LECTURES ON THE INFECTIVE PROCESSES OF DISEASE.

Delivered in the Theatre of the University of London.

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LECTURE III.—*Pathology of Septicæmia.*

AFTER describing the phenomena of septicæmia, so as to enable you to have before you a sufficiently well defined picture, first, of the effects which show themselves in animals in consequence of a dose of septic poison, and, secondly, of the corresponding symptoms in man, I proceeded to discuss the pathological questions relating to the septicæmic state under two heads; viz.: 1. The efficient cause of septicæmia—the septic poison; and 2. The nature of the pathological process. In the last lecture, I concluded what I had to say to you on the first of these subjects; viz., the genesis of the septic poison, and the important part taken by bacteria in its production. I have now to ask your attention to the nature and effects of the changes which it produces in the circulating blood.

In order that we may be in a position to enter on the study of this question advantageously, let me recall your attention to the main features of septicæmia in animals and in man, as I described them in previous lectures. We saw that it is characterised by (1) the loss of muscular strength, particularly of the heart and respiratory muscles; (2) by the marked tendency which exists to the development in various internal viscera, but more especially in the lungs and in those which send their blood to the portal vein, of a congestion, which has as its concomitant results capillary stasis and hæmorrhage and diffused infiltration of the affected tissues; and finally (3), by brain-disorder and fever.

The most important matter for consideration is that of the relation between the altered condition of the blood and the other phenomena. If, as has been suggested, the alteration of the blood-corpuscles be the primary fact, how does this change in their condition produce the other disorders? May it not be that some of these disorders are due to the immediate action of the poison on the nervous system, or on the tissues generally? I shall endeavour to show that, so far as concerns all those phenomena which belong to the circulatory system, we have good reason for attributing them to the pernicious influence exercised by the poison on the blood-corpuscles; for, in studying experimentally the pathological disturbances produced by agents which can act only in this way—i. e., by disintegrating the blood-corpuscles—we find that the morbid changes produced by them in the organs of circulation entirely resemble those of septicæmia. I found this statement on certain important observations which have been made very recently by Dr. Köhler,* at the suggestion of Professor A. Schmidt of Dorpat, whose name is well known to us all in connection with his investigations as to the coagulation of the blood. Let me first relate to you the facts as they stand. What has been observed is as follows. If, in a dog, a couple ounces of blood be taken from the femoral artery and allowed to coagulate, and, after the lapse of twenty minutes or so, the clot be broken up and kneaded with the fingers, and the carefully strained blood be reintroduced into the femoral artery of the opposite side, so as to mix very thoroughly with the blood-stream before it reaches the heart, it is found that this apparently harmless procedure is attended with the gravest consequences. In ten minutes, or even in a shorter time, after the injection, the animal is collapsed, as if poisoned; the pupil is dilated; even reflex action is much diminished; the heart beats irregularly, but strongly; and the respiration is difficult. These more violent symptoms pass off; but soon alvine disorders resembling those which I described to you in my first lecture present themselves. First, normal dejections are passed with more or less tenesmus; then follow liquid, mucous, and sanguinolent evacuations in rapid succession; the discharges become more and more bloody; and the animal, if not killed, dies in a state of complete prostration. If the examination of the body be made immediately after death, so as to avoid *post*

