Inflammation: an introduction to the study of pathology.

INFLAMMATION

recognising the relationship between phenomena, to deduce the laws which underlie and determine the individual cases of diseases—then, obviously, the study of the inflammatory process is the natural starting-point for a right understanding of that science and what it can teach us.

These considerations governed my treatment of the subject when, ten years ago, I was invited by Professor Allbutt to write the article on Inflammation for his new *System of Medicine*. I strove then to bring together all the data known to me bearing upon the subject of the reaction to local injury, and, cutting myself free from all the schools and established doctrines, I endeavoured conscientiously to select those facts which could not be gainsaid, and to draw from them the deductions which seemed most rational. There was here no attempt to bring forward anything that was new or that had not been already recognised by individual workers. At most it might be said that many of the facts brought forward, as also the method of approaching the subject, were new to the text-books. It has been a source of profound gratification that this article has from so many sources been accepted as authoritative, and that, when nine years later I came to revise it in the light of the abundant observations which had been published in the meantime, while there was much that might be added in amplification, there was little to correct. The teaching which in 1896 was to a certain extent novel is now in 1906 widely accepted. The revised article is here printed in book form in the hope that it may prove serviceable to the practitioner wishing to keep abreast of recent

place, that the nucleus plays an important part in this reaction. If, as Metchnikoff has shown, one of the larger amœbæ be cut in two, the region of injury becomes rapidly indistinguishable—the protoplasm of each moiety closes up, leaving no mark or scar: but of the two parts that which retains the nucleus grows and proliferates; the other disintegrates in a longer or shorter time. As I have shown in a recent address (6), from every consideration we are forced to regard the nucleus as the dominant constituent of the cell, controlling its higher activities; the nucleus is essential for continued growth and for reproduction. Or injury may induce changes in the protoplasm of the entire amœba: thus Miss Greenwood (7) points out that, without necessarily bringing about death, the interrupted current or an aqueous solution of thymol leads to a process of exudation or extrusion of clear hyaline spheres, or of spheres holding crystals and granules, from the surface of the organism—a process resembling that occasionally seen in the cells of an inflammatory area in higher animals. Nor is this all; apart from changes in the structure of these unicellular animals, differences may be seen in the behaviour of amœbæ towards foreign bodies. It would seem, according to Le Dantec (8), that amœbæ ingest non-irritating foreign substances indifferently, provided they be sufficiently small. Around each particle so ingested a vacuole is formed, and the fluid in this becomes increasingly acid, and at the same time digestive. Krukenberg (9), Reinke (10), and Miss Greenwood have conclusively proved these and similar food vacuoles in the amœba and other Protozoa to contain a pepsin or digestive ferment, which, as Le Dantec has shown by very delicate tests, exerts its action in an acid medium (the general protoplasm of the cell-body being alkaline); this digestive process leads to the solution of food-stuffs,

importance in connexion with the origin of certain of the pus-cells in the suppurative process of higher animals. The *third stage* is that of repair, of proliferation of the injured epithelium, return of the fixed cells of the tissue to their previous state, and emigration of the wandering cells.

A very similar progress of events occurs if the experiment be repeated upon the tail-fin of the young Newt. The same rapid alteration in the large branched connective-tissue cells (which become vacuolated as their long processes are drawn in and shortened), and the same immigration of motile cells from the surrounding connective tissue are to be seen; but here we now find the earliest evidence of vascular participation, for, according to Metchnikoff, complete arrest of the circulation may occur in the nearest vascular loop. By the next day the parts have returned to the normal condition.

If from these cases we pass to mild inflammatory disturbances affecting the non-vascular regions of animals far higher in the scale, we again discover a like process of events. For this purpose *the cornea* affords the tissue of election; in health it is absolutely non-vascular, perfectly transparent, and so thin that it can readily be examined microscopically. The cornea of mammalia, and indeed of vertebrates in general, is formed of fibres which run in layers parallel to the surface. These fibres, while roughly arranged side by side and parallel to one another in any given layer, are placed at an angle to the fibres of the layers above and below. Although free from blood-vessels the cornea is far from being devoid of channels along which lymph freely passes. Between the several layers there exist spaces in which lie the flattened connective-tissue cells of the organ; and, by means of numerous fine channels, these spaces around the cells are connected with similar

selves in the injured area purely on their own initiative; and that there must be an attraction, a chemiotaxis or chemiotropism, leading them actively to approach the region of cell-destruction.

(iii.) Or we may proceed a step further. A fairly severe aseptic injury can be produced by cauterising the centre of the cornea. In thus treating the pigeon's cornea Goecke (21) noted that the wandering of cells towards the damaged area is first visible twelve hours after the injury, and then proceeds from the periphery. Obviously the wandering cells are white blood-corpuscles, and pass from the peripheral vessels. In twenty-four hours the process and the accumulation of round cells reach their climax. Some of the new-comers break up, others, according to Goecke, show signs of division. But soon these foreign cells commence to wander away, and at the end of thirty-six hours scarce any are left.

Turning to the fixed cells of the part, it is deserving of note that, before ever a leucocyte has reached the injured area, the corneal corpuscles, bordering upon the area of cauterisation, show evident signs of enlargement and growth. On the second day there are indications of active proliferation; and these newly formed corneal corpuscles behave exactly like certain white blood-corpuscles, from which they are indistinguishable. The vexed question of the relative part played by the wandering white corpuscles of the blood and wandering young connective-tissue cells will be touched upon later. It is, however, well to impress upon the reader that, at a certain stage, what we may term histogenous and hæmatogenous wandering cells are wholly indistinguishable by our present methods of study. The fight has been particularly bitter regarding these cells in connexion with this very subject of experimental keratitis.

(iv.) The observations made upon these three more

simple cases help us materially to understand the series of events which occur in more intense inflammation of the cornea, such as that produced by injuring the surface and causing the entrance into the injured region of a small quantity of a pure culture of the pyococcus aureus. This may be accomplished by injecting the culture into the centre of the healthy cornea by means of the needle of a Pravaz syringe (Jacobs) (22). The micrococci so introduced grow rapidly, the growth so extending along the lymph-spaces that a branched mass of the microbes is produced, having the spot of inoculation as centre. Around the growth as it extends may be seen a sharply marked area in which the corneal corpuscles show evidences of degeneration; the nuclei stain faintly, and the corpuscles, speaking generally, have a shrunken appearance. Here, again, the first effect of a microbic, as of a simple chemical injury, is to bring about degeneration of the fixed cells of the tissue. Within eighteen hours the zone of proliferating cocci and cell-degeneration is well marked; and now the second stage begins to be clearly manifest, namely, the determination of leucocytes to the seat of injury. Within twenty-four hours there is a dense packing of these corpuscles around the central degenerated area, and great numbers of leucocytes may be seen converging along the lymph-spaces from the periphery of the cornea. This is the second stage of the process, the first stage of obvious reaction to the injury inflicted by the invading micro-organisms. If, as by Cohnheim[1] (23) in his original experiments upon the injury to the cornea, more careful examination be made into the stages of the determination of leucocytes, it can be seen that this determination is closely related to

[1] There can be no question that Cohnheim in his experiments induced not a simple keratitis but one which in the absence of aseptic precautions rapidly became infective and suppurative.

changes set up in the veins at the periphery of the cornea; they become more prominent, the region has a congested appearance, the smaller as well as the larger vessels are dilated, and there is abundant evidence that the leucocytes are passing out from the contained blood into the surrounding lymph-spaces. Indeed the accumulation of leucocytes shows itself first at the periphery of the cornea near the vessels, and gradually approaches the region of injury. Into the mechanism of this diapedesis, and into a fuller description of the changes that take place in the blood-current in these distended vessels, I shall enter later when discussing the changes in highly vascular regions. Suffice it to say here that no distinction can be made out between the behaviour of the leucocytes in the previous experiment, when they entered the wounded area from the external surface, and in this where the majority find their entrance from the blood; as in the previous case the part played was evidently active, so must it be here also. We cannot arrive at any other conclusion than that some attractive force leads to their determination towards the inflammatory focus. It is the polymorphonuclear leucocytes which at first most actively migrate. As Councilman (24) points out, in experimental pyococcic inflammation, as early as fifteen minutes after inoculation of the centre of the cornea a greater number than usual is seen in the conjunctiva. A more granular, more sluggishly amœboid form follows, most numerous in eighteen to twenty-four hours, while lymphocytes are not visible until the fourth day, and then do not so much pass out of the vessels as from the sheath of lymphoid tissue surrounding them. As we can easily show, by repeating the experiment, many of these leucocytes take up and contain numerous cocci, while other cocci remain free in the tissue-spaces. Many of the leucocytes degenerate and present a broken-down

appearance; and, as at the same time an increasing area of the corneal tissue becomes disintegrated, an *ulcer* appears. According to the virulence of the culture and the reaction on the part of the organism, the process may now extend, a larger and larger portion of the corneal tissue becoming affected; or, on the other hand, there may

