THE GULSTONIAN LECTURES,

ON

MALIGNANT ENDOCARDITIS.

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Lecture III.

Diagnosis.—Few diseases present greater difficulties in the way of diagnosis, difficulties which in many cases are practically insurmountable. It is no disparagement to the many skilled physicians who have put their cases upon record to say that, in fully one-half of them, the diagnosis was made *post mortem*. In spite, too, of able memoirs in the journals, the disease has not been much known, and it is only of late years that the text-books have contained chapters upon it. The protean character of the malady, the latency of the cardiac symptoms, and the close simulation of other disorders, combine to render the detection peculiarly difficult.

In the group of cardiac cases in which the disease attacks a patient the subject of chronic valvulitis, the matter is usually easy enough. The existence of fever of an irregular type, and the occurrence of embolism, generally suffice to make the case clear. It must be remembered that simple warty endocarditis not unfrequently attacks sclerotic valves, and may be accompanied by slight fever. Of course, in chronic heart-disease, irregular pyrexia may arise from other causes —local suppuration, cellulitis, etc.—which must be excluded.

In rheumatic fever, a disease in which the heart is more systematically examined than in any other, if with the occurrence of a murmur the symptoms become aggravated, and assume a typhoid or pyæmic type, the recognition of the complication should be easy. The onset of severe head-symptoms in rheumatism—delirium, with high fever and coma—requires to be carefully distinguished. Fortunately, the simple endocarditis common in this disease rarely, as I shall have occasion to show, passes into the grave form.

In pneumonia, a prolongation of the course, with the supervention of typhoid or septic symptoms, should lead to a very careful examination of the heart.

The greatest difficulty is met with in those acute cases resembling the malignant forms of the fevers; here the affection may simulate typhoid, typhus, cerebro-spinal meningitis, or even hæmorrhagic small-pox. Even with the detection of a heart-murmur, the judgment may have to be suspended, and many cases die with the general symptoms of profound blood-poisoning, before the development of any special features upon which a diagnosis could be based.

From typhoid fever, with which the cases are most often confounded, the mode of onset, the pyrexia, and the abdominal symptoms offer the chief points for discrimination. The onset of severe endocarditis is more abrupt, not so often preceded by a period of failing health and progressive weakness. In a large number of cases, cardiac pain or oppression and shortness of breath are mentioned as early symptoms. The fever rarely presents, in the early days of the disease, the regularity of typhoid, and from the outset may be very high. A sudden fall to the normal, or even below, may occur; indeed, irregular pyrexia is one of the most important diagnostic signs. The combination of diarrhœa, abdominal distension, and a rose-coloured eruption, points strongly to typhoid fever. The rash, when present, is usually petechial, a rare circumstance in typhoid fever. The development under observation of pronounced murmurs, particularly of aortic and regurgitant, is most suggestive of malignant endocarditis, and the occurrence of emboli would be a positive confirmation. Rigors rarely occur in typhoid fever, while they are common in endocarditis. It is well, however, to bear in mind that, in many of the most severe cases, death may occur, as in any of the infective disorders, without the development of the special symptoms necessary for a diagnosis.

Many of the cases present the clinical features of pyæmia, a condition which may actually exist, dependent upon the ulcerative lesions on the valves; and here the diagnosis lies between an ordinary septic infection from a wound, or auto-infection from a primary endocardial inflammation.

It is interesting to note the similarity of those cases of acute endocarditis in which death occurs in a few days, without the development of any other than the valvular lesion, with those instances of rapidly fatal acute periostitis and necrosis, and also with those cases of malignant septic infection from a slight external lesion.

It seems strange that difficulties should arise in the diagnosis between malaria and malignant endocarditis, but the records of cases plainly show that for weeks or months a condition of intermittent pyrexia may occur, simulating every type of ague. The paroxysms in regularity, in order of sequence, and in the accompanying general conditions, may fulfil every condition of a quotidian or tertian intermittent; and the development of cardiac symptoms, with breathing of the pyrexial type, may alone determine the nature of the case.

