THE CROONIAN LECTURES ON THE PROGRESS OF DISCOVERY RELATING TO THE ORIGIN AND NATURE OF INFECTIOUS DISEASES.

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LECTURE I.—THE ETIOLOGY OF INFLAMMATION.¹

Origin and Development of the Doctrine of the Infective Nature of Inflammation; Origination by Sir John Simon; Doctrine of Phlogogenic Organisms; and of the Resistance of Living Tissues; Cryptogenetic Inflammations.—Discovery of Specific Forms of Phlogogenic Microphytes; Researches of Ogston and Rosenbach.—The Staphylococci; Lesions Produced by the Staphylococcus Aureus; its Relation to Osteomyelitis; its Action on the Cornea, in the Subcutaneous Cellular Tissue, in the Kidney, and in the Lungs; its Relation to Ulcerative Endocarditis.—The Streptococcus.

THE task which I have undertaken—that of giving an account of the progress of knowledge relating to the origin and nature of infectious diseases, and the growth of this knowledge during the twenty years which have elapsed since I entered on the study of the subject—is one which I feel myself incompetent to discharge in a manner which will be satisfactory either to myself or to my audience. But the desire of the Council that I should attempt it was conveyed to me in such terms by Sir Henry Pitman, that refusal seemed difficult, and at once became impossible when enforced by the command of the President.²

The present course consists of four lectures, but the subject more naturally divides itself into three than into four. I shall therefore devote the first three lectures to two subjects, namely, (1) the causes of acute diseases and their mode of operation; (2) the reaction of the organism (of man or of the higher animals) against the operation of morbid agents. The fourth lecture will relate to specificity, that is, the relation between the distinctive character of specific diseases and those of the specific causes which produce them.

To-day I propose to discuss the etiology of inflammation, that is, the mode of action of those morbid microphytes which do not produce the diseases commonly called zymotic. I begin with this subject because the doctrine of inflammation has ever been the pivot upon which pathological doctrine on other subjects has turned. The definition of inflammation which I once gave (namely, that it is the response of living tissue to injury) still holds good, and probably will in all future time express what is meant by the word in pathology. In defining a morbid process it is not only necessary to set forth those characteristics which are well ascertained and constant, but to draw attention to those which are as yet subject to question or require further investigation.

PART I.—ORIGIN AND DEVELOPMENT OF THE DOCTRINE OF THE INFECTIVE NATURE OF INFLAMMATION.

Up to the year 1860, that is ten years before the beginning of the period to which these lectures specially relate, it was assumed without question that whenever inflammation occurs in consequence of an injury, whether chemical or mechanical,

¹ In printing this lecture a few passages, chiefly in the earlier part, have been omitted.

² I trust that it will be understood that I do not intend to lecture here on bacteriology, and that these lectures are not intended for specialists. My subject will be infective diseases and their causes. Of "microbes," or "micro-organisms" I shall speak, not as plants but as exciters of disease, and deal with them as they are known to the experimental pathologist, not as they are curiously contemplated by the botanist. My main purpose will be to show that, notwithstanding the apparent revolution which has taken place in our science in consequence of the discoveries of the past generation, the very ideas which are now dominant, especially those which have the best claim to acceptance, are, in so far as they are true, developments of ideas which were present to the minds of thinking working pathologists a quarter of a century ago.

the apparent cause of the morbid process is the real one. Since that time it has gradually become clear that in the majority of instances this is not so, and that however direct and simple may be the relation between the damage done and the reaction which follows, the result does not occur unless there be present at the seat of injury another condition, something analogous to the contagia which are the acknowledged indispensable agents in the production of specific diseases, so that in all these cases we have to distinguish between the contagium or proximate cause and the mechanical or chemical injury by the co-operation of which it is enabled to act. Now the pathologist who first referred to contagium as an element in the causation of inflammation was John Simon. He³ adduced many striking facts derived from clinical experience as reasons for believing that it is "a generic and essential property of inflammation; that its actions, or some of them, are always in their kind to some extent contagious." The most important of these facts were the readiness with which conjunctivitis can be produced by the introduction into the conjunctival sac of any kind of inflammatory product, the production of disseminated inflammations by intravenous injection of perfectly healthy pus, and in general all those cases in which traumatic inflammations (such, for example, as that produced by running a splinter of clean wood into the finger) give occasion to inflammation of the corresponding lymphatic glands. All such instances seemed to Mr. Simon to indicate that even non-specific, clean, uncontaminated inflammations are more or less contagious. It was, however, clear to him that even were it admitted that the property of contagiousness is generic, there must be a difference between common and specific, and he endeavoured, in so far as was then possible, to indicate its nature, referring particularly to the much greater dependence of specific contagia on individual proclivity and susceptibility, and to that antagonism between pus corpuscles and specific contagia which has of late years received its recognition in the phagocyte theory of Metschnikoff.