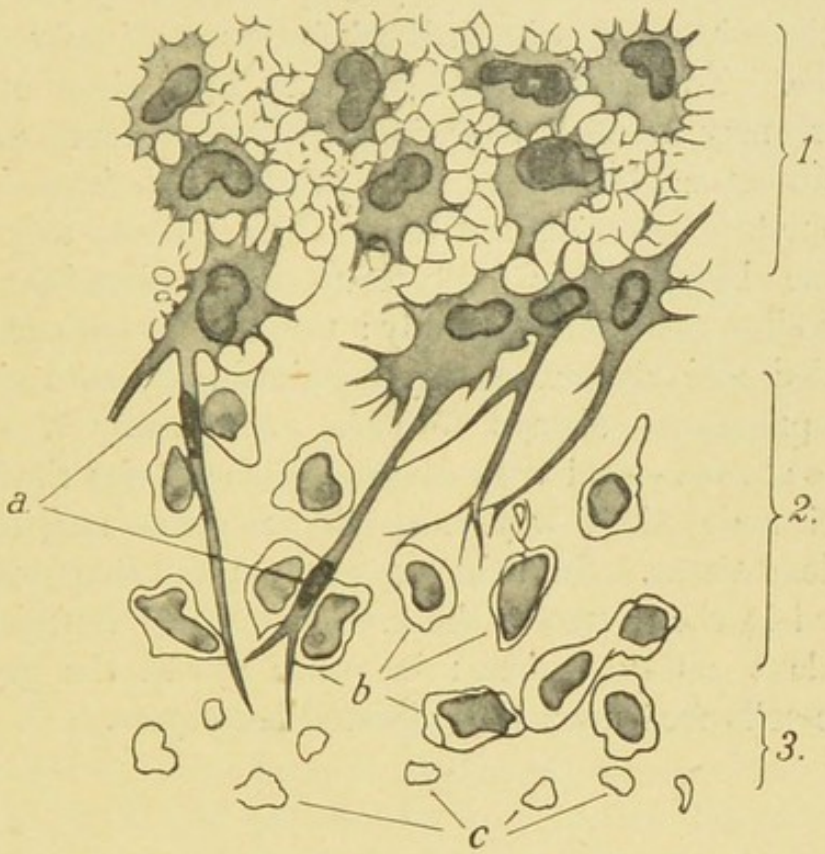

FIG. 3.—Mild grade of keratitis, commencing regeneration after forty-eight hours. 1. Peripheral zone of corneal corpuscles, showing enlargement with nuclear multiplication. 2. Zone of degenerating granular corneal cells (*b*). 3. More central area of cells (*c*) destroyed and broken up by the action of the caustic. *a*, Processes from proliferating corneal cells, with nuclei, advancing into region of irritation and degeneration.—After SENFTLEBEN.

be an arrest of the progress, the massing of the leucocytes preventing, as a barrier, the further extension of the micrococci into the lymph-spaces;[1] while at the same time there is an advance of newly formed capillary vessels into the previously non-vascular tissue. It is to be noticed that the blood-vessels at the periphery of the cornea are

[1] Into the details of this action I shall enter more fully later.

oozing by not completely closing one end of such a wound, and inserting there temporarily a "drain" of sterilised gauze, so that this fluid escapes immediately and primary union is facilitated.

Study of sections in these cases shows that the main part is played by the pre-existing cells of the part; of these a certain number (not so many as might *à priori* be expected) are destroyed immediately, and show all the signs of disintegration; a number relatively large have been injured only, their nuclei remaining intact, though their processes or some portions of the cell-bodies have been cut through. It is difficult to determine these injuries in the small cells of the cutaneous tissues; they are better seen in the peritoneum when slight inflammatory changes have there been induced. It can, however, be made out that the cells in the immediate neighbourhood of the wound became enlarged, and, without showing signs of division, prolong themselves (that is to say, send out prolongations) into the region of the provisional fibrinous cicatrix. In this way, before the end of the second day, there may be a more or less complete replacement of the primary unorganised cementing substance by organised growing tissue,—formed, in the first place, by the interlacing of processes from the neighbouring cells; in the second, and later, by a multiplication of these cells, together with a development of new capillaries, few in number, which branch off from the slightly congested vessels in the neighbourhood. Thus in this case the process of repair is characteristically associated with hypertrophy and the new growth of the fixed cells of the tissue; while vascular changes, exudation, and leucocytosis are relatively little marked. I have, however, never come across a case in which they have been entirely absent, save when the section has been truly extravascular—that is to say, when it has not penetrated into

the vascular region of the skin, and has affected only the epidermis and outermost layers of the dermis. In such cases the response to injury may show itself purely as a proliferation of the epithelial cells. As I have said, observations of this nature labour under the disadvantage that they must of necessity be discontinuous. I bring them in at this point, inasmuch as they represent the mildest condition of the inflammatory reaction. I have not personally observed this series of changes in tissues which permit of continued study under aseptic conditions; neither am I acquainted with any observations wholly fulfilling these conditions—made, that is to say, upon transparent vascular tissues subjected to the mildest aseptic injury and examined continuously under the microscope.

(ii.) The response to injury in the cases just mentioned was of the slightest. Let us now pass on to cases in which it becomes more pronounced; and in order to continue the comparative study of inflammation I would first describe the series of *events in a highly vascular and transparent region* in a low vertebrate animal, namely, in the tadpole's tail. If this be injured, either by the application of a caustic or by the introduction of a foreign inert body into its substance, a definite advance upon what was recognisable in the case of the axolotl, for example, is to be made out. Here the tail is very vascular, the wandering cells in the connective tissue are very few in number, while the blood is fairly rich in leucocytes, which are small relatively to the size of the vessels. The results of injury are a congestion of the vessels, noticeable within fifteen minutes, and a well-marked determination of leucocytes to the injured region. These cells, in the main, pass out from the vessels; the few leucocytes pre-existing in the tissue appear to play a very small part. Compared with the axolotl experiment

possibly he has misinterpreted certain of the appearances. On the whole, however, he draws a full and accurate picture of the successive stages of suppurative inflammation, and I may defer discussion to a later review of the action of the leucocytes and of the formation of fibrous tissue respectively.

However, before leaving this general description of the series of anatomical changes induced by injury, there is another phase of the inflammatory process set up by pathogenetic micro-organisms which must not be passed over—I refer to those cases in which, instead of ending in repair, there is *extension and generalised disease.* The stages preceding extension vary with the nature of the microbe; thus, in some cases, the reaction to the invasion of the microbe is mainly leucocytic (as with inoculations of the micrococci of suppuration), in others it is mainly exudative or serous, the congestion of the vessels being followed by abundant exudation of serum into the tissues. This is the case in inoculation of animals—such as rabbits, guinea-pigs, and fowls—with cultures of micro-organisms which are peculiarly virulent in their behaviour towards these animals. Such a serous or exudative inflammation is, for instance, well seen if the vibrio Metchnikovi be inoculated into the pectoral muscles of a fowl. Within twelve hours, it may be, the seat of inoculation becomes greatly swollen, and on section is found reddened and congested; while from it drains an abundance of relatively clear, faintly reddish serum containing but few leucocytes.

In such a case as this the micro-organisms appear to pass with ease from the centre of infection into the surrounding tissues, and thence into the lymphatics and general circulation, whence they may be obtained within twenty-four hours. Where there has been a well-marked abscess-formation in the region of invasion there, as

the arrest of pathogenetic microbes within the capillaries is often associated with a small accumulation of intravascular leucocytes and with degenerative changes in the vascular endothelium, the metastatic abscess, as such, forms not by accumulation of leucocytes in the occluded vessel, but around it; the leucocytes migrating from surrounding capillaries.

PART II

THE FACTORS IN THE INFLAMMATORY PROCESS

I.—THE PART PLAYED BY THE LEUCOCYTES

CHAPTER VIII

THE VARIETIES AND CLASSIFICATION OF THE LEUCOCYTES

As I have already shown, there is more than one form of leucocyte in the mammalian organism, and these several forms evidently possess different attributes, and act differently in the reaction to injury. Inasmuch as they have been variously classified—so variously, in fact, that it is often far from easy to collate the various descriptions and to discuss the forms distinguished by one observer in the terms of another—it is necessary to give the chief classifications of them and their relations.

The first to discriminate between the forms of white corpuscles in the blood was Wharton Jones (31) so long ago as 1846. He drew a distinction between

A. Granule cells—Finely and coarsely granular.
B. "Nucleated" cells—Non-granular.

These observations were confirmed and advanced by Max Schultze (32), who made out the following forms :—

1. Small round cells with round nucleus and little clear protoplasm.
2. Larger cells with round nucleus and more clear protoplasm.
3. Cells with finely granular protoplasm, and one, two, or more nuclei.
4. Cells with coarse granules in the protoplasm.

The distinctions drawn were, so far, purely morphological; and very little notice was taken of these varieties for a long period until Ehrlich (33), in a notable series of papers extending from 1878 to 1887, drew attention to the fact that the wandering cells of the organism react diversely towards the different aniline dyes, and possess diverse tinctorial affinities indicating chemical differences in the nature of certain constituents of the cell bodies. The granules of the previous observers were found to be variously affected by the dyes employed; they were shown not to be fatty, but—as Ehrlich put it—of the nature of a glandular excretion;[1] and comparing the effects of the two groups of aniline colours—that in which the dye is associated with the acid constituent of the salt and that wherein the dye forms the base (the "acid" and "basic" aniline dyes respectively)—he made out the existence of five forms of granulation associated with as many varieties of wandering cells. His table of cells, according to their granulation, is as follows:—

α. granulation—Eosinophil—Cells frequent in horse's blood, present constantly in small numbers in human blood; numerous in medulla of bones of rabbits, dogs, guinea-pigs, etc. Stain deeply with acid aniline dyes. Granules large and coarse.

β. granulation—Amphophil—Cells frequent in rabbits and guinea-pigs in blood; present also in medulla of bones. Stain both with acid and basic dyes. Granules fine.

γ. granulation—Basophil—Large cells found in the connective tissue, from the frog upwards, "Mastzellen"; in blood of man only in certain cases of leukæmia. Stain only with basic dyes. Granules coarse.

δ. granulation—Fine Basophil—The "mononuclear" leucocyte of human blood. Granulation fine. Stain with basic dyes.

