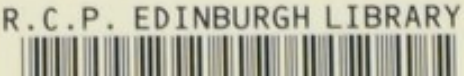
Chapters in pathology : being an outline of lectures upon some points in the pathology of elementary nutritive and circulatory derangements / by W.S. Greenfield and George Lyon.



CHAPTERS

IN

PATHOLOGY

BEING

AN OUTLINE OF LECTURES UPON SOME POINTS IN THE PATHOLOGY OF ELEMENTARY NUTRITIVE AND CIRCULATORY DERANGEMENTS

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PREFACE.

THE purpose for which this little work was undertaken was to give to the students of my class an outline of my lectures upon some elementary subjects in General Pathology.

There are some subjects with regard to which there has been constant difficulty, from the fact that the teaching in accessible text-books has been entirely at variance with the demonstrable facts, and with the everyday experience of the laboratory and the post-mortem room, as well as with clinical observation.

To a large extent the gradual advances of pathological science have come to be recognised and taught, but there are some common and elementary, yet fundamental, points upon which many otherwise admirable text-books are still far behindhand. It is especially to these points that attention is here directed.

In any work of greater pretensions, it would be desirable to give a fuller account of the work of various investigators, and to discuss their views. But for the student the ascertained facts, when they can be stated definitely, are the most valuable.

As regards the method of compilation, the work of preparing a digest of notes of my lectures was kindly undertaken by Dr George Lyon, and this was carefully revised by myself. But in order to keep the book within as small compass as possible, I have thought it desirable to condense or rewrite some parts. In any case, I must alone be held responsible for any errors or omissions.

W. S. GREENFIELD.

CHAPTER I.

ELEMENTARY CELL CHANGES IN RELATION TO DISEASE.

In studying the intimate causes and processes of disease which fall within the domain of General Pathology, it is convenient to consider first some of the more elementary changes which follow interference with cell life. Many of these changes are common to all living organisms.

We owe to Virchow the full recognition of the fundamental importance of the living cell in all the processes of life, whether in health or disease.

More recent discoveries of the complex structure of the cell, of its subtle mechanism and chemistry and of its manifold endowments, whilst they have shown us how much remains to be discovered, have served to emphasise the importance of the study of cell-life in relation to disease.

In whatever way the vitality of cells may be interfered with, some temporary or permanent alterations are produced. Changes in environment, direct physical agents, and cell-poisons, including of course toxins, may interfere with the normal function or normal metabolism of the cell or directly damage its structure, or, on the other hand, may excite it to abnormal activity.

To a large extent our knowledge of these changes in any of the higher animals must depend upon observations on dead tissues, or upon cells in abnormal conditions. It is only in a small number of instances that we can actually watch with the microscope the effects of interference at the time of their occurrence; as, for example, in leucocytes or other isolated cells, or in transparent membranes. Even then we can only see movements or visible structural changes.

To determine the minuter changes we must rely upon chemical tests or staining reactions. Our knowledge both of cell-structure and of the chemistry of cell activities is at present so very defective that our methods are crude and our classification of the changes necessarily imperfect.

But from what we know of cell-life in some lower organisms, we feel sure that structural alteration, using the term in the widest sense, is the almost invariable accompaniment of any interference with cell-life.

Even under normal conditions, the performance of function in the

healthy cell is often attended by perceptible physical change. There are alterations in shape, a flow of particles in the cytoplasm, and changes in the form and position of the nucleus. Such changes can often be readily watched in living cells, or their results detected in cells killed and at the same time fixed by reagents. The phenomena accompanying the stages of secretion and the cycle of processes during cell division give familiar examples. And beyond these, the high degree of activity and of mobility of many cells are well known facts.

But, in addition, there are complex chemical changes concerned in the processes of cell nutrition, secretion, and the other phases of active cell-life, of which we can only detect the gross results by direct chemical or staining tests. We may thus find varieties in the character and number of various granules in the cytoplasm, or changes in their chemical reactions at different periods of functional performance.

Histological study must, therefore, in many cases be the chief instrument of pathological investigation, however imperfect it may be. But its scope is widening with greater knowledge of cell-structure and life, and with improved methods and microscopes.

It is, then, of great importance at the outset of the study of Pathology to be impressed with the fact that since all the activities of life are ultimately carried out by those protoplasmic units which we call "cells," everything which concerns cell-structure and the phenomena of cell-life must be of especial interest to the pathologist.

Nor is it less important to bear in mind the constant activity of cells, and their ready response to variations in the conditions of life, and to stimuli of many kinds. It is only when realising this state of constant activity that the microscopic appearances in dead cells can be properly estimated or understood.

Cell-Structure.—Any lengthy consideration either of cell-structure or life would be out of place here, if indeed it were possible. But there are certain common facts which must be borne in mind, if even the simplest changes in disease are to be understood. A brief reference to some of the chief points in cell-structure which have a pathological bearing may therefore be of service, especially by drawing attention to those characters which may be altered by disease.

A cell may be defined as a mass of protoplasm definitely organised as a living unit. In all animal cells it contains a nucleus, which is the centre of cell nutrition, reproduction, and synthetic activity. The cell body or *cytoplasm* is usually a structure of granular appearance, apparently constituted by a reticulum or network, within the meshes of which lies a more fluid substance, the ground substance or cell-sap. In some cells the substance appears more homogeneous.

Whether the apparent network is a definite structure, or whether it is due to an arrangement of granules of different density is a disputed point. But it is convenient to assume that some loose fibrillar structure commonly exists. Surrounding it the cell-membrane or cell-wall may be recognised, though in many cells it is very indefinite, and it has not the importance which it attains in vegetable cells.

In many cells the more central part of the cytoplasm around the nucleus (the "endoplasm") is more homogeneous, whilst the more peripheral portion shows definite reticulation. This is especially marked in some secreting cells, and in ciliated epithelium.

In its staining reactions, cytoplasm has usually an affinity for "acid" dyes, such as eosin, but in some cases parts of its structure or granules contained in it may give a "basic" reaction, *e.g.*, in lymphocytes.

Within the cytoplasm are granules or droplets of various kinds. Some of these may appear to be definite constituents of the cell, others may be present only during some periods of secretion or functional activity, whilst others may be inclusions of various kinds.

Amongst these granules are some of albuminous nature, differing in their staining reactions and in their solubility by various reagents. Various nucleo-proteids, gluco-proteids, and other combined proteids are known to form some of these granules, but we are at present able to classify them only roughly as oxyphile or basophile in various degrees, or as giving a peculiar reaction with special stains.

Granules and globules of some fatty bodies, or of glycogen, and of pigment of various kinds, are also common.

Some of the particles are evidently inclusions; foreign bodies, remains of other cells and of hæmoglobin are common, especially in pathological conditions.

Changes in the characters, relative proportion, and staining of such granules as are normal, and the presence of abnormal granules are frequent in disease, and they must therefore be carefully observed.

Droplets of various size containing watery or serous or mucinous fluid are constant in some cells.

In addition, the cytoplasm often shows *vacuoles* which are evidently formed where active processes of intracellular digestion are going on. These vacuoles, whilst closely analogous to the persistent vacuoles of some unicellular organisms, do not commonly show so definite a structure, and in most cases appear to be only potential and temporary cavities. This will again be referred to under *Phagocytosis.*

For our present purpose other normal structures of importance, such as the *centrosomes*, which play so important a part in cell division, and *attraction spheres*, etc., need not now be described.

The **nucleus** must next be briefly considered. Usually rounded or elliptical, in some cases elongated, varying in size and position in

different cells and in the same cell in different phases of activity, it is capable in many cells of great changes in form. These may take place within a very short time, as in active leucocytes during migration or phagocytic action. It is true that in many cells the nucleus is found to be fairly constant in position and character in tissues examined after death, but we know that active changes are frequent whilst living, and that the nucleus may be permanently displaced (*e.g.*, in fatty cells) without affecting its vitality. Too much importance is often attached to such temporary variations in shape or position of the nucleus.

Nuclei capable of great variations in form ("*polymorph*") are well seen in the commonest kind of leucocytes (polymorphonuclear). A cell may contain more than one nucleus, even several, as in "giant cells" and "myeloplaxes." Such multiple nuclei may sometimes indicate a high degree of phagocytic power, but not necessarily.

At the periphery of the nucleus there is a denser meshwork or membrane, the exact structure and origin of which are disputed.

In structure the nucleus appears to be reticular, showing a meshwork of denser material called "linin," with a softer material between. But the special constituent "*chromatin*," arranged in granules or irregular masses along linin threads, is the most important feature. Its definite arrangements during mitosis, the formation of chromosomes, etc., and their variations in pathological mitosis are important in relation to tumour growth and to repair.

The chromatin—so called from its intense reaction with nuclear or "basic" dyes—consists largely of nuclein compounds, has a high percentage of phosphorus and resists gastric digestion.

In some cells the chromatin is so dense that it obscures the rest of the nucleus; in others it forms an opener network. Apart from the variations in amount and arrangement which occur in relation to mitosis, the chromatin alters in arrangement and in apparent amount during other active processes of cell-life. It is chiefly in conditions of degeneration or death that it becomes sufficiently scanty to allow the linin network to be readily seen. Whether indeed this linin network exists as a definite reticulum or only as an arrangement of rows of granules is not finally determined.

Chromatin changes form a considerable part of the discoverable nuclear alterations in disease. The modes of alteration will be more fully referred to in relation to cell-degeneration and death.

Embedded in the nucleus are one or more nucleoli, rarely more than five: though probably always present, their demonstration may be difficult. The true nucleoli are readily distinguished by their affinity for *acid* dyes, in striking contrast to that of the chromatin for basic dyes, so that in staining with hæmatoxylin and eosin a nucleolus is of bright red colour. This is true only of the true nucleoli or *plas-*

mosomes, not of the netknots or *karyosomes* which may often be seen, and are not separate structures.

The relations of nucleoli to disease changes have not been fully investigated.

Seeing that the nucleus controls or is necessarily concerned in all those parts of the life of the cell which relate to its maintenance, reproduction, and synthetic activity, its changes in disease are of the highest importance, and must always be carefully studied. A portion of cytoplasm in some unicellular organisms can, when detached, still survive for a time, and may carry on some katabolic processes, intracellular digestion for example, but it has lost its capacity for synthetic and anabolic functions, and for reproduction. We shall see that this loss of nuclear control may account for some of the changes in cytoplasm when the nucleus has been damaged or killed.

Within the nucleus as in the cytoplasm, other granules and the formation of clear spaces may be seen. These are, however, especially observed in degenerative changes.

Cell-Life and Activity.—Some of the relations of cells to general and local nutrition may next be briefly referred to.

Apart from the common duties of each cell, for which definite organisation and properties are provided: such as special secretion, metabolism and so on, a cell must maintain its own life, and reproduce its like when needed. In carrying out its own special function, every cell must also affect the more general metabolism of the body, both by what it removes or alters and by the residuary or by-products which it discharges. This holds good even of cells whose main purpose is to form or support structures of low vitality, such as fibres and laminæ.

To some extent all cells have also some influence upon the condition of the structures which immediately support them, and upon the local vascular supply. Some cells, *e.g.*, connective tissue corpuscles, are specially related to the maintenance of the supporting fibrous tissues. But the normal condition of these is dependent to some extent upon the performance of the function of the *special* cells, and the local vascular supply is determined by the demands of these special functioning elements. If this stimulus is withdrawn the normal blood supply is diminished: if it is increased, the supply also becomes greater, and in either case the supporting structures and the blood-vessels themselves are liable to nutritive change.

In other words, the integrity of any organ is largely controlled by the influence exerted by the cells which carry on its particular function. We shall see that this factor enters into many of the results of interference with cell-life.

Reaction to Stimuli.—In a large number of instances, and probably in all cells, special reactions follow special stimuli, physical,

chemical or other. The effects of tactile and electrical stimuli, and the existence of differing attraction by acid and alkaline solutions, are examples. In some cases these reactions are highly specialised. Of these special reactions those in relation to toxins and the properties of *phagocytosis* are best known and are of great importance. **Phagocytosis** is the process of ingestion of bodies, living or not, by a cell, and their intracellular digestion. This power, whilst most highly displayed by certain cells, is widely distributed. Not only free cells, such as the various kinds of leucocytes, but many fixed cells, such as endothelium of lymphatics and of bloodvessels, and even some epithelial cells, display this power. In carrying out the process we may see the cell advance or recede, and make repeated efforts for a considerable period—efforts so admirably regulated as to suggest intelligence on the part of the cell.

These processes will demand separate study. They can be easily watched, for instance, in the attack of leucocytes upon the malaria parasite ; an object lesson which gives an insight into the life and powers of the cell such as can hardly be obtained in any other way.

Connected with this phagocytic function, though displayed sometimes independently of it, is the power of **migration** possessed by some cells. The facts of migration will be more fully studied in connection with "inflammation"; but it is probable that the power, although mainly restricted to mesoblastic cells, is more widely distributed than is commonly believed. It is certainly not limited to polymorph leucocytes.

Finally, the power of cells to vary or increase their formative activity, and to produce new tissue by cell-division is constantly displayed both in repair and in new growth.

CHAPTER II.

INTERFERENCE WITH NORMAL CELL-LIFE.

To a large extent the ultimate processes of disease may be expressed in terms of their interference with normal cell-life.

When in any way the regular performance of nutrition and function are interfered with, as by defective nourishment, by physical agencies, such as cold, heat, or pressure beyond the capacity of resistance, or by the action of poisons, including toxines, there must be some injurious effect upon the cell.

This may be temporary, recovery may occur, and everything return to normal. But even then, the effect, although limited to interference with metabolism or secretion, may produce perceptible alterations. A cell, like a chemical factory in active work, consumes raw material regularly and gives a certain output of its products, including by-products and waste. If work stops, raw material may accumulate. So in the cell, the nutriment will not be used up, elaboration and excretion will be defective, and both unused and badly made up material may accumulate. And the more complex and highly organised the cell, the greater will be the possibility of disturbance.

There is, of course, often much more than this. A cell whose controlling centre is paralysed or under the influence of a narcotic has for a time lost its power of adaptation to its surroundings and of resisting physical agencies. It may therefore absorb fluid beyond its need and swell, or substances in solution which it usually rejects may soak into it.

Apart then from any direct chemical or physical action of the injurious agent upon it, the cell may, after such interference, show changes in size and shape and altered characters of its cytoplasm and of the contained granules, and these may reach a considerable degree if the damage be severe or prolonged.

Yet recovery may be complete, the abnormal material be removed, and the normal condition and characters be regained.

Such temporary disturbances of nutrition are common as a result of the agents already mentioned, including heat, toxines and some chemical poisons. And they constitute a large part of the group of changes designated "**cloudy swelling**" by Virchow, a name which merely indicates two of the most obvious visible changes common to cells in this condition.

It is important to remember that this cloudy swelling is not one disease or "degeneration," but is the expression of reactions common to cell-life: varying widely both as to their cause and in the nature of the changes which occur. It is natural that those cells which are most complex in structure and most delicately organised should usually be affected most readily and in the highest degree—and also that in some toxic diseases it should be most marked in the organs whose cells have a special affinity for the poison or take part in its elimination. Hence the heart muscle, some nerve cells and renal epithelium may be especially affected by diphtheria toxin, liver and other cells by phosphorus.

Such a change may then be only temporary, and should hardly be classed as a degeneration.

But the same poisonous or other injurious agents may act so intensely as to kill some cells whilst the rest recover. The cells, being dead, will decay and ultimately be disintegrated and absorbed. During this decay they will show various changes, the exact characters of which will depend on the physical and chemical nature of the cell, the action of the poison or other injurious agent upon it and the nature of the surrounding media.

Such death in the living body is called **necrosis,** and the various changes which follow are called "*forms of necrosis.*" They would more accurately be described as "*post-necrotic*" changes.

The cell may not, however, be killed outright. It may be so damaged at once that its proper function cannot be performed, and it then slowly decays. But in many cases decay is due to more slowly acting causes, such as defective nourishment, continued slight irritation or poisoning. Or it may arise solely from that ending of usefulness or power of maintenance which is the fate of all living organisms.

To such changes of decay the names **necrobiosis, degeneration,** and **atrophy** are given.

To state any absolute distinctions between these three groups of processes is impracticable. **Necrobiosis** should, so far as possible, be used only for those conditions in which the cell is in course of slow death. **Degeneration** implies that the cell or tissue continues to live, although in a crippled condition, and with changes in chemical and physical characters due to its defective vitality. **Atrophy** is especially applicable when the cell or tissue, although reduced in size and less active in function, is not much altered in its general chemical or physical characters.

It may be added that a cell, although it may have lost its power of performing its higher and specialised function, may still carry on a lower one, *e.g.*, secreting epithelium may be reduced to the task of lining a tube or cavity. Such a reduction or degradation of a cell or

tissue has not received any special name, although closely allied to what Virchow called "*Metaplasia.*"

In many cases it is difficult to say to which of these groups of defective vitality any particular instance should be consigned.

A further fact must also be considered. The cell or tissue which has lost its power of selection and of resistance may absorb materials from the surrounding lymph which alter its character. Or its substance may have acquired abnormal chemical qualities which produce unusual compounds, and these may accumulate. Or it may simply ingest more of some material which is natural to it than it can use.

In these and other ways there may be accumulation in the cell or tissue of some material with which it is said to be "infiltrated," and such **Infiltrations** are often described as special forms of disease.

It is obvious that in most of these processes of Infiltration there must be some defect of those powers by which the tissue selects what it needs and rejects the rest. Hence no sharp distinction can be made between infiltrations and degenerations, and most of the so-called infiltrations are simply the results of degeneration. The chemical nature of the accumulated material is only an accident of the change, and not its essence, and its recognition is useful chiefly to distinguish its nature.

In rare cases excessive or abnormal substances may find lodgment in cells or tissues, owing to some chemical affinity. This question will be referred to under gouty and waxy changes.

Some of these common changes may now be described under the old names, but the modern standpoint, that they are important mainly as expressions of altered cell-life, must be kept in view.

DEGENERATIONS AND INFILTRATIONS.

"Cloudy Swelling" (Parenchymatous Degeneration). Under this term are included, as already indicated, a great variety of changes dependent on interference with normal cell-life or metabolism. The common physical characters of the group are swelling and increased turbidity of the cytoplasm. It is thus a convenient generic term for a group of conditions.

This type of change in cells is well seen in diseases in which there is some soluble toxin circulating in the blood. The acute infectious diseases afford us the most striking examples, but similar changes may be induced by the action of various organic and inorganic poisons—*e.g.*, abrin, ricin, corrosive sublimate, etc. The cells most markedly affected are those specialised for any particular function, and the distribution of the change is governed by the nature of the toxin and its path of elimination. Thus in the case of the kidney the damage is mainly limited to the special excretory cells. Toxins, however, possess varying affinities for different cells. By what *modus*

operandi does the toxin produce its pernicious effects upon the cell-life? Grave disturbances of the normal cell metabolism are induced, but the explanation of these is for the present largely speculative. Does the toxin combine with some cell constituent, as has been proved in some cases, or does it replace one of the constituents of the cells in a way comparable to the replacement of oxygen in the oxyhæmoglobin molecule by carbon monoxide in coal gas poisoning? These are questions still to be elucidated.

Organs Affected.—The organs in which the most extensive changes are seen are the kidney, liver, and heart, but the special parenchyma cells of other organs may be similarly affected. The degree of affection of the different organs varies, but is mainly determined by the nature of the circulating toxin.

Physical Condition of the Organs.—The organ is swollen; the colour paler and more opaque; but this feature may be obscured by the presence of increased hyperæmia. The consistence is decreased, and the characteristic markings of the organ may be rendered less apparent.

Cell Changes.—The cells are swollen, and the intervening cement substance is usually loosened. In the cytoplasm we may recognise all transitions from a condition of increased granularity to complete disintegration. The granules are sometimes albuminoid in nature, and disappear on addition of acetic acid. These granules may sometimes represent a precipitation of substances normally contained in the cells, or of substances which have been absorbed from without. The swelling of the cell is dependent largely on the absorption of fluid from the surrounding lymph, which may accumulate in the cytoplasm in the form of clear globules. During the development of the changes, fatty granules or globules may make their appearance, and fatty degeneration is a common sequel of these preliminary alterations. In the more intense degrees which terminate in cell-death, the cytoplasm may undergo complete disintegration into a granular detritus.

The nuclear changes are inconstant, but are usually present to some extent. Commonly the nucleus becomes pale, poor in chromatin, and may be partially obscured by the granular condition of the cytoplasm. Whenever the cell-life has been irretrievably damaged, the nucleus is the seat of a variety of changes, similar to those which will be described under the subject of necrosis.

The less damaged cells may be able to perform some degree of their normal function, but this is usually gravely disturbed. Complete restitution of the cell to its normal integrity of structure and function on the removal of the noxious agencies is the general rule, but the cell-life may be so greatly deranged by the intensity or persistence of the toxic action that cell-death is the ultimate result.

FATTY DEGENERATION.

Fatty Degeneration may be defined as a retrogressive change associated with the formation of fatty granules or globules in the cell cytoplasm. It is often difficult to decide what amount of fat is to be regarded as normal for the organ or as evidence of fatty degeneration. Many cells of the animal body, especially in old age, may contain fat globules, when their presence is correlated to the processes occurring in the course of senile atrophy. Fatty degeneration occurs frequently in association with or as a sequel to the group of changes which have been described under cloudy swelling. Toxic conditions are thus a common cause of these two changes, but fatty degeneration represents the result of a more prolonged action of the toxin or of its greater intensity. Apart from the occurrence of fatty degeneration in the acute infectious fevers and in other bacterial intoxications (*e.g.*, septicæmias), this change may be widely distributed in its most extreme degree as the result of the action of some organic and inorganic poisons. Some metallic poisons and rapid alcoholic poisoning are potent factors in its production, but it is especially in phosphorus and chloroform poisoning that the greatest degrees are attained. (After the administration of chloroform as an anæsthetic to children, death has often supervened in several days, and the fatal issue can only be attributed by a careful exclusion of other possible causes such as sepsis, to a slow poisoning produced by this agent. Post mortem—widespread fatty degeneration is present, the liver and kidneys being the chief seats of the change. So great indeed may be the affection of the liver cells that many of them are transformed into masses of fatty detritus floating free in the intralobular capillaries or in the central veins of the lobules.)

Fatty degeneration is also a change common to all dead or decaying tissues. If pus cells or the cells in the air alveoli of a resolving pneumonia be examined, their cytoplasm will be found to contain oil globules. It is also a normal process in the involution of various organs. In all conditions of impaired general nutrition, *e.g.*, senility, grave anæmias and cachexias, fatty degeneration is a widely diffused change. In pernicious anæmia, however, there is much evidence to support the view that the cause is toxic in nature. In some diseases in which the metabolism is greatly deranged, *e.g.*, Diabetes Mellitus, there is occasionally very intense fatty degeneration of the organs. The blood in Diabetes Mellitus may be loaded with fat globules, a condition designated *lipæmia*, and as a consequence of this, fat embolism of the organs, especially of the lungs, may result. But it is at present uncertain whether the extensive fatty degeneration found after death from diabetic coma may not be of toxic origin. Localised fatty degeneration also occurs as a sequel to impaired local nutrition.

Examples of this are seen in the central parts of rapidly growing tumours, in paralysed muscles, and in the thickened inner coats of atheromatous arteries.

Physical Condition of the Organs.—The affected organs may be slightly increased in size, but this is never a striking feature. The colour is usually yellow or yellowish white. The consistence of the organ is decreased, and it is more friable than normal. The change may not be uniformly distributed throughout the organ, but may be localised to particular areas, producing a patchy or mottled appearance of the affected part. This is very characteristic in the heart in fatty degeneration of the myocardium. On section, the cut surface of the affected organ may be distinctly greasy.

Changes in the Cells and Tissues.—Although the change chiefly affects the special parenchyma cells of an organ, a similar change may sometimes occur in the formed tissues. The cells may be slightly swollen if the fat globules be numerous, but usually they are not increased in size. The fat may be in the form of fine granules or larger highly refracting droplets, which may subsequently fuse to produce large globules. The cells of an organ are not equally and uniformly affected. In the liver, at least in some cases of early affection, the change may be mainly localised in the cells which surround the central veins of the lobules. In the heart, the muscle-fibres which lie subjacent to the endocardium usually show the earliest and most marked degrees of fatty degeneration, and in this organ the arrangement of the fatty granules or globules in rows parallel to the long axis of the cell is often seen in the less acute forms. The basal portion of the secreting cells of the kidney may show the earliest transformation.

The nuclei may remain relatively unaltered, but whenever the change progresses to complete disintegration of the cell, there are always, of course, associated nuclear changes.

Chemical Reactions.—The fatty compounds are soluble in ether, but it is known that the degree of solubility of different fats in other menstrua, *e.g.*, alcohol, is of very varying degree. For the demonstration of fat special methods and staining reagents are used ; of these latter Osmic acid and Sudan iii and Scharlach R are the most satisfactory, but the reactions obtained with these reagents are occasionally misleading. Osmic acid stains fat intensely black, but some fatty compounds do not exhibit the reaction. Fatty granules and globules are stained of a characteristic orange colour by Sudan, but some substances of a non-fatty nature may be similarly stained. The organs and tissues may be examined fresh, by means of frozen sections, but for the more careful histological study, it is advisable to adopt Marchi's method or to use Flemming's solution or similar fixatives.

Chemistry of the Process.—The question of the origin of the fat in the cells in fatty degeneration is one which has long occupied the attention of physiologists and pathologists, but upon which no final conclusion can be stated. Only a general outline of the subject can be given. For the fuller statement of experiments and views, works on physiological chemistry may be consulted.

That many of the globules seen in cells and usually classed as evidence of fatty degeneration are not of fatty nature is shown by the action of reagents.

The quantity of fat in the tissues of an organ which has the characters of fatty degeneration may be found not to exceed that in healthy tissue, as was shown by Quain with regard to "fatty" heart.

Can the fat be formed by a process of splitting up of proteid, or of a combined proteid, *e.g.*, gluco-proteid, or is it carried to the cells by the blood stream?

Formerly the experiments were directed to the question whether albuminous bodies could be the source of the fat, but we now know that in the constitution of protoplasm the gluco-proteids and allied bodies form an important part, and it may be from the carbohydrate part of the molecule that the fat is derived.

In phosphorus poisoning fatty degeneration in the liver and other organs may rapidly reach a high degree. In slow phosphorus poisoning the nitrogen elimination may be greatly increased, whilst the fatty accumulation is taking place, care being of course taken to exclude the introduction of fat in food. But the result of recent experiments is to show that the total quantity of fat in the body is reduced, and hence some have concluded that the fat in the liver and elsewhere has been transferred from other parts. It must be said that this explanation does not fully account for the widespread changes found even in vessel walls in rapid phosphorus poisoning.

Analyses of tissues kept after death outside the body have thrown doubt upon the occurrence of a fatty metamorphosis in albuminous substances. Under these conditions one important difference is the absence of the circulating blood. But the most recent observations (of Waldvogel especially) tend to support the older view that a succession of changes occurs which may lead to the formation of fatty compounds by such autolytic processes. These results are certainly in harmony with what is seen in cells which are dead in the body, *e.g.*, detached epithelial cells and leucocytes in catarrhal and purulent effusions.

Results.—There may be recovery or there may be cell-death, *e.g.*, in chloroform poisoning. Fatty degeneration of the endothelium of capillaries may lead to their rupture and the production of minute hæmorrhages, *e.g.*, in Pernicious Anæmia. The function of the affected organ may be gravely impaired, *e.g.*, of the heart. In the liver and

kidneys, however, a considerable degree of fatty degeneration may be compatible with the performance of their function.

It is convenient to consider at this stage Fatty and Glycogenous Infiltration, changes closely associated with fatty degeneration.

Fatty Infiltration.—It has been customary to define Fatty Infiltration as a retrogressive change characterised by an accumulation or deposition of fat in cells whose vitality has been previously unimpaired. It is open to doubt whether fat is ever deposited to an abnormal degree in cells independently of some previous alteration. This change is frequently associated with fatty degeneration, from which in many cases it cannot be separated, and it may occur under the same conditions. Fatty accumulation is dependent either on an excessive ingestion of fatty or carbohydrate substances, or on their defective removal. The liver affords the best example of this change, and in this organ the fat accumulates especially in the peripheral cells of the lobules around the portal spaces. The liver cells no doubt serve as temporary storehouses for fat under normal conditions, but the quantity may come to be greatly in excess. Fatty infiltration of the liver is frequently present in alcoholism, especially in the more rapid forms, and also in chronic cases, especially in beer drinkers. It is then commonly associated with other structural changes. In Phthisis, the accumulation of fat in the liver cells is probably more of the nature of a true degeneration than of a simple infiltration.