In 1870 Mr. Simon, in republishing the article from which I have quoted, recognised in a note the probability that the doctrine which had a little before been set forth by Professor Halier that specific "contagia are in their essence living microphytes," was true. In my own essay on the Process of Inflammation, which formed part of the article Inflammation in the same edition of the *System of Surgery*, I differed from Mr. Simon in not regarding contagiousness as a property of common inflammation, but as distinctive of certain inflammations to which, on this ground, I applied the term "infective" or "secondary."⁴

The next year a very extensive series of researches was conducted by Dr. Klein and myself, in which we observed the fact that the presence of micrococci in groups or chains, as well as rodlike microphytes, was so characteristic of all such suppurations that we had no doubt that it was to them that these products owed their infecting character. During the next few years many investigations, chiefly experimental, were made which served to throw light on the part played by microphytes in the causation of inflammation. In 1873 Chauveau made an experiment, of which I gave a detailed account in my former lecture, which was of fundamental importance. The operation of *bistournage*, which is used in France for economic purposes as a means of arresting the circulation in the testis by torsion of the spermatic artery, and annulling the function of the organ in animals destined for the shambles, is never known to be followed by an inflammatory reaction, notwithstanding that the part is subjected to considerable violence; but if the animal is "prepared" by intravenous injection of microphytes derived from the pus of an infective abscess, the contamination of the blood which the organ contains at the moment that its circulation ceases converts the ordinary harmless manipulation into one fraught with danger to life in consequence of the

³ See article "Inflammation" in *System of Surgery*, vol. i, pp. 26 to 29.

⁴ As to the nature of the infective element contained in the exudation products of such inflammations, I was unable to say more than that they consisted of "particles of matter of the nature of which we can assert nothing, except that they are of extreme minuteness, are conveyed from a primarily inflamed part to other parts previously healthy, and there become foci of infective induration or suppuration, each of which is the product—if one may be allowed the expression—of a single seed." Holmes's *System of Surgery*, ed. 1871.

intensity of the local reaction which it produces. Subsequently Professor Kocher, of Berne, showed still more conclusively that the most severe injuries of bone—such, for example, as the destruction of the medulla by the actual cautery, or the introduction of caustic potash or croton into the medullary cavity, produced no suppuration under normal conditions, but that this effect might be determined at will by subjecting the animal to what might be called a septic regimen—that is, feeding it on putrid food. These and other similar facts served to make it extremely probable that organisms which, in the absence of the more exact knowledge which we now possess, we designated septic, were also at the same time “phlogogenic”—that is, possessed the power of determining suppurative inflammation when it would not without their intervention have occurred; but no proof was at that time given that they were capable of themselves of producing inflammation, or that they could exercise this power when separated from the inflammatory products in which they had vegetated.

Wesener, in a research of which I also gave an account in my former lecture, showed that cultivating liquids charged with ordinary saprophytes could be injected in large quantities into the peritoneal cavity, without producing any reaction whatever, provided only that the quantity so introduced was not too large to be disposed of by the efficient mechanism for absorption with which the peritoneal cavity is provided. On the other hand, it was found that if water were introduced into the peritoneum in such amount that it remained unabsorbed for several hours, death occurred from septic peritonitis, although no putrescible liquid had been used. Why this happens is easy to understand. The liquid becomes by diffusion charged with the soluble constituents of the blood, so as to resemble diluted serum—a liquid more suited for the rapid development of septic organisms than serum itself. The result is that the animal dies very rapidly of septicæmia. A process of inflammation is set up in the peritoneum, the surface of which is found at death to be lined with false membrane, while its cavity contains a fluid which is charged with leucocytes, and teems with septic organisms, which last also plug the lymphatics of the diaphragm, and are found in numbers in the circulating blood.

The inference to be drawn from these facts was obvious, but I do not know that even now the facts are so thoroughly impressed on the minds of pathologists as their importance demands. May I repeat that inference in the same words I used ten years ago? “Air enclosed in a serous membrane is harmless, water is harmless, septic organisms are harmless, provided that they are rapidly absorbed. The one thing fraught with danger is that liquid which is undergoing the process of putrefaction should remain in a cavity which although it is inside of the body as regards temperature, is yet outside in so far as it is beyond the reach of living tissue.”

I have now come, as regards the question of the dependence of inflammation on microphytes, almost to the point which had been arrived at at the date of my last lecture. In certain cases there was strong reason for believing that the origin of the process was microphytic, but, on the other hand, it was certain that, although the essence of the antiseptic treatment was supposed to consist in the exclusion of air-borne germs, such germs were in themselves absolutely harmless. The only way of reconciling these apparently contradictory principles was to be found in the hypothesis that among the organisms grouped together under the general term septic or non-specific there were some which were endowed not merely with the faculty of determining sepsis, and therefore capable of producing septicæmia if brought into relation with exuded liquid or effused blood enclosed within a living tissue, but also with the power of injuring and damaging protoplasm. In support of this hypothesis the only facts were those which were derived from certain forms of infective inflammation, which I at that time designated to you as cryptogenetic—a term which I borrowed from the late Professor Hüter. The term is one which does not need explanation. The type of such inflammations is the primary inflammation of the marrow, or spongy tissue, of bone, to which young people are liable without any assignable cause, and which, in many cases, gives rise to, or is associated with, secondary foci of inflammation, either in other parts of the skeleton or in internal organs, attended with the constitutional symptoms of

