THE LUMLEIAN LECTURES ON INFLAMMATION.

Delivered before the Royal College of Physicians.

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LECTURE I. PART II.—INJURY AND DAMAGE.

4. *The local disorders of the circulation, on which the objective signs of inflammation depend—namely, increased supply of blood with diminished velocity of the blood-stream, dilatation of the blood-vessels, exudation, and stasis—may all be explained either as direct or indirect results of a damaged condition of the vascular wall; but no satisfactory explanation has as yet been given of the mechanism of emigration of the colourless blood-corpuscles.*—In what has been said up to this point, I have endeavoured to present a general view of the effects of injury as they may be judged of, without making any effort to investigate them minutely. But we must not forget that these are made of finer details, to see which it is necessary to come nearer and to penetrate below the surface.

Our forefathers judged that inflamed parts were hot by feeling them; we know how hot they are by the thermometer. So as regards the other two Celsian characteristics. We know how a part swells and becomes red, by watching the process under the microscope. Without its aid, our knowledge of inflammation would be as vague as was Harvey's of the capillary circulation. Microscopical investigation has, no doubt the disadvantage that, the nearer we approach to our object, the narrower becomes our field of vision; and some people imagine that this is apt to associate itself with a corresponding narrowness of intellectual scope. If such a danger exist, the way to avoid it is not to change our method with our instrument. Whether we look at large things or at small—whether we occupy ourselves with general characters or with details—it is alike necessary to bear in mind that our business is with the pathological process itself, not with its results. The history of pathology, from the time of John Hunter to the present, seems to show that a great many of the mistakes that have been made may be attributed to neglect of this principle. The method which consists in inferring from the pathological anatomy of a disease its essential nature cannot be dispensed with; for, in many cases, it is the only method within our reach, but it is an imperfect and uncertain one; for, if we interpret our facts wrongly, we have no means of finding out our mistake. The only certain way of determining the nature of a diseased process is that which is employed in physiology. It consists in getting as close as we can to the seat of action—in taking care that our view is not obscured by surrounding objects, and of watching what happens with the utmost attention of which we are capable. I need not say that, as regards inflammation, this was the method employed by John Hunter, and, more recently, by the elder Thomson, C. J. B. Williams, Wharton Jones, Lister, and indeed more or less, along with the other method, by all who have worked to good purpose. That in later times, and particularly during the last ten or fifteen years, its relative importance has become so much greater, is due partly to the better appliances which we now possess for this close scrutiny of vital processes, partly to the more sceptical spirit of the time, which refuses to accord to inferences, however well founded, the same value as to direct observations.

As affording an excellent illustration of the method to which I have been referring, as showing how clear a view can be obtained at once of all the constituents of a pathological state or process, I would ask your attention to what may be learnt by the microscopical observation of a serous membrane under conditions which, although they apparently approach closely to the normal, yet depart from it sufficiently to determine inflammation. For this purpose, it is necessary that, during the whole period of observation, the membrane to be observed (the mesentery or omentum of a carnivore or a rodent) should be immersed in a liquid which represents as nearly as possible that of its own normal secretion; and that the temperature of this medium should be that of the body. I shall not describe the details of the experiment, but will content myself with stating that the arrangements are similar to those employed by Professor Stricker (*Handbook for the Physiological Laboratory*, p. 231) and myself in 1870; but that the *modus operandi* has

been since brought to much greater perfection by Professor Thoma, of Heidelberg ("Ueber entzündliche Störungen des Capillarkreislaufes bei Warmblütern," Virchow's *Archiv*, vol. lxxiv). As a result, he has been able to see the mammalian circulation in a state of unimpaired activity; the velocity of the blood-stream in all the blood-vessels being such, that even in the veins the axial blood-stream appears as a continuous thin red line, with a prismatic border perfectly free from corpuscles.

