**On the process of inflammation / by John Burdon Sanderson, M.D.**

With kind regards from the Author

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ON THE

# PROCESS OF INFLAMMATION.

BY

J. BURDON SANDERSON, M.D. F.R.S.

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# THE PROCESS OF INFLAMMATION;

BEING THE COMPLETION OF THE ESSAY ON INFLAMMATION IN VOL. I.

THE author who engages to give information to others on any subject with which he is supposed to be conversant, takes upon himself a serious responsibility. His first duty is to place his readers in complete possession of all the facts relating to the subject, which have been accepted by scientific men up to the time at which he writes, including in his statement such collateral information as is necessary for correctly judging of the grounds of their acceptance. But in addition to this primary obligation the reader has a right to expect that he will not be presented with a mere narrative of unconnected observations which he must himself arrange and apply to the solution of the questions at issue, but that the work of comparison and analysis shall be done for him, and those conclusions stated in clear language which have the best claim to be incorporated in the ever-changing body of scientific doctrine.

In the preparation of the following essay on the process of inflammation, I have made it my object to fulfil both these obligations without going beyond them, deeming that by doing so I should be most likely to make my performance of practical use. I have striven, above all, to be cautious in the selection and statement of facts, remembering how often misstatements, which find their way into the writings of those who assume to teach, are apt to retain their place long after the sources whence they were derived have been forgotten.

I have myself repeated most of the observations and experiments to which I have referred. I have done so, however, not so much in the hope of adding to them or correcting them, as for the purpose of making myself conversant with the methods and results.

It is hard to have to acknowledge that during the last ten

years no research of any importance relating to the questions which will occupy us in the following pages has appeared in this country. The fact that we have to submit to receive instruction at the hands of German pathologists, instead of meeting them on equal terms, unwelcome as it is, is very easy to account for. In the present position of pathology, the methods which in times past have been employed with such signal success in this country are exhausted. Although it would be a great mistake to say that all that can be learnt by the rough investigations which can be made in the *post-mortem* theatre is already known, yet it cannot be doubted that for some years past every important advance in the science of disease has been accomplished, not by the collection of isolated observations, but by the same methods of systematic experimental research which are employed in physics and chemistry. The Pathological Institutes of Vienna and Berlin have no counterparts in Great Britain. The want of them is not only disadvantageous but fatal to progress—partly because they are necessary for the effectual carrying out of experimental inquiries, partly because, without them, that education in the methods of exact research by which alone a real pathologist can be produced is impossible.

## Introduction.

By the 'process of inflammation,' I understand the succession of changes which occurs in a living tissue when it is injured, provided that the injury is not of such degree as at once to destroy its structure and vitality. With reference to their origin, all inflammations may be comprised in two classes—extrinsic and intrinsic. Of these two terms, the former is applicable to all those cases in which an injury, either sustained by the affected part or inflicted elsewhere, is the obvious cause of the morbid process; the latter to those inflammations which, from the concealment of their cause, are commonly called idiopathic. If, however, we desire to speak accurately, we must discard this word altogether; for there is no case in which it can be reasonably doubted that an injury must have preceded the earliest sign of local disorder, however little we may know either of the nature of the agent or of the mode of its action. We might advantageously substitute for idiopathic either of the words intrinsic or secondary; but inasmuch as there is no channel

by which an agent from within, i.e. from some other part of the body, could penetrate into a tissue, excepting by the blood-vessels or lymphatics, we are entitled to use the only word which fully expresses this view of the mode of introduction of the material cause, and to designate all so-called idiopathic inflammations *infective*.

From what has been said it may be readily understood that the primary inflammations naturally affect those parts principally which are exposed to external influences, while those of the other class occur by preference in parts and organs to which there is no access excepting through the circulation. These distinctions, however, are not constant, for there are many instances in which secondary inflammations affect external parts, and many others in which internal organs are the seat of primary inflammations, as for example when nephritis arises from exposure to cold. Much more important distinctions, however, may be based on a comparison of the structural changes which the two processes determine in the tissues affected; or, in other words, on their pathological anatomy. In making this comparison, there is one important principle to be borne in mind. *In all inflammations, the form of the lesion is dependent on that of the area of influence of the injury.* Thus, in those cases of primary inflammation in which it may be supposed that an impression received by afferent nerves distributed to mucous or cutaneous surfaces, is reflected to internal organs (as in the case of nephritis from cold, already referred to), the area of influence of the injury is wide enough to comprise whole organs, and the resulting lesions are of corresponding extent. In the strictly local inflammations, the correspondence in form between cause and effect is, of course, closer and more obvious, the area of a traumatic inflammation being larger than that of the injury which produces it, but of exactly similar form. As regards infective inflammations, the correspondence is not so plain, but the consideration of their pathological anatomy is sufficient to satisfy us that it is equally complete. It is the anatomical character of all infective inflammations that the lesions to which they give rise are disseminated rather than diffused. Particles of matter, of the nature of which we can assert nothing, excepting that they are of extreme minuteness, are conveyed from a primarily inflamed part to other parts previously healthy, and become foci of infective induration or suppuration (miliary tubercles, pyæmic

abscesses) each of which is the product—if one may be allowed the expression—of a single seed.

Although in a treatise on inflammation all the forms of the process ought to be discussed, I have thought myself justified in omitting the whole subject of secondary indurations and suppurations on the present occasion; not that I underrate its importance, but that the material for its satisfactory discussion is still wanting. The intimate pathology of the process of infective inflammation (e.g. tuberculous, scrofulous, or pyæmic) has been only very recently subjected to experimental investigation, so that, although pathologists are beginning to see the bearing of the facts already observed on clinical experience, the subject is not yet ripe for dogmatic exposition.

For a similar reason the consideration of those cases in which inflammatory processes originate at a distance from the locality directly affected by the injurious agent, must also be omitted; for the ideas we at present entertain with respect to them are not founded on experiment, but merely inferred by analogy, i.e. by comparison of what occurs with other known processes. The actual limits of pathological knowledge seem therefore to confine the scope of the present article to the discussion of those purely local inflammations which arise in a tissue in consequence of the direct application of injurious stimulation.

The purpose of this article is therefore to describe the effects of injurious irritation of tissues. Enumerated in the order of their apparent occurrence, they are (1) disorder of the circulation, (2) transudation of the constituents of the blood, and (3) altered mode of growth of the elements of the inflamed texture. As, however, it is more convenient to divide the consideration of these several derangements of function according to their seat than according to their nature, I propose to describe them under two headings—the first comprising all those changes which have their seat in the blood-vessels; the second, the alterations of the tissues.

## SECTION I.—CHANGES WHICH HAVE THEIR SEAT IN THE BLOOD-VESSELS.

### Part I.—Disorder of the Circulation.

When a grain of dust is accidentally introduced underneath the upper eyelid, much pain is felt, and the conjunctiva becomes vascular. This effect occurs so rapidly that it is difficult to suppose that the obvious dilatation of the vessels has been preceded by a preliminary state of contraction. On the other hand, we know from direct observation and measurement that if we irritate a minute artery, it contracts at the point of irritation. How are these two apparently opposed facts to be reconciled? Are we to suppose that, notwithstanding the shortness of the time that intervenes between the application of the stimulus and its effect, the apparent paralysis has been preceded by a transitory condition, or are we to believe that the condition of the arteries which leads to the increased activity of the capillary circulation is intermediate between that of complete relaxation and that of spasm?

Before entering on the consideration of this question, it will be well to give a short account of the vascular changes as they are seen in actual progress in the transparent parts of certain of the lower animals. For years the web of the frog's foot was the only field of observation. Now that, by the use of curare, we are enabled to obviate the difficulties arising from muscular movements, preference is often given to the tongue or the still more transparent mesentery.

When the mesentery is spread out (in the way to be hereafter more particularly described) for microscopical examination, the first change which is observed in the circulation, as a result of exposure to air, consists in dilatation of the arteries; the increase of width being accompanied by a corresponding increase of length, which manifests itself in more or less contortion. The dilatation begins immediately, and is ushered in by no antecedent stage of contraction. It is, however, progressive; the diameter of the artery gradually increases for ten or twelve hours, at the end of which period it is often twice as great as it was before; having thus attained its maximum, its size remains unaltered for many hours. This dilatation of the

arteries is followed by a similar change in the veins, but inasmuch as there is a considerable interval between the two events, a time occurs at which the arteries, instead of being sensibly smaller than the veins which correspond to them, far exceed them in diameter.

Along with these changes the rate of movement of the blood is also altered. At the beginning of the process the circulation is quicker than natural. Yet although the two changes go on at the same time the acceleration cannot be regarded as a result of the increase of calibre; for the inevitable consequence of dilatation would be diminution, not increase, of the rate of movement, supposing the activity of the heart and the resistance opposed by the capillaries of distribution to remain the same. The absence of any causal relation between the two is still more clearly shown by what is observed at a later period; for whereas on the one hand, as has already been stated, the dilatation lasts for many hours, the acceleration is confined to the first stage of the process. The rate of movement soon returns to the normal, and this is shortly followed by a change in the opposite direction; so that by the time the arteries are fully dilated the circulation is much slower than it was originally.

Such are the main facts as they occur in the frog's mesentery. In so far as every inflammation begins with increased activity of the capillary circulation of the affected part, which is followed by diminished circulation, they may be considered as representative. Nothing, however, can be learnt from them as to the relation between these changes and the variations which occur along with them in the degree of contraction of the vessels themselves. For the study of this relation we must have recourse to other tissues in which the conditions of vascular contraction are better understood than they are in the mesentery. But before doing so it appears necessary to give a short account of what is at present known as to the influence of the nervous system on the blood-vessels.

During the last ten years important additions have been made to our knowledge of the innervation of the arteries. Many new facts have been discovered, and others previously known are better understood. To attempt fully to discuss them would exceed the scope of this article. I shall, therefore, confine myself strictly to those physiological considerations which have an immediate bearing on the disorder of the circulation which manifests itself in inflammation. Until Bernard proved

by experiment that the nerves which preside over the arteries of the integument of the head are contained in the cervical portion of the sympathetic, the very existence of vaso-motor nerves was merely matter of inference. For a long time after that discovery, physiologists had no precise knowledge of the vascular nerves of the rest of the body. More recently, the mode of innervation of many other parts and organs has been demonstrated experimentally, particularly the right of the splanchnics to be regarded as the vascular nerves of the abdominal viscera, and the derivation of the vascular fibres of the upper and lower extremity from the sympathetic system, by means of communicating branches passing between that system and the anterior roots of the spinal nerves. By these researches the doctrine which has long been considered probable, viz. that all vascular nerves pass through the ganglionic nervous system, has been established. At the same time, it has been shown that although the vascular nerves are immediately derived from the sympathetic, their ultimate origin is to be found in the cerebro-spinal nervous system, as evidenced by the fact that when any part of the ganglionic cord is isolated by the division of its spinal attachments its vaso-motor functions are paralysed, the same vascular effects being produced as if the sympathetic were itself destroyed. We further learn that the vaso-motor nerves are not only subject, like other efferent nerves, to the direct action of stimuli, but that they may be excited in the reflex way by stimulation of certain afferent spinal nerves. And hence we are compelled to admit that the whole vaso-motor system is under the control of an excito-motory centre. The precise position of this centre is as yet uncertain. We know, however, that it is in the intra-cranial part of the cord: in the first place, because some of the afferent nerves in relation with it are cranial, and secondly because section of the cord immediately below the *medulla oblongata* produces paralysis of the whole vascular system. Of the afferent nerves above referred to, the most important is that which is now known as the depressor,* a branch of the vagus, the excitation of which by a feeble interrupted current leads to a general reflex acceleration of the flow of blood through the capillaries.

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* For a full account of this subject, see E. Cyon and C. Ludwig, *Die Reflexe eines der sensiblen Nerven des Herzens auf die motorischen der Blutgefässe.* Ludwig's *Arbeiten*, 1867, p. 77.

As in other parts of the nervous system, the special physiology of the vascular nerves is known almost exclusively by experiments, in which the effects produced by the stimulation or division of particular nerves are observed. The most important results of this kind of investigation are, that section of a vascular nerve produces congestion of all the tissues to which it is distributed; that excitation by the interrupted current, or by mechanical means, produces constriction of the minute arteries presided over by the irritated nerve, and consequent anæmia; *that excitation of a sensory nerve produces increased activity of the capillary circulation in the part in which the nerve originates*; and, finally, that all arteries manifest alternating states of contraction and dilatation, their rhythmical movements being entirely independent of those of the heart and of breathing, and ceasing when the vessel is paralysed by division of its nerves.*

Of these results, the one which has the most direct relation to our present inquiry is the third. It is founded, as regards mammalia, on the well-known researches of Ludwig and Lovén, of which I content myself with giving a very cursory account, referring the reader to the original paper for more complete information.

All of Lovén's experiments were made on curarised rabbits † in which respiration was maintained artificially, so as to avoid the disturbing influence of muscular movements. The nerves selected for excitation were the large nerves distributed to the external ear of the rabbit, and the *dorsalis pedis*. When the central end of a divided auricular nerve is excited by feeble induced currents, congestion of the corresponding ear follows in a period which varies from three to six seconds. This congestion is more intense than that produced by section of the sympathetic, and is accompanied with obvious dilatation of the arteries,

* Of these results, the first and second may be easily demonstrated in the rabbit by section of the cervical sympathetic followed by excitation of the peripheral end of the divided nerve; in the frog by section and excitation of the spinal cord. The effects of the excitation of the depressor nerve can only be shown in the rabbit. The modes of experiment required are described in my physiological lectures recently published in the *Medical Times and Gazette*.

† I have found, however, that all the facts observed can be demonstrated in animals under the influence of chloral (six grains or more in solution injected into a vein). In this way the experiment is rendered much easier and can be done without inflicting any pain on the animal.

varying in duration according to the degree of the excitation, and the time for which it is continued.* In the experiments in which the *n. dorsalis pedis* was excited, the *arteria saphena* was made the subject of observation. As this vessel in the rabbit is easily exposed in its long course down the inner surface of the thigh, derives its vaso-motor branches exclusively from the *n. saphenus*, and is distributed in great measure to the same region as the *dorsalis pedis*, it is particularly suited for the purpose. The results are as striking as in the other case. The vessel begins to enlarge and pulsate visibly a few seconds after the commencement of the stimulation. The dilatation soon attains its maximum and begins to subside, lasting only a very short time after the removal of the electrodes from the nerve.†

In the frog the vascular nerves which supply the web find their way by various channels to the arteries to which they are distributed, so that there is no single trunk by the division of which these vessels are completely paralysed. It is probable, indeed, that the distribution of the vascular filaments differs in different individuals, for while in some frogs division of the sciatic nerve in the thigh widens the arteries very distinctly, in others it produces no appreciable effect, either on the state of the vessels or on the activity of the circulation. There is a similar uncertainty in the results produced by exciting the peripheral end of the divided sciatic, which obviously, if that nerve always contained vaso-motor filaments, ought always to induce arterial contractions. In some frogs it is so, i.e. when the peripheral end is excited, the arteries contract markedly, and the circulation is suddenly arrested, but in others the effect is so inconsiderable as scarcely to admit of demonstration. If, however, the central ends of the divided sciatic be excited, the opposite effect—namely, increased activity of the circulation—shows itself with much greater constancy, proving that however variable may be the proportion in which vaso-motor filaments are contained in the sciatic nerve, the arteries of the web are always supplied more or less completely through other channels.