Etiology and Pathology.—With a view of obtaining data upon which to base statements regarding the etiological relations of malignant endocarditis, I have gone over the records of 209 cases. As before stated, 37 of these occurred in connection with pyæmia, traumatic or puerperal. Doubtless this number could have been very greatly increased had I examined files of special gynæcological and surgical journals, but my investigation did not lie so much in these directions. In 45 cases, there was no record of any previous disease which could be taken into account as possibly connected with the endocarditis. In 127 cases, there was a history of past or existing disease with which the cardiac trouble could, with a greater or less degree of probability, be associated.

One or two general considerations may first be mentioned. The period of middle life gives the greatest number of cases. Young children are rarely the victims; there were only three or four instances under 10 years of age, and not many more over 50. The cases occurring in connection with rheumatism presented an average younger age than the others; there were 36 instances under 30 years of age, out of 51 cases in which this point was mentioned.

Of 160 cases (exclusive of traumatic and puerperal), 99 were in males, and 61 in females.

Persons debilitated by exposure or other causes, or addicted to drink, seem particularly liable to be attacked; and in such subjects, during the course of an acute disorder, this complication is much more likely to arise.

As has been already referred to, the existence of sclerotic valvulitis is a very important factor in the etiology of severe endocarditis, a very considerable proportion of the cases occurring in individuals whose valves are thickened and crumpled from chronic inflammation.

The existence of a primary protopathic endocarditis must, I think, be allowed. In 45 cases, no history could be obtained of rheumatism or other affections with which endocarditis is known to be associated. Many of these cases were of the most malignant type; in 10, death took place within a week. A specific statement of the absence of rheumatism was generally given. The onset was usually like that of a specific fever, headache, vomiting, rigors, pyrexia, and often early delirium and unconsciousness. The very acute cases resemble severe typhoid or typhus, but, when more prolonged, a pyæmic condition may develop. In a number of these cases the disease has attacked persons with chronic valve-disease, some while under treatment, others in whom the compensation was complete and the old lesions only detected at the necropsy. In 5 instances, the ulcerative process attacked aortic valves, 2 of which were fused, and had undergone the fibroid changes always associated with this malformation.

In 127 of the cases, the endocarditis was associated with other diseases, some of the most important of which we shall now proceed to consider.

Rheumatism.—Since Bouillaud called special attention to the frequency of cardiac complications in this disease, its importance in the etiology of endocarditis has been universally recognised. And, as regards the simple form of endocarditis, the general statements are quite true, but, fortunately, the graver and fatal form is much less common, much less, I think, than is usually supposed. In 53 cases, there was a history of rheumatism, past or present. I included every case in which there had been the record of an attack, recent or remote. In only 24 did the symptoms of severe endocarditis arise during the progress of the acute or sub-acute disease. In 29 cases, there was simply a history of rheumatism, often years before, and no mention of the occurrence of joint-troubles at the time of the development of the endocarditis. Dr. Ogle called attention to the fact that ulcerative endocarditis occurred very often in persons in whom no rheumatic history could be traced. Of 21 cases which he reported, some of which were probably atheromatous, in only 3 was rheumatism mentioned. In only 3 also of the Montreal cases was there any positive history of rheumatism, either before or during the attacks. The following case, under the care of Dr. Ross, is a good example of the mode of onset.

B. M., aged 22, a healthy girl until three weeks before her admission to hospital, on January 4th. At that time she was attacked with

rheumatism of the wrists and ankles, not very severe, and she did not receive any treatment. A week from the beginning of the attack, she began to have chills, two or three a day, and she became feverish. During the next week she became worse, had occasional chills, not delirious; was brought to hospital on the 4th, in a very low state. On the 5th there was delirium and incoherence. Pulse 130; temperature 100°. Double murmur up and down sternum; joint-troubles not evident. On the 6th, 7th, and 8th, she remained in the same state, no chills; temperature ranged from 100° to 102°. On the 9th, she was more restless. On the 11th a grey membrane was noticed on the fauces. On the 12th, the membrane in the throat had extended, and covered the soft palate. Temperature 103°. On the 13th she died suddenly. The necropsy revealed a large deep ulcer at the aortic ring, nearly destroying one segment, and penetrating deeply between the auricle and the left ventricle. There were small infarcts in the brain, extensive recent diphtheria of fauces.

