Lumleian Lectures ON ENDOCARDITIS.

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LECTURE II.*

NON-MICROBIC ETIOLOGICAL FACTORS IN THE PRODUCTION OF ENDOCARDITIS.

I PASS NOW to consider certain etiological factors in the production of endocarditis, both of the valve cusps and of the chambers of the heart, which, though the exclusion of a chronic infective element must only be presumed at any time with great caution, appear to be outside the sphere of microbic activity.

Having spoken of the possibility of *congenital defects* in connexion with some cases of pure mitral stenosis I will take these first. It has been for a long time held that congenital defects in the heart are almost confined to the right side of this organ. Such defects as are found in the left side, if we except those gross defects which lead to such massive disturbances of the circulation that there are early and lethal results, have been too lightly passed over. There is good reason to believe that we have been too cavalier in our observations concerning the intimate anatomy of the heart valves, and of the aortic valve in particular, in relation to endocardial disease. Deviations from the normal in these delicate structures may well prove to be a determining factor in infection of a grade hitherto unsuspected. This possibility did not escape the eyes of older observers. Thayer reminds us that the recognition of the fact that bicuspid aortic and pulmonary valves predispose to disease is as old as Paget. Osler also pointed out the liability of these malformed segments to sclerotic endocarditis. Of seventeen cases examined by him all presented sclerotic changes, and the majority of them had, during life, the clinical features of incompetence.

Glynn, who gave the Lumleian Lectures upon infective endocarditis in the year 1903, refers in detail to a specimen obtained from a man aged 48 years, in which one of the two cusps was found to be torn and everted, and whose fatal illness started after a strain, during which it is presumed that the diseased cusp was damaged. I pointed out in 1909 that congenital defects that were compatible with good health and were outside the category of those grosser lesions which were to be recognized during life might still be of great importance in inducing active endocarditis. I cited cases of this as illustrated by defective inter-ventricular septum and patent ductus arteriosus, in patients of 31 and 42 years of age respectively. I drew special attention to the association of bicuspid aortic valves with bacterial endocarditis in 1905 when publishing the first cases of endocarditis due to Pfeiffer's bacillus. In 1909 I dealt with this point more fully, having found bicuspid aortic valves in two other hearts in the museum of St. Bartholomew's Hospital, each the site of bacterial endocarditis. In still a fourth specimen, from a case of pneumococcal endocarditis, the pulmonary valve cusps were only two in number. Since that date four other hearts have been added to the museum, all showing bicuspid aortic valves, and all affected by bacterial endocarditis. In addition, Dr. T. H. G. Shore, the curator, possesses three unmounted specimens of a similar kind, which he obtained from soldiers dying of this disease in France. It is very clear that the condition here dealt with is one of considerable importance.

In 1923 Lewis and Grant contributed a valuable paper to *Heart*, in which they treated of the normal structure of the aortic valve and especially of the relations of the aortic media to the annulus fibrosus. They describe in detail four cases of the condition of bicuspid aortic valve and seven further cases associated with bacterial endocarditis. There follows an analysis of 116 cases collected from the literature. Of these, 63 were males, 20 females, and in 33 cases the sex was not stated. These authors estimate that no fewer than 23 per cent. of males reaching

adult life, and possessing congenitally bicuspid aortic valves, die of active endocarditis. The moral of all this is, as Libman remarks, that it behoves us to be much more critical than we have hitherto been in our examination of diseased hearts in the dead-house. Interpretations of our findings must needs be very cautious since the matter is by no means easy. We must endeavour to distinguish (a) true congenital defects, (b) the sclerotic residua of effete infections by rheumatism, (c) the results of healed bacterial infection, and (d) sclerosis from purely mechanical causes. With so many possibilities before us it is obvious that the task is full of difficulties. I shall return to this matter in dealing with questions relating to pathogenesis.

PHYSICAL AND EMOTIONAL STRESS.

But if we have been cavalier in our consideration of these congenital defects and the anatomical strain which they impose upon these delicate structures, situate as they are at the very centre of the hydraulics of the circulation, may we not also have been somewhat cavalier in regard to *strain* of a functional kind? It has been the custom of late years to minimize the factor of physical and emotional stress in general in cardio-vascular disease, and therefore it has been largely discounted in the production of endocardial changes. This is a material age, and we have become accustomed to discount functional elements in the etiology of organic disease. We have been told that the healthy heart cannot be damaged by volitional effort. But whose heart is "healthy"? If a heart is found to be damaged after effort, then the onus of the damage is laid at the door of toxic agencies. But are we not all of us potentially, if not actually, "toxic"? And if this be so, does the doctrine of the heart's immunity from self-imposed strain carry any more practical application than that it is desirable, in order to reduce the effect of the strain to a minimum, that we should see to it that we are as little "toxic" as possible?