[1] J. Weiss has studied the micro-chemical reactions of the eosinophilous granules, and concludes that they are of albuminoid nature; since they were found not to be digested in gastric juice, he would ally them with the nucleins.

have the great advantage that by them it is possible to differentiate tinctorially the different forms of leucocytes present in the inflamed tissues. Schridde also sees every grade of development from the perivascular lymphocyte to the plasma-cell, though no relation between hæmal

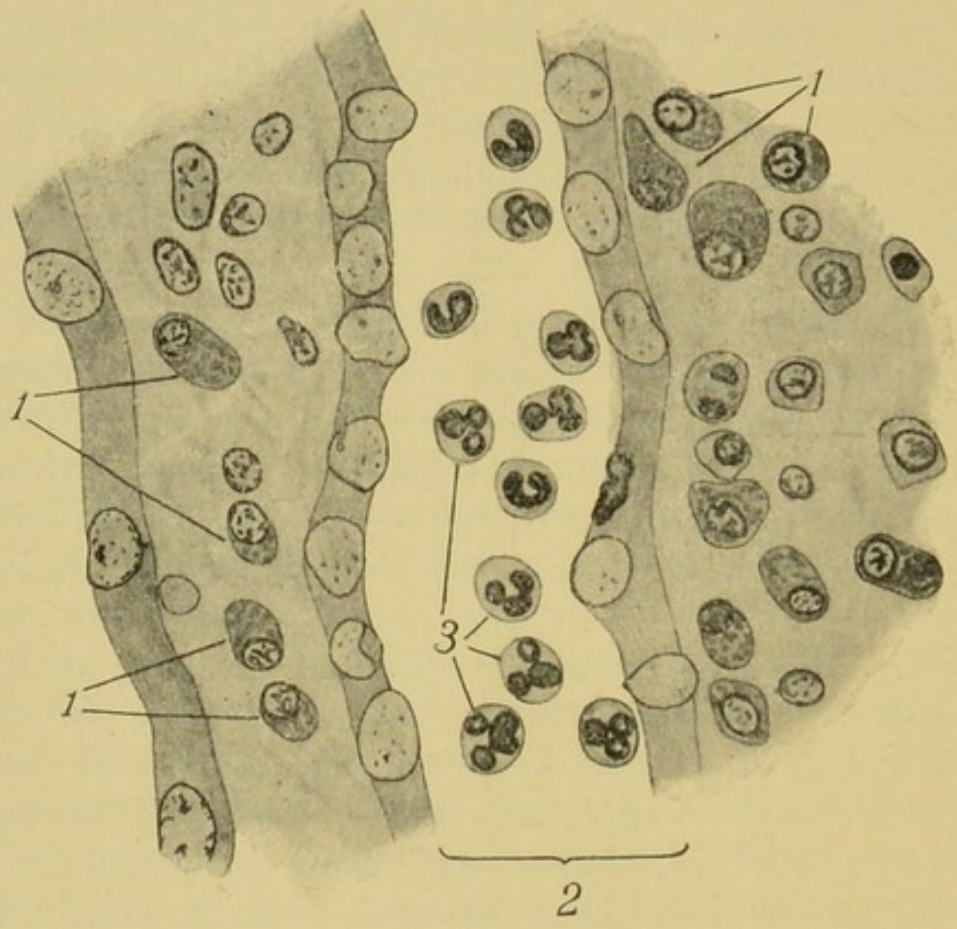

FIG. 5.—From a case of acute interstitial nephritis (man), drawn by camera lucida, $\frac{1}{12}$ Zeiss, ocular 2. Showing plasma-cells (1) in the interstitial tissue between the tubules. The epithelium of the middle tubule (2) is degenerated; the tubule contains polymorphonuclear leucocytes (3).—After COUNCILMAN.

leucocytes and this form of cell. He, however, goes further and finds three types of plasma-cells. The commonest of these is that with neutrophil granulations or weakly oxyphil. Rarer are those with acidophil or oxyphil granules (in which the oxyphilic character is somewhat less pronounced than is the case with the ordinary eosinophils); while the rarest of all are those

give origin, by direct division, to large, clear, mononuclear cells or leucocytes. These may be derived from the peritoneum generally, but the omentum is especially active in this respect. He identifies these cells with Metchnikoff's "macrophages," and Beattie has made a full study of the same. They are, according to him, the most characteristic form of leucocyte seen in peritoneal inflammation. After non-fatal peritoneal injection of the B. coli in the guinea-pig, he first observed an increase in the polymorphonuclear cells of the peritoneal fluid, which begins three hours after the injection and reaches its maximum in from six to thirty hours. Mononuclear leucocytes are first seen to increase in number about the eighth hour. On an average these are in numbers equal to or even greater than are the polymorphonuclears. From now onwards (in non-fatal as distinguished from fatal cases) they definitely preponderate. As during the next two days resolution proceeds, the polymorphonuclears become fewer and fewer until the few cells present in the exudate are almost entirely mononuclear. These mononuclear cells (the *hyaline* cells of the late Prof. Kanthack and Mr. Hardy, and of other observers) vary in size. According to Beattie there is every transition from small cells resembling lymphocytes with a round or kidney-shaped nucleus rich in chromatin, and with scanty protoplasm, up to cells four or five times as large, having a rounded or kidney-shaped nucleus which does not stain nearly as deeply as that of the smaller forms, but shows deeply-staining nodes of chromatin in the nuclear network. These larger cells have abundant cytoplasm, often showing extensive, fine vacuolation. In these respects the cells are identical with the swollen endothelial cells of the omentum. Nor are they merely passive agents—cells cast off in a moribund condition from the inflamed

and then detached from the wall, and various stages of the separation can be made out. Study of the sinuses of the spleen in typhoid (Mallory) shows the process very well; the lining cells swell to three or four times their original size and become separated, so that a sinus may become distended with these free cells. As they swell, their cytoplasm becomes vacuolated, and polymorphonuclears and other cells are seen to be ingested. Without entering into a discussion of the finer details of nuclear staining (*vide* Beattie's article) I would point out that the evidence now accumulating tends to the conclusion that Ehrlich's mononucleated non-granular

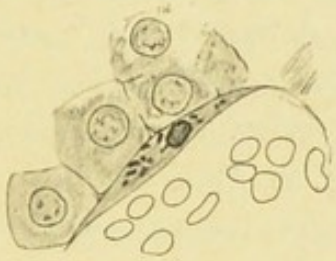

FIG. 7.—Endothelial cell of capillary of rabbit's liver, fifteen minutes after intravenous inoculation of culture of B. coli, showing bacilli ingested and undergoing disintegration. (The whole of the nucleus is not here in focus.)

blood-cells (33) are of endothelial origin.[1] Contrary, therefore, to Gulland, Saxer, and Uskow (55), I am of opinion that there is far from being a common origin for all the white blood-corpuscles; one group at least is of endothelial origin, just as another is of lymphoblastic. And thus, recognising that the former are capable of migration, it must be admitted that cells of this order seen in exudates may be of both local and hæmatogenous source.

A word may here be said regarding the fate of these large mononuclear cells. Evidence seems to show that

[1] With these I do not include the neutrophilic and other myelocytes seen in the blood in certain disorders: they, it need scarcely be said, are cells of a different order, clearly derived from the bone-marrow.

they do not, to any large extent, wander back into the blood-vessels. Various stages of degeneration of these cells may be recognised in the later stages of peritoneal inflammation; they tend to be extensively vacuolated, and thus the conclusion is that they in the main eventually disintegrate locally. While this appears to be true in connexion with bacterial inflammations, where more inert substances are taken up they clearly are capable of wandering in considerable numbers back into the circulation. Thus Metchnikoff points out that, if washed nucleated red corpuscles of the frog be injected into the peritoneum of a warm-blooded animal, large mononuclear cells containing the easily recognisable remains of the corpuscles can be detected after several days in the mesenteric glands, the vessels of the liver, and the spleen. Cells of the same order, which have not become free, evidently, according to Ranvier, take an active part in the formation of peritoneal adhesions. Muscatello, Graser, and Borst (56) unite in the opinion that the endothelium of serous surfaces can form connective tissue, though of late von Brunn (57) and Mönckeberg have strongly contested this view, at least as regards serous endothelial cells. Their objections are not, to me, wholly convincing. More recently Baumgarten (58) has brought forward what appears to be definite evidence that vascular endothelium under mild grades of irritation gives rise to fibroblasts and connective tissue.

Epithelial Leucocytes.—Mononuclear cells of endothelial origin seen in inflammation of solid tissues, noticeably in tubercle formation, are, from their general appearance, often spoken of as epithelioid cells. But if we employ the term epithelium, as is usual in English-speaking countries, to denote membranes derived from the primitive epiblast or hypoblast, this usage is apt to cause confusion. There are, however, true epithelioid

CHAPTER XI

SUMMARY OF PROPERTIES OF DIFFERENT FORMS OF LEUCOCYTES

AND here, though in so doing I to some extent anticipate and refer to matters to be discussed in some detail later, it is most convenient to sum up briefly the facts determined regarding the parts played by these various forms in inflammation.

Polymorphonuclear Leucocyte.—In acute inflammation, when the irritant is not too intense, this is the form most often attracted to the focus of irritation, migrating most rapidly and in the greatest numbers. It is the characteristic pus cell; is actively phagocytic, particularly for bacteria; secretes bodies of the nature of enzymes and, either while active or in the process of dissolution, liberates antitoxic and antibacterial substances. It may—(1) wander back into the lymphatics or blood-vessels; (2) undergo dissolution and disintegration *in situ*; or (3) be ingested by the proliferating tissue-cells and mononuclear leucocytes. It has nothing to do with tissue formation (66).

