is a retention in the body (in the blood and tissues) of the final products of nitrogenous metabolism. In a third class of cases more nitrogen is excreted than is taken in. The first class of cases includes those in which there is general well-being, in which the nitrogenous metabolism is not upset. The second class of cases includes those in which, owing to the extensive disease of the kidneys, elimination of the nitrogenous excretives is diminished, and so they are retained in the body. In the third class of cases the increased nitrogenous excretion is due either to resumption of the function of the kidney to a partial extent so that the retained nitrogen is excreted, or to increased breaking down of the nitrogenous tissues, or to both these events.

It is thus seen that the commonly accepted statement that the nitrogenous excretion is diminished in Bright's disease is not to be taken unreservedly. The question must be considered not only in relation to the amount of food taken, but also to the amount of retention of nitrogenous excretives in the body. In acute nephritis, during the period of great diminution of urine, there is a deficiency of food taken, but

the amount of nitrogen excreted with the urine is much less than that contained in the food. There is therefore nitrogenous retention. When improvement, however, occurs, the nitrogenous excretion increases—sometimes considerably—and this may be accounted for partly by the excretion of the retained products of nitrogenous metabolism, and partly by an increased activity on the part of the tissues. As an example, the following may be quoted (Von Noorden):—

A child with scarlatinal nephritis received daily about 8 grammes of nitrogen in the food. At the commencement of the illness, that is, during the acute stage, the amount of nitrogen excreted on three days was found to be respectively 3.2 grammes, 6.5 grammes and 4.5 grammes, that is greatly less than the amount of nitrogen taken in as food. When improvement, however, occurred, the amount of nitrogen daily excreted was largely increased, being 14.2 grammes and 16.1 grammes in two daily estimations.

In chronic nephritis, in many instances the amount of nitrogen in the urine is greatly diminished, to the extent, it may be, of several grammes daily. This applies more particularly to cases of chronic parenchymatous nephritis and to advanced cases of granular contracted kidney. In some of the latter cases, however, the nitrogenous excretion may be greater than the nitrogenous intake. Thus, in a case of granular contracted kidney in which 15.5 grammes nitrogen were present in the daily diet, 20.1 grammes nitrogen were found to be excreted. At a later period, however, in the same case, retention of nitrogen occurred. Thus, on the same diet, during a period of five days, it was found that instead of excreting 75.5 grammes nitrogen to maintain the nitrogenous equilibrium, only 53.18 grammes were excreted, leaving 24.32 grammes retained in the body.

Retention of the Products of Nitrogenous Metabolism.—The retention of the products of nitrogenous metabolism which has been mentioned above refers almost solely to the retention of urea. In some cases uric acid may be retained, but not commonly; while creatinin, some amount of ammonia salts

and of potassium salts, appear to be retained. Xanthin is fairly readily excreted, and ammonia salts are partly excreted and partly retained. The urea is increased in the blood. The normal amount obtained varies from 0.01 to 0.05 per cent.; in Bright's disease, 0.1 to 0.3 per cent. may be found. In uræmia the urea is in greatest amount, and may be as high as 0.8 per cent. Urea is also found increased in the tissues and in the œdema fluid, which may in some cases contain comparatively large quantities. Thus in œdema fluid 0.19 per cent. and 0.359 per cent. have been found. Retained urea, more particularly in cases of uræmia, is sometimes found in the secretions of the body, most commonly in the saliva, and to a much less extent, in the gastric juice, the milk and the sweat. The sweat may, however, contain an appreciable quantity of urea in cases of uræmia. The presence of urea in these secretions is sometimes referred to as "the vicarious excretion of urea." Its presence is due, however, only to the passage of a highly soluble salt into the liquid which is given out from the mucous membrane or glands.

The Blood in Bright's Disease.—This shows great variation. In cases where there is well-marked œdema the blood is in a hydræmic condition (p. 275), and the specific gravity of the serum is diminished, being from 1020 to 1025 as compared with the normal of 1029 to 1031. In the majority of cases no great change occurs in the corpuscles, but the red discs may be affected (p. 304). The alkalinity of the blood is greatly diminished, more particularly in uræmia.

The excretion of salts in the urine differs from the normal. There is a retention of potassium salts in the blood. The amount of chlorides in the urine is, as a rule, equal to the amount present in the food, but these are diminished when there is nitrogenous retention. The sulphates rise and fall with the amount of nitrogen excreted. This variation in the salts is to be ascribed to the renal condition.

Changes in the Urine in Disease.—The composition of the urine is frequently a valuable index in disease. Not only does

its composition show to an appreciably accurate extent the amount of proteid metabolism in health, but in disease as well there are substances present which are absent in health, such as blood, albumin, sugar and fat, which are valuable guides in the estimation of disease processes.

The normal amount of urine passed daily varies from 1200 to 1700 c.c., about equal to 1 c.c. per kilo. of body-weight per hour. The specific gravity varies between 1015 and 1025, and depends on the amount of urinary solids.

Composition of Urine :—

1. *Nitrogenous Substances*—		*Amount Daily Excreted*—
Urea . .	CH_4N_2O	33.18 g., or 84 to 87 p. c. of total N.
Ammonia .	NH_3	0.77 g., or 2 to 5 p. c. of total N.
Uric Acid .	$C_5H_4N_4O_3$	0.55 g. to 0.75 g., or 1 to 3 p. c. of total N.
Hippuric Acid .	$C_9H_9NO_3$	0.4 g.
Creatinin . .	$C_4H_7N_3O$	0.9 g.
Xanthin Bodies.		0.02 to 03 g. — or 7 to 10 p. c. of total N.

These nitrogenous bodies are not of the same significance from the point of view of disease. Whereas urea and the ammonium salts are derived solely from the proteid metabolism in the body, creatinin and hippuric acid depend on the kind of food taken, creatinin being derived from the creatin of flesh, while hippuric acid is derived mainly from vegetable food. Uric acid and the xanthin bodies may be grouped together, being partly derived from food and partly from proteid metabolism, and mainly from the metabolism of nucleo-proteid. They have therefore an important bearing on conditions in which nucleo-proteid is set free in the body (p. 437).

2. *Mineral Salts*—		*Daily Amount Passed*—
Sulphuric Acid .	SO_3	2 g.
Phosphoric Acid .	P_2O_5	3.5 g.
Chlorine.		7.5 g.
Sodium.		11.09 g.
Potassium.		2.5 g.
Calcium.		0.26 g.
Magnesium.		0.21 g.

These salts, however, are not of equal significance. Some, such as chloride of sodium and potassium, magnesium and calcium phosphate, are taken in with the food. The sodium chloride, however, differs from the phosphates in the fact that the amount excreted in the urine balances the amount taken with food; there is therefore a chlorine equilibrium in health. The phosphates are partly derived from food—more particularly vegetable food—but also are the result of proteid metabolism, and mainly of nucleo-proteid and of lecithin. Sulphates, on the other hand, are not taken in with food, and result from proteid metabolism. Part of the sulphates appear as metallic salts, and part are combined with organic substances and appear as ethereal hydrogen sulphates (p. 403). The sulphates in urine have therefore a peculiar significance. The amount present is proportional to the proteid metabolism occurring in the body.

3. *Urinary Pigments* (p. 402).

Composition of Urine in Disease.—It is evident that, in judging of the relation of the composition of urine to disease processes, there are several points requiring careful consideration. As regards *nitrogenous substances*, the amount of urea alone cannot be taken as a guide to the degree of proteid metabolism occurring in the body. All the nitrogenous constituents must be reckoned together. The total nitrogen in the urine does not, however, in disease or in health, give a correct indication of the amount of proteid metabolism, unless the amount of nitrogen in the food and that passed in the fæces be estimated. If this is done it is possible to determine, in a diseased condition, whether the nitrogenous equilibrium is maintained or not. The amount of urea present in the urine is an indication of a diseased condition only when it is greatly diminished or greatly increased. It is increased, for example, in pyrexia, which is the best example of an increased excretion of urea. There is, however, an increased formation of urea in many forms of renal disease, but, as in this case it is frequently retained in the body, the

amount in the urine is no gauge of the proteid metabolism. In this case, therefore, there is increased formation of urea and diminished excretion. Greatly diminished formation of urea and diminished excretion occurs more particularly in extensive destruction of the liver. A diminished quantity of urea in the urine, with an increased quantity of ammonium salts, especially when associated with the presence of lactic acid, indicates a diminished formation of urea by the liver. It therefore occurs more particularly when the liver is diseased, and most markedly in cases of destruction of the liver cells as in acute yellow atrophy (p. 384).

The amount of *uric acid* in the urine is not so important an indication in disease as is sometimes thought. It is partly a product of proteid metabolism, and is greatly increased, as far as is known, in only one disease—leukæmia. It is decreased in quantity in gout. Together with the other purin bodies it is increased by food containing nucleo-proteids, such as solid organs, sweetbread, thymus, liver, etc., taken as food (p. 437).

Oxalic acid is present in the normal urine, to the amount of 50 mgm., daily. It is mainly derived from the oxalates of vegetable food. It is increased in the urine when an excess of food containing oxalates is eaten, as well as in diabetes and in the obese. In diabetes, its increase is probably to be explained by an incomplete combustion of carbohydrates. *Cystin*, which is an amido-acid containing sulphur, may occur in certain individuals in excess, to the amount of 0.5 to 1 gramme daily. Cystinuria occurs in families.

While the sulphates and phosphates are increased by an increase in the proteid metabolism, the amount of chlorine in the urine is affected by the amount taken in the food, and in disease by the amount secreted in the gastric juice and by certain infective conditions. In the former case the amount of chlorine in the urine is increased, and in the latter case diminished (p. 45).

The amount of water daily excreted is sometimes greatly increased and sometimes diminished. It is increased in diabetes mellitus, diabetes insipidus, in granular kidney, in the early stages of albuminoid kidney, and after certain nerve attacks

(neuroses), such as those of migraine, epilepsy, hysteria and asthma. The increase in the urinary water, in these cases, is not due to the same cause. Thus, in diabetes insipidus and in neuroses, it appears mainly to be dependent on a primary nerve condition, perhaps directly affecting the vaso-motor system of the renal vessels. In granular contracted kidney and in albuminoid kidney the kidney substance is destroyed, and the increased amount of urine is partly due to more ready filtration through the diseased vessels, and in granular contracted kidney is aided by the condition of high arterial pressure present. In diabetes mellitus the polyuria is dependent on the sugar present, which increases transudation through the renal vessels. The urinary water is diminished in many conditions of disease. Physiologically, the amount bears an inverse proportion to the amount of water given off in the perspiration. Thus the urinary water is diminished in profuse perspiration. A similar effect is observed in profuse sweating in disease as well as when there is profuse diarrhœa, as in cholera and other acute intestinal conditions. A diminished quantity of urinary water is observed in pyrexia, and is in this condition associated with a general diminution of the activity of the tissues. The diminished urinary water which occurs in acute nephritis and in chronic parenchymatous nephritis results directly from the disease of the renal tissue whereby the transudation of the liquid is hindered. Such a diminution may occur when the general blood pressure is increased or diminished.

The specific gravity of the urine in disease varies within considerable limits from 1002 to 1050 or over. Very low specific gravity occurs in diabetes insipidus and after drinking large quantities of water, in both cases the proportion of urinary solids being low. A diminished specific gravity—1008 to 1012—occurs in chronic Bright's disease, owing partly to the diminution in the proportion of urinary solids, and partly to the presence of albumin. An increase in the specific gravity of urine occurs in concentrated urines from whatever cause, as in pyrexia, profuse sweating and diarrhœa, and in certain intestinal conditions in which there is a large amount

of unabsorbed liquid in the intestine. One of the main causes of increase in the specific gravity is the presence of glucose in the urine, as in diabetes.

Pigments in the Urine.—The most abundant yellow pigment in the urine is *urochrome*. It may be increased in disease, but this increase is of no particular pathological significance. *Urobilin* is another pigment, which exists in very small quantity in normal urine, probably as urobilinogen, which on exposure becomes oxidised to urobilin. Urobilin is one of the iron-free derivatives of hæmoglobin, and is identical with the stercobilin of the fæces. It is sometimes called normal urobilin as distinguished from pathological urobilin. Recent chemical research has, however, shown that the two bodies are probably identical. It closely resembles hydrobilirubin, which is a reduced product of bilirubin. Hydrobilirubin is said to contain more nitrogen than urobilin and to give a different spectrum. Urobilin is increased in the urine in different pathological conditions, and its source of origin is either bile or blood pigment. Thus, urobilinuria occurs in many cases of acute infective disease, as the result of large blood extravasations and of hæmolysis, in pernicious anæmia and in liver disease. It is also observed in acute and chronic alcoholism, and in the later stages of uncompensated valvular disease of the heart.

Uroërythrin is a red pigment giving the colour to the deposit of urates in the urine. *Urohæmatoporphyrin* is derived from blood pigment, and can be prepared by the action of reducing agents on hæmatin. It has been found in the urine in many different conditions, such as Addison's disease, cirrhosis of the liver, Hodgkin's disease; and in infective processes, such as acute rheumatism, pneumonia, pericarditis, peritonitis, measles, meningitis, and typhoid fever; as well as following the administrations of sulphonal.

Melanin is found in urine in cases of melanotic sarcoma; the condition is called melanuria. Other pigments in the urine are derived from aromatic substances, which are discussed in the next section.

Aromatic Substances in the Urine.—These substances are present in normal urine, and are increased in certain pathological conditions. The aromatic substances are derivatives of benzene, and are formed mainly by the action of putrefactive bacteria on proteids. In the body they arise almost solely from putrefactive decomposition or other bacterial action in the intestinal tract, or from foul abscess cavities in the chest, as occurs in bronchiectasis and empyema. Formed in the intestine, they are absorbed into the tissues, and before being excreted in the urine, usually undergo some transformations. A few are excreted unchanged. Still fewer undergo some form of destruction in the body, while the majority are excreted in the urine in combination with sulphuric acid as ethereal hydrogen sulphates. The amount of sulphuric acid, in combination with aromatic substances daily excreted in the urine, varies from 0.12 to 0.25 gramme; over 0.3 gramme daily being considered abnormal. The proportion of ethereal hydrogen sulphates to the total sulphates is as 1 to 12 or 15. The amount of aromatic substances in the urine is proportional to the extent of putrefactive processes in the intestine (Baumann). They are diminished in quantity in fasting dogs, especially if diarrhœa be artificially produced; and also in human beings when diarrhœa is produced by the administration of salts. The administration of so-called internal antiseptics appears to have no influence on the amount in the urine. The amount of these substances in the urine bears a direct relation to the amount and character of the food taken. They are only formed from proteids, and thus with a large proteid diet imperfectly digested, they are increased in the urine. With a large carbohydrate diet the amount is diminished. In disease they are increased in all forms of putrefactive decomposition in the intestine, both with and without organic disease, as, for example, in cancer of the digestive tract. They are also increased in other forms of cancer, such as that of the uterus and mamma, the new growths becoming infected with micro-organisms. In diabetes, owing to the large amount of proteid food taken, they are increased even to the amount of 0.5 gramme daily if the

food is imperfectly digested and absorbed. If digestion is good, they are not appreciably increased. In severe anæmias, such as pernicious anæmia and leukæmia, the amount of indican in the urine is increased; but in chlorosis, although in some cases an increase is observed, as a rule no such result occurs. The same irregularity in the increase is observed in jaundice, while the aromatic substances are diminished in inanition.

The decomposition of proteid gives rise among other substances to a series of bodies belonging to the aromatic group of organic bodies (p. 72). These may be classified as follows:—

1. *The Phenol Group*, comprising tyrosin, aromatic oxy-acids, phenol, cresol; and derivatives of these, such as phenyl-acetic acid and phenyl-propionic acid.

2. *The Indol Group*, comprising indol, skatol, and derivatives of these.

None of these bodies is formed in the normal metabolism of the tissues. Tyrosin is produced in pancreatic digestion, but all the bodies are the result of bacterial action. The substances to be discussed are of some importance in disease, and belong to both groups of aromatic substances. Benzene is oxidised after absorption to a hydroxyl-derivative of phenol with the formation of small quantities of pyrocatechin and of hydrochinon. The phenol compound combines with sulphuric acid, giving rise to a phenyl-sulphuric acid which is excreted in the urine in combination with sodium or potassium. In some cases the phenol combines with glycuronic acid and is so excreted. Traces of phenol (C_6H_5OH) and cresol ($CH_3C_6H_4OH$) are found in normal urine, about 0.003 gramme daily. Pyrocatechin and hydrochinon ($C_6H_4(OH)_2$) are found in small quantities in the urine, the former giving a dark green coloration on exposure to the air. Pyrocatechin and hydrochinon are found in large quantities in the urine in carboluria. Cresol is not infrequently oxidised in the body and excreted as cresyl-sulphuric acid.

Other compounds of phenol found in the urine are aromatic carboxy-acids. Thus phenyl-proprionic acid gives rise in the body to benzoic acid, which, uniting with glycocoll, forms hip-

puric acid, which is excreted in the urine. Another derivative is trihydroxy-phenyl-proprionic acid $(OH)_3 . C_6H_2C_2H_4 . COOH$: it is sometimes the cause of the darkening of the urine in "alcaptonuria." In this condition dihydroxy-phenyl-acetic acid has also been found, $(OH)_2C_6H_2 . CH_2 . COOH$, which is also called homogentisic acid. Alcaptonuria is a curious condition resembling carboluria, in which the urine when alkaline becomes brown, first at the surface and then throughout, till it is nearly black. It is not associated with any special diseased condition, although it occurs in families. The colour is due to the change in the aromatic substances in the urine produced by exposure to air. Some of the substances producing it may be derived from tyrosin.

Indol and skatol differ from the preceding group in containing nitrogen, and are excreted in combination with sulphuric acid. Indol is excreted as indoxyl-sulphuric acid in combination with potassium; this compound is called indican $(C_6H_4 . NH . CH . C . KSO_3)$. The daily amount varies from 0.005 to 0.02 gramme. Skatol is excreted as skatoxyl-sulphuric acid. Both bodies yield green, blue and red pigments on oxidisation.

Blood and Bile in the Urine.—The presence of bile in the urine has already been discussed (p. 368), and that of blood partly (p. 325). With regard to blood all that remains to be said is that the presence of blood in the urine in the form of red corpuscles, white corpuscles, serum and fibrils of fibrin occurs in disease of the genito-urinary tract of various forms—disease of the kidneys, lesions of the ureters, as by a stone, ulceration of the bladder and of the urethra. Hæmaturia may also occur from general disease, either during the excretion of poisons through the kidneys, as in phosphorus and cantharides poisoning, or as the result of the presence of free hæmoglobin in the blood. In the latter case, the colouring matter may be either in the form of hæmoglobin or of methæmoglobin.

Albuminuria.—The presence of albumin in the urine occurs in many different conditions. Physiological albuminuria is

described, but it is doubtful whether such a condition really exists. It is said to occur after prolonged muscular exercise, as in soldiers after a long march; also from the application of cold to the body. It may be that in such cases there is a temporary congestion of the kidneys leading to a congestive albuminuria. What may be considered a true physiological albuminuria occurs after the taking of large quantities of egg albumin in some individuals, the albumin being in part excreted in the urine.

The presence of albumin in the urine is in the great majority of cases a sign of disease, and may be ascribed to mainly three conditions:—(1) An alteration in the circulation of the kidneys, mainly in the production of congestion—*congestive albuminuria;* (2) as the result of a toxæmia—*toxic albuminuria;* and (3) disease of the kidney substance, as in Bright's disease—*renal albuminuria.*

The form of proteid found in the urine in albuminuria is almost solely serum albumin. In some cases serum globulin is also found, and fibrinogen is present in cases of chyluria only. The amount of serum globulin is very small, and is said to be greater in those cases in which the urinary water is diminished, and in amyloid disease of the kidneys. The amount of albumin varies according to the condition producing the disease. Thus it is usually slight in congestive and toxic albuminuria, while it is great in Bright's disease, in both the acute and chronic parenchymatous forms, and in amyloid kidney, but is small in granular contracted kidney. The amount of albumin present varies between 1 and 4 per cent.

1. *Congestive Albuminuria.*—Albuminuria may be produced experimentally, by suddenly increasing the blood pressure in the kidneys, but mainly by the increase of the pressure in the renal veins; ligature of the aorta below the kidney, and extirpation of one kidney; ligature of the aorta above the renal arteries; and compression of the trachea leading to asphyxia. Compression of the renal artery for a time, and re-establishment of the circulation, also leads to albuminuria,

probably by damaging the nutrition of the renal cells. In disease, congestive albuminuria is frequently noted, more particularly in mitral disease with venous stasis, and in asphyxial conditions with an increase of the venous pressure throughout the body.

2. *Toxic Albuminuria.*—This occurs in disease mainly in infective conditions. Albuminuria is a most constant sign in pneumonia, erysipelas, diphtheria, scarlet fever and smallpox. It is not so common in typhoid fever, in measles, dysentery, or rheumatism. It is said to be common in malaria. In these conditions the albuminuria disappears two or three days after the cessation of the pyrexia. Globulin is frequently present with albumin in febrile albuminuria, and may be one half or more of the total proteid present. It is probable that febrile albuminuria is due to the excretion through the kidney substance of bacterial toxines. Some of these, indeed, have a special action on the kidney substance, as shown in the production of cloudy swelling, seen more particularly in diphtheria and scarlet fever. Albuminuria may be due to the taking of poisonous chemical substances, such as cantharides, turpentine and mercurial salts. In all these cases the condition is due to the direct action of the poisonous substance on the kidney.

3. *Albuminuria due to Renal Disease.*—The albuminuria present in Bright's disease is due to the damage both to the glomeruli and to the renal tubules, whereby a greater or less quantity of the albumin of the blood plasma escapes into the urine. In this case, however, besides the damage to the renal tubules, the condition of congestion of the organ leads to albuminuria.

Several questions arise with regard to the effect of albuminuria in relation to Bright's disease. It is a loss of proteid to the body, and how far this loss is important has to be considered. Moreover, the effect of nitrogenous food on albuminuria is an important point. The amount of albumin lost is greatest in acute Bright's disease and chronic parenchymatous nephritis, and in the acute exacerbations occurring in granular contracted kidney. In chronic parenchymatous nephritis the loss may be considerable, and be extended over

weeks or months, but the amount lost varies considerably not only in individual cases, but from day to day, and at different periods of the day, even if the individual be on the same diet. In a case of parenchymatous nephritis, during twenty-four days 227 grammes of albumin were present in the urine, and thus lost to the body. This is equivalent to a loss of 9.4 grammes daily (Von Noorden and Ritter). This patient, however, was in a condition of nitrogenous equilibrium owing to the large amount of proteid of the food which was absorbed. The patient received 97 grammes of proteid a day, 87 grammes of which were utilised by the body. The loss of albumin in this case, therefore, was not felt by the individual. If, however, the food is deficient in proteids, the loss of albumin in the urine may be serious from the nutritional point of view.

Albumosuria.—Albumosuria, or peptonuria as it is sometimes called, is a condition quite distinct from albuminuria. Albumoses are sometimes found in the albuminous urine of Bright's disease; they are not, however, excreted by the kidney, but formed in the urine in the bladder or when passed. The amount of albumoses present in such cases increases in the urine on standing, and their presence is due to the action of the pepsin in the urine. The albumoses found in urine are either hetero-albumose (Bence-Jones' albumin) or deutero-albumose. As a rule they are present in solution, but in some cases they form part of the deposit in the urine. Hetero-albumose is precipitated at a temperature between 43° and 50° C., and is also precipitated by acid, the precipitate redissolving on heating. This form of albumin has been found almost solely in osteomalacia, and appears to result from the breaking down of the new cells in that condition. Most forms of albumosuria are due to the presence of deutero-albumose: in some cases proto-albumose has been found. In some cases it is supposed that the albumoses formed in peptic and pancreatic digestion do not completely undergo transformation into the proteids of the body during their absorption, and are thus partly excreted in the urine. Hetero- and proto-albumoses injected into the body pass out in the urine mainly as deutero-albumose. Deutero-albumose, when injected, passes out mainly as pep-

tone, while peptone is excreted unchanged. Albumosuria is as a rule a condition met with in infective processes, such as collections of pus, more particularly empyema, purulent bronchitis, tuberculosis of the lungs and lymph glands, and extensive ulceration of the skin and intestine. Albumoses are present in pus, and no doubt are the source of those found in the urine. The condition is present when no abscess is formed, as in some cases of pneumonia, septicæmia, typhoid fever, measles and scarlet fever, and it is probable that in these cases the albumoses formed by the infective agent are those which are present in the urine. Albumosuria is also present sometimes after parturition, in which case it is ascribed to rapid involution of the uterus. In phosphorus poisoning it has been noted. Albumosuria is mainly associated therefore with some toxic condition, and is, in the majority of instances, due to the formation of the substances in the tissues and their subsequent excretion in the urine.