Adiposity.—In this condition there is the conversion of ordinary connective tissue into adipose tissue. Apart from the excessive consumption of fats and carbohydrate with want of proper exercise and individual peculiarities of metabolism, it is seen after castration, in some forms of insanity, and as a sequel to some fevers, *e.g.*, typhoid fever. It is not uncommon after child-birth, and apart from the other causes mentioned, may possibly then be due to general changes in metabolism associated with lactation.

Local deposits of fat may be found around atrophied organs, *e.g.*, granular contracted kidney, or replacing atrophied muscle fibres, *e.g.*, in pseudo-hypertrophic paralysis. The use of the term fatty infiltration in relation to the heart has led to some confusion. This would be better designated adiposity of the heart, as the fat is not deposited in the muscle cells of the myocardium, but in the supporting fibrous tissue.

Glycogenous Infiltration.—Glycogen is found normally in many organs and tissues, *e.g.*, liver, muscle cells, and in most actively functioning cells. It may accumulate in excess, this condition having been especially observed in saccharine diabetes. The glycogen globules are found in the liver cells, in the secreting cells of the kidney, and in the circulating leucocytes.

Glycogen may occasionally be deposited in the cells of some tumours and in cartilage. In many acute diseases, *e.g.*, acute pneumonia, and in some chronic cachexias, glycogen globules are present in the circulating leucocytes or free in the blood plasma.

Glycogen is soluble in water, and after death is rapidly converted into glucose. It gives a golden brown reaction with Iodine, which disappears on heating and reappears on cooling.

Serous Degeneration.—This name has been applied to a retrogressive change characterised by the absorption of fluid from the surrounding lymph by cells whose vitality has been altered. It is often seen in association with cloudy swelling. In burns and inflammatory conditions of the skin, the epithelial cells often present good examples of this change. The cells are swollen and contain rounded spaces filled with clear fluid. Other degenerative changes in the cell are always present. It is doubtful whether it should be regarded as a separate form of degeneration.

MUCOID AND COLLOID DEGENERATION.

Under mucoid and colloid degeneration are included various changes closely allied to each other, and the distinctions drawn between these two types of degeneration are somewhat arbitrary. The name "*mucinoid*" might well be applied to this group of changes. Transition stages occur, and a differentiation on the basis of chemical reactions is quite artificial, as different members even of the same group may show no constancy in their chemical characters.

The distinctions of mucoid and "colloid" degeneration from one another were largely based upon the differences in solubility and some of the rough chemical tests, such as the reactions to acetic acid, tannic acid and alcohol.

It is now recognised that the normal mucins vary much in character, though all are gluco-proteids, and have a similar general constitution and common physical characters. "Colloid" material belongs to the same group of "mucinoid" or "mucoid" substances, varying in composition in different positions, but generally more stable, and in some cases, it is said, containing sulphur in larger proportion.

The ready transition of "colloid" to "mucoid" change is shown by the fact that when a gland which normally produces "colloid" material, *e.g.*, the thyroid, is excited to increased activity, the material formed becomes "mucoid." This change is often found in the thyroid in pneumonia and various fevers. Conversely, when in a mucous gland, or in any closed follicle lined with epithelial cells (*e.g.*, in tumours, tubules of kidney, etc.) the secretion is pent up and slow degenerative changes occur, the accumulated material often acquires "colloid" characters.

Both in "mucoid" and "colloid" degeneration, as in normal secretion, the process of formation is partly by excretion, partly by changes in the cells. In degeneration many of the cells, having accumulated droplets of mucoid material, then swell up, become detached and go to form part of the mass. Hence outlines of round masses partly fused together can often be seen.

It is probable that the transformations by which mucinoid substances are formed depend upon something in the cytoplasm of epithelial cells which fixes the proteid of the lymph in combination with carbohydrate. Hence in "catarrhal" inflammations the transudation of lymph through a mucous membrane leads to mucous instead of fibrinous exudation, except in rare instances.

Colloid transformation occurs in other closed secreting follicles than those of the thyroid gland, *e.g.*, often in the pituitary body, in which the successive stages of cell transformation can be well seen.

It may be pointed out that the occurrence of such "colloid" secretion in no way indicates any similarity in function on the part of these glands. The active secretion is merely stored in the colloid medium, just as we may keep active drugs in jelly. The formation both of mucoid and colloid material is due to the common mode of change in epithelial cells of certain kinds.

But it may be well to describe the characters of these degenerations as they are usually stated.

Mucoid Degeneration.—Mucoid degeneration of cells is characterised by the transformation of the cells into a soft, viscid, jelly-like substance. This mucoid substance may contain either "mucin" or some substance closely allied to it in chemical constitution (pseudomucin). Mucoid substance does not possess any constant chemical reactions which can be regarded as distinctive. Substances containing true mucin in alkaline solution are precipitated by acetic acid. They are also precipitated by alcohol. Mucoid substance which contains pseudomucin is not precipitated by acetic acid.

The epithelial cells covering the surface and lining the mucous glands of mucous membranes undergo this change to a considerable degree in all catarrhal inflammations. A similar change is seen in the cells of some other glands, *e.g.*, thyroid gland and kidney, and there may be formation of cysts filled with mucoid material. Mucoid degeneration occurs also in the cells of some tumours, most typically in compound cystic ovarian tumours. In these tumours the mucoid substance which fills the cystic spaces contains pseudomucin, which is not precipitated by acetic acid.

Colloid Degeneration.—This degeneration is characterised by the formation in epithelial cells of a structureless, homogeneous translucent substance, which is semisolid in consistence. Large colloid masses are formed by the fusion of transformed cells. Colloid sub-

stance has no constant and distinctive chemical constitution. It differs from mucin in not being precipitated by alcohol and acetic acid. It is, however, precipitated by tannic acid, which does not precipitate mucin. Colloid substance is usually stained of a characteristic orange colour by picro-carmine or picro-fuchsin.

This change is seen especially in cells which line closed cavities, the transformation taking place slowly. The spaces of the thyroid gland normally contain colloid substance, and there may be an abnormal formation and accumulation of it in some cases of goitre. This degeneration also occurs in some tumours, *e.g.*, in the so-called colloid cancers. Necrotic secreting cells of the kidney may undergo a colloid transformation, and fuse to form homogeneous casts.

Mucoid Degeneration of Connective Tissues.—The connective tissues normally contain mucins—which, indeed, seem to furnish a sort of gummy substance which may both help to unite the tissue elements and to allow of free gliding of surfaces.

In many conditions of defective maintenance of connective tissue, and in some processes of absorption, the formed fibres may be more widely separated or solid material (*e.g.*, matrix of cartilage) may diminish, whilst the whole structure becomes softer and more gelatinous.

Such a change may be seen in senile degeneration and in the softening of cartilage. In myxœdema it occurs in the skin and subcutaneous tissue, the intermuscular septa in the tongue and lips, and in the nerves and nerve-sheaths.

The change is therefore rather to be regarded as a process of degradation of the tissue towards a type allied to that in fœtal structures. It is in no way due to, or necessarily accompanied by, actual increase of mucin.

In some rapidly growing tumours such mucoid or myxomatous degeneration may occur to a high degree. This is especially seen in some sarcomas and in mixed adeno-sarcomas, *e.g.*, of the parotid and testicle, where transitions from cartilage to mucoid tissue may occur.

In cancers the change sometimes affects the stroma. And in some cancers of adenoid type, especially in the stomach, mucoid material is formed from the epithelial cells and soaks into the surrounding matrix. Such cancers form an important group of so-called "colloid" cancers.

HYALINE AND WAXY DEGENERATIONS.

A group of degenerations in which the structures especially affected are not the cells but the formed tissue elements, especially connective tissue fibrils and laminæ, may next be considered. Of these waxy degeneration is the most definite and important.

Waxy Degeneration (Amyloid, Lardaceous).—This is a

retrograde process affecting mainly the delicate fibrillæ of connective tissue, and characterised by alterations in their chemical and physical properties. The change probably never affects secreting cells. It usually affects first of all the walls of the minute arterioles. The fibrillæ of the connective tissue of the muscular coat usually show the earliest affection, becoming irregularly swollen and homogeneous. The change is usually widespread and is rarely, if ever, localised in its distribution. It commonly affects a number of organs at the same time, starting in the walls of the ultimate arterioles and thence spreading backwards and forwards along the vascular channels to affect the larger arterioles and the capillaries. This is the general rule, but rare exceptions may be noted. In the condition called diffuse waxy spleen, the change commences in the walls of the venous sinuses and pulp spaces ; and sometimes, though extremely rarely, in the kidney this change is at first localised in the connective tissue around the large collecting tubules in the papillæ. The walls of the affected vessels become swollen, and there is diminution in the size of the lumen. The degree of vascular obstruction, however, is not nearly so great as might be imagined from histological examination, for the lumen is still patent and can be injected.

The organs especially affected are the kidney, spleen, and liver, in order of frequency, and then the mucous membrane of the small intestine and the lymphatic glands.

In nearly every organ there may be the occurrence of this change, especially in the smallest arteries, but it is important to note that the lungs and central nervous system are remarkably exempt.

Changes in the Organs.—When the degeneration reaches any considerable degree, the affected organ becomes swollen, and waxy livers may reach a very large size. The organ is firmer than normal and more resistant, but somewhat elastic.

The waxy substance, seen best in the case of waxy livers and spleens, appears homogeneous and translucent. Minor degrees of the change may be detected only by histological examination.

Important secondary changes may be produced in the organs. In some positions the swelling of the vessel walls produces pressure on other parts, with consequent wasting. This is especially seen in the liver, where the columns of liver cells may be extensively atrophied.

The effect on the circulation and nutrient supply of the affected organ is not necessarily great, for the vessels retain some degree of patency, although their walls may be greatly swollen. In the kidney, before other changes are superadded, the quantity of watery excretion is increased and may be considerably so. This, although associated with increased transudation through the affected capillaries, is probably largely dependent on the arrest of the normal physiological contraction and relaxation of the afferent arterioles of the glomeruli,

in consequence of the atrophy of the muscle cells of the middle coat, or the condition of the walls may be a physical obstacle to contraction.

A similar tendency to increased transudation is observed in waxy degeneration of the intestine.

In the kidney waxy disease, if persistent, is usually followed by changes either of a degenerative or inflammatory nature in the organ.

Chemical Nature and Reactions of Waxy Substance—(**Historical.**—Waxy disease of the liver was long regarded as a variety of fatty liver. In 1840, Rokitansky called the condition "Lardaceous" disease, from the resemblance of some organs to bacon in appearance. Dr Budd of Bristol, in 1845, described the change in the liver as a "scrofulous" enlargement, from its association with tubercular disease, and called it "*waxy*" or wax-like. In 1852, the same observer showed that the waxy substance was deposited between the liver cells and not within them. Professor Miller of King's College, London, made an analysis of the substance for Dr Budd and found that it was of albuminous and not fatty nature. In December 1853, the disease formed the subject of a discussion at the Edinburgh Medico-Chirurgical Society, in which Hughes Bennett, Gairdner, and Sanders took part. The essential nature of the change was fully recognised by them. In 1854, Virchow discovered its reaction to Iodine and to Iodine and Sulphuric Acid, and on the supposition that this waxy substance was allied in chemical constitution to starch, he designated it "*amyloid.*" Later Friedreich and Kekulé found, as Miller had shown earlier, that on analysis the material was albuminous and not fatty or carbohydrate).

A waxy organ contains an increased quantity of proteid. Kekulé, on the strength of chemical analysis of a substance separated as a residue after artificial digestion, was led to the assumption of the presence of a definite chemical entity in waxy material. This substance he called *lardacein.* This is usually described as an albuminous body closely related to elastin and keratin in chemical constitution. But it is now known that it is slowly digested in gastric juice, hence it cannot be obtained in a pure condition.

Iodine—generally applied in solution—stains waxy material of a reddish-brown or mahogany colour. This is the common test of the post-mortem room for the presence of waxy disease. If weak sulphuric acid (5 per cent.) be poured over the cut surface of the organ after the previous application of the Iodine solution, a dull blue or slaty colour is produced, but this colour reaction shows variations, and may be difficult to obtain. Iodine also gives its characteristic colour reaction in microscopic sections, but more striking colour effects are obtained by the use of certain aniline dyes, *e.g.*, methyl and gentian violet, which stain waxy substance of a beautiful reddish violet colour, which is still more clearly brought out by the application of weak formic acid.

Diseases in which Waxy Degeneration occurs.—Waxy degeneration is never the result of ordinary malnutrition, but occurs only in certain chronic toxic conditions. These are especially—

(1) Chronic Tuberculosis (lungs, bones, joints).
(2) Constitutional Syphilis (congenital and acquired).
(3) Chronic Suppurations (especially of bones).

It has also been found in association with lymphadenoma (Hodgkin's disease) and leucocythæmia. In rare cases where there has been the history of repeated attacks of rheumatic fever with peri- or endocarditis, and no other discoverable cause, waxy degeneration has been found. In all these conditions there is probably the long continued action of some toxic substance. In chronic malaria it is also said to occur. Evidence of syphilis has not always been inquired into in the recorded cases.

There is not the slightest evidence that it follows Bright's disease, although this is so commonly stated.

Ultimate Nature of the Change.—Waxy degeneration is always characterised by the protracted period requisite for its development. The causal factors must be in operation at least for some months. There is only one case on record in which it was believed to have occurred within three months.

The facts that the degeneration occurs mainly, if not solely, in association with diseases in which there are toxins circulating in the blood, and that it especially affects the organs which are concerned either with the excretion or modification of toxins (kidney, spleen, liver) are very important evidence as to its probable causation. A similar change, or a change which is very closely analogous, can be produced experimentally in fowls and animals by repeated injections of living cultures of Staphylococcus pyogenes aureus. We must, however, admit that the pathogenesis of waxy degeneration is not fully elucidated.

There is no evidence that it is an infiltration of the tissues with a preformed substance circulating in blood. It seems quite a rational supposition that the nutritive functions of the affected tissues have been altered by the prolonged action of toxins, so that they combine with some constituent of the lymph or blood-plasma and produce this waxy substance.

Formerly several conditions were described as being "waxy" in nature, on the strength of a certain correspondence as to the waxy reaction produced by iodine. In Bright's disease homogeneous casts are often found within the tubules. These are formed by the fusion of necrotic or degenerated cells, and were called "waxy" casts, because they gave with iodine a somewhat similar reaction to that of waxy substance. But they do not give either the reaction with iodine and

sulphuric acid or that with methyl violet. Otherwise they have no correspondence with waxy degeneration, and should be called colloid casts.

Local waxy degeneration has been described, but it is very doubtful if the changes so described are ever analogous to the general form, and some are certainly of totally different nature.

Corpora Amylacea.—These bodies have no relation to waxy disease. They are more related to colloid degeneration, although they may give some kind of reaction with iodine. They are rounded or ovoid masses of varying size, or may be formed by the partial fusion of such. They often show a concentrically laminated structure resembling that of starch granules. They are found in the prostate, kidney, lung, central nervous system, and in old blood clots. Some so-called Corpora Amylacea in the spinal cord are produced artificially by preserving the cord in spirit. Corpora Amylacea are apparently often produced by the fusion of degenerated cells, and may subsequently become partially or completely calcified. The so-called amyloid tumours of the conjunctiva have no relation to true waxy degeneration.

HYALINE DEGENERATION.

This is a degeneration of connective tissue, and, like waxy disease, affects especially the delicate fibrillæ in the walls of the bloodvessels. The affected tissue elements become swollen, translucent, homogeneous, more resistant and less easily digested.

The term was applied by von Recklinghausen to numerous very diverse conditions in which the tissue became more translucent and more highly refracting, but it is better to restrict the name to a more limited group of changes affecting connective tissue.

Hyaline degeneration resembles waxy degeneration in its especial localisation in the ultimate arterioles and capillaries of the organs, but it is never such a widespread change. Its most common sites are the smaller arterial branches of the spleen and kidney, and the arterioles of the brain and spinal cord.

The change usually affects first of all the delicate fibrillæ of connective tissue of the inner coat, sometimes of the outer, the middle coat suffering far more rarely. The inner coat becomes very irregularly swollen, and the lumen may be partially or completely occluded.

Chemical Reactions of Hyaline Substance.—Unlike waxy substance, it is not stained characteristically or differentially either by iodine or by any of the aniline dyes. Picro-carmine and picro-fuchsin are the most useful stains for its demonstration, but the results are not invariable. In its early stages a pink colouration is usually produced with picro-carmine, later yellow. The picro-fuchsin reaction is in striking contrast with that of waxy degeneration.

Hyaline substance is very resistant to chemical reagents, in this respect much resembling keratin.

Calcification is a not uncommon sequel of hyaline degeneration of the arterial walls. This is seen in the arterioles of the spleen and kidney.

When we come to consider the ætiology of this process, we recognise two types which are both related to toxic conditions. As an acute process it occurs in some of the acute infectious fevers, *e.g.*, scarlet fever and diphtheria, and in some cases of acute septicæmia. This acute type may develop in a few days. The more chronic form is found in association with chronic toxæmias of an obscure nature: often in Bright's disease.

Some maintain that hyaline degeneration is an early stage of waxy degeneration, but there is no sufficient evidence in support of this view, and much against it. Apart from the different reactions, hyaline degeneration especially affects the inner or outer coats of arteries, waxy the middle coat.

Hyaline degeneration can only be recognised by microscopic examination. In the kidney a primary hyaline swelling of the arterioles may lead to their complete occlusion, with consequent atrophy in the corresponding areas of kidney substance.

A common necrotic change in muscle has been confused with hyaline and waxy degenerations. It was first fully described by Zenker in the abdominal muscles in typhoid fever. The necrotic muscle fibres become swollen and hyaline in appearance and break up into smaller masses, which are finally absorbed. It occurs in fevers, especially typhoid fever, in damaged or paralysed muscles, and infarction, *e.g.*, of the heart wall, a condition dependent on complete deprival of nutriment.

CALCIFICATION (PETRIFACTION).

Calcification consists in an abnormal deposit of earthy salts in the tissues. The salts are chiefly carbonate and phosphate of calcium, with a less proportion of phosphate than is found in bone. It is a common process in dead or decaying tissues. In old age, calcification of various cartilages, tendons, and of the arterial walls may be regarded as a normal accompaniment of senility. This change is of very common occurrence in fibrous tissue which has been the seat of chronic inflammatory and degenerative changes. Calcification of the arterial walls is met with under a variety of conditions. As a senile change, deposition of lime salts in the fibrous tissue of the middle coat is frequent, producing rigid "pipe stem" arteries. At an earlier period of life, patchy calcification of the fibrously thickened and degenerated inner coats of atheromatous vessels is a very common

pathological process, and is especially well seen in the aorta, although any atheromatous vessel may show a similar change. Hyaline degeneration of arteries is a frequent antecedent of calcification, and the cerebral vessels and those of the spleen and kidney are common sites of this subsequent calcification. A similar change is seen in the heart valves in chronic endocarditis and fibrous thickening. Widespread calcification, with the formation of calcareous plates, may occur in the pericardium or pleura from the remains of exudation.

It may be stated as a general law that any part within the body which is dead or useless may become calcified. A great variety of examples might be adduced, but the following will serve our purpose. Calcareous deposits are found in old blood clots, most commonly in veins (phleboliths), in dead fœtuses retained within the body (lithopædia), in caseous tubercular masses in the lungs and elsewhere, *e.g.*, the mesenteric glands. In old infarcts of the kidney and spleen which have not been completely absorbed, but remain as caseous masses encapsuled by fibrous tissue, lime salts may be deposited. This, however, is of more frequent occurrence in certain animals, *e.g.*, rabbit and dog, than in man. Experimentally in animals, calcification of the whole kidney may occur whenever it has undergone necrosis after ligature of the renal artery. In the kidney calcification of necrotic secreting cells and of casts formed by their fusion is not uncommon in man in chronic nephritis. But the most remarkable example of this is found in association with corrosive sublimate poisoning, not only experimentally induced in animals, but also in the rare cases of corrosive sublimate poisoning in man.

Recognition of Calcification.—The calcareous plates found in the pericardium or pleura, and in the inner coats of arteries are easily identified. In tissues and organs the calcified parts are yellowish white in colour, granular in appearance, and of a hard and gritty consistence. The lime salts are soluble in dilute acids, with the ebullition of carbonic acid if carbonate be present. The earthy salts are usually at first deposited as granules, scarcely ever in crystalline form. These fuse and form larger granular masses. In degenerated cells and connective tissue there may be a diffuse homogeneous infiltration. Calcified areas stain intensely with hæmatoxylin, and this is one of the most characteristic staining reactions.

Reason of Deposition.—The old view, that an antecedent fatty degeneration was necessary, cannot now be maintained, as it is not essential that any such degeneration should precede the deposition of lime salts. An excess of lime salts in the circulating blood or a resorption from bones when they undergo a considerable degree of destruction has never been proved. Virchow believed that the resorp-

tion of lime salts from bone and their deposition in other tissues were often essential factors in the production of calcification. This he designated "metastatic" calcification. But there is no sufficient evidence that this occurs. Chemical analysis of the blood plasma has failed to show an increase of lime salts either in excessive destruction of the osseous substance, or in corrosive sublimate poisoning in animals.

In all probability lime salts are never abnormally deposited in tissues whose nutrition is healthy, and no excess of lime salts in the blood will cause their deposition. There is always a sufficient amount in the blood to combine with the altered tissues. Whether the calcium salts combine with some fatty or albuminous substance is not certain.

GOUTY OR URATIC INFILTRATION.

In gout there occur deposits mainly consisting of acid urate of sodium. The deposition is preceded or accompanied by local malnutrition. The pathology of gout is still obscure, and there is a great diversity of opinion. The deposits occur in and around the joints, especially at first the smaller joints, and very commonly in the metatarso-phalangeal joints of the great toes. Similar deposits are also found in the cartilages of the ear and upper eyelid and in the subcutaneous fibrous tissues, where masses may be formed, the so-called "chalk" or "gout" stones (tophi). These gout stones in the subcutaneous tissues may be subsequently removed by large phagocytic cells. Rarer situations of these deposits are the heart valves and the interstitial tissue of the kidney. The tissue in which the deposit occurs is either cartilage or fibrous tissue. It is in the form of granules or acicular crystals of acid urate of sodium. Within the joints the deposit is always first seen in the superficial layers of the articular cartilage, looking as if the surface of the cartilage had been smeared with white paint. At first the cartilage cells are the seat of the deposit. They become swollen and show signs of division, and the surrounding ground substance may be partially dissolved. At a later period the cartilage matrix also becomes infiltrated. Other degenerative and inflammatory changes in and around the joints are apt to occur.

Chemical Tests.—(1) On the addition of an acid (*e.g.*, Hydrochloric Acid) to the deposit, uric acid crystals are produced.

Murexide Test.—(2) If a small quantity of the deposit be placed upon a watch glass, a little strong nitric acid added, and the whole evaporated to dryness on a water bath, an orange red residue is obtained. If a drop of ammonia be now added to the residue, a beautiful purple colour is produced.

Chronic lead poisoning tends to cause gout, and a deposit of urates may be found in the joints in such cases, even where there have been

no known symptoms of gout. In the cases where gout is associated with or follows chronic lead poisoning, chronic renal disease is also almost invariably present.

PATHOLOGICAL PIGMENTATION.

Pigmentary changes may occur together with or as the result of degeneration, but in many cases they are due to conditions of a widely different nature. It is, however, convenient to consider them together.

For purposes of study, the most convenient grouping is afforded by the nature and source of the pigment.

The three main groups are :—

I. **Albuminoid.**—When the pigment corresponds to the normal animal pigments, such as those of the skin, choroid, etc., this name may conveniently be used.

II. **Hæmatogenous.**—Here the source of the pigment is hæmoglobin, through changes in its hæmatin. And since most pigmentation from the bile has the same origin, the so-called **hepatogenous** pigmentation may be included in this group.

III. **Extraneous.**—Here the pigment is derived from foreign substances which are themselves coloured, *e.g.*, carbon as soot, coal, etc.—or substances which form compounds which give colour, *e.g.*, silver, lead, and perhaps arsenic.

There are some rare examples of pigmentation which do not fall under these groups, and will be considered separately.

I. **Albuminoid Pigments.**—Pigment is normally found as yellow or dark granules of melanin in various sites, *e.g.*, epithelial cells of skin, hair, retina, choroid coat of eye, and muscle cells of heart. This normal melanin pigment may, under certain conditions, show aberrations in quantity and distribution.

In the skin excessive pigmentation may occur under a variety of conditions. In old age, coincident with the atrophy of the skin, there is usually increased pigmentation of the epidermis. Pigmented patches of the skin may be the result of the application of blistering agents or may follow various skin eruptions. A patchy or more diffuse pigmentation of the skin is seen in various diseases and functional disorders. In Addison's disease there is increased pigmentation of the skin, especially where exposed to light or subjected to friction, and of the mucous membrane of mouth and tongue. In various uterine disorders local increase of pigmentation of the skin is frequently observed.

In "leucoderma" there is irregular distribution of pigmentation, some areas being devoid of pigment, others having an excess.

Apart from the skin, increased formation of normal melanin

pigment is found in melanotic sarcomas and cancers. The melanin granules, brownish or black in colour, are contained within the cells of the tumour, and also lie free in the intercellular substance. Sometimes the pigment becomes diffused in the blood plasma, and is excreted by the kidneys.

On the other hand, the presence of an abnormal quantity of melanin pigment in cells is associated in some cases with the occurrence of degenerative changes. During the atrophy of the heart which is natural to old age, there may be an accumulation of pigment in the atrophying muscle cells. The pigment granules are usually aggregated around the poles of the nucleus, but, when excessive, they may be scattered more diffusely throughout the cell. In ganglion cells pigment increases with advancing age, and is often seen to accumulate in some forms of degeneration.

Characters of Melanin Pigment.—Melanin occurs in the form of fine granules varying in colour from yellowish brown to black. It was formerly believed to contain little or no iron, but it frequently does even in normal pigments. There is a high percentage of carbon, and in some cases much sulphur. The source of the melanin pigment even under normal conditions is not definitely known, but it is believed to be elaborated by cells from albuminous substances.

In addition to an increase of melanin pigment under pathological conditions, pigments of a different nature are found in a rare form of tumour called Chloroma, and in the condition known as Xanthelasma or Xanthoma. The green colour of Chloroma is apparently due to the presence of a pigmented fat, and in Xanthoma the yellow colour is produced by a granular pigment belonging to the lipochromes.

II. **Hæmatogenous Pigments.** — The pigment is here derived from the hæmoglobin of the red blood corpuscles. When blood has been extravasated, or the red cells have been destroyed or their hæmoglobin discharged by various agencies in the circulating blood, the resulting pigmentation takes place especially in those organs in which effete hæmoglobin is normally altered.

The pigments which result from transformation of the hæmoglobin may be conveniently divided into two chief groups :—

(1) Those not containing iron. Of this group of pigments, *hæmatoidin* is the most common.

(2) Those containing iron. "*Hæmosiderin*" is the term used to designate the group of iron-containing pigments.

Hæmatoidin.—Hæmatoidin is identical in chemical constitution and characters with bile pigment (bilirubin). It occurs as ruby red rhombic prisms or acicular crystals, or it may be in the form of granular masses. It is insoluble in water, alcohol, ether, dilute acids, and glycerine, but soluble in chloroform, benzole and bisulphide of

carbon. It gives a play of colours with impure nitric acid (Gmelin's reaction). Hæmatoidin is not easily produced artificially outside the body. In the body it is slowly formed, several days being necessary, but once formed, it is very persistent and may be found at the site of old hæmorrhages years after their occurrence. Hæmatoidin is said by some to originate especially in situations where there is a deficiency of oxygen, or where the extravasated blood is not subjected to the action of phagocytic cells. It is often found in old blood clots, *e.g.*, after cerebral hæmorrhage, and in the walls of thrombosed veins.

"Hæmosiderin."—To a large extent this appears to be hydrated ferrous oxide, sometimes apparently in loose combination with proteid. It is usually in the form of brownish or black granules. Most commonly it is contained in cells, but it may be deposited in the intercellular tissues. It is this pigment which is usually deposited in the cells of the various organs as a result of hæmolytic changes, and by the action of phagocytes and malarial parasites on red blood corpuscles.

Although Hæmosiderin, the type of the group, may be regarded as hydrated ferrous oxide, the typical iron reaction may not be obtained for some time after the addition of reagents, either owing to some combination with albuminous substances or from the protective action of surrounding material.

