BACTERIAL OR INFECTIVE ENDOCARDITIS

THE GIBSON LECTURES FOR 1930.

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(*Continued from p.* 265)

LECTURE II.

In my first lecture I sought briefly to set forth certain fundamental differences between rheumatic cardiac disease and infective endocarditis.

In the former, although the evidence points strongly towards the agency of streptococci, yet the infecting organisms and their manner of action cannot be said to be generally recognized; in the latter the various infectious agents which are involved are clearly demonstrable.

In the former, the characteristic—indeed almost specific—anatomical changes spread to endocardium and pericardium as they do elsewhere to synovial surfaces, from alterations arising in the tissues beneath; in the latter, the infection seems to come from the surface.

In the former, endocarditis is but one manifestation of a wide-spread general process; in the latter, excepting in peracute septicæmias in which the cardiac lesions are mere incidents in a rapidly fatal process, the foci of valvular infection are the essential seats of the disease.

The commoner ætiological agents in infective endocarditis were set forth, and the opinion was expressed that it might not be unprofitable to consider separately the anatomical and clinical pictures resulting from each individual infection.

Following a short summary of the manifestations of rheumatic heart disease, the characteristics of streptococcal endocarditis were considered. It was pointed out that the endocarditis dependent on infections with *β Hæmolytic streptococcus* was generally a mere incident in a fatal acute septicæmia the primary focus of which was usually apparent, while infections with the milder non-hæmolytic forms of streptococcus, often insidious in origin, were followed by the characteristic phenomena of subacute infective endocarditis, the various features of which were discussed.

To-day I shall consider our experience with endocarditis due to the other commoner infective agents.

Infections with the Bacillus of Pfeiffer.
Influenzal Endocarditis.

The picture of subacute vegetative endocarditis is not entirely limited to streptococcal infections. Like phenomena are occasionally seen in infections with *Gonococcus*, *Staphylococcus albus* and possibly, though rarely, with *Pneumococcus* or *Staphylococcus aureus*. Endocarditis caused by the bacillus of Pfeiffer[67, 68, 69, 70] results in a picture which is indistinguishable from that of subacute streptococcal endocarditis. Of this infection there were nine cases in our series, seven with necropsy.

In all excepting one terminal infection in typhoid fever, the syndrome was the same. In three the organisms were obtained repeatedly during life. In two there was no necropsy. In the fatal cases they were demonstrated in the lesions at necropsy.

The *anatomical changes* were identical with those in subacute streptococcal endocarditis. The exuberant vegetations were packed with the characteristic small Gram-negative bacilli. The *distribution of the lesions* was essentially the same. The left side of the heart was involved alone in four of seven cases, the right alone in one of seven, both sides in two. As illustrated in Chart VI., the mitral and aortic valves were most frequently affected, in five of seven cases (71·4 per cent.); the tricuspid next, two of seven (28·5 per cent.); the pulmonary but once. In five of the nine cases (Chart IX.) there was a history of rheumatic fever; in all (Chart V.), a history or evidence of pre-existing valvular disease. Once the lesions were seated on an area of congenital disease, pulmonary stenosis.

There was one instance of serofibrinous pericarditis.

Acute myocardial changes were observed but once, a small abscess; fibroid, evidently rheumatic changes, were found in four of five cases.

TABLE VII.

Endocarditis due to Bacillus of Pfeiffer. Age Incidence.

Decades . .	I.	II.	III.	IV.	V.	VI.	Total
Totals . .	0	1	4	2	1	1	9
Per cent. .	0	11·1	44·4	22·2	11·1	11·1	

The incidence according to *age* and *sex* was much as in streptococcal infection. The *portal of entry* was always obscure. In rather striking contrast to the streptococcal series

there was evidence of oral sepsis but twice among these nine cases; once, peridental suppuration; once, infected tonsils.

The course was notably chronic—more so than with *Streptococcus viridans* infection. The duration was apparently of more than six months in seven of nine cases; of over a year in three. In one instance, a case of apparently eleven months' duration in which *B. influenzæ* had been cultivated from the blood during life as well as at necropsy, *Staphylococcus aureus* was also obtained at necropsy from the vegetations. It was not demonstrable in smears and was regarded as a terminal invader.