CHAPTER XVII

THE EFFECT OF DISEASE OF THE DUCTLESS GLANDS ON THE BODY

THE organs of the body comprise those—such as the heart and lungs — which have to do with the circulation and aëration of the blood; those concerned in the neuro-muscular system; and those concerned in the digestion and elaboration of the food taken into the body, such as the salivary glands, pancreas, liver and the glands of the mucous membrane of the gastro-intestinal tract. Connected with excretion are the kidneys and glands of the skin, and with generation are the ovary and testis. Besides these, with their specialised functions, there are certain ductless glands, the functions of which have been until lately very obscure. These are the thyroid, the thymus, the pituitary body, the suprarenal capsules, the spleen and the coccygeal and carotid glands.

The thyroid, thymus and pituitary body are primarily formed by the invasion of the stomodæum (ectoderm) in the embryo, the duct being obliterated. The suprarenal capsules are formed in connection with the Wolffian body, and consist of mesoblast. The spleen consists of mesoblast, which is also represented in the thymus and in the pituitary body.

The knowledge that a gland without a duct is of importance in the healthy body is the result of recent investigations into the effect on the body of the removal of the ductless glands. This effect varies with each gland, and has demonstrated the fact that some of the glands are essential to life. These are the thyroid, the pituitary body, and the suprarenal bodies; while removal of the spleen or thymus does not endanger life.

The removal of the thyroid induces a diseased condition in the body, which is the counterpart of the disease which occurs naturally—myxœdema. The removal of the pituitary body leads to definite symptoms in animals; while the result of the removal of the suprarenal bodies is to a great extent the symptoms which occur naturally in Addison's disease.

The effects of removal of the liver have already been discussed (p. 384). The presence of the liver is essential to life, and its removal has a profound effect on the chemical changes in the body. The effect of removal of the kidneys is discussed in Chapter XVI. The loss of a certain proportion of the kidney substance has also a profound effect on the nutritional or metabolic changes which occur in the body.

The salivary glands, as well as the mammary glands, may be removed without the production of symptoms; but the removal of the pancreas, a gland whose main function is apparently the secretion of a digestive juice acting on proteids and carbohydrates, leads to disease and the production of glycosuria—that is, to an effect on metabolism (p. 444).

The changes resulting from the removal or disease of the thyroid, the pituitary body and the suprarenal capsules, are partly due to a changed metabolism of the body, but are also shown in a profound effect on the nervous system, and in some cases on the circulation.

The Thyroid Gland.—The diseases which have to be discussed in relation to the thyroid gland are on the one hand myxœdema, cretinism and cachexia strumipriva; and on the other hand, exophthalmic goître (Graves' or Basedow's disease). The three first diseases show the same pathological changes, myxœdema being the natural disease in adults, cretinism the same disease in infants or children, and cachexia strumipriva, a similar condition which supervenes in man as the result of the total removal of the thyroid gland. In most of the symptoms myxœdema is in strong contrast with exophthalmic goître. Thus, in myxœdema, there is an increase in the size of the body, a dry skin, apathy leading to stupor, tremor, a low body temperature with a low blood pressure

and slow pulse due to a diminished cardiac action, and an atrophied thyroid: while in exophthalmic goître there is wasting, nervous or even maniacal excitability, tremor, an increased blood pressure and rapid action of the heart, with a normal temperature (sometimes pyrexia) and an enlarged thyroid.

Myxœdema occurs more commonly in women than in men in a proportion of about 6 to 1, and is accompanied by certain anatomical changes. The thyroid shows extensive fibrosis of the gland, which succeeds a round-celled infiltration. There is at first a proliferation of the cells of the alveoli, ending in degeneration and complete loss. The gland greatly diminishes in size, and is the chief part affected in myxœdema. The increase in size of the patient, which was at one time considered as due to mucin, is due mainly to an increase of fat. There is thickening in the skin round the hair follicles and the sebaceous and sudoriferous glands, which has been considered as probably inflammatory (Virchow). Associated with these anatomical changes, interstitial nephritis with a hypertrophied left ventricle is present in about one-third of the cases, and petechial hæmorrhages are sometimes found in the medulla oblongata. The gross face and body, spade-like hands, the gruff voice, slow speech, and general apathy, with the thinning of the hair and slow pulse, are characteristic of the developed disease in man. The disease was first described by Gull (1874), and in 1878 was connected with disease of the thyroid (Ord). Previously it had been shown that extirpation of the thyroid in dogs was fatal (Schiff, 1856), and it was found that complete extirpation of the thyroid in man for goître was followed by symptoms which were proved to be characteristic of myxœdema (Kocher). The disease in many of its aspects is also reproduced in dogs and monkeys by the removal of the thyroid, and it was found that the deleterious effects were prevented by a previous and successful grafting of a portion of healthy thyroid in the abdominal cavity of the animal (Schiff). No results follow the extirpation of the gland in birds, and the results in rabbits are frequently negative unless the accessory thyroids and parathyroids are removed.

Experimental Myxœdema.—After removal of the thoryid, the symptoms in animals commence at about the fifth day (from the second to the twelfth day). They commence earlier in young animals, and when the animal is exposed to cold. A sheep, for example, in which the gland was removed, lived for two years without symptoms; myxœdema, however, developed when the animal was sheared.

The symptoms which are observed in a myxœdematous animal may be classified as follows:—Affections of *motility* are shown in the development of tremor, of clonic spasms, sometimes of contracture, the onset of paresis and sometimes of paralysis. An affection of *sensation* is shown in the development of paræsthesia, which is followed by anæsthesia, while the reflexes are greatly diminished. *Mental operations* are affected, being slowly performed, and there is apathy and lethargy which may lead to coma. The *body temperature*, which may be raised and irregular at first, gradually falls and becomes subnormal. The *appetite*—voracious at first—fails, and may be lost (anorexia). There is a *diminished blood pressure*, with gradually increasing anæmia and leucocytosis. An effect on the *general nutrition* is shown by a mucinous degeneration of the connective tissue and an increase of mucous secretion from the membranes. The *spleen* is sometimes enlarged, and usually there is atrophy and falling out of the hair.

Not only, then, is nutrition affected as the result of the loss of the thyroid, but there is a profound effect on the central nervous system and on the circulation of the blood. It has moreover, been found that in animals without a thyroid the respiratory exchange is disordered, as when exposed to cold such animals show an immediate increase in the amount of carbonic acid given off, there being no delay, as in the case of the normal animal.

The diseased condition produced by removal of the thyroid gland is prevented (1) by grafting a portion of healthy thyroid into the animal before the operation, (2) by injecting a watery extract of the gland into the animal after the operation, or (3) by feeding the animal with the gland. Similarly, it has been shown that in the natural disease (myxœdema) occurring in man, the

symptoms completely disappear when an extract of the gland is either repeatedly injected under the skin or given continuously by the mouth. Extirpation or disease of the gland, therefore, removes something from the body which is essential to health and to life, the absence of this substance leading to a definite train of disease symptoms.

The Action of Thyroid Extract.—The active principle of the thyroid gland has a definite physiological action which is not

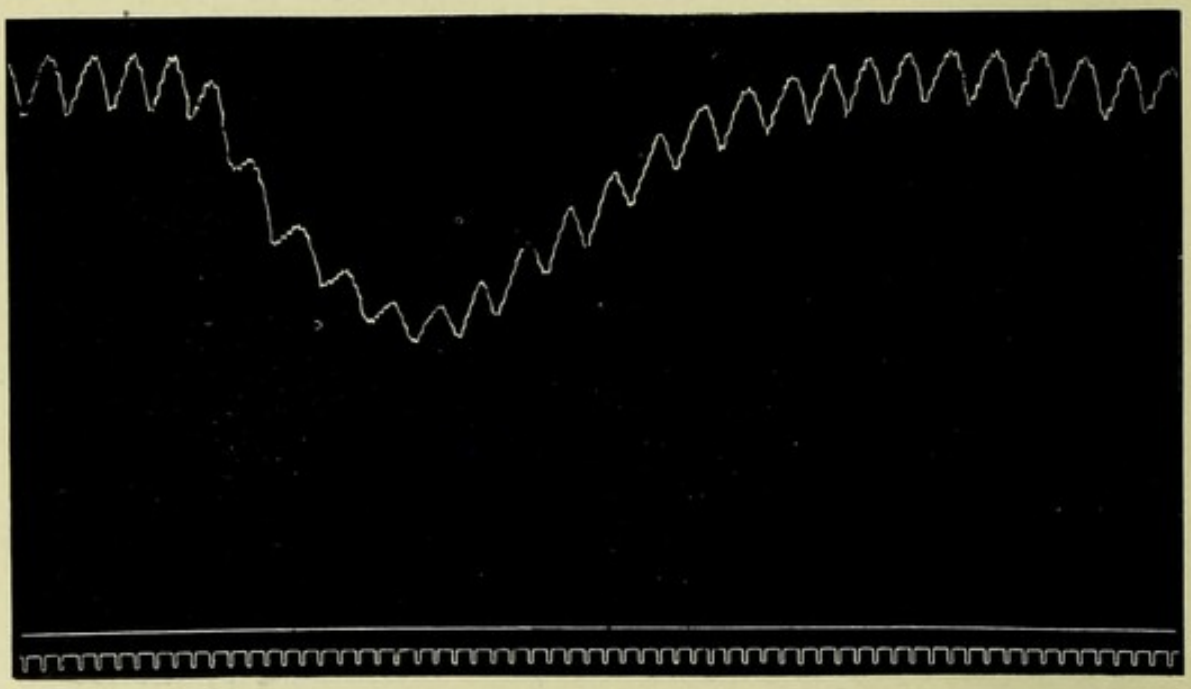


FIG. 107.—Effect upon the blood-pressure in the dog of the intravenous injection of decoction of thyroid.

Time in seconds. The line above the time tracing is the absciosa of the mercurial manometer. (Schäfer.)

destroyed by drying at a low temperature or mixing with water. Attempts which have been made to isolate the active principle have not been successful. It is regarded by some as a proteid. A crystalline substance, thyreo-antitoxine ($C_6H_{11}N_3O_5$) (Frænkel) has been described, as well as a body called iodo-thyrin, which consists of a proteid in combination with a large quantity of iodine. The exact nature of the active principle is, however, still unknown. It produces its effects in very small doses, and has a profound effect not only on the vascular system

but on metabolism. Injected intravenously in an animal, the watery extract of the thyroid gland causes a well-marked fall of blood-pressure (Fig. 107), due not to any alteration in the rate or strength of the cardiac beat, but to a dilatation of the peripheral blood vessels. In animals it has been found that thyroid feeding at first increases the excretion of nitrogen, but that this soon passes off, and nitrogen equilibrium is regained. In the healthy but obese human being, thyroid extract, when given by the mouth, produces a loss of weight due to the diminution in fat. It therefore increases metabolism in the body. It may produce a temporary glycosuria and an increase in the amount of urea excreted, especially when given in large doses. In such cases, too, an increased frequency of the cardiac beat is observed.

The most marked effect, however, of the action of the thyroid extract, is observed in cases of myxœdema and in cretinism. The regular administration of thyroid extract in myxœdema leads to the following results.

1. There is a great diminution in body-weight which may be as much as a loss of three stone in two or three months. This loss of body-weight is accompanied by the disappearance of the coarse features and husky voice.

2. There is a disappearance of the nervous symptoms, the tremor and the mental apathy.

3. Other nutritional changes are observed in the rise of body temperature, in the skin becoming moist and in the growth of the hair.

4. The effect on the circulation is observed by the slowed pulse becoming more frequent. A greatly increased frequency of the cardiac beat (120 to 140) may result from the action of thyroid extract in myxœdema.

The continued administration of the extract leads to a return to the normal condition; that is, all the effects of the loss of the thyroid gland disappear. For the maintenance, however, of the individual in this normal condition, the extract of gland has to be given continuously. It supplies something to the body which comes normally from the thyroid gland, and the loss of which by disease of the gland leads to the profound disturbances observed in myxœdema.

The pathological relation of myxœdema to exophthalmic goître is one of great importance. The symptoms have already been contrasted. In both conditions the thyroid gland is affected —atrophied in myxœdema, enlarged in exophthalmic goître. The enlargement of the thyroid gland is partly due to an increase in the size of the vessels which are sometimes hypertrophied, but mainly to the great increase of the secreting structure. The epithelium of the vesicles shows great proliferation, and the colloid secretion is more copious, and there is evidence of the formation of new vesicles. These anatomical changes are signs of an increased activity on the part of the gland, and are to be considered with the symptoms of the disease. Thus the increased frequency of the cardiac beat (tachycardia), the nervous excitability and the emaciation, are in direct contrast with the slow cardiac beat, the nervous apathy and the grossness of body in myxœdema, and might indeed be taken to represent the action of large doses of thyroid extract; and it must be considered a plausible conclusion that the symptoms of exophthalmic goître mentioned above are due to the presence in the blood and tissues of an excessive amount of the active principle of the thyroid gland. The disease exophthalmic goître cannot be produced in healthy animals by the injection of thyroid extract. This, however, is not a final argument against the view stated above. Whatever may be the fate of the active principle of the thyroid gland in the healthy body—and as to the details of this no knowledge is at present forthcoming—it is probable that, as in other instances, the tissues can act on the defensive against an excess of so powerful a substance; that is, the excess of the substance is destroyed in the body, and this may be the case in attempts to reproduce exophthalmic goître experimentally in healthy animals. There is probably in exophthalmic goître some other factor than the increased secretory activity of the thyroid gland, and possibly this is to be attributed to an affection of the nervous system. In many cases of the disease the thymus gland is enlarged and persistent, but the relation of this condition to the disease is unexplained, and the administration of thymus extract has no appreciable effect on the course of the disease. The influence of nervous shock

in initiating exophthalmic goître is an important fact, and the disease has been ascribed to an affection of the sympathetic nerves or to a disorder of the central nervous system, more particularly of the centres in the medulla. It has not as yet been shown that the central nervous system regulates the activity of the thyroid gland, but it may be that a change in the nerve centre initiates the excessive activity of the gland which is observed in exophthalmic goître, as indeed it might be supposed to initiate the diminished activity leading to atrophy which occurs in myxœdema.

The Pituitary Body.—The disease which has to be considered in relation to the pituitary body is acromegaly, in which there is evidence of a disordered nutrition as well as an effect on the circulation. There is an enlargement of the face and of the extremities due mainly to a thickening of the bones, which is practically an exaggeration of the normal prominences of the different bones. With this is associated some thickening of the integuments. The face becomes coarse, and the hands and feet become gigantic. The back is bowed, and the whole condition may be associated with great muscular strength, although in the later stages of the disease there is great muscular weakness. Thickening of the arteries has been described, and the pulse may be weak. Acromegaly is associated in many cases with an enlargement of the pituitary body, which is sometimes due to hypertrophy and sometimes due to the presence of a new growth. The disease is also sometimes associated with enlargement of the thyroid gland. Although the relation of acromegaly to the condition of the pituitary body is not yet definitely settled, yet the investigation of the functions of the pituitary body has led to the discovery that its integrity is essential to life. The anterior lobe of the pituitary body, which is derived during development from the epiblast, differs from the posterior lobe which consists of nerve tissue. The structure of the anterior lobe is somewhat like that of the thyroid, consisting of roughly spherical alveoli which contain a semifluid substance as well as nucleated cells.

Removal of the pituitary body in cats (Marinesco) and in

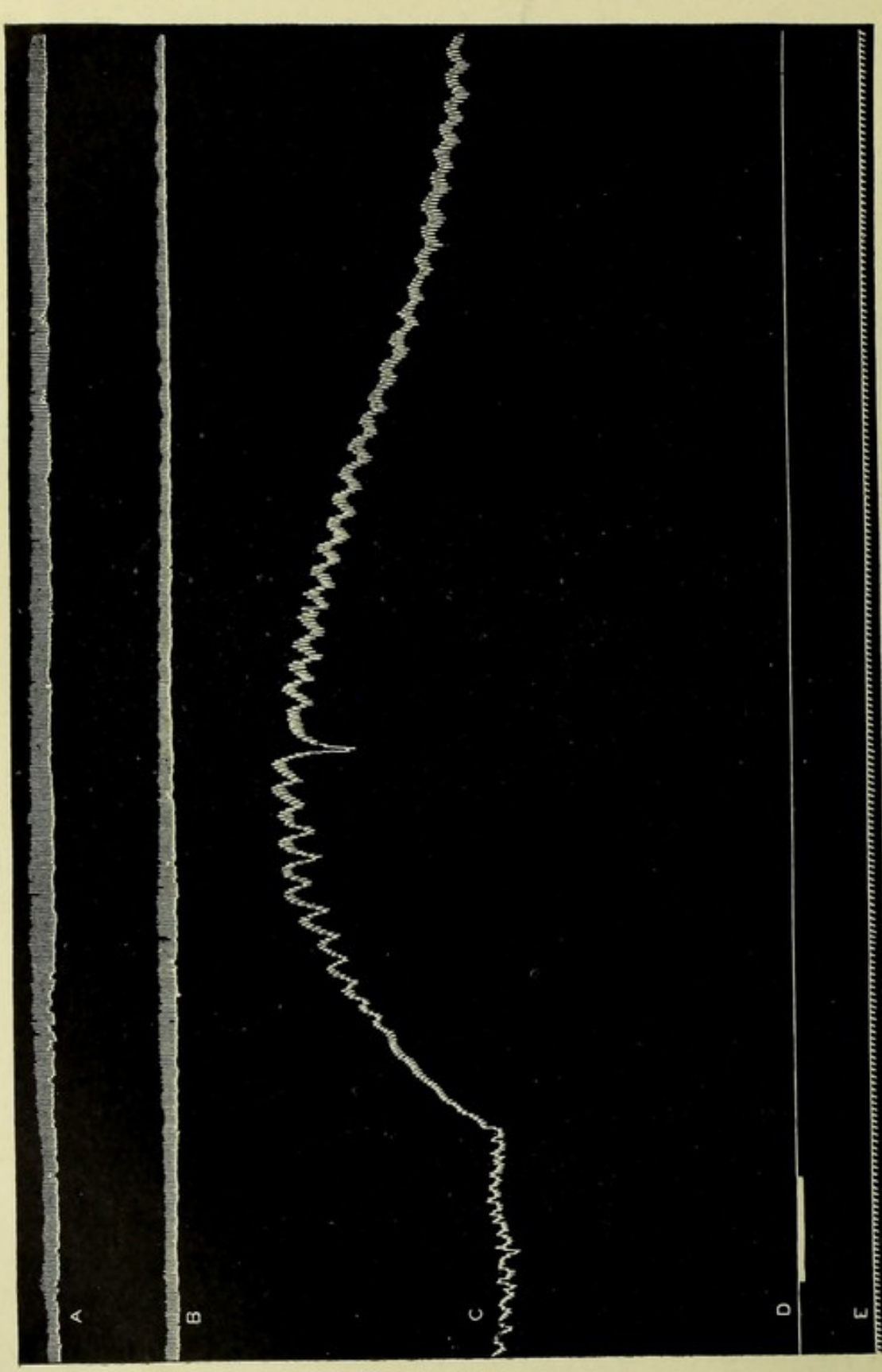


FIG. 108.—Effect of intravenous injection in the dog of boiled extract of pituitary body (equal to 0.07 grm. of dry pituitary). A, Tracing of auricle; B, of ventricle; C, of blood pressure in the femoral artery; D, pressure abscissa and signal of time of injection. (Schäfer.)

dogs (Vassali and Sacchi) leads to death within fourteen days. The symptoms observed are a diminution of body temperature, anorexia, lassitude, muscular twitchings, tremors and spasms and dyspnœa. The symptoms therefore show not only an effect on the nervous system but an effect on metabolism. To some extent the pituitary body appears in its functions to have some connection with the thyroid. Not only, as has been stated, is the thyroid sometimes enlarged in acromegaly, but in some cases following thyroidectomy the pituitary body has been described enlarged, although in myxœdema this is not generally the case. An extract of the pituitary body, however, has a different physiological action from that of extract of the thyroid gland; for whereas the extract of thyroid produces a fall of blood-pressure without any appreciable effect on the cardiac beat, extract of pituitary body causes a well marked rise of blood-pressure, with an augmentation of the heart beat (Fig. 108). Moreover, extract of pituitary body appears to have a direct action on the blood vessels causing their contraction. In both these respects it resembles suprarenal extract.

The Suprarenal Bodies.—Disease of the suprarenal bodies is observed in Addison's disease (Addison, 1855). This disease is characterised by a definite association of symptoms; such as great muscular weakness, a very feeble pulse and circulation, vomiting and pigmentation of the skin and mucous membrane of the mouth. These symptoms occur without any definite affection of the nervous system, such as paralysis of motion or sensation, or alteration of the special senses or of the mind. Indeed, Addison's disease in its progressive stages presents the features of an intoxication without pyrexia; the low body temperature, the profound weakness, and the extremely feeble circulation recalling symptoms which occur after the pyrexial stage of a known infection, such as typhoid fever, or like the apyrexial toxæmia of diphtheria.

The pigmentation occurs in the parts most exposed to pressure, and is due to an increase in the normal pigment of the part when it occurs in the skin. In the mucous membrane

of the mouth and tongue, although usually most marked where the parts are pressed upon by the teeth, it may be that the pigment is formed from the blood more directly than in the case of the skin. The suprarenal capsules may either wholly or in part be destroyed by atrophy, fibrosis, calcareo-caseous degeneration (tubercle), or by tumour. Of these the lesion most common in Addison's disease is calcareo-caseous degeneration, in which at death the original structure of the capsules is found destroyed.

Removal of the suprarenal bodies is fatal (Brown-Séquard,

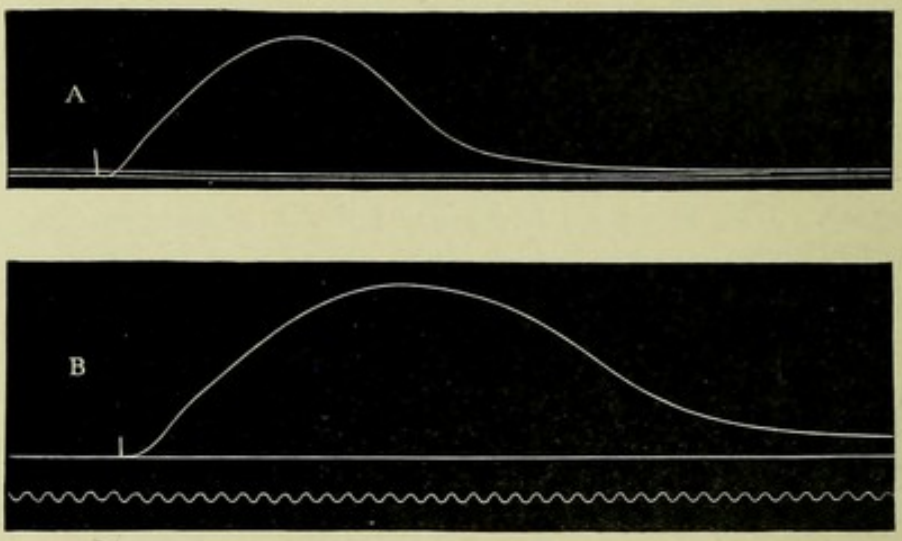


FIG. 109.—Effect of suprarenal extract upon muscle contraction in the frog.

A, Normal muscle curve of gastroenemius; B, curve taken during suprarenal poisioning, but otherwise under the same conditions as A. Time tracing, 100 per second. (Schäfer.)

1856), and the symptoms described as following the operation are: great muscular weakness, weak circulation and loss of appetite. Although Brown-Séquard did not observe pigmentation in his experimental animals, this has been said to occur in the slow experimental destruction of the capsules, as when they are inoculated with a micro-organism (the pseudo-tubercle bacillus). For the effects to be produced both capsules must be removed. The blood of animals dying after removal of the capsules is poisonous, not to normal animals, but to other animals in which extirpation of the capsules has just been performed, a statement which is not at present explained by the further work that has

been done on the suprarenal capsules. The toxicity of the blood of such animals has given rise to the idea that the function of the suprarenal capsules is to remove some poison from the system which accumulates when the capsules are taken away. This statement has no apparent connection with the physiological action of the extract of the gland.