In a larger number than in any other group, sclerotic valves were found, with the existence of which the past rheumatism could, in many instances, be connected. A primary rheumatic endocarditis was recognised by Latham, also by Graves and Stokes, and it is quite possible that some of the cases which I have grouped as protopathic represented instances of the kind in which, if life had been prolonged, joint-troubles might have supervened.

Cases of acute rheumatism sometimes occur in which there may be multiple miliary abscesses (Fleischhauer, Virchow's *Archiv*, Band lxxii), and a pyæmic condition similar to the case just narrated, but without the presence of endocarditis. Micrococci have been found in these abscesses, and the cases resemble those rare instances of idiopathic pyæmia. It is worthy of observation that a skin-eruption was most frequently noted in connection with the rheumatic cases, generally an erythema. In a case of Dr. Kirkes (BRITISH MEDICAL JOURNAL, 1863, vol. ii), it was observed on both face and hands. The occasional presence of a scarlet rash in rheumatism (Petor, *Union Médicale*, 1870), and in puerperal fever (Hicks, *Obstetrical Society's Transactions*, vol. xii), has long been recognised.

In chorea, with which simple endocarditis is so often associated, the malignant form very rarely supervenes.

Pneumonia, as Bouilland pointed out, is not unfrequently complicated with endocarditis, but the important part which it plays in the etiology of the malignant disease has not been generally recognised. In the cases I have reviewed, it stands at the head of the list of diseases in which secondary endocarditis of a severe nature develops, 54 instances having been noted, rather more than 25 per cent. of the total number of cases. For this I was quite prepared by our Montreal experience, for, in 11 of the 23 cases, the attack was associated with pneumonia. Of the occurrence of acute endocarditis in this disease, the statements are somewhat diverse. Bouillaud thought that, in a third or fourth of the cases in which there was left-sided pneumonia, there was inflammation of the serous membranes of the heart. Grisolle, in his classical work on pneumonia, states, on the contrary, that it is a rare complication, and this would certainly appear to be the conclusion of the Committee for Collective Investigation; for, in the report upon 1,000 cases, endocarditis is only once mentioned. My experience at the Montreal General Hospital is very different. I have notes of 103 *post mortem* on cases of lobar pneumonia, and the occurrence of acute endocarditis is noted in 16 cases, over 15 per cent. Of these cases, 11 were of the malignant form. An analysis of these shows that, in 6, the left lung was involved; in 5, the right; in 4, the upper lobe was affected; in 7, the lower. In 9 of the cases was there pericarditis; in 5 of the 11 cases, there was suppurative cortical meningitis. In the 54 cases which I have reviewed, in 36 the lung affected was mentioned, and in 26 the affection was on the right side, and only 10 on the left; figures which are opposed to the statement of Bouillaud, that it is in left-sided pneumonia that endocardial complication most frequently supervenes. In 15 cases, acute meningitis is mentioned, and, in one instance, the meninges of the spinal cord were also affected. The aortic valves seem more often involved than the mitral. In 17 instances, there were old sclerotic changes in the valves.

The clinical features of several cases in which the endocarditis came on during pneumonia have already been given. In many of them, as in the girl, M. D., aged 29, referred to in the second lecture, the patients are brought to hospital unconscious, and die within a few days, with symptoms of a grave cerebral disorder. In others, there is a history of ordinary pneumonia, and the case may pursue the usual course, and defervescence take place, when, in a day or so, fever of an irregular type recurs, and typhoid or pyæmic symptoms appear. The majority of the cases are of this kind. Again, some instances occur in connection with injuries, and the patient succumbs to a lobar pneumonia and endocarditis unconnected with any sepsis. Two of the Montreal cases were of this kind. In three or four cases, there were rheumatic symptoms preceding or accompanying the pneumonia, as in a case of Dr. Mussers, the remarkable temperature-chart of which is here shown.

