LECTURES ON THE INFECTIVE PROCESSES OF DISEASE.

Delivered in the Theatre of the University of London.

By J. BURDON SANDERSON, M.D., LL.D., F.R.S.,
Professor of Physiology in University College; and Superintendent of the Brown
Institution.

LECTURE II.—*Phenomena and Etiology of Septicæmia.*

As a basis for the study of the etiology of septic infection, which we hope to make to-day, I propose to give you an account of the symptoms of that condition as they manifest themselves, first, in the lower animals, and then as they present themselves in man.

By the term septicæmia I mean the aggregate of the effects which are produced in the animal organism when putrid matter is mixed with the blood-stream. By this definition, I exclude all characters which relate to the development of metastatic abscesses or of secondary foci of inflammation. Not that I for a moment question the very close relation which exists between the cause of septicæmia and that which gives rise to those forms of infection which we collectively designate pyæmia, but that I believe that the line of distinction between them, though faint, is yet clearly marked.*

Now, inasmuch as we cannot be certain, in any case of clinical septicæmia, that the symptoms or *post mortem* results are exclusively due to septic contamination, it is clearly necessary to take the experimental facts rather than the clinical as our starting-point, and in this we are fully justified by the historical development of the subject. It was by the experiments of Gaspard made at the beginning of the century, between 1809 and 1820,† that physicians and surgeons acquired the first conception of putrid infection. Gaspard's method consisted in injecting either into the veins, the serous cavities, or the cellular tissue of animals, various kinds of putrilage. When the dose was sufficient, the animals died three or four hours after injection; death being preceded by muscular collapse, vomiting, purging, and other signs of violent gastro-enteric disturbance. Gaspard arrived at no conclusion as to the nature of the poison which produced these symptoms, excepting that it was a product of putrefaction. Knowing that carbonic acid gas and sulphuretted hydrogen were among these products, he made experiments which showed that these bodies were not to blame. He also tried the effects of ammonia, with results which, although not entirely negative, afforded him very little aid in accounting for the effects observed. The experiments of Virchow,‡ made about the middle of the century, constituted his next important step in the investigation of the subject; for they afforded the starting-point for his still more important researches which have been made since. It was, indeed, at Virchow's suggestion that Professor Panum§ of Copenhagen (to whose work we owe the foundation of the accurate knowledge we now possess on the subject) undertook his investigations. Panum was followed by several eminent surgeons,|| particularly Professor Billroth of Vienna and the late Professor O. Weber, and subsequently by Professor Bergmann of Dorpat and his pupils.

The literature of experimental septicæmia is extremely voluminous; for the writers I have mentioned constitute a very small proportion of those who have contributed to it. It would be wearisome to endeavour to estimate the value of these contributions. It is sufficient to say that, of late years, Bergmann and Billroth (each of whom, as being at the head of a large surgical school, enjoys the opportunity of justifying each step of experimental investigation by clinical experience) have contributed in larger measure than most other writers to our knowledge of the subject.

The phenomena observed in an animal after the introduction of

putrid matter into the circulation differs according to the mode of introduction and the species selected. Thus the poison may enter the circulation directly, as when it is infused into a vein or artery, or indirectly, when it is injected into the cellular tissue or into one of the serous cavities. The most typical and characteristic effects have been observed in the dog; for it is in carnivorous animals that the symptoms and pathological results are met with which resemble and illustrate those observed in man; for the dog resembles man physiologically, and although much less readily affected by disturbing causes, it reacts, on the whole, in a very similar manner.

Gaspard, as I before stated, used simply putrid infusions or macerating fluid from the dissecting-room. In all more recent experiments, filtered solutions have been employed, so as to avoid those symptoms which are produced by mechanical interference with the circulation. I will now describe to you the symptoms observed when a fatal dose of a perfectly clear septic extract, such as those I now show you, is employed.