Physiological Action of Extract of Suprarenal Capsules. — An extract of the cortex does not contain any active principle, but an extract of the medulla contains a toxic substance not yet isolated. This substance is soluble in water, and is not destroyed by boiling for a short time. It has the following physiological action (Schäfer and Oliver). Large doses of the extract cause an acceleration and increase of the cardiac beat, with shallow and rapid respiration and a fall of temperature. Rabbits are more susceptible than guinea-pigs, dogs or cats. In certain doses the injection of the extract appeared to confer immunity against a subsequent fatal dose.

The extract has a definite effect on voluntary muscle (Fig. 109), the contraction of which it enormously prolongs, like the alkaloid veratrine. On the heart, when the vagi are uncut, it causes a slowing or stoppage of the beat. With the vagi cut, the auricular contraction is augmented as well as that of the ventricle. Suprarenal extract causes an enormous rise of blood pressure (Fig. 110), due to contraction of the arterioles, as shown not only by a blood pressure tracing but by means of the plethysmograph. This effect passes off in a few minutes, but during its continuance, owing to the firm contraction of the arteries, a stimulation of the depressor nerve has no effect in lowering the blood pressure. The extract acts locally when applied to the blood vessels, and not through stimulation of the vaso-motor centre. A corresponding organ which exists in certain fishes (elasmobranchs) yields an extract similar in action to that of the capsule of the higher vertebrates already described, so that it appears that this substance which has such a powerful physiological action is associated with the functional activity of the suprarenal body. It acts in extremely small doses, and a distinct physiological

FIG. 110.—Effect of intravenous injection of boiled extract of suprarenal, equivalent to 0.2 grm. of fresh suprarenal. Dog, both vagi cut.

A, Tracing of ventricle; B, of auricle; C, of blood pressure in the carotid artery; D, pressure abscissa and signal; E, time in half seconds. (Schafer.)

effect on the heart and arteries may be obtained by the administration in the dog of as little as one millionth part of a gramme per kilo. of body-weight (Schäfer). The repeated subcutaneous injection of suprarenal extract in the form of adrenalin chloride solution (1 in 1000) leads to glycosuria, like the injection of phloridzin (p. 442). It also leads to an increased nitrogenous excretion.

In Addison's disease, as far as can at present be stated, the destruction of the function of the suprarenal capsules removes from the body a substance which has the effect of causing a rise in blood pressure as well as an increase of the muscular contraction, and it is the loss of this body which appears to lead to great muscular weakness as well as to weakness of the circulation. The administration of suprarenal capsule extract in Addison's disease is said to be attended with useful but not curative results. The extract has been used for the stoppage of both local and internal hæmorrhage, the *rationale* of this treatment being the local effect of the extract on the arterioles.

CHAPTER XVIII

CHANGES IN METABOLISM

In the normal individual nutrition is maintained by the food eaten and the oxygen respired, as well as by the passage in the excreta of the products of metabolism of the tissues. The amount of food required varies in different conditions. It must consist of proteid, fat, carbohydrates, salts and water in certain proportions. The proteid supplies the nitrogenous food necessary for the tissues, while the fat and carbohydrates are the sources of heat and energy. Nitrogen in the form of urea and uric acid is excreted in the urine and in an unmetabolised form in the fæces. The combustion of fat and carbohydrates in the body gives rise to the formation of carbonic acid, which is discharged mainly by the lungs, and of water. The following table (Ranke), quoted in Halliburton's *Physiology*, is a table of exchange on a definite diet :—

EXCHANGE OF MATERIAL ON AN ADEQUATE DIET.

Foods.	Income.			Expenditure.		
	Calories.	Nitrogen.	Carbon.	Excretions.	Nitrogen.	Carbon.
		Grammes.	Grammes.		Grammes.	Grammes.
Proteid, 100 gr.	410	15.5	53.0	Urea, 31.5 gr. / Uric Acid, 0.5	14.4	6.16
Fat, 100 gr. .	930	...	79.0			
Carbo-hydrates, 250 gr.	1025	...	93.0	Fæces . .	1.1	10.84
				Respiration (CO_2)	0.0	208.00
	2365	15.5	225.0		15.5	225.00

The heat value of this diet is 2365 calories. This is rather below the average diet required, which ought to be about 3000 calories, as in Voit's diet, consisting of 105 grammes of proteid, 56 grammes of fat, 500 grammes of carbohydrates. In man, the least amount of nitrogen which is to be taken in with the food is 15 grammes, which is contained in about 100 grammes of proteid. If the food contains smaller quantities of nitrogen the tissues utilise their own nitrogen for metabolism and the body wastes. If the amount of proteid food containing nitrogen is increased, the excretion of nitrogen is also increased, and in all cases in health a condition of nitrogen equilibrium becomes established, in which the output of nitrogen is equal to the intake in the food.

Fats and carbohydrates permit of a smaller quantity of nitrogenous food being taken than would otherwise be necessary, so that they are considered as proteid sparers in the diet. For details on this and other points, works on physiology must be consulted. It is necessary, however, to consider certain points in relation to the constituents of food which have an important bearing on nutrition in disease.

Proteid Metabolism.—The character of the nitrogenous substances taken in as food is not a matter of indifference to the body. The proteid foods which serve to maintain the nitrogenous equilibrium are such as those contained in muscle, milk, eggs, and in cereals and leguminous seeds. These may be referred to as *native proteids.* They undergo the process of digestion in the stomach and small intestine by the gastric and pancreatic juices. Thereby they are rendered more soluble, being transformed into albumoses. These products of digestion are retransformed during their absorption by the mucous membrane of the intestine into the proteids of the body, albumoses as such not being present in the normal tissues. Proteids are therefore not directly assimilated by the tissues, and many of them when injected into the circulation are excreted in the urine, such, for example, as egg-albumin and albumoses.

Gelatin, which is a nitrogenous substance and undergoes a process of digestion in the stomach with the formation of bodies

allied to albumoses, is not a substitute for proteids in the diet, and, from a dietetic point of view, is to be considered simply as a proteid sparer, and as such is to be placed in the same class as fats and carbohydrates.

Nucleins and nucleo-proteids are constantly present in foods, and these bodies have some relation to the amount of uric acid in the urine, and of other bodies of the purin class.

The metabolism of proteids in the body is associated with the activity of the tissues, for although muscular work does not increase the amount of nitrogenous excretion, yet the urea and uric acid present in the urine are derived from the breaking down of the nitrogenous substances in the body. Urea (CON_2H_4) is not a direct derivative of tissue metabolism. It is not, for example, formed in the muscles which constitute a large part of the body and are constantly in activity. It is formed in the liver, probably through some precursor the exact chemical nature of which is not as yet known. It has, however, been shown that certain salts of ammonia, such as the carbonate, lactate and carbamate, are transformed into urea by the liver, as well as are leucine and glycine. The urea precursor in the muscles may be the lactate, since muscle activity gives rise to sarcolactic acid.

Nitrogen excretion as the result of proteid metabolism consists mainly of urea, to a certain extent of ammonium salts, and partly of uric acid and nitrogen "extractives." In health, metabolism of the proteids results not only in the excretion of the nitrogenous substances. It may be concluded that the proteid molecule gives rise in the body both to carbohydrates and to fat; so that proteid metabolism, both in health and disease, is a much wider question than the consideration of the amount of urea or ammonium salts which constitute some of the final products of the metabolism. Carbohydrates which result from splitting up of the proteid molecule, are utilised in the body and gives rise to carbonic acid and water. The fat is also partly utilised and partly stored. It cannot be too frequently insisted upon that in health and disease it is the protoplasmic cell that performs these chemical manipulations. Within the limits of health proteid metabolism may

be increased or diminished according to the special needs of the tissues. In disease a diminution of cell activity is frequently seen resulting from many different causes: from conditions of the circulation of the blood, from impoverishment of the blood, or from an action on the tissues of some toxic agent. An increased destruction of the proteids of the body, or, to speak more correctly, an increased proteid metabolism, is frequently observed in diseased conditions, and mainly as the result of the action on the tissues of some toxic agent. An increased proteid destruction, as it is called, gives rise to different conditions: (1) To glycosuria in special cases (p. 442), (2) to an increased formation of urea and ammonium salts, (3) to the formation of by-products, such as acetone, diacetic acid and β-oxy-butyric acid, and (4) to an increased formation of sulphates and phosphates.

The increased formation of urea is not always demonstrable in the urine, inasmuch as there may be retention of urea in the tissues. Such urea retention occurs in disease of the kidneys; whether primary, as in Bright's disease, or secondary, as in congestion occurring in venous stasis from whatever cause. More particularly is urea retention the case if œdema is present. In some cases, however, the increased proteid destruction in disease does not lead to an increased formation of urea owing to the ammonium precursors of urea not undergoing transformation in the liver. In such cases, therefore, a diminished amount of urea is excreted, and an increased quantity of ammonium salts, while there is an increase of these salts in the blood, and the presence of lactic acid in appreciable quantities both in the blood and urine.

Carbohydrates.—The carbohydrates are transformed in the alimentary tract into maltose which, however, is not absorbed as such by the tissues, but is first transformed into dextrose, which is the only sugar found in the body. The other carbohydrate found is glycogen. Inosit or muscle sugar, is not a carbohydrate. Blood contains 0.05 per cent. of dextrose. The relation of the absorbed sugar to glycogen has given rise to much experiment and controversy. The carbohydrates form but a small proportion of the body—not more than 1

per cent. This bears, therefore, a very small proportion to the amount of carbohydrate food which is taken. The absorbed dextrose is therefore utilised at once by the body for providing heat and energy. The glycogen in the body, which disappears in starvation and in muscular work, is also utilised for the same purposes; but all the glycogen in the liver is not derived from the absorbed sugar, and it has been shown that some, at any rate, is derived from proteid food. This is shown by the reappearance of glycogen in the liver on a proteid diet after the substance has been got rid of by severe muscular work, as well as in the formation of glycogen in the embryo chick, in the absence of carbohydrates. Fat given to an animal which has been starved and worked does not give rise to the appearance of glycogen in the liver. The administration of glycerine appears to prevent the loss of glycogen.

Fats.—Fat being emulsified, and to some extent broken up in the small intestine, the fat particles are absorbed by the intestinal mucous membrane, and undergo a transformation, no doubt in the cells, into the fat of the body, which is of different composition to the fats taken as food. Fat is stored up in the body in the connective tissues and in the liver, and is utilised as a source of energy and heat. Fats are also partly broken up (saponified) in the intestine, into glycerine and fatty acids, which combine with alkalies, forming soaps. All the fat in the body is not derived from fats taken as food. Some, at any rate, is derived from the proteids, and some from carbohydrates.

It is thus seen that the proteids form by far the most important food stuff necessary to man in that the transformation they undergo is not only one into the proteids of the body, but one in which they are broken up into a carbohydrate moiety and a fatty moiety. Moreover, the carbohydrates increase the fat of the body in a way not yet completely understood.

Of the salts taken in with the food, but little need here be said. Chloride of sodium is a necessity of vegetable feeders, and when the diet consists of foods containing an excess of potassium salts and phosphates. The relation of the salts

taken in with the food to the salts excreted is discussed under the heading of Urine Excretion (p. 399).

Changes in Metabolism in Disease.—The nutrition of the body suffers in disease from many different causes. The chief causes are the following:—

1. The amount and character of food, and changes in the processes of digestion.

2. Changes in the metabolism in the tissues of proteids, fats and carbohydrates.

3. Alterations in the circulation of the blood and in the composition of the blood.

4. As the result of disease of the glands of the body. *Ductless Glands*, Chapter XVII.: *Liver*, Chapter XV.: *Kidneys*, Chapter XVI.: *Pancreas* (p. 444).

5. Disease of the central nervous system (Chapter XIX.).

6. As the result of the circulation of poisons in the body.

The results of failure of nutrition are observed in the loss of body-weight, in changes in the body temperature, in changes in the excretory products, more particularly of the nitrogenous excretives and of carbonic acid, and in the presence of abnormal constituents or changes in the normal constituents of the urine.

A. 1. *Changes in Metabolism due to Food.*—Food may cause changes in nutrition if absolutely withheld, as in inanition or starvation; if greatly deficient, as in partial inanition, or if one or other of the essential food stuffs preponderate in the diet.

Complete Inanition.—The effect of abstention from food has been studied experimentally, and is observed in some cases of disease, such as stenosis of the œsophagus and of the pylorus, although both these instances may be considered in the majority of cases as examples of partial inanition. In complete inanition, which has been studied in the fasting men (Cetti, Breithaupt, Succi) as well as in animals, there has been observed a daily diminished loss of urea, which may, however, be at first excreted in greater quantity than normal, especially if a diet rich in proteid has been taken just previous to the fast. The

loss of urea and of nitrogen, as a rule, steadily diminishes and tends later to become more uniform: the average loss in the first ten days of starvation in well-nourished and healthy strong men being 10 to 11 grammes of nitrogen. The loss of urea is diminished if the body is fat. When no proteid or other food is taken, the continued excretion of urea is due to the metabolism of the tissues, which draw on their own resources of proteid for their activity. This, as the starvation continues, leads to wasting of the tissues and to their diminished activity. The tissues, however, after a certain period, appear to get accustomed to a lower normal nitrogenous metabolism, as shown by the fact that the excretion of nitrogen tends to become uniform after the first two weeks of fasting.

The loss of carbonic acid from the lungs is proportional to the weight of the body, to the amount of work done and, inversely, to the surrounding temperature. The amount excreted diminishes with starvation, and represents the combustion not only of proteid but of fat. The glycogen in starvation rapidly disappears from the liver and the muscles, so that the fat and proteids of the body are the only substances which give rise to the formation of carbonic acid by combustion.

The temperature of the body is at first maintained, but afterwards falls to subnormal. Artificial warmth, or the prevention of the loss of heat from the surface of the body, tends to prolong the life of the starving individual.

The loss of body-weight is due to loss of water in the urine, by the skin and from the lungs, and to the loss of the tissues in fat and proteid which is utilised in maintaining the processes of the body. The tissues of the body do not waste equally. The muscles and the fat are most affected, the former accounting for over 40 per cent. of the total loss of weight, and the latter for over 25 per cent. (Voit). The skin, liver and blood are the tissues next most affected, but their loss in weight is far behind that which occurs in the muscles and fat. The central nervous system and the heart show the least loss.

As regards the actual weight lost, particulars have been

obtained from the fasting men. Death occurs if the total weight lost is one-third of the original body-weight. Succi, in thirty days' fast, had his weight reduced from 62.5 to 52 kilos, a loss of 10.5 kilos, or over 23 lbs. The loss up to the fifth day was 5.1 per cent., and up to the tenth day 9 3 per cent., of the weight. Cetti lost, up to the fifth day, 7.7 per cent. of his weight, and up to the tenth day 11.1 per cent. of the original weight of 57 kilos.

The effect on the excretions is seen in the diminution and final cessation of the passage of the motions, which at first consist of the undigested remnants of the food eaten before the fast, and afterwards mainly of the secretion of the digestive juices and of some epithelium and mucus. The digestive secretions are greatly diminished in starvation. The saliva is less in amount, but the diastatic activity, although greatly diminished, is not completely lost. Very little gastric juice is secreted, and the amount of bile is also diminished. It is said that sugar does not completely disappear from the blood. The leucocytes of the blood are diminished in number.

The effect on the urine is shown in the diminution of the quantity excreted. The amount of urea has already been discussed. The urates are diminished in quantity, as well as the creatinin. The chlorides are much diminished. On the tenth day of Cetti's fast only 0.6 gramme was excreted in the urine in twenty-four hours, as compared with the normal of about 6 grammes. The urine also shows another change in the increased quantity of acetone present. The quantity of acetone present in normal urine is about 0.01 gramme in twenty-four hours, but in inanition the amount present may be nearly fifty times this quantity, as was observed during Cetti's fast. Aceto-acetic acid and β-oxy-butyric acid are also found in the urine, neither of them being present in the normal condition. Although acetone is a product of lactic acid fermentation, its presence in the urine in inanition must be considered as due to proteid disintegration.

Partial Inanition.—Complete inanition is rarely the result of disease. Partial starvation, however, not uncommonly

occurs, mainly from disease directly affecting the alimentary tract and its glands. The effect of partial inanition is due to an incomplete diet: that is, one deficient in all its constituents.

The nitrogenous exchange in partial starvation shows that, although the daily amount of nitrogen taken is below the normal amount of 15 grammes, the patient may store up some of this nitrogen, as the following example shows (von Noorden). The patient was a female with stenosis of the gullet produced by caustic alkali, and was unable to take a normal quantity of food for many weeks. During a certain period, the analysis of the nitrogen in the food and that excreted gave the following results: —

Daily Intake.		Daily Output of Nitrogen in Urine and Fæces.	Daily Storage of Nitrogen.
N.	Calories of Total Food.		
7.602	765	5.915 grammes.	1.687 grammes.
8.991	881	7.041 „	1.950 „
11.77	1000	8.180 „	3.590 „
13.67	1100	8.830 „	4.840 „

The nitrogen thus stored up is used for energy, but little fat being deposited.

The loss of weight which occurs in partial inanition as observed in disease varies considerably. As examples of severe cases, may be quoted: a case of stenosis of the gullet (non-malignant), in which the body-weight fell from 100 lbs. to 73 lbs. in six and a half weeks, a loss of about 27.5 per cent.; a case of severe ulcer of the stomach, in which the weight fell from 112 lbs. to 77 lbs. in five to six weeks, a loss of about 31 per cent.; and a case of pyloric stenosis due to ulcer, in which the weight fell from 161 lbs. to 86 lbs. in the course of two and a half years, or a loss of over 46 per cent.

The loss of weight in partial inanition depends on many

factors, not only on the amount of food taken, but also on the digestive power of the organs and the power of assimilation of the tissues. The loss is also more marked in fat people than in the lean and muscular.

What has been said as to the effect of complete inanition on secretion and excretion applies also to partial inanition, although to a less extent.

The body temperature in partial inanition is almost constantly subnormal, there being but little daily excursion of the temperature curve: such individuals experience cold extremities.

Preponderance of Proteids, Fats or Carbohydrates in the Diet.—Although 15 grammes of nitrogen is the minimum amount required for the maintenance of health, yet larger quantities are constantly taken. If the proteid in the diet is largely in excess of the requirements of the body, the excess of proteid appears in the urine as urea. The urea therefore increases in proportion to the amount of proteid food, and a nitrogenous equilibrium is established. An excess of proteid food thus leads to increased strain on the digestive and excretory organs and an increased metabolic activity on the part of the tissues, and the body wastes in many instances owing to the utilisation of the stored fat for the supply of energy and heat.

An excess of fat in the dietary, with a diminution of the proteid food leads to disintegration of tissue owing to the deficiency in nitrogen. There is a large deposit of fat owing to the excess of fatty food. Beyond a certain amount, which is about 2 ounces of fat daily, the extra fat is passed out in the fæces unaltered, or partly broken up into fatty acids which combine with calcium. With an excess of fat, as also with an excess of carbohydrates, and a diminution of nitrogenous food, there is a condition of partial inanition. Excess of carbohydrates, besides leading to digestive disturbance, leads to the deposit of fat.

B. *Changes of Nutrition due to Altered Processes of Digestion.*—The nutrition of the body may suffer owing to changes which occur in the digestive process in three directions, all of

which result in a deficient amount of food passing from the alimentary tract into the tissues.

1. There may be delay or obstruction to the passage of food along the alimentary tract. This occurs more particularly in obstruction to the passage of food by stenosis of the upper alimentary tract; for example, of the gullet, of the two orifices of the stomach, and of the duodenum; or to retention of the food in the stomach or small intestine owing to weakness (atony, myasthenia) of the muscular coat.

2. Alterations in the chemical processes of digestion occur in the stomach, where the gastric mucous membrane may secrete in some cases an excess of hydrochloric acid, in other cases, a diminished quantity. In the latter case, in addition, there may be fermentation of the food, more particularly of the carbohydrates, which are broken up into products not utilised by the body for its nutrition. Following changes in the pancreas, a diminished amount of secretion enters the small intestine; and in this, sometimes bacterial fermentation occurs.

3. A deficiency in the absorption of food not infrequently occurs, sometimes in functional disorders of the stomach and intestine, although not to any great extent, but more particularly when there is either portal obstruction, disease of the mesenteric glands, or of the thoracic duct itself.

When there is actual obstruction to the passage of food, as occurs particularly in stenosis of the œsophagus and of the pylorus, the effect on nutrition is well marked, and is that already described under the heading of Partial Inanition. With the delay of passage of the food due to deficient peristalsis, the failure in nutrition is not so marked as in actual obstruction, but is more marked when the stomach is affected than when the small intestine is the seat of the disorder. In such cases the loss of weight and the general effects of partial inanition are due not so much to the delay of food as to the deficiency of food taken.

Changes in the chemical processes occurring in the stomach may have a profound effect on the nutrition. Where an excess of hydrochloric acid is secreted, as in cases of gastric irritation and in some cases of ulcer, there is a rapid and efficient diges-

tion of the proteid food, but a diminished digestion of the carbohydrates not only in the early part of gastric digestion, but during their digestion in the small intestine, owing to the hyperacid stomach contents rendering the contents of the small intestine too acid. The digestion of fat is, however, not affected. In cases of hyperchloridia there is, as a rule, no profound effect on nutrition except in those cases where a deficiency of food has to be taken on account of the digestive distress. When there is a marked deficiency in the secretion of hydrochloric acid there may be the effects of partial inanition owing to the fact that the digestion of proteid foods is very poor, although the digestion of fats and carbohydrates is not affected. In the severe cases of hypochloridia, such as occur in gastric catarrh and in cancer of the stomach, bacterial fermentation of the food further increases the failure of nutrition, inasmuch as the carbohydrates are split up mainly into lactic acid, butyric or acetic acid. Deficiency in the amount of hydrochloric acid (hypochloridia) and of pepsin occur in catarrh of the stomach, cancer, and in atrophy: the effect on nutrition is profound, owing mainly to the diminished quantity of food taken, but partly to the inefficient chemical processes of digestion.

But little is known of functional alterations in the secretion of pancreatic juice, but when the pancreas is diseased, as in chronic pancreatitis, the secretion is deficient, and there is failure in nutrition due partly to the inefficient digestion of the food in the small intestine. The effect of the pancreas on nutrition does not relate solely to deficiency of secretion, as it has an influence on the metabolism of carbohydrates and the production of glycosuria (p. 444). Bacterial fermentation of the food may occur in the small intestine affecting mainly the carbohydrates. As a rule, however, no profound effect on nutrition is observed in such cases. Recent researches show that the mucous membrane of the duodenum and jejunum has an effect on pancreatic secretion. A substance, secretin, is extracted from the mucous membrane which, when injected into the body, sets up active pancreatic secretion (Starling). The bearing of these results in the explanation of disease cannot at present be estimated; but they are of great importance.

Changes in the absorptive processes may affect nutrition either slightly or profoundly. Thus absorption of the food is diminished in cases where there is deficient digestion of the food, as in cases of hypochloridia, and when there is weakness of peristaltic action. The failure of nutrition observed is, however, slight, and extended over a long period. When, however, there is organic obstruction to the absorption of food, the failure in nutrition is well marked. This occurs in portal obstruction, chiefly due to cirrhosis of the liver, and is one of the main causes of the failure in nutrition observed in that disease. It also occurs, however, in disease of the mesenteric glands and of the thoracic duct, which is commonly tuberculous in origin. Obstruction to the portal circulation affects mainly the absorption of the proteids and the dextrose, while obstruction in the mesenteric glands or thoracic duct affects mainly the absorption of the fats. In obstructed lacteal absorption the portal system cannot absorb the fats, but when the portal system is obstructed the lymphatics of the mesentery can absorb the proteids and dextrose, and this they may do to a greater extent than normally occurs.

2. *Changes in the Metabolism in the Tissues.*

A. *Proteid Metabolism.* — The general results of changes in proteid metabolism in disease are discussed under their appropriate headings, such as the pathological process of pyrexia, disease of the liver, and so on. There remains for special consideration the subject of uric acid.