The Prussian blue reaction is the common chemical test, and can be used for the demonstration of iron either in fresh organs or in microscopic sections. The reaction is best obtained by treating the cut surface of the organ or the microscopic section with a solution of ferrocyanide of potassium (20 per cent.), and then with weak hydrochloric acid (5 per cent.), or with a mixture of the two reagents. The iron-containing granules are stained blue or greenish blue. Other chemical tests for iron, such as ammonium sulphide or sulphocyanide of potassium, may be employed, producing respectively a black and a red colouration of the granules. This iron-containing pigment is often well seen within phagocytic cells in the air alveoli of the lung in chronic venous congestion.

Changes in Effused Blood.—The changes which commonly occur in effused blood may here be briefly mentioned. The series of changes which occur can best be followed by introducing blood into a serous cavity (*e.g.*, peritoneal sac or subdural space) of an animal. A considerable quantity of the blood plasma is quickly absorbed by the blood and lymph vessels, along with a certain proportion of unaltered red blood corpuscles, many of which soon appear in the lymphatics. The unabsorbed part coagulates or becomes more inspissated. The subsequent changes are largely due to the direct action of various cells.

Many of the red corpuscles break down or discharge their hæmoglobin, which soaks into the surrounding tissues. A part of this dis-

solved hæmoglobin is absorbed and eliminated by the kidneys as methæmoglobin or urobilin, but the unabsorbed part undergoes further chemical transformation, resulting in the production of hæmatoidin or hæmosiderin.

Other red corpuscles fuse together and their hæmoglobin is partly transformed into methæmoglobin, which later becomes further altered. A large number of them are ingested directly by various phagocytic cells. The various kinds of phagocytic cells will be mentioned in connection with the ingestion of bacteria. A word may be said as to their action on blood corpuscles.

The phagocytes ingest not only hæmatoidin and hæmosiderin granules, which may have been produced by a chemical transformation of the free dissolved hæmoglobin, but they also ingest red cells which are apparently unaltered, and red cells which have undergone disintegration into granular masses. Within the phagocytes the ingested red cells lie in vacuoles, but their hæmoglobin is soon dissolved and diffused throughout the cytoplasm of the phagocyte. The red cell then appears as a colourless globule, which quickly thereafter disintegrates and disappears. The dissolved hæmoglobin becomes transformed into granular pigment, mainly hæmosiderin, which accumulates in the cell. Many of the phagocytic cells become converted into passive masses of granular pigment. At first this granular pigment may not give the characteristic iron reaction, but after a few days the iron apparently becomes dissociated from its albuminous combination and then the reaction is obtained. The use of warm hydrochloric acid hastens the development of the iron reaction of these granules. Of the two types of phagocytic cells, the large mononucleated phagocyte displays the more active properties. As many as six red blood corpuscles, or even more, may be contained within its cytoplasm, in various stages of disintegration. In addition they ingest polymorphonuclear leucocytes, whose vitality has probably been injured in carrying out their phagocytic function. The ingested polymorphous cells lie within distinct vacuoles, where they are subjected to a digestive action. Their nuclei fragment into condensed masses of chromatin, which soon disappear, their cytoplasm disintegrates, and ultimately only the pigment granules which they may have contained remain imbedded in the body of the larger phagocyte.

These large phagocytes, although heavily laden with pigment granules, may retain their vitality, and by virtue of their amœboid activity they can migrate along the lymphatics and deposit their pigment in the lymphatic glands, or elsewhere in the body. A considerable quantity of pigment may be thus removed from the local site of extravasation.

A similar activity on the part of the cells is displayed towards all foreign particles. This is well seen in the case of tattooing of the

skin, partial removal of the extraneous pigment being effected by phagocytic cells, which deposit it in the associated lymphatic glands. In the lung, carbon particles are ingested by large endothelial cells and then deposited along the lymphatics and in the bronchial glands. The pigment may be carried to more distant parts, and be deposited in the liver or spleen.

Hæmatogenous pigmentation, as we have said, also occurs after the destruction of red blood corpuscles in the circulating blood, and after the liberation of hæmoglobin in the blood-plasma. In pernicious anæmia there is an excessive destruction of red blood cells, evidently occasioned by the action of some toxic substance. The resulting pigment, chiefly hæmosiderin, accumulates in the liver, kidneys, spleen and bone marrow. In the liver the granules of pigment are found especially in the peripheral cells of the lobules and in the capillary endothelium. In the kidney the secreting cells of the convoluted tubules and ascending limbs of Henle's loop are the chief sites of the deposit. In the spleen the endothelial cells of the pulp spaces and venous sinuses contain granular pigment, which may be aggregated into larger masses. A similar accumulation of hæmosiderin in the organs may occur whenever the red cells are injured or destroyed by any bacterial or other poison, but the accumulation in the liver rarely attains the degree which is reached in extreme cases of pernicious anæmia.

After malarial fever granular pigment containing iron is found in the various organs. The pigment directly elaborated by the malarial parasite from the hæmoglobin of the red cells which it destroys is by some regarded as of different composition. The pigment, in the form of dark or black granules, is ingested by the large mononucleated leucocytes, and is deposited in the connective tissue of the liver, spleen, pia mater and even the skin. It is contained for the most part within connective tissue corpuscles, but it may be also found within secreting glandular cells.

"Hepatogenous" Pigmentation.—Here the pigment is derived from bile. Bilirubin, the chief bile pigment, is, it must be remembered, identical with hæmatoidin, and is derived from hæmoglobin by the action of the liver cells. Biliary pigmentation occurs especially in chronic jaundice, due to some obstruction of the bile ducts. Part of the retained bile pigment which is absorbed from the liver by the lymph and blood vessels is excreted in the urine as urobilin. The bile pigment retained in the blood produces a diffuse staining of all the tissues and fluids of the body. The fibrous tissues are always most markedly affected. If the jaundice be persistent, granules of bile pigment are deposited in the liver cells, in the secreting cells of the kidney, and it may be diffusely in many other tissues. In some cases the pigment is biliverdin, or some other derivative of bile.

It is not uncommon to find some degree of jaundice in septicæmias and in other toxic conditions in which there is an excessive destruction of red blood cells. An increased amount of bilirubin is formed from the liberated hæmoglobin, and jaundice results in consequence of its absorption from the liver. At the same time there may be an accumulation of hæmosiderin granules in the organs. But in many cases, in fevers, etc., the jaundice is due to obstruction of minute bile ducts, or to breaking down of liver cells, and not to hæmolysis.

III. **Extraneous Pigmentary Substances.** — Foreign particles which accumulate in the tissues may be of various colours. They may be absorbed from the respiratory or alimentary tract, or rarely through the skin (*e.g.*, in tattooing).

The dust diseases of the lungs—the pneumokonioses—are the most common examples. The inhaled particles are of various kinds, *e.g.*, carbon (anthracosis) giving a black colour, iron (siderosis) rusty brown, etc. The particles are either carried direct by the lymph stream after passing through stomata, or are ingested by cells in the bronchi and air alveoli, which thereafter migrate and deposit them along the lymphatics and in the bronchial lymphatic glands.

The administration of silver preparations over a prolonged period in the treatment of certain chronic nervous or gastric diseases may produce chronic silver poisoning (*Argyria*). Silver as an albuminate is deposited as granules in the connective tissues of the skin around the sweat and sebaceous glands. The skin, on exposure to light, assumes a dull purplish colour. A similar deposit may occur in the epithelial cells and connective tissue of the kidney.

In chronic lead poisoning, a blue line on the gums around the roots of decayed teeth is sometimes a characteristic feature. This is due to the action of sulphuretted hydrogen on the lead compounds.

A distinctive staining of the skin and alimentary mucous membrane may be produced by various acids and corrosive poisons, but these need not be enumerated.

Pigmentation produced by Fungi.—A black discoloration of the skin of the external auditory canal is occasionally produced by the growth of the Aspergillus niger.

A brown scaly eruption of the skin, very common on the chest, is often seen. It is due to the growth of a fungus (microsporon furfur) in the superficial layers of the epidermis.

Finally, mention must be made of post-mortem discoloration. This is seen especially in the abdominal organs, which may present black or slaty blue patches of discoloration on the surface, due to the action of gases (sulphuretted hydrogen) on the hæmoglobin of the blood. Such discoloration is sometimes mistaken for the results of disease.

CHAPTER III.

ATROPHY.

ATROPHY is a term which is often applied to the wasting of organs and tissues, and to retrograde processes characterised by diminution in size or actual disappearance of the affected structures. Wasting may be a general process. Yet while all the organs and tissues in the body may suffer to some extent, the degree of affection varies considerably in different structures. On the other hand, the condition may be purely local in its distribution, affecting one organ or a group of organs, or an important constituent of one organ. This is a *local* or *partial* atrophy.

General Considerations.—In order that the activity of cells may be maintained at a normal standard, certain conditions are essential. The cells and tissues must receive a supply of nutriment sufficient in quantity and of a proper quality ; they must retain the power of self-nutrition and of normal regeneration or repair. Alterations in the environment of the cell to which it cannot adapt itself, such as abnormal temperature or pressure or defective oxygen supply, produce disturbances in cell-life which may impair this power.

The nutrition of cells may be impaired by exhaustion, as in old age, or by excessive use.

Many toxic substances may, if their action is severe or prolonged, permanently impair the vitality of cells and so check nutrition.

The trophic influence of the nervous system may be regarded as a well established physiological fact. But in many pathological processes it is very difficult to decide how far the effect of the nerve lesion is direct, or what part is played by impaired functional activity or by altered circulation.

From what has been said of the causes of degeneration it will be seen that those which are assigned as causes of atrophy are similar or identical. It is, in fact, rather a question of degree. The same cause may produce atrophy, degeneration, or actual death of a cell or tissue, according as its action is more or less intense.

In the changes which we call atrophic, there will be associated degeneration. Upon this ground some pathologists prefer to speak only of degenerative atrophy, and would restrict the term atrophy to conditions in which there is only diminution in the size of cells or in the quantity of tissue without degenerative changes. Such conditions,

if they occur at all, are extremely rare, and it is useful to retain the term as indicative of those conditions in which the reduction in mass is not specially due to degeneration, but is rather allied to the process of involution.

The cytoplasm of a wasting cell usually becomes clearer and stains less intensely. There may be increased pigmentation, as in brown atrophy of the heart, and fatty or mucoid degeneration are very common.

Imperfect regeneration of cells is often as marked a feature in atrophy as decrease in the size of the elements. The atrophy of the skin in old age is to a large extent dependent on inefficient repair. This lack of regeneration is also much in evidence in some diseases of joints in which the constant friction and pressure may wear away the articular ends of the bones, if the processes of renewal be impaired or abolished. In bones there may also be a progressive absorption, without a simultaneous formation of new Haversian systems.

A noteworthy feature in some atrophying tissues is the frequent degradation of the affected structures, a condition to which, when occurring in connective tissues, Virchow applied the term "*Metaplasia.*" This change can, of course, only occur among members of the same group of tissues. Cartilage frequently undergoes mucoid transformation, and a similar change is seen in the bone marrow, which becomes grey and gelatinous.

In glandular and muscular organs, the specialised constituents suffer especially, whilst the supporting connective tissue may become increased in amount, so that the organ acquires a firmer consistence. This is sometimes called *fibrous atrophy.* Such overgrowth of the supporting tissue at the expense of the specific elements of the organ, *e.g.*, muscle cells of heart, gland cells, etc., is a process common to all retrograde changes in these tissues, and is very characteristic of senile atrophy. During atrophy of the glands provided with ducts the secreting cells may become degraded so as to resemble those of ducts. Thus in the kidney the cells of some parts of the convoluted tubules may come to resemble those of the collecting tubules.

In atrophied organs and tissues, important changes are often found in the bloodvessels. These changes may either be the cause of the atrophic changes, or may be secondary, owing to the diminished demand for the supply of blood. For it is a general law that the arrangements for blood supply are proportioned to the demands which may from time to time be made for functional activity, and when this stimulus is permanently withdrawn or lessened, the channels of supply will become narrowed. Hence the lumen of the arteries of a functionless organ becomes diminished or entirely occluded by a fibrous thickening of their coats. The capillaries and veins undergo similar

changes. In general malnutrition and in prolonged anæmias, the superficial veins may become so thin and small that no vein of sufficient size may be found in order to perform transfusion.

Atrophy may be *general* or *local.*

General Atrophy.—In old age, general atrophy of many of the more special tissues of the body is to be regarded as physiological ; but if a like change occurs at an earlier age, it may be regarded as pathological (premature senility).

A general wasting or marasmus will follow entire deprivation or deficiency of nutriment. It occurs in famines, in cases of actual starvation, and in certain diseased conditions which interfere with the ingestion or absorption of food, *e.g.*, malignant disease of œsophagus, and disease of the mesenteric glands interfering with the absorption of chyle. In all cases of starvation, fatty and mucoid changes are widespread in the tissues, and the general body fat disappears. If the marasmus be dependent on an entire absence of food, there is often a special atrophy of the stomach and intestines in association with the general wasting. The intestinal walls become thin and translucent. In general wasting there is no uniformity of affection of all the organs and tissues. Apart from the disappearance of adipose tissue, the wasting of the muscles is always very striking. The bone marrow also undergoes great wasting. The tissues which waste least are the formed parts of bone and the central nervous system.

In severe or continued fevers, and in certain chronic diseases, *e.g.*, tuberculosis, constitutional syphilis, etc., a general wasting frequently occurs. In some cases of congenital syphilis in children, the wasting may attain an extreme degree, especially if the liver is diseased. The general wasting in these conditions cannot be solely ascribed to the diminished ingestion of food. A more predominant factor is probably the injurious action of various soluble toxins upon the cell nutrition, leading to increased metabolism and the supervention of various degenerative changes. Of interest in relation to the influence of toxic substances in producing atrophy is the general wasting which sometimes occurs after the use of antitoxic sera, and after the exhibition of thyroid extract.

But in most diseases attended by the action of toxins, the presence of fever, of interference with absorption and metabolism, and such causes as loss of sleep, diarrhœa, perspiration, etc., make it difficult to decide how much is due to toxic action alone.

Extreme wasting occurs in some cases of diabetes mellitus, but not in all.

Local or Partial Atrophy.—Atrophy may affect one organ, or a group of organs—*e.g.*, the lymphatic glands—or an important

tissue of an organ. We have to distinguish between true atrophy, characterised by retrogressive changes in organs and tissues which have reached full development, and some conditions, which are the results of defective growth or congenital deficiency, to which the terms *hypoplasia* and *aplasia* are respectively applied. But it is often difficult to decide whether the diminution in the size of an organ is to be considered as due to an arrest of growth or to atrophy consequent on disease.

The term atrophy is sometimes erroneously applied where the organ wastes from destructive change. A flagrant example is the application of the term "acute yellow atrophy of the liver" to a condition due to rapid necrosis of the liver cells.

Local atrophy may be physiological, dependent on the cessation or subsidence of function. This physiological atrophy is seen in the normal atrophy of the thymus gland, and of the female generative organs after the menopause.

Causes of Local or Partial Atrophy:—

(1) **Loss of Functional Activity.**—It is a general law that an effete and functionless organ or tissue wastes, and may ultimately be entirely removed. The muscles and the muscular organs afford the most striking examples. The muscles and bones of an extremity, whose function has been abolished in consequence of some deformity or partial amputation, always undergo atrophy. In pure cases of mitral stenosis the atrophy of the left ventricle is a direct consequence of diminished function due to the lessened quantity of blood to be propelled. Atrophy of a like kind occurs in the wall of the bowel below the site of an artificial anus. The atrophy consequent on loss or diminution of function is closely associated with lack of nutriment. The blood supply to a functionless organ is always diminished.

(2) **Excessive Use.**—Excessive use may lead to ultimate atrophy, but there is usually an antecedent hypertrophy. Examples of this are seen in cases of emphysema, where the extraordinary muscles of respiration, especially the sterno-mastoids and scaleni, are subjected to a persistent demand for increased function. Hypertrophy first occurs, but if the excessive use be continued, or the general nutrition fails, atrophy supervenes.

(3) **Pressure.**—Pressure is a common cause of local atrophy. John Hunter pointed out that continuous pressure produces atrophy, whilst intermittent pressure leads to hypertrophy. The pressure may be exerted from without, as in the erosion of the vertebral column or of the sternum by an aortic aneurism. In the case of the vertebral column, the bones undergo greater absorption than the more resilient intervertebral discs. On the other hand, atrophy of an organ may be the result of pressure from within, as in emphysema of the lungs. Pressure of one constituent of an organ upon another constituent

may cause atrophy of the latter. This commonly occurs in chronic venous congestion of the liver, in which atrophy of the columns of liver cells is the direct result of compression exerted by dilated capillaries. Atrophic grooves are frequently found in the livers of labourers and others who constantly wear a tight abdominal belt. And in old people, with distended intestines, the liver may be pushed up and compressed in its transverse diameter, and become somewhat folded, and atrophic grooves, often of considerable extent, are found running in an antero-posterior direction across the upper surface of the organ.

Pressure is directly antagonistic to cell-life, but its action is no doubt greatly aided by the compression of bloodvessels. In many cases pressure appears to stimulate the action of phagocytic cells.

(4) **Defective Supply of Nourishment.**—This is a frequent cause of atrophy; but whilst it often acts alone, in many cases it is associated with other factors. The lumen of arteries is frequently diminished in diseases leading to thickening of their walls, and the atrophy consequent upon the decrease in the blood supply is slowly progressive in its development. A striking example of this condition is the atrophic form of granular contracted kidney.

The absence of some special substance influencing nutrition may be responsible for the atrophy of some structures. The secretion of the normal thyroid gland is apparently necessary for the healthy nutrition of parts of the nervous system and of the special structures of the skin. In myxœdema, a disease consequent on atrophy of the thyroid gland, there is an atrophy of the hair follicles and of the sweat and sebaceous glands of the skin.

(5) **Neurotrophic Influence.**—We have seen that in so-called neurotrophic atrophy it is usually very difficult to say how far the wasting depends upon the interference with the vascular supply, upon loss of function, or upon the loss of the trophic influence of the nervous system. Atrophic changes in bones and joints are found in some nervous diseases. When the large ganglionic cells of the anterior cornua of the spinal cord are destroyed or diseased, wasting of the associated muscles ensues. In infantile paralysis the bones as well as the muscles of the affected extremity are found in after life to be smaller than those of the sound limb, and the condition does not appear to be due solely to the loss of muscular action, in other words, it appears to depend upon a direct influence on nutrition. Localised nerve lesions may lead to local atrophies of skin and hair, *e.g.*, in morphœa.

In leprosy, there may be great atrophy of the bones of the extremities of which the nerve trunks are affected, quite apart from the ulcerative or necrotic changes due to involvement of other tissues.

Changes in the Atrophied Organs.—The minute changes

in structure have been already considered. An organ whose special tissues have undergone atrophy is not necessarily diminished in size. A waxy liver may be much larger than normal, even although the liver cells in consequence of the pressure of the waxy capillaries are extensively wasted. The overgrowth and thickening of fibrous tissue in atrophied organs replacing the specific elements often leads to an increase in consistence. In some organs, the atrophic process is not uniform in its distribution, and the surface may be irregular or granular.

CHAPTER IV.

NECROSIS.

NECROSIS is local death of the tissues in the living body. The term necrosis is especially applied to conditions in which death of the cells or tissues occurs rapidly, and independently of any antecedent alteration in their structure. To the slower type of death, which is the ultimate result of other retrograde processes affecting minute elements, the term *necrobiosis* has been applied by Virchow.

It must be remembered that with our present knowledge the sole evidence of cell-death is the cessation of function and the presence of certain structural and chemical changes which supervene in the tissues in consequence of their death. This especially applies to the recognition with the microscope of the fact that parts have been dead before the cessation of general life of the whole animal.

Causes of Necrosis.—Death may be caused directly by the injurious agent, or by such interference with its vitality as renders it incapable of continued self-nutrition.

(1) **Arrest of Nutrition.**—An absolute arrest of the blood supply may lead to necrosis, where a gradual diminution would tend to produce atrophy.

Arterial obstruction is a frequent cause of necrosis, and is seen in many pathological conditions. In old people, with degenerated arteries and defective circulation, thrombosis in the narrowed arteries leads to senile gangrene, especially of the lower extremities, and similar effects may be produced by thrombosis from other causes.

Embolic obstruction of arteries is also an important cause of necrosis. The effects of arterial obstruction depend largely on the local circulatory mechanism and on the condition of the general circulation. But the consideration of these changes may be postponed, as they constitute an important group of phenomena connected with circulatory derangements in general. A temporary deprivation of the nutrient supply will in some cases produce necrosis. If the renal artery be ligatured for one hour, extensive necrosis of the vulnerable secreting cells may result.

In chronic ergot poisoning, and in Raynaud's disease, a symmetrical necrosis of the fingers and toes is occasionally the direct result of recurrent spasmodic contraction of the arteries.

Apart from the direct obstruction of arteries, anything which separates a tissue from its nutrient supply may lead to necrosis. As examples of this, the superficial exfoliation of bone which may follow separation of the periosteum by pus, and the extensive ulceration of the large intestine in dysentery when the mucous membrane is undermined, are sometimes quoted. But in both cases there are toxic conditions present which may be the real cause of the necrosis.

(2) **Physical and Chemical Agents.**—Pressure, if excessive or continued, may be a cause of necrosis, but is usually aided by other conditions, of which interference with the circulation is the most important.

The extensive necrosis of the tissues which occurs in severe crushing injuries may be due partly to the mechanical pressure and crushing, but much of it is a secondary result of the laceration and thrombosis of the vessels. Interference with the circulation is the potent factor in the production of necrosis due to tight bandaging. The persistent pressure of distended veins upon the skin may produce necrosis and consequent ulceration, as in varicose ulcers of the leg.

The effects of pressure are also seen in the formation of bedsores. These may occur in any case of prolonged pressure in conditions of debility, especially over the sacrum. The low vitality of the tissues is no doubt often aggravated by contact with decomposing urine or fæces.

In some cases of nervous disease, especially in acute myelitis, as from fracture of the spine, and also in some cases of hemiplegia, bedsores develop with alarming rapidity over any part of the paralysed limb which is exposed to pressure, *e.g.*, trochanters, internal condyles of the femur, where the knees are in contact, and on the heels or the toes where pressed on by bedclothes.

No doubt in many cases a part of this liability to bedsores may be from deficient sensation. A hot bottle may cause an extensive eschar. But a far lower temperature and shorter contact than that which would be efficient in health may produce the injury.

And in some cases, from the extreme rapidity of occurrence and the slight causes which may produce the necrosis, there can be no doubt that there must be loss of some trophic nervous influence. To these conditions the name of **acute decubitus** is applied.

Temperature.—Extreme degrees of heat and cold are inimical to cell-life, but their effects are intensified by the arterial contraction or thrombosis which they induce. Burns and frost bites are familiar examples. A moderate degree of heat, if too long continued, may produce necrosis, and this is especially the case if the tissues be deficient in vitality, as in the instances already cited.

Electricity.—Necrosis of the skin is often seen after exposure to the Röntgen rays. After the too prolonged local action of the

galvanic current, local necrosis of the skin may occur where the electrode has been applied. The necrosis induced by these agencies is probably the result of their direct action upon the tissues.

Chemical Agents.—The tissues may be killed outright by some chemical substances, *e.g.*, mineral acids, carbolic acid, and other caustics and corrosives. Their physical and chemical characters are frequently altered in a characteristic way. The various local actions of poisons on tissues may be studied in works on pharmacology and toxicology. The necrosis of the jaw following exposure to fumes of phosphorus has usually been regarded as due to a direct action on the periosteum, but of late this has been questioned. Some poisons may produce necrosis of cells in the organs by which they are eliminated, *e.g.*, corrosive sublimate in the renal epithelium.

(3) **Bacterial Toxins.**—The action of bacterial toxins in producing profound derangements in cell-life is their most important mode of disease production. In some cases the action is so intense that the cell is at once killed, or speedily dies. And the action of ferments may so alter the composition of the cell, or lead to reactions with material absorbed from the lymph, that very obvious changes occur in physical characters and in the staining with reagents.

Examples of such changes are seen in the hyaline swelling of cells and basement membranes due to some of the toxins generated by tubercle bacilli, and the local action of diphtheria toxin on the epithelial cells of the pharynx. Such local action is also seen in malignant pustule due to the anthrax bacillus.

But in addition to these local necrotic changes we sometimes meet with multiple minute areas of necrosis, "focal necrosis," in various organs, especially in those organs most concerned in transformation or elimination of the toxins, or those for which the toxins have especial affinity. In the liver, spleen, and kidney such focal necrosis may be found in typhoid fever, some forms of septicæmia and other infectious diseases.

The liver is the best organ in which to study such focal necrosis. The areas may be microscopic in size, but some are often large enough to be visible with the naked eye. They appear as small rounded areas of opaque white or yellowish white colour.

Similar necrosis may be produced by the action of the vegetable toxins, abrin and ricin.

In some cases careful examination fails to demonstrate the presence of any bacteria in the necrotic areas, so that the necrosis is apparently due to the direct action of the soluble circulating toxins upon the cells. In some cases, however, the focal necrosis depends on capillary thrombosis. This occurs in typhoid fever and some other conditions, in which, according to Mallory, there is the formation of fibrin around degenerated endothelial and phagocytic cells within the capillaries.

(4) **Influence of Nerve Lesions.**—Mention has been already made of the acute decubitus in transverse myelitis, in which there must be interference with the trophic influence of the nervous system, apart from the circulatory disturbances produced by pressure on exposed parts. In many nervous diseases the general vitality of the tissues is greatly reduced. Section or disease of the peripheral nerves may also lead to localised areas of necrosis, *e.g.*, perforating ulcer of foot in locomotor ataxy and necrosis of extremities in anæsthetic leprosy. In leprosy, however, the anæsthetic parts are exposed to mechanical irritation.

All these causal conditions may be greatly aided in their action by defective general nutrition, as in old people with weak hearts and diseased bloodvessels, and after prolonged starvation. Many diseases produce a diminution in the resistance of the tissues. This is seen in diabetes mellitus and scorbutus, and subsequent to the attack of certain fevers, *e.g.*, typhoid and typhus fevers.

Secondary Changes in Necrosed Parts.

The changes which occur in cells and tissues consequent on their death in the living body affect both their structure and chemical constitution. Cells which are specialised for function are the most vulnerable. In anæmic necrosis of the kidney, the highly specialised secreting cells always suffer first, while the cells of the collecting tubules and the capillary endothelium resist for a much longer period.

Changes in the Cytoplasm of Necrosed Cells.—The cytoplasm commonly becomes swollen and hyaline or homogeneous in appearance, with the consequent loss of its characteristic granularity or striation. The swelling of the cell is due to the imbibition of fluid and the transformation of the cytoplasmic contents into a homogeneous mass which may be of increased consistence, this being possibly due to the absorption of fibrin-forming elements or coagulable albumins from the surrounding lymph.

The belief that the coagulated material is fibrin rested mainly on the reaction with some stains (*e.g.*, Weigert's fibrin stain), but other albuminous substances may give a like reaction.

This transformation of the cytoplasm into a swollen homogeneous mass is of common occurrence in necrosed areas, *e.g.*, in secreting cells of kidney in infarction, in necrosed muscle cells (as in the so-called Zenker's degeneration), and in the cells of various organs from the action of toxins.

On the other hand, the cytoplasm of necrosed cells may become swollen and even vacuolated, lose its normal reticular structure, becoming more granular, and break down into a granular or fibrinous looking detritus. Such changes are frequently observed in the specific cells of the organs in intense toxic poisoning. The staining reactions

of necrotic cells vary. Commonly at first the cytoplasm is stained more intensely with acid dyes ; later, the staining capacity is lost, or it may show an affinity for basic nuclear stains.

Changes in the Nucleus.—An important and interesting series of changes occurs in the structure of the nucleus before its ultimate destruction and disappearance. The chromatic substance in some cases undergoes a rapid solution ("*Karyolysis*," "*Chromatolysis*"), so that the nucleus no longer possesses an affinity for basic stains, but remains for some time as a colourless body, in which there is the persistence of the linin network. The linin network soon after disintegrates and disappears. In other cases, however, the chromatin undergoes a preliminary fragmentation ("*Karyorrhexis*"). Two chief types of Karyorrhexis may be recognised for descriptive purposes. In one type the chromatin becomes condensed into a solid mass ("*Pyknosis*"), which subsequently breaks up into several smaller masses, usually six to ten in number. These chromatin masses become dispersed in the necrotic tissues, many quickly disappearing, but some persist till a later period.

In the other type of Karyorrhexis the nucleus usually becomes somewhat swollen, and the chromatin breaks up into a large number of small granules irregularly distributed throughout the nucleus, or it may be aggregated towards its centre or at the periphery. The nuclear membrane disappears, and the chromatin granules are diffused throughout the cell cytoplasm. Many of these granules persist for some time as chromatin remnants in necrosed tissues. It must, however, be stated that some granules in necrosed tissues, which are not chromatin, give a similar basic stain, and hence we cannot be sure whether they are chromatin or no.