The accelerating influence of excitation of the central end of

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* In my experiments, the dilatation had often disappeared ten or twelve seconds after the commencement of excitation.

† Chr. Lovén, *Ueber die Erweiterung von Arterien in Folge einer Nervenerregung.* Ludwig's *Arbeiten*, 1867, p. 1.

the divided sciatic on the circulation has been lately so carefully studied by Professor Stricker and Dr. Riegel that there can be no doubt of its nature. The method they employ consists in comparing the movement of the blood-corpuscles in a selected arteriole with that of a current of water containing particles of solid matter in suspension, which is so arranged as to pass through a horizontal tube fixed on the eye-piece of the microscope at such a distance from the eye-glass as to be distinctly seen by the observer. The apparatus by which this current is produced is so constructed that its rate can be varied at will, and its actual velocity at any given moment can be determined. The comparison is made by first fixing the attention on the arterial current, and then accelerating or retarding the test-current until the two velocities are equal. By this means it is obvious that any diminution or increase in the rate of movement can be appreciated with the greatest exactitude. With a view to the observation, the frog must be slightly curarised ($\frac{1}{2000}$th of a grain of curare in solution injected under the skin). The sciatic nerve having been divided on one side, the web is placed under the microscope, so that a small artery passes through the field in a direction which coincides with that of the test-current. As soon as the two movements have been brought to agreement, the central end of the sciatic is excited by a moderate current, immediately after which the acceleration begins, and goes on increasing so long as the irritation is continued, even when the observation lasts for half an hour, or longer.* In all Dr. Riegel's experiments the acceleration of the blood-stream was associated with some narrowing of the vessels. This observation was so carefully and so frequently made by him, that I should not doubt of its reality, even if I had not satisfied myself of its truth by repeating it. Its importance is obvious, for it affords the strongest ground for believing that in certain states of the arteries accelerated flow of blood may be associated with persistent reflex arterial contraction.

There are several instances known to physiologists in which contractions of arteries are produced which are not attended with increased activity of capillary circulation, but, on the contrary, with anæmia—as, for example, by excitation of the peripheral end of the sympathetic in the neck after division, in the

* Riegel, *Ueber die reflectorische Innervation der Blutgefässe. Med. Jahrbücher* 1871, p. 101.

rabbit, or by excitation of the spinal cord in the frog. If this were only the case when vaso-motor nerves are irritated directly, we could more readily understand it; but it also happens under conditions which so closely resemble those which we have been considering, that at first sight the results are difficult to reconcile. Saviotti has lately found that by exciting the cutaneous surface in various ways, e.g. by tapping on the integument of the belly, by pricking the skin of the same part or of the back, or by pinching the toes, very marked contraction of the arteries of the web of the frog's foot can be produced, which is attended not with increased but diminished progressive movement of the blood, amounting for the moment to complete arrest of the circulation. As I have said, this looks at first contradictory, but before we judge of its bearing on our present question we must call to mind that the conditions of Saviotti's and Riegel's experiments are not so comparable as they seem. It is well known as regards some at least of the modes of irritation employed by Saviotti, that they act not merely on the vaso-motor nerves but on the vagus heart-nerves. I need not remind the reader that tapping on the belly of the frog arrests the movements of the heart in diastole just in the same way as direct excitation of the vagus itself does. Consequently in Saviotti's experiment we are not merely obliged to admit the possibility that the arrest of movement is partly cardiac, but are tolerably certain that it must be so. This consideration is of great importance; for although there is no doubt that anæmic contraction of arteries is an ordinary consequence of direct stimulation of vaso-motor nerves, there is no case (except that of Saviotti's experiments) in which anæmia is produced by reflex irritation.*

Our knowledge of the innervation of the blood-vessels is, notwithstanding the progress which has been made during the last few years, too imperfect to enable us to harmonise all the facts. But the impossibility of constructing a complete theory on the subject does not prevent us from drawing some inferences which will be of use in enabling us to understand what happens in inflammation, at all events better than we should do without them. From what has been stated, it is tolerably clear that whatever difference there may be in other respects, there is one

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* Saviotti, *Untersuchungen über die Veränderungen der Blutgefässe bei der Entzündung.* Virchow's *Archiv,* vol. i. p. 592.

effect of exciting the sensory nerves distributed to any part which is pretty constant, viz. increased activity of the circulation; so that whether the actual quantity of blood existing in the part at any given moment be greater or less, the quantity of blood which passes through it in a given time is certainly greater.

In the commencement of the process of inflammation in the web of the frog's foot the successive changes are similar to those I have already described in the mesentery, but differ considerably according to the irritant employed. Most irritants, such as weak solution of caustic soda, dilute sulphuric acid, &c. produce dilatation first of the arteries and subsequently of the capillaries, with marked acceleration of the circulation—these conditions being followed by arterial contraction and capillary anæmia. But liquor ammoniæ and carbonate of ammonia in substance, appear always to occasion a certain degree of primary arterial contraction, which begins in one or two minutes after excitation, and is attended with retarded flow of blood through the capillaries, with distension of the branches given off by the artery nearer the heart, and increased activity of circulation in the neighbourhood of the irritated part. This state of things lasts for an hour or two, and is succeeded by dilatation and acceleration. In other words, ammonia and carbonate of ammonia produce results which are directly opposed to those of other stimuli. Croton oil appears to occupy an intermediate position between the first-named stimulants and ammonia, for while it always gives rise to acceleration of the flow of blood as a primary result, this change is sometimes associated with widening, sometimes with narrowing of the arteries. So that here, as in the case of reflex electrical stimulation of sensory nerves, the only fact which is constant is acceleration.

In order to judge whether the two kinds of acceleration we have been considering are of the same or opposite nature, the best way is to observe their action simultaneously in the same part. If, for example, in the web of the frog's foot the acceleration due to excitation of the central end of the sciatic is of the same nature as that of inflammation, we should expect it to be increased by local irritation; and, conversely, the effect of irritation, if already existing, to be heightened by exciting the nerve. The very careful experiments of Dr. Riegel show that it is so. Having found that after section of the sciatic the effects of

irritation were slightly retarded but otherwise unmodified, he repeated the observation in another animal, excited the central end, and then applied croton oil to both webs. On the injured side the accelerating effect of the croton oil lasted much longer than on the other, so that at the time stasis had already set in on the sound side, the circulation was going on more briskly than natural on the injured side.

As regards the precise nature of the modification of vascular contractility which is associated with the primary quickening of the capillary circulation, we cannot venture to speak in any terms more precise than have been already employed. The effect of local irritation is certainly not to paralyse the arteries leading to the irritated part, but rather to modify their *tonus* in such a way as to facilitate the flow of blood through them. For the present we must be content to leave the question open, for no good would be gained by endeavouring to conceal the insufficiency of our knowledge under a comprehensive theory.*

In all forms of inflammation of sufficient intensity, the circulation after a variable period of excitation becomes retarded. This effect is so closely associated with the other phenomena of

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* Many physiologists are of opinion that the arteries do not act merely as dead elastic tubes, but are endowed with powers of contraction analogous to those of the intestine. If this be admitted, it can be easily shown that the quantity of blood conveyed by an artery in a given time, and consequently the activity of the capillary circulation, might be increased by alterations in the contractility of the tube of a nature the very opposite of that of relaxation. Such a theory supposes that an artery, after it is distended by the injection of blood from the heart, does not content itself with returning to its state of elastic equilibrium, but that at a variable interval after receiving the systolic shock of the heart it contracts actively on its contents, just as a bit of intestine would do, and thus assists in propelling them. Admitting it to take place, the effect of such contraction would depend not merely on its intensity, but on the relative duration of the period of arterial distension as compared with that of the succeeding collapse. Thus if the contraction were so immediate as to happen while the artery was still acted upon by the heart, and consequently to coincide with what would otherwise be the period of greatest distension if the artery were a dead elastic tube (that is to say, about a tenth of a second or so after the shock), it is evident that it would tend to impede the circulation by increasing the resistance of the artery; but if, on the other hand, it were postponed until after the operation of the *vis a tergo* had ceased, it would not only keep up the flow of blood during what would otherwise be the period of greatest retardation, but would prepare the way for a more effectual filling of the artery at the next systole by previously emptying it of its contents.

the second stage of the process of inflammation, that it cannot be advantageously studied until they have been considered (see p. 745).

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## Part II.—Exudation of Liquor Sanguinis and Leucocytes.

It is now many years since it was taught by Dr. C. J. B. Williams, as the result of his own observations on the phenomena of inflammation in the web of the frog's foot, that in the second stage of the process, when the capillary circulation is becoming retarded, there is an apparent increase in the number of white blood-corpuscles in the vessels, and that they manifest a remarkable 'disposition to adhere to their walls.'* Dr. Williams attributed these appearances to the production in the vessels of inflamed parts, of young colourless blood corpuscles differing from those ordinarily met with in their consisting, not of cells (in the sense in which the word was then, and for many years afterwards understood, as implying the existence of nucleus, membrane and contents), but of masses of gelatinous consistence (p. 328). He considered that their tendency to adhere to the internal surfaces of inflamed vessels, and to creep along them, was due to their not having membranes (p. 331). He further observed that 'in the frog's web, after inflammation has continued for some hours, there appear outside of the vessels, especially where the strongest current encounters the most complete obstruction, white globules or corpuscles with specks in them, exactly like the pale granular globules within the vessels' (p. 335). He did not, however, suppose that the objects so exactly resembling each other which he saw outside and inside of the membrane respectively, were in reality identical; for although Dr. Addison had already maintained that pus globules and the white globules of the blood were indistinguishable from each other, and had represented that in inflammation the white globules first passed into the substance of the wall of the blood vessel, and were then thrown out from it, it appeared to Dr. Williams so difficult to understand their passage through the walls of vessels in which

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* *Principles of Medicine*, 3rd ed. p. 330.

no pores are visible under the highest magnifying powers, that such an explanation could not be accepted.

In 1846 the statements of Dr. Addison were confirmed by the late Dr. Augustus Waller. His paper on the subject displays such clearness in the description of the phenomena he observed as to leave no doubt in the mind of the reader that he actually saw what he represents. 'In some instances,' says Dr. Waller, 'the manner in which the corpuscle escaped from the interior of the tube could be distinctly followed; that part of the tube in contact with the external side of the corpuscle gradually disappeared, and at nearly the same time might be seen the formation of a distinct line of demarcation between the inner segment of the corpuscle and the fluid parts of the blood in contact with it. Any slight agitation then was capable of disengaging the corpuscle from the vessel to which it was now external,' &c.* This passage is taken from a description of one of Dr. Waller's experiments. I quote another which contains his explanation of the phenomena. 'In endeavouring to account for the fact of the passage of the corpuscles through the vessels, we find considerable difficulties. It cannot be referred to the influence of vitality, as it is observed likewise to take place after death. It may be surmised, either that the corpuscle, after remaining a certain time in contact with the vessel, gives off by exudation from within itself some substance possessing a solvent power over the vessel, or that the solution of the vessel takes place in virtue of some of those molecular actions which arise from the contact of two bodies; actions which are known as exerting such extensive influence in digestion, and are referred to what is termed the catalytic power' (p. 402). That the speculations and observations of Dr. Addison, even when so definitely confirmed by Dr. Waller's experiments, fell into oblivion, is to be attributed partly to the theories about cells which then prevailed, and partly to the extreme difficulty of the investigation. For it is to be remembered, to Dr. Waller's great credit, that neither curare nor chloroform, which have since so wonderfully facilitated research, were at his disposal, and that consequently anything like minute observation of the phenomena was rendered almost

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* Microscopical Observations on the Perforation of the Capillaries by the Corpuscles of the Blood, and on the Origin of Mucus and Pus Globules. By Augustus Waller. M.D. *Philosophical Magazine*, vol. xxix. p. 397, 1846.

impossible; for it was only by patiently waiting for short moments of tranquillity that the observer could see anything.

Before proceeding to the consideration of the discoveries which have rendered Professor Cohnheim's name so well known, it is desirable to give some account of the successive steps of investigation by which the true relation between the colourless corpuscles of the blood and other similar forms occurring in the tissues, either in health or disease, has been recognised. The common physiological property by which all these bodies are associated is that of spontaneous movement, manifesting itself either in progression or merely in continuous change of form. The bodies possessing this property are called in German by the terms *bewegliche Körperchen*, *Wanderzelle*, *Lymphkörperchen*, for which I propose to employ the English equivalent leucocyte,* understanding it to mean a mass of contractile living protoplasm. The importance of this definition in relation to our present inquiry is very great, for so long as a blood-leucocyte was supposed to be a cell, in the sense in which the term cell was used twenty years ago, it was quite impossible to understand how it could find its way through a structureless membrane; but from the moment that it was understood to be a mass of contractile material similar in all respects (which can be judged of by observation) to that which forms the body of an amœba, and endowed with a similar faculty of movement, the process became much more intelligible. Although the comparison between the movements of amœbæ and those of leucocytes is so familiar, it cannot be considered either an undue digression from the subject, or a waste of the reader's time, to recall to his recollection some of the facts relating to the mode of life of these organisms which fit them to serve as illustrations of the contractile corpuscles of the higher animals.

With this view the best examples which can be selected are the gigantic amœbæ which are known to biologists as the

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* Dr. Williams, in a recent note (*Med. Times*, Jan. 21, 1871), objects to the term leucocyte, that the body to which it is applied is not a cell, and suggests the adoption of a new word, viz. Sarcophyte, which corresponds more exactly with its anatomical characters and its physiological properties. I have nothing to advance in answer to Dr. Williams' arguments. Sarcophyte is clearly the more expressive and accurate word, but it is unknown; whereas leucocyte is well understood on both sides of the Channel. Moreover, the word cell, and its Greek equivalent, have so entirely lost their original meaning, that surely no misunderstanding can arise from their use.

Plasmodia of the Myxomycetes, and the more familiar forms which are closely related to the Monads. The myxomycetes, although possessing some of the characteristics of animals, have been always, on account of their development and mode of growth, associated with the fungi.* Like other fungi, they originate from spores. If the spores of *Physarum* (a genus of myxomycetes) are sown in water on an object-glass, and examined under the microscope twenty-four to thirty-six hours afterwards, the water is seen to be peopled with contractile corpuscles, each of which is at first provided with a single cilium, and contains, in addition to a contractile vesicle, a delicate vesicular nucleus, usually placed in the neighbourhood of the cilium. In its original state the corpuscle moves about so actively that the contractions of its substance cannot be studied; but after a while the cilium falls off or is retracted, and it then assumes in every respect the aspect and character of an amœba. Let us for a moment study its motions.

The mass is constantly changing its form. But as these changes go on in all parts of the hyaline substance of which it consists, simultaneously, the only way in which they can be understood is by confining the attention to one point at a time. If this is done it is seen that each act of movement begins by the budding out of a ray or process of contractile substance in a centrifugal direction. What next happens varies in different cases. Sometimes the projection subsides just in the same way as it was formed; at others the finely granular fluid, or rather labile matter, which occupies the more central parts of the corpuscle, streams into the offshoot, gradually widening it out, until it grows into a mass greater than the remainder, which it finally draws into itself. It is evident that the process last described must always be attended with locomotion, for each time it is repeated the whole mass rallies round a new centre, the position of which corresponds to the extremity of the offshoot. If the amœba always sprouted in the same direction, the progress would be continuous and rectilinear; as, however, there is no appreciable order in its efforts, its locomotion is correspondingly irregular.