But, in a very short time, the inevitable changes which are the signs of damage present themselves. If the attention be fixed on a vein, the blood-stream in it seems to flag almost suddenly. At once, the colourless corpuscles "fall out", like tired soldiers on the march, leave the mid-stream, and loiter against the vein-wall, afterwards sticking to it, just as Dr. Williams described the process for the first time in his Gulstonian Lectures in this College in 1841. We know now that the proximate cause of this loitering of the leucocytes against the internal surface of the vascular wall, is the retardation of the current: first, because, by the well known experiments of Schiklarsky ("Ueber das Blut und die Suspensionsflüssigkeiten," Pflüger's *Archiv*, vol. i, p. 603), it is shown that, from the relation which exists between the specific gravity of these bodies and that of the blood, this result is certain to happen; and, secondly, because, by altering the rate of flow, we can produce or abolish the phenomenon at will.

If this were a mere barren problem in vital physics, or even if I could tell you no more about it now than when, nearly forty years ago, Dr. Williams first described it accurately here, I might hesitate in doing more than to make a passing reference to it.

But we now know that it is most intimately connected with the central phenomenon of inflammation, the exudation from the slowly flowing blood-stream of corpuscular liquid. To show this, let me return to the narrative of what happens in the mammalian mesentery. There are three phenomena which demand our attention. The first is, the emigration of the colourless corpuscles. From the moment when these bodies cling to the walls of the veins, in the peculiar way that has been so long familiar, they begin to escape. How it happened that—to as good observers as any who now occupy themselves with the subject, aided by as good microscopes—this wonderful process remained hidden until both it and its meaning were brought to light by Cohnheim, we need not stop to inquire. To the student of the present day, to whom emigration presents itself as a commonplace and elementary fact in pathology, which is shown to him in the course of his first practical lesson on the subject, it seems incredible that it should have been overlooked; while older men, whose microscopes have perhaps remained under their glass shades for a generation, find it equally incredible that what they or their teachers failed to see thirty or forty years ago, can possibly be true now. Both err, in forgetting how slow and gradual is the process by which we come to a right understanding of objective facts. Let us be prepared to give equal credit to the past and to the present, accepting what is new, without losing sight of, much less rejecting, what is old.

The second of the three phenomena to which I referred just now is that of the accumulation of coagulable liquid on the surface of the inflamed membrane, and the separation of its fibrin; in other words, the inflammatory exudation. In other kinds of inflammation, the exuded liquid is discharged from the veins and capillaries into the intervascular parenchyma, where it accumulates or not, according as the mechanism of absorption is adequate or inadequate for its removal; the most important of the three objective signs of inflammation being the expression of defective drainage, or, what amounts to the same thing, excessive leakage from the blood-vessels. But, in inflammation of a serous membrane, no such drainage is wanted; the liquid exuded accumulates, not in the tissue, but in the serous cavity, and finds its way back to the circulation by the lymphatics (situated chiefly in the diaphragm), with which the peritoneal cavity is in communication. For this reason, the study of peritonitis under the microscope affords an opportunity, not elsewhere to be met with, of studying the nature of exudation, and of its relation to what precedes it. If the part of the membrane which is under observation be surrounded by a ring of glass, which rests upon its upper surface, the exuded liquid, instead of being washed away by the constant stream of warm liquid with which it is irrigated, collects on the surface, and soon forms a gelatinous clot, which adheres feebly to the surface of the membrane. You have, in fact, before you, in its simplest possible form, a croupous process.

If you remove this soft coagulum from the membrane and place it under the microscope, it exhibits the characters of blood-plasma which has undergone the same change; nor can there be a moment's doubt that the reason why it coagulates is the same in the two cases—namely, that a certain number of the leucocytes which have escaped undergo disintegration; in doing so, are dissolved in the liquid in which they

are suspended, and thereby communicate to it the property which it did not before contain—that of producing fibrin.

The third of the three microscopical phenomena which presents itself in the mesentery is that of capillary stagnation or stasis—a phenomenon which the earlier microscopical observers (as, *e.g.*, Dr. John Thomson) rightly regarded as of great importance. They were right in so regarding it, for two reasons: first, because it always occurs in inflammations which are of sufficient intensity; and, secondly, because it is in it that the process culminates—by destroying the life of the tissue in which it has its seat.