Relation of Uric Acid and Urates in Disease.—The amount of uric acid excreted from the body and its relation to the fluids of the body, are of great importance in certain diseased conditions, more particularly gout; and although knowledge is still imperfect on the subject, the following physiological facts have a bearing on pathology.

Origin of Uric Acid in the Body.—The uric acid excreted in mammals is no doubt in part due to the metabolism of proteids. Its mode of origin, as well as the organs forming it, has been much discussed. In birds, in which the nitro-

genous excretion is mainly in the form of uric acid, the liver is the seat of its formation, and its precursor is lactate of ammonia, inasmuch as after extirpation of this organ uric acid is no longer excreted, but lactic acid and ammonia. Urea also given to birds is passed out of the body as uric acid. Uric acid given to mammals is transformed by the liver into urea before being excreted. The commonly accepted opinion is, that in man uric acid is formed in the liver and possibly in the spleen, the precursors being possibly the same substances that are transformed by the liver into urea. It has, however, been asserted that the kidney is the organ which forms the uric acid. Analogy with birds would suggest that the liver is the organ concerned in its formation; but the process of formation in mammals may not be the same as in birds. Some, at any rate, of the uric acid is derived from the food. The uric acid in the urine is therefore of exogenous origin, that is, derived from the food; and endogenous, that is, derived from the metabolism of the tissues. The exogenous uric acid is derived mainly from those foods containing nucleo-proteids, such as solid organs, liver and sweetbread.

With uric acid must be considered the other substances which are classed as purin bodies. These bodies are hypoxanthin (mono-oxy-purin) ($C_5H_4N_4O$); xanthin (di-oxy-purin) ($C_5H_4N_4O_2$); uric acid (tri-oxy-purin) ($C_5H_4N_4O_3$); guanin ($C_5H_5N_5O$); and adenin ($C_5H_5N_5$). All these substances are closely united with nuclein or nucleo-proteid in the diet. The purin bodies of food are no doubt liberated during the digestion of the nucleo-proteid, as in the following table (Horbaczewski):—

Nuclein or Nucleo-Proteid.

Proteid. | Nucleinic Acid.

Phosphoric Acid. | $C_5H_4N_4-NH$—Adenin.
$C_5H_4N_4O-NH$—Guanin.
$C_5H_4N_4O$—Hypoxanthin.
$C_5H_4N_4O_2$—Xanthin.
$C_5H_4N_4O_3$—Uric acid.

It has been found that the purin-containing foods lead to an increase in the excretion of purin bodies in the urine as compared in the same individual when foods not containing purins are eaten, such as eggs, milk, butter, cheese and bread. The proportion of these bodies due to exogenous origin—that is, derived from food—may thus be ascertained.

Variations in the Amount of Uric Acid Excreted. — The amount of uric acid daily excreted varies between 0.2 and 1.4 gramme, the average amount being 0.8 gramme. The amount has been said to bear a definite relation to the amount of urea, so that a uric-acid-urea ratio is spoken of. There is, however no definite ratio, as in health it varies considerably with different diets. The ratio with a bread diet is 1 : 81, with beef 1 : 48 (Bunge, quoted by Hopkins). In normal conditions of diet and living, although there are great individual variations in the amount of uric acid excreted, the uric-acid-urea ratio is 1 : 35, or 1 : 40.

The amount of uric acid is increased in new-born infants, a considerably greater quantity of nitrogenous excretion being in the form of uric acid than is the case with adults. Other conditions in which the uric acid is increased are, excessive exercise, leukæmia (p. 455) and leucocytosis, and in the two last conditions the increase appears to be associated with the presence of an excess of white cells in the blood, which no doubt degenerate and give rise to free nucleo-proteid. The increase of uric acid in this case, therefore, pathologically is due to the same cause as the taking as food of a solid organ, such as the thymus and sweetbread. Pilocarpine and salicylates also increase the amount of uric acid in the urine, and the amount is diminished by rest and in chronic gout.

Solubility of Uric Acid and of Urates.— Uric acid does not exist as such in the tissues, nor in normal conditions in the urine. It combines with caustic alkalies to form neutral urates (M_2U : M = metal, U = uric acid) which do not exist in the tissues or urine. It combines with alkaline salts to form biurates (MHU), such as sodium, potassium and ammonium urates. This is the form in which uric acid is deposited in the tissues, as in gout. Uric acid also exists in the more soluble form of quadriurates

(H_2UMHU), and it is in this form in which the uric acid of birds is excreted, and presumably the form in which the urates exist in the human urine and the tissues (W. Roberts).

The study of the solubilities and deposition of the biurates and of the quadriurates becomes of great importance in the discussion of diseased conditions, more particularly of gout. The biurate investigated has been chiefly the sodium salt, and the following important facts have been ascertained (W. Roberts). Sodium biurate is soluble in 1000 parts of distilled water at 100° F. Its solubility is diminished by adding sodium salts to the solution, either by themselves or in such liquids as blood serum, lymph and synovia: a deposit is formed of sodium biurate. This salt is very slowly soluble in serum or synovia, as are the gouty deposits in cartilage which water dissolves quickly. Uric acid dissolves in serum (1 in 500) and in synovia as a quadriurate. On standing, however, the liquid soon deposits crystals of sodium biurate; the changes being accelerated by keeping the liquid at the body temperature. They are in proportion to the amount of uric acid dissolved. The deposit of sodium biurate from the solution of uric acid in serum is sometimes sudden and complete.

These results have been utilised to explain the deposit of sodium urate in the tissues in gout. Two conditions are necessary: an excess of uric acid in the blood (uricæmia), and the process of deposition or uratosis. The uric acid circulating as quadriurate is increased in the blood in gout. Circulating in tissues containing a large proportion of sodium salts, this excessive amount of quadriurate is suddenly transformed into sodium biurate, which is deposited in the cartilage of the joints affected. It is found that the tissues in which sodium biurate is deposited in gout are richer in sodium salts than those in which the salt is not deposited. Thus a larger proportion of sodium salts is found in blood serum, lymph and fibrous tissue (0.7 per cent.), in synovia (0.8 per cent.), and in cartilage (0.9 per cent.), in which sodium biurate is deposited in gout, than in the brain (0.2 per cent.), liver (0.08 per cent.), spleen (0.04 per cent.), and muscle (0.08 per cent.), in which deposits do not occur.

The deposit in gouty joints consists mainly of sodium biurate, which is encrusted on to the cartilage, and is found in the cartilage itself, but only superficially, gradually disappearing in the deeper parts. If the statements just made are correct, the deposition in the cartilage would occur in gout after imbibition from the synovia or blood vessels of the bone, and would be mainly a question of solubility due to the presence of an excess of sodium salts. It has been found experimentally that synovia, rich in uric acid, deposits biurate on the cartilage of dead joints in the same manner as is observed in gouty joints. It is this deposition which is supposed to give rise to the gouty paroxysm. A joint which has been affected with acute gout may be found afterwards to contain no deposit of biurate. It is supposed, therefore, that the deposit of biurate may be redissolved by the blood when this contains a diminished quantity of quadriurate. Whether the gouty paroxysm can occur without deposition of biurate is doubtful. Deposition of this salt is the main gross feature of the gouty attack. The analysis of tophi or deposits of biurates in fibrous tissues, shows that they consist mainly of uric acid and sodium, with a smaller quantity of potassium and still smaller quantities of calcium and magnesium phosphates, and sulphur. The amount of uric acid present is about 60 per cent. of the dried substance, of sodium oxide 9.3 per cent., and of potassium oxide about 2.95 per cent., the remainder of the substance consisting of small quantities of other minerals and of tissue, which is present in about 28 per cent.

There is no question of the deposition of biurate in the joints and tissues of gout. The amount present in the blood has been found to vary considerably. An excess was found in exudations, in blister fluid and in the blood by the application of the murexide test, or by placing fibres of linen in the liquids mentioned, with the addition of a trace of acid. Crystals of uric acid were formed on the fibres. It was thus considered (Garrod) that there was an excess of uric acid in the blood, and that this was accompanied by a diminished excretion. The amount of uric acid which has

been found in the blood in gout has varied between 0.025 gramme and 0.175 gramme per 1000. Similar variations in the amount of uric acid have, however, also been found in chronic plumbism and renal disease, pneumonia, emphysema and anæmia.

Other Changes in Gout.—In gout there are other changes in the body besides those which have been described in connection with uric acid. It has been found that the total nitrogenous discharge is diminished in gout, the difference between intake and discharge being between 2 and 4 grammes nitrogen daily. It is possible that this diminished output of nitrogen is associated with disease of the kidney (p. 395). The changes in metabolism are by no means always limited to variations in the nitrogenous substances of metabolism.

In some instances gout is associated with glycosuria (p. 446), with renal disease (granular contracted kidney) and with nervous symptoms, such as asthma. Whether those changes are to be ascribed or not to the presence of an excess of urates in the blood and tissues, is doubtful. The glycosuria would be ascribed to the general disorder of metabolism which occurs in the nitrogenous tissues. The explanation of the renal disease is not easy. It might presumably be due to some irritative substance which is excreted in the urine. It does not appear that the uric acid is the substance, as it is not excreted in excess in gout. By some the causation of the gouty kidney, as well as gouty asthma, has been ascribed to the circulation of some poison other than uric acid. There is no evidence, however, of the existence of such a poison, and at any rate the gouty kidney may be due to the same conditions which produce the gout, namely, dietetic irregularities.

In the majority of cases gout is due to the abuse of alcohol and food, more particularly animal food, both of which lead to general disorder of metabolism. It is, however, remarked that gout is hereditary in many instances; families showing this particular tendency of disordered metabolism which leads to the formation of an excess of uric acid. The inheritance may be passed on through the males of a family, a generation being frequently skipped.

Carbohydrate Metabolism.—Disturbances in the carbohydrate metabolism in disease are shown mainly in the occurrence of glycosuria, which exists in all degrees. Glycosuria has been experimentally studied, and the following facts have an important bearing on its natural occurrence in man. No distinction can at present be made between glycosuria and diabetes, although it is probable that the conditions may have different modes of origin.

1. *Puncture Glycosuria.*—Puncture of the floor of the fourth ventricle near the vaso-motor centre gives rise to glycosuria (Claude Bernard). With the glycosuria the glycogen of the liver disappears, being converted into sugar, which is thus in excess in the blood and is passed out in the urine. If glycogen is absent from the liver, as in a starved and worked animal, no glycosuria results. Other lesions of the nervous system are followed by glycosuria, such as injury to the vermiform process of the cerebellum, destruction of the cervical sympathetic ganglia and of some of the other ganglia, and stimulation of the central end of a divided sensory nerve. No glycosuria occurs on division of the splanchnic nerves.

One explanation of the occurrence of glycosuria after puncture of the floor of the fourth ventricle is that there is dilatation of the hepatic artery, which has the result of bringing some ferment to the liver cells, which, acting on the glycogen, converts it into sugar. In this case the condition would be due to stimulation of the liver cells. Whether this is so or not is not at present known.

2. *Toxic Glycosuria.*—Certain toxic substances cause the appearance in the urine of bodies which reduce Fehling's solution. These reducing bodies are either glucose or glycuronic acid. The following substances have this toxic action: phosphoric acid, lactic acid, hydrochloric acid, strychnine, curare, phosphorus, arsenic, carbonic oxide, butyl-chloral hydrate, morphine, hydrocyanic acid, chloroform, turpentine. In most of these cases the copper-reducing substance is not glucose, but glycuronic acid. Glycuronic acid, $COOH.(CH.OH)_4.CHO$ is related to glucose, which may be represented by the rational formula, $CH_2HO.(CH.OH)_4.CHO$. It appears in the urine

only in pathological conditions and is apparently an incompletely oxidised product in the metabolism of carbohydrates. In the urine it is in combination with ethereal sulphates or other similar compounds (p. 404), or with some alcoholic substances, such as chloral hydrate, butyl-chloral and chloroform. Glycuronic acid appears in the urine mainly as the result of the ingestion of these substances, and not as the result either of the ingestion of carbohydrate food, or as the result of disordered carbohydrate metabolism. It reduces Fehling's solution when present in the urine, and is distinguished from glucose, in not being fermentable with yeast.

The presence of glycuronic acid in the urine has, as far as is known, but slight connection with the occurrence of glycosuria. This is otherwise with a glucoside, phloridzin, obtained from the root bark of the apple and cherry, to which the formula $C_{21}H_{24}O_{10}H_{20}$ has been given. Phloridzin, when injected subcutaneously, or taken by the mouth, produces glycosuria, and its action does not depend on the amount of glucose it contains, but on an active principle, called phloretin, which is obtained from it. One gramme of phloridzin has given rise to the excretion of 97 grammes of sugar (Minkowski), so that the effect is out of all proportion to the amount of glucose the substance contains. It also produces an increased secretion of sugar in milk. The glycosuria is associated with a diminished quantity of glycogen in the liver, but is not solely or even mainly dependent on the metabolism of the glycogen, inasmuch as it persists after the glycogen of the liver has disappeared or been greatly diminished. Thus, in a starved and worked animal, phloridzin produces glycosuria, unlike puncture glycosuria. In this case the sugar must be derived from the metabolism of the proteids of the body, and that these are broken up more than normally is shown by the increased nitrogen excretion in the urine which sinks or falls with the excretion of sugar. It also gives rise, when given in large quantities, to an increase of acetone, and to the presence of diacetic acid and β-oxy-butyric acid (p. 448) in the urine, and finally causes death in coma.

It has been stated that in phloridzin glycosuria there is no excess of sugar in the blood, unlike what occurs in puncture

and pancreatic glycosuria, and the formation of sugar has been ascribed to the activity of the kidneys. It is not certain, however, that this is the case, and some observers have found an excess of sugar in the blood in phloridzin glycosuria (Pavy). Tying the renal blood vessels before the injection of phloridzin leads to the accumulation of sugar in the blood.

The mode of production of phloridzin glycosuria has not been explained. It is evident, however, that there is a profound effect on the nitrogenous metabolism of the body, and it is possible that phloridzin acts directly on these substances, causing a splitting up, with an increased formation of a carbohydrate moiety, which is excreted as sugar.

3. *Pancreatic Glycosuria.*—Total extirpation of the pancreas in dogs, cats and pigs, leads to glycosuria, sugar being present in the urine to the amount of 5 or 10 per cent., the blood containing as much as 0.46 per cent. of glucose (von Behring and Minkowski). This glycosuria is associated with the symptoms of natural diabetes in man, namely, excessive appetite and thirst, polyuria, wasting and weakness. Great quantities of acetone, diacetic acid, β-oxy-butyric acid, and ammonium salts are present in the urine, and death occurs in coma in from ten to fifteen days. The nitrogen excretion, as in phloridzin glycosuria, goes *pari passu* with the amount of glucose in the urine. Total extirpation in these animals leads, therefore, to a very complete reproduction of the symptoms of severe diabetes in man. If the organ is only partially extirpated, about one-third or even less being left, and this portion grafted on to the abdominal wall with its vessels so as to preserve its vitality, no glycosuria occurs, nor any of the symptoms or signs above stated. If the grafted portion be extirpated later, the symptoms described are observed. When a tenth part of the pancreas is left in the body, glycosuria does not occur unless carbohydrates are given with the food. In this way, therefore, the milder form of diabetes in man is reproduced (p. 446). Feeding with pancreas or injection of pancreatic extract does not relieve the symptoms of pancreatic glycosuria. The effect of extirpation is not dependent on the removal of the pancreatic secretion from the intestine since glycosuria, and the other signs do not

occur if the pancreatic duct be ligatured, or its lumen be obliterated by the injection of paraffin.

Twenty per cent. of cases of diabetes in man show disease of the pancreas (Frerichs), the disease being shown in atrophy of the organ, in fibrosis, or in cyst formation. It may be, however, that a gross naked-eye change does not necessarily occur in the pancreas when glycosuria results from disease of it. The pancreas consists of two portions: the acini of the glands connected with the ducts, that is, the parts secreting the pancreatic juice; and certain collections of epithelium-like cells which are unconnected with the gland ducts. It may be the latter cells which play a part in the carbohydrate metabolism. The diminution of secretion of pancreatic juice evidently has no effect in the production of glycosuria, and the suggestion has been made that the islets of cells in the pancreas yield an internal secretion which influences the carbohydrate metabolism. When this secretion is absent there ensues the presence of an excess of glucose in the blood, and so glycosuria. This, however, is at present only an hypothesis.

4. *Alimentary Glycosuria.*—This term is given to a slight glycosuria which occurs in certain healthy individuals after a meal rich in sugar, and it has been suggested that when a large quantity of sugar is taken it is absorbed, not by the portal vessels but by the lacteals, so that it is not transformed into glycogen by the liver. Starch when taken as food does not lead to alimentary glycosuria. Dextrose given in quantities of 200 grammes leads to glycosuria in half to one hour, the effect passing off in three to six hours and varying considerably in different individuals. Lævulose behaves in the same way as dextrose, while cane sugar is sometimes discharged unchanged, and sometimes as dextrose. Lactose appears readily in the urine after large quantities are taken. Puerperal lactosuria is an example of alimentary glycosuria. Suckling women also, after partaking of 50 to 100 grammes of lactose, not infrequently have lactosuria. The forms of sugar, called pentoses, also appear in the urine after administration (pentosuria).

It is evident that alimentary glycosuria is quite another condition from the glycosuria produced either by puncture, by

phloridzin, or by pancreatic extirpation, and that it is only a question of absorption and non-transformation of the sugars.

Glycosuria and Diabetes in Man.—As far as is known, these conditions occur naturally chiefly in man. The term glycosuria is frequently applied to the conditions where small quantities of glucose are excreted; diabetes to the severer forms where large quantities of glucose are present in the urine. No such distinction can be drawn from a pathological point of view, and all the conditions are to be considered as diabetes in a mild or severe form. The mild cases are those in which glycosuria only occurs when carbohydrate food is given, or when glucose is present in the urine with a moderate amount of carbohydrate—50 grammes, 100 grammes, or 150 grammes—in the daily diet. The severe cases are those in which glycosuria persists even if carbohydrates are withheld from the diet, and in these cases the carbohydrate present in the blood and tissues is not consumed. This glucose must be derived from the disintegration of the proteids of the body. It has been calculated that 100 grammes of proteid by the addition of H_2O and CO_2 may give rise to 113.6 grammes of glucose; or, in other words, one part nitrogen is equivalent to 7.1 grammes glucose (Moritz and Prausnitz). The excretion of nitrogen in the urine is greatly increased in diabetes, and may even be as high as 30 or 40 grammes of nitrogen daily: the normal being about 15.5 grammes as a minimum. This increased discharge of nitrogen is due partly to the taking in of more proteid food. Thus 200 grammes of proteid in the diet, which is not an excessive quantity for a diabetic to consume, would be equal to 32 grammes nitrogen in the urine. But the increased nitrogen discharge is also due partly to increased destruction of the proteids of the body with the formation of glucose, and due in part to the toxæmia. A patient weighing 49 kg. on a daily diet equal to 2320 calories excreted 34.5 grammes nitrogen. The sugar excreted in the same time was 271 grammes = 1110 calories. Only 1210 calories (2320 − 1110) was the amount of the diet utilised in the body, and this was equivalent to a daily loss of 2 grammes of nitrogen to the body.

Carbohydrates in the Urine.—In diabetes, glucose is the sugar which is almost invariably found. Occasionally small quantities of lævulose or maltose are discovered, and, in rare cases, glycogen, the presence of which has been ascribed to retransformation of the sugar in the kidneys. The amount of sugar which is daily excreted in cases of diabetes varies considerably, the average amount in severe cases, when carbohydrates are excluded from the diet, being about 100 grammes per day, but as much as 200 grammes, or more, daily may be found in the urine. The amount excreted from time to time in the day varies considerably. As a rule, less is found in the morning urine than in the evening, after the day's food has been taken. Inosit is sometimes found in the urine in diabetes.

Diabetic Coma.—The coma of diabetes is associated with symptoms which may also be present as a final stage of abdominal cancer and of pernicious anæmia. The main features are those of stupor of gradual onset, deepening into coma which ends in death, there being at the same time an affection of the respiration, which becomes more rapid and deeper, and an effect on the heart-beat, which becomes more frequent and weaker. The temperature is usually subnormal, and convulsions sometimes occur.

These symptoms are those of an intoxication, but the pathology of the condition has not yet been explained. The following facts may, however, have a bearing on the matter. The condition of the blood in diabetes is that of concentration due to loss of water from the body by the polyuria. This is also observed in diabetes insipidus. But more important than this is the diminished alkalinity of the blood which is due to an increase of acids, mainly of β-oxy-butyric acid (Minkowski). Aceto-acetic acid is also present, as well as acetone. The blood of diabetics shows between 0.154 and 0.576 per cent. of sugar, as compared with the normal variation of 0.05 to 0.12, and the amount of sugar bears a direct relation to the degree of glycosuria. By some, the phenomena of diabetic coma are ascribed to the presence of

β-oxy-butyric acid, but this body does not produce the symptoms of diabetic coma although it is said that the injection into animals of β-amido-butyric acid gives rise to the symptoms of diabetic intoxication (M. Gruber). It has also been suggested that some of the precursors of the acid bodies found in the blood may act as poisons. The symptoms may be produced by the injection into animals of dilute mineral acids, but this experiment has but little bearing on the subject. The perchloride of iron reaction of the urine, that is, the purple colour given with tinctura ferri perchloridi, is in many cases present at the onset of coma, but it may be absent; and, on the other hand, it may be present without coma ensuing. The increase of acetone in the urine in diabetes, and the presence of a large excess of aceto-acetic acid and β-oxy-butyric acid, is a sign of the decomposition of tissue proteids, and the amount of these substances is proportional to the loss of nitrogen from the body. Acetone may be found in diabetic urine to the extent of 2, 5, or 10 grammes a day. Of β-oxy-butyric acid, 30 to 50 grammes or more may be found daily, and the amount of this is diminished when a large amount of proteid food is given, so as to spare the tissue proteid.

C. *Fat Metabolism.*—The metabolism of fat in disease is seen in two different conditions: in a loss of fat which occurs in wasting, the result of a failure in general nutrition; or in an increase of fat which occurs in obesity. There is a physiological increase of fat at puberty and at the menopause, as well as at middle age in men. An increase of fat may otherwise be due either to an increase in the amount of food taken, or to a change in metabolism, in which, without an increase in the amount of food, more fat is deposited in the body.

The obesity due to over-eating is readily explained by the consideration that, after the needs of the body have been supplied as regards the necessary nourishment of tissues in relation to work and heat, the excess of absorbed food is deposited mainly as fat. This explanation does not apply, however, to many cases of obesity which are not due to over-

eating. Obesity follows castration both in the male and female; it is in many families hereditary and may in this case appear in youth, in adult life, or middle age. It is sometimes associated with chronic alcoholism, and occurs after infective disease, and is not infrequently associated with glycosuria. One obscure nervous disease, adiposis dolorosa, is associated with large deposits of fat in various parts of the body, and sometimes with atrophied thyroid.

Metabolism in the obese is diminished. There is a decrease in the body heat, a decreased consumption of oxygen and a decreased output of carbonic acid. There is not infrequently oxaluria, which may possibly be taken as a sign of diminished oxidisation. A complete explanation of the occurrence of obesity, when not due to an excess of food, is not forthcoming. It is, however, possible that the condition is due to a changed metabolism, by which, from the proteids taken as food or present in the body, a greater quantity of fat is formed than normal. By some the condition is said to be explained by speaking of a "retardation of metabolism."

3. A. *Metabolism in Disorders of Respiration and Circulation.*—Metabolic changes in disorders of respiration and circulation may be considered together, as in many instances the conditions are combined. The changes of respiration which here come for consideration are those in which there are respiratory defects leading to dyspnœa (p. 279), and secondarily to circulatory defects, such as venous stasis. The changes in the circulation to be discussed are those concerned in venous stasis, and are due to such primary conditions as valvular disease and dilatation of the heart, or disease of the lungs. Respiratory defects, such as result from destruction or incapacitation of a portion of the lung, as in pneumonia or tuberculosis, or from a loss of elasticity of the lung, as in emphysema, affect mainly the respiratory exchange in the blood. Venous stasis not only affects the respiratory exchange, but the activity of other organs in the body, and more particularly of the liver and kidneys, as they are so prominently concerned in meta-

bolism. The liver, for example, becomes congested and some atrophy and fatty degeneration of the cells occur, while the kidneys show mechanical congestion.