Elderly persons were more often attacked than in the other groups. There were 10 individuals over 50 years of age. In the Montreal cases, 3 of the patients had had pneumonia before; in 1 it was the third attack, and in every one of them there was a history of either drinking habits or previous bad health. In some cases, the pneumonia had partially or entirely resolved at the time of death, in others there was red, or, more frequently, grey hepatisation.

The relation of the meningitis to the pneumonia and the endocarditis is particularly interesting. The occasional occurrence of this complication in pneumonia has been referred to by many writers, particularly Grisolle, Huguenin (Ziemssen's *Encylopædia*, Band xii), and Greenfield (*St. Thomas's Hospital Reports*, 1878). In the 103 cases, I met with it in 8 instances, in 5 of which there was also endocarditis. The frequency of the association of these two conditions in pneumonia is illustrated by the figures already given: of 25 instances of meningitis in malignant endocarditis, 15 cases occurred in pneumonia. In all the specimens I have examined, there were micrococci in the exudation, and in three cases many of the capillaries and small arteries were filled with them; and it seems natural, where the endocardium is involved, to attribute the process to embolism from the valves. But the occurrence of an identical cortical meningitis without any valvulitis shows that it may be due to other causes than the endocarditis. As Huguenin suggests, it may be dependent upon the presence in the blood of infective material derived from the infiltrated lung-tissue.

In connection with these secondary or consecutive inflammations in pneumonia, it is interesting to call to mind the not unfrequent occurrence of pericarditis, and of croupous inflammation of the gastro-intestinal canal. Dr. Bristowe some years ago noted the frequent complication of croupous colitis; and, in 103 necropsies, I have met with this complication in 5 instances; and in one there was extensive croupous or membranous gastritis.

Diphtheria is rarely complicated with endocarditis, and I have only been able to find two or three instances in which severe symptoms were present; yet, in some works, endocarditis is stated to be not an uncommon sequence. Labadie-Lagrave (*Bull. de la Soc. d'Anatomie*, 1877) regards it as such; but it is probable that what he described as vegetations are only Albini's little nodules, the remnants of fœtal structures. In 108 necropsies in diphtheria, Telamon (*Progrès Médical*, 1879) did not meet with a single case of endocarditis; and my experience has been the same in 30 *post mortem* examinations, many of which were in adults.

In *dysentery*, a few cases have occurred. Litten (*Charité Annalen*, Band iii) has recorded an instance in which there was extensive ulceration of the aortic valves; and one of the Montreal cases occurred in connection with acute colitis.

In the *eruptive fevers*, grave endocarditis occasionally develops—in typhoid, in scarlet fever, and in variola; but, in the cases I have analysed, these diseases appear of very trivial etiological significance.

In *ague*, as Lancereaux (*Gazette Médicale de Paris*, 1862; and *Archives Générales*, 1873) first pointed out, simple or severe endocarditis may develop. In some of these cases, as in the remarkable one reported by Dr. Bristowe, to which I referred in the second lecture, the paroxysms of true intermittent fever, and those of the ulcerative endocarditis, seem to run the one into the other.[1] In most of the cases, there has been only a history of severe ague, and the endocarditis has followed repeated attacks. Dr. Greenhow (*Pathological Society's Transactions*, vol. xxx) has reported a very instructive case of the kind.

Dr. Goodhart (*Pathological Society's Transactions*, vol. xxxiii) makes the interesting suggestion that ulcerative endocarditis is more frequently met with at periods in which scarlet fever, erysipelas, pyæmia, and diphtheria prevail. The Guy's Hospital records certainly seem to show that the cases appear in groups pretty close together, and at a time when the diseases mentioned are epidemic. In Montreal, we have had occasionally a "run" of cases together; but I have not noticed the connection referred to by Dr. Goodhart.

Pathology.—I approach a discussion of the pathology of malignant endocarditis with some trepidation, partly due to a sense of incompetency, and partly from a feeling that the time is scarcely ripe for a satisfactory presentation of the subject; and yet there are signs which make one

[1] Dr. Bristowe informs me that, in the case referred to, he is inclined to regard the intermittent pyrexia as dependent from the outset upon the endocarditis, and not associated with malaria.

hopeful; and it would not be rash to predict that the knowledge twenty-five years hence will be as much in advance of to-day as our information on the subject is of the time when Dr. Kirkes made his memorable investigations. A serious difficulty exists in the circumstance that we have not to deal with a single form of disease—an entity—but rather with a special manifestation in many affections; affections, too, the pathology of which is, in most instances, by no means clear. No one can doubt that the more severe cases of endocarditis present in a typical mode all the features of those diseases which we call infective, and believe to be caused by the absorption of some poison, the development of which in the blood and tissues profoundly disturbs, and finally annihilates, function.