The first indication of disorder is that the animal shudders. If then the hand be placed on the back, the muscles are felt to twitch, but with this exception, it exhibits no sign of distress other than that it moves restlessly from place to place. If these movements are watched, it soon becomes evident that there is a great diminution of muscular power, for the gait becomes more and more unsteady, and in a short time it staggers and falls on its side. In the meantime, symptoms present themselves referable to the alimentary tract. Vomiting, violent tenesmus, followed by the discharge, first of feculent, then of sanguinolent and mucous dejecta in various stages of liquidity, are the phenomena which present themselves in every case, so constantly, indeed, that they are characteristic of this kind of poisoning. They are not, however, by any means necessarily fatal symptoms; for if the quantity employed be just a little below the lethal limit, the most violent gastro-enteric symptoms may pass off, the animal recovering its normal appetite and liveliness with wonderful rapidity. I mention this fact as proving that the septic poison has not the slightest tendency to multiply in the organism, and secondly, as rendering it extremely probable that, when death occurs, it is determined, not so much by the alvine disorder, which is so prominent a symptom, as by the loss of power of the voluntary muscles, and particularly of the heart. The conclusion, that when an animal dies of septic poison, it dies by failure of the circulation, is further warranted by what we observe of the temperature curve. When the dose is sufficiently large to produce well-marked gastro-enteric symptoms, but not sufficiently large to endanger life, the temperature rises gradually during the first four hours and as gradually subsides as the animal returns to its normal condition; but in fatal cases, it is different. Most frequently, it begins to rise at first, attains its maximum at 103 deg. to 104 deg. Fahr., *i.e.*, about a couple of degrees above the normal, and then subsides, at first gradually, then much more rapidly till life is extinguished. Now there is, so far as I know, no other interpretation possible for rapid sinking of temperature before death, excepting failure of the heart.

The appearances after death in animals septically poisoned are quite as characteristic as the symptoms during life. In the circulatory organs, the most remarkable change is observed on the internal surface of the left ventricle. It is found almost invariably that blood is extravasated in patches underneath the endocardium, sometimes on the papillary muscles, sometimes on or in the neighbourhood of the valvular curtains. Similar appearances occur in the right ventricle, but they are by no means comparable in number or extent to those seen in the left. On the serous surfaces of the pleura and pericardium similar points of ecchymosis present themselves. In the abdominal cavity, the spleen is enlarged and infiltrated with blood, and the mucous membrane of the stomach and small intestine so intensely injected that it exhibits in some parts an uniformly dark red colour, the depth of which is partly due to the intensity of the congestion, partly to the fact that the epithelium is detached and floats in the sanguinolent liquid with which this part of the canal is distended. That the other abdominal organs are also congested needs scarcely be added.

The pathological picture thus presented to us is, as compared with many that we are accustomed to see in the *post mortem* room, a simple one. The disorder which it indicates may be brought under two heads: first, there is an obvious tendency to congestion and capillary hæmorrhage; secondly, a localised congestion of the gastro-intestinal mucous membrane, which is so intense that we are tempted, with Bergmann, to speak of it as gastro-enteritis. Nothing, however, can be gained by calling it an inflammation. I much prefer to speak of it as intense congestion and capillary stasis of the mucous membrane, attended by shedding of the epithelium during life—a most remarkable condition, to the cause of which I shall have to recur in the next lecture.

* In these lectures no reference is made to the pyæmic process. The consideration of this subject is reserved for a future occasion.

† They were published in *Magenie's Journal* in 1822, vol. ii, p. 1; and in 1824, vol. iv, p. 1.

‡ Virchow, *Gesammelte Abhandlungen zur Wissenschaftlichen Medicin*, 1856, p. 219.

§ Panum, *Bibliothek for Læger*, April 1856, p. 253.

|| The references to these various researches are given in my paper "On the Preparation and Properties of the Septic Extract of Muscle", in the *Practitioner* for July 1877.