pyæmia. Another typical case of infective or disseminated inflammations coming into existence “cryptogenetically” is that in which pyæmia supervenes on valvular disease, without its being possible to suppose that any infective material has been introduced from without. Now, in these two cases the secondary lesions are of the same nature, though they differ in distribution, the most characteristic being the military abscesses, each surrounded by a border of hyperæmia, which are found in the medullary and cortical part of the kidneys, and appear to be due to the plugging of minute arteries. As regards all these secondary foci, whether their embolic origin could be made out or not, it was ascertained some fifteen years ago that they were characterised by the presence of aggregations of spheroidal microphytes, which, ever since Halier, we call cocci, and which, under the microscope, were clumped together in groups or colonies, which did not exhibit any definite arrangement. Considering that in these cases the microphytes in question must have come into existence and have grown under very special conditions, and that, however simple their morphological characters were, they were remarkably uniform, and that the pathological appearances were such as to indicate that they acted, not merely as foreign bodies, but possessed the power of exercising an injurious or disintegrating influence on the elements of living tissue with which they came into relation, pathologists thought it reasonable to attribute to them special pathogenic properties differing from those of ordinary saprophytes.

PART II.—DISCOVERY OF THE SPECIFIC FORMS OF PHLOGOGENIC MICROPHYTES.

Such, then, was the knowledge we possessed up to the year 1880, and now we come to a new departure, which consisted first in the demonstration that in all ordinary cases of acute suppurative inflammation, whether infective in the sense used by me in 1872 or not, the purulent product contains microphytes which are special to it; and, secondly, in the application of the methods with which about that time Dr. Koch had enriched pathology for separating species of microphytes from each other and obtaining pure cultures. It is gratifying to say that we owe the demonstration that all acute inflammatory products contain characteristic forms of microphyte to an English, or rather a Scottish, pathologist—Professor Ogston, of Aberdeen.⁵ For the working out of the phytological characteristics of Dr. Ogston's organism we are indebted to Professor J. Rosenbach, of Göttingen. The two researches may be referred to in connection with each other, provided that it is borne in mind that Ogston was first in the field. Ogston found that in the pus of acute abscesses the spheroidal microphytes which are always present are partly in chains or chaplets, and partly in collections (which I in 1872 described as mossy masses), in which the grouping of the individual spheroids resembled that of fish roe, or that of grapes in a bunch. This comparison led him to adopt as a name for the organism the term *staphylococcus*, which may be conveniently Englished as *cluster-coccus*. He further found that in 64 acute abscesses, all contained micrococci of some sort, 17 contained only chains, 31 only clusters; in the rest both were present. Both of these organisms were found to be capable of producing localised inflammation resulting in abscesses when liquids containing them were injected subcutaneously; but it appeared that the character of the abscess differed in the two cases, the *cluster-coccus* producing a well circumscribed abscess, whereas the *chaplet coccus* (which, following Billroth, he called *streptococcus*) always found its way from the inflammatory focus into the lymph paths leading from it. Nothing can be more interesting than the description which Ogston gives of the structure of a typically limited abscess in its early stage, namely, four days after the subcutaneous injection of a drop of the *cluster-coccus* culture. A nodule exists under the skin, of which the centre is yellow pus; then comes the pyogenic membrane infiltrated with leucocytes, and invaded by masses of *staphylococci*, and outside of this a zone of injured tissue in which the elements have lost their distinctness, but scarcely any microphytes are to be seen.⁶

⁵ Ogston: Report on Micro-Organisms in Surgical Diseases, BRITISH MEDICAL JOURNAL, 1881, p. 369 (aided by a grant from the British Medical Association).

⁶ That even so accomplished a pathologist as Dr. Ogston was able to make himself sure of the fundamental fact, that is, the existence of cocci

Staphylococcus is one of those microphytes which does not want air. It can be grown *in vacuo*. It is capable of digesting cooked meat and converting it into peptone, but it has no tendency to produce the chemical process called putrefaction—a fact which is evidenced by its not giving off any gas *in vacuo*. The cocci are very minute, so that although we used to be able to make them out in *præ-Kochian* days, we could never be quite sure what we were looking at. There is no difference between the two species of cluster-coccus either as regards the size or grouping of the organism. The only distinction between them is that one is golden yellow, the other opaque white.