mortem changes, appearances present themselves which any person acquainted with the signs of septicæmia would at once mistake for them. Let us suppose the animal to have been killed, and the body opened while the heart was still pulsating. The right ventricle is charged with fluid blood; it may, however, contain coagula, formed, of course, during life. The left ventricle exhibits the characteristic spots of ecchymosis on its internal surface. On opening the abdominal cavity, it is seen that the portal vein and all its tributaries are full of dark fluid blood; the liver is congested, and the mucous membrane of the gall-bladder beset with minute ecchymoses. The mucous membrane of the stomach is also congested and beset with ecchymoses, but otherwise little altered; so that its condition contrasts markedly with that of the duodenum, which, just as in septicæmia, is the seat of intense congestion. The liquid contained in the duodenum consists of blood-stained mucus more or less mixed with bile. Numerous shreds, of various sizes, of shed epithelium float in it, easily distinguished by their yellowish tinge. On microscopical examination, the liquid is found to consist of young cells, coloured corpuscles in great numbers, shreds of epithelium, and abundant masses of bacteria. The mucous surface is of intense dark red. On microscopical examination, it is seen that the villi are the chief seat of the capillary extravasation. The capillaries of the villi are choked with coloured corpuscles closely packed against each other. They sometimes exhibit extravasations, but not as a rule. The mesenteric glands are intensely congested and soaked with sanguinolent liquid. In the large intestine, the changes are much less marked, though any fecal matter contained in the bowel is of a pitchy blackness. Finally, the blood does not coagulate; but there are no signs of solution of the coloured corpuscles; i. e., the liquid part of the blood is not ruby-coloured, as it is in real septicæmia—an important difference between this result and that of septicæmia, the meaning of which will be more apparent as we proceed.

If anyone here present happened to attend the meeting of the Pathological Society in 1872 (*Pathological Society's Transactions*, vol. xxiii, p. 303), at which Dr. Klein and I exhibited to the Society the effects of the injection into the peritoneum or into the circulation of a very small quantity of peritoneal infective exudation-liquid, they will at once recognise the striking resemblance of the lesions of which I have now given a sketch with those then described. They resemble no less closely, as I have said, the infusion into the circulating blood of the virulent products of bacteria. In a word, the phenomena you have before you are those of intense septic toxicæmia; but (and it is to this fact that I would specially ask attention) they are produced, not by the introduction of any substance or contagium of extrinsic origin, but simply by the presence in the animal of the products of the disintegration I was going to say, but I must not anticipate—the products of the coagulation and exposure of its own blood. You have before you, in fact, an animal poisoned with its own blood.

To explain this action, I must ask your attention for a short time to some purely physiological considerations, which, however, if well founded, are of unquestionable pathological value and importance. Every bit of knowledge that helps the physician or surgeon to understand how it is that the hidden and intrinsic processes of disease go on, whether started by a morbid zyme from outside or not, is of value. Hence it is that an experiment like the one I have related to you, in which we are able to trace such a process, possesses a very great interest.

Every student is familiar with the inconvenient words fibrinogen and fibrinoplastin, by which Professor Schmidt of Dorpat has designated what he calls the fibrin factors, and is able to tell you that they are so designated because together they are supposed, according to what he pleases to call the newest views, to make fibrin. Your student would further tell you, if asked, that there is no fibrin in the circulating blood, that the fibrin of the clot is represented by the fibrinoplastin and fibrinogen of the liquor sanguinis; but that, somehow or other, although both of these factors are present, no coagulation occurs so long as the blood is contained in the vascular system; so that the immediate cause of the coagulation of the blood appears to be the withdrawal from it of the influence naturally exercised upon it by the living vessels.

The mode of the influence of the living artery or vein on its contents was, until lately, a mystery, to the solution of which the only clue was suggested by the observation that, in certain cases in which, notwithstanding that both "factors" were present, and that the liquid was no longer in the body, coagulation failed to take place or was unduly delayed, the desired result appeared to be brought about in some way or other with the aid of colourless blood-corpuscles. The only way in which this could be explained was by supposing that the corpuscles must contain some *tertium quid*, which, perhaps by a ferment-like action, determined, in the fibrin-producing constituents of the plasma,

* *Ueber Trombose und Transfusion, Eiter und septische Infection und deren Beziehung zum Fibrinferment.* By Dr. Armin Köhler. Dorpat: 1877.

those molecular changes of which coagulation is the visible sign.* Natural and simple as the suggestion seems, it was some time before it took more distinct form, and still longer before the agency of the colourless corpuscles in coagulation was established on the sure basis of experiment. Obviously, if the agent in coagulation be housed in the corpuscles, it must follow that, in order to its being free to act, at all events a certain number of them must be disintegrated. That such is really the case, we have now good reason for believing; but it has taken a long time and much laborious research to prove it. Let me now bring some of these reasons under your notice. I have to prove to you, first, that certain of the blood-corpuscles disintegrate from the moment that they leave the blood-stream; and, secondly, that if they are removed from the blood before this process commences, the concomitant process of coagulation is arrested.