The form of the adult plasmodium of Didymium, another genus, is shown in Fig. 396. It consists of a reticular film of grey

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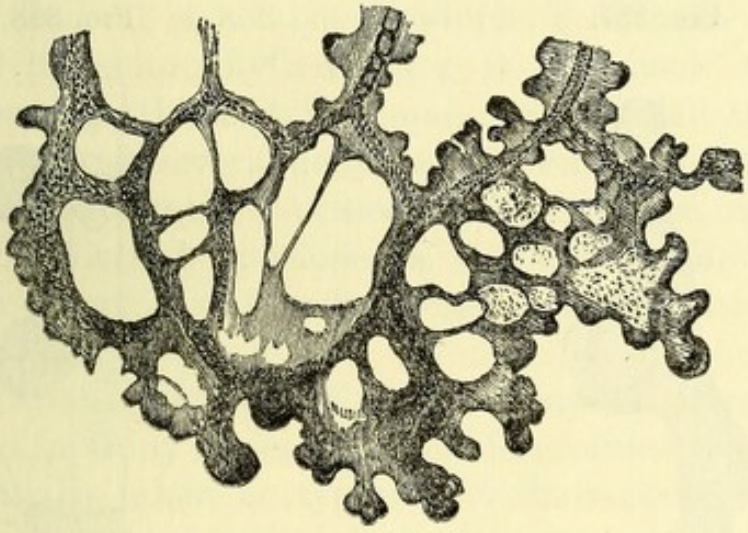
* L. Cienkowski, *Das Plasmodium. Zur Entwickelungsgesch. der Myxomyceten. Jahrbücher für wissenschaftliche Botanik*, vol. iii. pp. 325, 400.

fibres which spreads over the rotten leaves on which the plant vegetates, and would be regarded by the casual observer (if he recognised its claim to be considered a living structure at all) as undoubtedly a fungus. Under the microscope it is found to be neither more or less than an enormous mass of contractile protoplasm; for every part of it is constantly undergoing changes of form similar to those already described in the minute amœba, with which (as Cienkowsky's researches have clearly shown) it is organically continuous. As illustrative of the manner in which hyaline contractile material may shape itself into specific form without the intervention of cells, it is well worthy of our attention. Its mode of growth can be best

Fig. 396.

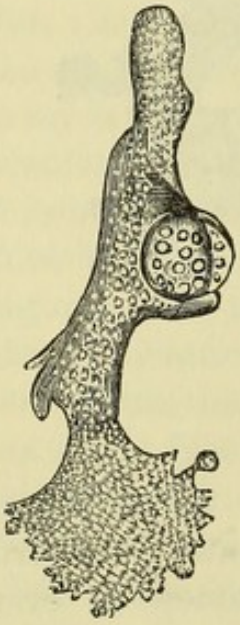


understood by observing what takes place at the edge of the network. Here it is seen that the filaments grow terminally, and that although there is amœboid movement in every part, this movement is much more active at the growing points than elsewhere. It is further seen that the process by which the growing end lengthens, is exactly similar to that by which the original amœba throws out rays. In each filament the outer part appears to be hyaline and contractile, the central part labile and granular; and when the process of elongation is carefully observed, it is seen to consist first of a budding out of the external substance, and secondly of an afflux (preceded by more or less marked alternations of ebb and flow) of the axial semi-fluid matter towards the growing point. The reticular arrangement of the filaments results from the fact that every marginal growing end meets with another, with which it unites so as to form a loop. The union, however, is not

instantaneous, but gradual. For a time the two ends are merely in contact, the labile axial matter being separated by a double septum of hyaline substance. Gradually the septum melts away, and a channel of communication is established in which the ebb and flow of currents can be distinguished.

The purpose I have had in view in giving this short sketch of the mode of life of the myxomycetes is to show that in contractile protoplasm the two functions of motion and growth are, so to speak, confused together in such a manner that the more closely we scrutinize the mode in which they are exercised the more difficult does it appear to distinguish them. No reference has as yet been made to another power which all amœbæ possess—that of absorbing the nutritive substances with which

Fig. 397.



A plasmodium beginning to surround a vegetable cell containing chlorophyll.

Fig. 398.

At the lower part of the figure a Vampyrella is beginning to adhere to a cell containing protoplasm and chlorophyll granules, which it is about to plunder. The other two cells have been perforated and their contents drawn into the bodies of the Vampyrellæ, which have retracted their processes.

they come into contact. This property is manifested in perfection in the colossal amœbæ we have been studying, which not only appropriate material derived from the soil with which they are in contact by their external surfaces, but surround their food with their own substance for the purpose of digestion (Fig. 397). I prefer, however, to seek for an illustration in the

history of those more minute forms which, from their close relation to the Monads, have always been regarded as animal.

I select as an example an amœba called by Cienkowski *Vampyrella Spyrogyræ*,* the specific name of which is derived from the confervoid alga on which it lives parasitically. Its appearance is shown in Fig. 398. It is granular towards the centre, hyaline at the surface, and the superficial part shoots out into pointed rays, or less frequently buds into obtuse promontories, in which an oscillation of granular matter is seen similar to that already described. It moves about apparently without purpose until it meets with a filament of Spyrogyra. It then adheres to the external cellulose membrane of the alga, and soon penetrates it. It thus comes into contact with the protoplasmic lining (primordial utricle) of one of the cells of which the filament is composed, which it at once proceeds to exhaust of its chlorophyll, drawing it into itself through the narrow opening which it has made in the cell wall. After having plundered several cells in this way, the amœba, much increased in size, entirely ceases its movements, and becomes enclosed in a distinct envelope, in the interior of which new amœbæ are formed by an endogenous process which it is unnecessary to describe.

Although the morphological relations of amœbæ are so various and in many instances so undetermined that no single example can be taken as typical, yet those above related may serve to render more intelligible the following general statement. It appears to be well ascertained that it is the destiny of every amœba, after it has enjoyed its active life for a certain time, to assume the immobile condition, in which it becomes invested in a membrane; and that as this transformation is always preparatory to its entering on the reproductive function, no amœba can itself be a parent. It is also certain that all amœbæ, so long as they continue in the active state, are endowed with a remarkable power of dissolving and absorbing the nutritive substances on which they live. In connection with this faculty, the exercise of which may be regarded as the final cause of all their movements, they are able, at one time, to surround the material to be digested with the substance of their own bodies, at another to penetrate membranes in which there are no visible

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* Cienkowski, *Beiträge zur Kenntniss der Monaden.* Schultze's *Archiv,* vol. i. p. 203.

pores, when such membranes are interposed between them and their food.

*Amœboid movements of leucocytes.*—The first precise observations on the amœboid movements of leucocytes were those of Professor v. Recklinghausen, contained in a paper on suppuration which appeared in Virchow's *Archiv* in 1863.

The publication of this research may be well considered as the commencement of a new era in histology,* not so much on account of the importance of the facts announced in it, as because the author enforced a principle which, at all events in its application to pathology, was at that time new, though it is now recognised by every one—namely that the elements of tissues, especially those in which life is most active, are so altered in the very act of dying, that the appearances they exhibit when dead and still more when disfigured by immersion in such liquids as acetic acid or water, are mere caricatures of their true aspects; for although the dead remains may be full of instruction, yet if we wish to know organic forms as they are, they must be studied either in the living state or at all events under physical and chemical conditions resembling those of life as closely as possible.

Guided by this principle of research, Recklinghausen was able to show, for the first time, that the changes of form of leucocytes are of the same nature as those of amœbæ, that they are capable of surrounding particles of any kind, if sufficiently small, with their own substance, and that they possess the power of moving from place to place. The first of these facts is established in his paper by observations on the pus corpuscles which are to be found in the liquid obtained by puncturing the anterior chamber of the eye of the frog a few days after keratitis has been produced by the application of nitrate of silver to the cornea. The description given of the movements as they are seen in the turbid humor aqueus, provided that it has

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* It is somewhat difficult to state to whom the merit of having discovered the amœboid movements of leucocytes is to be assigned. There is no doubt that they had been noticed by several anatomists before they were made the subject of special investigation. Among the more important early observations on the subject may be noticed those of Virchow on the corpuscles of hydrocele fluid (Virchow's *Archiv*, vol. xxviii. p. 238), of Lieberkühn on the fluid of ascites (Müller's *Archiv*, 1854, p. 15), and those of Messrs. Busk and Huxley on mucous corpuscles, in a note to their translation of Kölliker's *Microscopical Anatomy* (p. 46).

undergone no change either by evaporation or pressure, is as follows: 'The corpuscles differ very strikingly in their form

Fig. 399.

Amœboid leucocytes (after v. Recklinghausen).

from those from which the ordinary descriptions are taken. . . . No globular forms present themselves—only jagged ones, and the prongs vary both in length and number. But what strikes one even after very brief examination is, that each corpuscle is constantly changing its shape. While one prong withdraws itself into the body of the corpuscle, another juts out. Each prong is at first a delicate, homogeneous, somewhat shiny thread, but soon it thickens at the base, lengthening at the same time; then gradually the substance of the corpuscle tends more and more towards it, becoming smaller as the process gets larger, the whole thus assuming an oblong or protracted form. During this transformation . . . the tip of the process is rounded off and subsides into the contour of the corpuscle; or new delicate thread-like processes shoot out, which again undergo the same changes.' *

The ingestive power of leucocytes is proved by experiments in which Recklinghausen introduced milk into the lymph cavities of frogs, the result being that the blood leucocytes became 'choked with milk globules.' Subsequently he injected finely divided vermilion with like effect, and in this way introduced a method of research which has since been much employed by pathologists—that of distinguishing the blood leucocytes from those indigenous to the tissues, by feeding the former with some insoluble colouring matter injected into the circulation.

The proof of the faculty of locomotion is derived from another experiment which is in fact only a continuation of that already mentioned. Vermilion having been previously injected into a lymph cavity of a living frog, a rabbit's or dog's cornea, taken from an animal several hours dead, is introduced into it, and

* V. Recklinghausen, *Ueber Eiter- und Bindegewebskörperchen.* Virchow's *Archiv,* vol. xxviii. p. 157.

left there two or three days. The lymph sac of course becomes inflamed, and it is found on removing the fragment that whereas the centre remains transparent, the more superficial parts are turbid. And if the preparation is immediately submitted to microscopical observation under conditions consistent with the maintenance of life (i.e. immersed in a nutritive liquid), it is found that the turbidity is due to the presence of amœboid leucocytes in the cavities of the dead tissue. That these elements are derived from the purulent liquid in which the fragment is bathed, and must therefore have found their way into the positions which they occupy by migration, is evidenced not only by their vital movements and their containing vermilion granules, but by their exhibiting the size and other characters of leucocytes of the frog.*

Even at this early stage in the investigation, v. Recklinghausen recognised the bearing of his discoveries on several difficult questions relating to inflammation; as e.g. in explanation of the tendency of pus to find its way to the surface or into the great cavities of the body, and of the mode in which disseminated foci of suppuration originate; and he also brought them into relation with the notions entertained by earlier pathologists as to the part taken by blood-leucocytes in the formation of new tissues. He even went so far as to attribute the collection or accumulation of leucocytes on the surfaces of inflamed serous membranes to migration; but assumed that they must have originated by 'proliferation' in the neighbouring connective tissue, and must have followed pre-existing channels in their wanderings. Thus, although it may be said that he did not himself, so to speak, complete his own discoveries, and left it to others to develop them to their necessary consequences, there can be little doubt that he gave a new impulse to patho-

* This experiment has been since repeated in a variety of ways. The most striking is that of Prof. Lortet of Lyons, who found that when any porous substance is introduced into a suppurating cavity, the leucocytes penetrate into it in the same way as they do into the dead cornea. And if the experiment is so arranged that the porous material encloses a liquid (as e.g. when the swimming bladder of a small fish filled with water or saline solution is inserted into an abscess), the liquid soon becomes peopled with leucocytes. The same thing happens when a similar pouch, shaped out of vegetable parchment, is used. Lortet's experiment, as well as those of v. Recklinghausen, have been repeated in the Physiological Laboratory of University College during the past winter. More full information respecting them will be found in the author's lecture on *Leucocytes*, already referred to.

logical research, the effect of which has shown itself in the more brilliant achievements of Cohnheim and Stricker.

The experiment by which Cohnheim first demonstrated the escape of the blood leucocytes in the early stage of inflammation is as follows.* A male frog, which has been paralysed by injecting under the skin about $\frac{1}{2000}$ grain of curare an hour before, is secured on a plate of glass of convenient size for the purpose. A vertical incision is then made in the abdominal wall about half an inch in length, extending from the lower edge of the liver downwards. As much of the small intestine is then drawn gently out of the visceral cavity as is necessary in order that the mesentery may be evenly spread on a disk of glass which is fixed in a convenient position for the purpose. If the operation is performed with care and skill, it may be effected without bleeding and without in the slightest degree deranging the circulation.†

In order to obtain a general view, it is best to commence the examination with a low power. It is then seen that the arteries are smaller than the veins, the latter exceeding the former in diameter by about a sixth, that the arterial stream is quicker than the venous, that it is accelerated appreciably at each beat of the heart, and that in every artery a space can be distinguished within the outline of the vessel, which is entirely free from corpuscles. The arterial stream is so quick that the forms of the corpuscles cannot be discerned, but in the veins both coloured corpuscles and leucocytes can be distinguished, and from the first it is noticeable that while the former are confined to the axial current, the latter show a tendency to loiter along the inner surface of the vessel, like round pebbles in a shallow but rapid stream. So far all is normal, and may

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* Cohnheim, *Ueber Entzündung und Eiterung.* Virchow's *Archiv*, vol. xl. p. 27.

† The most convenient apparatus for the purpose consists of (1) A glass plate four inches long and two and a-half inches broad. (2) A common three-inch object-glass, to one side of which a glass disk four-fifths of an inch in width has been fixed with Canada balsam, in such a position that it projects by a third of its diameter beyond the edge of the object-glass near the middle. Around the adherent part of the disk there is an uncovered space of about one-tenth of an inch in width for the reception of the coil of intestine; and outside of this, an imperfect ring of cork to which the intestine may be pinned with fine needle-ends. The object-glass, with its disk, is fixed to a larger glass plate, at such a height above it that the free edge of the disk presses against the side of the frog's body, immediately below the incision, and is thus conveniently placed for the reception of the mesentery.

remain so for many hours, but in most cases changes occur in consequence of the exposure of the peritonæum, which are the beginning of inflammation.