Eosinophil Leucocyte.—This is also actively attracted, and that at an early period, towards the inflammatory focus, migrating from the surrounding tissues and also from the vessels, but it is never the preponderating cell present. In peritoneal inflammations it is found in great numbers in the omental vessels, and in sub-acute and chronic inflammations of certain tissues, such as the skin, may also be relatively abundant. Very rarely is it seen to ingest bacteria, so that, to all intents and purposes, it is non-phagocytic. Kanthack and Hardy (36) and Hardy and Wesbrook (67) have ascribed a secretory activity to these cells, associated with the

by Gabritchewsky (76) in diphtheria. As Roux remarks: "Ils ont fait de leur mieux en englobant les microbes,

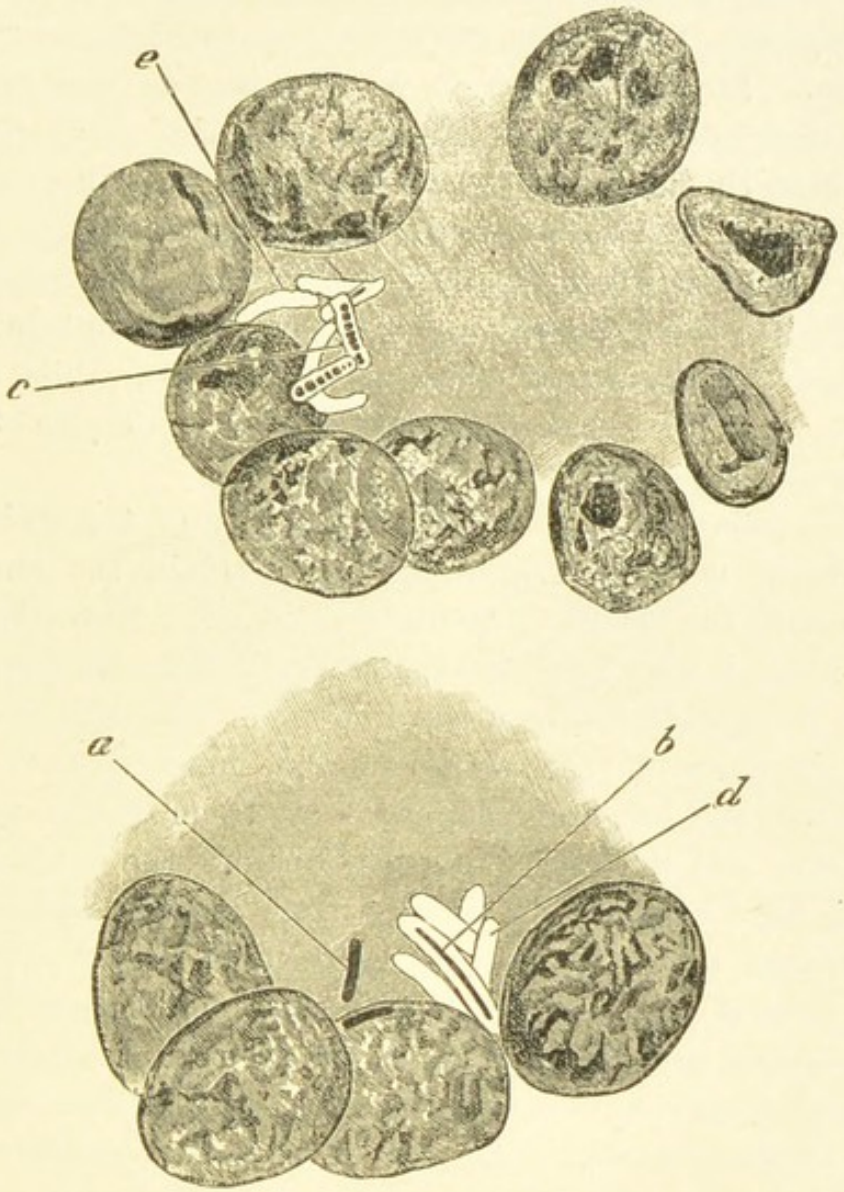

FIG. 10.—Two giant-cells, seen under high magnification (× 1515 diam.), from a rodent, the spermophile, inoculated with tuberculosis, to show stages in the destruction of the bacilli. *a*, unaltered bacillus; *b*, bacillus staining badly, and with greatly thickened capsule; *c*, bacillus granular and breaking up; *d e*, "shadows."—METCHNIKOFF.

mais ceux-ci se sont adaptés au milieu intérieur des cellules, et ils ont triomphés" (77).

In other less acute diseases, such as gonorrhœa, and in chronic maladies, such as in tuberculosis, leprosy, and

inflammation has been induced in both ears; in both the vessels round the seat of inoculation are greatly congested, but whereas at the seat of inoculation of the virulent organism there is a serous inflammation so intense that the skin is raised and separated from the subjacent tissues by a clear, transparent, reddish fluid which also infiltrates the deeper tissues, in the other ear there is not nearly the same amount of swelling and serous exudation; the region of inoculation is more opaque and solid. Upon more minute examination the serous fluid in the first ear is found to contain relatively very few leucocytes; the firmer mass in the second is composed of a huge aggregation of leucocytes.

Before proceeding farther it will be well to sum up the phagocytic hypothesis of inflammation as upheld by Metchnikoff and those who see in this phenomenon the all-important factor in inflammation and the repair of injury (as also in the production of immunity), in order that, having put clearly forward the tenets of those upholding the hypothesis, I may the more readily state wherein lies the strength and wherein the weakness of the doctrine.

This hypothesis may be summed up in the following theses:—

1. That certain of the leucocytes present in the blood and lymph, notably the polymorphonuclears (microphages) and the large mononuclear hyaline cells (macrophages), are capable under certain conditions of taking up bacteria which have gained entry into the system.

2. That in addition to these, the splenic corpuscles, the cells forming the endothelium of capillaries, and other fixed cells of mesoblastic origin, possess the same property, although they exert it to a less extent.

3. That these phagocytes seize upon and destroy living and active microbes under certain conditions.

excretion from the peritoneal endothelium; that Metchnikoff demonstrated that it was best explained by what he has termed "phagolysis"—by the rapid clumping of the leucocytes of the peritoneal cavity upon the omentum,

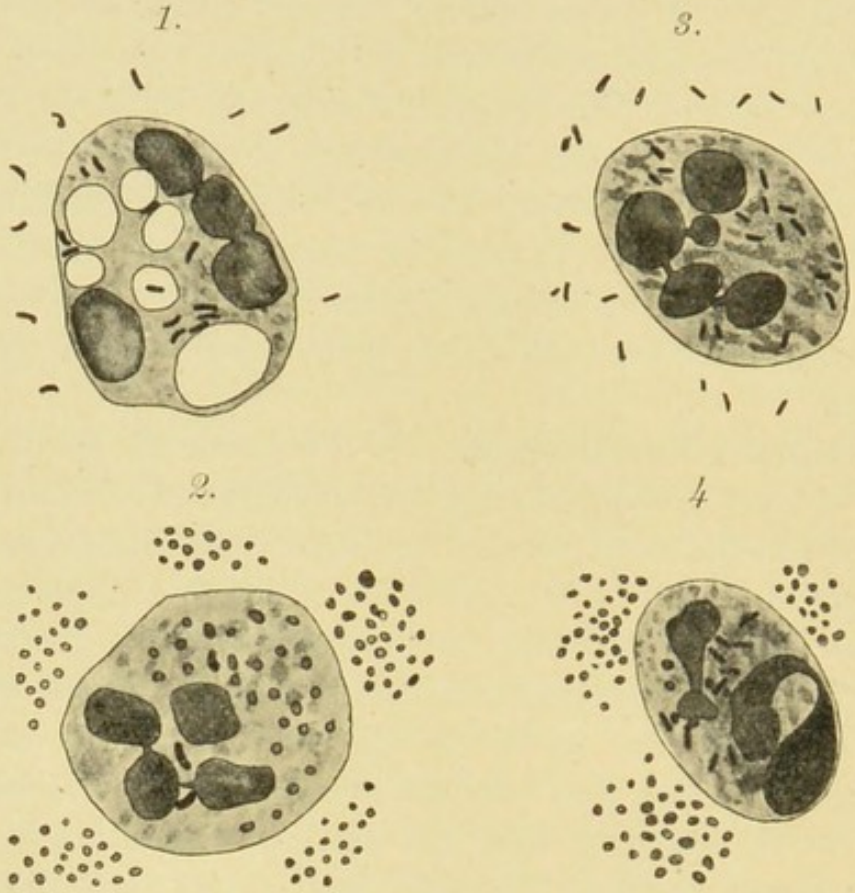

FIG. 12.—*Pfeiffer's Phenomenon.*—Effect of human blood serum upon spirillum choleræ (1, 2) and bacillus typhosus (3, 4) respectively.

In the two upper figures the blood-serum has been heated to destroy the intermediate bodies (immune bodies, opsonins). Leucocytes have been added, together with a suspension of the bacteria, and the mixture placed at 37° C. for fifteen minutes. It is seen that the polymorphonuclear leucocytes take up the unaltered bacteria. In the two lower figures are shown the effects of the *unheated* blood serum. In other respects the treatment is the same. Under the action of the serum the bacteria swell up and become spherical, losing their power of taking the stain. There is equally active phagocytosis. In the leucocytes are to be seen some unaltered bacteria. These have been ingested before the serum has acted upon them. —After WRIGHT and DOUGLAS.

followed by their dissolution and liberation of bactericidal substances; he has shown further that the phenomenon does not develop in connexion with body-fluids, such as the aqueous humour, containing few or no leucocytes; and that it does not occur if phagolysis be prevented;

It must be admitted that these observers introduced not a little confusion by speaking of certain cells as eosinophilous, which as a matter of fact, correspond in most respects to the neutrophil and amphophil polymorphonuclears of the mammal, to cells which in higher animals are definitely phagocytic. Mesnil and others have been unable to confirm these observations; but then they have not repeated Kanthack and Hardy's experiments according to the lines laid down by them; they have attempted other methods. It must be admitted that in the frog the experiment does not always succeed. I have, however, made and seen preparations in which this loss of granulation and coincident degeneration of the bacilli could not be denied. We have not been able to convince ourselves that in the mammal the coarsely granular eosinophil possesses a like excretory function, although Kanthack and Hardy convinced themselves that this was the case. In his last confirmatory article upon this subject Hardy (37) calls attention to the fact that after contact with bacilli the coarsely granular oxyphil cells of the frog are diminished in size, and, what is more, that as the cells crawl over chains of bacilli they leave behind them a slime. Bacilli coated with such a slime never grow. The observations of Durham and others indicate a little-understood alteration in bacteria preparatory to ingestion, which, indeed, would suggest that the leucocytes of mammals do afford some preparatory secretion. If, for example, a relatively abundant suspension of actively motile but not highly virulent bacilli be introduced into the peritoneal cavity of an untreated guinea-pig and a drop of the peritoneal exudate be examined, it is noted at a certain period that while many of the bacilli are moving freely in the fluid, and may impinge with impunity upon the lymphocytes and eosinophil cells present, those that come into contact with

action would cease. For ferment action to continue there must be some third substance present, which we may term the fermentator or complement, having an affinity for the atom group represented by the ferment plus side-chain, or atom-group, of the fermentescible substance. As the result of its presence, a second union takes place, and what had been the unsatisfied atom-group of the fermentescible substance of the above compound, becomes now attached to and combined with the fermentator. The ferment becomes free, once more unsatisfied, and ready to act again on the fermentescible substance. We may go farther and suppose that the atom-group or side-chain of the fermentator thus modified by combination with the atom-group from the fermentescible substance, may either remain attached to the fermentator (complement) or become liberated as a separate entity.