The fact that the colourless corpuscles break up in the process of coagulation can be made matter of direct observation in any liquid in which they can be observed alone, that is, without the coloured blood-discs. The liquid which has been used for the purpose by Professor Alexander Schmidt is the separated liquor sanguinis or plasma of the horse.† It may be well that I should state how this is obtained. As every one knows, blood does not coagulate at the temperature of freezing. If you allow blood from a vein or artery to fall into a tall jar, in which it is rapidly cooled, and surround the jar by ice, the blood does not coagulate, and what is observed is that the corpuscles fall to the bottom, so that, in the course of an hour or two, you have the column of blood divided into two parts, of which the upper consists of liquor sanguinis alone. As the subsidence of the coloured blood-discs begins very soon after the blood is drawn, it is possible to collect colourless plasma from the top stratum almost immediately with the aid of a pipette. If this liquid be examined without delay, it is found to contain scarcely any blood-discs, but any number of colourless corpuscles; and, if the observation be continued, it is seen that a certain number of these leucocytes rapidly undergo disintegration. In this process of disintegration, the corpuscle breaks up to granules, which hold together for a time in the liquid, but eventually dissolve and disappear. That the disintegration is intimately connected with the process of coagulation, Professor Schmidt infers from the fact that the first formed filaments of fibrin can be plainly seen to originate from the heaps of granular *débris* which the corpuscles leave behind them.‡

I need scarcely say that the fact of the participation of the colourless corpuscles in the act of coagulation could not be accepted on the ground of microscopical observation alone, however careful or minute. In order to arrive at certainty on the subject, it is necessary to adopt such a mode of investigation as will bring the matter to the test of crucial experiment. It must be shown, not merely that when the corpuscles are withdrawn coagulation is arrested, but also that if, after such withdrawal and suspension of coagulation, they or their contents are restored to the plasma, the power of coagulation, before absent or diminished, is restored. The proof of the first of these statements has been rendered possible by the discovery that in plasma the leucocytes, though quite incapable, on account of their extreme lability, of being stopped by any filter at the ordinary temperature, acquire at the temperature of freezing such firmness and consistence that they are held back by the ordinary method of filtration. This being the case, it is a comparatively simple matter to obtain uncoagulated plasma as nearly as possible in the same condition as that in which it actually circulates, free from leucocytes, provided that the physiologist can work at a low temperature. The filtrate so obtained is absolutely transparent, and is, as nearly as may be, deprived of its power of coagulating; for when brought into an ordinary room, and subjected to a temperature of 60 or 70 deg. Fahr., it remains fluid for several hours.

The second fact, namely, the restoration of the power of coagulation by the subsequent addition to the liquid of the constituent of which it has been deprived, may also be demonstrated by the same method of

filtration. The colourless corpuscles are, as I have described, collected on a paper filter. In order to obtain them free from adherent plasma, they must be washed with ice-cold water. If, then, the filter be washed a second time with water rendered slightly alkaline by sodic carbonate, a solution passes through, which, when added to the decorpused plasma, again restores to it its original coagulability (Schmidt, *Die Lehre*, etc., p. 47).

It has further been established by A. Schmidt that all spontaneously coagulable fluids contain, in addition to what he calls the *substratum* for coagulation (viz., the fibrin factors), a body which is endowed with the properties of a ferment, by which is meant a substance which by contact excites chemical action without itself taking part in it. The function or endowment of the blood-ferment, as it is called, is to excite the molecular changes which result in coagulation, without itself taking any part in the formation of the resulting fibrin.