As a result of these changes in the tissue elements, the physical characters and appearance of the dead part are altered. Certain names have been applied to these conditions, especially by Weigert, and they have been called "forms of necrosis." It would obviously be more correct to term them "post-necrotic." And their exact characters are of little importance, as they depend to a great extent upon the nature of the tissue and the surrounding conditions. The names—coagulative necrosis, colliquative necrosis, and caseation—are so commonly employed that they must be briefly explained.

When the necrosed tissues swell and become transformed into homogeneous masses of an increased consistence, in situations where lymph is readily absorbed, the term **"Coagulation-Necrosis"** has been applied by Weigert. In many of these cases a true coagulation does, no doubt, occur by the action of some ferment upon the albuminous or fibrin-forming constituent of the absorbed lymph. This change is characteristically seen in infarcts of the kidney and

heart-muscle, and in the tissues in many toxic conditions, *e.g.*, action of diphtheria toxin upon stratified squamous epithelium of the pharynx.

When the necrosed tissues undergo softening and liquefaction without decomposition, the condition is designated **"Colliquative Necrosis."** Softening of necrosed areas commonly occurs in the brain and spinal cord, *e.g.*, in embolic obstruction of arteries.

The areas of necrosis may come to resemble various kinds of cheese in appearance. To this change the term **"Caseation"** has been long applied. The classical example is seen in tuberculosis. But caseation may follow either "Coagulation necrosis" or a granular disintegration of the tissues.

Separation of Necrosed Parts.—Necrosed areas on free skin or mucous surfaces are commonly cast off as sloughs, with the subsequent formation of ulcers, *e.g.*, in typhoid and tubercular ulcers of intestine. This detachment is frequently attended or followed by suppuration wherever common septic bacteria can gain access. In solid organs and in situations where sloughing cannot occur, efforts are always made to remove the dead parts by active processes of absorption. There is the emigration of leucocytes possessed of phagocytic activities, the proliferation of fixed connective tissue cells, and the formation of new capillaries which permeate the necrosed area and aid in its absorption. The dead part, if small and aseptic, may be entirely absorbed and replaced by fibrous tissue, which may lead to deformity by its subsequent contraction.

In some cases, *e.g.*, infarcts of kidney and spleen, complete absorption may not take place, the unabsorbed parts persisting as yellowish-white caseous-looking areas encapsuled by fibrous tissue. In these areas lime salts may be subsequently deposited, *e.g.*, infarcts of kidney, old caseous tubercular masses in lungs and lymphatic glands.

If a dead part be exposed to the action of septic agents, it may undergo purulent softening and lead to an abscess, *e.g.*, in infarcts the spleen, where such secondary suppuration may follow a simple infarct. In most cases, however, suppuration only follows septic embolism.

Gangrene.—Any part, dying or dead, loses the power of resistance to organisms of putrefaction, and, consequently, if it be exposed to them, it undergoes decomposition.

Gangrene, in some instances, is a *primary* process, the direct result of the action of some organisms, *e.g.*, bacillus of malignant œdema and bacillus ærogenes capsulatus, which have the power of producing simultaneous death and putrefaction of the tissues. This condition is usually seen as a rapidly spreading gangrene of the

extremities. Hospital gangrene and cancrum oris are analogous examples. Many of the causal organisms are anærobic.

Secondary gangrene of dead parts is most commonly seen in situations normally exposed to the action of putrefactive organisms, *e.g.*, skin, intestinal canal.

Typical examples of this form of gangrene occur from obstruction of degenerated arteries by thrombosis, as in senile gangrene of the foot.

The fuller study of these conditions may be reserved for the section dealing with circulatory derangements.

In some cases of heart disease gangrene may occur at the tip of the nose or the ears as well at the extremities of the limbs. In these somewhat rare cases some other factors, either general or local, must be present, besides the effects of embolism or thrombosis. General impairment of nutrition, stagnation of the capillary circulation at the peripheral parts, and local irritation or infection may perhaps be sufficient causes.

It is in such cases that thrombosis in veins, *e.g.*, the subclavian or axillary or the femoral veins are also apt to occur.

In the alimentary canal, gangrene occurs after strangulation or intussusception of the bowel.

In the internal organs, *e.g.*, in the lung, gangrene is sometimes seen, dependent either on a direct infection from without, or on the presence of organisms in the circulating blood in conditions of diminished resistance. In the lungs it is sometimes a sequel of acute pneumonia, especially in persons suffering from diabetes insipidus or mellitus, or chronic alcoholism. In the brain, gangrene is always an indication of septic infection, usually extending from the ear or nose.

Gangrene may follow diseases producing great vital exhaustion, *e.g.*, acute infectious fevers. It is often difficult to say whether these are examples of primary or secondary gangrene.

It is customary to divide gangrene into two forms—the dry and the moist.

The putrefactive changes in dry gangrene, *e.g.*, senile gangrene of the foot, are not marked and may be entirely subsidiary.

The gangrenous parts become brown or black in colour in consequence of the transudation of blood pigment. Dry gangrene occurs especially in parts where free evaporation of fluid can readily occur, and where there is no excess of fluid in the part. The part becomes shrivelled and "*mummified.*"

Moist gangrene occurs especially in parts which are moist or dropsical. It is usually found either in gangrene due to infection or where there is a combination of venous and arterial obstruction. The parts become progressively softer, and there may be detachment of parts of the epidermis due to the evolution of gas, which forms

bullæ. This emphysematous condition of the tissues is very characteristic of the gangrene due to the Bacillus ærogenes capsulatus. There is much discoloration of the gangrenous parts, and the discharge of a foul smelling bloodstained fluid. Decomposition leads to the formation of toxic products, which are absorbed, producing a form of blood poisoning.

The gangrenous condition may spread, or it may become circumscribed by an inflammatory reaction on the part of the healthy tissues, which produces a line of demarcation and a protective barrier of connective tissue. In the latter case, the gangrenous part may be detached by sloughing.

The distinction between dry and moist gangrene sometimes stated by surgeons, that moist gangrene is synonymous with gangrene due to infection and dry gangrene to arterial obstruction, is, from a pathological point of view, inaccurate.

CHAPTER V.

CIRCULATORY DERANGEMENTS IN RELATION TO NUTRITION.

ABNORMALITIES in the circulation of the blood necessarily tend to affect the nutrition, although there is a large capacity of accommodation to altered conditions. And, conversely, any great change in the processes of cell-life, whether from damage or from increased activity, will lead to associated changes in the local circulation.

Many of the circulatory changes in disease are merely variations or exaggerations of common physiological actions, and depend on similar causes. Amongst them may be reckoned the occurrence of temporary hyperæmia from reflex excitement, and the effects of stimulation or of paralysis of vasomotor nerves.

Such conditions when occurring from pathological causes may be of some importance, but they do not play any large part in the more serious disturbances of nutrition, and they may be more profitably studied in works on physiology.

Far more important in pathology are two groups of alterations, viz., those due to mechanical obstruction, and those associated with the effects of irritation and damage to the tissues. The latter group of changes include those commonly associated with the processes of "Inflammation."

THROMBOSIS.

Before considering the phenomena of vascular obstruction, it will be convenient to speak of **Thrombosis**, since it is so frequently either the cause of obstruction, or occurs secondarily to it, and adds to its effects.

Thrombosis is the term applied to the formation of a clot in the heart or bloodvessels during life, and the mass thus formed is called a **Thrombus.**

The process by which a thrombus is formed is not necessarily identical with the coagulation which occurs in blood withdrawn from the body. Indeed, in many cases the mode of formation is obviously different. It is important to bear this fact in mind in relation to the conditions or treatment which may prevent the occurrence or spread of thrombosis.

Thrombosis occurs most commonly in conditions of physical or

vital change in the vessel wall, which lead to irregularity or roughening, or where the blood flow is impeded so as to cause eddies in the stream. Slowing of the circulation also aids its occurrence. The presence of foreign bodies, or conditions which act as such, may also cause it. Far more rarely it is due to the action of toxins or to changes in the blood itself.

We shall for the present consider only those instances in which the physical conditions and changes in the vessel walls are concerned, leaving the rarer conditions, due to blood changes, for separate consideration.

Characters of Thrombi.—Thrombi are usually divided into two chief groups—the *red* and the *pale* or white. These commonly differ not only in their composition, but in the conditions under which they occur.

In most cases, under the ordinary conditions of thrombosis, the thrombi which constitute the primary and essential part of the mass are formed slowly, and are pale in colour. This is practically always the case in thrombi formed whilst the blood is still flowing in the vessel. When, however, the flow is actually arrested, and a large quantity of blood stagnates, a red clot is formed as a general rule.

In some cases we may see a mixture of pale and red parts in a thrombus, often arranged in layers. Such a condition may be seen within aneurisms.

Pale Thrombi.—The term *pale* is not a good one, since decolorisation of a red thrombus may lead to pallor. And it may be added that, apart from the common pale thrombi, there are others which are of exceptional occurrence, due to special causes, which will be referred to later.

The important fact is, that some thrombi, or parts of mixed thrombi, are pale, dull white, and somewhat firm *from the earliest stages* of their formation, and that others are at first dark red and softer.

Red Thrombi are formed wherever there is rapid coagulation of stagnating blood, and are usually of considerable mass, filling the vessel in which they occur. Both in the mode of their formation and their characters they differ little from a blood clot formed outside the body, or in a mass of blood effused within it. In them are found red corpuscles, closely packed, with delicate fibrin threads between. The leucocytes are often in normal proportion, and are found unaltered, if the thrombi are examined soon after formation. In some cases there may be very little fibrin formation, the red corpuscles being closely packed together, and sometimes apparently fusing together into a sort of coralline mass.

But under the ordinary conditions of thrombosis, these red clots do not form at first, and are not the essential or important constituent in thrombosis.

In many cases of disease we can observe the changes and study them with the microscope. In the heart, when dilated or weakened, thrombi form especially in the right auricular appendix, and in the pouches between the muscular bundles, especially towards the apex of the left ventricle. Similarly, in any part of the heart where there is much stagnation of blood, and upon roughened parts, such as degenerated and calcified patches, thrombi occur. They also form the main part of what are called *vegetations* upon valves which have been the seat of inflammation.

But the mode of formation can be studied far better experimentally: by ligature or compression of a vessel, by introducing foreign bodies, or by damaging the vessel wall without narrowing it.

A study of thrombi in all these conditions has led to the conclusion that the essential primary change is the fusion together (or "conglutination") of bloodplates (*platelets*) into a mass and their adhesion to a damaged part.

So long as the blood continues to flow freely over the part of a thrombus first formed, bloodplates may continue to be deposited. When the circulation is entirely arrested, the blood coagulates *en masse*. Other changes, such as leucocyte accumulation, may also occur in the chinks between layers of a thrombus, or may take part in secondary processes. But under ordinary conditions they take no active part in the process of formation.

Having thus stated broadly the conclusions arrived at by comparison of the mode of formation in a large number of conditions, we may say a few words as to bloodplates themselves.

Bloodplates.—The nature of bloodplates has been the subject of much controversy, and even the fact of their normal occurrence in the circulating blood has been called in question, and the statements of physiologists upon the subject are still conflicting. It is not necessary to narrate the various points in the history of their discovery, or to discuss fully all the views entertained as to their nature. To a large extent the observations of Bizzozero, and the experimental work of Eberth and Schimmelbusch, are consistent with the known facts, so far as we have observed them.

If blood is drawn rapidly with precautions against change, there are seen a large number of minute discoid bodies, of fairly uniform size and character in the same individual, highly refracting, measuring from 2 to 2·5μ in diameter.

They rapidly alter, running together into granular masses, the individual platelets becoming irregular in contour, with a jagged outline. They can, however, be easily kept separate if the blood is rapidly dried, or if exposed to perosmic acid vapour, or if the blood is mixed with various preservative solutions. They stain readily with hæmatoxylin and most basic dyes, presenting characters

analogous to those of nucleoproteids. But their colour differs from that of the nuclei of the leucocytes seen in the same specimen, being usually paler and more bluish with hæmatoxylin staining. (For other staining reactions special books may be consulted.)

Their presence in normal circulating blood has been denied, some holding that they are a precipitate of nucleo-albumin from the plasma, which may occur within the circulating blood under abnormal conditions, and constantly when the blood is drawn. And it is even stated that they can be formed by precipitation from oxalate plasma kept at a low temperature. For our present purpose it is unnecessary to discuss the accuracy of these views. They are, so far as we are aware, contrary to all the known facts.

The other views of their origin are diverse. Some maintain that they are the extruded nuclei of nucleated red corpuscles, formed when the transformation of hæmatoblasts into the ordinary red cells takes place. Hence, it is alleged, they do not occur in birds or other animals whose red corpuscles are normally nucleated: a statement which needs corroboration.

For others they are the shells of red corpuscles from which the hæmoglobin has been discharged, or, again, the discharged nuclei of leucocytes. No sufficient evidence exists for either of these views, and there are many reasons against the latter view. But at present the source of the platelets is not determined.

Nor can we discuss the question of their relation to the formation of fibrin in ordinary coagulation. According to some they are identical with "*prothrombin*."

Reactions of Bloodplates.—As seen under pathological conditions, their reactions are striking. If blood from a severed artery is allowed to flow freely and a bundle of glass threads inserted into the stream, the threads become covered with a mass of fused platelets, which have all the characters of a pale thrombus. (Bizzozero.)

Their reaction within the vessels has been fully studied by Eberth and Schimmelbusch, whose experimental results are in accordance with what is seen in the process of thrombosis.

The general result of the experiments of Eberth and Schimmelbusch may be outlined. So long as the bloodflow is active the platelets run in the axial stream with the red corpuscles. When retardation is produced the leucocytes, as is well known, fall out into the peripheral layer. As slowing becomes more considerable bloodplates also fall out, and at a certain period before entire arrest of the flow, they accumulate in large numbers in the peripheral layer of the stream, whilst many of the leucocytes may return to the more central part. When total arrest of flow occurs, all the corpuscles again become mingled.

During the period of retardation, if there is any irregular or

roughened part on the vessel wall, many of the bloodplates stick to it and fuse together. And at some points, especially where retardation is great and there is any eddy in the stream, many fuse together into masses, which narrow the channel and adhere at points to the wall. These reactions of bloodplates correspond with what is usually seen during the early formation of thrombi, and with their characters. In some of the veins we may find parts of the channel partially occluded by fused bloodplates, and leucocytes almost entirely absent. Those leucocytes which remain show no alteration in character which in any way suggests that they are taking an active part in the process.

The various phases of change can be well seen in the veins of an organ in which gradual stagnation of the circulation has been produced by ligature or embolism of arteries. For example, they are well seen in the veins in experimental infarction of the kidney studied at different periods after the obstruction.

We may now review some of the commonly observed facts as to the sites and conditions under which thrombi may occur.

Thrombi in the Heart.—In the heart clots are commonly found after death ; and it is necessary to distinguish between true thrombi and post-mortem clots. The latter are either dark red throughout or show parts which are paler or yellowish, especially in the part which has been uppermost after death. The paler parts of post-mortem clots are softer and more easily broken down, less stringy, and of more distinctly yellow or whiteish colour, whilst the ante-mortem clots are buff coloured, more firmly adherent to or entangled with the heart wall, and of greater toughness.

But it is not always easy to determine what part of the clot has been formed during the act of dying, especially if the period of heart failure is prolonged. In such cases there may be thrombi formed some time before death, continuous with clots formed both during and after death, the processes going on continuously. Clots in the cavities, especially of the right side, are not uncommon where the process of dying has been protracted, and it is often difficult to say whether these so-called "agony" clots have been formed during the act of dying or after death. These clots are yellowish in colour, translucent, gelatinous or slightly stringy in consistence, and are usually only loosely attached to or simply entangled with some part of the cardiac wall. They are frequently attached to some ante-mortem thrombus in the appendix, and they may extend through the tricuspid orifice into the right ventricle. In the ventricular cavity they are commonly adherent to some part of the wall towards the apex, mainly by becoming entangled between the columnæ carneæ, and they may also adhere to thrombus formed behind a flap of the tricuspid valve. The clot may also extend for some distance into the

pulmonary artery, and formerly when this was observed at the post-mortem death was ascribed to thrombosis of the pulmonary artery. These paler clots are mainly composed of masses of fibrin threads and entangled leucocytes.

When the heart is acting weakly, and especially if its cavities are dilated or it is the seat of disease, thrombosis may occur at any time, but is usually limited until the final failure occurs.

The commonest sites of thrombosis are the auricular appendices, and between the columnæ carneæ of the ventricles, especially towards the apex, situations in which slowing of the current and eddies in the stream are most apt to occur, and in which also there are great irregularities on the wall.

The right auricular appendix is by far the commonest site of such thrombi, and they occur there very commonly in cases of mitral valvular disease. Parts of these may become detached and be the cause of embolism of the branches of the pulmonary artery.

Valves which are the seat of acute inflammatory changes or of chronic fibroid thickening are very common sites of thrombosis. The thrombi are usually small and pale, and consist almost wholly of a mass of fused blood platelets firmly adherent at the base to the altered valve. These are called *Vegetations.*

In septic endocarditis the vegetations are usually larger than in rheumatic endocarditis and may reach a considerable size and even obstruct the orifice of the valve. This fact may be due to the greater alteration in the valves produced by the bacteria and toxins, or to the direct local action on the blood. Such thrombi may contain large numbers of bacteria, and as they often readily crumble or break off they produce multiple septic embolism.

Thrombosis in Arteries.—Thrombosis of such degree as to obstruct arteries is comparatively rare, owing to the rapidity of the blood stream. Thrombi may occur upon roughened or calcareous patches in the aorta and great vessels. Where there is great narrowing of the lumen of an artery, together with irregularity, as in advanced atheroma of the cerebral arteries, thrombosis may occur, and when once it has commenced it may spread to other diseased arteries. But even when the narrowing is very great, thrombosis may not occur. In syphilitic disease of the intima, however, thrombosis occurs with much greater readiness, and may take place before the lumen is greatly narrowed.

Obstruction by embolism or by ligature may also be causes of thrombosis, but in ligation of arteries the thrombus is often inconspicuous. That which occurs in the proximal side of the ligature is pale, firm and conical, and is slowly formed. On the distal side, if formed at all, it is red, loose, and rapidly formed, and may fill the vessel for some distance.

When thrombosis occurs in arteries from embolism or other causes, the clot may to a large extent be absorbed. The thrombus may at first fill the lumen, but as it often adheres only at one side, the blood finds its way past it as the clot shrinks, and the thrombus thus adherent to part of the wall is then called a "*parietal*" thrombus. Similarly, blood may find its way into chinks in any thrombus, and then coagulating produce red layers or masses amongst the paler and firmer parts.

In Capillaries thrombosis is especially associated with acute inflammatory conditions or with changes in the blood, and will be described later.

In Veins, as we shall see, thrombosis is especially common, both when they are dilated and varicose, and when the circulation is feeble. Injury to a vein or disease of its wall may also lead to its occurrence. The thrombosis usually begins in the pouch of a valve, to which it partly adheres. Projecting into the bloodstream, it grows by gradual accretion of bloodplates until it fills the lumen, and then a rapid coagulation, with formation of red thrombus, takes place up to the junction with a larger vein. Here a similar process is repeated, and the thrombosis may gradually extend in this way from a small superficial vein in the leg up to the femoral and iliac veins, and even to the inferior cava.

Such a spread of thrombosis is especially apt to occur if the heart's action is weak. But it is, no doubt, often favoured by certain conditions of the blood and by general debility, or by local disturbance or damage. Such thrombi occurring in ill-health and wasting disease are sometimes called *marantic* thrombi. But many of these socalled marantic thrombi are probably of infective origin—for instance, in many cases of "white swelling" of the leg following parturition. A common starting point of such thrombi is at the junction of the external iliac and femoral veins. This has been attributed to local pressure.

In all the conditions which have been mentioned, the two factors which especially determine the occurrence of thrombosis are retardation of bloodflow with the production of eddies, and local conditions of nutrition of the vessel wall.

The presence of actual disease of the vessel wall is probably not essential to the occurrence of thrombosis. It has been thought that the fact that blood may remain uncoagulated in a ligatured vessel or in a glass tube whose walls have been oiled was evidence that some roughening or disease was essential. But, as we have seen, the process of formation of a thrombus in circulating blood, from which a large number of bloodplates can accumulate, introduces a different factor. Undoubtedly, irregularity or disease of the surface in contact

with the blood is usually present, and to this the bloodplates first adhere.

Apart from these common causes of thrombosis, there are other rarer conditions which may produce it. These are especially the action of substances which produce changes in the blood corpuscles or plasma, or the presence of abnormalities of the blood itself.

The transfusion of "dissimilar" blood—that is, of the blood of another species of animal—or injection of various tissue extracts and some animal poisons may bring about coagulation. Bacterial toxins may also cause coagulation, and so also may the direct action of some chemicals. In these cases, the chemical process may be similar to that by which coagulation commonly occurs, but it may be by direct coagulation of some of the albumins.

Further, in inflammation we sometimes find masses of red blood corpuscles fused together, forming a socalled coralline thrombus, apparently due to a change in the blood corpuscles themselves.

And in leucocythæmia masses of leucocytes—usually of abnormal kinds—may block the vessels, forming leucocyte thrombi.

Changes consecutive to Thrombosis.—A thrombus may, as we have said, soften and disintegrate, either with or without the action of bacteria. In most cases, it is partially or entirely absorbed by changes in the vessel wall and the thrombus, which gradually transform the whole into a fibrous cord. These changes will be more conveniently considered under "Repair."

CHAPTER VI.

MECHANICAL OBSTRUCTION OF THE CIRCULATION.

MECHANICAL obstruction to the flow of blood may affect either the veins or the arteries. If the veins are obstructed, the outflow from the parts is of course checked: if the arteries, the supply of blood is diminished.

The terms employed to designate the conditions thus produced are unfortunately used in different senses and for diverse conditions.

The term **hyperæmia** or excess of blood, although limited to *local* conditions, as distinguished from **plethora** or general excess of blood in the body, is applied both to conditions where the blood accumulates from defective outflow and those where it is poured into the part in excess. And in the latter case it is used whether there is merely arterial dilatation, as from vaso-constrictor paralysis, or where there is general relaxation of all the vessels in the part. And the term "*congestion*" is also used in much the same way as "*hyperæmia*" to indicate the local condition of engorgement. Hence the terms "passive" congestion or "passive" hyperæmia are employed to indicate the condition due to accumulation from obstructed outflow or impediment to the circulation in the part, and "active" congestion or hyperæmia when there is increased supply.

It is obvious that there may be combined conditions. A local dilatation of the minute vessels in any part may lead to engorgement, with no obstruction to outflow or increased afflux of blood. And we may have present both obstacles to the outflow and increase in the inflow of blood.

For conditions due to dilatation of the minute vessels of the part, the venules and capillaries especially, the term *congestion* would be convenient; whilst those due to venous obstruction might well be called *venous engorgement*, and those associated with increased afflux of blood, *active hyperæmia*. But any such restriction in the use of terms is not yet generally accepted.

In like manner the term **Anæmia** is used in widely differing senses, and includes conditions of the blood itself as well as states of bloodlessness in a part due either to diminishing or cutting off the supply, or to actual loss of blood. We shall consider this term more fully later.

VENOUS OBSTRUCTION.

When from any cause the outflow of blood from a part is impeded or entirely arrested, if the inflow still continues, the venules and later the capillaries will become distended, full of blood, and from defective aeration of the blood the part will become livid, and if at the surface, cold and numb.

A venous, *i.e.*, unaerated, condition of the blood causes a bluish colour. Hence the term "*cyanosis*" or blueness.

Such a "cyanotic" condition may be *general*, either from a mixture of venous and arterial blood or defective aeration. In some congenital malformations of the heart the former produces a general blueness or lividity of the extremities of the body called "*congenital cyanosis.*"

But the term **cyanotic** has come to be applied to the more local and partial conditions consequent on accumulation of venous blood, as well as to those due to defective aeration. Hence "cyanotic atrophy," "cyanotic induration" and like names mean conditions due to prolonged venous obstruction.

General Venous Obstruction.—General venous obstruction is common in heart disease.

In many conditions where there is an impediment to the free flow of the blood through the right side of the heart, there will be general obstruction in the systemic veins. This especially occurs when the mitral valve is incompetent or stenosed, and prevents the free exit from the pulmonary veins, thus checking the entire capillary circulation through the lungs, and preventing the right ventricle from emptying itself. Such a condition of the pulmonary circulation will limit the general aeration of the blood, and the general cyanotic condition will be still further intensified.

The effects of such obstruction in the right heart are so often seen in mitral valvular disease, and in other conditions of long standing cardiac failure or dilatation, that such terms as "cardiac kidney," "cardiac liver," etc., are often used to denote the condition of these organs produced by the chronic venous engorgement.

Apart from this, there are other general or local conditions which may aid local stagnation of blood, and are especially important in relation to **chronic venous congestion.**

Before considering these more general and lasting conditions, it is convenient to consider the causes and the local effects of checking the outflow from veins.

Local Venous Obstruction.—1. Veins may be obstructed by various causes of external compression, as by ligature, bandage,

or the pressure of a tumour or aneurism. Folding of the vein may also be a cause of narrowing, and thus lead to obstruction.

2. Conditions of the vein walls, such as thickening from disease, or dilatation may retard the flow.

3. Obstruction may occur within the vein, especially by the formation of a thrombus, or very rarely by some foreign body, such as a parasite or a detached piece of tumour.

A vein may be obstructed suddenly and completely, as by ligature. More commonly, even in the case of thrombosis, the complete closure takes some little time, and in some cases, such as compression by tumour, the process may be very gradual. Usually, when the narrowing has reached any considerable degree, thrombosis occurs, and rapidly causes total obstruction.

The immediate effects will, of course, vary with the acuteness and completeness of the obstruction. But in all cases there will be an effort to relieve the local distension by opening up collateral communications, with which most parts of the body are amply supplied. And even where these are minute, a great amount of enlargement of other veins is possible, so that it is rarely that the severe effects are prominent. Obstruction of the entire renal or splenic vein, or of their main branches, or of the ophthalmic veins, give examples of severe results.

Before considering these, we may briefly refer to the phenomena attending the collateral venous substitution.

For the most part the systemic veins are so abundant and anastomose so freely, that numerous obstructions will have little effect on the circulation in the part. It is only when large venous trunks or the main vein of an organ are occluded that the effects will be considerable. Even if the superior or inferior vena cava is blocked, ways are found for conveying the blood by circuitous channels to the heart.

But in order to carry the blood by these tortuous routes, a much larger number of veins are brought into use. The bloodflow is no longer directed in a defined channel, as the pressure leads to the opening up of any communicating vein.

Veins are constructed to carry a far larger amount of blood than normally circulates in them. But when overstretched their valves become useless, and they stretch still more. Moreover, in those positions where they are ill supported, as where they are not surrounded by solid tissue, they can and do more readily dilate unchecked. Hence the greatest distension occurs in such veins as those of the subcutaneous tissue or of mucous membranes, in the abdominal walls, and in the plexuses which lie within the body cavities.

Hence we find that when the inferior vena cava is obstructed,

numerous veins become greatly dilated and visible over the abdomen, and there are similar dilatations of the deeper veins.

The walls of these veins, although they become thickened, are so stretched in length that they are thrown into folds, and large masses of varicose veins may thus be produced.

When the obstruction occurs slowly, the possibility of complete collateral venous return is greatly increased. Thus, in very extensive obstruction of the circulation through the liver in cirrhosis, and even in cases of complete obstruction of the portal vein by tumour growth, the blood may find its way into the systemic veins, and little or no effect may be produced by the obstruction apart from those due to the changes in the liver itself. The channels by which the blood escapes are partly those known as the supplementary circulation of Sappey, which include the minute anastomoses through the capsule and ligaments of the liver, especially if there are adhesions between the liver and the diaphragm. The communication of the coronary veins of the stomach with the œsophageal veins and with minute branches from other veins, form one important route of escape. Hence there may be varices of considerable size around the lower part of the œsophagus, and varicosity of the submucous veins in the œsophagus itself, which sometimes lead to the formation of minute ulcers which may perforate the veins and cause serious or fatal hæmorrhage.

One common result of increased intravenous pressure, especially where the veins are ill supported, is to lead to thickening of their walls. The mode in which this thickening occurs will be more fully considered later.

Acute Venous Congestion.—This is not often seen as a result of disease in such positions as to lead to serious or permanent effects. But it may occur under the conditions already stated.

Its phenomena can best be studied experimentally, as by obstruction of the renal vein or some of its branches, or of the splenic vein, or in various positions where the changes can be directly observed, such as the frog's leg, etc. Experiments upon the tongue of the frog or in the mesentery are not satisfactory, as other changes are induced by the stretching or exposure. Hence Cohnheim's results on the tongue of the frog cannot be accepted as conclusive evidence upon the nature of the changes.