Respiratory Exchange in Cyanosis and Dyspnœa.—In simple forms of cyanosis, such as are observed in uncomplicated mitral disease and in congenital cardiac disease, the respiratory exchange in the lungs is not deficient and is not markedly different from the normal. Sufficient oxygen is taken into the blood and a corresponding quantity of CO_2 discharged. The duskiness of the extremities—fingers, nose and ears—is explained by the slow circulation of the blood in the capillaries of these parts. The oxygen is taken up completely by the tissues from the blood, leading to the dark colour of the part. There is no general deficiency of oxygen, therefore, but only a local deficiency due to an increased absorption of the oxygen of the blood by the tissues. When, however, there is a respiratory defect, either primary or secondary to the cardiac lesion, associated with the resulting dyspnœa, there is a deficiency of oxygen taken into the blood and an excess of CO_2 present, and this is the condition present in dyspnœic and asphyxial states. The deficiency of oxygen and the increase of CO_2 vary considerably in amount and in proportion, not only to the amount of lung damage, but to the degree of compensation possible (p. 290) When into a small portion of lung the air enters with difficulty, the blood from the pulmonary artery supplied to that area does not efficiently discharge its CO_2 or take in oxygen. This blood, therefore, mixing with the blood from other efficiently acting parts of the lung, diminishes the total oxygen in the blood. The main compensation in chronic lung conditions for this diminished quantity of oxygen is that the tissues adapt themselves to a lessened supply of oxygen (p. 292).

Effect of Cyanosis and Dyspnœa on Digestion and Proteid Metabolism.—In all but severe cases the secretion of the digestive juices and absorption go on practically normally.

When, however, in conditions of deep cyanosis there is congestion of the stomach, the amount of hydrochloric acid in the gastric juice is greatly deficient. As a rule, the absorption of carbohydrates and proteids is good; that of fats is diminished in some cases.

There are no very accurate data for discussing the proteid metabolism in dyspnœa and cyanosis in man. In experimental dyspnœa in dogs an increased proteid metabolism is observed, ascribable, it is supposed, to death of a certain number of cells of the body, but it cannot be said with certainty that a similar increased metabolism occurs in man. On the whole, it may be said that the nitrogenous excretion is not increased. This cannot be taken as an accurate indication of the amount of urea which is formed in dyspnœa and cyanosis, for there is no doubt that some of the urea is retained in the body, more particularly in the œdema fluid. Uric acid is not increased except in very severe cyanosis, or just before death. An increased quantity of urea is found in the urine in some cases when diuresis is produced by digitalis. Cases may be divided into three groups (Kobler, quoted by von Noorden).

In the first group, the diuresis produced by digitalis is accompanied by an increased excretion of urea and to some extent of uric acid, as in the following table:—

Daily amount of Urine .	420	400	730	1100	740 c.c.
Urea	9.01	9.28	20.44	23.43	17.83 grammes
Uric Acid . . .	0.53	0.52	0.74	0.98	0.75 „

Thus, with the diuresis, there occurred an enormous excretion of urea which is to be considered as the excretion of the urea retained in the body.

In the second group of cases, while digitalis produced diuresis, the amount of urea was but slightly affected:—

Daily amount of Urine .	500	1050	2200	1850	550	620 c.c.
Urea	10.9	14.8	15.6	13.5	11.5	12.6 grammes
Uric Acid . . .	0.29	0.32	0.4	0.5	0.15	0.22 „

In the third group of cases there was but little diuresis, but the urea was greatly increased.

Daily amount of Urine .	320	200	700	450	510 c.c.
Urea	8.64	5.88	21.42	12.82	13.43 grammes

The increased excretion of urea did not last longer than two to four days, and it may be greater than the figures given above.

The excretion of ammonium salts increases with that of the urea, while that of creatinin, in severe cases of want of compensation, is diminished.

With the consideration of the nitrogenous excretives, must be taken that of lactic acid, which is present not only in the blood but in the urine. It is observed not only in dyspnœic and cyanotic conditions in man, but also experimentally in dogs, as in artificially produced dyspnœa and in poisoning by carbonic oxide, phosphorus, morphine, amyl nitrite, cocaine veratrine, curare and strychnine. The amount in the urine appears to be proportional to the degree of dyspnœa, and its presence may possibly be due to an affection of the liver, the normal amount of lactic acid and ammonia not being transformed into urea. Glycosuria is not observed in dyspnœa or in cyanosis in man, but it is present in dyspnœic conditions experimentally produced in dogs. The oxalic acid in the urine is increased.

4. B. *Metabolism in Anæmias and in Leukæmia.*

1. *Anæmias.* — The conditions included under this head are (Chapter XI.), chlorosis, pernicious anæmia, acute anæmia following hæmorrhage and secondary anæmias. The conditions are widely different pathologically, and have one common factor, the diminution in the amount of hæmoglobin in the blood. Pernicious anæmia and many secondary anæmias differ from chlorosis and acute anæmia in that there is some toxic condition present. The changes in metabolism to some extent depend on this factor.

(*a*) *The Oxidisation Processes.*—A diminution in the amount of hæmoglobin in anæmia, of whatever kind, would lead to

the supposition that the oxidisation processes of the body are diminished owing to a deficiency in the oxygen-carrying substance in the blood ; but the rate of exchange of oxygen and CO_2 has not been found to be widely different from the normal. In anæmia experimentally produced by bleeding in dogs, it has been found that the respiratory exchange is not different from the normal, and experiments performed in pernicious anæmia, chlorosis and in secondary anæmia, show a like result, as well as in leukæmia. Inasmuch as the oxygen carrier is diminished in amount, it is evident that there must be some compensation for the loss of hæmoglobin, and the compensation probably is due partly to increased activity of the heart, and partly to increased rapidity of the breathing. In this case, although the hæmoglobin is diminished, what is present does its work more quickly than in normal conditions, owing to the increased rapidity of circulation of the blood and the increased rapidity of the respiratory exchange in the lungs. In the tissues in anæmia, the hæmoglobin parts with nearly all its oxygen, so that the venous blood is more deficient in oxygen than it is in normal conditions. There may be, however, a degree of anæmia in which the hæmoglobin is not sufficient to keep up the normal respiratory exchange, and in such cases, which mainly occur in pernicious anæmia or severe secondary anæmia, there is some evidence of diminished oxidisation in the tissues. Thus, lactic acid may be found in the urine. It is present in experimental anæmia, but in human anæmia its appearance is very irregular. The fatty degeneration of the glands and heart muscle which occurs in anæmia is no doubt due to the anæmic condition, and has been explained as the result of deficient oxidisation (p. 202). Such degeneration, however, only occurs in severe forms of anæmia, and is possibly associated with an increased and imperfect metabolism of the tissues.

(*b*) *Effect on Digestion and Proteid Metabolism.*—The secretion of hydrochloric acid in chlorosis is, as a rule, not diminished. The percentage varies between 0.26 and 0.58 gramme. In twenty-five cases examined by von Noorden, eight showed an increase of hydrochloric acid, eleven showed the normal quantity, and six showed a diminished quantity. In severe

pernicious anæmia, on the other hand, the secretion of hydrochloric acid may be greatly diminished, and in the acute exacerbations it may be present in the gastric juice in only very small quantities. Both in chlorosis and in pernicious anæmia the absorption of fat may be affected.

Proteid metabolism is not affected in chlorosis to any great extent, and the nitrogenous equilibrium is readily maintained, as shown in the following table of three cases investigated (von Noorden):—

	Duration of Experiment.	Daily Nitrogen in Food.	Calories per kilo Body-Weight.	Nitrogen in Urine and Fæces.	Daily Nitrogen Stored in the Body.
Case I.	7 days.	12.83 g.	38	12.82 g.	+0.06 g.
Case II.	7 days.	13.06 g.	37	12.68 g.	+0.38 g.
Case III.	9 days.	12.92 g.	37	12.21 g.	+0.71 g.

In acute anæmia, however, produced experimentally by bleeding dogs, an increased excretion of nitrogen was found soon after the loss of blood, and a similar increase has been observed in severe pernicious anæmia. This increased proteid destruction in pernicious anæmia is, however, not to be ascribed to the condition of anæmia, but to the condition of intoxication present. In pernicious anæmia, the amount of uric acid excreted is diminished in relation to the other nitrogenous substances, but there is no change in the chlorine equilibrium. There is a diminution in the chlorides in the urine after hæmorrhage.

2. *Leukæmia.*—What has been stated about the respiratory exchange in anæmias applies to leukæmia, which, strictly speaking, is not an anæmic condition until the disease is well advanced (p. 315). Proteid metabolism in leukæmia exhibits certain peculiarities which contrast strongly with those in anæmia. There is increased proteid metabolism which is very irregular in extent in individual cases, the destruction of proteid being apparently in some relation to the number of leucocytes in the blood. Albumoses are found

in the blood and their amount is increased after death. An analysis of leukæmic blood by Freund and Obermeyer (quoted by von Noorden) shows that the percentage of albumoses is about 1.23 as follows:—

	Composition (Percentage) of	
	Leukæmic Blood.	Normal Blood.
Water	89.58	77.9
Total Solids	10.42	22.1
Proteid and Hæmatin . .	7.2	21.27
Albumoses	1.23	...
Fat	0.71	0.16
Lecithin	0.31	
Cholesterin	0.21	
Salts	0.98	0.78

As regards the mineral constituents, phosphates, sodium and sulphates, are greatly increased; while chlorides, potassium, calcium, ammonium and iron are greatly diminished. Besides this, the chief chemical characteristic of leukæmic blood is the presence of albumoses, and a large quantity of lecithin, fat and cholesterin, which, with the phosphates, are derived from the white blood corpuscles, these being included in the analysis.

The amount of urea, in so far as it has been examined in leukæmia, does not appear to differ from the normal, but the main feature in the nitrogenous metabolism is the presence in the urine, although not in the blood, of a greatly increased quantity of uric acid. Thus the amount daily excreted in leukæmia is between 1 and 2 grammes (sometimes 4 or 5 grammes) so that the usual amount is nearly double the normal (0.7). Out of eighteen cases of leukæmia in which the uric acid was estimated by various observers (quoted by von Noorden), the amount daily excreted was in three cases normal or below the normal, and in the remaining cases varied between 0.915 gramme

and 1.06 gramme. The nitrogenous extractives (xanthin bodies) are found increased in the blood and in the urine in many cases. The amount of xanthin bodies found is between 6 and 15 cg., 2 to 3 cg. being the normal amount daily excreted. The increased quantity of uric acid and xanthin bodies present in the urine is due directly to the disintegration of the white cells of the blood, their amount being proportional to the number of white cells. The substances are derived from the nuclein base present in the white corpuscles.

CHAPTER XIX

CHANGES IN THE NERVOUS SYSTEM IN DISEASE

THE changes which occur in the nervous system in disease are manifold and require special consideration, not only on account of the predominating action of the nervous tissue on the other tissues of the body, but also because disease processes affect the structures in a peculiar manner owing to their anatomical and physiological arrangement. The diseases which affect the nervous system may be grouped as follows :—(1) Infections, (2) degenerations, whether due to toxic action or inherited, (3) gross lesions, such as injury, vascular lesions (hæmorrhage and softening) and new growths. It is not, however, within the scope of this work to discuss the particular effects either of infective processes or of such lesions as tumours of the nervous system, but rather to discuss the processes of disease of the nervous system ; that is, the manner in which different parts are affected, and the results.

I. *Arrangement of the Nervous System.*—The central nervous system is composed of nerve cells contained in the gray matter of the brain and spinal cord, and in the spinal ganglia (ganglia of the posterior roots), and of projections from these cells which are in physiological but not anatomical connection with other cells.

The nervous system is therefore composed of cells and branches called a neurone, which is anatomically distinct, but is physiologically connected with other neurones. The arrangement of the neurones is shown in the diagram (Fig. 111). Broadly speaking, they are arranged in two different series or projection systems, as they are called : one, efferent or motor, the other, afferent or sensory.

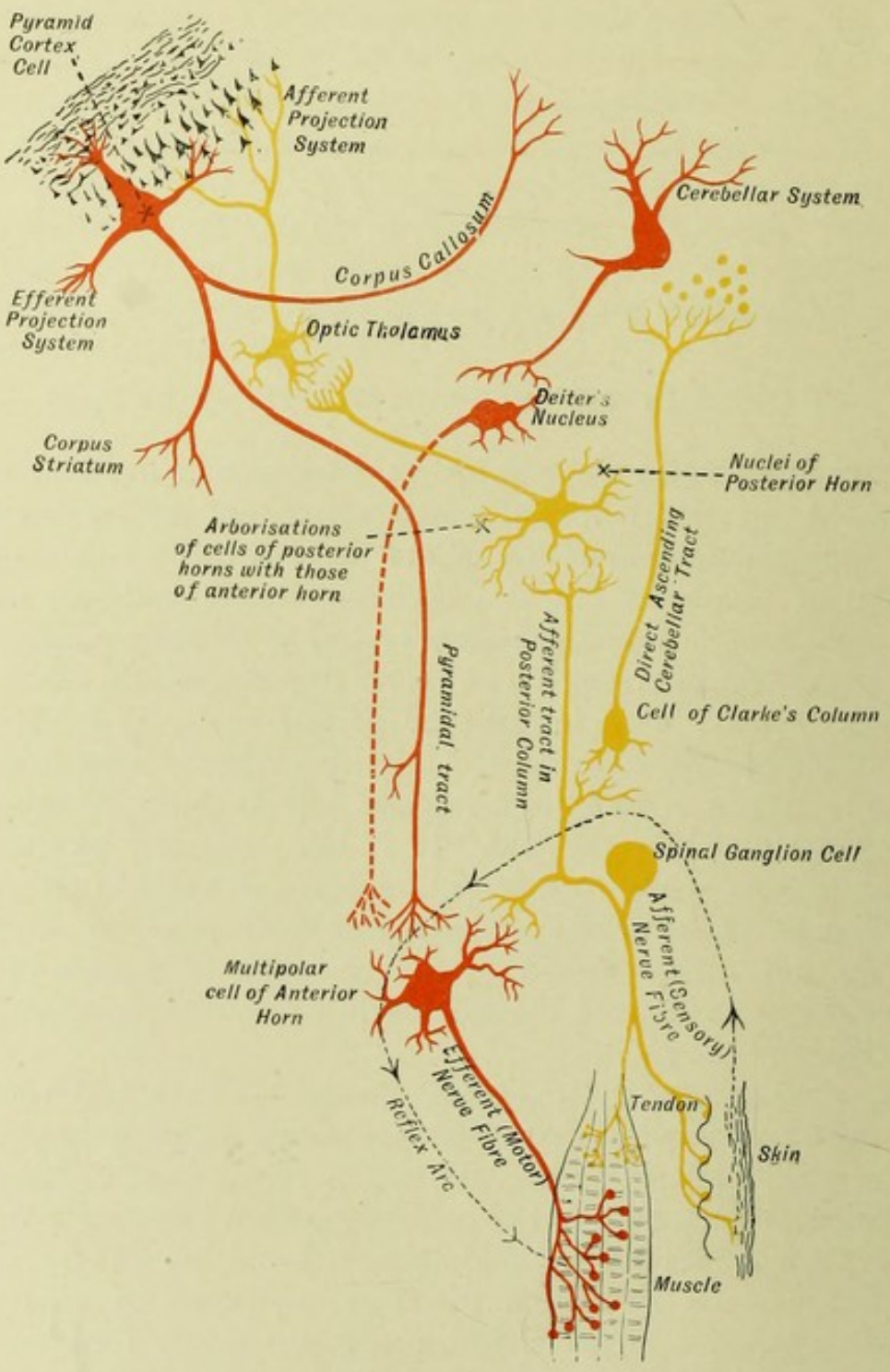


FIG. 111.—Diagram to show the three systems of neurones, illustrating the path of sensory (yellow) impulses to the cerebrum and cerebellum, the path of outgoing (red) impulses from the brain in a voluntary movement and the association of the afferent and efferent projection systems in the gray matter of the brain. The path of a simple spinal reflex is shown by the dotted line. (F. W. Mott.)

Efferent Projection System of Neurones.—The efferent neurone is divided into an upper motor neurone, starting in the cortex, and a lower motor neurone, starting in the multipolar cells of the anterior cornua of the spinal cord. Commencing in the pyramidal cells of the Rolandic area of the cortex, there are first the branches of the cell, which connect it with other convolutions, namely, the association fibres. The axis cylinder or axon passes from the cell, and gives off in its passage through the brain (through the internal capsule and the tegmentum), branches which pass into the corpus callosum—commissural fibres—which terminate by breaking up into smaller branches (arborisations) in the cortex of the other hemisphere. Other branches pass to the corpus striatum; while the main branch passes to the medulla, and most of it crosses into the cord on the opposite side (crossed pyramidal tract), while some passes down the cord on the same side (direct pyramidal tract). The axis cylinder ends by breaking up into arborisations round the branches of the cells of the anterior horns. The upper motor neurone, although an anatomical entity, has by its branches numerous connections with the cells of other parts of the cortex of each hemisphere and with the corpus striatum, as well as with the cells of the lower motor neurone. The lower motor neurone arises in the multipolar cell of the anterior horn. The branches of this cell are in physiological connection with the terminations of the axis cylinder of the upper motor neurone, and with the cells of the posterior horns of the cord. The axis cylinder passes to the muscle. The cell of the lower motor neurone is also in physiological connection with fibres passing from the cerebellum above.

Afferent Neurone.—The afferent neurones are more complicated than the motor. The lowest afferent or sensory neurone commences in the nerve cell of the spinal ganglion. The axis cylinder from this bifurcates, one part passing to the skin and tendon as a sensory nerve fibre, and the other passing into the cord, where it has very numerous connections. After it enters the cord it passes upwards and is connected by means of collateral branches and arborisations with the motor cells of the anterior horn, with the cells of the posterior horn

and with the cells of Clarke's column. The axis cylinder sends branches upwards in the direct cerebellar tract, and is physiologically connected with the cerebellum. The main part of the axis cylinder of the spinal ganglion cell passes upwards in the cord to the nucleus gracilis and nucleus cuneatus of the medulla, where it ends in arborisations in physiological connection with the nerve cells of the nuclei. The axis cylinders of the cells of the nucleus gracilis pass upwards on either side of the brain, and terminate round a cell of the optic thalamus. The axis cylinder from the cell of the optic thalamus passes upwards, and ends in arborisations round the branches of the cells of the cortical grey matter, as well as round the branches of the motor pyramidal cell. The sensory fibres in the cord are, therefore, mainly exogenous. A small tract, called the "comma" tract (Fig. 116), is probably endogenous, arising from the cells of the gray matter and passing downwards.

It is obvious from the above description that, although the arrangement of the nervous system is conveniently divided into efferent or motor, and afferent or sensory, systems, yet the arrangement is an extremely complicated one, more particularly on the sensory side, and that this complexity is still further increased by the consideration of the higher functions of the brain, such as those comprised in ideation and psychomotor activity.



FIG. 112.—Normal pyramidal Bett's cell, cortex cerebri, stained by the Nissl method. ×700. The Nissl granules are seen occupying the body of the cell and extending also into the processes. (F. W. Mott.)

The Nerve Cell.—The structure of the nerve cell is that of a protoplasmic cell, with a large oval nucleus and nucleolus situated in the centre of the cell (Fig. 112). The cell is divided into two parts, one of which, forming the body of the cell (the so-called trophoplasm), is continued directly into the axis cylinder. Round the nucleus, and continued into the branches, there can be demonstrated by appropriate staining with methylene blue, certain bodies called Nissl bodies or

granules, sometimes referred to as kinetoplasm. These granules are composed, in all probability, of nucleo-proteid, inasmuch as they contain phosphorus and are not digested by pepsin. The axis cylinder, composed of protoplasm, is covered, in the brain and spinal cord, by a myelin sheath, which consists of phosphorised fat. Outside the brain and the cord the myelin sheath is still further covered by the nucleated sheath of Schwann, which is continued in the peripheral nerves. The myelin sheath is developed after the axis cylinder, but its physiological relation to the axis cylinder is not understood. The cellular sheath of Schwann is formed of mesoblastic cells and plays some active part in the regeneration of nerves.

II. *Conditions of Nutrition of the Neurones.*—A nerve cell, after it has undergone a certain degree of degeneration, cannot be regenerated, as is the case with other cells. Owing, however, to the individuality of the nerve cell and its branches (the neurone), the cell once dead cannot be replaced. The axis cylinder can, however, be regenerated if one part of it is destroyed, if the nerve cell is still intact. The duration of life of the nerve cell becomes, therefore, of great importance in the study of the general pathology of nerve disease; not only its inherent vitality, but its vitality as affected by inheritance, by the action of poisons and by the conditions of circulation of the blood and its composition.

The earliest change which is seen when the nerve cell undergoes degeneration, is the disappearance, either partial or complete, of the Nissl bodies, as definite bodies stained by methylene blue. This is referred to as chromatolysis (Figs. 113 and 114). Sometimes the granules appear to be diffused through the protoplasm of the cell in fine particles. They may disappear altogether, a cell being diffusely stained by the reagent. This, according to recent research, may be considered as the first effect of injury to the nerve cell, and if it is correct to consider the granules as consisting of nucleo-proteid, chromatolysis must be considered a great change, considering the important relation that nucleo-proteid has to the nutrition of the cell, and its importance in other pathological conditions (p. 331). It is considered that a condition of chromatolysis may be

recovered from. More advanced degeneration of the nerve cell is seen in the contraction and distortion of its branches, in vacuolation of the protoplasm, the nucleus occupying a

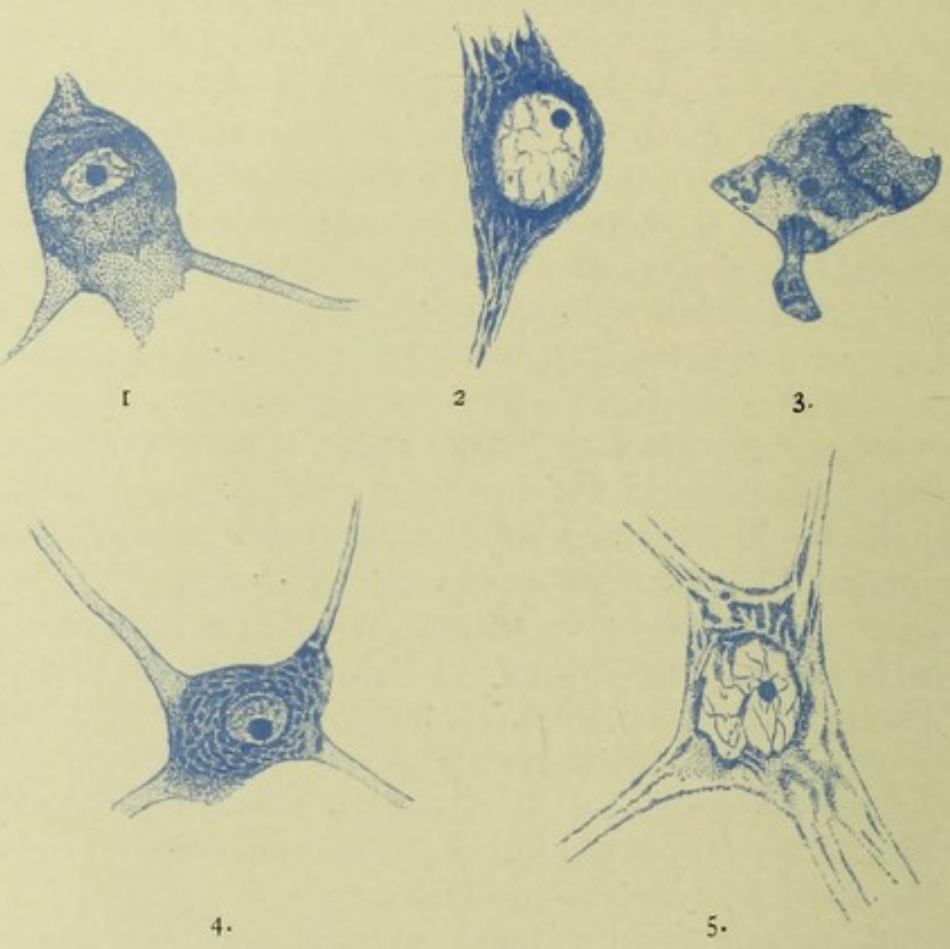


FIG. 113.—Degeneration in nerve cells, stained by the Nissl method. (F. W. Mott.)