It is necessary to distinguish between sudden and occasional strain on the one hand and prolonged strain on the other. There seems good reason for believing that both physical and emotional strain, if prolonged, may lead to endocardial disease, both of the sclerosing variety and, with or without this, of the active bacterial type. Since prolonged strain is inseparable from *fatigue*, this element may also be included in this group of etiological factors.

The recent experiences of those who have had charge of ex-soldiers suffering from endocarditis of the bacterial sort throws much light upon this matter. Reports concerning these cases are to hand from careful observers in nearly all the belligerent countries, but are not yet complete in many important points. So far as the observations go, however, we have strong confirmation of the view taken here. The cases reported have been almost entirely aortic in disposition, there has for the most part been no evidence of previous disease of the valves, and the type of soldier affected, and his war record, suggest strongly that the factor of strain has been considerable. In this country Starling and Carey Coombs have made memorable contributions on the subject. Starling, in a report on fifty-two cases of infective endocarditis in ex-soldiers, in half of which the disease was of the chronic type, says of them:

"the disease occurs in individuals of fine health and physique who have had little or no previous illness. The majority of those suffering from it have undergone a considerable degree of physical stress—e.g., those who were serving in the fighting line in the years 1916-17. The infection is primary in the endocardium. The *post-mortem* appearances show no evidence of previous rheumatic endocarditis."

Carey Coombs, in his equally important paper, is led to almost identical conclusions. He says, as the result of his analysis of thirty cases of post-war chronic endocarditis of the bacterial type:

"the predisposition of the ex-soldier to endocarditis lenta is not due to infections of the heart prior to enlistment, since approximately four-fifths of the cases, even after the Ministry of Pensions had scrutinized their histories, failed to disclose any evidence of such infections. . . . The facts as to lesions and diseases contracted during service are, of course, open to the criticism that it is quite impossible to assess in figures the liability to injury of the various 'portals of entry' of infection; but it does seem reasonable to conclude that the reason why soldiers have become victims of endocardial infection does not lie in their liability to be invaded by micro-organisms through any particular tract. . . . There is, however, a very remarkable

* Delivered before the Royal College of Physicians, London, on March 25th.

fact, only imperfectly presented by the statements that 80 per cent. of the men were engaged in the more strenuous forms of military service, and that the average duration of service was 3.05 years, or nearly three-fourths of the whole length of the war. The fact is one which is not susceptible of arithmetical statement. It is this, that almost without exception the men whose military service was followed by the development of endocarditis lenta were men of fine physique and morale: men who joined the army early, served with all their might, and exerted themselves to the utmost limit of their physical power. . . . Looked at from the obverse side, the same fact is equally striking. At the bases and elsewhere, both at home and overseas, there were large numbers of men of indifferent physique serving in the army; yet I have not so far encountered a single example of chronic endocardial infection amongst such men."

Carey Coombs does not miss the obvious point that excessive fatigue may predispose the body to infection, and thinks a biochemical link between fatigue and infection may be suggested by Walker Hall's work on the effect of dilute acids in accelerating blood cultures in nutrient broths.

Strain and fatigue overlap with arterio-sclerosis, with which in most cases hyperpiesia goes hand-in-hand. Upon these factors in the production of chronic endocardial disease I do not propose to dwell.

MARANTIC AND TERMINAL INFECTIONS.

I agree with Irving Simons, to whom we owe an excellent critical review of the whole subject of endocardial infections up to the year 1914, that the lesions occurring in the heart in cases of the so-called cachexias lack clinical significance, and are to be regarded rather as marantic thromboses than as true endocarditic manifestations. This statement refers to most of the positive *post-mortem* findings in cases of chronic nephritis, tuberculosis, cirrhosis of the liver, and carcinoma. They are to be distinguished, however, from cases of terminal septic endocarditis occurring in patients suffering from these same diseases, a class which, in my original survey, I included in the "latent" group. Although they usually are latent, it would be better to call them "terminal," since the word "latent" is more properly used for those cases of chronic infection which only come under observation as the result of one of the accidents incident to the disease, and especially embolic infarction.