A comparison of such experimental evidence and of observations in disease show that the following changes occur.

The parts of which the veins are thus rapidly and totally obstructed become swollen and livid. External parts become cold and numb. The venules and capillaries are greatly distended; and where they have little external support, hæmorrhage from rupture of the capillaries commonly occurs.

In the kidney, if the entire renal vein is tied, the whole organ becomes engorged, and this may be followed by diffuse hæmorrhage throughout its substance. If only a branch is ligatured, the corresponding zone is the seat of the hæmorrhage, but there is usually some general venous engorgement also, possibly from the interference with the vein at the time of operation. The appearance of the part on which the obstruction has taken effect is of a uniform engorgement and hæmorrhage, and at first sight resembles the effect of arterial obstruction; but, on closer inspection, it shows striking contrasts, which will be more fully discussed under the head of "Infarction." The hæmorrhages are most abundant in the boundary layer between the tubules, and into the glomerular capsules from the capillaries of the glomeruli. It may be added that the hæmorrhage becomes more considerable after the lapse of a few hours, when the vessel walls may have undergone some degeneration.

Hæmorrhage from acute venous obstruction in disease is not common. It may be seen in the retina in obstruction of the ophthalmic veins. In rapid thrombosis of the longitudinal sinus, hæmorrhage into the pia over the vertex of the brain sometimes occurs; and in thrombosis of branches of the pulmonary veins, from tumour invading the root of the lung, it may be sometimes seen. Possibly some of the hæmorrhagic infarctions in the spleen in leucocythemia may have a like origin.

The *swelling* of the part is at first due largely to the general distension of all the minute venules and capillaries, but later it is added to by the accumulation of transuded lymph—in other words, by **dropsy** of the part.

At first sight, it seems natural to expect dropsy to occur when veins are obstructed, and clinical observation confirms the belief in its occurrence. Thus thrombosis of the femoral vein may lead to dropsy of the leg. Pressure upon the straight sinus or veins of Galen by a tumour may cause hydrocephalus, *i.e.*, dropsy of the lateral sinuses. Pressure on the portal vein may cause ascites, and so on.

And these results are supported by the well-known physiological facts that a large part of the watery fluid of transuded lymph is normally absorbed into the veins, and, on the other hand, that increase of intravenous pressure would tend to increase lymph transudation.

Experimental study has not, however, supported the view that venous obstruction alone causes local dropsy, or is always efficient in the absence of other causes. Ranvier's well-known experiments showed that obstruction of the crural veins or even of the inferior cava might be unattended by dropsy in the hind limbs, unless vasomotor paralysis of the arteries were superadded, this causing increased afflux of arterial blood, in addition to the venous obstruction. To a large extent these experiments have been supported by other

observers. But whilst this probably indicates that in healthy active animals the venous outflow may be speedily supplemented, it is very rarely that we have to do with healthy human individuals when veins are blocked.

These experimental results are to some extent supported by observation in human disease. We have seen the inferior cava completely obstructed by thrombosis, which had spread from the right external iliac vein during typhoid fever, and the only sign of dropsy during life was some swelling of the right leg shortly after the thrombosis commenced, and this entirely disappeared later.

The additional factors of gravity, weakened force of the heart, and defective muscular movement, which play so important a part in the venous flow, together with the general conditions of malnutrition of the blood and tissues in disease, may be needed to produce any marked dropsy.

The question of leucocyte emigration as a result of venous obstruction has been much disputed. The changes in the relative positions of the leucocytes in the bloodstream when the flow becomes slower have already been considered. When there is no other abnormal condition than the check to the bloodflow, such leucocyte emigration as may occur is very scanty, if it occurs at all. And if it occurs at later periods, it is related rather to the general nutritive changes than to the slowing of the stream. It is certainly not an important result of the process.

Apart from the occurrence of hæmorrhage, the nutritive effects of acute venous obstruction are comparatively slight. The only instance usually cited as evidence of the possible occurrence of necrosis due to this cause is intussusception of the bowel. But in this condition there is also some obstruction of the arteries, stretching and compression of the tissues, and the exposure of the damaged part to septic infection from the contents of the intestines, all of which might determine the necrotic changes which occur.

Where the collateral circulation is not fully re-established, the part will become the seat of *chronic* venous congestion, which may next be considered.

Chronic Venous Congestion.—The commonest cause of any chronic obstruction to the venous outflow from a part is some central condition, *i.e.*, in the case of the systemic circulation, some state of stagnation in the right side of the heart due to any of the causes already mentioned. More rarely, the cause is some persistent obstruction of the main vein of some organ, or of the superior or inferior cava. But, as we have said, even these may be compensated in course of time. And when any other large vein of an organ is obstructed, it is rare to find serious consecutive results.

But when there is a serious obstacle to the return to the right side of the heart lasting for some years—still more when the pulmonary circulation is also engorged, as in disease of the mitral valve—gradual changes occur both in the lungs and other organs.

The effects of the obstruction in mitral valvular disease are usually greatest in the lungs. The right heart becomes hypertrophied, and drives the blood with greater force into the pulmonary artery. The outflow of blood may be mainly obstructed (*i.e.*, there will be no backward pressure) in the pulmonary veins if there is only mitral stenosis, but to some extent the acquired hypertrophy of the left auricle will exert some direct pressure during systole upon the column of blood in the pulmonary veins. Still more will this occur if there is considerable mitral regurgitation. The effect of this may, of course, be expended mainly on the walls of the larger pulmonary vein branches, but must tend to retard the circulation through the lungs.

Of the systemic veins, the hepatic, splenic, and renal are commonly most affected. The direct and close connection of the hepatic veins with the inferior cava, the absence of valves of importance, and the low pressure in the portal vein, all render hepatic venous engorgement easy. The spleen, serving as a sort of reservoir for the liver, and affected secondarily by it, also suffers from the obstruction ; but the effects are usually partly compensated by the higher pressure in the splenic artery, and by the muscular and fibrous structures of the spleen, which resist expansion. Hence in the spleen, the dilatation of the venous sinuses and venules may be great, and lead to atrophy of the lymphoid tissue, whilst the organ may not be much enlarged.

The kidneys often suffer to a considerable extent, probably because of the relatively large size of their veins, and the complex course of the arterial blood through the glomeruli.

Apart from these organs, there may occur chronic venous congestion elsewhere. But its degree and effects vary to a large extent with the presence or absence of *accessory causes.*

Of these, gravity is important. Next to this, the amount of local support to the veins, whether from position or from the laxity of the surrounding tissues. Muscular movement is also very important, the flow in the veins of the limbs being largely aided by the movement of the muscles. Hence the value of moderate exercise in conditions leading to local stagnation.

Of the other conditions which act generally in increasing or diminishing the effects of central obstruction in heart disease, two are of great importance. The force of the arterial flow determines to a large extent that of the venous. Hence, an increase in the power of contraction of the left ventricle will, if the local conditions are favourable, aid the venous return.

But a condition of perhaps greater importance is that of the respir-

atory movements, which act both by sucking the blood into the large systemic venous trunks, and aiding the circulation through the lungs. Hence, so long as the obstacle at the mitral orifice can be overcome, and the left ventricle has power enough to propel the blood, careful respiratory exercises greatly aid the general circulation.

Changes in the Vessels and Tissues.—We have seen that the effect of continued obstruction to the flow in the veins is to produce stretching and elongation, and also dilatation, so that they become varicose. This is observed throughout the vessels down to the capillaries when they are defectively supported. In the bronchial mucous membrane and in the alveolar septa in the lungs this varicosity may reach a high degree.

In all veins and capillaries such persistent increase of pressure tends to cause thickening of their walls. In the larger veins the thickening of the inner coat resembles in character that of the intima of arteries in atheroma, and as in that disease the patches of thickening may degenerate in the deeper parts and become calcified. Calcification may also occur in the media.

In the smaller veins the fibrous thickening is more general. In the capillaries, if they consist, as some believe, of endothelium only, the thickening is in fibrous filaments or laminæ around them. But if, as is more probable, and the view is supported by modern research, they have also an extremely delicate layer of fibrils around them, it is this which becomes thickened. In any case in advanced chronic venous congestion, the capillaries may show a distinct double contour, not due to the endothelium only, in parts where normally no such structure is seen in health.

In some positions the distension of the venules and capillaries leads to atrophy of surrounding tissues. To some extent the defective nutrition may aid in the occurrence of the wasting. But we have direct evidence that the pressure may be the main cause, especially in the liver, where the liver cells in the centre of the lobules waste first, owing to the fact that the central veins and their immediate tributaries suffer to the greatest degree from the engorgement of the hepatic veins.

In the spleen the venules and venous sinuses may become distended to such a degree that both the spleen pulp and its cells and the lymphoid tissue of the Malpighian bodies may in parts entirely disappear. This is especially well seen towards the surface of the organ. In the spleen the fibrous tissue of the trabeculæ and capsule and the muscle cells in them are often markedly increased.

In the kidney the direct pressure is mainly expended upon the veins, especially the interlobular veins and venæ stellatæ, but the glomerular capillaries become dilated and their walls thickened. The intertubular plexus does not usually become dilated to any marked

degree, possibly because the flow through the glomeruli is inactive. Some atrophy of the renal epithelium is common, possibly owing to impaired activity of function.

In some positions dilatation of veins may lead indirectly to destructive changes. Thus especially in the lower limbs "varicose ulcers" may occur. And at the lower end of the œsophagus, similar ulcers may be formed and lead to serious or fatal hæmorrhage. This is one of the causes of hæmatemesis in cirrhosis of the liver.

It is probable that in the formation of such ulcers, the occurrence of thrombosis and hæmorrhage and local damage also play some part, although the tissues may have suffered directly from the pressure of the distended veins.

Hæmorrhages from dilated venules and capillaries are apt to occur, especially when they are unsupported. In the lung, minute hæmorrhages into the air cavities frequently occur in chronic venous congestion, and the consecutive changes, including the absorption of the blood pigment, play an important part in the changes commonly seen in that condition. Similarly, there may be hæmorrhage from the bronchial mucous membrane. Moreover, the swollen and congested condition of the bronchioles renders them more liable to irritation and catarrh, and the narrowing of the lumen by the swelling aids the occurrence of emphysema.

In the kidney, minute hæmorrhages may take place from the engorged glomerular capillaries, and some of the pigment may remain in the tubules as melanin casts. Any greater amount of hæmorrhage in chronic heart disease is usually due either to embolic infarction or, far more rarely, to thrombosis in the renal veins.

In most cases, if the organ is capable of distension, venous congestion causes enlargement. This occurs in the liver and spleen, and to a less degree in the kidneys.

The organ may also become firmer than normal, and to this condition the name of "cyanotic induration" has been given. It has been supposed that it was due to fibrous overgrowth, which was thought to be favoured by the greater lymph supply in venous engorgement.

Microscopic examination of such organs does not support this view. The distended condition of the vessels of itself makes the organ feel firmer. Such fibrous thickening as occurs is almost entirely in the walls of the vessels, though sometimes the distended branches of the hepatic vein in the liver show fibrous thickening around them. In the *spleen*, such fibrous thickening as occurs in the trabeculæ corresponds to that produced by increased strain. In the *kidney*, in very long standing cases, there may be slight fibrous thickening of the basement membrane around wasted tubules, such as occurs in other fibrous atrophy.

In the *lung* the case is somewhat different. Here considerable

fibrous overgrowth may occur along the lines of the lymphatics. But this is directly proportioned to and consequent upon the accumulation of blood pigment in the lymphatics, and resembles that which occurs as a result of the absorption of carbon or other particles.

To a large extent the apparent hardness of the tissues is merely the result of the distension of the capillaries and lymphatic spaces. In the *heart*, in long standing mitral valvular disease, the wall of the right ventricle, which is hypertrophied, may be extremely firm and fibrous looking, suggesting the presence of fibrous overgrowth in addition to the muscular hypertrophy. But on microscopic examination there may be evidence of the latter only. And a simple experiment shows that a similar apparent induration may be due merely to distension of the vessels. If the coronary arteries of a healthy heart are forcibly injected with water by inserting the nozzle of a tap into the aorta, a condition closely resembling it may be produced.

The term "cyanotic atrophy" is sometimes applied to the condition found after long-standing venous congestion of the liver. When the liver cells have to a large extent been destroyed by compression, and their functional activity to a great extent abolished, the organ may shrink irregularly and become much smaller than natural. Many of the distended capillaries, having become functionally useless, also waste. This especially occurs when the blood in the portal circulation has found other channels of escape, and the hepatic veins have become much distended. To some extent such atrophy of the liver may be due to the thickening and shrinking of the peritoneum and capsule when there has been ascites.

In rare cases there may be actual expansile pulsation of the liver when the hepatic veins are thus greatly dilated, but in most instances the pulsation is due to the impulse of the heart transmitted through a liver which is displaced downwards by the dilated right ventricle.

Finally, other changes may be found in the tissues in chronic venous congestion, which may be briefly mentioned. Pigmentation is not uncommon, *e.g.*, of liver cells, lungs, and in the skin around varicose ulcers. This is mainly due to alterations of effused blood. In parts which are the seat of chronic venous congestion the vitality of the tissues is lowered. This is well seen in the mucous membranes, *e.g.*, mucous membrane of stomach, intestine, and bronchi, which are very prone to undergo chronic catarrhal changes.

Hypostatic Congestion.—This term is applied especially to a condition of the lungs which is seen in debilitated conditions of all kinds, including old age, fevers, heart disease, etc., especially in those confined to bed.

The lungs, especially in the posterior parts and in the lower lobes, become engorged with blood, œdematous, and often partly collapsed.

And in such conditions some pneumonic consolidation, "hypostatic pneumonia," often follows. The pneumonia shows usually a broncho-pneumonic type, combined with the congestion, œdema, and collapse.

But since **hypostatic** implies that the congestion is due to the dependent position of the part—in other words, to the action of gravity—the term is inaccurate. We have seen that gravity does co-operate in the production of local stagnation from a general cause.

But several factors, in addition to gravity, co-operate in producing hypostatic congestion and pneumonia. Expansion of the lower and posterior parts of the lung is normally less effective in the recumbent posture than in the erect. Added to this, distension of the stomach or of the other abdominal contents often impede the free descent of the diaphragm. If there is bronchitis, catarrhal secretion gravitates into the lower bronchi, especially if the patient is lying on the back, and this aids the occurrence of collapse of the lung. Added to this, weakened heart action aggravates any obstruction to the flow in the pulmonary circulation. To these and other physical causes the condition is largely due.

One important lesson taught by these considerations is that by changes of position to one or other side, the freer play of the thorax on the opposite side should from time to time be ensured, when possible, in all bedridden patients.

CHAPTER VII.

ARTERIAL OBSTRUCTION.

ARTERIAL obstruction leads to an important series of circulatory and nutritive changes. It is convenient to study separately — (1) the circulatory disturbances; (2) the nutritive changes in the part which is deprived of its normal blood supply.

The local anæmia which arises in consequence of arterial obstruction is usually designated by the term *Ischaemia.* In local anæmia or ischæmia the cutting off of the blood supply is not necessarily complete; frequently, indeed, it is only partial. But most of the serious effects are caused by arrest which is practically complete; and it is these which we shall especially consider.

As with other tubes, the flow in an artery may be stopped by squeezing it or by blocking its bore, or by anything which thickens its walls and thus narrows its channel.

These possible causes of ischæmia may be briefly considered.

1. *Excessive contraction of the muscular coat* of arteries may be produced either by stimulation of vaso-constrictor nerves, or by direct action upon the muscle cells.

In most cases the contraction is not of sufficient degree or duration to lead to serious nutritive disturbance. We have already considered the results of some degree of contraction, when persistent, in leading to atrophy and in aiding necrosis. Chronic lead poisoning is one of the causes of such continued partial contraction.

Excessive heat or cold, electrical stimulation, and some poisons—such as lead, ergot, and suprarenal extract—can produce arterial contraction. But of these possible causes, ergot poisoning is the only one which, when repeated or continued, produces serious damage solely as a result of the contraction.

Vaso-constrictor nervous action rarely leads to serious nutritive disturbance. It is chiefly in Raynaud's disease, where there is repeated spasmodic contraction of the arteries, due to changes in the nerves, that gangrene may result.

2. *Changes in the walls of arteries* which narrow or occlude them. Atheroma and syphilitic disease are especially frequent causes, owing to the thickening of the coats; but the obstruction is usually rendered complete by thrombosis.

3. Compression by tumour, or infiltration by new growth, and ligature or compression of an artery may have a like effect.

4. Obstruction of the lumen of the artery by a thrombus, formed *in situ* or carried from a distance. This is the commonest cause of serious arrest of the arterial supply.

Obstruction produced by the carriage of a bit of clot from a distance was called **embolism,** or throwing in, by Virchow. The term is also applied to a similar result produced by the carriage of any body thus "thrown into" a vessel. The subject of embolism may now be more fully considered.

Embolism signifies, as we have said, the obstruction of a vessel —usually an artery—by some solid or semi-solid mass carried by the bloodstream. The mass or body is called an **embolus.**

The nature of emboli varies. In the great majority of cases, the embolus is only a fragment of a thrombus; or, in rare cases, the entire thrombus may be detached and carried away.

Of the common and important sources of such emboli in the systemic arteries, by far the most frequent are "vegetations" or thrombi on the mitral and aortic valves of the heart. Sometimes, however, part of a thrombus formed in a dilated left ventricle may break down and be carried away. Far more rarely, a thrombus formed upon an atheromatous patch in the aorta may be the source of embolism.

The mass thus detached is carried by the blood along the artery until it reaches a point where the vessel is too narrow to allow of its passage, and there it becomes impacted. Not uncommonly the embolus lodges at the origin of a branch of the artery or where it bifurcates.

After its impaction the embolus may be partly broken up and portions carried still further into smaller branches, thus producing multiple obstruction. This is especially liable to occur if the embolus is caught in a branch and does not at first entirely block the vessel.

But whether the obstruction is at first complete or no, it usually becomes so by the occurrence of thrombosis, which may spread back to the nearest collateral channel, and forwards into the obstructed artery.

It is difficult to form any accurate estimate of the relative frequency of embolism in the different systemic arteries, since it is only when the obstruction leads to definite symptoms during life or to permanent effects which can be seen after death that we have evidence of its occurrence. Thus while we may feel sure that the small arteries of the lower limbs must receive emboli more frequently than those of the spleen or kidney, the effects are so

transient as to be unobserved, unless a large artery is blocked, or subsequent changes, such as aneurism, follow in the artery.

Embolism of the pulmonary artery and its branches may arise either from thrombi in the systemic veins, *e.g.*, varicose veins of the legs, pelvic veins, etc., or from thrombi formed in the right side of the heart. In chronic heart disease, especially of the mitral valve, or in any condition which leads to failure of compensation, thrombosis frequently occurs in the right auricle, especially in the appendix. The detachment of parts of such thrombi and their carriage into the pulmonary artery is the commonest cause of what is called "pulmonary apoplexy" or infarction.

Thrombi in the radicles of the portal system or any of its tributary veins may be carried to the branches of the portal vein within the liver and there become impacted. These emboli are very commonly septic, and the changes produced are to a large extent due to this fact.

While thrombi are the common sources of emboli, there are, in addition, other rarer sources, *e.g.*, air, fat, tumour cells, parenchymatous cells, animal and vegetable parasites, and foreign bodies.

Air Embolism.—Much importance was formerly ascribed, on insufficient evidence, to the occurrence of air embolism. With the exception of the very rare cases in surgical practice, where a large quantity of air is aspirated through an open vein into the right side of the heart, air embolism has not been proved to occur. In such cases air bubbles are found mixed with the blood contained in the large veins near the heart, in the right chambers of the heart, and in the pulmonary capillaries.

Formerly the discovery of gas in the blood at the post-mortem examination was regarded as constituting sufficient proof of air embolism. This can, however, be no longer maintained. Most of the cases which have been carefully investigated have proved to be dependent on the presence of a gas-producing bacterial organism.

Fat Embolism.—Although fracture of the long bones may lead in some cases to the passage of the fat of the marrow into lacerated veins, it is very rare to find any definite and characteristic symptoms. Fat embolism of the pulmonary capillaries in these cases does in all probability occur, though to an insignificant extent. There are, however, cases on record in which death has been due to extensive fat embolism of the lungs, not only after fractures of the long bones, but also as the result of the forcible manipulation of bones in the attempt to break down firm joint adhesions.

Fat embolism of the pulmonary capillaries, and to a less extent of the glomerular capillaries of the kidney, is found in some cases of diabetes mellitus, in which minute oil globules are present in the blood plasma. Fatty disintegration of the liver cells around the central veins of the lobules is believed in some rare cases to be a cause

of fat embolism of the lungs. The existence of such a source of fat emboli has been recorded in a few cases of chloroform poisoning, characterised by very extreme fatty disintegration of the liver cells.

Whenever there has been extensive fat embolism of the pulmonary capillaries, the lungs always show the presence of multiple ecchymoses, œdema, and localised pneumonic patches.

Emboli of Tumour Cells.—Emboli of tumour cells are usually capillary in size, and cannot therefore be easily recognised. Emboli of larger size are sometimes found impacted in larger vessels, *e.g.*, in branches of the portal vein in the liver, and in branches of the pulmonary artery. These masses of tumour cells (sarcoma and cancer) effect an entrance into the bloodstream by the erosion of a vein or artery. After transportation and impaction, the tumour cells may proliferate and produce metastatic new growths.

Animal and Vegetable Parasites.—Although some animal parasites affecting man have their habitat in the blood, *e.g.*, Filaria Sanguinis Hominis, Malaria parasite, and Bilharzia Hæmatobia, they are not known to cause embolism.

Of much greater importance are the socalled septic emboli containing pathogenic bacteria. By far the most important classification of emboli is into two groups—the *bland* and the *septic* or infective. Septic emboli, composed of or containing masses of bacteria, are very commonly capillary in size, and give rise to multiple obstruction. The two chief sources of septic emboli are the valvular vegetations in septic endocarditis and infective thrombi of veins. Septic emboli give rise to all the mechanical effects of bland emboli, with the addition of important lesions dependent on the specific action of the contained organisms. Aneurisms may be produced in arteries by the action of septic emboli. The consideration of the other effects of septic emboli belong to the subject of *pyæmia*.

It must be clearly understood that in what follows in relation to the effects of embolic obstruction of arteries, we speak entirely of bland or non-septic emboli.

One or two very rare forms of embolism may be briefly mentioned.

Crossed or Paradoxical Embolism.—Although emboli usually follow the normal course of the bloodstream, there are some rare exceptions. The term "*Crossed Embolism*" is applied to cases in which emboli derived from the systemic veins pass through a patent foramen ovale into the left auricle, and are distributed in the systemic arteries. Such a condition is, of course, extremely rare.

Retrograde Embolism.—When the embolus is carried in a direction opposite to that of the normal bloodflow, the condition is called retrograde embolism. This is of very rare occurrence, and has been observed only in veins, especially in the inferior vena cava.

The phenomenon is not easily explained on physical grounds; and the most feasible explanation is to regard it as due to a temporary reflux of the blood in the vein, in consequence of some hindrance to the return of blood to the right heart, *e.g.*, tricuspid incompetence, increased intrathoracic pressure, etc.

Effects of Arterial Obstruction.—In whatever way the complete obstruction of an artery is brought about—whether by embolism, thrombosis, or compression—the general effects are the same so far as the circulation is concerned. And whilst we may especially refer to the results of embolism as affording the commonest instances of rapid total obstruction, it must be remembered that similar circulatory and nutritive derangements will follow any other kind of obstruction.

The phenomena may, for purposes of study, be divided into the **circulatory** and the **nutritive.** These occur side by side; but the circulatory changes commence sooner, and are for a time the more striking, so that they may be considered first.

Circulatory Phenomena following Obstruction of an Artery.—The phenomena following ligature of an important artery, *e.g.*, the superficial femoral, are well known. The limb at first becomes blanched, cold and numb, and pulsation in the peripheral branches ceases. During the ensuing period, special care is needed to maintain the temperature of the limb and to avoid damage.

But after a few hours the limb again becomes warm, and for a time may be warmer and redder than its fellow and may be slightly swollen. The pulsation has now returned in the distal branches. Sometimes at first the pulse is larger than in the sound limb, from defective tone in the arteries.

After a time these conditions subside; and the circulation returns to normal.

These phenomena correspond to those which invariably follow arterial obstruction.

The explanation of these changes is that when the arterial supply to any part is cut off, there is a natural provision for the restoration of the supply from other arteries by anastomosis. By the enlargement of these anastomoses, the blood supply may rapidly be restored to the part. This change is known as the establishment of **collateral circulation.**

We are not now considering the reasons *why* the collateral channels enlarge and carry blood to the part. It is sufficient for the present to emphasise the fact that such an effort is made *in all cases* to restore the arterial supply, so that it may be regarded as of constant and universal occurrence.

It will be necessary to state in some detail the grounds for this statement, since the subject is one which has been much obscured by erroneous observation—or rather neglect of experimental observation —and by the substitution of speculation for direct research.

Before entering upon any discussion, there are one or two facts which may conveniently be referred to.

Anastomoses.—The anastomoses between arteries vary greatly in their abundance and directness in different parts of the body—in some they are obvious and large, as in the forearm and hand and at the base of the brain ; in others so small and indirect, that they are only discovered when the communications are enlarged. And in some positions they are so scanty as to be incapable of anatomical demonstration. They may even be mainly capillary. But there is scarcely any part in which some possible communications do not exist. The apparent exceptions will be considered later.

Many experiments have been made to determine the exact channels of anastomatic supply after ligature of various arteries. Even the abdominal aorta has been tied in dogs, and the collateral circulation re-established. The only point which concerns us here in these observations is that the communications opened are often extremely abundant and tortuous, and if the arteries are defectively supported as, *e.g.*, in the spinal canal, a condition allied to varicosity may arise.

Collateral supply is usually established by *enlargement of existing vessels*. We have little evidence of the formation of new vessels in acute conditions of arterial obstruction, although we shall find that there are grounds for the belief that new vessels may be formed to supply a part of which the arteries are more slowly obstructed.

The vessels not only enlarge, their coats proliferate and develop so that they come to resemble in all respects normal arteries of the same size.

But there are certain *conditions essential* to the effective and rapid establishment of collateral circulation, and in their absence the supply may be incomplete or may be delayed till too late to prevent damage to the tissues.

Of these conditions the most important are :—

(1) The arteries must be capable both of expansion and growth. If they are degenerated or calcified, they may not do either. (It is quite possible that the existence of tonic spasm of the peripheral arteries, such as occurs in Bright's disease, may in some cases hinder the normal changes in arteries after ligature and in other operations. The point is worthy of careful attention.)

(2) A sufficient pressure of blood is needed. Whether we regard the collateral enlargement of vessels as a purely physical process or no, it is certain that a want of sufficient propelling force in the heart tends to failure of collateral supply. It must be remembered also that

if the heart's action is weak there will be a tendency to venous stagnation, and that thrombosis may occur in the vessels of the part before the fresh supply is available.

(3) The channels for collateral supply must be open. If, for example, two arteries which normally compensate each other are both blocked at or near the same time, no sufficient source of supply will be available. This condition may arise from multiple embolism.

(4) As with all nutritive processes, their normal occurrence may be prevented or delayed by debility, and by general conditions of ill-health.

Infarction.—We have said that there are in nearly all parts of the body possible sources of collateral supply. There are, however, some parts in which these are almost wanting, or those which exist are so insufficient that they cannot enlarge rapidly or completely enough to prevent serious damage to nutrition. Or it may be that the circulatory arrangements are such that if the blood does not follow the normal channels, it may derange the circulatory mechanism of the organ. Examples of this are seen especially in the kidney and the spleen.

To those arteries which he regarded as practically devoid of anastomoses, Cohnheim gave the name of terminal or **end** arteries. The view upon which this name was based cannot now be fully accepted, nor can the inferences drawn from the supposed total absence of anastomoses. The term may be retained to indicate arteries inadequately supplemented by anastomoses.

The following are the more important examples of "end arteries": —(1) The renal artery and its branches, especially the interlobular cortical branches. (2) The splenic artery and its branches. (3) The arteries supplying the basal ganglia of the brain and the grey matter of the spinal cord—the arteries distributed to the surface of the brain and spinal cord possess more abundant but still imperfect anastomoses. (4) The central artery of the retina. (5) The large branches of the coronary arteries of the heart. (6) The superior mesenteric artery. (7) Branches of the pulmonary arteries, especially those distributed to the surface of the lungs and the free margins of the lobes.

The branches of the portal vein within the liver are also imperfectly provided with anastomoses.