According to this conception of ferment action, which is the ferment—the intermediary body (fixateur) or the lysin, complement or cytase? Clearly, I think, the former; the cytase can only be regarded as the fermentator, the substance essential for the final act in the process. And this view is supported by Wright's phenomenon, in which the bacterial bodies must have the intermediary body (opsonin) in association with them before they can be acted upon by the cells. Possibly it is a matter of convention which we shall term the enzyme or ferment, whether the intermediary body or the third substance essential for the completion of the process. Yet it seems more just that the active factor in the process should receive the name; just as, with Pawlow and Bayliss and Starling (115), and in opposition to Metchnikoff and Delezenne (116), I would lay down that in tryptic digestion the enterokinase is the true ferment, and would regard the trypsinogen as the

is seen when virulent anthrax bacilli are inoculated subcutaneously into an ordinary rabbit and into one that has been rendered immune: in the former the exudation is of a serous nature, in the latter little fluid is exuded from the vessels—a clear indication that, in the development of the immune state, not merely the leucocytes, but also the capillary walls, at the least, become altered in their behaviour to the toxins. The effect of the quality of the irritant is observable upon comparison of the results of inoculation of various microbes. Some cause little exudation of fluid. These are in general of low pathogenetic quality, but not always; certain virulent microbes (such as those of tetanus) lead, when inoculated, to relatively little effusion of fluid from the vessels. On the other hand, it may be stated definitely that where in a moderately dense tissue the injection of a pure culture of a micro-organism leads to well-marked exudation, the micro-organism is of high virulence.

Can any meaning be ascribed to this effusion, or, to express the same idea in words which shall not offend those who fear the semblance of teleological ascriptions, has the increased pouring out of fluid into the tissues as the result of irritation, been of proved benefit to the species, so that those individuals have survived who have manifested this reaction and have conveyed it to their offspring? Is it an attempt at increased nutrition in the injured region? It has been suggested, in accordance with Virchow's conception of inflammation, that the injury, stimulating the surrounding fixed cells, leads to increased local metabolism; and that the exudation is a means of bringing to the region the increased nourishment demanded by the increased cellular activity. But inasmuch as exudation is most marked in those cases where there is most profound and rapid cell destruction,

2. Foot subjected to venous obstruction; 28·5 c.cm of lymph containing 2 to 3 per cent of solids.

3. Foot inflamed; 28·5 c.cm. of lymph containing 7 per cent of solids.

The figures in the third case—of inflammation—do not represent the whole exudate. So thick was the lymph that it tended to clot and obstruct the canula, and there was, in addition, much œdema and swelling of the foot. But obviously, as Ainley Walker (119) points out, from twenty to thirty times more proteid matter may drain away from an inflamed than from a healthy region.

In addition to the proteins the inflammatory lymph may contain other substances worthy of more than passing note. Of these the more important are ferments, the results of proteolysis (notably fibrin and its precursors, nucleo-albumins and albumoses), and in many cases mucin, together with bactericidal substances, and, where bacteria are present, the products of their growth. Various extractives have been noted. Exudates rich in cells and disintegrated tissue-products—pus, for example, —may contain glycogen, fats, and, as Klotz working in my laboratory at M'Gill University has recently shown (120), a very definite amount of soaps.

The presence and amount of these substances depend largely upon the intensity and character of the inflammation. Thus the total quantity of proteins, and the proportion of fibrin, albumin, and globulin present, vary within wide limits. The following table[1] of observations made by Halliburton (121) shows well this variation in proteins, and the difference existing between inflammatory exudations and dropsical effusions:—

[1] These figures are thoroughly in accord with those of other analyses by Reuss, Hofmann, Mehu, and Letulle (122).

average of the former was 5·43, of the latter 6·2 per cent; without exception, the percentage in the blister-fluid was found the higher. It may be laid down (Miller) that fluids with the specific gravity of 1018 or higher, with at least 4 per cent of albumin, are of inflammatory origin; or from 1010 to 1015, with albumin up to 3 per cent, are due to venous stasis; of less than 1010, with albumin under 1 per cent, are due to hydræmic conditions.

The Cells of the Exudate.—Much study has, of late years, been devoted to cytodiagnosis, to the diagnosis of inflammatory and other conditions by a study of the cells present in the removed fluids. It cannot, however, be said that, for our present purposes, much has been elicited beyond this, that abundant polymorphonuclears indicate an active inflammation; a preponderance of lymphocytes, either a tuberculous infection or sub-acute inflammation of other nature of some little duration, though it has also been noted that in the early stages of a tuberculous inflammation (*e.g.* in a rapidly developing tuberculous pleurisy) there may also be an abundance of polymorphonuclears.

Fibrin.—Between the amount of fibrin present in exudations and the amount of peptones there is an inverse ratio. Peptones are especially developed in connexion with suppurative inflammation; and the more an inflammation tends to be suppurative the greater is the breaking down of the fibrin, as also of fixed and wandering cells, and the more evident the production of peptones, or more correctly of albumoses, until in chronic abscess-formation of fair extent these pass into the general circulation, and are excreted and recognisable in the urine.

Into the discussion of the mode of formation of fibrin I need not enter here, intimately connected as the

if suitably stained by employing van Gieson's stain, or thionin.

The researches of Leo Loeb (128), conducted in my laboratory, possibly throw some light upon this subject. Taking a little lobsters' blood in which coagulation has been delayed by the addition of a solution of adrenalin chloride, and placing this upon a slide, then covering this with a second slide and pulling the one slide over the other so as to exert traction, it can be seen under the microscope that the cells, arranging themselves in rows, become transformed into a system of threads, and here and there the threads can be seen passing through a cell or even through the nucleus of a cell; the cells often become spindle-shaped and may either be so drawn out that their protoplasm forms long threads, or fine fibrillar threads may be seen actually passing through several cells. Loeb produced a similar transformation into fibrils by traction upon the protoplasm of exploded cells. It is worthy of note that, during either process, the cell-granules disappear, and these fibrillæ have staining and other reactions which connect them both with fibrin and with connective tissue. Many of them, for example, stain well by Mallory's connective-tissue stain. In other words, these observations of Loeb favour the view that the conversion of the protoplasm of connective-tissue cells into fibrillæ is the result of tension and traction, *i.e.* of physical agents, and that the same is true also of the development of the threads of fibrin. If the same process be at work in both conditions, there is little wonder that it is difficult to draw a sharp line of distinction between the intra- and extra-cellular process in tissues where both are occurring at the same time.

Leaving out of account coagulation-necrosis as not occurring in direct connexion with exudates, it may be

reinforcing a weak point and, by the adhesions, preventing generalised peritoneal infection. From this aspect alone, the great omentum can only be likened to a brooding abdominal providence. But, when these adhesions organise, the omentum, now firmly attached, forms a band or bands of most dangerous import; now constricting a coil of the intestine and so causing obstruction, or kinking the bowel, or leading to internal hernia and volvulus. In short, the late results of adhesions may be very serious.

The fibrin so thrown out, while it may (1) be dissolved by the action of bacterial products, or (2) undergo complete absorption by the cells and fluids of the body with *restitutio ad integrum* of the affected areas, may also (3) form a frame-work upon which new tissue-growth occurs with replacement by organised connective tissue. This new tissue-formation in inflammation we shall discuss later.

Passing now to the ferments and ferment-like bodies present in the exudate, I may briefly state that these are not only generated and excreted by the pathogenetic bacteria present, but are liberated by the breaking down of the wandering cells. Abundant evidence of the existence of bacterial ferments capable of acting upon proteids, gelatine, sugars, etc., is supplied by the study of the growth of these microbes outside the body. No less than six such enzymes are said to be produced by the B. pyocyaneus, for it has been shown that dead cultures of this organism will liquefy gelatine, coagulate milk, and redissolve the coagulum, invert cane sugar, split up fats, and decompose proteids. That ferments also originate from the wandering cells has been demonstrated by Leber (28), who, placing pieces of copper in the anterior chamber of the eye, thereby produced a purulent collection devoid of microbes, and showed that the exudate

passage of the mass through the walls may therefore be an "artefact."

Kolossow (136) has demonstrated that the endothelial cells of the intima of vessels are not absolutely independent units, and that they are connected one with the other by numerous fine brides or bridges of cytoplasm. Between these bridges are the stigmata; stomata—larger spaces—are not normally present between capillary endothelial cells. He holds that, normally, the cuticular portions of the cells are in apposition, but that with distension the stigmata from being potential become actual spaces, through which the migration of leucocytes and the escape of fluid may take place.

There is this further difficulty in the assumption that these are actual spaces—that in acute inflammation the exuded fluid contains a smaller quantity of proteids than does the blood-plasma. It is true, no doubt, that the stigmata are so small they may possibly act like the pores of a filter, and consequently may not permit the free passage of certain constituents of blood-plasma. To enter into the large subject of the nature of lymph would be to pass too far afield; I can here only say that taking into consideration the abundant evidence we possess of the activity of endothelial cells—influenced also, it may be, by loyalty to my old master Heidenhain—I have not become convinced by the brilliant researches of Starling that these cells have no selective activity, governing to some considerable extent the quality and the quantity of the exudate.

We have not a little evidence that these cells play an important part in the vascular phenomena of inflammation. To their power of taking up microbes and acting as phagocytes I have already referred; into their connection with the slowing of the blood-stream I shall enter later. Here I would point out that microscopically these cells

It must be acknowledged that there is much which would seem to support this view of the passivity of the leucocytes. No one is prepared to attribute active movements to the red corpuscles, nevertheless in inflammation a certain number of these escape through the vessel-walls. In the inflammation affecting some organs, notably the lungs, the number effecting a passage is very considerable. If, then, the red corpuscles emerge passively, why should not the emergence of the white be passive also? Add to this the very important observations made by Cohnheim, that where the circulation is arrested by compression of the artery there diapedesis ceases. This, if invariably true, would seem to indicate that when once by changes in the vessel the leucocytes adhere to the wall, the further passage through that wall is due to the *vis a tergo* of the blood-pressure.