The first abnormal phenomena observed have been already fully discussed—those of increased activity of the capillary circulation. On dilatation of the arteries of the mesentery follows a corresponding though less marked enlargement of the veins. During this stage the observer who desires to note the subsequent changes, must select for that purpose a vein of about $\frac{1}{300}''$ in diameter, the exact width of which it is desirable to measure either with the micrometer, or by marking its outline as projected on a sheet of paper with the drawing prism. For a couple of hours or more (the time varying in different animals) nothing whatever is to be observed except that although the vein gradually enlarges while the velocity of the venous current shows no abatement, the capillary circulation becomes more and more active; but sooner or later a change occurs which must be watched for with the utmost attention. This consists in a marked and almost sudden diminution of the rate of the current in the vein, in which that in the capillaries necessarily participates: it is the forerunner, and in some sense the cause, of the emigration which we desire to witness.

Simultaneously with the retardation, the leucocytes, instead of loitering here and there at the edge of the axial current, begin to crowd in numbers against the vascular wall, as was long ago described by Dr. Williams.* In this way the vein becomes lined with a continuous pavement of these bodies, which remain almost motionless, notwithstanding that the axial current sweeps by them as continuously as before, though with abated velocity. Now is the moment at which the eye must be fixed on the outer contour of the vessel, from which (to quote Professor Cohnheim's words) here and there minute colourless button-shaped elevations spring, just as if they were produced by budding out of the wall of the vessel itself. The buds increase gradually and slowly in size, until each assumes the form of a hemispherical projection, of width corresponding to that of a leucocyte. Eventually the hemisphere is converted into a pear-shaped body, the stalk end of which is still attached to the surface of the vein, while the round part projects freely.

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* See Dr. Williams' Gulstonian Lectures, published in 1841, in the *Medical Gazette*.

Gradually the little mass of protoplasm removes itself further and further away, and as it does so, begins to shoot out delicate prongs of transparent protoplasm from its surface, in nowise differing in their aspect from the slender thread by which it is still moored to the vessel. Finally, the thread is severed, and the process is complete. The observer has before him an emigrant leucocyte, which in all appreciable respects resembles those which have been already described in the aqueous humour of the inflamed eye.*

The experiment I have described, even if the phenomena are not observed with that care which is necessary in order to obtain a satisfactory result, is yet very convincing. For even if one fails from want of patience to watch an individual corpuscle through the successive stages of its escape, there are other obvious facts which are too significant to be misunderstood. The accumulation of innumerable leucocytes round veins which were before entirely free, the absence in these bodies of the faintest indications of any process by which they could be supposed to be developed where they are, the obvious identity of the leucocytes outside with those inside, the pedicles by which at all stages of the process many of the corpuscles hang on to the outer surface of the vessels—all these are facts which make it impossible to admit either that the corpuscles have been formed in the situations which they occupy, or that they have migrated from any other quarter excepting from the blood-stream.

In his observation on the same process in the tongue of the frog,† Professor Cohnheim follows the method originally em-

* From the description given above, it might be inferred that the experiment is one of great simplicity, whereas in practice it is attended with very considerable difficulty; so much so, indeed, that most persons who have tried it have found failure more frequent than success. The principal sources of difficulty are, 1st, that the time occupied in the first stage of the process, during which the circulation is going on with unabated velocity, is extremely variable; 2ndly, that if, from weariness or inadvertence, the attention of the observer is diverted from the selected vein at the commencement of the process of migration, he is very unlikely to succeed in seeing what he desires to see afterwards; for, inasmuch as leucocytes are escaping simultaneously in various parts of the mesentery, they soon accumulate in such numbers that their mode of exit can no longer be distinguished. Yet, notwithstanding these difficulties, no one who has time and patience enough need fail; great care in manipulation is required, but no extraordinary dexterity.

† Cohnheim, *Ueber das Verhalten der fixen Bindegewebskörperchen bei der Entzündung*. Virchow's *Archiv*, vol. xlv. p. 333. From comparative observations made recently, I am led to recommend the tongue as decidedly a better subject for study than the mesentery.

ployed by Dr. Waller, excepting of course that the animal is curarized, and that in order to facilitate the observation the mucous membrane is partially removed. The process of migration goes on in the tongue just as in the mesentery; but (to quote once more from Cohnheim) 'with such promptitude and certainty, and if the expression may be allowed, with such elegance,' that he feels tempted to prefer the former to the latter as an object of experiment.

From these facts Cohnheim concludes 'that all such corpuscles as are formed in the first stage of an acute inflammation certainly originate from the vessels,' but admits that they do not enable us to arrive at any determination of the question whether or not pus-cells originate in other ways in the later stages (p. 350).

The bare fact of emigration when first announced took every one by surprise. Notwithstanding, it was very soon accepted by pathologists, partly because their minds were prepared by the previous discoveries of v. Recklinghausen, partly because Cohnheim's statements bore upon them the stamp of straightforwardness and accuracy. Unfortunately many of Cohnheim's adherents have not been content with receiving the fact, but, as so often happens in similar cases, have attributed to it a wider significance than that assigned to it by the discoverer himself. The passage I have quoted above affords evidence that the doctrine commonly spoken of as Cohnheim's—that pus-corpuscles originate entirely and exclusively from the blood, and that the tissues have nothing to do with their production—is in reality not his.* He evidently sees as plainly as others that, although in the commencement of every acute inflammation the first generations of pus-corpuscles may be emigrants, there is nothing in the facts which contradicts the previously accepted belief, supported as it is by so overwhelming a mass of evidence, that the later generations are the offspring of the inflamed tissues.

I have now said all that appears necessary on the subject of the migration of leucocytes. It remains to notice in few words the parallel process of exudation of liquor sanguinis. The idea

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* I am aware that Prof. Cohnheim has since expressed himself much more positively than in the passage referred to. It is therefore the more important to show what impression was left upon his mind by the facts at the time he observed them.

that the escape of liquid from the blood into the inflamed parts is a main characteristic of inflammation is an old one; nor indeed is it very easy to see how it could be overlooked, for the swelling which is one of the four cardinal symptoms could not be otherwise explained. It is, therefore, not worth while to occupy space in stating evidence to show that every inflamed part becomes soaked with a liquid which is derived directly from the circulating blood. Nor is it expedient to refer to the doctrines which prevailed when the microscope was first used as an instrument of pathological research, as to the independent origin of pus-corpuscles and other cellular inflammatory products in exuded blood-plasma, excepting in so far as is necessary in order to explain that when we use the term exudation, we mean simply the *act* by which the liquor sanguinis sweats out of the vessels, not either the exuded liquid nor the structural elements which were at one time supposed to be spontaneously generated in it. The important relations of exudation with the other phenomena of inflammation will be fully considered under other headings.

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## Part III.—Stasis.

Another change occurs in the blood-vessels in inflammation, which, as it is subsequent as well as subordinate to those already mentioned, has not yet been adverted to. We have seen that in the mesentery as well as in the tongue of the frog, the vascular enlargement which is produced by irritation is for a certain time associated with an acceleration of the blood-stream, or at all events with no appreciable diminution of its velocity; but that, at an uncertain moment, the current begins to slacken, while the leucocytes hug the vascular wall and finally find their way out. If the part is arranged for observation in a manner conducive to the maintenance of the circulation, the retarded current may go on for a long time without any material alteration; but eventually it is apt to become slower and slower and more and more oscillating, until it ceases, in which case the condition long known as stasis is brought about. This does not, however, consist merely in arrest of the current, for it is observed that in those vessels in which

stasis has occurred, the blood is not merely motionless, but much altered in its aspect. It appears as if it were made up entirely of coloured corpuscles without liquor sanguinis, and these are packed together in the choked capillaries in such a manner that their individual forms are scarcely distinguishable. The nature of this change was most carefully investigated by Professor Lister in his well-known paper 'On the Early Stages of Inflammation.'* The principal results of his inquiries are as follows:—He believes that the accumulation of the corpuscles is due to a property they themselves possess of cohering together; and that they attach themselves to each other in the inflamed vessels in exactly the same way that they cohere in rolls in ordinary blood after its removal from the body. He does not, however, suppose that this cohesiveness of the corpuscles is greater in the blood of inflamed parts than in other blood;† for he finds in the first place that vessels leading to or from areas of stasis manifest no tendency to cohesion on the part of the corpuscles; and, secondly, that blood taken from inflamed parts differs in no respect from healthy blood, as regards the mode in which its corpuscles arrange themselves on the object-glass. These facts seem plainly to indicate that the cause of the phenomena is to be looked for, not in the condition of the blood, but in that of the vessels—in other words, that the corpuscles draw to each other, not because they are themselves in an abnormal state, but because the living tissue by which they are surrounded is altered. This conclusion is rendered even more certain by the recent experiments of Dr. A. Ryneck in the Physiological Laboratory at Gratz. He has shown that all the phenomena of stasis can be produced by irritation in the webs of frogs, in which milk or defibrinated blood of mammalia has been substituted for the circulating fluid. To demonstrate this, fresh milk must be injected under a pressure of from two to three inches by a canula into the *bulbus aortæ* of a curarized frog, the *sinus venosus* having been previously opened. The milk having passed through the systemic circulation, finds its way out at the venous opening, completely displacing the natural contents of the vessels. If, then, the web is touched

* *Philosophical Transactions*, 1858, p. 645.

† Loc. cit., p. 669. 'The adhesiveness which the red corpuscles acquire in inflammatory congestion, though varying in proportion to the degree of irritation, is never greater than occurs in the blood of a healthy part when withdrawn from the body.'

with a rod moistened with ammonia, the phenomena of stasis occur in the irritated part; the capillaries become crowded with milk-globules, exhibiting the appearance of grey cords. When defibrinated blood is used, the results are even more striking, for in this case the choked vessels soon exhibit in every respect the same appearances as in ordinary inflammation.

These results seem to make it perfectly clear that the local changes which lead to the production of stasis must have their seat either in the walls of the vessels, or in the tissues which immediately surround them. To determine this more precisely, Dr. Ryneck varied this experiment by first filling the vessels with an indifferent liquid, such as solution of common salt of proper strength, so as to remove the blood; then subjecting their internal surfaces for a few moments to an agent which, by virtue of its chemical action, might be expected to modify or destroy its vitality; and finally, after replacing the injurious liquid by milk or defibrinated blood, observing the effects of local irritation. Solution of chromic acid, chloride of gold, and sulphate of copper, were found to be well adapted for thus acting on the vessels. The results were decisive. No stasis was produced by irritation in webs which had been thus treated.*

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## Part IV.—Structural Changes in the Capillaries.

Until a few years ago, it was supposed that the capillaries take no part in normal or abnormal nutritive processes, excepting in so far as they act as passive filters through which liquor sanguinis transudes. This belief was first shaken by the discovery of Stricker that when the capillaries of the *membrana nictitans* of the frog are examined alive (i.e. when the structure is placed under the microscope in aqueous humour immediately after excision), they exhibit changes of form and size which can only be accounted for by supposing them to be contractile.†

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* Ryneck, *Zur Kenntniss der Stase des Blutes in den Gefässen entzündeter Theile.* Rollett's *Untersuch. aus dem Institute für Phys. u. Histol. in Graz.* Leipzig, 1870, p. 103.

† Stricker, *Ueber die capillaren Blutgefässe in der Nickhaut des Frosches.* Sitzungsberichte der Wiener Akademie, 1865, vol. li. part ii. p. 16. *Studien über*

The activity of the life of the capillary wall has been more completely demonstrated by the further researches of the same pathologist, especially those carried out by him in combination with Leidesdorf, as to traumatic inflammation of the substance of the brain.*

In his first inquiry, published in 1866, Stricker showed that in the brain of the common fowl, when examined five or six days after mechanical injury, the vessels of the injured part exhibit changes which may be best described as consisting in budding or sprouting of the capillary wall. The structureless or hyaline substance of which the capillary appears to consist, is found to have undergone thickenings here and there of such a nature, that instead of being evenly cylindrical, it exhibits projecting irregularities or knobs. Of these knobs some retain their original form, while others grow out into branched or undivided processes, in a direction at right angles to that of the capillary, which sooner or later unite with similar outgrowths springing from other capillaries, so as to give rise to a connecting mesh-work of fibres. In the early state all these formations are beset with numerous fat granules, exactly similar to those which exist in the well-known exudation-corpuscles of inflamed brain substance; so that wherever the knobs are of a globular form, they look as if they were exudation-corpuscles, embedded in and continuous with the substance of the capillary. Very recently these observations have been repeated by Dr. Jolly of Munich,† under Professor Stricker's guidance, who has found that the alteration of the capillaries begins within a day after the injury. The first change consists in an infiltration of the capillary wall with fat granules, and has its principal seat in the neighbourhood of the nuclei. As the process advances, the granulation increases, and the alterations of form already described begin to manifest themselves.

Although a similar process has not been made out in other tissues when in a state of inflammation, there are various facts relating to the condition of the capillaries in such tissues, which are in accordance with it. Thus in the process of healing by the first intention, the formation of new vessels takes place by a

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*den Bau und das Leben der capillaren Blutgefässe,* loc. cit. vol. lii. part ii. p. 379.

* Leidesdorf und Stricker, *Studien über die Histologie der Entzündungsherde.* Sitzungsb. der Wien. Akad. vol. lii. part ii. p. 534.

† Jolly, *Ueber traumatische Encephalitis.* Stricker's *Studien,* 1870, p. 38.

mode of budding from the old capillaries, which is very like that we have been considering. Little processes sprout out from capillary loops in the neighbourhood of the wound, which are still entire, and grow towards similar processes which spring from other loops. The two growing points, as soon as they come into contact, melt together, just in the same way as the growing ends of the marginal filaments which we studied before in the plasmodium of the myxomycetes. Thus the main difference between the process of healing and that of traumatic encephalitis lies in the circumstance that in the latter the outgrowths from the capillaries are apparently not tubular, and do not become vessels. So also in the pyogenic membranes of very small abscesses, the newly formed capillaries, although they become looped, originate by outgrowth in the same manner.*

Since the discovery of the emigration of blood leucocytes, it has often been argued that their escape from the capillaries would not be possible unless the capillary membrane were porous; and then, this being admitted, the fact that the capillaries can be filled to distension with transparent injection-masses (such as the so-called soluble prussian blue) without the slightest extravasation, has been used as a reason for regarding migration as an impossibility. There seems to me to be no doubt that if the porosity of the capillaries were a necessary inference from the fact of emigration, the objection made would be a valid one. But from the account which has been already given of the vital properties of the capillary substance, the reader will see that any such assumption would be premature. The capillary is not a dead conduit, but a tube of living protoplasm. There is therefore no difficulty whatever in understanding how the membrane may open to allow the escape of leucocytes, and close again after they have passed out; for it is one of the most striking peculiarities of contractile substance that when two parts of the same mass are separated, and again brought into contact, they melt together as if they had not been severed.†

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* For a full description of this subject, see Wywodzoff, *Experimentelle Studien über die Vorgänge bei der Heilung per primam intentionem. Medizinische Jahrbücher*, 1867, p. 3.

† 'The griding sword with discontinuous wound
Passed through him, but th' ethereal substance closed
Not long divisible . . . . . .
. . . . . for spirits that live throughout

## Part V.—Summary.

We have now arrived at a point in our inquiry at which we may perhaps advantageously pause, and endeavour to bring the various parts of the process we have considered into closer relation with each other.