The obstruction of a branch of one of these arteries, especially in the case of a solid organ, such as the spleen or kidney, may lead to changes in the part whose artery is blocked, which have been called "**Infarction,**" and the affected area is called an "**Infarct.**" Some explanation of the origin of these terms is necessary.

In the course of his studies on embolism, Virchow observed that

when such arteries were obstructed, the part supplied by them often became swollen and engorged with blood. Microscopical examination showed that every part of the tissue seemed to be crammed with red blood corpuscles, hence he called it a hæmorrhagic "infarction" or *stuffing*, and to the area the name of red or *hæmorrhagic* infarct was applied.

But it is a matter of common observation that in the spleen and in the kidney wedgeshaped areas corresponding to an obstructed artery are as commonly seen to be pale and bloodless, or showing only some reddening at the periphery. To these the name of *pale* or *white* or *anæmic* infarcts was given.

And it became a question whether there was really any connection between the two kinds of infarct. Virchow regarded the pale infarct as a later stage of the red, the decolorisation being, he thought, due to secondary changes in the blood and in the necrosing tissues.

Later, it came to be maintained that the common effect of arterial obstruction, in the kidney at anyrate, was to produce only pale infarcts, the colour being due to anæmia. And for a long time it was believed by many pathologists that where a red or hæmorrhagic infarction occurred, it was due to *venous* rather than to arterial obstruction.

And it has been commonly alleged that the presence of redness and hæmorrhage was always of late occurrence, due either to the rupture of vessels after they had degenerated, or to secondary irritation or inflammatory hyperæmia around.

The subject has also been complicated by the theories of Cohnheim and others as to the cause of the vascular engorgement and hæmorrhage, which did, as they allowed, actually occur. Cohnheim regarded this engorgement as due to reflux into the veins of the part, in consequence of the lowered pressure in those veins and their tributaries, which no longer received blood from the arteries.

Experimental Production of Infarction.—Amidst these conflicting statements as to common facts, and discussions of theories as to their causation, the only possible mode of arriving at the truth is that of direct observation, and especially by experiment.

Virchow himself made many experimental observations. Of other early observers, Bernard Cohn deserves especial mention for the accuracy of his work. His treatise has been much neglected, perhaps because his observations did not accord with current theories. Cohnheim, and later Litten and other of Cohnheim's pupils, did much to advance the subject; and of more recent investigators, Von Werra deserves mention. In fact, on looking into the history of the subject, we find abundant material for accurate knowledge on most of the doubtful or disputed points.

Repetition of the experiments is easy; and what will here be stated

as to the events following arterial obstruction and their sequence, and the nature of the changes found, is based on repeated careful observation of the actual process.

[*Note.*—It seems necessary to give some explanation of the grounds upon which statements are here made which are not in accordance with the views commonly entertained.

I regret that this explanation must be of a somewhat personal nature, but my object is to show that there is nothing original in the experiments referred to.

In the summer of 1874, when in Paris, whilst attending the courses of Hardy, Professor of General Pathology, and Charcot, then Professor of Morbid Anatomy, Professor Vulpian carried on a course of experimental pathology, supplementary to Professor Hardy's course.

I there saw experiments made by Professor Vulpian and his assistant, Dr Carville, on artificial embolism, chiefly in dogs; and, later, the specimens were demonstrated by Professor Hardy.

The following method was employed:—Tobacco seeds, suspended in normal saline solution, were injected forcibly upwards towards the aorta from the crural artery. In some cases the spleen was exposed whilst the animal was still unconscious by drawing it out through a small incision in the abdominal wall, so that the changes immediately following the injection could be watched. In other cases the animal was allowed to live for varying periods, and the organs then examined.

I was anxious to repeat and extend these experiments, but for a number of years no opportunity was afforded me of doing so. Finally, as it was found impossible to obtain a licence to repeat the experiments in dogs, I was fortunate enough to obtain the assistance of Dr George Mackay, who carried out the experiments in Berlin, and sent me the specimens. The animals were killed at various periods after the injection.

More recently, these observations have been repeated and extended in a series of experiments made in my laboratory under my direction by Dr Duncan Forbes—the experiments being somewhat more varied, in order to determine some further points. Some of the experiments were made on rabbits; and, owing to the smaller size of the arteries, begonia seeds were employed instead of tobacco seeds. Moreover, some other experiments—such as simultaneous ligature of renal vein and artery—were made to test the validity of the observations of Litten and others.

So far, then, as it has been possible, the subject has been restudied by actual experiment, and any statement made as to the changes which occur may be regarded as confirmed by personal observation. There is, it is true, little that is new or which had not been recorded many years ago.

The experiments are easy to repeat and to demonstrate. Even in the case of the kidney it can be sufficiently exposed after artificial embolism to watch the sequence of events during life.]

In addition to the production of infarcts by embolism, other modes of arterial obstruction may be employed. The entire renal or splenic artery can be ligatured or compressed for various periods. Sometimes a branch of the renal artery can be separately tied. The renal vein may be tied alone or together with the artery. Detachment of the

capsule, ligature of the ureter, etc., may also be readily effected. By means of such control experiments, the changes can be and have been fully studied.

It may be added that the changes thus produced by artificial obstruction of the arteries correspond in every important detail with those seen in the human subject in disease.

The effects observed after such arrest of circulation may now be detailed.

Phenomena following Artificial Obstruction of Arteries—Entire renal artery.

Ligature of the renal artery is followed by gradual swelling of the kidney, which becomes engorged with blood. There may, perhaps, be a transient anæmia, but it can rarely be observed. The kidney swells, becomes darker in colour, and after two hours the enlargement is very distinct. Both swelling and engorgement continue for several hours, until the kidney may become nearly twice as large as its fellow. After sixteen to eighteen hours the engorgement usually reaches its maximum, and there ensues a gradual diminution in size and loss of colour, until complete pallor supervenes. Still later, the entire organ shrinks and becomes transformed into a caseous mass, in which partial or complete calcification may occur.

These changes may be watched during life to some extent, but they are more exactly determined by killing animals at various periods after ligature of the artery.

During the earlier stages of the vascular engorgement, the hyperæmia is most marked in the parts of the organ adjoining the pelvis and calyces, and in the superficial parts of the cortex near the capsule. In these regions, also, hæmorrhage is most apt to occur.

The changes found with the microscope will be more fully described later. Amongst the earliest are great distension of the capillaries in the medulla, especially near the boundary layer, and of some capillaries in the cortex. Later, hæmorrhages also occur, especially after thrombi have formed in the veins.

To what is the vascular engorgement due? We have seen that it commences early and continues for several hours. There is now no doubt that it is due to collateral afflux of blood through minute communications which normally exist between the vessels supplying the ureter and the pelvis of the kidney with those in the medulla, and between branches from the lumbar arteries which supply the fat surrounding the kidney with the vessels in the capsule of the organ.

Let us now briefly consider the evidence that the source of the blood is arterial, and that it is not due to a reflux through the veins.

Cohnheim, basing his theory upon what he believed he had observed in the tongue of the frog, attributed the refilling of the vessels to a reflux through the veins. That such reflux would be liable to occur was suggested by the fact that as the pressure in the veins is mainly that communicated from the arteries, it must fall when the arterial flow is arrested. The higher pressure in the inferior cava would, he thought, necessarily force the blood back into the renal veins, and thus refill the capillary system.

But experiment shows that this hypothesis, however plausible, is not in accordance with the facts. Litten and others have demonstrated this. For if the renal vein be divided, blood continues to flow from it. If the renal artery and vein are both tied, the engorgement not only occurs, but is greater than if the artery alone is tied. So that the blood cannot come from a reflux into the vein.

But if the other accessory sources of supply already mentioned are cut off, the engorgement no longer occurs. Separation of the ureter by a ligature and stripping off the capsule entirely prevent the collateral afflux, and engorgement no longer occurs, even if the renal vein be left open. Under these conditions the kidney becomes and remains pale and bloodless.

In other words, the source of the hyperæmia resulting from obstruction of the artery is *collateral supply*.

More complete investigation has shown that the collateral circulation thus established is insufficient to maintain the outflow through the veins, and that thrombosis is apt to occur in them and thus increase the engorgement.

It will be remembered that the normal course of blood in the cortex of the kidney is a complex one. Nearly all the branches of the interlobular arteries open into the glomerular capillaries. The blood, after traversing their loops, emerges by the efferent vessels, which then again break up into capillaries which supply the tubules.

Any blood supply which comes through the vessels in the capsule is mainly distributed by capillaries which unite with those of the intertubular plexus. It is perhaps possible that it may pass into the glomerular arteries and follow the normal course. But it is more likely to fill some of the capillaries of the intertubular plexus, and if it passes into the glomerular capillaries, to do so in reverse order through the efferent vessel. As under such conditions the blood cannot escape, the result will be distension of the glomerular vessels, and often consequent rupture. This is what we find actually occurs.

One point of considerable interest suggested by these facts is the possibility of the formation of a compensatory supply to the kidney when the arteries are greatly narrowed by disease. In some cases of granular contracted or "cirrhotic" kidney the capsule is abnormally adherent both to the kidney and to the fat around. And it can

be shown by injections that numerous vessels pass from the surrounding tissues through the capsule into the cortex. We have especially observed this in cases where the change in the kidney was due to chronic thickening of the arteries, with obstruction and atrophy of many glomeruli. It seems as if, under these conditions, the gradual establishment of collateral supply, with formation of new vessels, may be of normal occurrence.

Obstruction of Branches of the Renal Artery.—We have seen that the common result of embolism in man is to produce "infarcts" in the kidney, wedgeshaped areas having their base at the surface, and extending at the apex into the medulla, where they usually involve a part of the pyramid. Only very rarely do we meet with similar areas limited to the medulla. These "infarcts" are sometimes red, more commonly pale, often yellowish, with a zone of red surrounding them if they are at all large. This reddened zone is usually much more distinct in the medulla, where it may show numerous red streaks along the lines of the tubules which sometimes look like hæmorrhages.

The nature of these changes can readily be studied in animals by the method of artificial embolism already described. It is possible to see the changes to some extent by exposing the kidney before or after the embolism, as colour changes may be visible to some extent through the capsule. But this introduces sources of error, and it is better to remove one kidney, or to kill the animal at various periods after the embolism.

In dogs the tobacco seeds are often arrested in some of the arched vessels from which the interlobular arteries of the cortex arise, and lead to obstruction of a group of these arteries. The seeds are found *in situ*, so that there can be no doubt of their relation to the territory supplied.

Such experiments confirm the results obtained from obstruction of the entire renal artery. There is an early and progressive effort to replace the blood supply by collateral afflux. This is most marked in the medulla, especially if the obstruction involves the supply to the pyramids. All the capillaries and smaller vessels become distended with blood, and rupture of many capillaries in the boundary zone follows, some of the blood passing into the collecting tubules.

In the subcapsular area there is also rapid filling of the vessels through communications which pass through the capsule. After some hours, there may be hæmorrhages between the capsule and the cortex.

At the margin of the infarct adjoining the healthy cortex there is rapid filling of the intertubular capillaries and of those glomeruli which are nearest to the collateral supply. The distension of the glomerular capillaries is often great. After eighteen hours, it is often found that hæmorrhage has occurred from these distended capillaries

into the capsular space, and the capillary tufts are found later to be separated from the glomerular capsule by a mass of altered blood, mixed with degenerated cells.

The extent to which the blood penetrates into the capillary system of the obstructed area varies considerably. Sometimes it appears to refill a considerable part. At other times the occurrence of secondary degenerative changes in the epithelium and the swelling due to transuded lymph seem to occur before the capillaries can be refilled, and only some broken-down corpuscles and traces of absorbed hæmoglobin appear in the more central parts of the infarct.

It is important to notice that in this case also there is no evidence of refilling of capillaries through the veins. In those regions where such refilling should occur most readily, there is an entire absence of it.

Moreover, the collateral engorgement, when it has once set in, continues after the veins have become filled with thrombi.

Thrombosis in the veins corresponding to the affected area gradually occurs, and is usually complete in from twenty-six to thirty hours. It is during this period, whilst the collateral engorgement is continuing and thrombosis is setting in, but the reparative changes have hardly commenced, that hæmorrhage from the distended capillaries is most apt to occur.

The secondary changes in the infarct, the gradual necrosis, and the processes of absorption are similar to those occurring in other parts. (See sections on necrosis and on wound healing.) The collateral engorgement corresponds to, or is continuous with, the hyperæmia associated with wounds and their healing. So long as there are active changes of absorption going on, it will to some extent continue, and may extend. Ultimately, with absorption or enclosure of the damaged area, it will entirely subside.

In the case of non-septic embolism, which we have been considering, there is but little emigration of polymorph leucocytes into the infarct. In fact, for the most part they appear to play but a small part in the processes of absorption.

If, however, there has been any exposure of the surface, or any source of sepsis in the infarct, leucocyte immigration occurs. In septic embolism it reaches a high degree.

Infarction of the Spleen.—The effect of arterial obstruction in leading to vascular engorgement in the part supplied by the obstructed artery is also well seen in the spleen. When artificial embolism of branches of the splenic artery is produced in the manner already described, if the spleen be exposed through an incision in the abdomen, there will be seen livid bands running transversely to its length, sometimes completely across it. The band or bands corre-

spond to areas supplied by branches of the artery. These livid bands, which may become visible within five minutes after the embolism, gradually swell, and become of deeper red colour.

Whether produced by embolism or ligature, splenic infarcts are invariably red or hæmorrhagic at first. The difference from the kidney appears to be due to the fact that the blood can easily penetrate the meshes of the spleen pulp. It is difficult to state to what extent the condition is one of mere vascular engorgement or of actual "hæmorrhage," the structure of the spleen not always allowing of ready distinction.

What is certain is, that after a large part of the infarct has been absorbed, and the shrunken part surrounded by a thick fibrous capsule, the outlines of degenerated Malpighian corpuscles crowded together can sometimes still be discerned.

Decolorisation of the infarct, mainly by changes in the hæmoglobin and subsequent degeneration and partial absorption, with final encapsuling by fibrous tissue, are the common sequels of infarction in the spleen.

Effects of Arterial Obstruction upon Nutrition.—The effects of arterial obstruction upon the nutrition of a part will depend entirely upon the question whether an efficient collateral circulation can be established or no. It is only where the arrangement of the vessels does not permit the establishment of an adequate collateral supply of blood that necrosis is the usual result.

We have already referred to the necrosis which follows obstruction of the renal arteries and their interlobular branches, and of the splenic artery and its branches. A similar result follows obstruction of the branches of the coronary arteries of the heart, of the central artery of the retina, of the basal arteries of the brain, and of the superior mesenteric artery. Obstruction of the branches of the pulmonary artery does not, as a rule, lead to necrosis.

The changes which occur in the tissues consequent on their death have already been described, so that little remains to be added (*vide* chapter on Necrosis). The most highly organised tissues are the least viable, and are therefore most susceptible to the injurious influence of arrest or diminution of the blood supply. The ganglion cells of the spinal cord die after the arrest of their blood supply for half an hour.

The different vulnerability of various tissues can be most conveniently studied in the kidney. Necrosis of all the epithelium of the convoluted tubules results from one and a-half to two hours' obstruction of the renal artery. The collecting tubules, especially the larger ones, enjoy a greater immunity, and the least vulnerable are the bloodvessels and supporting tissues, which retain their vitality after at least six hours obstruction of the renal artery.

Later Changes in Infarcted Areas.—Recent infarcts of the spleen and kidney are, as we have seen, always partially or completely hæmorrhagic. After the subsidence of the swelling and vascular engorgement, they become transformed into necrotic masses of an opaque white or yellowish white colour, either firm or soft in consistence. Finally, the dead parts are partially or completely absorbed by means of emigrated leucocytes and new bloodvessels which are projected from the surrounding living tissues into the dead areas. If the infarct is not completely absorbed, *e.g.*, in large infarcts of kidney and spleen, a caseous mass remains, surrounded by a capsule of fibrous tissue.

Pulmonary Infarction.—Pulmonary infarction has been the subject of much controversy. Infarcts of the lung or, as they are sometimes called, pulmonary apoplexies are usually multiple and vary considerably in size. They are situated beneath the plural surface, and very commonly at the free margins of the lobes. It is rare to find an infarct imbedded deeply in the substance of the lung. Infarction is commoner in the lower than in the upper lobes. The infarcts are usually wedge-shaped, the base being directed towards the pleural surface, above which they may project. They are firm in consistence, dark red or purple in colour and well defined from the surrounding parts. On microscopic examination, the alveolar capillaries are greatly distended with blood and the air spaces are filled with red blood corpuscles. In some air spaces fibrinous masses may be found. All the tissues in the area of infarction are infiltrated with blood, but there is usually no evidence of necrotic changes such as occur in other infarcts.

Causes of Pulmonary Infarction.—Most pathologists are agreed that pulmonary infarction is due to obstruction, usually embolic, of branches of the pulmonary artery; but there are some who consider the evidence inconclusive, or who regard other causes as more probable.

The experimental evidence is not conclusive. Artificial embolism of the pulmonary artery does not always lead to infarction, as Virchow and others have shown. Moreover, the condition in which pulmonary apoplexy commonly occurs is one in which there is great engorgement of the venous and capillary systems throughout the lung, and in which either venous thrombosis or hæmorrhage might readily occur. Indeed, it is difficult to assert that in some cases venous thrombosis may not be the cause, as the condition of the affected area in the lung is almost exactly like that produced in the kidney by obstruction of a branch of the renal vein.

Hæmorrhage, either into the bronchi or into the air cavities, cannot be accepted as a possible cause, for in all cases when such

hæmorrhage occurs during life, the inspiratory and expiratory movements scatter the blood in such a way as to produce areas of collapse surrounded by over distension of air cavities, the result being an entirely different condition of the lung.

There is, however, positive evidence in favour of the embolic causation of pulmonary infarcts.

In nearly all cases they occur in heart disease, especially of the mitral valve, where there has been dilatation of the right auricle, and especially of the appendix. In these cases we not only constantly find that thrombi have formed in the appendix, parts of which can readily be detached, but we find that the branches of the pulmonary artery corresponding to the infarcts contain thrombi of which some parts are evidently older than the rest, and older than those in the corresponding veins. These older parts sometimes exactly correspond in their characters and shape to those in the appendix.

Comparison of the blood in the artery and in the vein connected with the infarct in recent cases will usually show that the artery has been obstructed longest.

It must, however, be allowed that the evidence that the source of the engorgement in pulmonary infarcts is entirely collateral is not so clear as in other cases. A greatly engorged condition of the capillaries and high venous pressure are certainly present in most cases of its occurrence. And in most of the cases which we have observed, where the source of the embolus was a thrombus in one of the systemic veins, it has so happened that heart disease has also been present. All that these cases have shown was that emboli from other sources were effective in producing the obstruction of the artery.

Subsequent Changes in Pulmonary Infarcts.—In many cases pulmonary infarcts are terminal phenomena. There is usually a complete absence of necrotic changes in them. The lung tissue is probably not so easily injured as many other tissues by the loss of a proper supply of nutriment, and, in addition, a better collateral blood supply may be provided through the bronchial arteries. Lymph may also readily soak through the tissue. It is rare to find in the lungs a permanent record of previous infarction, apart from some localised overgrowth of fibrous tissue, which may contain pigment derived from disintegrated red blood corpuscles.

Infarction of the Heart.—Thrombosis in diseased coronary arteries is a much commoner cause of obstruction than embolism. There is very little anastomosis between the branches of the coronary arteries after they enter the muscular substance of the heart. Infarcts of the heart are most frequently found in the substance of the interventricular septum and in the anterior wall of the left ventricle towards the apex. The branch of the left coronary artery which supplies these

regions is most frequently the seat of disease and consequent thrombosis. The areas of infarction are irregular in shape, firm, and the central part is usually of an opaque white or yellowish white colour. Around the periphery there is commonly a hyperæmic zone. The necrosed muscle fibres are absorbed and replaced by fibrous tissue.

Obstruction of Arteries of the Brain. — Blocking of some of the cerebral arteries by embolism or thrombosis is a common source of cerebral softening. The anatomical arrangements which favour or prevent collateral supply in different parts are well known. Only one or two points of interest may be noted.

The first is that the collateral hyperæmia is rarely marked, and the occurrence of hæmorrhage due to it extremely rare. It can, however, occur. It is only when we see the brain within a few hours after the obstruction that we may find the pia reddened over parts of the surface. The reasons for this absence of visible engorgement cannot be discussed here.

The second point is that in the case of the cerebral cortex the area of softening is always very much smaller than that supplied by the obstructed artery, if there is a healthy condition of the vessels. Total obstruction of one middle cerebral artery may lead to softening, which is limited to the parts of convolutions supplied by its most central branches, namely, those adjacent to the lower part of the ascending frontal, all the remainder obtaining sufficient collateral supply from other arteries.

If, however, as in persons with degenerated arteries or a weak heart, collateral supply cannot readily occur, parts of the entire arterial territory may become softened.

In the brain, a large part of the necrosed area becomes liquefied, and is absorbed, leaving only—if large—a cavity containing milky fluid. Even where the destruction has been extensive, the chief obvious effect may be shrinking of the part.

In the *spinal cord*, obstruction of arteries, if acute—as in the experiments on embolism—is commonly followed by hæmorrhage, especially in the grey matter of the anterior cornua. Softening may be extensive; and there appears to be much more tendency to leucocyte emigration and other evidence of irritation than elsewhere.

Such embolic obstruction of the spinal arteries is almost unknown in human disease.

ACTIVE HYPERÆMIA.

When there in an increased afflux of blood to a part, the condition is known as active or arterial hyperæmia. This is generally due to dilatation of the afferent arterioles; but dilatation of the capillaries, apart from any arterial dilatation, will lead to a similar result.

The bloodflow in the capillaries and venules of the hyperæmic area

is accelerated, and the amount of blood which flows through it in a given period of time is increased. The capillaries become dilated in consequence of a rise of the intracapillary pressure; and the phenomenon of capillary pulsation, or even of venous pulsation, may sometimes be observed.

Causes.—Active hyperæmia may be purely physiological. Thus actively functioning organs demand an increased supply of blood. The arteries dilate, and furnish them with the requisite supply of nutriment.

Under pathological conditions, active hyperæmia may be due to some interference with the nervous mechanism which controls the contraction and dilatation of arteries, or to the influence of agencies which directly induce relaxation or paralysis of the muscle fibres of the arterial wall.

It is well known that paralysis of the vaso-constrictor nerves is followed by dilatation of the arterioles, as, for example, in the common experiments of the section of the cervical sympathetic nerves. But it is much more difficult to determine the influence which stimulation of the vaso-dilator nerves plays in the production of arterial hyperæmia.

The erythemas of the skin which are sometimes seen in the area of distribution of an injured nerve, and from the action of some toxins, have been attributed to the stimulation of vaso-dilator fibres.

The local hyperæmias which follow the application of vesicants, *e.g.*, mustard or cantharides to the skin or mucous membranes, probably depend on the directly injurious action of the substances upon the vessel wall, apart from any reflex action through the cerebrospinal vaso-motor centres. It is supposed that they act either directly upon the muscle fibres, or indirectly by the intervention of a local vaso-motor apparatus in the walls of the vessels. Whenever the vascular wall is damaged in any way, there is a great liability to the occurrence of vascular dilatation. Exposure of the frog's mesentery to the air is quite sufficient to set up an active hyperæmia. The rashes of fevers, the localised erythemas in other conditions, and the wheals of urticaria may all be adduced as examples of local hyperæmias, dependent on damage to the vascular walls by toxins circulating in the blood.

The nutrition of the vascular walls is also damaged, or the nervous control deranged, by rendering the vessels anæmic, even for a short period. A previous local anæmia is usually succeeded by vascular dilatation and hyperæmia. A simple experiment will demonstrate this fact. If a finger be rendered anæmic by the application of a tight ligature, it will be seen that, on removal of the ligature after a short time, the previously anæmic finger becomes temporarily hyperæmic. A temporary hyperæmia also follows the anæmia produced by the application of cold.

The arterial dilatation and hyperæmia consecutive to local anæmia may, under certain circumstances, be so considerable as to lead to actual rupture of the vessels. This is sometimes seen when a distended bladder is too quickly emptied by a catheter. The ill-supported vessels in the mucous membrane become so rapidly dilated and distended with blood, that rupture, with the production of extensive hæmorrhage into the bladder, may follow.

Dilatation of the arterioles may be occasioned by various other agencies. The application of moderate heat to the skin causes a local hyperæmia, even when the nerves to the arteries have all been cut. The arterial dilatation has therefore not been induced reflexly through the vaso-motor centres. Some drugs, *e.g.*, nitrites, which produce relaxation of nonstriped muscle, will lead to arterial dilatation.

Most of the conditions which give rise to arterial hyperæmia are transient in their action.

Reference has been already made to the *collateral hyperæmia* which occurs when an artery is obstructed.

CHAPTER VIII.

INFLAMMATION.

THERE is no subject in the whole range of pathology or of medicine which has been the subject of so much controversy as inflammation. Indeed, the doctrines of inflammation may be said to have dominated medical and surgical science and practice, and to have been the main stimulus to pathological research. There are few morbid conditions which have not at some time been included under the name.

Even now there are many differences of opinion as to the exact limits of the processes which should be called "inflammatory." Many pathologists would prefer to get rid of the term altogether, as one which has become useless and misleading.

But since the name has been so long employed, and has become so closely allied with the descriptions of disease, it seems better to endeavour to use it in some commonly understood sense, without attempting too exact a definition. For all practical purposes the changes so described are the series of reactions which follow irritation or injury: reactions which we now know to be to a large extent protective and designed to prevent or to repair the mischief. But amongst the various changes produced by any injury there will be found some actual damage, directly or indirectly produced, so that the two groups of change, the effects of the injury, and the efforts to oppose and to repair its results, are seen side by side in what we call inflammation.

It is needless now to dwell upon the history of the doctrines of inflammation or the controversies to which the subject has given rise. For the older pathologists, the commonly observed facts of redness, swelling, heat, pain and so on naturally appeared the most important. And since the occurrence of suppuration was so commonly associated with acute inflammation, it was regarded as a result, and its study formed part of the subject.

With the work of Virchow the matter came to be regarded in a somewhat new light. For him, the local phenomena of inflammation were largely those due to irritation of cells and interference with their metabolic activity. They might swell and divide and furnish pus corpuscles, or become so damaged as to necrose. The vascular changes could only be regarded as either a part of, or secondary to, these tissue changes.

The rediscovery of leucocyte emigration by Cohnheim introduced a new phase of the subject. The nature of and mode of formation of pus corpuscles was still the subject on which attention was especially centred. The demonstration which Cohnheim afforded of their origin in emigrated leucocytes led, for a time, to the view that leucocyte emigration was the central fact of inflammation. Cohnheim's observations on the changes in the vessels were also of great importance, and to a large extent form the basis of our present ideas of their reaction in inflammation.

Still later came the work of Elias Metchnikoff on phagocytosis, to which we have already referred. The phagocytic activity of leucocytes and of other cells came to be regarded by many as the essential and central fact in the inflammatory process, all the other phenomena being regarded as merely auxiliary to this.

Gradually, too, the fact that suppuration was not an essential of the reaction to irritation, but was only a special result of the conflict with some bacteria or toxins, led to the separation of its study from that of inflammation in general.

We must recognise the enormous value to pathology of the specialised research which has followed the effort to establish one or other view of the essential nature of inflammation. But if we regard the processes as a whole, we find in all of them a series of reactions combined for the common object of removing or antagonising the irritant and of preventing and repairing damage. In some cases one process is most active, in others another. From the moment of injury to the complete restoration to such health as is possible, we find a succession and co-operation of these reactions, all united to a common end. It is these which we propose to study under the name of **"Inflammation,"** including under the name the processes of temporary repair after injury.

Causes of Inflammation.—It is usual to state that anything which causes serious damage or irritation to the tissues may excite those changes which are grouped under the name "Inflammation." But the actual disturbance of nutrition or the injury inflicted may be very slight, provided that anything is present which is capable of producing damage, and therefore demands protective action. The presence of certain toxins excites leucocyte emigration and the associated changes almost before the toxins have had time to do any harm.

But viewing the process as a whole, the cause of inflammation may be said to be anything which calls for the exercise either of protective or reparative cellular reactions.

Amongst the most important of the causes we must place bacteria and their toxins. But other irritants may be effective.

The cause and the reaction may be localised, we then speak of a

"*focal*" inflammation. Or it may be *diffuse*, acting over a wide area. In some cases such diffuse inflammations are due to multiple foci of local irritation, in others, to a widely acting irritant, a toxin for instance.