To avoid confusion, it is necessary to regard the process as consisting of two stages; the first transitory; the second definitive. Transitory stasis is only a local exaggeration of that general retardation of the progressive motion of the blood which we have already studied. Permanent stasis is, as everyone who has watched the circulation in the transparent parts of the frog knows, associated with two other changes in the capillaries. One of these is what has unfortunately been called diapedesis—namely, the often sudden extravasation of a number of coloured blood-discs from a capillary; the other is that strange adhesion of the coloured discs to each other inside the capillaries, so that they look like rods of red coral, which was carefully studied by Mr. Lister twenty-five years ago. Of the truth of the principal conclusion to which these researches led Mr. Lister—namely, that stasis is not due to alteration of the circulating blood, but to a change in the channels through which it has to pass—there can be no doubt; for, in addition to his own most ingenious experiments, it has been since shown that when, in the living animal, corpuscular liquids, such as milk, are substituted for blood, stasis occurs in injured parts, in a similar manner and under similar conditions. I shall have again, in my third lecture, to refer to these facts in their historical relations; for there can be no doubt that, as I have had occasion to state before, they led their discoverer to anticipate the advances which have been made since. What I would now desire to emphasise about stasis is not so much the antecedent changes which give rise to it, as its effect on the tissues which surround the obstructed vessels. Stasis is the mechanism by which inflammation kills, and thereby gives occasion to further pathological changes, of which necrosis is the starting-point.

Time does not admit of our studying other examples of inflammation microscopically. I trust that this one instance, in which I have endeavoured to give as clear an account of what happens as I could, will suffice to show that, just as to the naked eye the visible effects of injuring a vascular part are heat, redness, and swelling, so these have their microscopical counterparts in vascular dilatation and exudation, and in the escape of the fibrin-forming elements of the blood; and that these culminate in capillary stasis. From it, all the destructive after-effects of inflammation have their point of departure. What I have now to do is to show that all these separate results of injury are—not so much by virtue of their dependence on each other as by their common relation to one and the same proximate cause—like the naked-eye phenomena, not disorders of nutrition, but simply signs of damage.

And, first, as regards the retardation of the circulation. As no reason exists why there should be any general retardation of the blood-stream, the condition which determines the local retardation must also be local; and, if so, it must depend on changes of diameter of the blood-vessels, or on increased resistance from other causes in the capillaries. As regards the former, we know by direct observation, first, that there is in inflammation no narrowing either of arteries or of veins; and, secondly, that in all inflammations the quantity of blood which flows through an inflamed part is, in the initial stage of the process, vastly increased. It has been proved by exact experiments, that the blood-stream through an inflamed limb may exceed the normal flow in the proportion of something like four to one. (Cohnheim, *Vorlesungen*, vol. i, p. 222.) Further, we know by measurement that capillary veins and capillary arteries of inflamed parts are much wider than natural, and that many channels come into view which were before invisible. From all these facts, it is evident that, so far as concerns the first stage in the process—the stage during which exudation is going on with greatest activity—the diminution of the velocity of the blood-stream can be due to no other cause than the widening of the blood-way.

If we now proceed to ask, Why do the blood-vessels widen? we get an answer from physiological experiment, which seems to carry us back to John Hunter. They dilate simply because they have lost a power which they possessed before (I am afraid we must be content to call it a vital power) of resisting dilatation. The loss of a vital power is evidence of damage. A damaged blood-vessel in relaxed, for the same reason that a damaged heart or a damaged intestine is relaxed.

