THE LUMLEIAN LECTURES ON INFLAMMATION.

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LECTURE II. PART II.—ETIOLOGY OF INFLAMMATION.

1. *The exudation of a normal inflammation is not infective.*

The proposition that a normal inflammation has no tendency to extend beyond the limits of the injury of which it is the physiological effect, has already been illustrated; but it is further desirable to state what grounds exist for concluding that the introduction into the circulating blood of a relatively large quantity of exudation (which, so far as the organism as a whole is concerned, is the most important effect of a considerable local inflammation) does not produce secondary inflammations elsewhere. To arrive at this conviction, all that is necessary is to consider what actually happens. In the beginning of every acute inflammation of a vascular tissue, a large quantity of liquid leaks from the blood-vessels, and is discharged into the intervascular spaces. This liquid does not at first accumulate where it is effused, but is at once drained off by the lymphatics, which, in consequence, become distended with lymph. In an admirable series of experiments by Dr. Lassar ("Ueber Ödem und Lymphstrom bei der Entzündung", Virchow's *Archiv*, vol. lxi, p. 516), in which diffuse inflammation of the cellular tissue of the limbs was induced experimentally for the purpose of studying the mechanism of absorption, the amount of this drainage was estimated at different stages of the process. For this purpose, a cannula was inserted in one of the principal lymphatic vessels leading from the inflamed part, and the lymph collected. It flowed at the rate of about an ounce per hour—in such abundance, that, in the twenty-four hours during which the exudation was at its height, the quantity which would have entered the blood could not be estimated at less than a pound—*i. e.*, something like half the weight of the animal's blood. Now, inasmuch as a local inflammation of this kind rapidly subsides, and leaves no trace behind it, and is not attended by any serious constitutional disturbance, it is tolerably clear that the mere admixture of a large proportion of inflammatory exudation with the blood is not in itself a matter of very serious moment, and that whatever impressions may exist in our minds as to the toxic properties of pus-corpuscles must be discarded. So long as these structures retain their integrity, there is no reason to suppose that the mere fact of their having escaped from the blood in consequence of injury of the vascular wall, unfits them for re-entering the circulation.

In the early stage of the inflammatory process, there is every reason to believe that the process of absorption goes on exactly as in health, with the exception that as many ounces have to be drained away in the one case as drachms in the other. Subsequently, as the percentage of solids, and particularly the number of corpuscles contained in the lymph increases, the drainage diminishes, partly owing to partial obstruction of the lymph-paths by coagulation, partly because less is exuded.

2. *No organisms endowed with inflammation-producing phlogogenic particles exist in the atmosphere or in the ordinary aqueous liquids with which our bodies come into contact.* In dealing with this proposition, we have the same sort of evidence as with reference to the first; *viz.*, that these supposed delinquents may be brought into contact with living tissues of all kinds without producing any local disturbance. But, before attempting to show this, I would ask you kindly to bear in mind that we have to do exclusively with the case of inflammation. I presume that no one here doubts that the air contains, or may contain, the seeds of specific diseases; and there are strong reasons for believing that these seeds are organisms. Whether they are or are not, does not at present concern us. My proposition is, not that there are no such things as air-contagia, but simply that its particles are not phlogogenic; and the first point to be settled is, how we are to bring these particles into contact with living tissues so as to test their properties effectually. As regards the air, one method which appears to me to be very conclusive, consists in passing large quantities of air through living tissues. In the rabbit, the subcutaneous tissue may be kept distended for days, by frequently renewed injections of unpurified air, without producing any inflammation; nor is the effect more serious if the same tissue

be ventilated by a continuous current of the same air for a number of hours, even when that air is derived from a *post mortem* theatre; whence it seems clear that, so far as the tissue is concerned, air is tolerably harmless; for, by this mode of ventilating a tissue, floating matter can scarcely fail to be deposited.