We have learnt that in inflammation the circulation is at first accelerated and increased, subsequently retarded and diminished, that the latter condition is attended with exudation of liquor sanguinis, emigration of leucocytes and stasis. In the study we have already made of these phenomena we have been led to believe that their origin is partly local, partly general. Thus, with respect to the leading vascular change in inflammation, viz. the acceleration of the blood stream, it has appeared to be established on satisfactory grounds that it is a consequence of an impression received by the centripetal nerves of the injured part, and reflected by the vaso-motor centre through the centrifugal nerves to the vessels; so that, although our understanding of the mechanism by which this result is brought about is as yet very imperfect, we can have little doubt that it is due to changes having their seat in the nervous system. On other grounds we have seen reason to suspect that most of the subsequent phenomena have no direct relation to the dis-

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Vital in ev'ry part, not as frail man,
In entrails, heart or head, liver or reins,
Cannot but by annihilating die;
Nor in their liquid texture mortal wound
Receive, no more than can the fluid air.
All heart they live, all head, all eye, all ear,
All intellect, all sense; and as they please,
They limb themselves; and colour, shape, or size
Assume, as likes them best, condense or rare.'

*Paradise Lost*, Book vi.

Since the above was written I have had the opportunity of witnessing the very admirable and ingenious experiments lately exhibited at the Royal Society by Dr. Norris. A membranous film is formed by dipping a metal ring, a foot or more in diameter and held horizontally, into a vessel containing solution of soap. It is then shown that soap-bubbles, glass rods, and other objects with wetted surfaces, can be pressed through the film without its being ruptured. The conditions of this experiment are so entirely different from those which exist in the living tissue, that I cannot regard it as affording any explanation of the passage of leucocytes through the walls of the capillaries.

turbance of the circulation as their cause, but rather to intimate changes in the properties of the living substance with which the blood comes into contact in its passage through the affected part. We shall probably best accomplish the end we have in view by assuming in the first instance that the essential phenomena of inflammation are referable either to disordered vascular innervation or to a local disturbance of the life of the inflamed part. We shall then be able to consider, with respect to each of them in succession, in how far it is referable to one or other of these proximate causes. The assumption, even if it do not turn out to be a true one, will materially help us in bringing facts into connection, and in determining their relative significance.

We have first to inquire into the causes of the slowing of the blood-stream which always succeeds the primary acceleration. Does it happen because the access of blood from the heart is retarded? or is it a combined result of the subsidence of the previous acceleration and of dilatation of the smallest vessels? The main reason for believing that it is due to diminished supply of blood from the heart, and therefore presumably to a condition of the arteries the reverse of that which leads to the previous afflux, is that in certain cases it is attended with visible narrowing of the arteries. The most positive observations on this point are those of Saviotti already referred to. He has made careful comparative experiments as to the vascular effects produced in the web of the frog by acids, alkalies, metallic salts, neutral alkaline salts, croton oil, cantharides, and other irritants; and he finds that in every case the diminution of the capillary circulation is attended with narrowing of the afferent arteries. Just as in the case of the previous dilatation, however, the relation between contraction of the capillaries and slowing of the blood-stream is not constant either as regards their degree or the time at which they occur. This want of correspondence is in itself sufficient to show that the former canot be regarded as the cause of the latter. And we are the more disposed to adopt this view when we consider that the contraction can be completely accounted for otherwise. During the primary afflux of blood the arterial dilatation extends not merely to those branches which lead directly to the inflamed area, but to those which convey blood to its immediate neighbourhood. Soon, slowing and stasis occur at the centre, the increased afflux still continuing, in consequence

of which the collateral capillary channels become more and more enlarged. Eventually the arterial determination of blood subsides; less blood flows, but the capillaries still remain open, and therefore the artery which feeds them having less resistance in front, contracts to a diameter smaller than that which it originally possessed. In other words, notwithstanding the obstruction which exists at the seat of inflammation, the effect produced is not, as might be expected, dilatation, but contraction of the afferent artery, because the resistance is far more than balanced by the increased facility of circulation in the surrounding zone of congestion; so that the pressure of the blood against the inner surface of the artery, and consequently its expansion, is considerably lessened. The diminished circulation in an inflamed part is therefore not to be regarded as a consequence of the diminished afflux of blood *a tergo*; for the narrowing of the arteries is a merely secondary effect of the disturbance of the circulation. We must, therefore, in accordance with the assumption with which we started, look in the direction of the local changes for its cause.

It follows from what has been said that the slowing of the capillary circulation is merely the first stage of stasis, the beginning of the process of which stasis is the end. For if it be granted that they are both of exclusively local causation, it would be unreasonable to separate them; the more so considering that in all cases in which we have the opportunity of observation, the former is found to pass by insensible gradations into the latter. So far, therefore, as relates to the local changes in inflammation, i.e. to those which occur within the range of the immediate action of the injurious stimulus, we see that the process consists first in gradual arrest of the capillary circulation, and secondly in exudation of certain constituents of the blood. When we proceed further to inquire in what relation these two stand to each other, by comparing the circumstances under which they are actually observed, we come at once to the conclusion that they are so closely and inseparably associated that neither can be considered as consequent or antecedent, and hence that both must be dependent on the same proximate cause.

In the present state of our knowledge it is not possible to elucidate the nature of this cause completely. There are, however, certain experimental facts which enable us to approach its solution somewhat closely, and which will, on this ground,

serve as a basis for future investigation. Thus, if a ligature is tightened round the thigh of a frog, so as to arrest the circulation, and ammonia is applied to the web, the blood gathers from all sides towards the irritated part, until the capillaries within the area of irritation become choked with closely packed blood-corpuscles, and present all the appearance of stasis. If at the same time the other web is irritated in a similar manner, a comparison can be made of the effects produced. So far as the state of the capillaries is concerned, there is no difference whatever between them; the similarity becoming still more striking if the circulation is restored in the ligatured limb by removing the thread. Both webs then exhibit the ordinary results of irritation.*

In this experiment we have the process of inflammation reduced to its simplest form. Taken in combination with the observation of Dr. Ryneck, related in Part III., that neither exudation nor arrest of the capillary circulation can be produced in vessels through which certain poisonous metallic solutions have been passed, it shows that the agent in all the visible local effects is the living substance with which the blood comes into contact as it flows. Beyond this point we lose the guidance of direct observation, and must for the present content ourselves with stating that in an injured part the walls of the capillaries become so altered that the liquor sanguinis, instead of transuding from the smaller arteries in quantity just sufficient to balance the absorption, leaks abundantly from the vessels; and that in many cases this is subsequently associated with squeezing out of the leucocytes, or even of the coloured corpuscles.†

What the nature of this sudden change in the living sub-

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* This experiment was first made by H. Weber in 1852 (*Experimente über die Stase an der Froschschwimmhaut.* Müller's *Archiv*, 1852, p. 361). It was repeated by Prof. Lister (loc. cit. p. 667) in 1857, and subsequently by other pathologists.

† That the change by which the capillaries become leaky has its seat in the vascular walls rather than in the adjoining tissue, is rendered probable by a recent observation of Dr. Ryneck, who has found that if an irritant is applied to the web of a frog, in which solution of common salt is circulating instead of blood, it becomes infiltrated at the seat of irritation to such an extent that a prominent tumour is formed, which eventually spreads over the whole of the division of the web acted upon. This experiment shows that exudation cannot be a consequence of increased attraction between the tissue and the circulating liquid, for in the case of salt solution such an attraction cannot be supposed to exist.

stance is, we know not, and should gain nothing by speculating. Apart from all theory the fact stands out clearly that, independently of any visible alteration either in the vessel itself or in the structural elements in its neighbourhood, the constant effect of injuring a living tissue is to divert a part of the liquor sanguinis from its natural course, and determine its soakage from the vessels which before held it, into the surrounding parenchyma.

Another question presents itself, the consideration of which cannot be left out, although it does not at present admit of any satisfactory answer—viz. that of the immediate cause of the emigration of leucocytes, and the relation of this phenomenon to exudation of liquor sanguinis. Why, as the blood-stream slackens in an inflamed part, leucocytes should separate from it and tend towards the internal surfaces of the veins and capillaries, we must admit ourselves altogether unable to explain. The fact that if blood freshly taken from the circulation of a frog or newt is received in a capillary tube or under a cover-glass, the leucocytes emigrate from the clot as soon as it is formed, and collect in numbers in the surrounding serum, affords an opportunity of watching the process under conditions much simpler than those which exist in the circulation.* As yet we are as little able to explain the one as the other. There can, I think, be little doubt that of the two stages in the process of emigration—viz. the long known loitering of leucocytes along the sides of the vessels, and the newly-discovered penetration by them of the vascular walls—the first is the essential one, and that whenever an explanation is found of the former, it will serve as a key to the comprehension of the latter.

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* For a description of this process see my lecture on *Leucocytes*, already quoted.

## SECTION II.—CHANGES WHICH HAVE THEIR SEAT IN THE TISSUES.

*Introduction.*

In the preceding section we have seen that the process of inflammation centres in the discharge of liquor sanguinis from the capillaries. We have now to consider the influence which the exuded liquid exercises on the elements of the tissues. The textural changes, although they may differ considerably according to the structure and function of the part affected, are all of such a nature as to indicate increased activity of cell life. Considering that the condition of an organ which is the seat of inflammation differs, so far as observation teaches us, from the ordinary state only in being soaked with exuded liquor sanguinis, it is natural to attribute the supervening over-growth and over-multiplication of cells to the exudation. As, however, many pathologists believe that these effects have an extremely different signification—that they are the results not of the direct stimulation of the cells, but of impressions reflected to them by an unknown nervous centre, supposed to preside over nutrition—we shall, after we have completed those anatomical descriptions which will constitute the most important part of the present section, place before the reader the grounds which exist for believing that whatever other influences may co-operate with that of changes in the nutritive medium in which the tissues are immersed, this is in itself sufficient to account for the textural germination. (See Part III.)

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### Part I.—Structural Changes which occur in the Connective and Supporting Tissues in Inflammation.

Under this title I include all those tissues which are not concerned in any function excepting those expressed in the definition. With reference to the present inquiry they are divisible into vascular and non-vascular. The vascular tissues include

bone and the varieties of connective tissue in the strict sense; the non-vascular, cartilage, tendon and the cornea.

*Non-vascular connective and supporting tissues.*

In studying the process of inflammation in tissues which derive their supply of nutritive material from blood-vessels at a considerable distance, we have the great advantage of being able to separate entirely those phenomena which are proper to the tissue-elements from those which belong to the circulation. For this reason it is not surprising that the non-vascular tissues have at all times, since the earliest attempts to apply exact methods of research to pathology, been favourite fields for this investigation, and that of late years in particular, the most fruitful and at the same time decisive discussions which have taken place have related to the structural changes produced by artificial irritation in the cornea.

*Inflammation of the cornea.*—The reader who desires to know more of the earlier researches relating to traumatic keratitis will find the information he requires in special treatises on that subject. For the elucidation of the question which now engages our attention it appears scarcely necessary to carry our inquiries beyond the past ten years; for the better modes of investigation which have been introduced since 1863 by v. Recklinghausen and Cohnheim have given to subsequent observers so great an advantage over their predecessors, and placed the subject in a light so entirely new, that it has become necessary to begin the work afresh. The result has been to confirm the truth of the previous discoveries, and to establish the doctrine of textural pyogenesis, which was so admirably developed in the article on the process of inflammation contained in the previous edition of this work, on a more solid and extended basis.

Professor von Recklinghausen's method of examining the cornea of the frog is as follows:* The anterior chamber is first punctured so as to let out a drop of aqueous humour, which is placed on the object-glass; the cornea is then excised and placed in the drop with Descemet's membrane uppermost. The preparation thus obtained is examined without a cover-glass, in a closed chamber in which the air is saturated with

* V. Recklinghausen, loc. cit. p. 157.

moisture, so that no evaporation can take place, and consequently no alteration in the density of the liquid in which the cornea is immersed.* The healthy cornea is absolutely transparent, and when it is examined under the microscope in the manner described, no structure can be distinguished. This homogeneity, so essential to the function of the cornea, is a condition inseparable from life; if the observation is continued till the tissue begins to die, its structural elements gradually come into view—first the epithelia, then the lymphoid elements proper to the tissue, then the cornea-corpuscles. The explanation of the fact is, that whereas in life the elements of which the cornea is formed, affect light exactly in the same degree, their respective refractive powers are slightly altered in the act of dying.

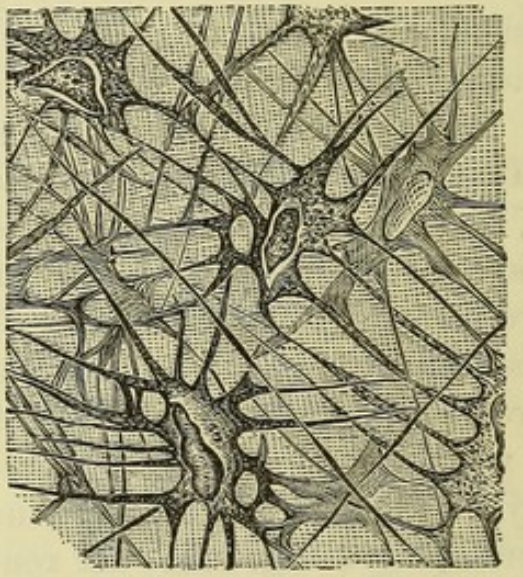
If a cornea is examined in the same way, which has been irritated a quarter of an hour before by the application of a point of caustic to its surface, the conjunctival epithelial layer can at once be distinguished, along with a few leucocytes, underneath and among the epithelial elements. If an hour or two has elapsed, the proper cornea-corpuscles are visible, as dark stellate or spindle-shaped spots on a transparent ground. Of these some are homogeneous, and can be distinguished from the surrounding substance by a slight difference of shade. In others, which are finely granular, the processes or rays are subject to slight variations of contour. These amœboid movements of the rays, although very sluggish as compared with those of young protoplasm in general, are rendered much more active by subjecting the preparation to a stream of blood-serum; for which purpose Professor Stricker employs the serum of the same animal which has furnished the cornea.

In order to follow the inflammatory process in its further stages, another method of preparation has been found by Stricker to be advantageous. The cornea is immersed for a few minutes in a weak solution of chloride of gold ($\frac{1}{2}$ per cent). It is then washed with water slightly acidulated with acetic acid, and exposed to daylight. When the frog's cornea is examined in this way at various periods after irritation, the

* The following statement is founded on the admirable research of Mr. W. F. Norris, conducted in the Vienna laboratory under Stricker's guidance. Norris and Stricker, *Versuche über Hornhaut-Entzündung.* Stricker's *Studien*, 1870, p. 1. I retain the terms employed by the authors, although in the light of more recent anatomical discoveries they are open to criticism.

progress of the changes of which the beginning has been already sketched, may be studied with great advantage. In the normal cornea, when so treated, the stellate corpuscles with their nuclei can be very distinctly seen. The latter are irregularly defined, of large size in relation to the protoplasmic mass in which they are embedded, and contain one or two nucleoli. In the stellate masses themselves the caudate processes or rays are the most striking and obvious features. In a cornea excised three hours after irritation, some of the corpuscles exhibit no change excepting that their outlines are more strongly marked; in others there seem to be, in addition to the irregular nucleus above referred to, one or more spheroidal bodies which are embedded in some other part of the corpuscle. This appearance affords

FIG. 400.