This, however, is not a safe deduction to draw from the experiment referred to. When the artery of an inflamed area is compressed the stoppage of the blood-stream not only reduces the pressure, but also affects the quality of the blood and the conditions of the vessel-walls; moreover, it must profoundly affect the vitality or at least the activity of the contained leucocytes. These considerations alone render the experiment valueless as a proof of the passive nature of the diapedesis. Again the passage outwards of red corpuscles does not occur in the earliest stages of reaction to irritation; it never precedes the diapedesis of the leucocytes (save where there is gross injury), but follows it. A capillary or small vein in the inflamed frog's web, for example, may be seen wholly filled with corpuscles, the peripheral zone being quite annihilated, and numerous red corpuscles lying in immediate contact with the walls; nevertheless at first leucocytes only emigrate. This difference must be due to some special property of these cells. The leucocytes

in the blood-stream are not necessarily globular passive agents, but are capable of independent movement. Leber (28), in his long series of studies, has pointed out that if, with due precautions, a hooked glass tube (closed at its outer end where it catches into the incision in the wall) be inserted into a large vein no thrombosis may be set up around the intravascular portion, and yet, upon removal, a large collection of leucocytes may be found in the tube, attracted by a drop of mercury placed, along with normal salt solution, within it. (Mercury is a substance which within the tissues leads to an accumulation of leucocytes.) Here, then, there must be active attraction and active movement of the leucocytes within the blood-stream. And Lavdowsky (147) has described very exactly what other observers had also noted, namely, that in inflammation the leucocytes in the outer zone of the blood-stream do not simply adhere passively to the wall, but move backwards and forwards before they attach themselves and emigrate, as though seeking for a point of less resistance. At times this movement is in a direction opposite to that of the blood-current. Further, Councilman has called attention to the suggestive fact that in the process of migration the nucleus is always directed to the objective point and, with a small surrounding of cytoplasm, is the first part of the cell to pass through the capillary wall. More than one observer has seen a relationship between the labile, broken-up character of the nucleus of polymorphonuclear leucocytes and their function of passage through minute orifices in the capillary walls.

If both within and without the vessels the leucocytes can be actively amœboid, it is strange that they should be passive in the process of diapedesis which to the eye has so characteristically amœboid an appearance.

As above stated, the compression of the artery passing to an inflamed area is in most cases sufficient to arrest

diapedesis in that area, and I have suggested that this arrest may be due to the altered environment of the leucocytes. Now, if an embryonic form be taken, in which the tissues would seem to possess greater inherent vitality coupled with less sensibility, the arrest does not necessarily occur. Thus, Metchnikoff has noted that diapedesis of the leucocytes can be followed in the tadpole's tail, after the animal has been curarised to such an extent that the heart has ceased to beat and the blood in the capillaries has been brought to a standstill.

It is evident, therefore, that with our present knowledge we must regard the diapedesis of the leucocytes as an active migration, and must look upon the blood-pressure, the disposition of the blood-stream, and the altered condition of the endothelium of the dilated vessels as adjuvants in the process. The slowing of the blood-stream and the diminished pressure in the inflamed capillaries render it more easy for the leucocytes to accumulate close to the vessel-wall; the dilatation of the vessels and consequent thinning of the walls, with the opening, perhaps, of larger spaces of cement substance or stigmata between the individual endothelial cells, render it more easy for the leucocytes to accomplish the passage; but the movement from within the capillaries to the tissue-spaces outside is an active process due to amœboid movement of the leucocytes themselves. The continuity of the vessel-wall once destroyed, other cells — red corpuscles—may be pressed passively through the walls.

If this view be accepted, we are bound to look beyond Cohnheim's limit of changes in the vessel-wall for the stimulus which, originating in the area of irritation, acts upon the vessel-wall and the leucocytes in contact with it, and, having first set up changes in the former, so reacts upon the latter that they emigrate; or, to put it in other words, are attracted out of the capillaries

in a peptone solution, in order for it to be attracted towards and move into a more concentrated solution, this last must be five times as strong as is the former. This is in conformity with the psychophysical law of Weber-Fechner: that sensibility increases in arithmetical ratio when the stimulus or excitation increases in geometrical ratio—or, in other words, reaction is in proportion to the logarithm of the excitation. The only possible explanation that I can see of the above observations of Ruffer, Roger, and Sidler is that the passage and want of passage of the leucocytes out of the vessels depends upon the ratio of diffusible bacterial products present in the blood-stream and in the tissues respectively. Where the products are localised at one focus in the tissues, the leucocytes are attracted out of the unaltered blood, and there is active diapedesis; where there was already a solution of the bacterial products in the blood, the ratio of difference between the percentage amount of toxin in blood and tissue may be insufficient to stimulate the leucocytes; no diapedesis then ensues.

As is well shown in the experiment with symptomatic anthrax, the presence of the bacillus and its products in the circulating blood did not prevent inflammation at the region of local injection; inflammation and exudation were abundantly manifest—there was, in fact, a more extensive exudation than ever. The irritant—that is to say, the toxic products of the bacilli—at the point of injection was in no wise hindered from exerting effects upon the fixed cells of the vessel-walls, and promoting all the changes in calibre and condition of the walls and in the blood-stream characteristic of inflammation. But with vascular changes, if anything more prominent than in the case where local inoculation alone had been practised, the leucocytes stayed within the vessels. Now the only cause to which we can attribute this abstention of the

affecting the nerve centres—in this case the posterior root-ganglia—may be the main factor in the development of an intense inflammatory process in the areas governed by those centres—a process so far unassociated with the presence of bacteria, although the appearances suggest infection. Another example is to be found in the acute nephritis which at times rapidly follows the passage of a catheter or the impaction of a stone in the urethra. It is not unlikely that many of these sympathetic inflammations are not direct, but secondary. Thus, the first noticeable symptom of catheter fever is suppression of the urine. Such suppression might be brought about either by reflex contraction of the renal arteries, or, contrariwise, by reflex great dilatation and congestion of the vessels of the kidneys. If it be caused by the former then the nephritis can only be regarded as secondary, and as due to the injury done to the organ by the stoppage of its blood-supply for some little time. Undoubtedly in many cases of catheter fever the nephritis is infective, but in some the condition supervenes so rapidly that it is difficult to believe that we have to deal with an ascending infection. Where there is infection it develops in such a way that we are led to see that the altered condition of the organ under various influences has favoured the inflammatory process.

From the multitude of the factors involved, these examples, taken separately, afford at most only a great probability that the nervous system can directly originate inflammatory changes. There is, however, the clearest proof that the nervous system does possess this power, and this is afforded by the results of certain observations upon hypnotic effects. In some persons susceptible to hypnotic suggestion, the suggestion that a red-hot substance has been placed upon the hand will, in the course of a few minutes, lead to great reddening of the

cases rich in mucin, and although our knowledge of the changes in the matrix is scanty, the fact that the tissue-cells in general show little evidence of storage of mucoid or mucinogenous material, renders it probable that what mucin is formed is either excreted or elaborated between the cells. Connective-tissue fibrils, as part of the matrix, become swollen and fused into hyaline bands or masses, in which the individual fibrillæ are no longer distinguishable: in acute inflammation the next stage is the dissolution and disappearance of this collagenous matter. In chronic disturbances they are especially prone to hyaline change.

CHAPTER XXII

REGENERATIVE CHANGES

In the lower animals, as we know, injury and actual removal even of a large portion of the body may be followed by the complete reproduction of the lost part. In man, however, this reproduction of lost tissue is reduced to its lowest point; the higher the tissue the less, and the less perfect, the reproduction. Speaking generally, the tissues which show the greatest potentiality for reproduction are the least highly organised—those composed of similar units. The "connective tissue"—the lowest and most widely distributed—retains the largest powers of proliferation and hyperplasia.

In ordinary inflammation, hypertrophy and hyperplasia[1] of the connective-tissue cells are absent at the focus of irritation. Here degeneration is predominant. It is in the peripheral zone, away from the maximum concentration of the irritant, that (as shown in case after case of Leber's long series of studies upon injury to the cornea) the connective-tissue cells show signs of enlargement and proliferation, that they become more swollen and prominent, send out large processes, and may exhibit signs of active mitosis. It may be urged that this

[1] By hypertrophy in the strict pathological sense is indicated increase in *size* of the individual elements of a tissue, by hyperplasia increase in the *number* of these elements.

ing abundant instances to the point, demonstrating, for example, that the internal secretion of the thyroid directly stimulates growth, and that the growth of the mammary glands during pregnancy is not of nervous origin, or in any way connected with nervous control, but is due directly to the influence of substances diffused into the maternal blood from the growing fœtus during pregnancy. Professor Starling (169) in describing his series of experiments affords a useful resumé of cognate examples.

The difficulty of determining the origin of the growing cells in inflammation has formed the greatest trial of the pathologist throughout an entire generation, and yet longer; nor can we now assert without chance of dispute what cells are mainly concerned in the formation of new tissue. When we examine newly formed granulation-tissue we can distinguish cells of more than one type—(1) small round cells with polylobular and fragmented nuclei, (2) other cells containing oxyphil granules, (3) larger cells with a single nucleus and a relatively large quantity of protoplasm, and again (4) cells of varying but generally large size, varying in shape, but on the whole having the appearance of spindle-cells with single oval nucleus and abundant protoplasm. These can be made out easily.

The first two forms of cells are clearly hæmatogenous leucocytes. Further study of their fate shows that they disappear; they play no further part in the organisation of the tissue save that, as is well shown by Scheltema and Nikiforoff (170), many of them are absorbed by the growing connective-tissue cells, and thus would seem to aid in their nutrition. The last form likewise presents, as such, no difficulties. These are fibroblasts—cells in the process of growth into connective tissue. But what is their relationship to the previous form,—to the round mononucleated cells with fairly abundant protoplasm,—

phenomena of inflammation. Or they may be of more gradual onset, associated with evidence of over-stimulation and increased activity of the cells.

4. Fatty, cloudy, hydropic, and mucoid are the most frequent forms of degeneration affecting the tissue-cells in acute inflammation; hyaline in chronic; other forms are rare.