The blood-ferment is obtained from freshly coagulated blood by a method which resembles that by which, as I explained in my last lecture, I obtained my septic extract from putrid infusions; viz., by first subjecting the blood to the prolonged action of strong alcohol, and then extracting the precipitate with distilled water. The solution of the precipitate, which as so prepared has no toxic properties, exhibits a very remarkable power of exciting coagulation in coagulable liquids in which the process was previously delayed or restrained. If, for example, you receive bullock's blood into a vessel containing already a strong solution of Epsom salt, and allow the blood and solution to mix, you obtain a liquid which does not coagulate. If, after allowing the corpuscles to subside, you decant off the supernatant liquid, you have, of course, the plasma of the blood diluted with water holding magnesian sulphate in solution. If now you dilute this plasma sufficiently with water, it coagulates, because, as has long been known, the inhibitory power of the sulphate is neutralised by dilution. But, if, in adding the water, you stop short of this degree of dilution, you readily obtain a liquid which, although, so to speak, on the point of coagulation, yet does not coagulate. Such a liquid is well adapted to exhibit the influence of any such body as we suppose the ferment to be. It is evident that it contains the substratum for coagulation; for it consists of liquor sanguinis and magnesian sulphate. Yet it does not coagulate until the required fillip is given to it by the addition of the ferment.

These facts admit of no explanation excepting the one given to them by general consent, namely, that, in addition to the substratum, the action of a ferment is necessary for coagulation, and, this having been admitted, the explanation at once suggests itself to the mind that it is in the leucocytes that the ferment is produced, and that this is one reason why they must be disintegrated, in order that coagulation should take place. The filtration experiment affords evidence that this explanation is correct; for it is found that, whereas plasma which contains its leucocytes is as rich in fibrin as the corresponding quantity of blood, plasma which has been deprived of them contains no ferment whatever. But we have already had the proof before us that this is not the only way in which they contribute to the formation of fibrin; for it has been shown that their absence not only prevents coagulation, but that the quantity of fibrin formed is proportionate to the number of corpuscles present. Hence they are not merely exciters of coagulation, but also furnish part of the material out of which fibrin is built up (*loc. cit.*, p. 51).

These considerations, relating to the participation of the leucocytes of the blood in the act of coagulation, readily afford us a way to understand the fact from which we started; viz., that blood which has been allowed to coagulate and then strained off from the clot and reinjected acts as a poison. Why does it do so? Obviously, because it contains disintegrated leucocytes, and thereby determines to a greater or less extent intravascular coagulation. Intravascular coagulation as a mode of rapid death is familiar to every one: a clot in the right ventricle, extending into the pulmonary artery; arrest of the circulation in the lungs; life extinguished by a process in which the phenomena of collapse are mixed with those of asphyxia. In some of the experiments on the reinjection of cruor, this effect was observed. The animal died collapsed and half asphyxiated, and, on opening the thorax immediately, it was found that the still beating heart contained a firm clot, which extended into the pulmonary artery. But, in those cases of longer duration in which the *post mortem* appearances corresponded so very closely with those of septicæmia, coagulation had indeed taken place, but the obstruction was not in the great vessels, but in the smallest arterioles. The contrast between the two kinds of coagulation was striking enough, the one inducing a systemic, the other a local effect; the one affecting the circulation close to the heart, the other near to the capillaries.

It will be remembered that the cruor was infused into the arterial

* For the facts known in 1873, as to the influence of the colourless blood-corpuscles on coagulation, see the article on the Blood in the *Handbook for the Physiological Laboratory*, p. 173.

† Professor A. Schmidt has lately published a complete summary of his sixteen years' labours in the investigation of the coagulation of the blood, under the following title: *Die Lehre von der fermentativen Gerinnungs-Erscheinungen in der eiuissartigen thierischer Körperflüssigkeiten*. Dorpat: 1876.

‡ A similar process may be readily studied in the coagulation of blister-fluid, a drop of which may for this purpose be subjected to observation in a "moist chamber" on the "warm stage" of the microscope. Pericardial fluid, collected from the body of a horse or ox just slaughtered, can be used for the same purpose. Schmidt's microscopical observations relating to the coagulation of plasma are to be found in detail in a paper published in *Pflüger's Archiv* in 1875, p. 560, entitled "Ueber die Beziehung der Faserstoffgerinnung zu den körperlichen Elementen des Blutes". He concludes, from elaborate observations, that those of the colourless corpuscles which, on account of their containing coloured granules, may be regarded as transitional (*voher Körnerkugeln*), take a much more active part than the rest in the fibrin-producing disintegration.