Next we come to exudation and escape of leucocytes. We have

already seen how the retardation of the stream, particularly in the veins, is a condition *sine quâ non* of emigration. As regards leakage, we have also seen that, on the large scale, leakage is an immediate result of injury; that, in injured parts, the blood-vessels begin to leak at once—*i.e.*, immediately after the injury; so that the element in the act of exudation which remains unaccounted for is the penetration of the vascular wall by the semifluid protoplasm of the leucocyte. Now there are two senses in which a vital phenomenon may be said to be explained or accounted for. The best and most satisfactory is, when we can deduce it from the operation of those properties of matter which are operative outside of the organism. From attempting this we are precluded by want of knowledge, or, more accurately, by want of the means of investigation. We have, therefore, to fall back on the less perfect method, which consists in placing the fact along with others which it resembles. In the present instance, we refer the penetration of the vascular wall of injured parts to the more general fact (of which the examples are very numerous) that leucocytes themselves, and other amoeboid bodies which resemble them, possess the power of intruding their own substance into that of dead tissue, and, indeed, of any material capable of imbibition with which they are brought into contact in an active state. The mechanism by which the necessary contact is established has been explained. As to the mode of penetration, we have to content ourselves with identifying it with other well-known but equally unexplained processes.

And, finally, as regards stasis: to understand its relation to the other effects of injury, and to the injury itself, we must bear in mind, first, that it does not form part of the inflammatory state, but is rather a sequela or consequence; and, secondly, that the lagging, the stagnation of the blood-stream, and the final choking of the capillaries with blood-discs, occur only here and there in the inflamed area; and that, when we are able to localise the action of the noxa, we find that stasis, if it occurs, is limited to the parts most directly acted upon—*i.e.*, most injured. This localisation suggests what on other experimental grounds we know to be the case; *viz.*, first, that stasis is the expression of a higher degree of injury than that which is required to produce the inflammatory state (*i.e.*, redness, heat, and swelling); and, secondly, that the localised retardation of the circulation which leads to it is the result of a change in the capillaries which renders it more difficult for the blood to pass through them than in the normal state. On the subject of this increased resistance, and the conditions which lead to it, a most important series of experiments have been recently made by Professors Glax and Klemensiewicz of Graz,* who have profited by the fact that in animals the vital properties of the tissues can be maintained by artificial circulation of properly arteriased blood, for the purpose of ascertaining to what extent the capillary resistance is modified by the introduction into the circulating liquid of extremely small percentages of injurious substances, particularly metallic salts. These experiments prove, not merely that the effect of such injury is to produce leakage, but that it shows itself immediately in diminishing the quantity of blood flowing through the blood-vessels of the injured part in a given time, under absolutely constant pressure. These beautiful experiments, though they fail to tell us why a spoiled capillary resists the passage of blood more than a sound one, afford us most exact information as to the condition which leads to this increased resistance. They justify us in saying that although, in the order of time, stasis is a consequence of exudation, the two phenomena owe their relation to each other to their being both alike the direct effects of injury; the former being the sign of a less, the latter of a greater, degree of damage.

I now desire to submit to you one or two consequences which follow from the view we have taken of the nature of the inflammatory state. The first is, that the only direct after-effect of inflammation is necrosis, that being dependent on the arrest of the circulation; and that the processes of restitution of structures which have thus ceased to live cannot, with any regard to accuracy, be regarded as parts of inflammation, or as in any way different from those by which the same structures are restored when destroyed by other agencies. The determining cause in the one case, as in the other, is the power of renewal inherent in the adjacent undestroyed tissue. The second point is, that the process of inflammation is essentially a terminable process—*i.e.*, one which has no tendency either to spread or last beyond the limits of the proximate cause. To this deduction I attach great importance, because it is the foundation of what I shall have to say in my next lecture as to the ætiology of inflammation. For, if it be accepted as true, it necessarily follows that, if we meet with an inflammation which does *not* cease on the removal of its assigned cause, there must be another latent noxa at work, of which we had before taken no cognisance.

* Glax und Klemensiewicz, "Beiträge zur Lehre von der Entzündung", *Sitzb. der k. Acad. der Wissensch.*, vol. 84 (iii Abth.), p. 216

An uncomplicated inflammation is neither reproductive nor infective, neither benignant nor malignant. If it have any tendency, it is the tendency to leave off as soon as the occasion for it ceases.