1. Pyramidal cortical cell from a monkey five days after ligature of two carotids and one vertebral, showing swelling of the cell with diffuse homogeneous staining, owing to the stainable substance being scattered through the protoplasm of the cell as a fine dust.

2. Pyramidal cell of a dog after ligature of two carotids, one vertebral and one subclavian. There is great swelling of the nucleus, and advanced chromatolysis, most marked at the periphery of the cell.

3. A cortical pyramidal cell in acute softening, produced by ligature of the cerebral arteries. The cell is dead and phagocytes are adhering to it.

4. Spinal motor cell of rabbit, acute botulin poisoning. Swelling of nucleus, commencing chromatolysis.

5. Spinal motor cell from a case of negro lethargy with hyperpyrexia. The Nissl granules have disappeared and the staining is diffuse.

peripheral position and even being extruded. From such a condition the nerve cell does not recover.

(*a*) It is an important fact that the nerve cell may be

affected by an injury to its axis cylinder. Besides the changes in the portion of axis cylinder which is severed from the nerve cell and which will be described later, there is, so to speak, a reaction backwards on the cell itself, and this is shown

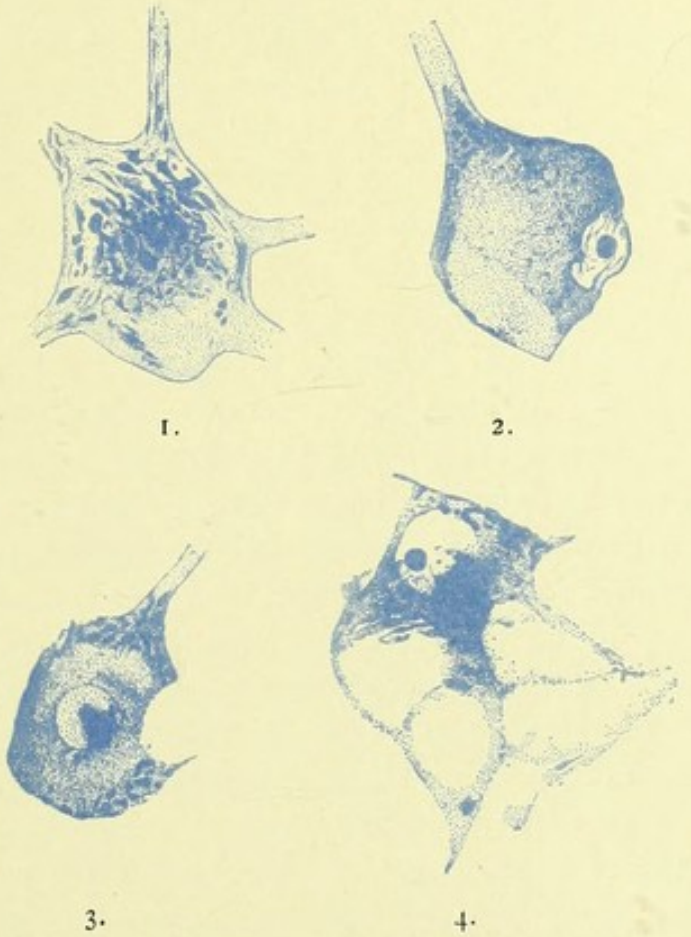


FIG. 114.—Degeneration of the cells of the anterior horn of the lumbo-sacral enlargement in a case of alcoholic paraplegia. (F. W. Mott.)

1. Shows commencing chromatolysis; disappearance of the Nissl granules.
2. Shows advanced chromatolysis, and eccentric position of the nucleus.
3. Shows chromatolysis as well as a concavity at one side, indicating rupture of the nuclear membrane and death of the cell.
4. Shows swelling and eccentric position of the nucleus, and extensive vacuolation of the protoplasm of the cell, indicating death.

by chromatolysis and by a displacement of the nucleus towards the periphery of the cell. This change does not persist in experimental cases, but reparation takes place, the nucleus coming back to the centre of the cell and the Nissl granules reappearing. If, however, the injury to the axis cylinder be great, such as when the portion of the nerve is

cut or torn away, the cell of origin undergoes degeneration and atrophy occurs.

(*b*) The nerve cell is also directly affected by poisons—chemical, bacterial, and those developed in the body, as in auto-intoxication. Thus, in strychnine poisoning and in tetanus, there is chromatolysis with the diffusion of the Nissl bodies throughout the cell. The cell becomes enlarged, probably by hydration, and there is enlargement and pallor of the nucleus. Chromatolysis is also observed as the result of the action of abrin, ricin, the toxine of the bacillus botulinus, of rabies, pellagra, lathyrism and ergotism. This change is also observed in artificially-produced hyperthermia, if the temperature of the animal, for example, is raised to 109.5° or over. There is swelling of the cell and its branches, a diffused staining by methylene blue and an irregular nucleus. In some cases of hyperpyrexia in man, a similar change is observed.

(*c*) The nutrition of the nerve cell depends to some extent on its systematic activity. Disuse may lead to degeneration, and degeneration or interference with the functional activity of one system produces an effect on the functional activity of another. An illustration of the first point may be seen in the results of the changes following amputation of a limb. The long disuse of the nerve which follows in this case leads to its atrophy and that of the cells of origin. After amputation of a limb, for example, both anterior and posterior roots may be found degenerated, as well as the main nerve of the limb. An illustration of the second statement is seen in the result of dividing the posterior roots. Division of the posterior roots from the third cervical to the third dorsal inclusive rendered the upper limb insensitive, as was to be expected. But the animal was incapable of performing the finer voluntary movements, showing that the loss of the afferent impulses had affected motility, although the efferent path from the cerebral cortex, as tested by stimulating it, was normal. Section of the posterior roots also causes a loss of tonus in the muscle. This interdependence of efferent and afferent systems in the performance of normal functions is of great importance in the consideration of nervous disease. Section of the posterior

roots may, indeed, cause chromatolysis in the motor cells of the anterior horn of the cord. Other examples may be given of the effect of injury to one neurone on the functional activity of another, or in causing its degeneration; such, for example, as the atrophy of the cells of the lower motor neurone when the upper motor neurone is partially destroyed by disease, as in hemiplegia.

III. *Anatomical Results of Destruction of a Neurone at one or other part.*—The results which follow destruction of the neurone must be considered as to whether the cell is first destroyed, or the axis cylinder.

Injury to the Axis Cylinder.—The effects of injury to the axis cylinder have been studied after section of a peripheral nerve, of a nerve root, or of the spinal cord itself. Complete transverse section of a *mixed nerve* leads to simultaneous degeneration of the nerve fibres below the lesion down to their endings—either motor or sensory. Upwards, the nerve fibres degenerate as far as the next node. The effect on the nerve cell has already been described. The degeneration of a nerve below the lesion is spoken of as Wallerian degeneration, and is of the same character whether the axis cylinder is severed in a peripheral nerve, in a nerve root, or in the brain or spinal cord. The degeneration is characterised by a breaking up of the myelin sheath into droplets (Fig. 122), the lecithin being decomposed and finally disappearing; while the axis cylinder becomes irregularly broken up, and finally disappears. Some proliferation of the nuclei of the sheath of Schwann occurs. If the two ends of the divided nerve are sutured together, regeneration occurs, the axis cylinder growing down from the proximal end of the divided nerve and developing a myelin sheath. The function of the nerve may in time be restored. Section of an *anterior root* leads to a similar Wallerian degeneration below the injury, affecting, however, in this case, only the efferent fibres of the mixed nerve. Some slight degeneration upwards towards the cord is observed, and a change occurs in the nerve cells, but these changes are insignificant compared to the changes below the lesion.

Section of the *posterior roots* has, however, a different effect

to the foregoing, owing to the entrance of the afferent fibres into the cord. By reference to the diagram (Fig. 111) it will be seen that section of the posterior root separates the axis cylinder from the cell of origin in the spinal ganglion. Wallerian degeneration occurs in the part of the root attached to the cord, and in the cord along the tracts in which the afferent fibres run. These tracts are shown in the diagram (Fig. 115). The afferent fibres pass up the cord in the posterior columns: (*a*) in the column of Goll, the nearest to the posterior median fissure; (*b*) the column of Burdach outside this; and (*c*) in one smaller column, the tract of Lissauer, which is between the column of Burdach, the apex of the posterior horn, and the crossed pyramidal tract; (*d*) a fourth tract passes down the cord, as the "comma" tract in the column of Burdach. The comma tract represents afferent fibres descending the cord, and when it degenerates it is called a descending degeneration, inasmuch as it passes downwards. The tract of Lissauer is a lateral tract of afferent fibres. The main afferent fibres run in the columns of Goll and Burdach, and the parts represented in these columns are, starting from the posterior median fissure, fibres from the lumbar and sacral regions contained in the column of Goll; fibres from the dorsal region, partly in the column of Goll and partly in that of Burdach; and fibres mainly from the cervical region in the column of Burdach. The tracts of degeneration produced by section of the posterior nerve roots diminish as they proceed upwards, many of the axis cylinders no doubt ending in the cells of the gray matter. The degeneration extends upwards as far as the nucleus gracilis,

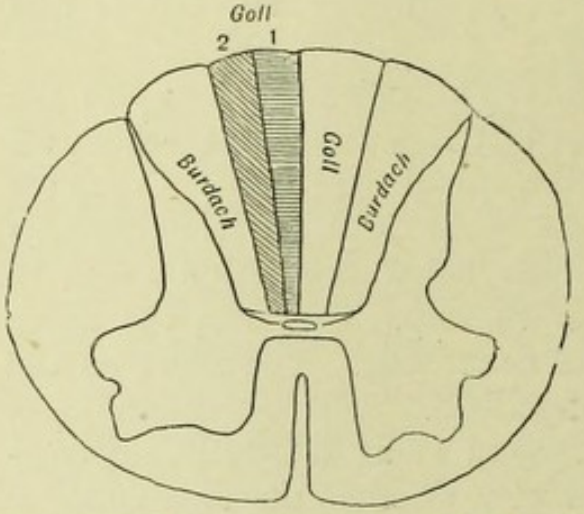


FIG. 115.—Degeneration in the column of Goll after section of the posterior roots on one side. (Kirke's *Physiology*.)

The section is taken high up in the cord: all the degenerated fibres are seen in the column of Goll on the same side. (1) Nearest the posterior fissure indicates the degenerated fibres from the lowest nerve roots; (2) the degenerated fibres from nerve roots higher up in the cord.

and nucleus cuneatus in the medulla, which is the termination of the lower sensory neurone.

Section of the *spinal cord* itself leads to degeneration both upwards and downwards, since both afferent and efferent axons are separated from their nerve cells. The degenerations which occur upwards are those which result from section of the posterior roots (Figs. 116 and 117). Those occurring downwards result from separation of the efferent axon from its nerve cell: these degenerated tracts are seen in the crossed and direct pyramidal tracts. A descending degeneration occurs in

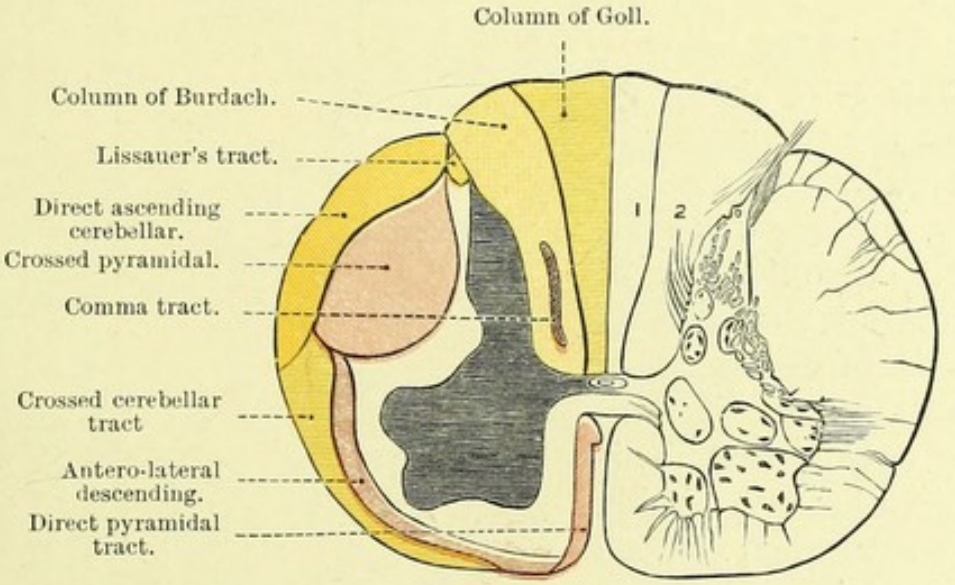


FIG. 116.—Section of spinal cord in the cervical region, showing the tracts of white matter in one half, and the groups of nerve cells in the other. (After Sherrington, from Kirke's *Physiology*.)

the comma tract, which is afferent. Another descending degeneration is the descending degeneration of the cerebellar tract of the antero-lateral column. Two other ascending tracts require to be mentioned: namely, the direct cerebellar tract and the antero-lateral ascending tract (Gowers). Both these are, as will be seen by reference to the diagram (Fig. 111), separated from their nerve cell of origin.

Tracts of degeneration in the brain and spinal cord also result by the removal of the cells of origin of the axon. Thus, removal of the cortex in the motor area (Rolandic area) results in degeneration of the upper motor neurone as far downwards

as the cells of the anterior horns (lower motor neurone). This tract of degeneration is seen in the pyramidal tracts of the brain and cord. In the cord, both the direct pyramidal and the crossed pyramidal tracts are degenerated. Some degenerated fibres are found in the lateral tract of the cord on the same side as the lesion.

Removal of one lateral half of the cerebellum in animals, leads to degeneration, on the same side, of the circumference of the antero-lateral column, the area of degeneration diminishing as it proceeds downwards. This degeneration probably only occurs when Deiter's nucleus is injured or destroyed. Degenerated fibres have also been found in the anterior roots.

The functional changes which result from these degenerations are subsequently considered (p. 483). Some changes concerning the chemistry of degeneration must now be taken into account.

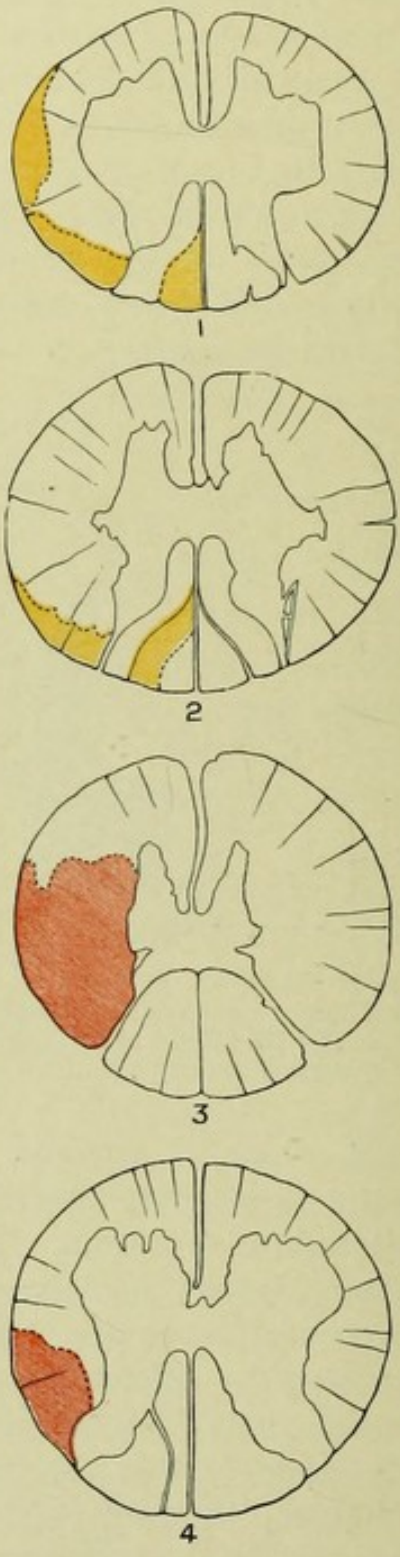


FIG. 117.—Diagrams showing the tracts of degeneration following left hemisection of the cord in the thoracic region in a monkey. (Kirke's *Physiology*, after F. W. Mott.)

The tracts of degeneration are all on the same side as the lesion—ascending, yellow; descending, red.
1 and 2 are above the lesion: (2) just above the lesion in the thoracic region, shows degeneration in the outer part of Goll's column (see Fig. 115), and in the direct cerebellar tract: (1) in the cervical region shows that the degenerated tract in Goll's column now occupies a median position. Degenerations in the direct cerebellar tract and in Gower's tract (antero-lateral ascending) are also seen.
3 and 4 are below the lesion: (3) is just below the lesion in the thoracic region; a large area of degeneration is seen in the crossed pyramidal tract: (4) is lower down in the lumbar enlargement. The area of degeneration in the pyramidal tract is smaller.

IV. *Chemical Changes occurring in Nerve Degeneration.*—The chemical changes which

occur in degeneration, both of the central nervous system and of the peripheral nerves, mainly concern, as far as is known, the myelin sheath. This consists, in part, of a substance called protagon, which is supposed to be a compound of lecithin and cerebrin. Lecithin ($C_{42}H_{84}NPO_9$) is a complex fat which yields, on decomposition, glycerine, stearic acid, phosphoric acid and choline. The formula for choline is $N.(CH_3)_3C_2H_6O_2$ (p. 73). Some decomposition of protagon probably occurs in normal conditions in nerve tissue, but the choline, which is hereby liberated, is not found in the urine and is probably oxidised in the body.

That some chemical change occurs in the myelin sheath in degeneration, is seen by the reaction of osmic acid, which is most conveniently applied to the nerve tissues in the form of Marchi's fluid (one part of 1 per cent. osmic acid and two parts of Müller's fluid). The normal nerve fibre, both in and outside the central nervous system, stains a light colour with a greenish tinge by this fluid. When, however, it has degenerated, the myelin, which is mostly in the form of droplets, stains a black colour just like the reaction of osmic acid on ordinary fatty tissue. The change which has probably occurred is therefore the formation of a fat not containing phosphorus. It has been found that, in a cord, one half of which only showed degeneration, ether extracted from the degenerated half a larger quantity of fat than from the undegenerated; the amount of phosphorus, however, from the degenerated portion being less than from the normal. Probably part of the fat formed in the process of degeneration comes from the decomposition of the proteid of the axis cylinder (Mott). These results led to the investigation of the presence of choline in the cerebro-spinal fluid in various forms of degeneration. The physiological action of choline is shown mainly in a fall of arterial blood pressure, due partly to an action on the heart, but mainly to a dilatation of the vessels of the splanchnic or intestinal area. This action is independent of the influence of the cord or splanchnic nerves, as it occurs after section of the cord and of these nerves. An extract of brain also produces this result, which has been ascribed to the presence of choline. It may

therefore be that choline is a normal result of the metabolism of nerve tissue, and that its presence in appreciable quantities in degenerated nerve tissue is only an excess of the normal condition. The cerebro-spinal fluid and blood, in cases of general paralysis of the insane, when injected into an animal, causes a fall of blood pressure due to choline (Fig. 118). If atropine is injected, there is no fall, but a rise. From the cerebro-spinal fluid the choline has been separated by chemical means. Choline

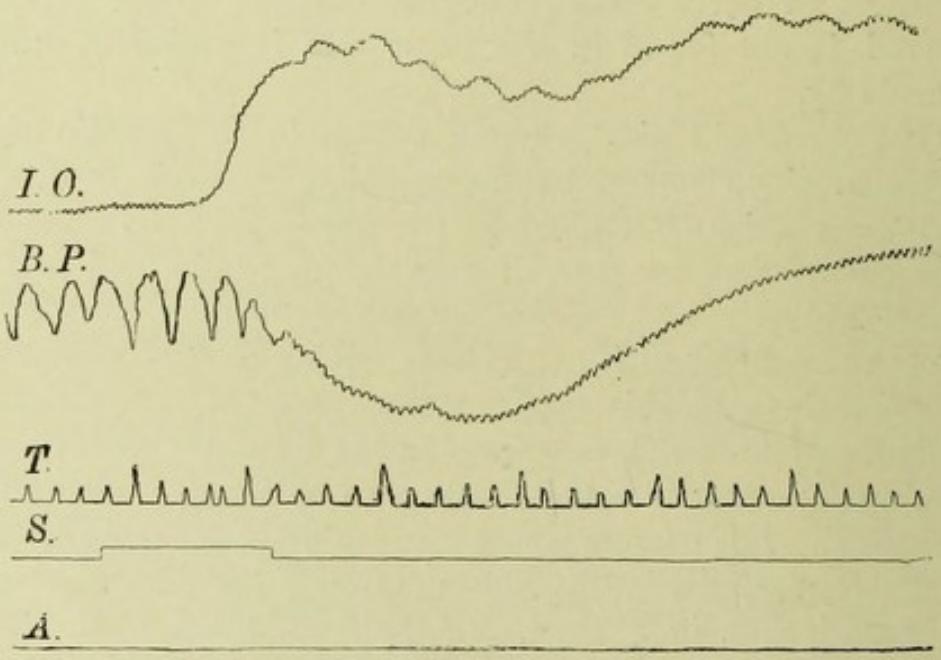


FIG. 118.—Tracing of intestinal oncometer (I.O.) and arterial blood pressure (B.P.) in a cat. T, time; S, signal; A, abscissa.

Ten cubic centimetres of cerebro-spinal fluid from a case of general paralysis were injected. The fall of blood pressure is at first mainly cardiac in origin, for the oncometer tracing first follows the fall of arterial blood pressure passively; it, however, soon rises, indicating dilatation of the peripheral vessels. The same effect was produced in the same animal by injecting 2 c.cm. of 0·2 per cent. solution of choline. (Mott and Halliburton.)

has also been found in cases of combined sclerosis, beri-beri and in degenerated peripheral nerves (Mott and Halliburton).

The cerebro-spinal fluid in general paralysis is also peculiar in containing, in some instances, an appreciable quantity of nucleo-proteid, which has produced coagulation after intravenous injection into animals. This nucleo-proteid would, no doubt, be liberated during the degeneration of the nerve cells.

Diseases of the Neurones as they occur in Man.—The diseases

of the neurones as they occur in natural disease in man are not so simple as the results observed in experimental lesions of the nervous system, the majority of cases of disease being due to one or other form of intoxication. The parts of the nervous system affected are by no means uniformly the same, although certain types of affection may be described.

The first grouping to be made is into primary and secondary degenerations. Secondary degenerations have practically been already discussed. They are due to severance of the axis cylinder from its cell of origin. It is thus a Wallerian degeneration, the part of the axis cylinder severed from its cell being affected. The secondary degeneration is thus commonly observed in peripheral neuritis in those fibres in which the axis cylinder becomes ruptured. It is also observed in transverse lesions of the cord, whether produced by pressure, by disease—such as myelitis—or by an injury; and it is observed as the result of injury to the efferent fibres of the upper motor neurones in the brain, as in hæmorrhage and thrombosis or embolism of the middle cerebral artery. Tracts of degeneration in the spinal cord which result from a transverse lesion are those which have been described as resulting from a section of the cord. The degree of degeneration, however, varies in disease according as to whether the lesion is completely transverse or only partially so. Again, in the brain, the degeneration of the efferent fibres down as far as the lower motor neurone, occurs as the result usually of rupture of the fibres, such as occurs in hæmorrhage affecting the internal capsule or the corona radiata.

1. *Peripheral Neuritis.*—There remains for more detailed consideration the degeneration which occurs in peripheral neuritis. Degeneration of the peripheral nerves due to, disease is always the result of one or other form of poisoning. The commonest causes are chronic alcoholism, plumbism, diphtheria and beri-beri. It may, however, occur as the result of the intoxication occurring in influenza, typhoid fever, pneumonia, erysipelas, septicæmia, malaria, gonorrhœa, and syphilis, but it is not common after these diseases. It occurs in some cases of diabetes, gout and rheumatism, and

results from poisoning by arsenic, mercury, phosphorus and silver, among inorganic substances; and ether, carbon disulphide, nitro-benzene, aniline and carbonic oxide, among organic substances.