Such is the *prima facie* case established in 1883 by Rosenbach in favour of the yellow cluster coccus, or, as it was also at that time called, the "osteomyelitis coccus." The reason why it received the latter designation was that about the same time that Rosenbach was working with it Dr. Becker published a preliminary communication in which he gave that name to a micrococcus which he had obtained in a state of pure culture from the pus of infective or dyscrasic osteomyelitis, and which he regarded as the specific cause of that disease. So that, although Rosenbach appears to have been the first to recognise the causal relation of the microphyte to suppuration, Becker has a fair claim to be regarded as a discoverer, inasmuch as his description was the one first published; it was not, indeed, until 1884 that Rosenbach's well-known monograph was published. But in the meantime the clinical fact of the almost constant presence of the microphyte in the products of acute inflammation and the experimental fact that it is capable, under favourable conditions, of producing localised suppuration had been accepted with even too much confidence as well-established facts in pathology. What we have now, therefore, to do is to inquire what the real value of the clinical and experimental facts I have referred to is. We shall find that the question is by no means so simple as at first sight it seemed, and that, although during the seven years which have elapsed since Rosenbach's book appeared the literature of the subject has assumed very large proportions, the question of the true relation between process and microphyte has scarcely even yet been fully elucidated.⁷

PART III. LESIONS PRODUCED BY THE YELLOW CLUSTER-COCUS.

Krause⁸ confirmed Rosenbach as to the identity of the cluster-coccus of common suppuration with that of infective inflammation of bone, and his excellent experimental results were also of interest.

M. Rodet's⁹ results as to the production of osteomyelitis by the intravenous injection of the yellow cluster-coccus, and the resemblance of the disease so produced to the infective myelitis in man, have been confirmed by later observers, particularly by MM. Lannelongue and Achard.¹⁰ These pathologists find that although when osteomyelitis is produced by

in all acute abscesses, and to state numerically the prevalence of each in the cases which came under his observation, was due to his having taken the trouble to make himself master of the best technical methods which were then known. In like manner, Rosenbach's success (Rosenbach, *Die Mikroorganismen der Wundinfektionskrankheiten des Menschen*, Wiesbaden, 1884) in investigating the generic characters of *staphylococcus* and the distinctions of the two species, *aureus* and *albus*, would not have been achieved had not Koch discovered the method of culture on solid media. A *staphylococcus* culture can be obtained by sowing pus in which it is growing on the surface of a suitable solid medium—solution of meat peptone, to which agar enough has been added to enable it to gelatinise. This is effected by streaking the surface with a sterilised platinum loop which has been charged with the pus. In twenty-four hours a linear opacity shows itself in the position of the scratch, which soon acquires the appearance of a streak of yellow paint. If the *staphylococcus* were sown on nutrient jelly instead of on agar, it would liquefy it, so that in a short time the yellow crust would fall to the bottom.

Although the cluster-coccus is the most important of the microphytes which appear to have to do with the suppurative process, Rosenbach designated three other organisms in addition to streptococcus as having subordinate claims. But it will be most conducive to the purpose we have in view to confine ourselves as far as possible to the pathogenic properties of the yellow cluster coccus, bearing in mind that no sort of microphyte has any interest for us whatever, excepting in so far as it can be proved to be a mischief-maker.

⁷ Krause, *Die Mikrokokken der Osteomyelitis*, *Fortschritte der Medicin*, 1884, II, p. 221, 261.

⁸ *Revue de Chirurgie*, 1885, pp. 273 and 636.

⁹ Lannelongue et Achard, *Étude expérimentale des Ostéomyélites à Staphylocoques et à Streptocoques*, *Ann. de l'Institut Pasteur*, 1891, p. 209.

the infusion into the circulation of cultures of *staphylococcus* inflammation may begin superficially, that is, under the periosteum, it usually begins in the medulla, or spongy tissue, a favourite seat of origin in animals not fully grown being the lower end of the femur, at the junction of the diaphysis with the epiphysis; so that when, as in some of Rodet's experiments, the most obvious lesions are arthritic, the joint affection is found to be dependent on disease of subjacent bone. Thus the cluster-coccus might reasonably enough be called the myelitis coccus, were it not that occasionally it kills by infecting the kidneys and other viscera without harbouring in the bone marrow.

Among the earlier experimental investigations which were made during the years which immediately followed the publication of Rosenbach's work, few were carried out more satisfactorily than that of Dr. Lübbert, of Würzburg, as regards the care bestowed on the clinical, bacteriological, and anatomical parts of the inquiry.¹¹