5. The ultimate fate of the necrosed cells varies as the situation, intensity of irritant, and specific character of the irritant.

6. Cell-proliferation is so constant an accompaniment of certain forms of inflammation that it is impossible to regard this as an adjunct and not as an essential part of the process.

7. The tissues which show the greatest potentiality for reproduction in consequence of inflammation are those which are least highly organised.

8. The origin of fibroblasts and new connective-tissue cells is still in some details a matter of controversy, but this much would seem to be clearly demonstrated: That while the larger proportion of the fibroblasts are derived from the pre-existing connective-tissue cells of the part, others may have originated from histogenous wandering cells that have migrated from some distance. Free hæmatogenous leucocytes (polymorphonuclear and eosinophil) do not give rise to new tissue; whether lymphocytes can do so is still under debate. Not a few observers have declared that the plasma-cell can elongate, become spindle-shaped, and eventually develop into a connective-tissue cell. Schridde shows that while it is true that these may take on the form of spindle-cells within the tissue, they maintain throughout their specific granulation and are at all periods distinguishable from the connective-tissue cell proper. They come to rest, that is, within the tissue, but do not become converted into

and in place of a thin layer of exudate tending to undergo coagulation and form a scab, there is a surface accumulation of pus, without coagulation. With the

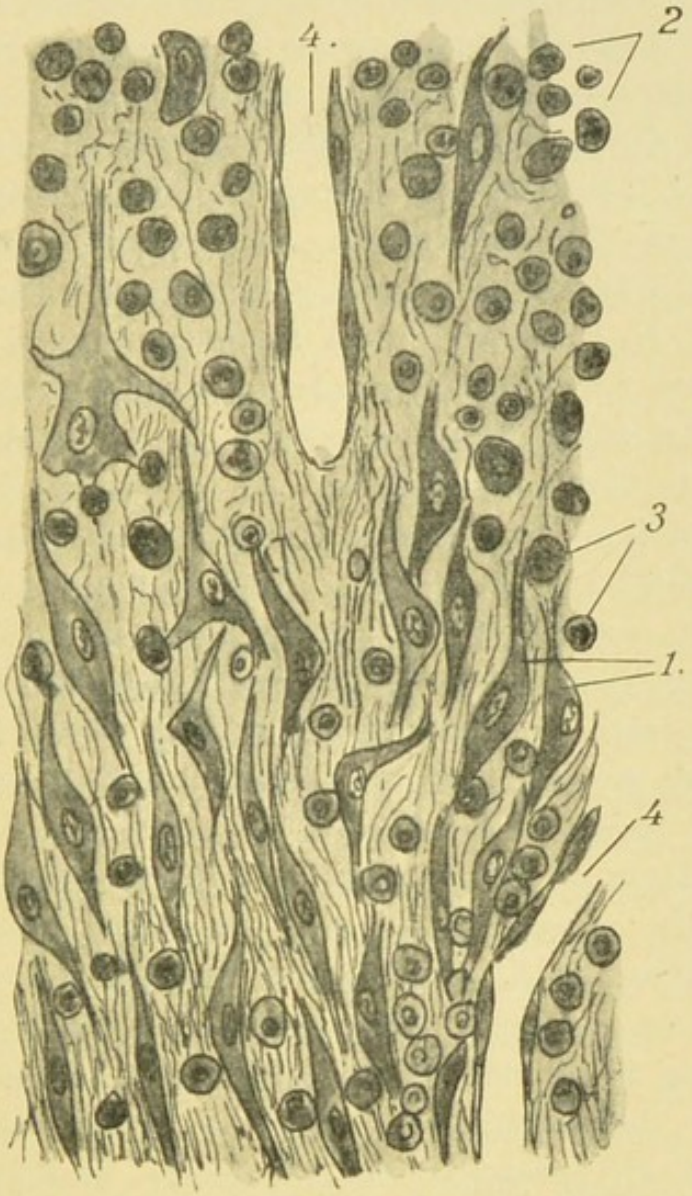

FIG. 19.—Granulation-tissue seen from the deeper toward the upper surface. 1. Spindle-cells, most abundant in deeper portions, where they are also becoming swollen; 2. Polymorphonuclear leucocytes, most abundant towards outer surface; 3. Lymphocytes; 4. Capillaries.—After RIBBERT.

present aseptic methods of treating wounds we are not accustomed to see now any abundant development of pus over an exposed wound. Formerly it was different, and a distinction was made between laudable and foul

pus; the former being bland, creamy, and of sweetish odour; the latter discoloured and foul through the abundance of putrefactive microbes, and accompanied by progressive breaking down of the tissue bordering on the wound. "Laudable pus" seems to us to-day a misnomer. With modern methods pus is regarded as matter out of place and far from praiseworthy. And yet more than one recent observer has shown, by direct experiment, that pus of this nature on an exposed surface has properties which we cannot describe as other than laudable. It has been shown to act as a barrier. Add to such pus covering a granulating wound a suspension of some known pathogenetic microbe, and, unless these be added in excess, they do not set up general infection; they are not to be detected in the underlying tissue. Pus is definitely bactericidal. It would seem that the underlying, newly formed granulation-tissue partakes also in these bactericidal properties (Jürgenlünas (179)).

For beneath this surface layer new tissue begins to form. The process of growth is seen to originate in the immediate neighbourhood of, if not in direct connexion with, the layer of dilated capillaries immediately bordering upon the wound. As already described, these project outwards towards the exposed surface, and from them are developed or projected new capillary loops. As these form there is a rather remarkable clearing in their immediate neighbourhood. The abundant leucocytes and fibrin (if present) or cell-debris disappear, and whether by phagocytosis, autolysis and dissolution, or by re-migration of the still active leucocytes into the vessels, the area immediately around the capillary loop becomes relatively free. From the first series of capillary loops other capillaries are projected, until the whole surface of the tissue, when cleansed, if necessary, of overlying pus, is seen to be covered with a finely granular or coarsely

irritants, initiating a series of changes in connexion with the surrounding vessels. The changes seen in the cord and in the kidney differ in degree only, not in kind.

We must thus recognise at least two types of inflammatory fibrous tissue-development; the one *productive* or *hyperplastic*; the other, as I have termed it, *replacement-fibrosis*. In the latter the amount of new fibrous tissue developed appears to be in proportion to the extent of the destructive process; in the former, continued irritation leads to an overgrowth not related to previous tissue-destruction.

(1) *Productive Fibroses.*—Among these are to be included various localised fibroses, such as the focal areas of new connective-tissue growth set up by the presence of certain micro-organisms, notably those causing the more chronic types of infective granulomas, as, for example, the tuberculous nodules of the tubercle bacilli; syphilitic gummas; the nodules caused by the presence of leprosy bacilli; the extensive tumour-like masses set up in man and cattle by the ray fungus or actinomyces; the new growths around certain pathogenetic blastomycetes or yeasts, more particularly studied by Gilchrist (181) and other American observers. Similar tubercle-like nodules may be formed around certain pathogenetic moulds (aspergilli) (Boyce (182) and others), and we encounter them also around minute larval nematode worms.

Not unlike these are the *capsular* fibroses, those cases of connective-tissue development forming around the irritant, whether infective or no. Here the zone of tissue-formation is a development of so much new material laid down irrespective of previous tissue-destruction; the thick capsules forming around chronic abscesses and phthisical cavities; around impacted bullets, or, as frequently observed in the lungs, around inhaled

particles taken into the tissues by the agency of the leucocytes.

Here also must be included the fibrous overgrowth due to inflammation of *serous* surfaces, including in this the fibroid thickening of those surfaces and the development of organised inflammatory adhesions. The new formation in some of these cases may be most extensive, more particularly in conditions known as chronic hyperplastic serositis, or as Nicholls (183) has termed it, hyaloserositis; the liver, spleen, or pleura may be covered by a thick layer of dense, hyaline, almost porcelain-like connective tissue laid down in successive layers which may be a centimetre or more in thickness.

With these are to be included the general productive fibroses of inflammatory origin affecting the substance of different organs. Such, for example, is the chronic interstitial pneumonia following upon chronic pleurisy, in which bands of fibrous tissue are laid down along the lymphatics passing from the pleural surface. And here also we may include the generalised interstitial fibrosis of so-called chronic parenchymatous diseases, such as we see, for example, in productive parenchymatous nephritis, in which, secondary to the inflammation of the tissue-cells proper of the organ, there is an overgrowth of the fibrous stroma. It is to be noted that some at least of these later cases must be regarded as admixtures of productive and replacement conditions, there being a coincident destruction of the parenchymatous cells.

(2) *Replacement-Fibroses.*—Here we can distinguish certain well-defined types, though all may be termed cicatricial. Wherever we have breach of continuity in a part, there is a tendency for that breach to be filled up by new tissue. In some cases this new tissue is a regeneration of the higher specific cells of the injured organ. In general, however, it may be laid down that

the more highly differentiated a tissue, the less is the capacity of its cells to regenerate, so that, more often, it is the lower, humbler connective tissue that repairs the breach. Under this heading, therefore, we place cicatrices of various orders, and include, as already stated, the replacement of *dead* tissue seen in a simple infarct, where there has been sudden death of the tissues (necrosis), and the replacement-fibrosis seen where tracts degenerate in the spinal cord, and other cases in which fibrosis follows necrobiosis, *i.e.* slower death of the tissue preceded by atrophy and degeneration. Possibly this is the right place also to include the organisation of thrombi; that is to say, of masses of coagulated blood within the vessels. When the blood thus coagulates, its cells largely break down, so that the fibrinous products may be regarded as non-living necrotic tissue. While this, in part, undergoes absorption, if it be not infected, a portion at least becomes organised by granulation-tissue spreading into it from the vessel wall, and so, eventually, is replaced by a fibroid mass.