I now pass on to consider that large and important, but heterogeneous, group of cases of endocarditis variously termed "ulcerative," "malignant," "infective," or "bacterial." The limits of this group are ill defined. At one end of a possible series into which they may be placed they fuse with the rheumatic group. Poynton and Paine, together with some other workers, describe a "malignant rheumatic endocarditis," considering that the rheumatic virus alone—in their judgement a specific streptococcus (the *Diplococcus rheumaticus*)—is responsible for such cases. At the other end of such a series are cases in which the endocardial lesions may be regarded as little more than intracardiac thromboses occurring in the course of a pyaemia.

A CONFUSING NOMENCLATURE.

The present nomenclature is avowedly very unsatisfactory. "Ulcerative" has the double objection that, even if we leave out of account for a moment Poynton and Paine's cases of malignant rheumatism, a process of ulceration occurs in severe forms of acute rheumatic endocarditis, as may be seen not infrequently in the *post-mortem* room, whereas by no means all cases of the bacterial group are associated with ulceration. Indeed, the absence of ulceration is an important feature in some of the more chronic cases. "Malignant" is an ugly and forbidding word to use, and however high may be the mortality in the fully fledged cases within this group some patients do certainly weather through. To both the words "infective" and "bacterial" the objection applies equally—that the rheumatic cases are presumably of this nature, despite our ignorance of the cause of the infection, and the syphilitic cases certainly are. The tendency during recent years to change the word "infective" for "bacterial" is curious, seeing that we have no knowledge of infections which are not bacterial. Beyond sharing the general dissatisfaction with any and all of these names, I am not anxious to introduce a new one. But I have a leaning towards a still older name than any of those now used, reactionary though it may sound to speak of

"septic" endocarditis. The word commits us to nothing in regard to pathogenesis, yet is expressive of the main differential features between this form of endocarditis and the rheumatic and syphilitic forms. Irving Simons regards the term "septic" as unfortunate, in that the lesions in many cases are not suppurative. But suppuration is by no means a necessary part either of acute or of chronic sepsis. Witness our use of the term in such conditions as "puerperal sepsis" and "focal sepsis"; in neither of these expressions does the word "sepsis" necessarily connote suppuration.

Unfortunately the confusion in words does not end here; confusion has of late years also invaded the terms by which we designate the type of disease as regards the intensity of the morbid processes involved and the duration of them. Although the words "acute" and "chronic," like a good many very common words, cannot be accurately defined, there is general consensus of ideas as to what they mean when applied to diseases. They are a convenient estimate of the two combined qualities already mentioned—intensity and duration. Now everybody seems agreed on the use of the word "acute" in relation to certain cases of bacterial infections of the type I am now discussing, but the cases that are not acute have been called "chronic," "subacute," and "slow" by different authors. As between "chronic" and "slow" there seems to be no difference. Schottmüller's account of the cases which he described under the name "endocarditis lenta," and which appeared in 1910, the year following the accounts contributed in this country by Osler and myself, makes it clear that he was dealing with the same kind of case which we called "chronic endocarditis." Individual cases of this chronic type had been described earlier than this, as by Bristowe, Lenhartz, and others. In the same year Libman introduced the term "subacute bacterial endocarditis," and by a rapid series of papers, embodying observations and reflections of fundamental importance, has succeeded in establishing this term, for a time, as synonymous with both the earlier names.

Most of those who have considered the matter, and have contributed to our increasing knowledge of the subject, fail to distinguish between the cases originally designated "chronic" and Libman's subacute cases. And so it comes to pass that these two terms are, for the most part, used indiscriminately. Strangely enough, if there is any tendency to make a distinction between these two terms it is to use Libman's new term for a class of case which, on analysis, seems to be of even slower development and less intense symptomatology than the class of cases formerly called chronic. I shall refer to this point again, because of its important bearings upon pathogenesis.

ACUTE SEPTIC ENDOCARDITIS.

Acute septic endocarditis was recognized clearly by Wilks and others. Wilks introduced the excellent term "arterial pyaemia," and the words very aptly express the main features of the disease. Little or nothing has been added to our knowledge of this group of cases since Wilks's time. The heart and heart valves share in a general infection. The micro-organisms concerned are highly virulent in character—*S. aureus*, *Strep. pyogenes* (vel *haemolyticus*), the pneumococcus, and less often the gonococcus.