Pure cultivations of *staphylococcus* were for the most part derived from osteomyelitis. Sterilised salt solution, in which pure colonies of *staphylococcus* were suspended so as to form an opalescent liquid, were introduced either into a serous cavity or into a vein. If the peritoneum was the channel employed, the injection killed the animal in a few hours; or, if it survived the immediate effect of the injection, gave rise to secondary inflammations of internal organs, both of these effects being, of course, due to the entrance of the microphytes into the circulation through the lymphatics. The nature of the infective lesions and the fate of the organism in the circulation could be better studied after injection of the diluted culture into the venous system. Lübbert found that whereas shortly after injection the microphytes can be readily detected in the blood, they are not many hours in disappearing entirely, and are then found in numbers in the urine. Still later they are neither forthcoming in the blood nor urine, most having without doubt been eliminated by the kidneys from the body. Of the small minority that remain there are, however, quite sufficient to do mischief. In the kidney, which in cases of infective endocarditis and osteomyelitis in man, are the favourite seat of secondary foci, on stripping the capsule, yellowish patches, more or less prominent, are seen on the external surface of the organ, while in section the cortex shows nodules of various sizes, most of them milary. Of these grey spots, some are obviously abscesses, but the most minute are glomeruli, of which the afferent arteries and capillaries are choked with micrococci, these organisms also occupying the space between the tuft and the capsule. Here and there spots of necrotic tissue are met with surrounded by a zone of purulent infiltration, and it is then seen that the micrococci occur both incorporated in the pus corpuscles and in the intercellular liquid. In the medullary part the linear streaks are chiefly due to plugging of the uriniferous tubes with cocci. Sometimes a vein is beset with cocci which penetrate into its wall, as shown in the diagram. In the heart there are opaque nodules as large as pin heads, some of which are superficial—that is, subjacent to the serous membrane or endocardium—others disseminated in the muscular substance. Each is surrounded by a zone of hyperemia, beyond which the muscular fibre exhibits signs of degenerative change. These minute abscesses are for the most part in relation with emboli in capillary arterioles.

As regards the medulla of bone, Dr. Lübbert added nothing to the observations of Rodet as to the development of osteomyelitis, and was, indeed, unable to confirm them. But that question has, as I have already stated, been completely settled since by Lannelongue.

I will first ask your attention to the changes which result from the local action of the cluster-coccus, as observed in the cornea and subcutaneous tissue, in respect of which I will refer to a series of very valuable researches which have lately been carried out in the Pathological Institute at Bonn, under the direction of Professor Ribbert,¹² to the important paper of Dr. Hess,¹³ and to an equally important investigation by Dr. Hohnfeldt.

Staphylococcus in the Cornea.—The cornea can be infected by introducing the undiluted culture into the wound made by a needle. The microphyte grows into the corneal tissue as it does in any other suitable medium, the only difference being that the colony assumes a form which is determined by the structure of the tissue. It consists for the most part of a system of subordinate colonies, which are arranged more or less distinctly in rows or tracts which branch from a central tract, but take their direction from that of the tissue, the whole forming a continuous system which has the puncture as its starting point. Each mass is sharply defined and surrounded by a zone of altered tissue, in which, if the preparation has been stained, the corneal tissue is relatively pale and the corneal corpuscles appear to be wasted. The paleness is chiefly owing to change in the nuclei, which not only stain less but are less sharply defined. It is easy to recognise in this zone the atrophic state which was described by Cohnheim in 1877, as the first stage in trigeminal keratitis. It can be observed distinctly 18 hours after infection. About this time the migration of leucocytes goes on so rapidly that by the end of the first day the zone of atrophy is bordered by an outer zone of infiltra-

¹¹ Lübbert, *Der Staphylococcus pyogenes aureus und der Osteomyelitis coccus*, Würzburg, 1886.

¹² Jacobs, *Beitrag zur Histol. der acuten Entzündung der Cornea*, *Inaug. Diss.*, Bonn, 1887.

¹³ Hess, *Weitere Untersuchungen zur Phagocytenlehre*, *Virch. Arch.*, 1887, CX.

tion. The leucocytes are most abundant at the junction of the two zones. Here, indeed, they are closely packed, but further away from the colony they run in tracts corresponding to the lymph splits of the tissue. The elements themselves show signs of disintegration in the neighbourhood of the atrophic region, but are elsewhere normal. The result of the process so begun is that the whole of the tissue which is infected by the cluster coccus, and which corresponds in extent to half the cornea or more, is destroyed: in other words, that a corneal ulcer is formed, on the floor or surface of which there are now no micrococci. At the edge of the ulcer the epithelium shows the signs of reparative growth, that is it is thicker than normal and many of the cells exhibit karyokinesis, while in the subjacent corneal tissue the reparative process is going on in the way also described by Cohnheim at the same time. The Bonn pathologists have, however, no doubt that in this process the nuclei which are seen in karyokinesis in the corneal tissue really belong to the fixed corneal corpuscles. In these facts we have the clearest evidence that the cluster coccus is able to vegetate in the cornea and thereby damage its structure, and that this damage is followed by the normal reaction, that is, the immigration of myriads of leucocytes. Why do these leucocytes appear on the field? Metschnikoff says that they appear there for the purpose of devouring the microphytes. As to the fact that they do incorporate them there is no manner of question. This point was not specially studied by the Bonn pathologists, but has been thoroughly worked out by Dr. Hess, whose observations are positive on the subject. The question what this means, that is, whether any such teleological meaning is to be attached to it, we shall have to discuss in a future lecture.