The information yielded by similar experiments on unpurified watery liquids is, in one respect, more satisfactory—*viz.*, that we have here to deal with media, in every particle of which we can very readily prove the actual existence of germs, in such a state of viability as to require only a suitable soil to ensure their development. Dr. Wegner, ("Chirurgische Bemerkungen über die Peritonéal Höhle," Langenbeck's *Archiv*, volume xx, page 51), who is the author of the ventilation experiment to which I have just referred, has tested these liquids, both on the cellular tissue and the serous surfaces, with similar results. I will ask your attention specially to those which relate to the peritoneum. When water, charged with septic bacteria (bacteria which had grown for this purpose in a "cultivation liquid", *i. e.*, a solution of nutritive salts) was injected into the peritoneal cavity of a rabbit, in quantity less than two ounces, it produced no effect whatever; and when the animal was killed the next day, it was found that the whole of the liquid was absorbed, and that the peritoneum was in a normal state. Whither had the organisms gone? Had they disappeared from the peritoneum, or were they reposing harmlessly on its surface? The examination of the lymphatic vessels of the diaphragm, which, as is well known, serve as the ordinary drainage-channels for the peritoneum, showed that for the most part they had been absorbed; for these vessels were full of bacteria, which had been arrested on their way from the peritoneum towards the venous system; but neither in the lymphatics nor in the peritoneum, did they occasion any inflammatory change. Similarly he found that, when a large quantity of liquid (warm 0.75 per cent. solution of salt) was led, by means of suitably arranged drainage-tubes through the peritoneal cavity, in a continuous stream for many hours, so that the membrane was exposed for a long time to whatever phlogogenic influences the liquid conveyed, no effect whatever was produced. So long as the liquid was constantly changed, there was no infection, no inflammation. If it were allowed to remain stagnant in the peritoneum in larger quantity than could be absorbed, these results followed inevitably. Hence, while a liquid which is actually charged with septic organisms is harmless if its quantity be such that it can be rapidly absorbed, common water, if it accumulate, will produce a fatal peritonitis.

It may thus be considered to be established that septic bacteria or their germs, in a viable state, are not necessarily phlogogenic; and I may, therefore, pass at once to my third point.

3. *Whenever an inflammation becomes infective, it owes that property to chemical change in the exudation-liquid, of which the presence of microzymes is a necessary condition. Conversely, septic organisms which are infectious owe their infectiveness to the exudative soil in which they have grown.* To illustrate these propositions, I will pursue the study of peritonitis a little further.

In experiments which I made a dozen years ago, I showed that, in rodent animals, peritonitis induced by the injection of irritant liquids is always infective. The exudation products of such inflammations were found to be septic, notwithstanding that the irritant used (*e.g.*, tincture of iodine) was not only free from germs, but destructive of them. This was understood to mean, that the first effect of the iodine was the effusion of liquid into the peritoneal cavity; the second, the infection of this liquid by formed ferments, which found their way into it, not from the atmosphere or from external media of any kind, but from the alimentary canal. A knowledge of the exact conditions which lead to this result, is obtained by simplifying the mode of experiment. We have already seen that water, whether contaminated with septic organisms or not, may be introduced into the peritoneum in limited quantity without effect. But, if water, which has just been boiled and cooled, be injected with antiseptic precautions in larger quantities—*i. e.*, in quantity so large that it cannot be rapidly absorbed—the result is entirely different. The water which is thus injected accumulates in the serous cavity, charges itself by diffusion, first with the salts, subsequently in increasing proportion with the proteids of the blood, and thus becomes a most favourable soil for the development of septic organisms, which, in their turn, act infectively or phlogogenically on the blood-vessels and living tissues with which they come in contact. A septic peritonitis ensues, which kills the animal by septicæmia in twenty-four or thirty-six hours.

This simple experiment serves, I think, to illustrate the fundamental principle that, although the seed is indispensable to the coming into existence of the infective process, the question whether that seed becomes morbid or not, depends, not on the seed itself, but on the soil. But there are other examples equally striking.