Briefly stated, the theory of acute endocarditis which at present prevails, and the only one to which I shall refer, is, that it is in all its forms, an essentially mycotic process; the local and constitutional effects being produced by the growth on the valves, and the transference to distant parts of microbes, which vary in character with the disease in which it develops. This very attractive theory can be adjusted to meet every requirement of the case, though as yet lacking certain of those substantial data necessary for full acceptance, but which, having been furnished of late years in other diseases, we may reasonably hope will in time also be forthcoming for this.

Let us see, first, what has been done, and how far the facts at our disposal seem favourable to this view. The constant presence of micro-organisms seems undoubted; only, in the simple acute form, we need more careful observations with our improved methods. Some good observers have not been able to find them (Orth, *Lehrbuch der Speciellen Pathologischen Anatomie*, Lief. i, 1883); others declare them to be invariable constituents of the verrucose outgrowths (Klebs, *Archiv für Exper. Pathologie*, Band iv; Köster, Virchow's *Archiv*, Band lxxii). The careful application of such a satisfactory mode of staining as recommended by Gramm should readily determine this question. A study of the endocarditis of puerperal and traumatic pyæmia will be most likely to yield important information, as here the conditions are simpler, and the relation of the micro-organisms can more readily be determined. The cardiac complication in these cases is only part of a general process, excited by a local lesion, and is entirely secondary and subsidiary. Micrococci arranged in chaplets are constant constituents of the vegetations, and, in the case of puerperal fever, they have a close resemblance to those found in the peritoneal exudation. The well known observations of Koch, Ogston, and others have shown the relation of microbes to pyæmia; and the recent culture-experiments of Rosenbach ("Micro-organisms bei den Wund-Infections," *Krankheiten des Menschen*, Wiesbaden, 1884) go far towards demonstration for man what Koch had previously done in the case of the pyæmia of the mouse. In these cases, a study of the modes of growth of the micrococci of the endocarditis, and of the effects of inoculations, and a comparison of these with similar observations in the organisms of the original lesion, or of the metastatic foci, should yield results of great value in the interpretation of the phenomena of secondary endocarditis.

In rheumatic fever, we are still too far from any accurate knowledge of its intimate pathology to dwell on the possible connection of any organism peculiar to it, and the endocarditis common in its course. Klebs (*Archiv für Experiment. Pathologie*, Band ix) distinguishes the microbes occurring in rheumatic cases from those of the septic forms.

In pneumonia, micrococci undoubtedly abound in the exudation of the air-cells, and their mode of growth in gelatine is peculiar, but the numerous experiments on artificial production are not yet conclusive. The evidence is accumulating which places pneumonia among the infective disorders; and it certainly is a seductive view to take of its pathology to regard the local pulmonary lesion as excited by the growth of micrococci in the air-cells, and the various consecutive inflammations, the endo- and peri-carditis, the pleurisy, the meningitis, the membranous gastritis or colitis, as due to the penetration of the organisms to deeper parts, and their local development under conditions dependent on the state of the tissues. The processes are all of the character described as croupous, and have as common features the presence of micrococci in a coagulable exudation. We have still, however, to settle the identity of the organisms of the air-cells with those of the consecutive inflammations; but we may reasonably hope ere long to have some positive data from investigations in this disease, which, more than any other, offers favourable opportunities for the solution of these problems.

In diphtheria, as we have seen, mycotic endocarditis rarely occurs; and, in the few instances observed in association with scarlatina, variola, erysipelas, and other affections, we lack positive information with regard to the characters of the micro-organisms.