Staphylococcus in the Subcutaneous Cellular Tissue.—For subcutaneous injection the cluster coccus is used in the form of an emulsion, obtained by diluting a pure culture with salt solution. In Hohnfeldt's experiments¹⁴ the local effects were observed from four hours after injection. By the end of the third day the cocci had collected into colonies. Long before this many of them were incorporated, not only in leucocytes, but also in the epithelial lining cells of the capillaries. A little later the leucocytes in the abscess cavity exhibited obvious signs of degeneration, and the coccus vegetation extended beyond the zone of infiltration into the lymph spaces, but not to any considerable extent. The process of reparation did not begin until after the expiration of the first week. It was marked by the formation of new tissue, that is, of epithelioid cells with large distinct vesicular nuclei and distinct nucleoli, immediately outside of the leucocytic infiltration. In these cells various stages of karyokinesis could be seen, particularly single and double stars, indicating great activity of germination. But it must be remembered that before this work of new growth, of reparation of damage, begins the mischief-makers have disappeared. As in the case of the cornea, so here, their work consists first in killing the living elements of structure within their reach, and secondly in determining the initial phenomena of the inflammatory process, that is, active congestion, exudation, and emigration. This accomplished, they disappear. Whatever be the proximate cause of this cessation of growth and disappearance, we may, I think, properly connect it, as we always have connected it, with the multiplication of leucocytes. We shall return to this question later.

*Staphylococcus in the Kidney.*¹⁵—We have seen (and the fact is familiar to every one) that the favourite seat of secondary infective inflammatory foci, in cases of osteomyelitis and of infective endocarditis, is the kidney. Similarly, when our microphyte is introduced into the circulation, it is in the kidney that it localises itself. Twenty-four hours after the injection of a syringe of staphylococcus emulsion, the organ shows streaks of grey in the medullary part. These streaks are simply collections of cocci which have plugged the blood vessels, whether arterial or venous it is difficult to determine. The cortex is beset with very minute dots not larger than poppy seeds, each of which represents a colony or group of colonies, many of which exceed the convoluted tube in width, and therefore must have grown *in situ*. Each is surrounded by a zone of spoiled tissue, and that by a zone of cellular infiltration, outside of which the tissue is normal. Later, each of these colonies becomes a small abscess, around which you have the double zone, atrophy or necrosis inside with cocci in the atrophied part, infiltration of leucocytes outside, then tissue showing signs of regeneration. Towards the end of the third day, or later, these appearances become more distinct, that is, the abscess cavity is bounded by a zone of cellular infiltration, and that by a zone of nearly normal tissue, in which there may be karyokinesis of the epithelium of the convoluted and other tubes, as well as of other tissue elements, probably vascular, occupying the interstices between them. It is to be borne in mind that this unequivocal evidence of proliferation does not present itself until at least three days after infection, long after the cellular infiltration has attained its height, and consequently that there is no causal relation between germination of the tissue and pus formation. The order of process is therefore, first necrosis, secondly emigration, and lastly proliferation of fixed elements indicated by karyomitosis. We surmised this to be the case before, we know it to be so now.

Staphylococcus in the Lungs.—For the study of the action of the cluster coccus on a vascular tissue the alveoli of the lungs afford advantages not to be met with elsewhere; for in the lungs the relations between fixed elements of tissue and those which emigrate from the blood vessels are relatively easy to appreciate. In the rabbit there is no difficulty in introducing staphylococcus into the alveoli; all that is necessary is to inject an emulsion into the trachea with a subcutaneous syringe. What happens is this: You get an exquisite lobular pneumonia. In twenty-four hours the base of the lungs is beset with minute indurations, varying in size from that of a hemp-seed upwards, which are more or less confluent and follow the course of the bronchi. In the indurated parts the alveoli are full of cells, which, I need scarcely say, are of two kinds, namely, small cells with one or more irregular-shaped nuclei—for example, leucocytes—and larger epithelial elements distinguished by their vesicular nuclei. From the first these cells contain cocci. Both kinds take part in the process of incorporation, but the epithelial elements much more than the leucocytes. At first the leucocytes are very numerous, but later they find their way into the bronchial tubes and the

alveolar contents become more and more epithelial. Along with this occurs that process of coalescence by which in the lungs multinuclear or giant cells come into existence, all of which, like the smaller epithelial elements, contain incorporated cocci. What happens to these cocci? They all disappear, but before they disappear they die. The proof of this has been given by Lühr.¹⁶ By bringing a calcined platinum needle into contact with a freshly-exposed surface of the inflamed lung and streaking with it the surface of an agar plate the characteristic colonies are obtained any time up to the third day after infection; but they become less and less abundant, until after the fourth day none can be obtained, however carefully or repeatedly the experiment is made. At this period cocci are still visible in the alveolar cells, but soon they dwindle and lose their characteristic uniformity of size and contour.