Both the intensity of the reaction and the proportion of each group of changes vary with the *nature* of the "*noxa*" or exciting cause, and with its *intensity*. And to a considerable extent, both the damage inflicted and the character of the reaction will depend upon the capacity of the individual or of the tissue to react, in other words, upon the degree to which it is susceptible of injury, and upon the possession of defensive powers.

Thus, if the nutrition be already impaired, some irritants which would be without effect in health may cause serious disturbance of nutrition, and thus lead to the reactions of inflammation.

Processes of Inflammation.—Restricting our study at first to the changes observed in a small area or "focus" of inflammation, it is convenient first to give a general outline of the leading phenomena, and afterwards to discuss some of them more fully.

These phenomena are most conveniently observed in a transparent membrane, *e.g.*, web of frog's foot, mesentery. Inflammation of the web is readily induced by the application of a minute drop of any irritant, or by snipping off with scissors a small piece of the cuticle. Dilatation of the bloodvessels speedily ensues, and the bloodflow through the part is accelerated, a condition of active hyperæmia. Soon, however, this stage of active hyperæmia is followed by a period of sluggish flow of the bloodstream, seen first here and there in the dilated venules. This is the period of so-called stasis. Some of the venules become greatly and irregularly dilated, and in some of them actual cessation of flow and thrombosis may occur. During this period, there is an increased transudation of lymph through the vessel walls, leading to swelling of the inflamed area ("inflammatory œdema"). The transparent membrane has now become red and swollen, and an increasing opacity may render the observation of the further processes difficult. Leucocytes have already begun their emigration from the vessels into the surrounding tissues, and in a few hours the tissues may be crowded with leucocytes which have passed through the vessel walls. These leucocytes migrate in the tissues towards the focus of irritation in a definitely purposive manner.

Red blood corpuscles may escape from the bloodvessels either by diapedesis or by actual rupture of the vessel wall. Diapedesis of red blood corpuscles is a purely passive phenomenon. The successive extension of the process from the centre of the damaged area towards the periphery can be observed.

If the irritant be removed, the process may be arrested and the phenomena subside, *e.g.*, in temporary exposure of the mesentery of the

frog to the air, unless the tissues have suffered grave damage. On the other hand, if degenerative and necrotic changes occur in the tissues as a result of the action of the irritant, the process continues until the irritant is removed or antagonised and repair is effected.

In all parts there is usually some degeneration of the tissue, especially of highly endowed tissues which are very susceptible to the action of injurious substances. If the irritant be at all intense in its action, degenerative changes of various kinds also occur in the supporting tissues. Damaged and necrotic tissues are absorbed and removed by various means (phagocytic cells and the action of peptonising ferments). Repair is also begun. There is the formation of new capillaries by a process of budding, and proliferation of the fixed cells of the part. The reparatory processes may be seen commencing early, in the later stages they predominate.

We may now consider separately the several groups of phenomena, especially as to the vascular and circulatory changes, the lymph transudation and leucocyte emigration, and lastly, the changes especially affecting the fixed tissue elements, both degenerative and reparative. But it must be borne in mind that these may go on side by side.

Vascular Phenomena.—Under this head we include the changes in the vessels themselves and in the flow of blood.

The vascular phenomena, although they may not be absolutely essential to the process, are amongst the earliest and most striking. And they aid greatly the more essential processes of lymph transudation and leucocyte emigration, and pave the way for absorption and repair.

The successive development of these vascular phenomena can be watched under the microscope in a transparent vascular membrane, such as the web of a frog's foot, or the mesentery of warm-blooded animals. Dilatation of the bloodvessels rapidly follows the infliction of the injury. This dilatation is most evident in the capillaries and veins; the arterioles may also dilate after, it may be, a primary evanescent contraction, but the dilatation is so slight that its early occurrence is denied by some observers. There is an increased influx of blood, and the bloodflow in the capillaries and veins is accelerated. This is the stage of active hyperæmia.

Dilatation of the capillaries by diminishing the peripheral resistance is of itself, apart from any arterial dilatation, quite sufficient to determine the occurrence of the increased influx of blood and the accelerated flow. The diameter of the capillaries, as shown by Lister, may only be increased by one-fifth to one-quarter, but the sectional area would thereby be increased by nearly one-half. Dilatation of the vessels occurs even when all connection with the cerebrospinal vasomotor centres has been severed. The injurious influence of the

irritant must therefore be exerted either directly on the vascular walls or by the intervention of a local vaso-motor apparatus.

This stage of active hyperæmia may only last for one to two hours (observations on web of frog's foot), and is succeeded by the period of stasis, during which the bloodstream becomes sluggish in its flow. The slowing of the bloodflow is first observed in some of the irregularly dilated veins. As the rate of bloodflow becomes diminished, the leucocytes drop out into the clear peripheral plasmatic stream. This alteration in the disposition of the bloodstream consequent on slowing is a purely physical phenomenon. The velocity of the axial stream is always greater than that of the peripheral stream, and the corpuscular elements of the blood circulate in the axial stream so long as the requisite velocity is maintained. But whenever the rate of the bloodflow is reduced to a certain degree, the leucocytes, being of lower specific gravity than the red blood corpuscles, tend first of all to fall out into the peripheral layers of the stream. A mixing up of all the corpuscular elements occurs when the flow becomes still slower. Sometimes complete stagnation of the blood ensues, and the capillaries and small venules appear to be filled with a mass of fused red cells. The leucocytes which accumulate in the peripheral layers of the stream are seen here and there to adhere to the walls of the vessels, and some now begin to migrate through the vascular walls into the surrounding tissues. This is especially observed in the venules, to a far less extent in the capillaries.

When we come to seek the cause of the slowing of the previously accelerated bloodflow, we must direct our attention to the important structural and functional changes which have occurred in the vascular walls. In consequence of their damaged nutrition, the normal elasticity is impaired, and they stretch unduly. This stretching is more evident in the venules than in the capillaries. The rise of intravascular pressure which results aggravates the condition, and as the dilatation of the minute vessels becomes progressively greater, the volume of blood which flows into the veins is greater than they can wholly remove. Furthermore, the blood has now to overcome an increase of frictional resistance. This arises in consequence of structural changes in the lining endothelium. The endothelial cells become swollen, the intervening cement substance is loosened, and they now project into the vascular lumen. The *vis a tergo* thus becomes dissipated in overcoming the increase of frictional resistance. The leucocytes appear to become "sticky," and tend to adhere to the altered walls. The red blood corpuscles also which come in contact with the walls, as shown by Lister's classical experiments, seem to undergo changes which render them more viscid and more difficult of circulation. There is another factor which may aid the occurrence of slowing. During this time an increased amount of fluid is escaping through the vessel

walls, and the blood plasma in the vessels may become more inspissated.

Escape of Red Corpuscles.—It is usual to speak of the passage out of red corpuscles from the vessels as "*diapedesis*"; and it is supposed that they can pass through the unruptured vessel walls: either between the endothelial cells or through openings formed by leucocytes. Such modes of escape, whilst not impossible, are certainly rare. The openings made by the leucocytes are very minute, and close after their passage.

Both from direct observation and from the condition in which the blood appears, it is obvious that the commonest mode of escape is in a little jet, from the sudden bursting of a capillary. Hence we find the red corpuscles in little clumps near, but not close to, engorged vessels in early inflammation of the omentum. The openings by which they escape close rapidly after the pressure is relieved. Of course we do not deny the existence of other modes of escape.

Whilst some such escape of the red blood cells is common in an inflamed area, it may be very scanty. Usually most escape at the early periods before leucocyte emigration has become active, and in the case of serous membranes before the surfaces are coated with lymph or separated by exudation.

In some cases, however, the quantity of red corpuscles is so great that the exudation is hæmorrhagic, this occurring especially in some constitutional conditions; more rarely from a special action of the irritant upon the bloodvessels.

Increased Transudation of Lymph. — An increased transudation of lymph may be observed quite early in the process. It is usually well marked when the bloodflow is becoming slow. The increased quantity of fluid which transudes is spoken of as inflammatory œdema or exudation.

A large exudation may occur with great rapidity. The quantity depends to a large extent on the influence of certain mechanical factors. In situations where the degree of external pressure is inconsiderable large accumulations may occur, *e.g.*, in the pleural sacs. In the pleural sacs little external resistance is offered to the outpouring of fluid, and the facility for accumulation is enhanced by the compressibility of the lungs. On the other hand, if the surrounding tissues be dense and non-elastic, *e.g.*, in solid organs, the quantity of fluid never attains a high degree. The nature and intensity of the irritant also exert a considerable influence. Some kinds of bacterial irritants cause a large exudation from the bloodvessels, whereas others produce an insignificant amount, but there may be a great emigration of leucocytes.

The quantity of the exudate also depends on the condition of the patient. Thus in some conditions of anæmia, in which there are an

altered composition of the blood plasma and changes in the vessel walls, transudation occurs with greater facility. Differences in susceptibility to the action of invading bacteria are also responsible for variations in the quality and quantity of the exudate.

Character and Composition of Inflammatory Exudates.—Inflammatory exudates are always richer in proteid constituents than ordinary lymph and dropsical transudates. The amount of proteid, however, never equals the amount in the blood plasma, except in some cases where the exudate becomes subsequently concentrated by the absorption of the watery constituents. The exudate, though coagulable, does not necessarily coagulate in every situation. Coagulation is usually observed upon free serous surfaces, such as the pleura and pericardium, and in aseptic wounds. Its occurrence depends upon the presence and amount of fibrin ferment. But in some cases coagulation is prevented or the coagulum softened by ferments, especially those produced by some bacteria. This action is well seen in suppuration.

It must be remembered that the inflammatory exudate may contain also substances which have special antitoxic and antibacterial actions. The consideration of these belongs to the subject of immunity.

As to the causes of the increase in and altered characters of the transudation of lymph (or as it is termed "exudation" when occurring in inflammation), the differences from the normal process are no doubt partly physical. There is a difference in the relative pressure which may aid the increase of transudation. But the increased porosity of the vessel walls and the swelling of the endothelium will also diminish the resistance to transudation and lower the selective capacity.

But we cannot even by these changes fully account for the great differences in the character of the exudate caused by different toxins, nor explain the differences in the exudation in different serous cavities from a common cause.

The increased transudation no doubt serves some useful purposes. Free irrigation of the injured tissues must often be beneficial. Irritant substances, such as bacterial products, are diluted and partly removed. It may be that in some cases harm is done by aiding the spread of bacteria or irritants, *e.g.*, along the channels of lymph absorption or over serous and mucous surfaces. Moreover, the fluid may aid the ready absorption and distribution of locally manufactured toxins, which may exert an injurious influence on important organs such as the kidneys or heart. Locally, however, the toxins are diluted, so that they act on the tissues with less concentration. If antitoxic and bactericidal substances are present in the exudate, they will tend to neutralise the toxins and antagonise the micro-organisms. The exudate also loosens the tissues and thereby facilitates the migration of the leucocytes. In the early stages of inflammation, when the

destructive changes predominate, the exudate is not of much use as a source of increased nutriment, but in the later stages, when the proliferative and reparative changes have begun, it may help to nourish the tissues.

The formation of fibrin is of great benefit in many cases. On serous surfaces, for example, it tends to localise the area of inflammation and to bind together apposed surfaces: and it furnishes a sort of scaffolding for the reparative processes.

The Emigration of Leucocytes.—We have said that Metchnikoff and his followers look upon the part played by the leucocytes as the essential and constant factor in the process. In other words, they regard the inflammatory process as essentially a reaction on the part of the leucocytes against the irritant. The emigration of leucocytes is undoubtedly one of the most striking features in the process. It is well known that the migration of leucocytes through the vessel walls was discovered by Addison in 1843, and again by Waller in 1846. These observations escaped the notice of pathologists until Cohnheim, in 1867, again demonstrated the fact, although he did not recognise that it was due to active amœboid movement on the part of the leucocytes themselves. But his work laid the foundation of most of the later discoveries on the nature of inflammation.

Phenomena of Leucocyte Emigration.—Leucocyte emigration may be observed two hours after the application of the irritant in frogs. The leucocytes fall out into the peripheral layers of the bloodstream. Some of them are seen to attach themselves to the vessel wall. Delicate protoplasmic processes are then protruded, and by a gradual amœboid movement the entire corpuscle finds its way through the vessel wall. If the process is carefully watched, it is seen that the part of the leucocyte which lies within the vessel is globular or flattened, whilst the parts which are protruded are actively changing their shape.

The rapidity of the passage of a leucocyte varies with the animal, the time of year, and the activity of the circulation. If the circulation is slow, it may be accomplished in eight to ten minutes, but sometimes it may require one to two hours. In warm blooded animals it may be accomplished more rapidly. There is no sufficient ground for the belief that any preformed openings or stomata are needed to allow of the passage. The spaces between the endothelial cells, especially when the cement substance is softened, would allow of ready passage. And we know that leucocytes can penetrate thick layers of epithelium, and pass readily through other tissues. It is not improbable that contractile movements of the endothelial cells may aid the passage.

The *site* of the emigration is usually from the venules, more rarely the capillaries, and very rarely through the arterioles. Nor is it only through the smallest venules: we often find leucocytes passing

through those of 50μ or more in diameter, so that other structures than endothelium must be penetrated. Emigration is often abundant at the site of junction of branches of the veins.

Having escaped from the vessels the leucocytes migrate in various directions, especially towards any noxious or effete material. In this way a large number of leucocytes coming from a wide surrounding area may accumulate at one small focus.

So long as there is any work for them to do, leucocytes will continue to emigrate, it may be for months or years.

Inflammation in Extravascular Parts.—Keratitis.—Before considering more fully some of the problems of leucocyte emigration, we may inquire what changes occur in the inflammation of extravascular parts, such as the cornea or cartilage.

Much attention has been paid to artificial keratitis, not only on account of the ease with which the changes could be observed, but because it seemed possible to determine in the cornea the course of the changes in the fixed cells and tissues apart from the blood-vessels, and also to decide the nature and origin of pus corpuscles. Practically, it is difficult to produce injury of the cornea without exciting such a degree of conjunctivitis that the changes in the cornea are obscured. In some cases the injury can be restricted to a limited area.

It will be remembered that the cornea is composed of flattened fibrous laminæ, which run parallel to the surface, and between these are lymph spaces in which lie flattened connective tissue cells, the corneal corpuscles. The lymph spaces communicate freely with each other and with the lymphatics surrounding the vascular loops at the periphery of the cornea, so that although devoid of bloodvessels there is a free supply of lymph. In the rare cases in which injury is inflicted without exciting inflammation (as in Senftleben's experiments by injecting chloride of zinc solution), the corneal corpuscles may be destroyed and shrivel and parts of the fibrous laminæ be softened, without other reaction. Repair may then be effected by the proliferation of the healthy corneal corpuscles around, which send offshoots into the necrosed area, and gradually restore the structure.

But in nearly all cases, and especially if septic bacteria are present, changes are seen both in the damaged area and at the periphery of the cornea. An area of opacity surrounds the focus of damage, due in part to the direct immigration from the surface of leucocytes which have come from the conjunctival vessels. If the irritation is more severe, the vessels surrounding the periphery of the cornea become swollen and engorged with blood, and leucocytes migrate from them through the lymph spaces to the area of damage, or to the spot where bacteria or toxins lie. Together with these changes there is distension of the lymph spaces with lymph, and swelling of the connective tissue fibrils.

Speedily, too, the formation of new capillaries which penetrate the corneal structure is observed. The further changes are analogous to those to be described later under the head of "Repair."

Hence it is evident that the inflammatory phenomena in the cornea correspond with those seen in vascular parts, so far as the occurrence of hyperæmia, lymph transudation, and leucocyte emigration are concerned. Moreover, the kind of leucocytes which emigrate and the periods of reaction correspond with those seen in other parts.

We may now consider more fully some of the problems of leucocyte emigration.

Nature of the Leucocytes which Emigrate.—It was formerly believed that the multinucleated leucocytes (or "polymorphs") alone possessed the power of amœboid movement, and were the only leucocytes which could emigrate from the blood-vessels. This view is still entertained by some. But a study of the cells found in inflammatory exudations shows that at some periods and in some conditions a large number of other cells which closely resemble the other common forms of leucocytes may be present. And the possibility that they also may come from the blood was suggested. Moreover, it is certain that some of the large mononuclear leucocytes of the blood have a high degree of amœboid and phagocytic activity.

As the statements made by different authorities as to the characters of leucocytes vary, it may be well to give a brief outline of some common elementary facts so far as they concern the changes in inflammation.

The leucocytes normally present in the blood are—

(*a*) *Polymorphonuclear.*—These—the commonest kind, forming about 70 per cent. of the total—have a multipartite or lobed nucleus, the segments of which are variously arranged and united by delicate threads. The cytoplasm contains numerous fine granules, often called neutrophile, but faintly oxyphile with eosin.

(*b*) *Eosinophiles.*—These, whilst resembling in most respects the polymorphs, do not usually show so great a degree of division of the nucleus, and are distinguished by the coarse oxyphile granules in their cytoplasm. They are much more fragile, and readily break down with discharge of the granules.

(*c*) *Lymphocytes*, having a relatively large rounded nucleus, which stains deeply, and scanty cytoplasm in which some fine basophile granules may be present, especially towards the periphery.

Larger lymphocytes, with similar characters, but having more cytoplasm, are also common.

(*d*) Between these large lymphocytes and the larger mononuclear cells, which are sometimes called *hyaline*, or simply "large mononuclear," it is difficult to draw any absolute distinction. These

"*hyaline*" leucocytes have often a large, somewhat ovoid or reniform nucleus, which stains less intensely than that of the lymphocytes, and their cytoplasm is for the most part devoid of granules, hence the name "hyaline." Whilst normally present in small numbers in the circulating blood, they may be greatly increased in some conditions, and they display great phagocytic activity. As seen in blood films, they vary greatly in form, a fact probably associated with their amœboid activity. And they often show vacuoles in their cytoplasm.

From the fact that they may be present in large numbers in the circulating blood when some kinds of phagocytic action are required, *e.g.*, in malaria, and that when they are abundant the ordinary lymphocytes may not be proportionally increased; and, conversely, that a great increase in small lymphocytes may in no wise determine any increase of these large mononuclear cells, the inference might be drawn that the two kinds are distinct in nature and origin. We have also much evidence that such mononuclear cells can originate from serous and possibly vascular endothelia, and from other mesodermal structures.

But at present we cannot establish any sufficiently absolute distinction between these and the larger lymphocytes. Forms which appear to be intermediate are also frequently met with.

Mast Cells, characterised by the presence of large granules with basic or metachromatic staining are usually described as a normal type of leucocytes. Whether they are really so is questionable; in any case, there is little evidence that they take any part in the active processes of inflammation.

Evidence of the Emigration of Leucocytes other than the Polymorphs.—The only conclusive evidence would be that from direct observation of the passage through the vessel wall. It is true that the passage can rarely be seen during life. But on microsopic examination of the tissues from an inflamed area, fixed immediately after death, leucocytes of a particular kind may be found to have accumulated in the venules, and to show various phases of migration. Some may be flattened against the inner wall of the vessel, others protruding processes, and yet others in various stages of passage through the wall or escaping into the tissues. The peculiar characters of the various leucocytes are readily seen by differential staining.

It might, of course, be suggested that the leucocytes were migrating *into*, and not out of, the vessel. But the various phases of migration are so well known that there is no difficulty in determining the direction in which they are travelling.

Apart from this, if large numbers of any kind of leucocytes are

found to accumulate around the vessels in the positions where emigration usually occurs, and if they cannot be traced to other sources, there is strong ground for the belief that they have escaped from the blood, especially if certain exciting causes lead to such an accumulation in the tissues, together with a corresponding increase in the circulating blood. This is especially the case if they are leucocytes which are known to be normally generated in the bone marrow and carried from the bone marrow by the blood. And still more, if we find evidence of a concurrent increase in their formation in the bone marrow itself.

But it must be remembered that a marked increase of any particular kind of leucocyte in the blood is not essential, although it frequently occurs, since the blood only acts as a means of carriage, and if the cells which escape are rapidly replaced, they need not accumulate in the blood itself. The great increase of the polymorphs in the blood in some suppurative inflammations may be due to their enormous and widespread generation in the bone marrow, and to the large number which are used up in some infective inflammations, *e.g.*, in pneumonia.

As to the *lymphocytes*, direct observation has shown that they do emigrate (Councilman, Maximow, and others), but many of those present in an inflamed area can be traced to proliferation in adenoid tissue and local migration with the lymph stream.

As to the *eosinophiles*, the evidence of their emigration is derived from the study of tissues fixed immediately after death at various periods after infection. Their increase in the blood, especially in some diseases due to animal parasites, and the large numbers which may be present outside the vessels in some inflammatory foci, made the fact of their emigration almost certain. Recent observations have afforded positive proof of their emigration. Thus E. L. Opie has shown that after intraperitoneal injection of Bacillus pyocyaneus and some other bacteria, the eosinophile leucocytes speedily begin to accumulate in venules in the mesentery, especially in those of 30μ to 40μ in diameter, and at the end of 4 hours were found to be actively emigrating. By the end of 8 hours their number had considerably diminished. They were not observed to ingest the bacteria, or to discharge their granules.

During the earlier periods of their emigration, the number in the circulating peripheral blood was greatly diminished. This was followed by gradual replacement, and in 4 or 5 days the number might become considerably increased, but in 6 to 8 days it fell to normal. Evidence of an increased formation in the bone marrow was also found.

As to the *larger mononuclear cells*, apart from those derived from lymphocytes, the evidence is not so clear. It is true that they may increase greatly in the blood at some periods of inflammation, *e.g.*, in

pneumonia, and they may also become much more numerous where phagocytic action in the blood itself is demanded.

On the other hand, the presence of large numbers in the inflammatory exudation at certain periods is not usually accompanied by any corresponding increase in the blood itself. Moreover, the period of their predominance coincides with that at which active proliferation of endothelial and other fixed cells is going on.

Further, in serous membranes we find all transitional forms between endothelial cells which are actively germinating and some of the free mononucleated cells, and both kinds of cell show the same phases of vacuolation and of active phagocytosis with regard both to other cells and to bacteria.

There are, therefore, grounds for the belief that some, at any rate, of these free mononuclear cells have not emigrated from the blood, but have been formed either from lymphocytes derived from adenoid tissue, or by the proliferation of endothelial or other cells. All grades of transition are seen between the pleural endothelium and such free mononuclear phagocytes in pleuritic effusions.

The **relative proportion of the different kinds of leucocytes** in any inflammatory exudation, and also the period of their occurrence, vary with the nature of the excitant, and probably also with the intensity of its action and with the kind of animal. But within certain limits there is a remarkable concurrence in the results of many different observers experimenting on various animals and in many sites with the bacteria of some of the common wound infections, such as staphylococci and bacillus coli.

Of the more recent observations those by Dr J. Martin Beattie with the bacillus coli may especially be cited.—*Journal of Pathology and Bact.*, June 1902.

The results are in accordance with those of other recent workers, but they especially illustrate the periods at which different kinds of leucocytes are present.

The method of observation was that employed by Metchnikoff, viz., the introduction of active cultures of the organisms, and the removal from time to time at fixed periods of a small quantity of fluid from the peritoneal cavity, by means of a fine pipette. Control observations can be made in healthy animals, and also by killing the animals at various periods and examining the tissues.

The results as to the preponderance of certain cells at different times in one group of experiments with bacillus coli in the peritoneum of the guineapig were as follows :

Polymorphonuclear Leucocytes.—These are numerous three hours after inoculation, their number increasing and becoming especially abundant in from 12 to 24 hours. In fatal cases, *i.e.*, where the power

of resistance is low, they may go on increasing in number till death, which may be delayed till 96 hours.

Usually, however, they diminish after a period of 36 to 48 hours, and by 84 to 96 hours they become very scanty. After this time they may entirely disappear, although in rare cases some few were present at 150 hours.

Coarsely Granular Eosinophiles.—These were present only in small numbers. They were found 4½ hours after inoculation, becoming more abundant in 9 to 24 hours, and they might still be present at 150 hours.

It must be remembered that these leucocytes are relatively more abundant in guineapigs and rabbits than in man.

Mononuclear Leucocytes.—These include small and large lymphocytes, and the "hyaline" or large mononuclear leucocytes. They appear in the lymph in 3 hours after inoculation, but at first are scanty. Between 18 and 24 hours the number becomes greater, and this increase continues whilst the polymorphs decrease, until between 54 to 84 hours the mononuclear cells form almost the sole leucocytes present. This increase is maintained until 150 hours, or even longer.

As regards the phagocytic action in these experiments, the bacilli were rapidly taken up, especially by the polymorph leucocytes, and in some cases all had been ingested in 4½ hours, in others at various periods up to 9 hours. Subsequently, but not until about 18 hours, there was ingestion of the polymorph by the large mononuclear leucocytes. This process became marked during the period between 27 and 48 hours, after which it diminished.

It may be added as the general result of other observations, *e.g.*, in the cornea by Councilman, that the larger clear mononuclear cells are those which appear especially between 18 and 24 hours, the lymphocytes not being found in any number until 74 hours. This certainly accords with our own observations in inflamed tissues.

In the experiments of Opie, to which we have referred, the large mononuclear cells were found to have made their appearance at the end of 16 hours, and to become numerous in 24 hours, by which time they had ingested many of the eosinophiles.

The Causes of Leucocyte Emigration.—What is it which excites the activity of the leucocytes and causes them to emigrate? And by what influences is their course directed after they have escaped from the vessels? It is evident that the physical conditions of the circulation or the pressure do not account for the phenomena. The movements are actively amœboid, and they are in some way related to the performance of special functions.

A partial solution is afforded by the known phenomena of "chemiotaxis." Plasmodial organisms are known to be attracted by some substances of a certain chemical constitution, and to be repelled by others. When attracted, the condition is one of *positive*, when repelled, of *negative* chemiotaxis.

By the introduction into the tissues of capillary tubes or capsules, containing various substances, the degree of attraction exerted upon leucocytes by them has been studied. A large number of different substances have thus been tested. Leber, who especially investigated the action of some chemical compounds, found that mercury, copper, turpentine, and some others exert a positive attraction. Quinine, chloroform, glycerine, alcohol, etc. act negatively. Moreover, the degree of concentration produces variations: a strong solution of some substances may repel, whilst a weak may attract. The acid or alkaline reaction also have some effect.

With regard to bacteria, it is found that the toxines of most of the common septic bacteria of wound infections, and also diphtheria toxine, when not too concentrated, attract leucocytes ; but, if concentrated, they may repel them.

When thus attracted, leucocytes may not only wander for considerable distances, but may penetrate dense tissues to reach their object. Then they may migrate through the corneal epithelium to the surface.

But although a chemical attraction may be regarded as one of the important influences determining emigration, there are other stimuli which excite leucocyte activity. Like other living cells, leucocytes are sensitive to physical stimuli of various kinds. This physiotactic activity includes the reaction to light, heat, electricity, and to tactile stimuli. And the facts which are known as to the effects of other kinds of stimuli on some unicellular organisms make it probable that there are other less known agencies to which they are sensitive.

Metchnikoff has pointed out that the altered condition of the endothelial cells of the bloodvessels, their swollen condition, and possibly contractile movements on their part, may excite the tactile sensibility of leucocytes and stimulate their movements. Such contraction of the endothelium would also aid the escape of the leucocytes.

Both within the blood, as in the search for and attack upon malaria parasites, and in their actions when traversing the tissues, we see the display of a high degree of selective power by the leucocytes. They perform varied evolutions in the effort to grasp and ingest their prey, and the movements are apparently so purposive and so regulated as to suggest some degree of intelligence on the part of the leucocyte. In other words, they are sensitive to and react in accordance with a variety of stimuli.

Phagocytosis.—We have already referred to phagocytosis, or the action of living cells in incorporating and digesting various foreign

substances, including inanimate particles such as carbon, living cells such as red blood corpuscles and polymorph leucocytes, and various bacteria and animal parasites. Some further consideration of the subject is essential in relation to the processes seen in Inflammation.

It had long been recognised that leucocytes, like other living cells, will ingest foreign particles, and that they aid in the absorption of material which has become effete. This action was seen in the absorption of the tail of the tadpole, and in the removal of myelin granules in degenerating nerves.

We owe to Elias Metchnikoff a large part of our knowledge upon this subject. In a series of researches, carried on during many years in all parts of the animal kingdom, and with many varied experiments, he has shown conclusively that this power of living cells is a universal endowment of animal life, and that it is of the greatest importance in the defensive powers, without which the maintenance of life would be impossible. Whether we accept Metchnikoff's conclusions in their entirety or no, we cannot but regard this action as one of the chief factors in immunity from disease.

The substance of Metchnikoff's researches will be found in his work on "Immunity," but some of his earlier observations in relation to Inflammation are embodied in his "Lectures on the Comparative Pathology of Inflammation," which should be read by all who wish to gain a fuller insight into the subject.