(To be continued.)

CROONIAN LECTURES ON THE CLIMATE AND FEVERS OF INDIA.

Delivered before the Royal College of Physicians of London.

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LECTURE I. PART II.—ETIOLOGY OF FEVERS.

(Concluded from page 415 of last number.)

Facts and Modes of Action of Malaria.—Briefly to summarise the facts about malaria and the methods by which it acts—whatever it be, it seems to be influenced by local and climatic conditions; its activity increasing generally with proximity to the equator, though there are parts of North India, as well as of Europe, where it is most active. Though prevalent in low-lying, marshy, or water-logged ground, or on soil drying up after rains, or on land that is rendered damp by interrupted drainage, it is also found on dry, sandy, or rocky ground, where there is little or no moisture or vegetation of any kind. Of this there are many examples in Europe and in India. Still, water seems to be the prime causal agent, especially when stagnant and near the surface. Water seems to not only determine the generation of malaria, but to hold it in solution. The natives of India attach little importance to atmospheric states, but believe that the water of pools and tanks, or even of streams flowing through certain jungles or marshy places, is charged with the fever-poison, and many believe that the milk of buffaloes or cows fed in these places has the same effect. I have myself heard natives assert this. Malaria is more active near the surface of the ground, in valleys, deep dry ditches or moats, old tanks filled with refuse, silted-up beds of rivers, obstructed watercourses; decreasing in energy with height, it ceases to exist above certain altitudes, variously given at from 1,500 to 5,000 feet. How high it permeates the air above the sea-level surface is not known; but the top of a hill, even the upper room of a house, is less dangerous than the ground-floor. It occurs in some of the hill-stations of India; but, as there is constant communication with the plains and valleys, fever may be the result of importation. It moves like mist and rolls up the hill-sides, nay, overtops those of a certain height, may be dissipated by or travels with the wind, probably some miles, but no one can say how far, though to a greater distance over land than over water, especially salt water, which is supposed to have the power of absorbing and retaining it. Crews of ships lying at a considerable distance to leeward of a malarious shore have been affected by the off-shore wind; and it is said that ships have generated it from certain cargoes of green wood, coals, and other vegetable matter, from rotting timber or bilge, which have developed fever of great severity. Steeping of hemp, jute, and indigo, or other vegetable matter, has had similar effects. Villages and camps have been affected when to leeward of swamps, even at a considerable distance. It is said that burning fires, smoke, or a belt of trees, will arrest its progress; that it clings about trees—hence the danger of sleeping under them; that the growth of trees will destroy or prevent it; and that some trees—the eucalyptus, for example—have a special antagonistic power; but there is probably nothing more in this than the rapid growth of these trees, which makes them quickly available as shelter. A screen of gauze or muslin is said to be protective; a musquito-curtain will keep out malaria as well as insects! A very high temperature does not always cause, it may even prevent it, though the other necessary elements seem to be present. Malaria is more active at night than in the day—more likely to affect those who are exposed to it at that time, during sleep, on or near the ground. It affects the weak sooner than the strong; those of a phlegmatic, lymphatic, or melancholic, rather than the sanguine or nervous temperament; the sickly and ill-fed before the robust; it spares no age; new comers are more liable to suffer than those who have been acclimatised; it affects all races, but it would appear that the negroes in some parts of the coast of Guinea acquire a toleration which has been referred, possibly

without sufficient reason, to the colour of the skin. There are certain tribes in the Terai and other forest districts of India who acquire some immunity; the non-Aryan races, inhabiting Assam, suffer, it is said, to a greater extent from malarial disease than the Aryans in the same province. The Tharoos live where it would be death to others, but even they are not altogether exempt.