We may thus classify the forms so far brought forward as follows:—

A. Productive or Hyperplastic Fibrosis:

1. Localised { focal, capsular.
2. Serous and adhesive { local, generalised.
3. Interstitial.

B. Replacement-Fibrosis.

1. Cicatricial.
2. Post-necrotic.
3. Post-atrophic.

C. Mixed Fibrosis: both processes being in evidence.

only be the manifestation of local increased activities of cells. In animals it is quite possible, nay probable, that, where the irritation is not too severe, the increased metabolic changes in the cells tend towards katabolism and liberation of heat; but if so, this is so slight, and the heat is so rapidly diffused into the circulating blood that thermometric measurements fail to give evidence of its existence. It may thus be left out of consideration for practical purposes.

4. The increased temperature of superficial areas when inflamed is due, not to the production of heat in the part, but to the increased quantity of blood passing through it. When the congestion is so great that stasis ensues, there may be actual decrease in the temperature of the part.

5. The maintenance of high external temperature may exert a favourable effect upon the duration and progress of specific inflammation. Thus Filehne (192) has shown that the course of experimental erysipelas in rabbits is more rapid and more benign when they are kept at a high temperature than at a low. We possess no clear evidence that this is due to the unfavourable effect of the heightened temperature on the growth of the microbes. Pasteur's well-known experiments (193) upon the production of anthrax in fowls (ordinarily insusceptible to this disease) by lowering their temperature can be explained on other grounds. We have abundant evidence that heightened temperature promotes vascular dilatation: the experiment of Filehne may therefore supply a further demonstration of the favourable effects of dilatation of the vessels and hyperæmia in the inflammatory process; indeed the use of hot air and electric light baths for this purpose are now strongly commended from many quarters.

6. Low external temperature, or the application of cold to the surface, contracts the vessels: hence, upon

PART III

GENERAL CONSIDERATIONS

the outermost layers of the derma is most often of a vesicular or œdematous character; when it affects the deeper layers of the derma the serous infiltration is less evident.

Yet another example of the influence of position in modifying form is seen in enteric fever. In this malady, the lymphoid tissue forming Peyer's patches becomes the seat of excessive cellular infiltration and proliferation, undergoes necrosis, and is cast off, leaving the well-known ulcers. The lymphoid tissue of the neighbouring mesenteric glands likewise undergoes great infiltration and enlargement, but necrosis rarely implicates the whole of a gland: notwithstanding the previous extensive inflammation, the glands commonly recover their normal appearance and size.

Beyond this there are few broad principles to be laid down concerning the relationship between forms of inflammation and position that do not essentially depend upon the structure and functions of the tissues. Much can be said concerning the intimate connexion between position and liability to inflammation; but this and the allied and most important subject of the protective mechanisms of sundry tissues against injury are away from our present point.

C. The Relative Intensity of the Irritant is a more frequent and potent cause of variation. I have already in several places referred to the ratio between the resistant powers of cells and the intensity or virulence of the irritant as it affects the inflammatory process, and have shown how much that was previously vague has been made clear by bacteriological research; while, at the same time, it has brought home the truth that there is a single process of inflammation, the manifestations of which while varying merge insensibly the one into the other.

CHAPTER XXVI

ON SYSTEMIC CHANGES CONSEQUENT UPON INFLAMMATION

The results of an acute local inflammatory process are not confined to the immediate locality, but associated alterations in the system at large have long been recognised; yet while recognised these systemic changes have been but little studied: I cannot pass the matter over in silence, but my setting forth of it must necessarily be very brief and imperfect.

I cannot here say more upon the effect of local irritation on the nervous system than that, apart from direct reflex action leading to changes of nervous origin in the region of injury and the reflexes affecting associated regions, the higher centres, and through them the system at large, may become affected by paths that it is not always easy to trace.

The disturbances of the nervous system which accompany local injury can be but vaguely and indefinitely described. As regards the secondary effects, the most suggestive work of the late Prof. Roy and Dr. Cobbett (195), and more recently of Crile (196) upon *Shock*, indicate that there is here a rich field for yet further research. Of the changes in the general circulation, and more especially in the circulating blood, thanks to the observations of von Limbeck (40), Rieder (196), Löwit (198), and Sherrington (199) we possess more

CHAPTER XXVIII

ON ADAPTATION: CONCLUSION

It will be seen that the picture of inflammation here given is very different from the old view in which the dominating idea was that inflammation is essentially an injurious process leading to cell- and tissue-destruction. Here we regard the *irritant* as capable of causing cell- and tissue-destruction, and so long as the irritant is in action so long may this destruction continue. But inflammation itself we regard as the series and sum of the reactive processes set up in the tissues, and then bringing about, not destruction, but the very reverse. Taking as our definition that inflammation is the response or reaction to injury, we are inevitably led to see that this response results in counteracting, or more exactly in tending to counteract, the deleterious effects of the irritant; the inflammatory process tends towards repair. It may not result in repair, for, as we have pointed out in several instances, too often the reaction is either inadequate or excessive. The exudation may possess but slight bactericidal powers, or may be poured out in such quantities that the microbic irritant, instead of being retained in the region of injury, is conveyed outside that region; the wandering cells, instead of destroying, may undergo destruction; they may incorporate bacteria, but not be able to annihilate them;

deficient or excessive in their action. Within physiological limits, the reaction to a given stimulus is nicely balanced and adequate; when the stimulus is excessive, the reaction is liable to be imperfect. The iris accommodates and adequately protects the retina within certain limits, but, if the eye be exposed to too intense a light, the iris fails to arrest all the rays and the retina suffers. And so it is that, in inflammation, when the stimuli are excessive and so have become irritants, the tendency is for the reaction not to be perfectly balanced, and the ultimate result to be an incomplete counteraction of the disturbance. But, to repeat, if we recognise purpose in the one set of cases, we must recognise it in the other.

All, it will be seen, depends upon what is our conception of "purpose" in vital phenomena. That conception is teleological if and when we regard it as primary —as what may be termed an intelligent endeavour on the part of the tissue to accomplish a certain object—a predetermined end. To suppose that, in inflammation, the vessels dilate and bring about increased exudation *in order to* flush out the irritant, is an utterly wrong and baseless idea. If, on the other hand, our conception is along these lines—that in the course of evolution those individuals survived who, by chance, let us say, happened to manifest this reaction on the part of their vessels in response to stimuli of a certain order, whereas those who did not were more unfavourably placed and so succumbed; that they conveyed the same power to their descendants who also possessed this advantage over individuals incapable of affording the reaction; then we can conceive the development of a race possessing a mechanism for countering a given stimulus by a given reaction, a race in which provision is made, or gained, for dealing with a given order of events; then it will be seen that what primarily is accidental becomes secondarily purposeful

(1900), is of great interest as showing the gradual change in opinions on these topics. Another discussion well worth reading is that held by the Pathological Society of London in 1892 (*B.M.J.* 1892, i. 373, 492, 591, 604) and *Trans. Path. Soc.* 1892). —93. Buchner. *Arch. f. Hyg.* 1890, x. parts i. and ii.; *Ctbl. f. Bakt.* 1889, v. 817; *ibid.* 1890, vi. 1; *Fortschr. d. Med.* 1892, x. 319 and 363; *Ctbl. f. Bakt.* 1894, xvi. 738, etc.; art. "Immunity," *Encyclop. Medica*, Edinburgh, 1900, v.—94. Vaughan, Victor C., and M'Clintock. *Med. News* (N.Y.), 1893, 701. See also Kossel, H., *Ztsch. f. Hyg.* 1894, xvi. and *Arch. f. Anat. u. Physiol.* Physiol. Abth. 1894, 200.—95. Tizzoni and Cattani. *Berl. klin. Wochenschr.* 1894, 64, 189, and 732.—96. Ehrlich. *Gesammelte Abhandlungen*, Berlin.—97. The leading papers on bacteriolysis will be found in (84).—98. Ribbert. *Der Untergang pathogen. Schimmelpilze im Körper*, Bonn, 1887.—99. Denys and Havet. *La Cellule*, 1894, x. 1.—100. Buchner. *Münchener med. Wochenschr.* 1894, xli. 469 and 497.—101. Bail. *Berl. klin. Wochenschr.* 1897, xxxiv. 887.—102. Schattenfroh. *Arch. f. Hyg.* 1896, xxvii. 234; 1897, xxxi. 1; 1899, xxxv. 135. —103. Van der Velde. Ref. in *La Cellule*, 1894, x. 1.—104. Jacob. *Ztsch. f. klin. Med.* 1897, xxxii. 466. See also Hahn. *Münch. med. Wochenschr.* 1897, xliv. 134; Lachtchenko, *Arch. f. Hygiene*, 1900, xxxvii. 290; Trommsdorf, *ibid.* 1901, xl. 382. —105. Löwit. *Vorlesungen ueb. allgem. Pathologie*, Jena, 1897. —106. Bordet. *Ann. de l'I. Pasteur*, 1899, xiii. 15; 1901, 232; *ibid.* 303.—107. Lubarsch. *Ctbl. f. Bakt.* 1889, vi. 841. —108. Gengou. *Ann. de l'I. P.* 1901, xv. 68.—109. A criticism of the facts bearing upon these experiments is given in Jacoby, M., *Immunität und Disposition*, Wiesbaden, 1906, an excellent study of the immunity problem.—110. Pfeiffer. *Ztsch. f. Hygiene*, 1894, xvi. 268; *ibid.* 1896, xviii. 1.—111. Bordet. *Ann. de l'I. P.* 1895, ix. 462.—112. Wright and Douglas, *Proc. R. S.* 1903, lxxii.; 1904, lxxiii. 128; 1904, lxxiv. 147; see also Bulloch and Atkin, *ibid.* 1905, clxxiv. 379.—113. Bulloch. An admirable account of these researches upon Opsonins and Opsonic Treatment is given by Bulloch, *Practitioner*, 1905, lxxv. 589, together with full literature to date. A brief but clear account is also given by Ross, G. W., *B.M.J.*, 1906, 2.—114. Woodhead. *Bacteria and their Products*, London, Scott, 1891. —115. Pawlow. *The Work of the Digestive Glands*, transl. by W. H. Thompson, London, Griffin, 1902, 160; Bayliss and Starling. *Journ. of Physiol.* 1904, xxx. 61. 116. Metchnikoff and Delezenne. *C. R. Soc. de Biol.* 1902, 282.—117. Samuel.

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