Phagocytosis is accomplished by leucocytes and other cells in the same way as unicellular organisms ingest their food. The prey is grasped or surrounded by pseudopodia and thus incorporated, and is gradually absorbed by intracellular digestion, such parts as resist digestion being usually extruded. In most cases the digestion is carried on in vacuoles which are formed within the cytoplasm, the substance which is undergoing digestion being often surrounded by a clear space containing fluid. Sometimes numerous vacuoles may be seen in one cell, each containing a mass in various stages of digestion. There can be no doubt that the digestion is effected by some kind of ferment; but its exact nature has not been determined, although many experiments have been made.

In the human body the phagocytic processes are effected both by leucocytes and by various fixed cells. Vascular and lymphatic endothelium show a high degree of phagocytic activity. But liver cells, renal epithelium—especially that lining some sections of the urinary tubules—the epithelium of the pulmonary alveoli and bronchi, and also other epithelial cells of mucous membranes, possess the power in varying degrees. Probably there are few cells engaged in active nutrition which cannot thus ingest foreign particles or organisms.

In relation to inflammation, and especially where bacteria are present, the earlier and more active part of the process is effected by

leucocytes. In the case of most of the common bacteria of wound infections (staphylococci, streptococci, bacillus coli, and pneumococci in particular), the polymorph leucocytes are the first to act. Some other kinds of infective bacteria are not ingested by them, or only to a small extent, the larger share in the process being taken by mononuclear cells. The polymorphs can also ingest red blood corpuscles, particles of dead or useless material such as necrosed cells, and foreign particles such as carbon.

But the processes of intracellular digestion within the polymorph leucocytes appear to be often very incomplete, and they sometimes seem to serve mainly as agents for the collection and carriage of the material to be removed or destroyed. They may carry it to the surface, as in granulating wounds, or may migrate with it into the lymphatics, and thence to the glands. Bacteria after ingestion may prove to be living and active, and capable of growth.

The more complete processes of destruction are usually effected by mononuclear cells (either leucocytes from the blood or derived from other cells) and by fixed cells, especially lymphatic and vascular endothelium. Metchnikoff calls these larger mononuclear cells *macrophages*, as distinguished from the *microphages* or polymorph leucocytes.

From the period when mononuclear leucocytes appear in the inflammatory exudation they are found to ingest the polymorph leucocytes, red blood corpuscles and any free bacteria. The polymorph leucocytes may be loaded with bacteria when ingested. Within the larger cells the bacteria lose their staining reactions, often becoming for a time oxyphile before they disintegrate and disappear. The nuclei of the ingested polymorph leucocytes become fragmented, the cytoplasm dwindles and is finally absorbed. Red blood corpuscles shrink or are broken up, their hæmoglobin may be absorbed, or may leave a residue of pigment within the phagocyte. Where several red cells are ingested by one phagocyte this is especially apt to occur.

Similar processes are carried on by the phagocytic endothelial cells. Such phagocytic cells may become considerably enlarged by the accumulation of foreign material within them.

Even within the larger phagocytes, bacteria may resist digestion for considerable periods, and in some cases it is possible that they may proliferate within the cell and overcome it ; or they may lie dormant, and be carried by the leucocyte to other parts of the body, where they may again become active.

It is probable that the larger part of the phagocytic action by which dead cells are removed is ordinarily effected by the mononuclear cells. The polymorph cells are especially active where bacteria are present. But some bacteria, notably those of typhoid

and tubercle, are chiefly dealt with by mononuclear cells, and in those diseases the polymorph leucocytes play but a small part.

It is believed by some that, in addition to their directly phagocytic action, leucocytes may form and excrete materials which are bactericidal, or which aid in paralysing bacteria, or overcoming their resistance. It is well known that substances are present in blood serum and lymph and in the other fluids of the body, which arrest movement and cause agglutination of bacteria, or which act as antitoxins.

But it is not certain that these substances are generated by leucocytes; some of them are more probably derived from other cells. However derived, they aid in the general defensive reactions, and facilitate the phagocytic action.

After the completion of their functions, the polymorph leucocytes may, as we have seen, be ingested by other cells, or be discharged from the surface, or may again enter the lymphatics or, more rarely, the bloodstream. It is believed by Metchnikoff that some of them undergo a process of direct cell division after escaping from the vessels. But it is very doubtful whether this power, if it exists, is often exerted, and still more doubtful whether polymorph leucocytes ever share in the formation of new tissue.

The mononuclear cells may also migrate and find their way to the lymphatics and lymph glands, where foreign particles which they contain may be deposited. Such of them as re-enter the blood may ultimately lodge in various parts, especially in the bone marrow and the spleen, where they are arrested.

The question of their share in formative processes will be considered later.

CHAPTER IX.

CHANGES IN THE FIXED TISSUE ELEMENTS IN INFLAMMATION.

We have thus far considered chiefly those changes which are related to the transudation of lymph and blood cells. The changes in the fixed tissues, especially in the vascular and supporting structures, and in the more special constituents, must next be mentioned. These changes are of two kinds, *degenerative* and *proliferative*. They proceed side by side with the changes already studied. The proliferative processes destined to effect absorption and repair commence at an early period, though somewhat later than the leucocyte emigration.

Degenerative changes may not be prominent in an inflamed area. They may be present in consequence of the direct action upon the tissues of the agent which excites the inflammation. Some of these changes have already been considered under "*necrosis*." Amongst such agents are caustics, burns, etc., which may lead to intense and widespread necrosis, and crushing or laceration of wounds. Severe and widespread necrosis may be caused by some bacterial toxins, as in malignant œdema. But, as a rule, the damage produced by bacteria and toxins which excite inflammation is to a large extent microscopic, although it may spread widely. In most of the acute and subacute inflammations with which we have to deal, as in all wound infections, and in the various inflammations of serous membranes and internal organs, there are present bacteria which not only proliferate but continue to generate toxins so long as they are not destroyed or removed. Some degree of progressive damage due to their continued action goes on side by side with the protective processes.

It is often difficult to say to what extent any degenerative change is due to direct damage or toxic action. In the case of many cells which have a high degree of organisation and which carry on special functions, such as secreting gland cells or nerve cells, the interference with their normal metabolism and function, and the altered relations of lymph supply, may suffice to cause degeneration or wasting. Such secondary results of inflammation may lead to partial atrophy in a secreting gland, such as the kidney or testicle.

In any severe or continued inflammation it is common to find that cells undergo fatty or mucoid degeneration, connective tissue fibres

and laminæ become swollen and loosened, and mucoid or hyaline degeneration may occur in fibrous and elastic structures.

Proliferative Changes.—Where any severe damage has been inflicted on the tissues, or where from any cause they have lost their vitality or become useless, changes occur by which they are either absorbed or removed ; or, if this cannot be effected, they are enclosed in a sort of capsule of fibrous tissue which shuts them off from the healthy parts.

The processes by which this absorption is effected are to a large extent the same as those by which temporary repair and cicatrisation are begun. It is possible that the repair of an injury may be direct. Growth of the cells of a tissue may reform the structure and unite severed parts. Such direct union may occur in severed nerves or tendons or in epidermis. But where, in addition to an injury, inflammation has been excited, other preparatory steps are usually needed. Portions of damaged tissue may need removal, there may be gaps to fill, surfaces to be united, or some remodelling of the structures may be required in order to adapt them to the new conditions. Moreover, there may be masses of coagulated fibrin or of blood-clot to be loosened and absorbed.

The earlier proliferative changes in the fixed tissues are merely such as subserve absorption and temporary healing, and pave the way for more complete restoration and repair. At a comparatively early period signs of commencing proliferation, especially swelling and mitotic figures, may be seen in vascular endothelium and connective tissue corpuscles, and also in simple epithelial cells (*i.e.*, those which serve to line tubules or cover surfaces).

The vascular and connective tissues begin to show such changes in about twelve hours from the period of injury. During the earlier periods the vascular proliferation becomes predominant, and may first be considered.

To a large extent the changes are the same wherever absorption and repair occur. Whether we study the healing of wounds, the repair of fractures, the closure of arteries after ligature, the absorption or organisation of thrombi, the union of serous membranes after inflammation, the removal of damaged or dead parts or foreign bodies, or their enclosure by fibrous tissue, we find that there is not only a general correspondence in the processes, but a remarkable uniformity in the period at which they commence and in the general method of procedure.

We can therefore study the processes in a great variety of conditions.

Experimental observations have the advantage that, by noting the changes at fixed intervals of time, we can determine the exact periods of their occurrence.

Many investigators have studied the effects of the introduction of foreign bodies, such as ligatures, bone, pith, sponge, capillary tubes or capsules containing toxins or irritants, and ingeniously constructed glass chambers. Wounds and serous inflammations and artificial thrombosis also serve the purpose. Our own observations mainly refer to the latter group, and especially to serial incised wounds made at definite periods. Experimental results in the lower animals can be compared with those in the human subject in a variety of instances where the time of the injury is known. Operation wounds, thrombi of known duration, and serous inflammations of definite origin furnish valuable data for comparison.

Proliferation of Bloodvessels.—The earliest and most important step towards absorption and temporary repair is the growth of new bloodvessels. It can be well seen in the process of absorption of a mass of coagulated fibrin on a serous membrane. New vessels, at first capillaries, grow out from the other vessels into the fibrin, and, uniting, form a ramifying network within it. These vessels form channels by which fresh fluid and leucocytes can be poured into the mass, serving to soften and digest it. Through them also the absorbed material can be carried away. The method adopted by nature is similar to that by which a piece of waste land is drained and irrigated and prepared for cultivation, or new roads and drains are made to prepare for building. But beyond this the vessels serve as a sort of scaffolding upon which layers of connective tissue can be built up. Or, to pursue the analogy of reclamation of land for building, walls or pavements can be constructed alongside the new roads.

We have seen that the bloodvessels of the inflamed area are engorged with blood, and that their endothelium is swollen. The vessels are thus in a condition favourable to proliferation.

The **mode of formation** of new vessels is by a budding of the endothelium. At first the buds take the form of solid processes of nucleated protoplasm of somewhat conical shape projecting outwards from the wall of a vessel. From these processes long delicate threads run outwards amongst the tissues or exudation, like the rootlets of a plant. By successive divisions of the protoplasm, new endothelial cells are formed, which separate and open out a new channel continuous with the lumen of the vessel, which then progressively enlarges.

The new vascular buds or rootlets are at first difficult to distinguish from other cells. As the development proceeds and the lumen is opened out, the appearance in transverse section is that of a hollow ring, thicker on one side ; and in some the cross section of a nucleus may be seen.

As they extend outwards, these rootlets give off branches, which

unite with similar twigs from other capillaries, and thus form a ramifying network.

A large number of such budding capillaries may sometimes be seen at the margin of a healing wound. The evidences of proliferation of the vascular endothelium—such as swelling of the cells and mitotic figures—may be abundant at twenty-four hours, and by thirty-six hours numerous young capillary buds may have been formed.

As their development proceeds, the new capillaries become surrounded by other cells, which form a sort of adventitia. Some of these may arise by proliferation of the capillary endothelium itself. Others may be the offspring of connective tissue cells, which also grow out alongside the capillaries. Or they may be derived from wandering cells of various kinds.

The new capillary network may extend by successive branching and formation of new loops to cover a wide area, if there is much exudation to be removed. And in cases of persistent granulation tissue, the capillaries may remain for a long time, as in the wall of a sinus. In many cases, the thinness of their walls, composed as it is of one layer of endothelium and a few adventitious cells, and the want of support around them, allow of ready dilatation and of rupture with consequent hæmorrhage.

But in most cases the early formed capillaries are not persistent. As the process of absorption becomes complete, most of them waste and disappear; and if any further vascularisation is needed, it is effected either by a new set of vessels or by a few which become more fully organised.

Proliferation of Connective Tissue.—In any case of injury demanding repair of any kind of connective tissue, signs of commencing proliferation of the cells may be seen in about twelve hours. The fibres have often become somewhat swollen and loosened, and here and there a cell shows some swelling and the formation of mitotic figures in the nucleus. In twenty-four to thirty-six hours these have become more abundant, but there is not such marked proliferation as that seen in the capillaries. The rapidity and degree of formation of new cells is in inverse ratio to that of the capillaries. When there is little disturbance, and small need for absorption, the formation of new vessels is of small amount, and the connective tissue growth predominates. Where there is much damage or irritation, the further development of the connective tissue may be retarded.

The new formation of the simpler connective tissues in repair is mainly by the direct outgrowth of protoplasmic processes from the cells. These penetrate the tissues in much the same way as the capillary buds, and develop into branching or flattened cells and reform connective tissues. Such outgrowths can be seen in severed

tendons and simple incised wounds, whose edges are in close apposition and free from septic or other irritation.

Commonly where inflammation has occurred, the process is less simple. Masses of cells are formed, some only of which are obviously the direct offspring of connective tissue corpuscles. The nature and relations of these will be considered later.

Epithelial Cells.—Simple epithelial and endothelial cells may replace those which have been damaged or destroyed, either growing over the surface from adjacent parts, or being reformed from some cells which have remained attached. In this way a serous membrane may again be coated with a healthy layer, a gland tubule may be relined, or a mucous or epidermic surface be again covered. If the supporting structure is much damaged or if inflammation continues, the renewed growth may be delayed until a more normal condition is restored. But even at an early period efforts may be made to reform the covering layer of cells. In healing skin wounds many epidermic cells grow over the edges of the wound at an early period, and perish or become entangled in the lymph. As soon as order is restored the growth rapidly covers the surface as a thin pellicle. Similar changes are seen in healing ulcers of mucous membranes—*e.g.*, of the intestine after typhoid fever. To what extent special epithelial structures or gland cells are repaired is a different question. In this respect there is great variety in different organs. In many cases the more special cells are not reformed, but are replaced by epithelium of simpler type.

CHAPTER X.

ABSORPTION AND CICATRISATION.

IN order to study more fully the steps of the healing process and to discuss some special points, it will be convenient to consider one example. The process of absorption and organisation of the fibrinous exudation upon a serous membrane such as the pericardium illustrates most of the commoner phenomena of wound-healing and cicatrisation.

Selecting an example where there is a large quantity of coagulated fibrin, and where the process of healing has been going on for a week or two, we may follow the successive steps in sections through the heart wall and the exudation. Similar changes occur on both serous layers. We may select the epicardium.

At the part furthest from the heart there will be coagulated fibrin, and the earlier steps may be seen, and as we advance towards the heart the older and more complete changes are found. By comparing the condition at each level with the changes seen in wounds or other healing structures where the duration is known, we can fix approximately the time needed for each successive step.

The changes are progressive and show no sharp line of division. But we may, for convenience, divide them arbitrarily into three or four layers or zones, proceeding from without inwards towards the heart.

1. In the most external zone we see unaltered or somewhat granular fibrin, with here and there one or two capillaries penetrating it, these becoming more abundant as we pass more deeply. Around the capillaries are a few cells, some being polymorph leucocytes, others mononucleated cells of various size. The fibrin immediately around has become somewhat softened and has altered in staining reactions.

2. More deeply the capillaries are more abundant; some are dilated, and may have ruptured. The spaces in the fibrin are larger, and the cells surrounding the vessels and migrating from them are more abundant and more varied in type. Some larger phagocytic cells are seen, and other more flattened cells, some of which may lie alongside the capillaries. Signs of proliferation of the capillary endothelium and the formation of two layers of cells may be present.

3. At a deeper level the fibrin has to a large extent disappeared, or here and there may be little masses, considerably altered in character, and evidently becoming rapidly absorbed. The capillaries are

partly surrounded by flattened cells, and between the vessels are masses of cells, some closely packed together, others branching and forming a more reticular structure. Here and there some fibrils may also be seen. This cellular structure corresponds with the "granulation tissue" of wound healing.

4. Nearer to the surface of the heart a fresh structure appears. At first are some long branching cells, and then layers of cells of much larger size, which on section appear spindle shaped with long processes, but are really flattened. These cells form bundles or layers, which lie more or less parallel to the surface of the heart, becoming denser from closer packing as we near the heart. These large flattened cells are the true "fibroblasts." As they grow, connective tissue fibres and laminæ are formed between them, and the cells become less distinct, until, when the fibrous laminæ have become dense, only the nuclei are visible. In other words, the cells form connective tissue corpuscles.

In this part of the structure the bloodvessels have become much less numerous. Here and there are seen vessels which run directly outwards from the heart, perforating the fibrous layers at right angles. They are more completely developed than the earlier capillary vessels, and form much larger loops.

At a later period these capillaries are also to a large extent obliterated, mainly by proliferation of their endothelium, or remain as very narrow channels. But it is not uncommon to find that some of them have anastomosed with those from the opposite serous surface, a fact which may be demonstrated by injections.

At its deepest part the newly formed tissue is firmly united with the thickened epicardium. To a large extent the outline of the normal surface has been obscured by the outgrowth of vessels and connective tissue, which are continuous with the newly formed structure on the surface. A similar cell growth and tissue formation has occurred within the epicardial structures, although many fat cells, nerve fibres, etc., may appear fairly normal.

Here and there, however, some of the pericardial endothelium may remain. In the early stages of inflammation the endothelial cells are partly detached, but some of them proliferate, and may send branching processes into the exudation. They may also take part in the formation of phagocytic cells, as in the peritoneum. As the process of healing becomes more advanced, the endothelium may again grow over the surface ; and where the inflammation has been less intense and persistent, or where there has been little fibrinous exudation, the normal endothelial covering may to a large extent be replaced. So that, in many cases, adhesions between the two layers of pericardium —as in other serous membranes—may be only partial, and may be almost wanting.

It will be understood that in many sections the processes are more irregularly distributed. We have described one in which the healing process has been continuous and uniform.

We may now consider some of these changes more fully, especially with reference to the origin and function of some of the structures mentioned.

The *capillaries* arise solely by budding from pre-existing capillaries. There is no evidence that they can, as in the embryo, originate in separate areas and subsequently unite with other capillaries. Nor is there any evidence of their origin from connective tissue corpuscles.

The cells found scattered in the more superficial parts of the fibrin are emigrated leucocytes. If bacteria or toxins are present, polymorph leucocytes will be present, and may be abundant. In tubercular exudations, lymphocytes may be found in large numbers. The other mononuclear cells have already been discussed. Those which are seen in the most superficial layers have probably emigrated from the capillaries.

The more abundant cellular masses corresponding to "granulation tissue" must be more fully considered. Of the cells which compose the mass many are irregularly rounded or polygonal, have a single nucleus which is often deeply stained, and a varying amount of cytoplasm. Others are more irregular and branching, their nuclei may be paler and may be more or less completely divided. A few are larger flattened or branching cells, more resembling connective tissue corpuscles. And lastly, there may be multinucleated or giant cells, although these are rarely seen in the pericardial exudation. Such cells are most constant and abundant when resistant substances such as bone, crystals, or foreign bodies such as ligatures require absorption ; or where, as in tuberculosis, special irritants are present.

That many of these cells may be present only for a time and for the completion of special absorptive or phagocytic reactions is very probable. Their possible origin from the blood or from other tissue cells has already been considered.

The more difficult question is whether they have any share in the production of permanent tissue, especially of connective tissues, or whether, if they do not themselves form tissue, they may remain as free cells, such as are often present in connective tissue, or may aid in the formation of endothelium of lymph spaces.

At present these questions can hardly be considered settled. Maximow, whose work upon the subject is the most exhaustive recent research, gives to the mononucleated cells which resemble large lymphocytes and hyaline leucocytes the name of *polyblasts*. He considers that many can be definitely shown to have emigrated from the blood, although this is not their sole source. They do not, he be-

lieves, take any important share in the formation of connective tissue, although they may, where true fibroblasts are present, take some part, or may even, although rarely, themselves become fibroblasts. To a large extent they either disappear, or remain as free cells amongst the fibres. On the other hand, Metchnikoff maintains that such cells do undoubtedly develop into connective tissue—for example, in the formation of the granulation tissue of tuberculous growths.

It seems probable that under certain conditions cells corresponding to the polyblasts of Maximow do develop into a sort of connective tissue, but that they are not the usual source of the definite fibrous tissue of repair. In many conditions of interstitial inflammation, we find what is called "small-celled infiltration." The "small cells" are identical in character with mononuclear leucocytes and the allied forms which are seen in the exudation at the later periods of inflammation. Where there is persistent irritation, and especially in the presence of bacterial irritants, such cells may develop a type of connective tissue closely resembling lymph-gland or "adenoid" tissue. At later periods the cells may partly disappear, the fibrillar structure, somewhat thickened, alone remaining. In some cases, such adenoid tissue appears to be formed around a centre of infection as a sort of protective barrier to prevent its further spread.

Where, as appears sometimes to be the case, such cells settle down amongst newly formed connective tissue, they seem to act rather as lymphatic structures than as formative connective tissue cells. Since these cells have their origin in the cells of lymph-gland structures and in lymphatic and other endothelium, it is not unreasonable to regard them as still retaining their capacity for the new formation of similar tissue.

Multinucleated or *Giant* Cells.—Multinucleated cells are often present in granulation tissue, but rarely reach any large size except in special conditions. In certain processes of bone formation and removal they may be numerous, especially where absorption or remodelling are being carried on. Where hard bodies are attacked, *e.g.*, a mass of urate crystals in the subcutaneous tissue in gout, or foreign bodies, such as silk ligatures, etc., they may be well developed. Their maximum growth and peculiar secondary changes are best seen in tubercle, but here they acquire special characters from the action of the toxins, such as their central degeneration and the dense fibrous investment which may surround them.

The mode of formation of giant cells is much disputed. Probably the modes observed in tubercle cannot be taken as evidence in other conditions. No experimental proof has been given of their origin in wound-healing from lymphatic or vascular endothelium, sources which can be readily demonstrated in tuberculosis. Ordinarily, they appear to arise either by fusion of some mononuclear phagocytes into a sort

of plasmodium, or more rarely by the proliferation of one endothelial cell, *e.g.*, in the peritoneum. The latter mode of origin is denied by some.

Fibroblastic Cells.—The large flattened cells which form layers in the deeper part of the organising exudation are derived mainly, if not entirely, from pre-existing connective tissue cells. As seen in the vertical section of the pericardium they appear spindle-shaped. Similar cells are found uniting the edges of wounds and gradually forming interlacing fibres, the appearance in a section resembling that of the stitches of darning. The type of connective tissue to which they correspond is the ordinary white fibrous tissue of fasciæ, tendons, etc. Where other kinds of connective tissue are formed, the character of the fibroblastic cells varies with the special type.

In their earlier stages such fibroblastic cells may be difficult to distinguish from other rounded cells of granulation tissue. But they can often be seen to develop as offshoots from other cells, taking at first the form of long protoplasmic threads. Their resemblance to new capillary buds at this period has no doubt led to the view that the connective tissue is sometimes derived from the vascular outgrowths.

The mode of formation of the connective tissue filaments which lie between these cells has been disputed. Formerly they were regarded as a sort of excretion or "periplast," but investigation by more recent methods supports the view that they originate in delicate fibrils which are formed within the cytoplasm, which subsequently form masses of densely packed fibrils closely welded together.

Whatever the mode of formation, it appears to be similar to that by which white fibrous tissue is formed during normal growth.

A general idea of the rate of healing may be gained from a series of small incised wounds in dogs. The period at which some signs of swelling and mitosis may be seen in connective tissue corpuscles is, as we have said, about 12 hours; but in wound-healing definite proliferation is not usually seen till about 36 hours, and then chiefly around the vessels. In 48 hours the growth has become much more marked, and long branching processes are seen shooting out. Between 70 and 75 hours there are not only masses of undifferentiated cells, but some flattened cells are forming regular layers. In about 100 hours numerous bundles of cells are seen uniting the edges and interlacing across the wound. In 7 days many of the bundles have become fibrous, and the earlier capillaries may have disappeared. New epidermic cells may be abundant in 48 hours, and may entirely cover the surface in 100 to 120 hours.

Healing in Bone.—Whilst the changes described as following pericarditis serve as a type of the general processes of absorption

and temporary healing or cicatrisation, these may to some extent be modified by special conditions, especially where some specialised type of connective tissue is concerned. Thus we find that in the repair of fractures a considerable part of the granulation tissue undergoes changes resembling those of ossification, the cells becoming transformed into osteoblasts, and the intercellular substance altering in character and becoming impregnated with lime salts. The "callus" thus formed is subsequently absorbed and replaced by more regularly formed bone with definite Haversian systems. This permanent bone is usually formed in the same way as in regular ossification, and the new bone is so arranged that its laminæ and trabeculæ are adapted to the new conditions of support or strain.

One fact of great interest is that in some parts of the granulation tissue formed from the periosteum in the repair of fracture in the lower animals, nodules of cartilage are produced, and in these the true ossification occurs later. It has been questioned whether this can occur in man; but since a like transformation of periosteal tissue to cartilage often occurs in other pathological conditions, it must be regarded as possible, although opportunities for observing the change in man must be very rare.

Healing in Vessels.—In the closure of vessels and the absorption of thrombi special changes occur which are due to the intervention of the vascular endothelium. This is well seen in the case of the thrombi which may be formed at the site of ligature.

The endothelium grows over the surface of the thrombus, forming a complete covering. As the vessel contracts upon the clot, the two layers of endothelium grow together. Where there are chinks between a thrombus and the vessel wall, endothelium also covers the detached part, and if a parietal thrombus contracts and the lumen of the vessel is thus reopened, the endothelium forms a continuous coating, and the only result of the thrombus is a thickened patch at one side of the vessel. Such restoration is commoner in arteries than in veins. To what extent the endothelium of the vessel aids in direct absorption, and whether to any large extent it penetrates the clot, are less certain. The endothelial cells in contact with the clot often show marked proliferation, and contain remains of blood pigment. Probably they may also penetrate the clot, and may possibly form new capillaries within it.

But the masses of cells which press upon and aid the absorption of the thrombus are to a large extent formed by the growth of cells of the intima, together with those of the endothelium.

Within two or three days after ligature of an artery, irregular thickenings of the intima, looking like buds on section, are seen pressing upon the thrombus. At first they appear to be devoid of vessels,

but as they enlarge they become distinctly vascularised by the penetration of vessels which grow into them from the vasa vasorum. That this is their source can sometimes be demonstrated in fortunate sections which happen to pass through the entire length of these vessels.

In many cases the thrombus is completely absorbed, the buds from the opposite walls coalesce, the tissue becomes more fibrous and contracts ; but where the vessel is large, especially in veins, the process of absorption may be slow, and the more central part of the thrombus degenerates and becomes fatty or even partially calcified before it can be absorbed. In such cases the more central part may be found to be penetrated by a few capillaries only, and some multinucleated cells may be formed in contact with the degenerated remnants.

In the fibrous tissue which is formed we do not see large fibroblastic cells arranged in layers as in wounds ; the cells are smaller and more branching, and the fibres interlace irregularly.

In other tissues, whilst the same general principles are maintained, the nature of the fibrous tissue will be found to vary with that of the organ or structure concerned.

"Interstitial" and "Parenchymatous" Inflammations.—To some extent the changes found in "Interstitial inflammations" are similar to those in cicatrisation. The fibrous overgrowth occurs especially along the lines of normal fibrous tissue, and is often extensive in that which surrounds the vessels. But it must be remembered that such interstitial and chronic "inflammatory" changes may be merely hyperplasias due to some special strain, or may result from the action of chronic infective irritants. Or they may be merely the associates of chronic degenerative or absorptive changes analogous to senile fibrous atrophy. In other words, they are not, strictly speaking, "inflammatory" at all.

"Parenchymatous" inflammation is sometimes contrasted with interstitial. In the former, the special functioning cells—such as gland-cells, muscle fibres, and so on—are especially involved. Under this name a variety of changes are included. Degenerative changes due to the direct action of toxins, decay and degeneration, whether following disuse or altered metabolism or impaired vascular supply, are all included under this title.

That purely parenchymatous changes may occur from the action of some toxins has already been stated. But in nearly all instances of a socalled subacute or chronic parenchymatous inflammation, there is no such limitation of the change to the special cells of an organ. The supporting framework and the vessels are necessarily involved to a greater or less degree ; and it is often difficult to determine which group of structures has been first affected.

Permanent Repair and Restoration of Tissues.—Each group of tissues, whether general or special, possesses powers of restoration after damage or destruction. The capacity is more highly developed in the lower animals, and is greater in young and growing tissues. Whilst there is, as we have seen, a great power of repair in the connective and vascular tissues, the new tissue often fails to attain the perfect type of the normal.

In the other more specialised tissues, the general law holds good that they are replaced only by growth from tissue of the same kind. The method of reformation is usually the same as that by which they grow normally or increase in order to meet an increased functional demand. The study of this subject can, therefore, better be associated with that of the processes of Hypertrophy and Neoplasia.

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