If we compare the pathological appearances of septicæmia in the dog with those which present themselves in other creatures, or that produced by direct infusion into the blood with those which are seen when the poison is injected subcutaneously, we find that the only fact which is common to all cases is the general tendency to capillary hæmorrhage and congestion. This tendency is the expression of a change which the blood itself has undergone—a change which has its primary seat in the corpuscles. The evidence that this is so we shall have before us subsequently; but I may now refer to some of the peculiarities presented by the blood on microscopical examination. There is no doubt that the hue of septic blood is, *ceteris paribus*, darker; and that its corpuscles have a tendency to collect themselves together in clumps, not in rolls: a fact which may, perhaps, be partly attributable to their having undergone a change of form.

The changes of colour and appearance are in relation with the still more important fact that many of the corpuscles are in a state of partial solution in the liquor sanguinis, to which they communicate a red colour. The verification of this discharge of the colouring matter is by no means so easy as we might expect. The only effectual method is to receive the blood into a strong solution of sodic sulphate, or some other suitable neutral salt, in such proportion as to prevent any solution of the corpuscles after death, and at the same time to prevent coagulation. When, in normal blood so prepared, the corpuscles are allowed to subside, the supernatant liquid is, of course, almost colourless; in septicæmic blood, it possesses a bright ruby tinge. In consequence of the change of the corpuscles which this indicates, a large quantity of colouring matter is actually lost in septicæmia, being discharged either by the bowels in the blood-stained evacuations, or by the physiological transformation of the hæmoglobin into bilirubin. Accordingly, it has been found that animals recovered from septicæmia are in the highest degree anæmic.

I shall now claim your indulgence for a few moments while I refer to the symptoms and results of septic infection in man, in doing which I shall attempt nothing more than is necessary to make the meaning clear to you that I intend to convey in employing the word. There are but few instances in clinical experience in which effects are produced by the introduction of septic matter from outside which can be compared with the experimental effects of infusion into the circulating blood of an animal. In the ordinary case of septicæmia—as, for example, in a case of compound fracture, in which the tissues of the injured limb are infiltrated with exudation-liquid which has undergone septic change—the poison has been elaborated within the organism; for, although it is perfectly true that those septic changes would not have occurred unless a doorway had existed for the contamination of the wound, it is not the less obvious that the poison by which the system is affected did not come in from outside, but was generated in the spoiled tissues.

Clinical septicæmia and experimental septicæmia, therefore, differ as regards their mode of origin. They agree, however, in the fact that in both septic poison is mixed with the blood-stream. Do they agree as regards these phenomena?

This is a question difficult to answer; for this reason, that the characteristics of the septicæmic state are difficult to appreciate. The onset of septicæmia in man, as in the dog, is insidious, and contrasts in this respect with the exacerbation of pyæmia, especially in the absence of rigors. The initial pyrexia, although in some fatal cases it leads on to a condition of hyperpyrexia, is in others of short duration, and passes into a state of collapse, in which the bodily temperature tends to fall below the normal. Again, the symptoms which relate to the alimentary canal are much less characteristic than in animals. Nausea, vomiting, and diarrhoea are seldom wanting; but they never attain such intensity as we have seen them to present in the carnivora.

Of the *post mortem* results of surgical septicæmia, it is very difficult to obtain exact information. There is sufficient, however, to show, first, that the same tendency presents itself to capillary congestion and stasis of the alimentary mucous membranes, and the same appearances are seen in the lining membrane of the heart and of the serous membranes; and, secondly, that cases occur in which secondary inflammatory changes are as conspicuously absent.

And now let me say a single word about puerperal septicæmia. Considering that the anatomical conditions present in the puerperal state are in themselves so favourable to direct entry into the circulation of septic matter, we should expect to find, in the records of obstetrical practice, cases more comparable with experimental septicæmia than in surgery. The cases in question—happily rare and exceptional—are those in which the patient dies without any signs of inflammation, either in the uterus itself or in surrounding structures, and in which septic symptoms may appear even as early as twenty-four hours after delivery. These symptoms are simply failure of the circulation,

dyspnœa (the dyspnœa of muscular adynamia), collapse, and death. There are other forms in which symptoms relating to the nervous centres are present, which I do not forget, but content myself with merely mentioning. After death, nothing excepting intense congestion of internal organs, coagula of blood in the vessels before death, and the signs of capillary hæmorrhage. These rare cases afford instances of as pure blood-poisoning from the element of purulent infection as if the patient had a dose of some virulent liquid infused into her veins.