The onset of the disease is usually abrupt, the symptoms severe throughout, fever is high, rigors are common, and the course of the disease is rapid. A few doubtful recoveries occur. Death usually takes place in from ten days to a month, but there are fulminant cases which terminate in three or four days, and some, of less than the ordinary severity, which drag into the second month. The disease sometimes complicates osteomyelitis, erysipelas, pneumonia, puerperal sepsis, and less often some other acute local infections. I deal with it here thus briefly so as to give my groups of cases more clear definition.

Septic Endocarditis of the Right Side of the Heart.

Among the cases of acute septic endocarditis which I have observed of late was one in which the tricuspid valve was affected, and this valve alone. Since I regard the case as presenting the clinical picture to be expected in this somewhat rare condition, I will give a brief note of it.

A bar manager, aged 42 years, was admitted to St. Bartholomew's Hospital on the sixteenth day of an acute illness which was ushered in by shivering and headache. The man was seen by his doctor on the second day of his illness and put to bed, where he had been ever since. He became delirious on the third day and was transferred to a nursing home. About this time a patch of pleuritic friction was noted near the region of the right nipple, which disappeared in less than a week. There were no physical signs of pneumonia. The temperature chart, which was brought to the hospital with the patient, showed that there had been a fairly continued fever for four days after the record was begun, the temperature reaching 103° to 104° . It fell, but not by crisis, on the eighth day of the illness, and remained nearly normal for three days. It then rose sharply, with a rigor, reaching 104° to 105° . The delirium, which had subsided with the deferescence of the fever, returned. There was no headache. From the twelfth to the sixteenth days there were daily rigors, with profuse sweats.

On admission the patient was very ill, with low delirium, dry cough, and slight cyanosis. Examination of the chest yielded a soft systolic bruit near the apex, and a few rhonchi over both lungs. There was a leucocytosis of 10,800. A lumbar puncture gave normal fluid. A blood culture was sterile. Agglutination tests were negative. Complement fixation test for tubercle bacilli was negative. There were no choroidal tubercles seen. No abnormal coliform organisms were found in the stools. The urine was sterile. The spleen was not palpable. No petechiae were present. Rigors continued almost daily, with high quotidian intermittent fever. On two separate occasions definite areas of crepitation, with soft pleuritic rub, were found, one in the right flank and one in the left axilla. There were no sputa. The frequency of the respirations was constantly raised. These, and the persistence of the apical systolic bruit, were the only physical signs elicited. Two further blood cultures were negative, but on the thirty-third day of the disease the blood yielded a growth of pneumococci. The patient, very ill at all times, died on the thirty-fifth day of his disease. At the *post-mortem* examination recent vegetations of the septic type were found on the tricuspid valve, and both lungs contained recent infarcts. There was about a pint of blood-stained serous fluid in the right pleural cavity. This fluid and the heart's blood both showed pneumococci in film preparations.

The chief diagnostic feature in a septic endocarditis of the right heart, whether tricuspid or pulmonary, is the association of the signs of endocarditis with multiple pulmonary infarction. The intensity, and the duration, of the disease process depend, as in left-sided cases, upon the virulence of the infecting microbe. The case just mentioned, being pneumococcal in nature, approximated to the acute forms of septic endocarditis. In a case which I included in my first series the micro-organism was a salivary type of streptococcus, and the infection was grafted upon a congenitally stenosed pulmonary orifice. The patient was a young adult, and her illness dated from the extraction of a septic tooth under local anaesthesia. In the first three months of her disease she had twenty-two attacks of pleurisy. Although she was known to be the subject of congenital heart disease of a mild type, the real nature of the disease was not recognized, and the repeated bouts of pleurisy, from which, however, she seemed to recover well, and a persistent pyrexia, led to her being sent to a tuberculosis sanatorium. Eventually her blood was cultivated and a streptococcus of the type *S. salivarius* was isolated. After an illness lasting for some nine months, and very thorough treatment, she recovered.

CASES INTERMEDIATE IN INTENSITY AND DURATION.

Between this group of acute cases and the group of chronic septic cases, which I shall take in more detail, there occur cases which I originally termed "subacute"—that is, cases in which the onset was less abrupt, the symptoms less dramatic, and the course less rapid. The causative micro-organisms are less virulent; the gonococcus and the pneumococcus are found in them at times, but more often the cocci approximate to those found in the chronic cases. Those cases termed by Lenhartz and by Poynton and Paine "malignant rheumatism" are of this class. So also, quite frequently, are those young adults who give a clear history of rheumatic fever in childhood or in the teens, and who present clear signs of residual valvular disease. The duration of these cases is from about three to six months. In view of the present confusion in the use of the term "subacute," I think it better to give no name to this group, but to be content to regard them as an intermediate class between the acute and the chronic cases. In any individual case we may, if we feel unhappy without a label, strain a point and call it chronic.