blood-stream of a limb, and not into a vein; consequently it had to pass through the capillary system of the limb, and so become intimately mixed with the circulating blood, before it arrived at the heart. It is this fact which affords the key to the understanding of the result. The tendency to coagulation developed itself slowly, and affected the whole mass of the blood, its effect being to increase the viscosity, and not to produce clots. It was only in a few cases that visible plugs could be distinguished even in very small arteries; but the change in the properties of the blood showed itself in the production of stasis in those parts of the circulation in which stasis is most apt to be produced.

That the organs which send their blood to the portal vein were specially distinguished admits of a probable physiological explanation. In those parts, the difference between the arterial and venous pressures is less than anywhere else in the circulation, excepting in the lungs. But it may be asked, admitting that the circulation of cruor produces embolism of capillary arteries, and that this is, on the whole, more likely to occur in the abdominal organs than elsewhere, how does this explain the localisation of the congestion of the mucous membrane in the duodenum and jejunum? For the answer to this question I need only refer to the facts relating to capillary embolism, of which I gave you an account here two years ago. We then saw that, whenever a terminal artery is obstructed (*i.e.*, an artery which is so exclusively distributed to a particular territory, that that territory receives no blood from any other source), the result is, that the capillaries become choked with blood; and that, by the exudation of the liquor sanguinis of the stagnant blood into the adjoining tissues, the relative number of corpuscles increases, so that in the end you have the capillaries completely plugged with coloured blood-discs, just as they are in the capillary stasis of inflammation. Hence the fact that, both in septic gastro-enteritis and in that produced by the injection of cruor, the villi are the special seat of the injection may be readily understood; for it is obvious that the artery of a villus must necessarily be terminal. If it be choked, the capillaries of the villus will fill with blood as completely as those of the frog's tongue after obstruction or ligature of its principal arteries.

The value and significance of the experimental results we have been considering appears to me to lie in this: not that an analogy is established between septicæmia and the effects of corpuscular disintegration, but that they afford evidence that the particular symptoms produced are not specific, *i.e.*, are not dependent on any specific attraction between, *e.g.*, the mucous membrane of the duodenum and the septic virus, but on a physiological process for which all the conditions exist inside the organism. Thus, by simplifying the problem of the pathological nature of the conditions, we resolve the question of its action into a question of the disintegration of the colourless blood-corpuscles.

The analogy which we have now seen to exist between septic intoxication and the effect of the reinjection of cruor, however remarkable it may be, must not mislead us to the conclusion that the two processes are identical; that is, to the inference that the whole effect of the septic poison is due to the premature disintegration of leucocytes. The symptoms which seem to me to stand apart from the rest in this respect are those which relate to the nervous system, and the pyrexia. As regards the former, their mode of production must for the present remain an open question. There are clinical facts relating to the subject, but they are not sufficiently definite to be dwelt on here. As regards the pyrexia, I think it very unlikely that it is produced by the disintegration of the leucocytes. It seems to me much more probable that the damage done by the septic poison has a wider range, and affects all the more unstable forms of protoplasm, that is, all the more active structures of the body; and that, in accordance with the view of fever which I submitted to you in my lectures here four years ago, the pyrexia which it produces is the expression of that general damage.

[To be continued.]

STOMATOPLASTY.—In a case of cicatricial contraction of the jaws, in which the mucous membrane of the cheek as far as the masseter, and the gums, were extensively destroyed, Dr. Gussenbauer replaced the mucous membrane by a pedunculated horizontal flap cut from the skin of the cheek, and turned so that the epidermic surface looked towards the interior of the mouth. At a second operation, the bridge of tissue connecting this flap with the exterior was divided, and fastened to the anterior part of the mouth. Finally, the defect in the exterior of the cheek was repaired by skin taken from the submaxillary region in the neck. The result of the operation was the restoration of the normal movements of the jaw. The case may be regarded as a typical one of the contractions which result from ulcerative stomatitis, noma, and injuries.—*Archiv für Klinische Chirurgie*, Band xxi; and *Centrallblatt für die Med. Wiss.*, Dec. 29.