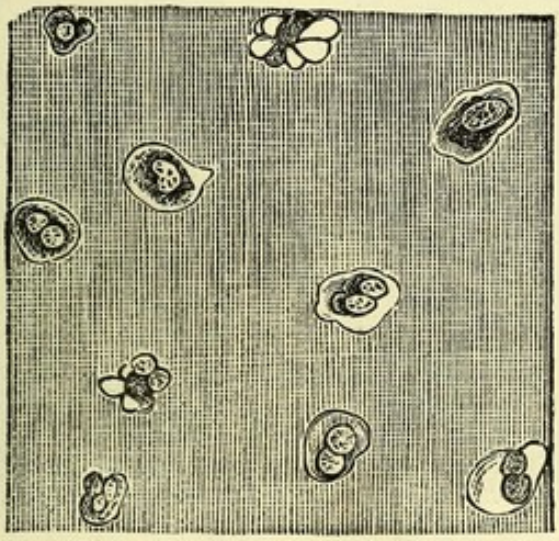
Cornea of frog excised three hours after irritation.

the earliest sign that the process which has been hitherto called 'proliferation' is beginning, that is to say that the mode of life of the protoplasmic mass is changing from the normal quiescent state which fits it to take part in a permanent tissue, to the state of reproductive or germinating activity—that new bodies are being formed within the body of the parent mass, to which such terms as 'germs' or 'offspring' are applicable. A part of the original living substance of the element begins a new life, much more active than it before possessed, and a new organic development. Since the introduction of the method of observing structural changes in living tissues, pathologists have learnt that it is a constant characteristic of the change we are considering, that the rejuvenescent part or

substance acquires the property of contractility. In other words, that all protoplasm when assuming new life, and beginning new organic development, is endowed with the faculty of amœboid movement. Of the words which have been employed to denote this change, viz. rejuvenescence, proliferation, germination, the last appears preferable as being the least technical and the most expressive.

We return to the further steps of the germinative process in the inflamed cornea. Between the fifth and twelfth hours after irritation the cornea-corpuscles become more and more distinct and granular, while their processes become thicker and shorter, until at length many of them lose altogether their

FIG. 401.

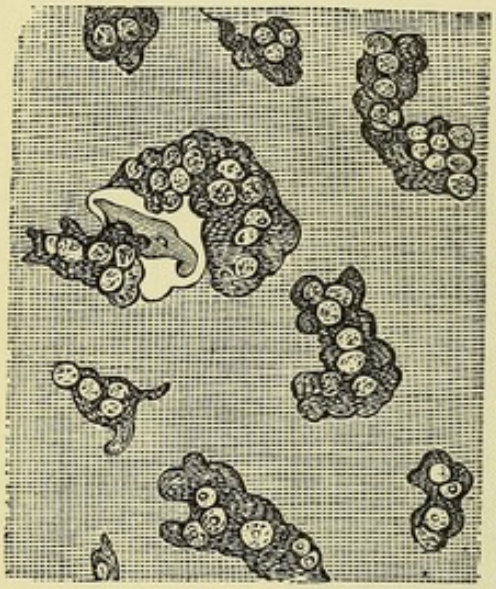


Altered corpuscles of cornea excised eight hours after irritation.

characteristic stellate, or caudate, outline, and are converted into irregular clumps. If the cornea is examined in this stage, after treatment with chloride of gold, it is seen that in those parts in which the structural changes are most advanced the normal character of the tissue is entirely lost. The beautiful network produced by the interlacing of the normal corpuscles is no longer visible; in place of it the field is scattered over with clumps of irregular form, in some of which the caudæ are represented by rounded knobs, while in others the outline is almost spheroidal. Most of these bodies are so granular that their contents cannot be distinguished, but in others the newly formed germs are plainly visible. The number of these germs varies according to the stage of irritation, so that in the same cornea, clumps containing a numerous offspring may be seen in one part, while in others the germination is only beginning.

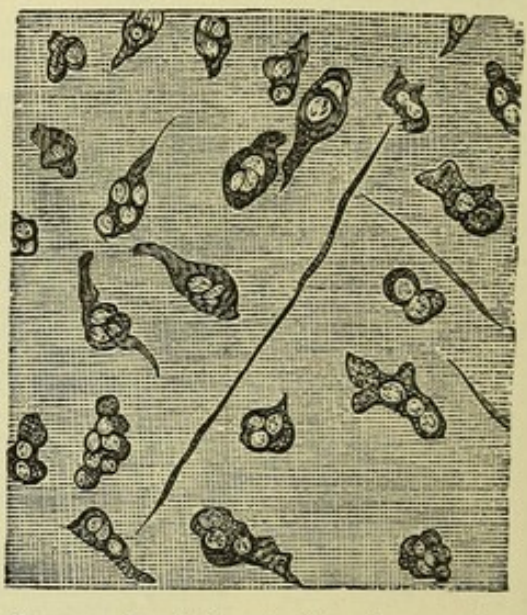
That the interpretation suggested by these appearances is the true one, that the clumps containing numerous round corpuscles are really of the nature of mother-cells, the observer can best assure himself by returning to the method of examination first described, that is to say by placing the inflamed tissue under the microscope alive, at the same time stimulating the elements in question to increased amœboid movement by irrigation with serum. It is then seen that the germs change their relative position with the movements of the mass of protoplasm in which they are enclosed, just in the same way

Fig. 402.



Cornea sixteen hours after irritation. Amœboid masses containing numerous newly formed elements.

Fig. 403.



Cornea about twenty-four hours after the insertion of a fine ligature. Masses containing young elements in the neighbourhood of the thread.

as the granules and ingesta do in the body of an amœba, rolling one over another in such a manner as would not be possible if they were not really contained in the mass.

Hitherto nothing has been said of pus-corpuscles, that is leucocytes, because in the stages of keratitis we have been considering they bear no part. The cornea has lost its perfect transparency, but is not as yet turbid; the few leucocytes which are met with are those which are indigenous in the tissue. There is as yet no suppuration; to arrive at an opinion as to how the formation of pus commences we must follow Professor Stricker a stage further. The difficulty of the observation lies in the rapidity with which the process takes place; for from the moment that the cornea begins to be clouded, its

tissue is so beset with growing and multiplying elements that it is difficult to distinguish them, so that the only way by which a conclusion can be arrived at is by combining the results of a number of observations made on different corneas at the stage of commencing opacity.* From such observations it may be learnt, first that the opacity is due to the presence of leucocytes which are so numerous that it is out of the question to regard them as the offspring of those which are indigenous in the tissue; and secondly, that among them there are many of the original branched or stellate corpuscles, some of which are only slightly changed in outline or aspect. But in addition to these more or less normal corpuscles, the masses above described, containing groups of germs, also occur in great numbers, while among them, and in the very parts of the cornea where they are most numerous, the leucocytes are most crowded and there are fewest fixed corpuscles. If these are facts it can scarcely be doubted that there is a relation between the metamorphosis of the stellate corpuscles and the formation of leucocytes; in short, that the little spheroids which are contained in the amœba-like masses are young pus-corpuscles, and that even in the cornea suppuration must be regarded as at all events in part, a process of germination.

We have next to consider to what extent emigration is also concerned in traumatic keratitis. According to Professor Cohnheim, it is the only way in which the pus-corpuscles are produced, this conclusion being mainly founded on negative observations. He has failed to observe the germination process we have been describing, and does not believe in it. He finds that in every form of traumatic keratitis, whatever be the nature or mode of application of the irritant, the stellate corpuscles remain absolutely unaltered, both as regards their position and arrangement, and their structure, and that the leucocytes to which the opacity is due are neither enclosed in other elements nor show any indication of being in different stages of development; whence he naturally concludes that they cannot have originated where they are found, and must have been introduced from outside. He has further observed, and

* The reader who is acquainted with Professor Cohnheim's researches on keratitis will notice that they commence at the point to which we have now reached, so that it is not difficult to understand that, although he employed the same modes of examination, he failed to observe the structural changes which have been described in the preceding paragraphs.

the fact has been confirmed by many other pathologists, that if keratitis is produced in a frog whose blood-leucocytes have been charged or fed with aniline or vermilion by injecting either of these pigments in a state of extremely fine division into the circulation, corpuscles can be distinguished in the inflamed cornea, which from their being pigmented must necessarily have migrated from the blood. In some cases the marginal part of the cornea, that part which of course is nearest to the vessels, is so full of immigrant leucocytes that the blue or red coloration can be distinguished even with the naked eye. These facts of course afford conclusive evidence of migration, but they contain no disproof of tissue-germination, for even Professor Cohnheim himself admits that in all stages of the process there are many leucocytes which are not coloured.

The only positive argument against germination is that founded on the remarkable experiment known as that of the 'salt frog.' This experiment consists in slowly injecting a weak solution of common salt by the abdominal vein, until blood ceases to flow from its peripheral end which is left open, so that the whole of the natural circulating fluid is replaced by the saline solution. In this condition the animal may be kept alive for several days. If then, immediately after the injection, the cornea is irritated, no opacity is produced, because, according to Cohnheim, the blood from which they spring is absent. During last summer this experiment was carefully investigated in the Vienna Pathological Laboratory. It was found that even if the injection is continued, according to Cohnheim's direction, until the liquid which issues from the open end of the vein appears colourless, the minute capillaries as seen in the mesentery still contain liquid which is rich in leucocytes, so that whatever be the explanation of the want of opacity of the cornea, it is not due to the absence of these structures from the circulation; it is much more reasonable and natural to suppose that the result of the experiment is to be accounted for by the peculiarly abnormal condition of the animal.

*Inflammation of cartilage.*—The changes which occur in the permanent structural elements in consequence of irritation, are much more easily studied in cartilage than in the cornea, on account of the facility with which this tissue can be prepared for microscopical examination; it has therefore from the commencement of the inquiry afforded to the pathological observer the most accessible evidence in support of the belief that such

structural changes form an essential part of the process of inflammation; and particularly as regards the question of the origin of pus, the obvious difficulty of supposing that the young elements which occupy its cavities when it is inflamed have penetrated into those cavities from some other quarter, has made the case of cartilage the strongest that can be cited against any exclusive doctrine of emigration. For this very reason it is unnecessary to devote much space to the discussion of inflammation in cartilage, for it is certain that if we can show that germination is the rule in every other tissue, no one will suppose that cartilage is an exception. The normal cartilage cell, like every other active cell, is a mass of protoplasm containing a nucleus. As in the case of the cornea, each mass is enclosed in a cavity of similar form to itself, which is hollowed out in the interstitial substance; the difference being that whereas in the cornea the cavities communicate with each other by the innumerable tubular prolongations which correspond to the rays of the stellate cells, in cartilage they have no such prolongations and are entirely closed. When cartilage is irritated, as for example by scraping its surface, the cells in the neighbourhood of the irritation enlarge and consequently expand their capsules. The protoplasm of which each cell consists becomes more granular, and soon it is found that the mass contains two corpuscles in its interior instead of one, and that each has a gathering of protoplasmic matter around itself. This process of division is repeated in each segment until every cavity contains a mass of nucleated cells, which at length assume characters corresponding with those of newly formed pus-corpuscles, while at the same time the original interstitial substance gradually wastes away, and is finally represented by a sponge-like stroma, in the holes of which the groups of young cells are contained. In this process we have a typical example of germination; the permanent cells which have for their function the maintenance of the unchanging life of the tissue, are replaced by a more numerous progeny of transitory mobile cells—i.e. leucocytes—which live at the expense of what remains of the tissue and eventually destroy it.

*Inflammation of tendon.*—As a non-vascular tissue, extremely rich in cellular elements, tendon has almost as great advantages as cartilage for the study of the inflammatory changes which such elements undergo at a distance from the vessels. The splits (*Henle'sche Spalten*) which exist in tendon between the

parallel bundles, are lined with chains of staff-shaped, nucleated cells, each of which is in contact with its neighbours by its ends, and consists of a cylinder of protoplasm, including a nucleus. The changes which these cells undergo have been recently very completely studied in rats and guinea-pigs by Dr. Güterbock, who finds that by a kind of cleavage of the nucleus that body assumes a botryoidal or necklace form, to which the scanty covering of protoplasm models itself. Eventually new cells (young pus-corpuscles) are formed by the complete division of the nucleus. Here, as in other cases, the participation of the elements of the tissue in the germinative process, can only be judged of at the very beginning, i.e. about eight hours after the injury. At a later period it is so difficult to distinguish the results of similar changes in the connective tissue from those proper to the tendon itself, that no conclusion can be arrived at.*

*Vascular connective tissue.*

The most positive information we possess as to the nature of the inflammatory changes in vascular connective tissue is derived from the examination of the process in the frog's tongue, for there is no other organ in which the tissue in question can be placed under the microscope under conditions so completely normal. The mode of experiment has been already referred to.

The textural changes have been lately described with great minuteness by Professor Cohnheim,† and still more recently his description has been critically examined by Professor Stricker.‡ The curarized frog is conveniently placed on its back, the tongue being extended by a ligature attached to each of its two tips, and the ligatures so fixed that the organ can be set free and replaced in the mouth at the end of each period of observation. The tongue can thus be placed readily under the microscope, with its papillary surface upwards. As, however, the submucous tissues could not be well seen through the mucous membrane, it is desirable to strip this membrane off, over a small extent of surface, an operation which can be effected with scarcely any bleeding, and has the additional advantage that it affords a con-

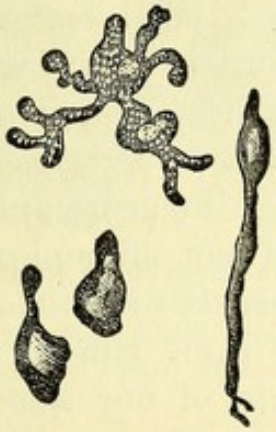
* Güterbock, *Untersuchungen über Sehnenentzündung.* Stricker's *Jahrbücher,* i. p. 22.

† Cohnheim, loc. cit. p. 344.

‡ Stricker, *Ueber die Zelltheilung in entzündeten Geweben,* loc. cit. p. 18.

venient and practical method of irritating the parts to be examined. If these preliminary arrangements have been successfully carried out, and sufficiently high powers are employed in the examination, it is seen that in the meshes between the capillaries of the inter-muscular spaces there are bodies of the most varied form and slightly turbid appearance—the so-called connective-tissue-corpuscles. According to Cohnheim these

FIG. 404.