CHRONIC SEPTIC ENDOCARDITIS.

It is to the *chronic cases*, however, that much attention has been directed of late years, and deservedly so. The experience of the ex-soldier in this connexion is, given no other experience, very striking and very helpful in our understanding of endocardial diseases. But in civilian work also there is a growing recognition of the importance of these cases, and of the urgent necessity of detecting them as early in the course of the disease as possible. I shall deal with some of the main points of clinical interest as these have appealed to me, deferring matters of pathological importance until my next lecture.

Chronic septic endocarditis is a disease of adult life; its maximum incidence comes during the third and fourth decades. It is nearly twice as common in males as in females, a disproportion which exists quite independently of the war cases. It is a very insidious disease; it is not at present possible to estimate, except approximately, the date of its origin in the great majority of cases, nor, in those few cases in which we have good evidence of recovery, can we say when it ceased to be an active disease process. But allowing for these things, it is probable that the disease lasts, on an average, about six to nine months. Not a few cases reach twelve months, and there are reliable records of cases lasting two and two and a half years. Proofs are accumulating that there are recurring cases, also that spontaneous cures occur. Of these cases I shall say more later.

The earliest symptoms of the disease are undoubtedly of the toxic kind. *Chills or sweats* are perhaps amongst the earliest recognizable symptoms; but an accidentally discovered pyrexia, as following influenza, frequently leads to observations that discover something seriously wrong in many of the cases. Pyrexia is almost always present at some time or other in the course of the disease. It has little or no recognizable features to guide us. It is rarely high. Apyrexial periods are not uncommon, even when the temperature is taken every four hours, an important point in the general observations. Rigors are quite unusual.

VARIATIONS IN THE PYREXIA.

Exacerbations in the pyrexia are often concomitant with embolic events, and especially with embolism in branches of the splenic artery; the attendant perisplenitis is probably the main source of the fever in this case. That the pyrexia frequently ranges higher with the occurrence of embolic infarction was pointed out by Douglas Powell in his Lumleian Lectures in 1899, when he showed temperature charts illustrative of this fact. But I do not know that attention has been drawn to the fact that the pyrexia not seldom falls to a lower level after these exacerbations and remains there for several days. This is not the result of decreased ability to react to the toxæmia, because the patients often feel fitter during this period of lower pyrexia following an exacerbation. It certainly looks as though the mechanism of embolic infarction results in some instances in the manufacture of antibodies to the infecting agent. It would be interesting to examine the patient's blood for these substances by complement fixation or by other means after such a process, and compare the titre with that obtained at other times. I have wondered if the process of embolism in this disease is not sometimes of service to the patient, as well as being, at other times, the direct cause of a tragic end. Provided the infecting microbe is not so pathogenic as to overthrow the local resistance altogether and lead to an abscess—which is rarely the case—and provided the embolus does not occur in a vital part like the brain—an all too common contingency—it is quite possible that the extraordinary slowness with which the disease sometimes progresses may in part be explained by such a view. I have been struck by the fact that in the two cases in which I have seen the largest spleens—in both the organ was visible on inspection of the abdomen, and its lower border lay well below the umbilicus—the general condition of the patient was well maintained for months together. In one of these cases the spleen had increased so greatly in size during a stay of five months in the winter in the open air at the South of France that on the patient's return I wondered if she had developed leukaemia. In the other case my opinion was asked because, though a diagnosis of septic endocarditis had been

made provisionally, the very large size of the spleen had actually thrown doubt upon it. In this latter case the effect of splenic infarction, as estimated by attacks of pain in the upper and left side of the belly, was seen in striking fashion in the temperature curve, as also was the subsequent improvement in the general symptoms. Remissions in the disease are often attributed to some special line of treatment which is being pursued, such as the use of a vaccine. Before such a conclusion can be accepted it is important to inquire if the remission be not possibly correlated to splenic infarction.

SOME IMPORTANT SYMPTOMS AND SIGNS.