Malaria is very intense in the belt of low swampy forest ground at the foot of the Himalaya mountains, where the porous soil has a substratum of clay, by which the water is brought near the surface, and where there are dense vegetation and a high temperature; in certain jungle districts, and water-logged land, and where the tides encroach; in the river-valleys, deltas, and debouchures of rivers; and near rice and other cultivation in some stages, though the danger from fresh rice cultivation is probably exaggerated; in the Sunderbunds of Bengal, where the mud is covered with dense jungle and frequently washed by the tide; in the jungles lying at the foot of hill-ranges, and along the sea-coast where salt and fresh water mingle, and where organic matters decompose amid moisture and heat. But it is scarcely less active on high and arid ground, as in the Deccan, Sind, Bikaner, Peshawur, the Punjab, Bhawalpore; but even in these localities, subsoil, damp, and organic matter seem to be at the bottom of it; though there are places, it must be admitted, which seem so dry and devoid of vegetation, and with the water at such depths below the surface, that it is difficult to believe that the explanation holds good—as it probably does; for, though there may be no great quantity of water, the subsoil is impregnated by a certain amount of stagnant moisture, which is probably the worst of all. It often appears with great intensity, after excavation and turning up of soil, in land that has recently been broken up, or has been denuded of jungle; whilst, on the other hand, cultivation, draining, and cropping seem to diminish or destroy it. The worst malarial dysentery that I have ever seen followed the clearing of some jungle during the last Burmese war. There are localities in India now comparatively healthy, that were formerly dangerous. Malaria is at its worst in the drying-up season after the rains and the beginning of the cold season; whilst, in the dry hot weather, and during heavy rains when the ground is covered with water, or when the land has been for some time cultivated and populated, or covered with trees, it is less severe. Volcanic, rocky, sandy, granitic soils or surfaces, have been thought to favour it, but it seems impossible to ascribe it to any particular soil.

Heyne, in a paper on the Hill-Fevers in India, shows that fevers prevail where granite rocks and ironstone are found in large quantities, and attributes it to magnetic or electric fluid disengaged in excess. Martin thought ferruginous hornblende might be the cause. Volcanic soils and exhalations were supposed by Sir W. Napier and Parkins to cause fever in Sind. Sulphurous vapour has also been suggested. Kuler attributed the endemic fever to limestone rocks. Gordon says: "Fever may occur on rocks, and on the detritus of rocks, as at Gibraltar, Malta, Ascension, the Ionian Islands, Hong Kong, and Cape Coast Castle, when the rock is rotten, and gives out vapours as the sun falls on it after rain." At Port of Spain in Trinidad, the residents enjoy comparative immunity from fever, though the place is surrounded by a swamp; and yet the same persons, if they take up their abode for a single night in La Vantile hill, in the immediate neighbourhood overlooking the Bay of Trinidad, suffer from fever in its severest form. So at Hong Kong, and at Cape Coast in Africa, climatic fevers are severe and deadly, though the soil is dry and hard in both places. At both, the underlying rock consists of decomposing ferruginous granite; and the alternations in meteorological conditions are great and sudden. In Sind and the Punjab, the soil is mostly sandy or alluvium on clay. At Kurrachee it is magnesium limestone, yet malarial fever, neuralgia, and cachexia are common.

Indian experience, however, supports the view expressed long ago by Pringle, that the chief determining cause is stagnant subsoil water at certain temperatures; for when such water moves, however slowly, the evidences of malarial poisoning are less marked. To the stagnant water must be added a certain combination of air and decomposing organic matter. What part may be taken respectively by vegetable and animal matter in the production of malaria is not known, but it is impossible to conceive of miasmata arising from organic decomposition in a tropical marsh, that is not a mixture of both; for low forms of animal life teem among the vegetation in such places, and the slime and ooze of a swamp drying up must contain quantities of animal matter, dying and dead. This may explain the more virulent character of some miasmata, and account for varying phenomena. Those given off from rocky soils, having less of the animal element, may account for differences that characterise the fevers of those regions.*

* Jackson attributed paroxysmal fever to vegetable emanation, typhus and its congeners to animal emanation, miasmata.