The imperfect sketch I have just given will, I trust, be sufficient to make it clear that what I mean by septicæmia is a constitutional disorder of limited duration, produced by the entrance into the bloodstream of a certain quantity of septic material. It must, therefore, be regarded not so much as a disease as a complication—differing from pyæmia not only in the fact that it has no necessary connection with any local process either primary or secondary, but also in the important particular that it has no development. Pyæmia is a malignant process which goes on and on to its fatal end; but, in the case of septicæmia, inasmuch as the poison which produces it (as I hope to show to-day) has no tendency to multiply in the organism, there is no reason why the morbid process should not come to an end of itself, unless either the original dose is fatal, or a second infection takes place from the same or another source.

Having arrived at this point, we are in a position to enter on the discussion of the *How* and the *Why* of septicæmia: first, of the *cause* of septicæmia, viz., the morbid poison; and, secondly, of the *mode of operation* of that cause, viz., the pathological process which underlies the phenomena. I will, therefore, to-day occupy your attention with the question: What is it in septic liquids which renders them virulent, and how can we characterise their virulence? I shall begin by once more drawing your attention to this preparation. This perfectly transparent liquid is strongly charged with septic poison, so much so that a dose of a couple of drachms, mixed with the bloodstream of a dog, would certainly produce death. It is obtained by first treating putrid infusion of muscle with strong alcohol at a boiling temperature, then getting rid of the alcohol by filtration and evaporation, and finally extracting it with water. Consequently, it is the aqueous solution of the alcoholic precipitate. The bodies which are dissolved or suspended in it are, therefore, bodies which, insoluble in alcohol are soluble in water. Hence, although it may, notwithstanding the boiling alcohol, contain some proteid matter, it contains no albumen. I can easily show you that tyrosin is present in it, by the beautiful colour it gives with Millon's reagent. No doubt it also contains other analogous products of the breaking up of proteid; but to us the fact of chief interest is that, although the quantity you see would leave but a trace of solid residue if evaporated, it contains the *septic poison*.

Now, with reference to this liquid, which has been proved by experiment to be possessed of virulent properties, and with respect to other equally virulent preparations, I have to prove to you, first, that they contain neither bacteria nor their germs; and, secondly, that we have the strongest reason for believing that the virus itself cannot be produced without the agency of bacteria.

Considering that our virulent liquid is prepared as I have described, it might at first sight appear out of the question to suggest that bacteria could have anything to do with the production of the toxic effects; for it seems very difficult to imagine the existence of any living organisms, however little susceptible, in a material prepared by the action of boiling alcohol. But (without referring at present to the statement made by M. Pasteur the other day, to the effect that although bacteria themselves may object to being boiled in alcohol, it is a matter of indifference to their germs), there are many reasons why it is necessary to exercise the most sceptical caution before you venture on the statement in respect of any liquid that it is germ-free or sterile. I must, therefore, occupy a short time in discussing the value of the means which we possess of proving with respect to any liquid that it is germ-free, *i. e.*, free from living matter capable of germinating.