Clubbing of the fingers has, since Cotton's observations published in 1922, become a valuable help in diagnosis. This observer, working in Lewis's clinic, found that of 63 out of 798 cases of structural heart disease in pensioners in whom this sign was present, 44 proved to be cases of chronic septic endocarditis, and of the remaining 19 cases 4 were regarded as doubtful instances of the same disease. This observation has found corroboration from many sources. Starling thinks that in the majority of cases the occurrence of clubbing indicates that the disease has been present for some time. It is clear that the association of this sign with acquired valvular disease must put us on our guard.

I referred in my original account of the disease to the frequency of *pains in or about the joints*. I do not think sufficient attention has been paid to these symptoms by subsequent writers. There is a point of great importance in connexion with the manner of their appearance, and that is their suddenness. A second important point is the difficulty that patients often have in locating them; and a third is the absence oftentimes of any recognizable effusion when the affected part is a joint, so that I have sometimes spoken of these pains as being arthralgic rather than arthritic. The situations of these pains are very numerous; the regions of the foot and ankle are the most common, then perhaps the hip and shoulder. But the wrist, the back, and the sacrum are not uncommon. The abrupt onset of the pain, and the fact that in not a few cases critical examination discovers a dusky red patch of tender skin in the neighbourhood of the pain in those cases in which the affected part is not a deep structure, makes it probable that the origin of the event is embolic. Many of these pains, even if there be associated swelling, are of quite short duration, passing off completely and leaving no residue, either subjective or objective. In the investigation of a doubtful case, if no history of these pains be given by the patient, inquiry should be made, because it not seldom happens that the event has been considered of no special significance owing to its transient character.

The *ephemeral cutaneous nodes* of French physicians—now generally called after Osler because of the detailed description given of them by our late gifted and lamented colleague—have been proved to possess all the pathognomonic value which he attributed to them. I know of no feature in a suspected case which possesses such dire significance. Again, owing to their fleeting nature, inquiry should be made for these lesions if they are not present when the patient is first seen. No doubt they, too, own an embolic source. The most common situation for them is the pulp of the finger or toe. They also occur on the thenar and hypothenar eminence. I have described analogous lesions as occurring occasionally in the bed of the nails, where a thin splash of red may be seen, accompanied by exquisite tenderness if pressure be made upon the affected part. These nodes arise suddenly, with sharp pain, as though the finger has been pricked; indeed, patients often examine the part carefully to make sure that some sharp object, like a thorn or a splinter, has not been the cause of the sensation. One patient, a typist, found that she could not use a particular finger for two or three days because of the tenderness caused by pressure on the keys of her instrument. A few hours after the onset of the pain an erythematous patch appears, pinkish at first, and later dusky red, with oftentimes a centre of white skin rather suggestive of an urticarial wheal. There is usually slight swelling of the discoloured skin. The redness disappears, and the tenderness also, in about one to three or four days.

The presence of *petechiae* in the skin is quite a different sign from that last described; though of much less diagnostic value it is still very important. As I have pointed out, a favourite and early situation for these lesions is about the neck and clavicles; other common situations are the chest, forearms, legs, and buttocks. Needless to say, two or three scattered petechiae may be very easily overlooked unless the possibility of their presence is specially borne in mind and the body is scoured for them in a good light. Like the nodes just referred to, these petechiae are short-lived; they tend to appear in small crops. We have no proof that they are embolic in origin.

There is general agreement that a *leucocytosis*, at least of any considerable degree, is not a feature in these chronic cases. Indeed, the type of count is very apt to be round about 9,000. In my second series of cases the actual figure averaged 9,300. But a leucopenia is quite common. This contrasts markedly with the leucocyte count in the acute cases, in the second series of which the figure averaged 22,000.

The degree of *anaemia* varies much. It may be so great as to raise the question of pernicious anaemia, especially when a marked leucopenia is present. But the proportionate reduction in haemoglobin seems to be invariably greater than the reduction in red cells. It is to be noted that some patients retain their blood, and especially their content of red cells, surprisingly well under treatment, especially if kept in the open air. I have seen an erythraemia in one well marked case, but the haemoglobin content was well below 100 per cent.

Pallor of the skin is a striking sign in the chronic cases, though if this be marked, and particularly if the curious tint of the complexion to which Libman has given the term "*café-au-lait*" be present, the case is generally of considerable standing. As in the case of the actual blood content, however, it is surprising how well some of these patients keep their complexion for a long time if treated in the open air.

EMBOLIC EVENTS.