I would ask your special attention to these observations because they serve to exemplify in a very remarkable way how the same process, that is, the action of staphylococcus on living tissue, may vary in its character according to the anatomical and physiological endowments of the tissue acted on. In the alveoli of the lung they come into relation with a tissue in which the capillaries are protected only by a scanty covering of epithelium—in which active congestion and exudation and emigration can be excited with extraordinary facility—and the encounter between microphyte and cell occurs in the presence of oxygen. In the kidney there is no oxygen, and the organisms appear in the first instance as capillary emboli. The want of oxygen is favourable to the vegetation of the microphytes, and, accordingly, a colony grows wherever a single coccus is deposited. By virtue of their aggregation the individual cocci are effectually protected from any influence of their environment which might tend to check their growth, and are enabled to exercise on that environment their own characteristic toxic influence—each colony surrounding itself, as we have seen, with a zone of necrosis. In other words, the microphytes are, within a limited sphere of action, in the majority; whereas in the lung, by disseminating and because the presence of oxygen is unfavourable to their growth, they are in the minority. In the one case they die and rapidly disappear; in the other they hold their ground and become the centres of infective abscesses.

We have already seen that in the cornea, where for very similar reasons the cluster-coccus grows just as it does in a tube culture, each colony is surrounded by a necrotic or atrophic zone, just as it is in the kidney; and the immigration of leucocytes from the conjunctival border is an event subsequent and secondary to this damage. There is another case which not only serves to exemplify the same principle, but is in itself full of interest. The case I mean is that of infective endocarditis. By clinical observation we know that mitral valvular disease is associated with the presence of infective inflammations in other parts, and that, on the other hand, ulcerative endocarditis is antecedent to general infection. Recent researches have proved that, in these forms of endocarditis, our cluster-coccus is more frequently concerned than any other, and it has now been shown experimentally that by introducing this microphyte into the circulation it is able to fix itself on the heart valves, and that having done so it is capable of destroying the epithelial lining and penetrating the subepithelial tissue. Why does it fix itself there rather than elsewhere on the internal surface of the vascular system? Probably because the surface is most remote from capillary blood vessels, that is, from the influence of actively living cells. Be that as it may, it is important to note that the action of the cluster-coccus on the endocardium is the same as on the cornea. It grows slowly, but holds its ground. It slowly damages a tissue which, when once spoiled, has no power of recuperation.

SUMMARY.

I have now completed the case against staphylococcus. It has been shown that its primary influence is to impair and ultimately annul the vitality of whatever living tissue is brought within the range of its influence. It has further been shown that it induces in all vascular tissues congestion, exudation, and migration of leucocytes (that is the first stages of the process of inflammation), and that it is very readily incorporated in actively growing cells, whether epithelial or derived from the circulating blood. From the fact that in the lungs and elsewhere the infiltration of the tissue with leucocytes, and the abundant development in it of young cells,

¹⁴ Hohnfeldt, Ueber die Histogenese der durch Staphylokokkeninvasion hervorgerufenen Abscesse, *Beitr. zur pathol. Anat. von Ziegler u. Nauwerck*, 1883, iii, p. 343.

¹⁵ See Lübbert, *loc. cit.*, pp. 74-102.

¹⁶ Lühr, Ueber den Untergang des Staph. pyog. aur. in den Entzündungsprocessen der Lunge. *Inaug. Diss.* Bonn. 1887.

appears to be distinctly connected with the absence of the destructive effects which are observed under opposite conditions, it may be fairly inferred that these processes are protective—that is, that although they are themselves constituents of a morbid process, they conduce to the destruction or elimination of the *materies morbi*; but in the facts before us there is nothing to justify the conclusion that the incorporation of microphytes in cells is the chief or only way in which the human or animal organism exercises its protective influence.

THE STREPTOCOCCUS.

It must be borne in mind that there are other organisms which stand in the same or in a similar relation to the process of inflammation. I have referred to streptococcus only, as regards which it has been shown by a large body of evidence, clinical and experimental, that its action resembles staphylococcus in most respects. The question of the difference between them has been lately satisfactorily dealt with by MM. Lannelongue and Achard in the research to which I have already referred. The results to which they have come are these. The visceral lesions produced by the chain-coccus differ only in degree—that is, in their being less intense—from those due to the cluster coccus. Each is capable of producing osteomyelitis experimentally, and may be the cause of it clinically.

That two microphytes which are so easily distinguished in the laboratory should be almost indistinguishable in their action is a fact which evidently bears on the view to be taken of the relation between a microphyte and its morbid action. This we shall have the opportunity of considering in relation to another phlogogenic microphyte—namely, the lung coccus, which plays so important a part in several infective inflammations.

PUERPERAL ECLAMPSIA.

By ROBERT BARNES, M.D.

I HAVE read with much interest the discussion on puerperal eclampsia started by Dr. Galabin at the recent meeting of the British Medical Association at Bournemouth. As I was not able to assist at the meeting I trust that I may be allowed to take part in the discussion in the *BRITISH MEDICAL JOURNAL*. I think I am not exceeding the bounds of just criticism in saying that almost every point brought forward by the speakers at the discussion is fairly set forth in the *System of Obstetric Medicine and Surgery* by myself and Fancourt Barnes. Reviewing the principal points expounded by the speakers, the following seem most directly to challenge observation.