The first means that suggests itself is microscopical examination. A dozen years ago, we should have expected by means of it to have arrived at something like certainty; for at that time, the evidence of the microscope in respect of any liquid that it was absolutely free from organised particles would have been taken as conclusive. If I had been able to say, I have examined any liquid under a twenty-fifth or a fiftieth, and find nothing, I should probably have felt justified in asserting that nothing living was contained in it. Now, it is entirely otherwise. I am quite willing to admit with Dr. Tyndall that, in deciding the question of the presence or absence of living matter capable of germinating, the microscope has no voice—not because we are less competent than we were formerly to see them, not because the germs themselves have become less visible, but because the accepted conception of a “germ” is different. By my own experiments in 1870, I

found that distilled water in which I discovered nothing microscopically, nevertheless, in the sense in which germs are now commonly spoken of, contained germs. Since that time, Professor Tyndall has rendered every one familiar with the notion that similar germinal particles exist in the air. I fancy that most persons who talk about atmospheric germs have not taken the trouble to realise what sort of objects they are talking about. Objects, indeed, they cannot with any accuracy be called, for an object is a thing of which we can take cognisance by some of our senses, aided or unaided. Professor Tyndall has given a definition which, I venture to think, may with advantage be provisionally accepted. A "germ", says he, is that which when sown produces an organism. As regards the germinal matter of the atmosphere, he has told us that he has not seen atmospheric germs, nor does he believe that any one else has seen them. This I take to mean nothing more than that they lie so completely beyond the powers of our present instruments, that their existence is for the present matter of inference, not of direct observation.

The microscope failing, how are we to proceed? I have here two specimens of distilled water, each of which is contained in a hermetically sealed tube. There is no apparent difference between them, and none could be discovered by the most searching microscopical examination. They are, however, different: one is fertile, the other sterile. The only differential test we can employ is a physiological one. To apply it, I must have two test-glasses, and, after having sedulously cleansed them, subject them to high temperature for the purpose of destroying all trace of whatever contaminating material may adhere to the surface. I must then charge each with a suitable liquid, *i.e.*, with a liquid solution which contains all the materials necessary for the support of the life of bacteria in such chemical form as to be most favourable to their vigorous vegetation. The best sort of liquid for the purpose is that originally employed by Pasteur in his invaluable researches. It may, however, be modified for the particular purpose in view in various ways. The mixture now most frequently used is the one of which the composition is given in the table.

If now I add a drop of the one specimen of distilled water to the tube A, and a drop of the other to tube B, I become aware of a difference of property between them which I could not by possibility have discovered otherwise. If, after having made the addition and closed the mouth of each with cotton-wool (which may, if I choose, be carbolised), I place both tubes in a warm chamber at a temperature between 80 deg. and 100 deg. C., and observe them from day to day, I shall find that A remains clear; tube B, even at the end of twenty-four hours, shows some appreciable trace of opalescence, an opalescence which gradually increases.

The method I have described, as used for the testing of water, may be applied in any case in which an answer is wanted to the same question, and particularly to the examination of any *infective material*, in respect of which the question arises whether or not it owes its infectiveness to the presence of living germinal matter; and it is the only method we possess of obtaining the required information. It is a mode of experiment which, especially in its application to liquids which to the microscope appear free from living particles, is well calculated to impress upon one's mind the impalpable nature of germs, so much so that persons who have but little time for reflection might be excused if, by contrast with the visible germs which were in the field some dozen years ago, they deemed these ultra-microscopical ones as also hypothetical. The realisation of their existence has, however, become much more easy by the beautiful subsidence experiments of Professor Tyndall and M. Pasteur. In the case of water, M. Pasteur has found that, if a quantity of apparently faultless distilled water contained in a tall cylindrical vessel be placed in a cellar, or other place where the temperature is not liable to vicissitudes, and allowed to stand there for several weeks, it can be proved by the method of testing I have already described that the surface-layers are barren, while the deep layers still retain their contaminating power, but possess it in a much higher degree than before subsidence. This admirable experiment shows us not only that water which is apparently pure contains particles in suspension, but also that among those particles are to be found some which are potentially (*i.e.*, in the sense of Dr. Tyndall's definition) germs. All the particles contained in the water, whether organised or not, are included in the invisible sediment, so that, even if we could see the particles so as to acquire a knowledge of their size, we should be as completely without information as we are now as to the size of the germ-particles; for in each visible particle any number of such ultra-microscopical germs might be contained.