Next to the evidence of endocarditis, consideration of which I take later, *embolism* is undoubtedly the most constant of all the signs of the disease. It was recorded in 142 of my second series of 162 cases. The vessels affected were, in the order of frequency, those of the spleen (108 cases), the kidneys (98 cases), the brain (26 cases), and the arteries of the limbs (13 cases). To these situations must be added the retina and the skin. Embolism, or one of its sequels, is not infrequently the event which brings the patient under observation, and in many instances of apparently mysterious signs and symptoms it is this process which offers a satisfactory clue to the problem. Be it remembered that the size of the detached fragment of material may vary from something microscopic to something so large as to obstruct a vessel of considerable size.

1. *The Spleen*.—This is the most commonly affected of the internal organs. The more chronic the case the more common is it to find the spleen enlarged during life; indeed, it is probably correct to say that in chronic cases a palpable spleen is an invariable finding. Early in the disease, and when the organ is as yet not palpable, pains in the upper left quadrant of the belly or hereabouts are highly suggestive. These pains, associated with fever, and perhaps referred to the flank, are sometimes mistaken for pleurisy; when friction is present, as it may be, the error is difficult to avoid. But pleurisy may actually be present in addition. I have only once seen a pleurisy with effusion (which was aspirated) complicate the splenic infarction. Although, as already mentioned, in some of the slow cases the size of the spleen may be very considerable, we must not conclude, from our knowledge of the great frequency of infarction in it, that this is the only factor in the enlargement. There is doubtless the general factor of toxæmia, and there is also the factor of anaemia. Unlike the spleen in acute septic endocarditis, the organ is generally quite firm, and the infected areas almost never suppurate; the nearest approach to this seen *post mortem* is some degree of grumous softening; even this is uncommon.

2. *The Kidney*.—If we consider in connexion with this

organ that the glomerular lesions, which are so characteristic a feature, are embolic in nature, as they probably are, then it is likely that the kidney is affected by the embolic process quite as often as the spleen. The frequency of embolism here must not, as has often been pointed out, be judged only by the appearance of a haematuria; in many cases the number of red blood cells passed in the urine is so small as to call for microscopical search, and this should be undertaken very frequently. I have pointed out that a small haematuria may be missed, but a brief albuminuria consequent upon it may be detected; intermittent albuminuria should, therefore, suggest renal infarction just as intermittent haematuria does. The process of renal infarction is generally, but not always, painless. In one case under observation the renal emboli were accompanied by severe lumbar pain, so much so that calculus and tuberculosis were both suspected. We owe especially to Gaskell and to Baehr our knowledge of the intimate changes in the kidney, only ascertainable by microscopical examination. These investigators described a form of glomerular change which they regard as peculiar, and to which Libman, in particular, has come to attach great significance. Indeed, according to the last-named observer, the discovery of the hyaline-like change in portions of the glomeruli which is the end-stage in the Gaskell-Baehr type of nephritis enables us to say with confidence that an associated sclerotic heart valve is the result of a "healed bacterial endocarditis." If this conclusion be borne out by other workers, and we may regard the lesion as almost a specific effect of septic endocarditis, its value in *post-mortem* interpretations will be very great.

3. *The Brain*.—Cerebral embolism is by far the most serious of all the common events of this nature. It not infrequently brings a latent case very rudely into prominence; it often determines the fatal ending, and not seldom at a stage in the disease when, on all other counts, a hopeful period of quiescence has arrived in regard to the toxic process. Experiences like these it is which lead the physician to speak with caution even in the face of definite improvement in the general state, including quite lengthy periods of apyrexia. Death in this disease may be accidental and mechanical as well as the natural termination of an intractable toxæmia. The most common clinical result of cerebral embolism is hemiplegia, with aphasia if the hemiplegia be right-sided. Monoplegias are much less common. The resultant cerebral shock is usually considerable, and the outlook, even immediately, is grave. I have twice seen a second hemiplegia on the other side, the interval between the two attacks being in one case only three days, in the other case twelve months. The sequence, originally described by Douglas Powell, of haemorrhage following the septic embolus, is common, as *post-mortem* experience shows, but acute cerebral softening, short of actual haemorrhage, is perhaps quite as common a finding. Irritative cerebral effects occur as well as paralytic, and these may sometimes be correlated *post mortem* with subarachnoid haemorrhages. I found ten such lesions recorded in 118 *post-mortem* examinations. In none of four cases in which choreiform movements were present was there, unfortunately, any opportunity for *post-mortem* examination.