On a former occasion, seven years ago, I gave an incomplete account of certain experiments of my friend, Professor Chauveau, which I had then recently witnessed, and still regard as among the most valuable ever made with reference to the questions which now interest us. (Chauveau: *Microbiose et Gangrène*. Paris, 1873.) M. Chauveau's observations were founded on an operation which, under the name of *bistournage* of the testis, has been for centuries practised in the south of France, for economical purposes; and which, although extremely simple, is more scientific and better adapted for the end—that of annulling the function of the testis, with as little injury to surrounding parts as possible—than any of the operations which are practised in this country. The procedure is as follows. The organ, with its serous and fibro-muscular coverings, is freed from its attachment to the dartos; then twisted on the spermatic cord, so that its lower end is upmost; and finally rotated round the cord, as an axis, four or five times—the whole being accomplished without the aid of any instrument, and with wonderful rapidity. If the animal be killed and the arteries be injected, it is found that the spermatic artery is empty beyond the twist of the cord. Consequently, the circulation of the testis is completely cut off. The result, stated shortly, is that adhesions are promptly established between the organ in its new position and the dartos, as well as between the two layers of the tunica vaginalis; and that, in these adhesions, new vessels are formed. These, however, never extend into the dead organ, which consequently undergoes degeneration and atrophy. For our purpose, the value and interest of *bistournage* lies, first, in the evidence it affords—evidence based on ready-made experiments to be numbered by hundreds of millions—that, under favourable conditions, the inflammatory effects which result from fairly severe injuries of vascular tissue are strictly limited to the parts directly injured; and, secondly, as affording the opportunity of determining the nature of those conditions by observing the effect of varying them. Here, as in respect of every traumatic inflammation two factors had to be considered. The strict limitation of the inflammatory effect to the parts directly injured might be due entirely to the absence of septic organisms, or entirely to the circumstance that the surrounding structures were so little injured that they suffered thereby no appreciable damage. Experiment showed that both factors were operative. If, instead of allowing the organ to become grafted in its new position, the process of union were interrupted by repeated manipulation, an inflammatory process was set up between the dartos and the external surface of the fibro-muscular tissue, which resulted in suppuration; whence it was manifest that, without any change of the condition of the parts, as regards the exclusion of germs (for the integument remained perfectly healthy), the phlogogenic effect was increased in proportion to the injury inflicted. But this effect was not comparable to that which was produced when, without any modification of the operative procedure, means were taken to secure the existence in the circulating blood, and consequently in the blood-vessels of the organ, at the moment that its circulation was arrested, of infective material. This was accomplished by infusing into a vein a sufficient quantity of diluted pus, derived from an infective abscess, to impregnate the blood with septic products, without risk of fatal septicæmia. In an animal so prepared, the devitalised organ, instead of becoming engrafted, itself became the nucleus of an inflammatory tumour, which rapidly extended to surrounding parts, and resulted in the deaths of most of the animals experimented on, either by septicæmia or by diffuse suppuration.

Following on the lines of Professor Chauveau's investigations, Professor Kocher of Bern ("Die acute Osteomyelitis mit besonderer Rücksicht auf ihre Ursachen", *Deutsche Zeitschrift für Chirurgie*, vol. xi, p. 118) has materially extended their bearing by showing that, when septic products enter the circulation in what may be called the normal channel—i. e., the channel by which they are constantly entering the circulation in greater or less numbers, they exercise a similar power, not of producing inflammation in undamaged tissues, but of transforming the normal effects of injuries into infective processes. The structure chosen for these experiments was bone. Having first found that in a healthy animal the most active irritants or caustics can be, if antiseptic precautions be used, injected into the medullary cavities of bones without extension of inflammatory changes beyond the limits of the injury, he repeated the experiment under special conditions as regards diet. Having produced a normal osteomyelitis in the way above described, and observed the animal during the first week, at the end of which its condition was perfectly healthy, he substituted for its ordinary food a diet of putrid material, charged with septic organisms. The result was in entire accordance with Chauveau's observations—namely, that the impregnation of the blood with material absorbed from the intestine converted the normal into an infective osteomyelitis. The dog became ill, and was subsequently killed. The medullary cavity of the injured bone was converted into an infective abscess. A

result of this kind, perhaps, scarcely needs comment or explanation. We have already learnt that the presence of septic organisms (provided that they have not been bred inside the organism) is not necessarily attended with any danger. We have now learnt that they become sources of danger at once, when they are brought into relation either with devitalised organs, or with extravasated serous liquids of any kind, and particularly with inflammatory exudation.