It is not necessary here to discuss all the conditions produced by these various intoxications. The nerve change in diphtheria has already been considered (p. 86). A few general

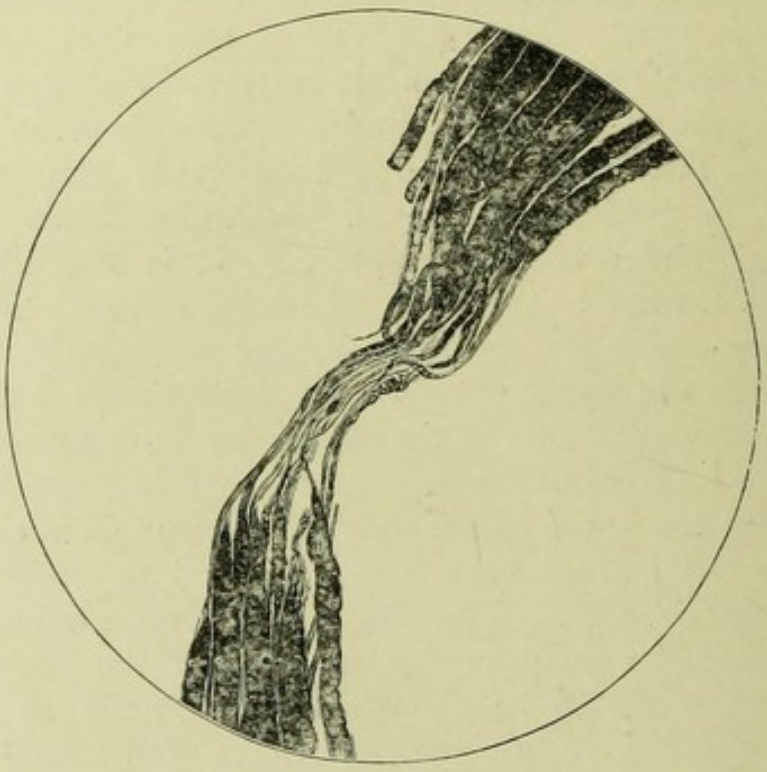


FIG. 119.—Nerve degeneration in diphtheria (experimental).

The figure shows a bundle of nerve fibres in one of the anterior roots of a rabbit, paralysed by the intravenous injection of albumoses from the spleen of a patient dead of diphtheria. At one part the nerve fibres have lost their white sheath; the primitive sheath and, in some cases, the axis cylinder being intact. Stained with osmic acid.

points in relation to the pathology of peripheral neuritis may, however, be mentioned (Figs. 119-122).

(*a*) In different forms of intoxication, a selective action of the poison appears to be evidenced. In chronic plumbism, a frequent form of peripheral neuritis, there is an affection of certain branches of the musculo-spiral nerve, causing a paralysis of the extensors of the hand and dropped wrist; there is no affection of the sensory nerves, and the lesion may be

symmetrical. In alcoholic neuritis, the nerves specially affected are those of the extensors of the ankle, causing dropping of the foot. Both in lead poisoning and in alcoholism other parts may be affected. Thus, in lead poisoning a general affection of the nerves may be present, or the nerve cells of the brain may be affected, as in encephalopathia saturnina. In chronic alcoholism, again, the neuritis may be general, and there is a distinct effect frequently on the cells of the spinal

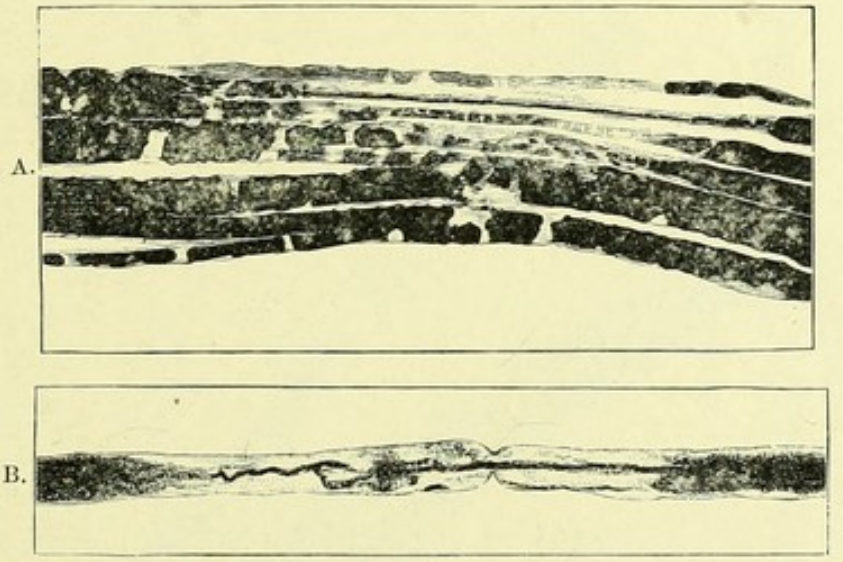


FIG. 120.—Nerve degeneration in diphtheria (experimental).

A. is a bundle of fibres in the phrenic nerve of a rabbit, paralysed by the intravenous injection of extract of diphtheritic membrane. The white sheath is broken up irregularly, and has in part disappeared. In one fibre the axis cylinder is seen intact.

B. Portion of a single nerve fibre from the nerve to the vastus in a rabbit paralysed by the intravenous injection of albumoses from a case of diphtheria. There is disappearance of the white substance on each side of a node, while the axis cylinder is ruptured and has become tortuous.

Stained with osmic acid.

cord, which show vacuolation and increased pigmentation, as well as on the cells of the brain. It is thus evidenced that, although the poison may select some particular nerve for its action, yet this selection is only part of a general intoxication, and is possibly determined by occupation, as, for example, occurring in plumbism in the arms of painters, and in alcoholic neuritis in the legs, which bear more stress than the arms.

Moderate degrees of neuritis, such as occur in neuritis from arsenic medicinally administered, or in diabetes, affects the legs more than the other parts of the body; and in

rabbits, in which experimental diphtheritic paralysis has been produced, the degeneration in the nerves of the muscles of the legs is much more marked than in the nerves of the rest of the body, more particularly than in those of the forelegs.

(*b*) The question arises whether the degeneration of the nerve in peripheral neuritis is due to a local toxic action of the poison on the nerve fibre, or to a primary effect on the

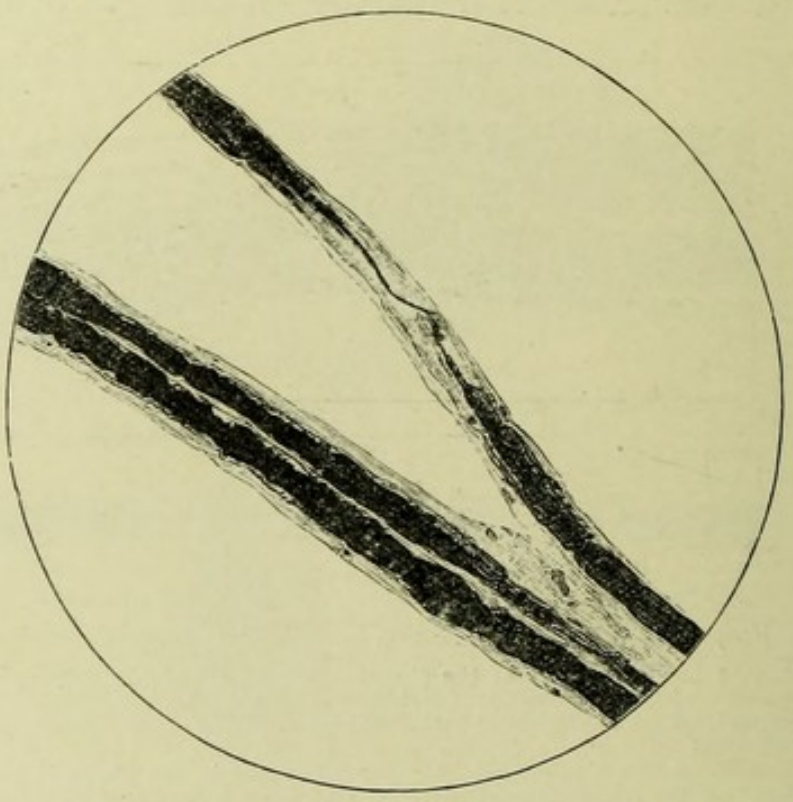


FIG. 121.—Nerve degeneration in alcoholic neuritis.

Three nerve fibres are shown from the nerve to the left tibialis anticus. In the uppermost fibre the white substance has disappeared from part of the fibre, and the axis cylinder is tortuous and ruptured. The second fibre shows a loss of white substance in one part, while the third fibre is normal. Stained with osmic acid.

cell of origin, whereby the trophic influence of the cell on the axis cylinder is removed. This point cannot be at present decided, but in experimental conditions, more particularly in diphtheria, the nerve degeneration appears to be out of all proportion to any change visible in the cells of origin. In diphtheritic paralysis in man, however, changes in the cells are frequently present, as they are in alcoholic neuritis and in some cases of chronic plumbism.

(*c*) The pathological change in peripheral neuritis is mainly a degeneration of the nerve fibre, which, after rupture of the axis cylinder, leads to Wallerian degeneration below the rupture (Figs. 121 and 122). In some cases, however, there is an increase of connective tissue round the nerve bundles, and this is described as a special variety of peripheral neuritis, and called interstitial. It is very much open to doubt whether, as some appear to believe, this increase of interstitial tissue is the cause of the nerve degeneration by compression. It is more likely to result from the action of the poison itself, which produces the nerve degeneration.

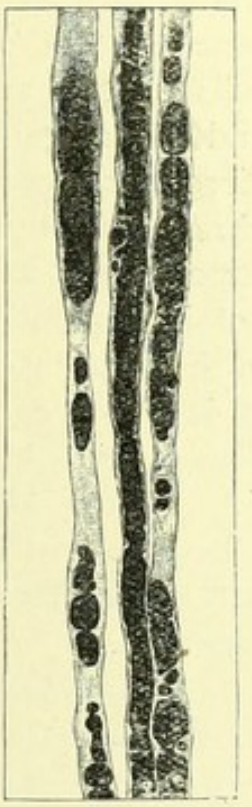


FIG. 122.—Nerve degeneration in alcoholic neuritis.

Three nerve fibres form the nerve to the right vastus internus. The middle fibre shows slight breaking up of the white substance: the other two fibres show extensive breaking up with destruction of the axis cylinder (Wallerian degeneration). Stained with osmic acid.

2. *Diseases of the Efferent Projection System of Neurones.*—The diseases here to be considered are those in which the axons of the upper efferent neurone are affected, as in spastic paraplegia (primary lateral sclerosis); those in which these axons are affected as well as the cells of origin (amytrophic lateral sclerosis)—both these lesions are, however, mixed, more than one system being affected; and those in which the cells of origin of the efferent neurone are affected, such as acute and chronic anterior poliomyelitis and bulbar palsy (mainly glosso-labio-laryngeal palsy); and polioencephalitis.

(*a*) *Affection of the Upper Projection System of Efferent Neurones*—In spastic paraplegia the lesion is mainly in the pyramidal tracts of each side, being most marked in the lower part of the cord and diminishing upwards. The lesion is a degeneration of the axons, and appears to be—in some cases, at any rate—associated with changes in the nerve cells; indeed, the condition does not appear to differ pathologically from the condition in peripheral neuritis. Cases do occur in which the nerve cells do not appear affected, but

the affection of the nerve cells which occurs in some cases would bring the disease pathologically in line with amyotrophic lateral sclerosis, which is a degeneration of the whole of the efferent neurone system affecting the cells of the anterior horns, and the lateral columns (the direct and crossed pyramidal fibres) right up to the motor cortex (Fig. 123). The lesion not infrequently commences in the upper part of the cord. It is to be considered as a disease in which degeneration follows changes in the cells of origin in both upper and lower efferent projection neurones.

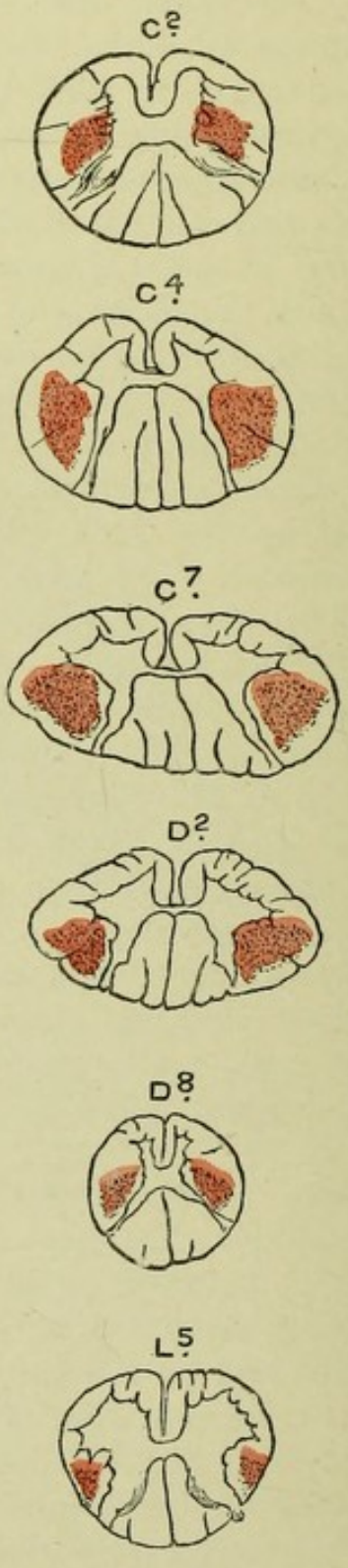


FIG. 123.—Amyotrophic lateral sclerosis.

The figure shows the tracts of degeneration in the cord: they occurred chiefly in the crossed pyramidal tracts. There was also some degeneration in the anterior commissure and in the antero-lateral columns in parts. In addition, the following changes were found in the nervous system:—
(1) Diminution and degeneration of the cells of the anterior horn in the cervical and lumbar enlargements.
(2) Atrophy of the peripheral nerves and the muscles.
(3) Degeneration of the large cells of the motor cortex and of the efferent tract through the capsule, pons, medulla and in corpus callosum. Also atrophy of cells of 9th, 10th, 11th and 12th nerve nuclei in the medulla. (F. W. Mott and A. F. Tredgold.)

(*b*) *Affection of the Lower Projection System of Efferent Neurones.*—In acute anterior poliomyelitis there is a primary effect on the cells of the anterior horns, leading to their granular degeneration and then to atrophy. The result is degeneration of the axons of the cells, which extends through the anterior roots right down to the muscles. This is a simple instance of degeneration of the whole of the lower efferent projection neurone. A similar affection occurs in the cranial motor nerves, and is referred to as polio-encephalitis.

The condition, however, in chronic anterior poliomyelitis (progressive muscular atrophy) does not appear to be so simple (Fig. 124), as some consider that besides the degeneration of the nerve cells in the anterior horns there is some degeneration in the lateral columns (Gowers). Many observers, however, have found no such degeneration, showing that the upper efferent neurone is unaffected. In the majority of cases there is degeneration in the anterior roots, and there are many degenerated fibres in the peripheral nerves. The muscle fibres undergo atrophy, the cross striation being retained for a long time.

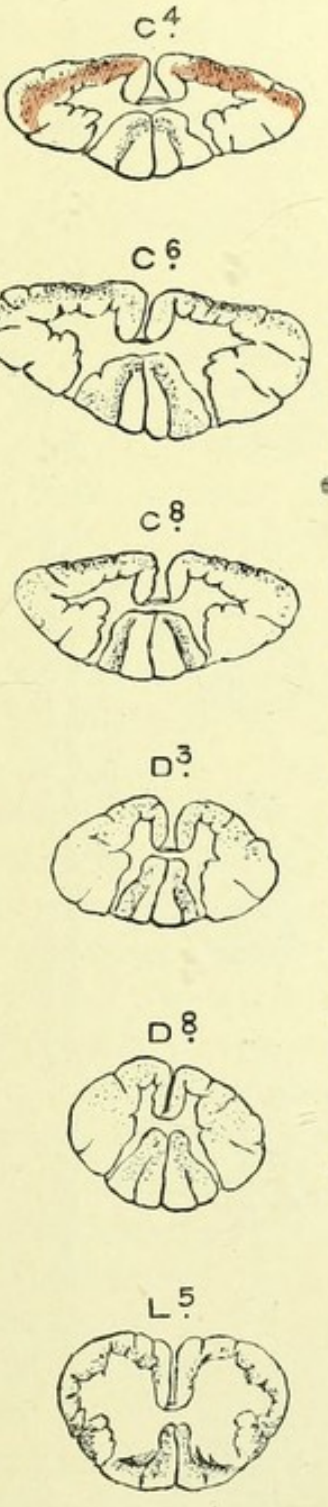


FIG. 124.—Progressive muscular atrophy. (Mott and Tredgold.)

There was extreme degeneration of the anterior horn cells in the cervical enlargement, with atrophy of the anterior roots. There was no change in the cells in the dorsal and lumbar regions. The figure shows there was slight sclerosis in the posterior columns throughout, and in the crossed pyramidal tracts in the lumbo-sacral region.

The changes in bulbar palsy come into line with those described in anterior poliomyelitis. In none of these conditions is the afferent projection system of neurones affected. Progressive muscular atrophy, bulbar palsy and amyotrophic lateral sclerosis are closely related, if not identical in their pathological processes.

3. *Diseases of the Afferent Projection System of Neurones.*—The best example of these is seen in tabes dorsalis, which may be described as "a primary progressive degeneration of the first afferent (sensory) projection system of neurones," the change which occurs being a degeneration of the posterior spinal roots and the posterior columns of the spinal cord (Fig. 125). The trophic centre of the first afferent neurone

FIG. 125.—Tabes dorsalis.

The degenerated tracts are in the posterior columns only (columns of Goll or of Burdach). In addition, the posterior roots are degenerated. (Mott and Tredgold, from Green's *Pathology*.)

FIG. 126.—Combined scleroses, chiefly amyotrophic.

The degeneration in the pyramidal tracts is shown as in Fig. 123. This extended upwards to the pons. In addition, there is degeneration in Goll's and the antero-lateral columns, and in the projection fibres of the motor cortex. The cells of the motor cortex showed no change; but those of the anterior horns in the cervical and lumbar regions were atrophied, as well as the cells of the glosso-pharyngeal and hypoglossal nuclei. There was atrophy of fibres of peripheral nerves. (F. W. Mott and A. F. Tredgold.)

exists in the spinal ganglion. It is noteworthy that in tabes no pathological changes have been found in these cells; so that whether the degeneration is dependent on some change in the cells or is a primary degeneration of the axons is unknown. In tabes there is degeneration not infrequently in the peripheral nerves, and changes in the muscle spindles. The posterior roots are invariably affected, but the extent of degeneration of the axons of the afferent neurones in the cord varies with the locality in which the disease commences: (*a*) In most cases of tabes the changes begin at the lower part of the cord and extend upwards; (*b*) in some cases the changes commence in the cervical region; and (*c*) in other cases they are in the brain and bulb (Marie).

The tract of Lissauer (Fig. 116) degenerates early, as well as the fibres which terminate round Clarke's column of cells. As a rule the disease begins in the lumbar roots, and in the cord degeneration is seen in Burdach's and Goll's tracts. Fibres which are frequently not degenerated are—Flechsig's median oval area, the commissural bundle zone and the posterior external angle of the posterior column. The extent and position of the tracts of degeneration in the posterior columns depends on the nerve roots affected. In the column of Goll, for example, the fibres become degenerated, more particularly if the fifth lumbar and first and second sacral roots are diseased. If these roots are not affected the tracts degenerated are mainly in Burdach's column. Thus in the rare condition of cervical tabes Goll's column remains practically undegenerated. Although the main stress of disease falls on the first afferent projection system of neurones, yet there is an affection of the cerebral nerves and ganglia. Thus there is degeneration of the optic nerve, which is followed by an affection of the ganglion cells of the retina and a spreading of the degeneration towards the corpora quadrigemina and the internal geniculate bodies. The glosso-pharyngeal fibres may be degenerated as well as the auditory nerve, and the cells of the cerebral cortex may show some slight change.

All the changes just described as occurring in the brain are affections of the afferent neurones. Affection, however,

of the efferent neurones in the brain may be present, mainly in the nuclei of the oculo-motor nerve, followed by degenerations in the nerves of the eye muscles, and in the nucleus of the hypoglossal nerve. These are the chief two motor affections which occur in tabes. In some cases, weakness of the extensors of the forearms has been observed. Although tabes, therefore, is mainly an affection of the afferent neurones in the spinal cord, the changes in the brain bring it into line with another disease—general paralysis of the insane—in which there is extensive disease of the afferent neurones, and to some extent of the efferent.

In ergotism, which is produced by the presence of ergot in rye bread, there is an affection of the nervous system in which the efferent neurones escape, the sensory nerves being affected. In some cases the posterior columns of the cord have been found affected, as in tabes dorsalis. The posterior root zones are said to be affected in the cases exhibiting most pain.

4. *Combined Degenerations or Scleroses.*—In the conditions to be discussed, the seats of degeneration are not all completely worked out, owing possibly to the scarcity of accurately made post-mortem examinations. In *ataxic paraplegia*, there is a combined sclerosis of the lateral and posterior columns. The lesions in the latter tracts resemble those in tabes dorsalis, the posterior roots not being affected, however, to so great a degree; but the cross pyramidal tracts are mainly affected in the lateral columns and also the direct cerebellar tract. In this case, therefore, there is a degeneration of both the afferent and efferent projection system of neurones. A subacute combined degeneration affecting the same parts as in ataxic paraplegia, may occur. It is probably of toxic origin. A similar anatomical condition to ataxic paraplegia exists in *hereditary ataxy* (Friedreich's disease). Here the degeneration differs from that of tabes in that the posterior nerve roots are less affected and Lissauer's tract usually escapes degeneration.

In *pellagra*, which results from eating diseased maize, mainly in Italy, and in *pernicious anæmia* there is degeneration of the posterior and lateral columns of the cord

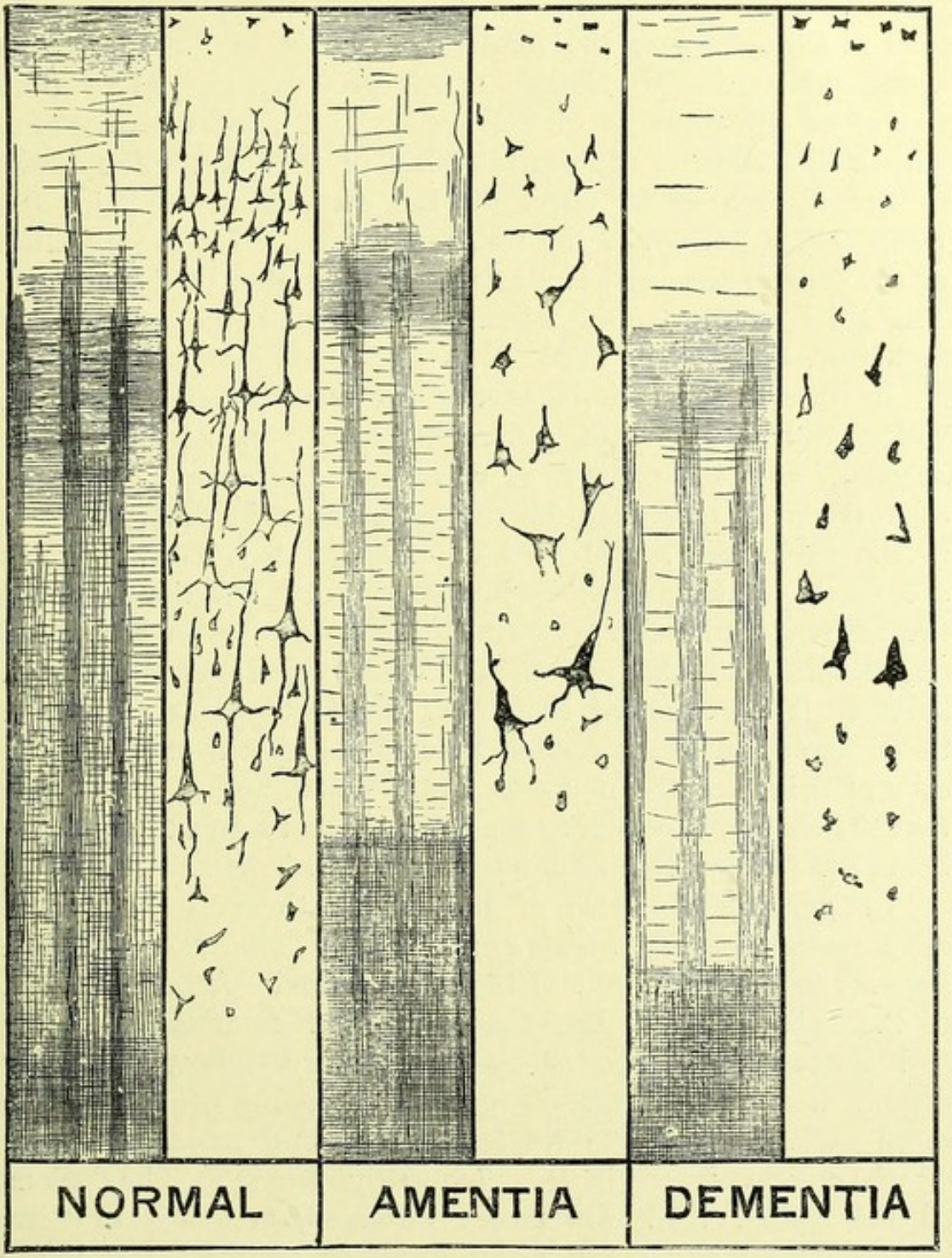


FIG. 127.—The diagram represents the relative degeneration of fibres and nerve cells of the cerebral cortex in amentia and dementia as compared to the normal. (F. W. Mott.)

associated with atrophy of the motor cells of the anterior cornua.