A CASE OF RUPTURE OF THE INTERNAL AND MIDDLE COATS OF THE POPLITEAL ARTERY, AND COMPLETE RUPTURE OF THE POPLITEAL VEIN, FOR WHICH PRIMARY AMPUTATION OF THE THIGH WAS SUCCESSFULLY PERFORMED: WITH REMARKS.

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THE comparative rarity of partial rupture of the popliteal artery will, I hope, impart sufficient interest to the following case to justify me in bringing it under the notice of the British Medical Association. The particulars of the case are these.

James Collins, aged 19, a muscular well built young man, of fair complexion, was sitting on the front seat of an omnibus; the retiring angles of his knees were in close correspondence with the projecting edge of the seat. A runaway horse and cart came rushing up and dashed into the omnibus. The cart was a railway cart with a high curved cover, and one corner of this cover struck against the patient's left knee and drove it backwards, so that the recess of the popliteal space must have come violently into contact with the edge of the seat. The patient was admitted into the London Hospital on Friday, May 8th, 1874, at 7.30 P.M., shortly after the accident. The left knee showed signs of severe contusion; but, on examination, Mr. Bowkett, the house-surgeon, did not detect any abnormal mobility. There was no evidence of a dislocation. There was not much effusion into the cavity of the joint, and the patient could bend it with only a slight amount of pain. The right knee was bruised. By 9 P.M., the swelling had greatly increased, and the patient complained of partial loss of sensation below the middle of the leg. On measurement, the circumference of the left limb, three inches above the upper border of the patella, was found to be seventeen inches, whilst that of the other side was only thirteen inches. At 11 A.M., the next morning, he was seen by myself. Great swelling existed above and below the left knee for some distance. The knee-joint was distended. The limb was perceptibly cooler than its fellow. The posterior tibial artery at the ankle yielded the faintest possible thrill, so faint, indeed, that most of those who examined the case could not perceive it. On auscultating the limb over the course of the popliteal artery, I detected a peculiar low clicking sound, much resembling the ticking of a watch under a pillow. The diagnosis formed was probable rupture of the popliteal artery and vein, either partial or complete. There was too much swelling to determine the existence of any accompanying fracture. It was decided to send for the friends, and to recommend amputation in the course of the afternoon. At 3.30 P.M., the patient was seen also by my colleague Mr. Hutchinson, who concurred in the diagnosis, and strongly advised the patient, who seemed at first unwilling to consent, to submit to the loss of his limb. By this time, the swelling had invaded the thigh and the leg farther, both upwards and downwards, and the foot was assuming a mottled aspect. The consent of the patient and his friends having been obtained, I amputated the thigh at the lower third, adopting a modification of Teale's method, which I have practised for some years. The anterior flap was rounded at the angles and cut rather shorter, whilst the posterior flap was cut rather longer, than the corresponding flaps in Teale's amputation. The greater portion of the anterior flap consisted of skin and fascia only. On completing the removal of the limb, we found that the areolar tissue underneath the skin of the posterior flap was infiltrated with dark blood for some distance, and, as it seemed possible that the part had been bruised and might slough, it was thought advisable, as a precautionary measure, to take away an inch more of the femur, so as to obviate all chance of subsequent protrusion. Accordingly, the periosteum was stripped up for an inch and the bone sawn off. Subsequently, however, not the slightest sloughing action took place, the blood previously effused undergoing absorption. Four or five ligatures were required; the flaps were brought together with wire sutures, simple dressing was applied, and the patient was sent to bed.

The progress of the case was scarcely interrupted by any unfavourable symptom. Both the temperature and pulse had a high range for a few days, as might have been expected, the former reaching 102 deg. and 103 deg., the latter 120; but, within a week, the temperature was at 99 deg. and the pulse 100. By the 18th, the flaps had united by first intention, except at the lowest part; and, by the 28th, the ecchymosed portions had regained the aspect of health. In the middle of June, the patient was going about on crutches, and, in another month, he was sent to the seaside, his stump being entirely healed. On his