4. *Micrococci which have found their way into the circulation may serve as vehicles for the dissemination of infective malaria.*—The last of my four points relates to the purely mechanical part which micrococci seem to play in the dissemination of infective material. To illustrate this, I must revert to the experiments before referred to relating to the absorption of liquid from the peritoneum of the rabbit. I mentioned how, after injection into the peritoneal cavity of liquid charged with bacteria, the lymphatics leading from the peritoneum are found to swarm with bacteria, and these organisms also abound in the blood. If the animal be killed, say, ten days or a fortnight after the injection, yellowish opaque deposits are found here and there in the internal organs—particularly in the lungs, liver, and kidneys—which have been conveyed by the blood-stream to the places in which they are found.

If, instead of charging the circulation with harmless bacteria grown outside, you produce an acute peritonitis, the effect is the same mechanically, but pathologically very different. In both cases, the peritoneum contains liquid charged with septic organisms, which, in both cases, are conveyed therefrom by the lymphatics into the blood-stream; but in one case they enter the circulation incapable of doing any harm excepting such as may result from the plugging of capillary arterioles; in the other, they carry with them a phlogogenic virus, by virtue of which, wherever they lodge, they become the starting-points of infective abscesses. Now, as I observed before, it is not to be imagined that the particles by which infection is disseminated throughout the organism, so as to produce multiple abscesses in muscles and viscera, consist exclusively, or even chiefly, of aggregations of micrococci. All that can be maintained is that, wherever they exist in the circulation, they certainly take part in the process of dissemination; and we are strengthened in this conclusion by what is now known of ulcerative endocarditis, in which the circulating blood becomes (sometimes very suddenly) impregnated with infective material by the instrumentality of fibrinous matter separated from the mitral valve. In these cases, life is destroyed, not by the mere mechanical plugging of the arteries, but either by septicæmia, or by a slower process characterised by the development of miliary abscesses in the muscular tissue of the heart, liver, spleen, kidneys, and other internal organs. That the little emboli which here act as if they were seeds of infection consist chiefly of masses of micrococci, we know from direct observation, for they are found—as it were *flagrante delicto*—at the very spots where the mischief has been done, and surrounded by the evidences of its nature.

Still more remarkable is the history of the secondary lesions found in internal organs during the development of small-pox, which have been so thoroughly studied by Dr. Weigert (*Anatomische Beiträge zur Lehre von der Pocken*, part ii, p. 3, Breslau, 1875). He has shown that, early in the suppurative stage of small-pox—i. e., before the secondary fever commences—cylindrical masses are to be found, on microscopical examination, in various organs, particularly in the liver, spleen, lymphatic glands, and kidneys, which consist simply of capillaries plugged with micrococci. At a somewhat later period, though the organs are still to the naked eye perfectly healthy, each plug is surrounded (in the section) by a zone of altered tissue, the change consisting in wasting of the nuclei of the cells. Up to this time, the process has given rise, to use the ordinary language, to no surrounding vascular reaction; but eventually the devitalised tissue becomes the seat of infiltration with leucocytes, and is thus converted into a circumscribed miliary abscess, with a surrounding border of hemorrhagic congestion.

So far as relates to the mechanism of the process, it is almost as plain as it was in the case in which we produced the same results experimentally in the rabbit by injecting bacteria into the peritoneum. In small-pox, the micrococci, which take so prominent a part in the development of the cutaneous eruption, find their way (probably by the lymphatics) in myriads into the circulation. We have no evidence that they carry with them the specific contagium of the disease. All that is proved is, that they lodge in the capillaries of the internal organs. What they do there may well depend on circumstances. It may probably be assumed that in all cases they do some damage to the tissues in their immediate neighbourhood; but we have no evidence that in every case each capillary embolus becomes the nucleus of an infective abscess. Whether this happens or not will probably depend on the quantity and progress of the cutaneous suppuration, and on the degree in which the circulation becomes impregnated with septic material.