Connective tissue corpuscles of the tongue of the frog.

bodies take no part whatever in the inflammatory process, the steps of which, as he observed it, correspond to those we have already described when speaking of inflammation in the mesentery. To determine this question, of such importance in its general bearing on inflammation of connective tissues, Professor Stricker has subjected these corpuscles to the closest scrutiny. He finds that while some of them are oblong or fusiform, others are of the extremely irregular form figured by Cohnheim, and that corpuscles of the latter class may be watched for hours (in one instance in the same individual for ten hours continuously) without changing their place. But he does not admit that they are motionless; on the contrary, he states that they undergo changes of form of so marked a character, that there can be no mistake about their existence. Thus they swell at one part, shrink in others, sometimes budding out into processes, which are again retracted; at others assuming forms which seem to indicate that they are on the point of dividing. Yet notwithstanding the most careful and patient observations, Stricker has not succeeded in seeing a single act of division completed. In the oblong corpuscles the amœboid changes are less active, and limited to the extremities. Sometimes it was observed that the tip gathered itself up as if it were just

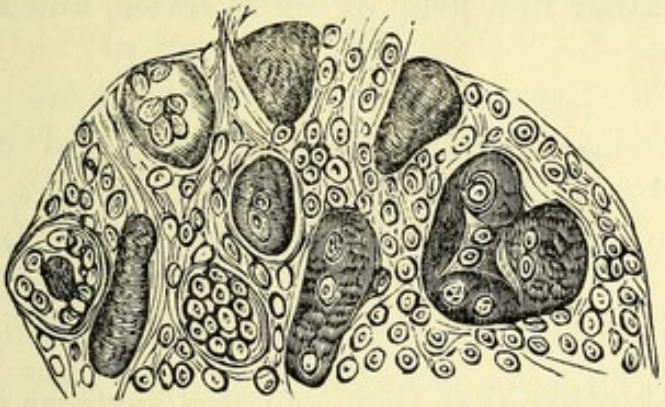
about to separate from the rest, but again subsided into its original condition.

In several of Stricker's experiments the process of emigration was going on with great activity, and the tissue becoming fuller and fuller of leucocytes during the whole period that he was engaged in observing the phenomena above described in the connective-tissue-corpuscles. It therefore appears perfectly clear that, in the particular case of the tongue of the frog, these corpuscles have at first nothing to do with the process of suppuration. On the other hand it seems highly probable that if it had been possible to pursue the investigation to a later stage, the changes of form which he describes would have resulted in actual division. The lesson to be learned here, as in other cases, seems to be, that although in acute and rapid suppurations the leucocytes are mostly if not all emigrants, there is reason to believe that at later periods other modes of pyogenesis come into operation. At the same time it must be borne in mind, that in the present state of our knowledge this is rather a matter of inference than of observation. The grounds for believing it are in the first place the facts we have already considered with reference to the cornea, and secondly the structural alterations which are met with in examining tissues in the more advanced stages, and less acute forms of inflammation—all those anatomical facts, in short, which formed the original groundwork of the doctrine hitherto taught of the textural origin of pus ; with reference to which many of Cohnheim's followers seem to have forgotten that they are quite as true and quite as significant as ever. For in every limited inflammation of the subcutaneous tissue, and in the neighbourhood of every subcutaneous abscess, a region is found outside of the focus of suppuration, in which the connective-tissue-corpuscles present alterations which are so distinct, that it is impossible for any one who is conversant with them to doubt that they signify that the tissue is germinating.*

* The experiment of M. Lortet, already referred to (p. 750), affords the pathological student the opportunity of satisfying himself, by a single observation, that in traumatic inflammation of the subcutaneous cellular tissue, pus is formed both by tissue-germination and emigration. The swimming-bladder of a fish, previously filled with solution of common salt, is inserted beneath the skin of a rabbit. After thirty-six hours the animal is killed, and the lesions are investigated. It is then seen that while the bladder is full of corpuscles which can only have migrated from the blood vessels, there is abundant evidence of the commencement of germinative pyogenesis in the surrounding texture.

*Inflammation of muscle.*—There is no vascular tissue in which the phenomena of germination can be more satifactorily studied than in muscle. The process was first examined by Waldeyer, and subsequently by Otto Weber (Fig. 405). Still more recently

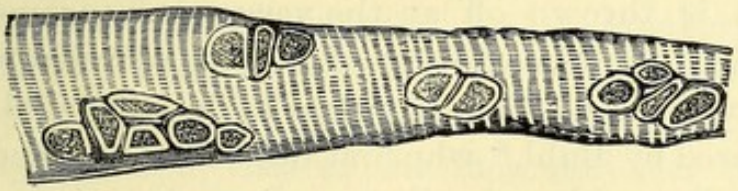
Fig. 405.



Cross section of human muscle from the neighbourhood of a wound. The dark masses represent the remains of muscular bundles. In other parts of the section the sheaths are filled with young elements, which have displaced the muscular substance. The interstitial connective tissue is also in a state of germination. (After Otto Weber).

it has been made the subject of an extended series of experiments by Dr. Janovitsch Tschainski,* under the direction of Professor Stricker. In traumatic inflammation of muscle, the fixed corpuscles of the fibre-sheaths undergo alterations which resemble those we have already noticed in connective tissue, and, as in the other case, they are much better seen in parts at a little distance from the seat of injury than in its immediate neighbourhood. Thus, in experiments in which muscle was cauterised, Dr. Janovitsch found that the inflammatory changes could be studied most advantageously in the

Fig. 406.



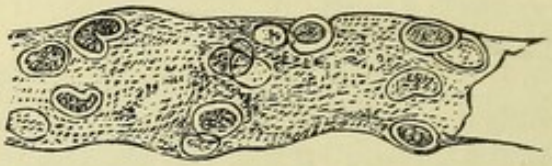
Multiplication of nuclei in the sheath of an inflamed muscular fibre.

outer zone of redness and swelling. In this situation the muscular substance, when examined twenty-four hours after irritation, is found to be for the most part unaltered, the transverse striæ

* *Ueber die entzündlichen Veränderungen der Muskelfasern.* Stricker's *Studien*, p. 86.

being well marked and of natural appearance. The aspects of the corpuscles vary according to the stage of change. Some are merely enlarged, each consisting of a single nucleus embedded in a fusiform clump of finely granular protoplasm. Of the rest some exhibit two nuclei, others a greater number, which are arranged either in a heap or in a series, and are generally

Fig. 407.



Empty sheath beset with young elements.

so close to each other that their opposed surfaces are flattened, the whole being held together and surrounded by the protoplasm already mentioned. In the later stages the young elements multiply to such an extent that they eventually occupy the whole of the sheath, the natural contents having gradually disappeared.

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## Part II.—Structural Changes which occur in the Epithelial and Glandular Tissues in Inflammation.

*Epithelial tissues.*—The appearances observed in suppurating mucous membranes have always been regarded as affording, next to those in the cornea and in cartilage, the strongest evidence of the textural origin of pus. For in a great many kinds of catarrh, large cells have been met with in the purulent liquid which is thrown off at the very commencement of the process, which contain groups of bodies entirely resembling young pus-corpuscles. These remarkable epithelial elements were considered by Buhl,* who first described and studied them, as mother-cells or brood-cells; and most pathologists since have regarded them in the same light. But more recently, since the discovery of emigration has induced a tendency in the minds of some persons to conform all the details of the inflammatory process to one type, Steudener and Volkmann† have maintained that the bodies in question are not the off-

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* Buhl, Virchow's *Archiv*, vol. xvi. † *Centralblatt*, 1868, No. 17.

spring of the cells in which they are enclosed, but strangers which have intruded themselves from without. Here, as in so many other cases, the only way of solving the question was, if possible, to observe the phenomena in the living tissue, i.e. to see the process of intrusion or extrusion actually going on under the microscope. This, however, was evidently a matter of great difficulty. In Professor Billroth's* admirable essay on inflammation the reader will find an account of a number of efforts made by him for the purpose without satisfactory results. The question seems, however, to have been now settled in favour of the original doctrine of Buhl, by the very recent researches of Dr. Oser† in the Vienna laboratory.

Although in general epithelial structures derive their nourishment directly from the blood, there are some which are entirely remote from vessels. Of these the epithelium covering the cornea and that of the epiploa are the best examples. If the normal epiploon‡ of the rabbit or guinea-pig be treated with weak solution of nitrate of silver, and then exposed to the light and examined without further preparation, it is seen that in the most delicate parts it consists merely of a network of hyaline fibres of connective tissue paved on both sides with flat epithelia; and that in the centre of most of them a little mass of protoplasm can be distinguished. We have here, therefore, an epithelial structure of the simplest kind which is entirely out of relation with the capillaries, and is thus remarkably well fitted for studying the independent behaviour of epithelial elements in serous inflammation. If a little iodine or solution of nitrate of silver be injected into the peritonæum, and the omentum be examined twenty-four hours after, it is found that the fibres of the network are no longer covered with a continuous pavement, but that a number of elements hang about it, most of which differ considerably from the original epithelia, though some still resemble them. The most striking difference is that of the increased size of the protoplasmic mass. Instead of a faintly granular body, scarcely so large as a leucocyte, you have a clump twice or three times as large, which if examined under the proper conditions displays

* Billroth, *Mancherlei über die morphologischen Vorgänge bei der Entzündung. Medizinische Jahrbücher*, vol. iv. 1869, p. 1.

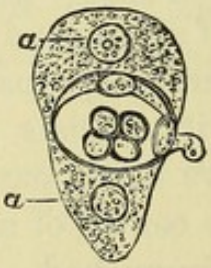
† Oser, *Ueber endogene Bildung von Eiterkörperchen an der Conjunctiva des Kaninchens.* Stricker's *Studien*, p. 74.

‡ Cornil et Ranvier, *Manuel d'Histologie pathologique.* Paris, 1869, p. 74.

amœboid movements. Some of these rapidly growing cells contain single nuclei, others two or a greater number of spheroidal corpuscles corresponding in form and size to those which either float free in the peritonæal liquid, or are enclosed in the coagulum of reticular fibrine with which the affected surface is more or less covered.

In this case it is at all events certain that some of the changes observed have nothing to do with migration, for the membrane in which they occur is non-vascular. But it is obviously only a matter of inference, that we have before us an actual formation of pus by epithelial germination. We shall find, however, additional ground for believing that this interpretation is the true one, by comparing the account given above with the very exact observations of Dr. Oser on the conjunctiva already referred to. In his experiments the

FIG. 408.




An epithelial element from the anterior surface of the cornea of a rabbit, which had been irritated two days before with weak ammonia. *a a*, Nuclei. One of the five young elements contained in the central cavity is in the act of escaping through the wall of the cell.

membrane in question was examined at periods varying from a few hours to four or five days after irritation with solution of ammonia of various strengths. The first stage of the process consists in the growth of the protoplasmic or living part of the epithelial element, and the consequent disappearance of the external investment; the second in the condensation of the granular material at one, two, or a greater number of points, into little spheroidal corpuscles, which as they become more distinct appear to detach themselves gradually from the remaining granular matter, until eventually they all lie free in one cavity. Finally the spheroids show themselves to be leucocytes by their amœboid movements; and, on one fortunate occasion, were seen by Dr. Oser making their way out of the mother-cell and then moving about in the surrounding liquid.

In both the cases referred to, it is to be borne in mind that the fact of germinative pyogenesis does not exclude that of migration. Indeed, as regards the serous membranes, there is the strongest reason for believing, that in certain forms of acute peritonitis the leucocytes contained in the peritonæal liquid are all emigrants. Thus in the peritonitis which is produced in the frog's mesentery by exposure, it is quite impossible to suppose that the dense layer of corpuscles which, in the advanced stage of the experiment, covers the surface of the membrane, can be derived from any other source than the circulating blood. Again, the anatomical appearances which present themselves in the most acute forms of suppurative peritonitis with which we are acquainted clinically, even though we may be disposed to admit that they might be brought into harmony with an opposite theory, can be explained much more naturally and easily in the same way.

*Glandular tissues.*—The question next to be considered is that of inflammation of glands. There is no glandular organ in which traumatic inflammation has been so completely studied as in the liver; some observers finding, in the anatomical changes which result from experimental irritation, proof of the dependence of these changes on migration, while others, particularly Holm, believe that the liver-cells undergo transformation into inflammatory products, and that pus-corpuscles may be produced in hepatic mother-cells. Dr. Hüttenbrenner has recently repeated the experiments of Holm,* as well as those of Koster,† (who may be regarded as the most important expositor of Cohnheim's doctrine in its relation to inflammation of glands), and has confirmed the results obtained by both of his predecessors. He concludes that in the liver, if the irritant is such as to produce alterations which are confined to the immediate neighbourhood of the injury, the liver-cells germinate, and believes that the few pus-corpuscles which are formed under these circumstances originate endogenously. If, however, an abundant suppuration is produced, as e.g. by the injection of ammonia, it is found that the pus corpuscles are collected round the blood-vessels in a manner which certainly indicates that they are emigrants, or that the capillaries are concerned in their production. In support of the same view

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* Holm, *Experimentelle Untersuchungen über die traumatische Leberentzündung. Wiener Sitzungsb.* vol. lv part II. p. 439.

† Koster, *Entzündung und Eiterung in der Leber. Centralblatt*, 1868, p. 17.

we may refer to the observations of Billroth* on mastitis and orchitis. In a patient who died in puerperal fever with minute abscesses disseminated throughout the mammary gland, Billroth found that the young pus-cells occupied the inter-acinar vascular network just in the same way as Koster described in the liver. Again, in an inflamed testicle taken from a patient who had died of secondary pyelitis consequent upon stricture, and had often before been treated for gonorrhœal orchitis, the connective tissue between the seminal canals was the seat of interstitial irritation, and beset with an infinite number of young cells, the glandular structures remaining themselves unaltered. In both of these cases the accumulation of leucocytes round the vessels is certainly remarkable. But before we agree to the explanation offered by Billroth we must take other considerations into account. It is to be borne in mind, that in both instances the inflammation was of a secondary, that is to say infective, character. In all inflammations of this class it appears quite as reasonable to suppose that the limitation of the morbid changes to the immediate neighbourhood of the blood-vessels is due to the fact that the infective agent is introduced into the tissue by the blood-stream, as to attribute it to emigration of leucocytes.

For the present this question must remain open. All that we are justified in concluding is, that although even gland-cells under certain circumstances may be alienated from their natural secreting function, and excited into reproductive activity, this germination does not play any important part in the formation of pus.

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## Part III.—Influence exercised by the Form and Mode of Action of the injurious Agent on the Character of the resulting textural Changes.

Although if we be careful to distinguish what is essential to the process of inflammation, viz. the altered state of the vessels, from the phenomena which accompany it, and the textural germination which it produces, its characters will appear to us to present very slight variation, yet the visible results by which

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* Billroth, loc. cit. p. 30.

it manifests itself differ widely in different cases. It is therefore necessary, in order to complete the present subject, to consider in what degree these differences correspond to differences in the causes which produce them.

*Vesication.*—If a hot iron is applied to the skin at a sufficient temperature, it at once destroys its vitality. If the temperature be a little below that which is necessary to produce this result, the blood contained in the vessels coagulates, and the tissue eventually dies. At a still lower temperature the skin retains its vitality, but blisters are formed at or around the injured part.

If the mesentery of a guinea-pig is touched with a heated surface, and the effect observed under the microscope, it is found that stasis is produced which is co-extensive with the surface of contact. It is tolerably certain that in like manner, in vesication of the skin by heat, the circulation of the heated part is abruptly brought to a standstill. As, outside of the area of stagnation, it goes on at first with unabated then with increased vigour, while the walls of the capillaries are probably acted upon by the heat in such a manner as to render them more permeable, we can readily understand how it happens that liquor sanguinis is exuded more rapidly and more abundantly than in ordinary inflammations. From the researches of Dr. Samuel of Königsberg it seems probable that the effects of liquid vesicants agree with those of heat in all the respects which have been referred to; so that the peculiarity of the mode of action of vesicant agents in general, would seem to lie in its suddenness and in the faculty which they possess of at once producing those changes in the capillary wall which in ordinary inflammation require a longer time and a more gradual process for their production. In this way the exudation of liquor sanguinis, instead of being deferred until the slowing of the circulation has commenced, begins immediately, and, favoured by the primary arterial afflux, and the increased intra-vascular pressure consequent on the sudden capillary obstruction, is so abundant that the liquid collects in blisters.