With this method of subsidence, another has been combined by Professor Tyndall, which teaches the same lessons in a still more striking manner. I refer to the exploration of the suspended particles of a

liquid by the observation of the track of a beam of sunlight, or other light of comparable intensity transmitted through it. Such a beam in pure water is invisible, but, in passing through common water, exhibits a beautiful luminous track. To learn anything with reference to germs we must, as before, combine the physical with the physiological test, and it is in this combination that the beauty of Professor Tyndall's experiment consists. Each experiment must, in short, consist of two parts or stages. In the first, we observe, as regards a certain specimen of water, that it is opalescent to the beam, and that it has also the power of contaminating. We then make a second observation after subsidence, in which we find that the beam track has become invisible and the liquid sterile. What do we conclude from this? That the particles which have fallen have carried with them the germinal material; not, however, that they are that material, and nothing else.

These facts relating to subsidence are undoubtedly of great interest and importance in several respects. Thus, for example, they render it extremely probable that by perfect subsidence, it would be possible to render water pure, not only of those grosser defilements which in our town water-supply systems we get rid of by subsidence reservoirs, but of the much finer particles—chiefly, no doubt, organic—of which the opalescent beam track affords the most striking evidence. My object in referring to them was not, however, to propose a new method of purifying water, but to show the bearing of the same considerations on the question whether or not the particles which form the sediment that falls to the bottom after prolonged subsidence, and render the luminous beam opalescent, are likely to be pathogenic entities—in the current language of the hour, not only germs, but disease germs. This intention may serve as an excuse, in case an excuse seems required, for having occupied you so long with matters which might appear at first sight to have little to do with pathology.

As I showed just now, the value of the subsidence experiment, whether in relation to air or water, hangs exclusively on the *physiological* test with which it is associated. By itself, the fact that air or water is opalescent, means nothing *quod* germs. To give it meaning, you must prove that what subsides when sown produces an organism. So, as regards our septic extract, the extract can be prepared as transparent as distilled water. But even when so prepared, the liquid still contains particles, particles not so small as to be invisible by the microscope, yet so small that nothing can be made out of their form. When the liquid is examined with the aid of the luminous beam, the presence of these particles is indicated by an opalescence which, as in all similar cases, may be distinguished from that due to fluorescence by the circumstance that, when viewed through a Nicol's prism in the proper direction, the light which emanates from it is seen to be polarised.

Now, some years ago, it occurred to me that it would be desirable, if possible, to ascertain whether, if these particles could be separated from the liquid, they could be proved to contain in themselves the virulent property of the liquid. I did not particularly care whether they were germs or not. Indeed, I thought it quite out of the question that they should be germs for the reason already mentioned, *viz.*, that they had come out of boiling alcohol; but I thought that they might be morbid particles, and the method that I adopted for separating them was that of filtration through porous porcelain. I have recently published those experiments, which prove that by filtration of this kind the liquid can be deprived of its virulent properties.

Now this is an experiment of the same kind as that of subsidence. A merely mechanical property of the virus, the fact that it consists of particles, and, although apparently in solution, is not really so, is used in the one method as in the other for the purpose of separating these particles. But what is proved by it? As it stands, nothing more—and that is no doubt important enough—nothing more than that the virulent material is not able to go through a porcelain filter.

It is not proved that the particles before referred to as visible under the microscope, are the only particles which are stopped; indeed, I am quite certain that this is not the case, for I can get rid of them by less perfect filters which do not deprive the liquid of its toxic powers. Consequently, there is no evidence that the individual particles which were first in question have a claim to be regarded as morbid elements. It is, of course, still more certain that they are not germs, for the most careful observations have established the conclusion beyond the possibility of doubt, that if the liquid be prepared with the proper precautions against after contamination—by which I mean contamination any moment between that of preparation and use—it is absolutely sterile both before and after filtration.

DR. CARLO GHINOZZI, Professor of Clinical Medicine in Florence, and principal editor of *Lo Sperimentale*, died on the 15th instant.