1. It seems to be taken for granted, by Dr. Galabin especially, that nephritis and the attendant albuminuria and uræmia cause the convulsions. He states indeed the "form of nephritis associated with eclampsia appears to be especially severe in its effect of diminishing the excretion of solids, and that in the puerperal woman reflex excitability is naturally increased in preparation for the process of labour." Where is the proof that the kidney is inflamed? Because there is sufficient evidence of inflammation in acute and chronic Bright's disease, one credential of which is the presence of albumen in the urine, does it follow that whenever there is albumen in the urine the kidney is inflamed? If it be urged that there is further evidence of inflammation in the state of the kidneys revealed by necropsy, it may be objected that there is a wide difference between the conditions of cases that end fatally and cases that recover. Not to insist too much upon this distinction, it is not unreasonable to submit that some of the cases ending fatally do so greatly because the kidneys are too completely disabled by inflammation or other change; whilst the numerous cases that recover do so because the kidneys are only functionally affected. A strong argument in support of the latter proposition is this: the rapidity, even suddenness, of the recovery of the kidney power when the cause of the convulsions—the pregnancy—is removed. Is there any analogous example of acute inflammation of an organ passing away in a few hours

or even minutes? More than this, disease of the kidney is not constantly found, even in fatal cases. Depaul (1854) stated that in the necropsies he had made, the kidneys were perfectly healthy or simply congested. It is further certain that in some of the cases in which disease was found, this was of chronic character antecedent in origin to the pregnancy.

2. Let us now examine the relations of albuminuria to eclampsia. Dr. Byers puts the case as follows:—"Does the kidney affection cause the eclampsia, or does the eclampsia give rise to the abnormal state of the kidney; or, finally, is there some primary cause occasioning the convulsions, and at the same time giving rise to the kidney lesion?" Dr. Braxton Hicks has advanced the view that the convulsion may cause the albuminuria, but this theory has met with little support." Dr. Byers thinks Dr. Hicks's view is disproved by the fact that no albumen has been found in the urine of many patients after an epileptic attack. The argument is altogether strained.

It is enough to reflect that epilepsy is not puerperal eclampsia. The cases are essentially distinct. Dr. Hicks shows clearly the fallacy of Dr. Byers's argument in the *BRITISH MEDICAL JOURNAL* of October 3rd. In the discussion under comment Dr. Byers adverted especially to the researches of Leyden. This pathologist found that when the kidneys in three fatal cases of eclampsia with albuminuria had remained for a time in spirit the fat in great part disappeared, and then the organs on microscopic examination appeared to be normal, and accordingly inferred "that this fatty condition is not a degeneration but an infiltration." That is to say that, even in some fatal cases, the appearance taken to show inflammation really indicate an exaggerated physiological condition similar to that which I have described in the mucous membranes of the pelvic organs.

The believers in the nephritic theory think their case is confirmed by the observation of granular casts and epithelial scales along with albumen in the urine. But this is a fallacy not difficult to explode. Under the dominant vascular tension of pregnancy (and this is open to direct observation in the living subject) the mucous membrane of the pelvic organs undergoes an intense degree of hyperæmia which may be called congestion, but which it would be absurd to call inflammation. This hyperæmia in the cervix uteri and vagina is marked by deep red and purple coloration, by tissue engorgement, by the profuse shedding of epithelial scales and exudation of muco-albuminous fluid. These appearances, indeed, constitute one of the most obvious objective signs of pregnancy. It is quite legitimate to infer that a similar condition exists in the kidney which is within the sphere of similar influences. And, be it noted, we find these conditions present in cases free from excess of albumen in which the pregnancy and labour run a healthy course. This is described in the work referred to, but there is the confirmation of strong analogy in the researches of Tarnier, De Sinéty, Leyden, and others as to the changes wrought in the liver in pregnancy. These changes I have myself observed, and, working with me, the late Dr. Sutton at the London Hospital and Dr. Ewart at St. George's Hospital have made similar observations.

3. What, then, are the essential factors of eclampsia? It is clearly not necessary to invoke disease, inflammatory or other, of the kidney, since clinical observation proves that eclampsia may break out in subjects whose kidneys are sound; it is equally clear that albuminuria is not the cause, since eclampsia breaks out where no albumen is detected in the kidney. The theory that the immediate cause of the convulsion is some poison circulating in the blood rests upon strong physiological and clinical evidence. True, what that poison is has not been shown. Urea is found in the blood and is wanting in the urine. Gegenbauer and George Harley were among the first to attest it. In one case in which I bled the patient, Dr. Bernays found urea and uric acid in the blood. This does not prove that urea is the active poison. All that is known positively is that the kidneys, and the liver often in similar cases, are checked in their function of elimination. What the kidneys ought to excrete is retained in the blood. The noxious elements have certainly not been clearly identified. For this reason I have proposed the word "urinæmia" as not committing to an absolute dogma; and even this term