*Relation between inflammation and the reparative process.*—When the local injury is so intense as to destroy the vitality of the affected part at once, that part becomes surrounded with a zone of inflamed tissue from which it eventually separates, leaving behind it a granulating surface. To understand this process of demarcation and separation, it is in the first place to be borne

in mind that the exuded liquid contains the fibrine-producing elements of the blood, and that contact with dead substance at once determines coagulation of all such fibrinogenous liquids. Accordingly, the first step in the process of reparative separation is the formation, in contact with the dead part, of a more or less solid stratum of fibrine, in which stratum the production of new capillaries and granulation-tissue commences.

What is this granulation-tissue? It consists entirely of young cells, which if they agree with leucocytes more or less in size, differ from them both in structure and arrangement. The neoplastic granulation- or embryonal-cell (as it is often termed) is a mass of protoplasm with a round or oval well-defined central nucleus. It exhibits very slight amœboid movements, and has a marked tendency to endogenous multiplication by division of its nucleus—a process which goes on with such activity that in carefully prepared sections of young granulations it may be studied in all its stages under the microscope with great facility. The arrangement of granulation-cells is determined by that of the newly formed capillary vessels around which they are grouped. At first irregular, it becomes more and more definite as the new growth is transformed into cicatrix, or into that adenoid texture which is the material of chronic inflammatory induration. It is scarcely necessary to add that the process we have been describing and that of healing by the first intention are essentially the same.

*Suppuration.*—Before endeavouring to explain how it is that leucocytes, after escaping from the vessels, tend to collect together in groups so as to form foci of suppuration, i.e. abscesses, I would refer to two of the vital endowments which they possess when in the active, that is amœboid state, as perhaps having an important bearing on the question; viz. the power of surrounding concrete matter with which they come into contact with their own substance, and secondly that unexplained tendency which they possess to escape from the blood-current, and to move away from it in a direction at right angles to the axis of the vessel from which they have escaped.

When a bit of fresh cellular tissue is inserted under the skin of a living animal, and allowed to remain there for several days, it becomes soaked with a liquid teeming with living amœboid leucocytes, all of which possess the ingestive faculty just referred to. It has not as yet been experimentally demonstrated that these leucocytes actually prey upon the nutritive con-

stituents of the slough, but it certainly appears as if they determined its liquefaction.

Again, when an abscess is produced by embedding a thread steeped in an irritant liquid in some tissue, leucocytes collect in numbers around the foreign body, which soon floats loose in a collection of pus. As the cavity is considerably larger than the irritant, there must have been destruction of the natural tissue. It is surrounded by a zone of reproductive inflammation (pyogenic membrane), in which the neoplastic process already described is going on in full vigour.

In both of these instances the abundant genesis of leucocytes at and around the lesion, which gives rise to the formation of a suppurative focus, manifests itself in absorption or liquefaction of the original tissue. The two conditions stand to each other in a relation so close that we may venture to infer that the latter is a consequence of the former.

The growth of an abscess once formed is explicable on the same grounds as migration in general. Whatever cause determines the rapid filling of a bladder full of liquid inserted under the skin (p. 776), will also account for their accumulation in the cavity of an abscess, independently of any special action of its lining. With reference to this point, however, there is much probability in the supposition that the newly formed and dilated vessels of the so-called pyogenic membrane, favour by their structure and arrangement the extrusion of leucocytes.

Why one inflammation is suppurative and another not is a question we are unable to answer, excepting in so far as an answer is contained in the statement that on the whole those inflammations which are most intense and concentrated, provided that the injury done falls short of the production of instant stasis or necrosis, are most suppurative. In other words, so long as blood freely circulates, the quantity of pus produced in an injured part varies according to the intensity of the lesion.

The existence in leucocytes of a power of absorbing tissues with which they are brought into contact is probably the explanation of the destructive tendency which is so important a character of all intense inflammations.* The absorption and liquefaction of the original texture is as peculiar to and inseparable from the process of inflammation as the germinative

* On this subject see ADDENDUM, p. 789.

changes which we have been describing. That it is analogous to ordinary absorption cannot as yet be stated, for we do not yet know whether the wandering leucocytes which are found in healthy connective tissues have to do with that process or not. The only other kind of liquefaction which it could be compared with is the putrefactive, but with this it has not the slightest analogy. For in no single particular, excepting that both result in disintegration, do they resemble each other. Suppurating tissues, so long as they are protected from the influence of external media, do not show the slightest tendency to septic decomposition.

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## Part IV.—Direct Influence of abundant Supply and frequent Change of Nutritive Liquid in stimulating Cell Life.

It is well known that if a portion of living structure is removed from its natural position and inserted or engrafted into some other part of the same or of another animal, in such a manner as to be in complete contact with living vascular tissue, the ordinary nutritive changes may go on in the engrafted fragment independently of the direct influence of the nervous system. Hence it may be inferred that if an adequate supply of normal nutritive fluid is the only condition which is necessary to determine the continuance of the ordinary nutritive changes, it is by no means improbable that the modification of this process which goes on in inflammation, may be determined in a corresponding manner by subjecting the tissue to the action of such a fluid as is discharged from congested vessels. With some such considerations as these in view, Stricker * devised an experiment consisting essentially in the insertion of a fragment of living tissue into a cavity of which the walls are in a state of active inflammation. A somewhat similar experiment had already been made by v. Recklinghausen in 1863. He introduced the cornea of a frog, immediately after excising it, into a lymph-sac of the same animal, and observed that if the cornea were left in this situation long enough for the cavity to

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* Stricker, *Ueber die Beziehungen von Gefässen und Nerven zu dem Entzün - ungsprocesse*, loc. cit. p. 31.

inflame and suppurate, the marginal part of it became charged with leucocytes, which, by virtue of their amœboid movement, penetrated in vast numbers into its tissue. But as v. Recklinghausen had not inserted his healthy cornea into a cavity already inflamed, and moreover had not observed the structural changes which took place, his experiment was not available for the solution of the question. The method adopted by Stricker is as follows:—He irritates one eye of a frog by cauterizing the cornea through, then excises the cornea of the opposite eye, and inserts it beneath the *membrana nictitans* of the irritated eye, finally uniting the edge of that membrane with the opposite margin of the cutis by ligatures. After twenty-four hours the transplanted cornea is removed and examined, and is found to exhibit inflammatory changes, which although they are on the whole less advanced than those found in an unexcised cornea, at the same period after irritation, are equally characteristic. In different experiments there were differences both in the degree in which the cornea-corpuscles were altered, and still more in the number of pus-corpuscles, but in all the appearances corresponded with the description which has been already given of the effects of direct irritation.

These results scarcely admit of misinterpretation; they are, however, rendered much more decisive and satisfactory by varying the conditions of experiment in such a way as to show that the changes observed are not due to the penetration of leucocytes from the liquid in which the cornea is immersed, and secondly that they are not a mere result of its transplantation into an unnatural position. The first of these objects is readily attained by dividing the cornea immediately after excision, plunging one half in water so as to kill it instantly, and then placing the dead and the living portion together, underneath the *membrana nictitans* of the opposite eye. It is then found that whereas the same inflammatory changes as before go on in the living half, the other half remains inactive. The second result is attained by the observation of what happens when, instead of first cauterizing the eye which is destined to be the recipient of the transplanted cornea, it is left uninjured. At the end of twenty-four hours the cornea-corpuscles are found quite unaltered, and so distinct that the plan is strongly recommended as a method of demonstrating their normal characters.

These varied results seem therefore to show, beyond the possibility of dispute, that the structural changes in the cornea

of the frog cannot be dependent either on any influence exercised by the nervous system, or by transmission of the irritative effect from one structural element to another, so that we have good ground for concluding with Professor Stricker that they result exclusively from the stimulating influence of the exuded liquid. The precise physical or chemical conditions are as yet unknown, and are at the present moment subjects of further investigation.

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## CONCLUSIONS.

1. In every inflammation which attains its full development the changes which manifest themselves in the inflamed part are of three kinds, distinguished from each other according to the organs which are concerned in their production. They are either (1) effects of disorder of the vascular nerves and centre; (2) effects of alteration of the properties of the living walls of the capillaries; or (3) effects of the stimulation of the living cells by transudation of liquor sanguinis.

2. Of these three orders of phenomena the second only can be regarded as absolutely essential to the existence of inflammation, which may, therefore, in the strictest sense, be said to have its seat in and about the veins and capillaries, it being there that the earliest and most constant effects of irritation or injury manifest themselves.

3. The nervous and vascular effects of local irritation cannot be directly described as successive stages of one process; for the determination of blood to the seat of injury which is the sole result, and, if I may so speak, purpose of the vasomotor disturbance, has no relation to the local vascular changes, excepting in so far as it tends to make the exudation more abundant. Exudation of liquor sanguinis, although favoured by increased arterial afflux, may occur without it, and as a rule continues after the afflux has ceased. The vascular and textural changes, on the contrary, may be regarded as successive stages of one process, for they are connected by a causal relation—the exudation of liquor sanguinis, in which the former ends, being the determining cause of the latter.

4. The mode in which an injury changes the living substance of

the vascular walls so as to make them permeable to the blood is unknown. The nature of the change itself is also unknown, the only clue which we have to its character being that afforded by the structural alterations to which it leads in certain organs, and particularly by those which are observed when the process of reparation, attended with the formation of new capillaries, is commencing. (See pp. 757 and 778.) From these appearances we are led to infer that the primary change consists in the transition of the material from the formed to the plastic condition; from a state in which it is resistant, because inactive, to one in which it is more living and therefore more labile.

5. In all living tissues the effect of inflammation manifests itself in a modification of the action and properties of individual cells. In cells which form part of permanent structures the protoplasm increases in quantity and becomes more or less contractile. Subsequently, it is converted entirely or partly into young cells, either by cleavage or by endogenous germination.

J. BURDON-SANDERSON.

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## Addendum.

The destructive effects of inflammation are traced with a master's hand in the following paragraphs, reprinted from the article on the same subject which appeared in the former edition of this work. After pointing out that both for pathology and practice it is needful that the student recognize the reality of destructive changes as an essential part of inflammation, Mr. Simon continues:—

'Let him examine inflamed muscle, as, for instance, in the post-mortem examination of a compound fracture or of a recently made stump:—He will find the structure weakened, so that it easily gives way with pressure or traction; he will see, under the microscope, that the substance tends to fall into irregular fragments; that its natural striation is more or less replaced, first by an almost homogeneous appearance, and afterwards by an appearance of aggregated granules; that, with these granules of albuminous matter into which the muscle has resolved itself,

there is mixed, even from an early date in the inflammation, a noticeable quantity of minute oil-drops; that often these oil-drops appear before the disintegration of muscle has made much progress, and then arrange themselves in such mutual relation, transverse or longitudinal, as to suggest that the sarcous elements have changed themselves, particle by particle, into oil; that little by little the oil-drops multiply to such an extent as to be the chief visible objects—the limitary membrane of a fasciculus seeming now to be almost filled with finely-divided oil, diffused through some scanty connective albuminous material; that the limitary membrane, within which the muscular material is thus emulsionised, tends also itself to undergo dissolution, and let its proceeds confuse themselves with the similar débris of neighbouring fasciculi, till more or less bulk of muscle is reduced to a state of oleo-albuminous liquidity.

'And from this point, if the observer have opportunity of watching the changes which lead to convalescence, he will see that gradually the liquefied material diminishes in volume; that, in proportion as it vanishes, the adjoining parts adapt themselves to the altered relation; that eventually only a scar-like puckering of substance—a kind of tendinous intersection—remains to mark the place where muscular material has irrecoverably melted away.

'Let him examine inflamed bone, as, for instance, in a carious vertebra:—He will see that the structure breaks down under his finger, and offers scarcely any resistance to a knife; that the microscopical texture is rarefied—cancelli, canals, lacunæ, being all larger than natural, and the solid framework all scantier; that the material is tending to break into its component parts, and to undergo changes which admit of its being removed by the circulation. In many cases (for example, under the irritant pressure of an aneurism) he will find that a quantity of bone has thus gone, leaving no trace behind—gone of course, only after having first become liquid; and it appears that, when bone is inflamed, the first step towards this disintegration consists in a breach of the ordinary union between the mineral and cartilaginous constituents, with a primary removal of the former, and a chemical change of the latter. If there be discharge from the inflamed part, there will be found in it bits of bone, chemically and microscopically demonstrable.

'Let him examine inflamed nerve—as, for instance, near to where it has been cut in amputation:—He will find, says Dr.

Lent, the medullary cylinder of each nerve tubule falling, as it were by cross-cuts, into irregular pieces—at first large, but as the process advances, getting smaller and rounder, and assuming the character of oil; till at last the tube-membrane is filled with oily material, which gradually undergoes removal.

'Let him examine the hard textures of an acutely suppurating joint:—He will find the strongest ligaments in course of being reduced to an incoherent state—either actually pulpy and half-liquefied and in course of removal, or ready to break with the least traction; he will find (unless proper splintage have been used to prevent it) that dislocation is occurring from this cause; he will find, if the inflammation have been primarily synovial, that the cartilage is smoothly melting away at its surface into the fluid which bathes it, or, if the disease have begun subarticularly, that the cartilage, where superjacent to carious bone, is irregularly eroded and perforated; and throughout, with the microscope, he will find, wherever there are evidences of advancing disintegration, that the softening material is abundantly marked with oil-drops.

'Let him—not in post-mortem examinations, for which there are no opportunities, but during life—observe the results of inflammation of the sclerotic, and ask himself why it is that staphyloma so often follows this disease. He will infer that here, as with other cases which we have considered, the inflammation must have so disorganised the texture, and so enfeebled its normal rigidity, that it can no longer give sufficient resistance to pressure from within, or save itself from being bulged by what now becomes an almost dropsical excess of fluid secretion within the globe.

'Above all, let him examine the products of inflammation furnished by mucous and serous membranes, and by glands: the expectorations of bronchitis, the hawkings of common throat-catarrh, the urine of scarlatina, the acute effusion of serous cavities, and, after death, the inflamed organs themselves. Let him once thoroughly recognise the destructive acts of inflammation, as illustrated in the simple cells of gland or epitheliated membrane; and the whole of this argument will be compendiously before him. He will find cells (especially where they are squamous) shed as dead material, without their first undergoing any appreciable alteration. He will find all others undergoing change in a more or less marked degree—change, of which the essence consists in a loosening and eventually a dis-

integration of texture, with increased imbibability by fluid, and gradual accumulation of oil; so that the cell, while undissolved, appears of larger than natural size, its wall less defined, its nucleus dimmer, its contents more granular and oily than in health. Sometimes a cell is thus converted into a mere heap of oil-drops held together by little intervening or surrounding material; sometimes there will be more albuminous matter, perhaps in a granulated or dotty form; sometimes there will be more evident fludity of contents; but in any case the cell, if retained within the body, tends to break up and contribute with its neighbours to the making of an oleo-albuminous fluid, in which there exist but scanty and evanescent remains of the original cell structure.'

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