4. *Plugging of arteries in the limbs* is probably more common than is thought. Unless the arteries be carefully examined a bout of pain and some swelling, say, in the wrist and hand, or in the foot, is sometimes considered to be arthritic in nature, when it is really the result of embolism in the radial or one of the branches of the posterior tibial artery. That the arterial pulse is not often obstructed for long, and rarely completely obstructed, adds to the deception, since coldness of the part beyond the partial block, still less gangrene, does not occur. We must suppose that the absence of these last-named effects is due to the friability, not to say softness, of the embolus, allowing of rapid disintegration, or channelling, or both. All this is in marked contrast with the results following embolism, if this takes place, in (non-septic) mitral stenosis, when gangrene is not at all uncommon. A common sequel to these septic emboli in vessels in the limbs is *aneurysm*, the development of which helps to explain, no doubt, the absence of serious nutritional changes in the part supplied by the affected vessel.

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I have twice seen *mesenteric embolism*. In one case there was an attack of abdominal pain, followed in three days by a swelling about the size of a golf ball, and situate just to the right of the mesial line and a very little below the level of the navel. Despite the unusually discrete nature of the lump and its peculiar situation, the case would doubtless have been considered one of acute appendicitis had it not been that about the time of this occurrence the patient became suspect on the score of a possible septic endocarditis. A positive blood culture determined the diagnosis. In the other case a surgical colleague removed a small aneurysm from the right ulnar artery near its origin from the brachial. A routine digital examination of the rectum had discovered the presence of two small firm lumps, lying close together, and felt easily through the mucous membrane of the bowel. They were thought to be enlarged glands. A *post-mortem* examination later revealed the fact that these were healed aneurysms on the superior mesenteric artery. There was a third small aneurysm on the hepatic artery. Death had occurred from haemorrhage into the cerebellum, no doubt secondary to another embolism in this situation.

Aneurysm of the *ophthalmic artery* occurred in a case under observation by Foster Moore and myself.

RELATIVE IMMUNITY OF THE HEART.

The *state of the heart* in chronic septic endocarditis deserves a note. The salient feature, and one upon which there is general concurrence, is that it maintains its functional capacity in a very striking manner. Indeed, it may be said with truth that this is not a disease of the heart at all, but of the endocardium; hence my expression in my first lecture, "*Endocarditis vera*." This fact contrasts markedly with the state of things seen in a rheumatic endocarditis, where to a large extent the converse applies. Many of the patients in the disease now under consideration enjoy complete cardiac sufficiency for months after they fall victims to their infection. This is no doubt the reason why so many of them do not come under our notice until long after the initial stage of the process is past. Soldiers remain in the firing line, doctors continue their arduous profession, farmers proceed with quite heavy labour, until one or other of the accidents of the disease leads them to report themselves. Even then it is often difficult to persuade them to consider themselves ill. This retention of cardiac efficiency, combined with that buoyancy and optimism which I have called "*spes endocarditidis*," renders these patients oftentimes difficult to treat. A doctor, casually mentioning to his partner that he could not see the print on the extreme right side of his newspaper, submitted to a cursory examination; it was found that he had the cardiac signs of aortic incompetence and a retinal haemorrhage; on fuller examination a diagnosis of septic endocarditis was not difficult. He refused treatment and carried on his work. A month later he attended a difficult confinement, using forceps. He woke the next morning to find himself hemiplegic, became comatose a week later, and died.

It is generally agreed that such evidences of heart failure as auricular fibrillation do not occur in these cases—another testimony to the same fact. This relative absence of myocardial involvement tends to persist to the last in many of the cases, though there is considerable divergence in the figures given by different authors as to the frequency of terminal heart failure. This divergence probably depends upon the fact that when small numbers of cases are dealt with the type of case which bulks most largely in the series from which the figures are calculated determines the figures. Taking my two series together, I found death with cardiac failure to occur in from 40 to 50 per cent. But both series contained a good many examples of the old rheumatic type of case. Yet in the groups which chiefly include ex-soldiers death has been due to heart failure in much the same proportion as this. Cotton gives 47 per cent., and Starling gives 60 per cent., in their two series respectively.

Renal failure is admittedly the most frequent cause of death next to heart failure. After this, in probable order of frequency, come *cerebral causes* (and especially coma following embolus), *exhaustion* from the prolonged toxicity, and *pneumonia*.