In the way of experimental investigation of the properties of the micrococci, not much has been done of a satisfactory nature. Heiberg (Virchow's *Archiv*, Band lvi) placed bits of vegetations from a puerperal case beneath the skin and in the peritoneal cavity of a rabbit without effect. Eberth (*Ibid.*, Band lvii), Birch-Hirschfeld (*Archiv der Heilkunde*, Band xvii), have produced panophthalmos in the rabbit by inoculating the cornea; and I was able to produce well marked mycotic keratitis in the same animals with fresh material from the valves of two cases. H. Young, of Manchester, inoculated rabbits with pus from an abscess in ulcerative endocarditis, and was able to detect micrococci in the blood.

No conclusive culture-experiments have yet been made. Grancher (*Journal de Médecine de Paris*, December 20th, 1884) has cultivated a microbe from the blood, taken during life with all necessary precautions, but apparently not in series, and no inoculations of animals were made. Cornil (*L'Abeille Médicale*, December 22nd, 1884) has made cultures on gelatine, but apparently no special results have been reached.

How do the micrococci reach the valves? In cases of puerperal and traumatic septicæmia, the external lesion is undoubtedly the source of infection which is conveyed through the venous system; and, in these cases, it will be remembered that the right heart is most often affected. In other instances, where the skin is unbroken, we must suppose them to gain access by the lungs or intestines, most probably the former; and, in these instances, the left heart is the chief seat of the mycosis. Whether they reach the valve with the general blood-current, as Klebs supposes, or through the coronary arteries, as Köster holds, cannot be considered settled; but, from the position of the early vegetations in a non-vascular region of the valves, and from the fact already referred to, that colonies of micrococci can be seen directly upon the endocardium, it seems probable that Klebs's view is the correct one. He suggests, in explanation of the fact that the lines of closure of the valves are the usual seat of the process, that the micrococci, circulating with the blood, are here closely pressed into the endothelium by the firm apposition of the flaps. Whether or not in any given case endocarditis will arise, depends greatly on the condition of the valve-tissue. In a case of pneumonia or other disease—such as pyæmia—in which we may suppose microbes circulating in the blood, the endothelium of normal valves may be able to resist their invasion, or, even if they do lodge and penetrate, the conditions may not be favourable for their growth; but, where an individual is debilitated, and the tissue-tone lowered, or if, as often seems the case, the valves be diseased, then the micrococci find a suitable nidus, and excite, by their growth, an endocarditis which may be of a malignant type. As Dr. Goodhart suggests (*loc. cit.*), patients with chronic sclerotic valves are walking mushroom-beds, in common times without spawn, but in periods of epidemics taking in germs by various channels, which fertilise in some cases into ulcerative endocarditis; in others, to suppurative processes. Certainly, on paper, so to speak, the view which I have thus imperfectly and hurriedly discussed seems plausible enough, and meets the requirements of the case fairly well; but let us, in conclusion, follow an important rule too much neglected, and get a definite outline for our ignorance. In the first place, we do not yet know, with sufficient accuracy, the frequency of the occurrence of microbes in simple endocarditis. Are they constantly present, or only in forms associated with special diseases? Secondly, we want full information of the various forms of micro-organisms occurring in secondary endocarditis, and of their relation to the microbes assumed to be the cause of the primary disease. And, thirdly, we are only at the threshold of inquiries relating to the culture of these organisms, to the macroscopic characters of their growth, and to the possible experimental production of endocarditis.

I cannot conclude without thanking my late colleagues at the Montreal General Hospital, by whose kindness I have had command, not only of the pathological, but also much of the clinical, material upon which these lectures were based; and lastly, sir, you will allow me to express my sincere regrets that my efforts have not been more worthy of such an intensely interesting subject, and of the distinguished audience which I have had the honour of addressing.

An industrial exhibition for the working classes of East London will be opened by the Princess Louise on May 4th. The exhibition is a philanthropic scheme, and loans of works of art and other objects of interest are invited as well as subscriptions to the prize fund. The secretary is Mr. A. McLagen, 505, Commercial Road East.

The third edition of Dr. W. H. Day's work on *Headaches* has been translated into the Russian language by Dr. J. J. Trusevitch, Surgeon to the Russian Imperial Navy.