In *syringomyelia*, the anatomical basis of the disease is a destruction, due to disease, of the grey matter, and to some extent of the columns of the cord. This may be associated with a dilatation of the central canal of the cord. The result of the disease is an effect on the conduction of pain and temperature, but not of the sense of touch; while the affection of the cells of the cord leads to a degeneration of their axons. The chief feature of the disease is, however, the affection of sensation.

In two degenerations of the nervous system there is a widespread affection of different parts, namely, in *insular sclerosis*, and in *general paralysis of the insane*. Insular sclerosis is characterised by the appearance in different parts of the brain and spinal cord of areas of degeneration which are focal, so that there is interruption or affection of both the afferent and efferent tracts. There is also an associated degeneration of the peripheral nerves, chiefly of the cranial nerves. It is remarked that these areas of sclerosis give rise to no secondary degeneration upwards or downwards, but the cells of origin of the neurones are affected, and it is probable that the change is primarily a parenchymatous one, the sclerosis being secondary; though the opposite view is held.

In general paralysis of the insane there is widespread degeneration of the neurones; not only of the association systems in the brain, but of the afferent and efferent neurones of the spinal cord. The tangential and commissural fibres and association fibres of the cortex are almost uniformly degenerated, and there is general atrophy of the brain, more particularly of the frontal and parietal lobes. Atrophy of the cranial nerves is also frequently present. The lesions of the spinal cord which are observed, are degenerations in the lateral and posterior columns, or an insular sclerosis. The nerve cells of the cortex are degenerated. Nissl granules have disappeared and the cells are small and irregular in outline, the branches showing distortion. The cells eventually undergo disintegration, the nucleus becoming irregular or

destroyed. The peripheral nerves show parenchymatous degeneration, especially in the lower extremity, and there are frequently degenerative changes in the voluntary muscles, in the heart and other viscera of the body. There is no disease which produces such widespread degeneration of the nervous system as general paralysis of the insane. In some instances the early stress of the disease is on the spinal cord, the lesions of tabes being first developed. In other cases the first stress is on the brain.

Effect of Disease of the Efferent Projection System of Neurones.—1. *Disease of the Lower Projection System.*—The diseases comprise those affecting the cells of the motor nuclei of the brain and of the anterior horns (cells of origin), and those affecting the peripheral nerves.

The effect of disease of the *peripheral nerves* is only in a few cases in disease similar to section of a nerve. If there is complete severance of a nerve there is loss of power (paralysis) and of sensation in the parts supplied by the nerve. Subsequently the muscles waste and give the reaction of degeneration. This is an increased excitability to the galvanic current and a decreased excitability to the Faradic current, the application of which in advanced cases produces no contraction of the muscle. Normally, the application of the negative pole to the tested part gives a contraction with weak currents when the current is closed (cathode closing contraction, C.C.C.). With stronger currents, there is a contraction with the positive pole (anode) on the tested part, when the current is broken (A.O.C.). With still stronger currents there is an anodal closing contraction (A.C.C.). In the reaction of degeneration the changes that take place are that the anodal closing contraction (A.C.C.) becomes more marked than even the C.C.C.; while the cathode opening contraction, which requires in health stronger currents than are bearable, becomes more marked than the A.O.C. The reaction changes as the disease progresses, and in the later stages there is only a sluggish and prolonged response to galvanism. Vaso-motor palsy is also observed in the part affected. It is noteworthy that if the two ends of the divided

nerve be sutured together soon after division regeneration of the nerve takes place, with more or less complete return of motor power and of sensation. Sensation returns before motility. If, however, the suturing does not take place for some long time after the division, say for months or years, no return of motor power occurs, but the sensation may return and the rapidity with which sensation returns after suturing of the ends of the nerve in some of these cases is certainly remarkable. The absence of the return of power under the conditions described is to be explained by want of regeneration of the efferent axons. Two factors influence the delay or absence of a return of motor power. One is, if the muscles are completely degenerated, even a regeneration of the axons would not cause a return of power. But another factor is the effect on the cells of origin after the axon has been divided (p. 462); the cells of the anterior horn being affected, the diminished nutrition of the axon delays or prevents its regeneration.

In peripheral neuritis, as seen in disease, all degrees of loss of motor power following the nerve lesion are observed. It is not common in such cases to find complete degeneration of the nerve. In most cases the degeneration is partial, fibres or bundles of fibres being affected and lying amidst normal fibres and bundles. There is a paresis of the affected muscles without an actual paralysis except in advanced cases; this is true of many cases of alcoholic and diphtheria neuritis. The muscles supplied by the affected nerve undergo fatty degeneration, usually only in proportion to the degree of nerve degeneration, and the reaction of degeneration is observed if the nerve-muscle is extensively affected. The knee jerks are lost owing to the affection of the reflex arc. There is sometimes vaso-motor palsy. The loss of sensation varies considerably. It is never so extensive as in primary affection of the sensory projection system of neurones, but is usually patchy and shown by loss of tactile sensibility in various parts, almost exclusively the distal, the trunk usually escaping.

Affection of the *cells of origin* of the *lower projection system* of efferent neurones leads to paralysis of the muscles, their flaccidity, to a loss of knee jerk on the side affected, to the

reaction of degeneration and to a vaso-motor palsy. No further comments need be made on these points. The effect, however, varies somewhat as to whether the disease occurs in children during the growing period or in adults. Thus in infantile palsy, in addition to the changes already described, there is an arrest in growth of the part affected, an arrest which affects all the tissues of the limb, including the bone and joints. This arrest of growth has been ascribed to a trophic influence, but this is a question somewhat difficult to decide. It has been said that the cells of the anterior horns exercise a trophic influence over the tissues of the limb which is supplied by nerves from them, but it may be that the defective nutrition shown in arrested growth—or rather diminished growth—is due to the paralysis, that is, to the absence of the contraction of muscles and to the altered blood supply due to the vaso-motor paralysis.

In anterior poliomyelitis occurring in adults, these trophic changes are not observed. The change in progressive muscular atrophy (degeneration of the anterior horn cells) differs from that in infantile palsy, from the fact that the muscles do not show a typical reaction of degeneration. This is, however, present in a modified form in many cases.

2. *Effect of Disease of the Upper Projection System.*—The result of degeneration of the axons of the cells of origin of the upper motor neurone is the production of paresis or paralysis of the part and wasting of the muscles from disuse. No reaction of degeneration occurs, but there is a diminished excitability of the muscular tissue to electrical stimulation. Vaso-motor palsy occurs, but the main results besides the paresis of muscles is spasm and contracture of the affected part, and an increase of the knee jerks. Increase of the knee jerks is due to the fact that, the normal inhibitory influence of the brain being removed, the reflex arc associated with the knee jerks becomes more excitable.

The explanation of the spasm which occurs mainly in spastic paraplegia, but also in secondary degeneration following hemiplegia, is not so simple, and still awaits elucidation. In spastic paraplegia the development of the spasm and

spastic gait is a very slow process, and, although present when the individual is quiescent, the spasm is increased and frequently brought out by a voluntary movement. It has been ascribed to the removal of inhibition from the cerebral centres which normally have an inhibitory influence on reflex movement. This would mean that volitional impulses passing from the cortex in a case of spastic paraplegia, would be imperfectly conducted down the pyramidal tracts, down some of the axons not at all owing to their degeneration, and that more powerful impulses than normal, passing down the unaffected axons, would stimulate the cells of origin of the lower motor neurone to an exaggerated effect on the muscles. This, however, is a purely theoretical consideration, and is not supported by any experimental or pathological evidence. Another explanation of spasm is that it is due to a reaction of the cerebellum which normally exercises a tonic influence on the muscles, the axons of cells in the cerebellum being in relation with the cells of the anterior horns. In spastic paraplegia, the influence of the cerebral centres being removed or diminished, there is over-action on the part of the cerebellum leading to increased tonus of the muscles resulting in spasm.

Affection of the cells of origin of the upper motor neurone leads to very varying results, as is seen in disease of the cortex. Destruction of the cells leads to palsy of the parts supplied from the cells, with some slight degree of loss of sensation. There is no reaction of degeneration, but wasting of the muscles may be observed, mainly from disuse. Irritation of the cells leading to increased activity also occurs, leading to impulsive movements of varying kinds (p. 490). In amentia and dementia there is degeneration of the cells and the fibres in varying degree. This is shown in Fig. 127.

Effect of Disease of the Afferent (Sensory) Projection System of Neurones.—Sensation is affected by interruption in any part of the path of afferent impulses. The degree, however, of affection varies in individual diseases.

In disease of the *peripheral nerves*, the loss of sensation is not complete except in the case of severance of the nerve. In

peripheral neuritis in which a mixed nerve is affected, sensation may not be affected, and when affected, the loss is not complete. Affection of sensation is seen in numbness and tingling and in the loss of tactile sensibility.

A profound affection of sensation occurs in tabes dorsalis and in other affections in which the posterior columns of the cord are affected, as well as in syringomyelia in which the gray matter of the cord is affected, and in some cases the posterior columns. In tabes dorsalis, the loss of sensation is over the part supplied from the affected area of the cord and posterior root. There is loss of tactile sensibility or delayed sensation of touch, a loss of sensation to pain as well as loss of sensation of heat and cold. In addition, there is a loss of muscular sense; that is, a loss of co-ordination, so that the individual walks with his eyes on his feet, cannot walk in the dark and sways in the upright position with the eyes closed (Romberg's sign). The gait is ataxic; hence the name of the disease—locomotor ataxy. In syringomyelia, there is loss of sensation which is of a peculiar and characteristic kind. Over the parts affected, there is loss of sensation to pain and to temperature, while tactile sensibility is retained, and this is the chief condition in which this combination of results obtains. It may occur in other central lesions of the cord: but these are rare.

It is in tabes and syringomyelia that *trophic changes*, or trophoneuroses, occur with more frequency than in any other nerve condition. They also occur in general paralysis of the insane, but only when tabes co-exists with it. In tabes, there is an affection of the bones which leads to their spontaneous fracture, more particularly of the long bones and those of the limb affected by the disease. The bony tissue is worm-eaten and atrophied, new tissue in some cases being deposited round the articular edge of the bones. The inorganic elements of the bones, more particularly the phosphates, are diminished from 66 to 24 per cent.; while the organic are increased from 33 to 76 per cent. Atrophy of the bones occurs also in old age and in malignant disease, but this is probably a result due to a general defect of nutrition, whereas in tabes the bones

affected are those of the limb showing the signs of the nerve disease. It is the same case with a joint disease (Charcot's disease), which is mainly an atrophy of the heads of the bones and the cartilage, with an increased secretion of thin fluid somewhat like synovia. Osteophytic growths are not uncommon round the edge of the bone, and are possibly not a part of the trophic disease, but are the result of irritation produced by moving the joint. The vertebral column is also affected, and the foot. The tabetic foot has a truncated appearance, like that of a Chinese lady. The arch has disappeared, and the condition appears to be due to atrophy of the bones of the foot. In syringomyelia, similar trophic changes occur in the bones and joints, but they are more common than in tabes. Scoliosis is a common symptom. Perforating ulcer of the foot is more common than in tabes, Friedreich's disease, or in other nerve conditions, although it may occur as a sequel of compression of the nerves and spinal cord, of injury to the nervous system and of peripheral neuritis. The trophic changes which are observed in tabes and in syringomyelia are clearly associated with an affection of the sensory tract; but whether they are due to an affection of trophic centres, or where these are situated, is as yet unknown. It is possible that the nerve cells, associated with trophic changes, are in the grey matter along the whole length of the cord, and that there are no definite centres, such as exist for other actions in the medulla oblongata. It has been suggested that the trophic changes are associated with paralysis of the vaso-motor nerves or centres, a suggestion which it is impossible to reconcile with the extreme damage which occurs in a Charcot's joint. It has also been considered that the sensory fibres from an articulation form a reflex arc through the vaso-motor centre with the vaso-motor nerve fibres, and that the atrophy of the bone and joint is due to irregularity of the impulses transmitted through the bone and articulation, whereby a deficient nutrition is produced, and so atrophy.

Other trophic lesions are observed in diseases of the nervous system. Thus, following injury to nerves, an affection of the joints of the part is described, which may begin with effusion,

but passes on to stiffness of the joints and to fibrous ankylosis. Wounds of nerves are followed in some instances by a glossy skin over the part affected, red blotches occurring in the skin as well. Pemphigus also sometimes follows injury to nerves.

Herpes zoster is an eruption of the skin following the distribution of nerves, which is accompanied by great pain, and is associated with acute disease of the spinal ganglion.

Besides the effects which have been already described as resulting from disease of one or other part of the projection systems of neurones, there remains for consideration certain special effects observed as the result of disease mainly of nerve cells. These are tremor, spasm and convulsions.

Tremor.—Tremors are to-and-fro movements of the limbs and of the head and neck which occur in very various conditions. They are observed in specific diseases of the nervous system, such as paralysis agitans, disseminated sclerosis and general paralysis of the insane. In the first case the hands are affected more particularly; in the second the parts are those affected by the sclerosis, more particularly the hands and arms, the head and neck and the ocular muscles (nystagmus); while in general paralysis tremor affects not only the facial muscles, but the hands. Tremor is also observed in the hands in Graves' disease, in the hands and head in old age (senile tremor), and, more particularly in the arms, as the result of poisoning by alcohol and mercury, and in convalescence from acute disease. It also occurs as the result of shock and fright.

Tremor may be spontaneous and continuous, as in paralysis agitans, and also in senile, alcoholic and mercurial tremor. As a rule, however, even if not initiated, tremor is exaggerated by voluntary movement, more particularly in disseminated sclerosis, mercurial tremor and Graves' disease. The part of the nervous system affected in tremor is the nerve cell or centre. Disease of the efferent nerve does not lead to tremor. The afferent nerve acts as a conductor of impulses in tremor due to shock or fright. This may be called reflex tremor.

Tremor is due to an irregular discharge from the nerve cell

to the muscles in conditions in which the vitality of the nerve cell is diminished, as in general paralysis, alcoholic poisoning and in the convalescence from acute disease. The rate of tremor varies. The movements occur three to seven times per second in paralysis agitans, and are rather more frequent in disseminated sclerosis and alcoholic tremor.

Spasm and Convulsions.—One form of spasm, namely, that associated with degeneration of the pyramidal tracts, has already been considered. In this case the spasm is associated with removal of the influence of the cells of the upper efferent neurone on the cells of the lower motor neurone. This spasm is *tonic*, that is, produced by a slow and prolonged contraction of the muscles. Spasm may also be *clonic;* that is, produced by a rapid contraction and relaxation of the muscles. Tonic and clonic spasms are produced by a direct effect on the motor nerve cell of the upper or lower efferent neurone, either by a direct effect on these cells or by a reflex effect. A direct effect on the cells is observed in certain special diseases such as epilepsy, hysterical convulsions, puerperal and renal eclampsia, toxic convulsions and asphyxial convulsions.

In epilepsy there is a period of tonic spasm, followed by clonic spasms, due to the discharges from the cortical motor cells. These discharges are recurrent, producing the epileptic fits. In hysterical convulsions similar cortical discharges occur, but they are more irregular. Convulsions due to renal or puerperal conditions are possibly due to the effect of some poison on the nerve cell, although they may be associated with an altered cerebral circulation. In asphyxia, convulsions are due to the effect of a deficiency of oxygen and an excess of carbonic acid on the nerve cell, while a definite toxic effect on the nerve cell is observed in strychnine and picrotoxine poisoning, in tetanus and in infective disease in children. In the first three cases the convulsions are mainly of spinal cord origin.

Reflex convulsions occur mainly in children, and are observed in rickets and in intestinal disturbances, whether due to the indigestion of food or to the presence of worms.

Spasms due to mechanical irritation of the cells occur

mainly from pressure on the cortex, or as the result of some local inflammation.

Effect of Changes in the Circulation on the Brain and Spinal Cord. — The conditions of circulation of blood in the brain have certain peculiarities which it is necessary to discuss separately, and which bear a distinct relation to certain nervous diseases. The arteries in the brain and spinal cord are end-arteries; that is, are vessels whose branches do not anastomose with those of neighbouring arteries, but break up into capillaries continued into the veins. There is no evidence that the arteries have vaso-motor nerves, and it appears that in the brain, at any rate, the cerebral circulation "passively follows the changes in the general arterial and venous pressure." A rise of general arterial pressure accelerates the flow of blood through the brain, and a fall slackens it. Increase of pressure in the vena cava would, therefore, impede the cerebral circulation. The brain, however, is not passively supplied by blood according to the conditions of the general circulation, inasmuch as the supply of blood is controlled by centres in the medulla. When more blood is required, the heart is accelerated and the pressure in the carotid artery raised. The influence of gravity is counteracted by means of an increase in the cardiac beat and by the general vaso-motor mechanism. If, as in some cases of disease, such as shock and exhausting disease, there is weak action of the heart and a paralysis of the vaso-constrictor mechanism, the influence of gravity leads to a collection of the blood in the great abdominal veins, and diminution or cessation of the circulation in the brain, thus leading to syncope. Leonard Hill considers that hyperæmia of the brain does not exist as a pathological state. Anæmia of the brain is, however, observed, and has already been partly discussed in the discussion on Cheyne-Stokes respiration (p. 289). Local anæmia of the brain is produced by embolism (p. 348), and results in disease of the cerebral tissue. The subject of anæmia of the brain has been studied experimentally by embolic occlusion of the arteries, or by ligature of the cerebral arteries. The effect of the production

of anæmia of the whole of the brain leads to loss of consciousness and a general motor paralysis; sometimes with epileptiform convulsions, dilatation of the pupils and nystagmus. The muscles become rigid and there is hyperexcitability. Ligature of the four cerebral arteries in cats and monkeys leads to tonic spasm, and if after this operation absinthe be injected, there is an increase of the spasm, instead of the usual effect of the production of clonic spasms. In dogs, recovery takes place after ligature of all the four arteries (that is, both carotids and both vertebrals) owing to the fact that a collateral circulation is established through the superior intercostal artery and the anterior spinal artery. For some days, however, the dogs remain paretic and demented, and in this condition the nerve cells show distinct changes, such as the loss of the Nissl granules and the swelling of the cell as well as of the nucleus, which may become eccentric or may even be extruded (Fig. 113). The conditions of circulation in the brain may, to some extent, explain the loss of consciousness which occurs in syncope and in epilepsy. In animals in which no collateral circulation is established after ligature of the cerebral arteries, the nerve cells degenerate, showing a diffused staining by the Nissl method and destruction of the processes of the cells.

The spinal cord is also sensitive to alterations in the amount of blood supplied to it. Thus, if the abdominal aorta be compressed from one quarter to three quarters of an hour, a temporary paraplegia occurs, which disappears when the circulation is restored. If, however, the compression of the aorta lasts for one hour or more, the paraplegia is permanent, and an examination shows that the cells of the grey matter are affected, chromatolysis occurring with atrophy of the nucleus, while those tracts of the cord in direct connection with the grey matter degenerate, the pyramidal tracts and the afferent tracts coming from the spinal ganglion not being affected.

Causation of Degeneration of the Nervous System.—Local disease of the nervous system or of the surrounding parts leads to a local effect, which may be associated with a degeneration of the neurones in the manner already described. Degeneration

of one or other part of the nervous system, apart from local disease, also occurs, and the causation of this must be briefly considered. It is a wide subject, which includes the changes occurring in insanity as well as in primary degeneration of the neurones. The causes of these changes are still a matter of discussion, but a prime position in the consideration of their causation must be ascribed to *heredity ;* and it may be said that diseases of the nervous system are the chief diseases of the body in which heredity plays a prominent part. This is seen, for example, in the inheritance of insanity, of epilepsy, of neuroses, such as migraine and asthma, and in the inheritance and in the occurrence in families of such diseases as Friedreich's ataxy. But heredity plays a still further part in the predisposing to nervous disease, inasmuch as the inheritance of nerve conditions is not only interchangeable, but, in an apparently normal individual with a nerve history, a disease other than that of the nervous system will bring out the hereditary defect, as is seen, for example, in epilepsy, in puerperal mania and in many other forms of insanity. An infective disease is frequently the initiating cause, as, for example, scarlet fever in epilepsy and typhoid fever and influenza in mental derangement. A second great predisposing or initiating cause of nerve disease and degeneration is *toxic*, and besides the diseases already mentioned, such as ergotism, pellagra and lathyrism, which are due to specific causes, the two poisons which are most frequently concerned in the production of nerve disease are alcohol and syphilis. The effect of an excess of alcohol is seen first in blunting of the intellectual faculties, the production of emotional disturbances and the production of inco-ordination of movement—effects which are quite separate from the causation of alcoholic neuritis, or the effect of the poison on the internal organs. Syphilis is a disease which affects the nervous system in three different ways—gummata are formed ; arteries may become diseased ; and, without either of these specific lesions, degeneration of the neurones may occur, as in tabes dorsalis and general paralysis of the insane.

What other poisons may act in producing disease of the nervous system is not known, but it is evident that some of the

diseases of the central nervous system are infective in origin; either a primary infection, or secondary to some general infection or intoxication. These diseases more particularly are acute anterior poliomyelitis, acute polio-encephalitis and acute myelitis not due to pressure. An affection of the peripheral nerves is due in the vast majority of instances to one or other form of intoxication (p. 471).

The question of the tissue immediately and primarily affected in many chronic diseases of the nervous system is one in which it is very difficult to arrive at definite conclusions. In many of these diseases, there is, in addition to degeneration of the nerve elements themselves, sclerosis of the tissue around (the neuroglia), as well as, in many, disease of the vessels in the perivascular spaces of the brain. The question arises, which of these changes, the nerve degeneration, the sclerosis, or the vascular changes, is the primary? Modern research tends to the conclusion that the nerve degeneration is the primary change, the other lesions being subsidiary. There is, for example, no reason why, if the sclerosis were primary, it should affect a definite tract in the nervous system; and the same remark applies to any vascular changes. Sclerosis, like fibrosis (p. 220), arises from irritation, and it is a question whether it arises from the poison producing the nerve degeneration or from the chemical products of the nerve degeneration (p. 468). This cannot at present be decided: but it may be pointed out that the virus of syphilis and alcohol are common causes of fibrosis elsewhere in the body. In some instances vascular degeneration and sclerosis appear to go *pari passu* with the nerve lesion.

The Effect of Nerve Disease on the Body and on Metabolism.—In all cases of prolonged disease of the nervous system there is an effect on the general nutrition. This is associated not only with fatty degeneration and infiltration of the heart, but with a similar change in the liver, and sometimes in the voluntary muscles, more particularly of the diaphragm. Individuals with chronic nerve disease are predisposed to the invasion of infective micro-organisms, and death not uncommonly occurs from such causes, either, in paralysis of the bladder, from cystitis leading to pyelitis and pyonephrosis; by an infected bed sore

of a paralysed part; or more generally by an infection of the lungs.

In conditions in which there is a generalised paralysis of muscles, the nutrition of the whole body suffers. This is readily understood when it is considered how large a part the muscles play in the general metabolism of the body.

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