The clinical phenomena, indistinguishable from those in subacute streptococcal infections, were, in general, milder and slower in their development. Petechiæ were noted in one-third; the spleen was palpable in two-thirds of the series. Mild periarticular pains were complained of in one-third; clubbing of the fingers were noted in 44·4 per cent. Albuminuria was universal, and red blood corpuscles were found in the urinary sediment in two-thirds of the series. Acute embolic glomerulonephritis, similar to that in streptococcal infection, was found in three of the seven cases with necropsy.

The anæmia was not so striking as in streptococcal endocarditis, and leucocytosis (Chart X.), when present, was less marked—indeed it was often absent. The average low and high counts were 5020 and 14,880.

The result, fatal in all of the series, was preceded by myocardial insufficiency, a circumstance which may be accounted for by the relative benignity of the infection, the extreme chronicity of the course, and the universality of preceding rheumatic heart disease.

Summary.—Our small series of endocarditides due to the bacillus of Pfeiffer, like those of other observers, pursued a relatively slow, chronic course indistinguishable from that of subacute endocarditis due to streptococci. While those instances which we have followed to an end appear to have been fatal, one must ask whether, in so relatively benign an infection, there may not be others from which recovery occurs.

Pneumococcal Endocarditis.

Next to *Streptococcus*, *Pneumococcus* (Chart I.) is generally recognized as the most frequent ætiological agent in infective endocarditis. There were two and forty cases in our series, eight and thirty after omitting four purely terminal infections

(12·41 per cent. of 306 cases). To the usual picture presented by endocarditis due to *Streptococcus*, pneumococcal endocarditis offers a sharp contrast.

The acute septicæmia so commonly demonstrable during a pneumonia is not, as a rule, accompanied by endocarditis, but when pneumococci nest on a cardiac valve, the symptoms are usually more or less characteristic—acute, stormy and, as a rule, rapidly fatal. The process is, almost invariably, an acute, ulcerative endocarditis, especially notable for the early and extensive destruction of tissue resulting in erosions of the valves with aneurysms, rupture or burrowing ulcers. If death have not already occurred as a result of the intoxication or the usual meningitis, these acute destructive changes may be manifest clinically by the appearance of valvular insufficiencies associated with sudden evidence of the increasing cardiac burden.

Biological classification of pneumococci.—In nine and thirty cases, including six mentioned in my former publication,[71] the biological grouping of the pneumococci was as follows:—Group I., 13; Group II., 12; Group III., 2; Group IV., 12.

Anatomical distribution of the lesions.—As with streptococcal infections, pneumococcal endocarditis affects, usually, the left side of the heart alone (81 per cent. of our series). The right side alone was affected in but 8·1 per cent. The involvement of the aortic valves (Chart IV.) was, however, more frequent (70 per cent.)* than that of the mitral (59+ per cent.), in contrast to the greater frequency of mitral involvement in streptococcal endocarditis. The relative frequency of involvement of tricuspid and pulmonary valves was similar to that in streptococcal endocarditis—tricuspid, 16·2 per cent.; pulmonary, 2·7 per cent.

Pre-existing valvular disease (Chart V.), the rule in streptococcal endocarditis, 70 per cent. of our series, was the exception in pneumococcal infections, but 37·5 per cent. of forty cases. *Pneumococcus*, then, infects normal valves with greater frequency than does *Streptococcus*. More striking yet was the rarity of mural endocarditis in the left auricle, which was observed in but four of thirty-seven cases (10·8 per cent.), in two of which, at least, there was no evidence of previous rheumatic involvement. There

* This is in agreement with the figures of Netter[72] and Preble,[73] and in conflict with the experience of Menetrier[74] and Locke,[75] who found more mitral involvement.

is, then, a sharp contrast between streptococcal and pneumococcal endocarditis, in the greater frequency in which the former is seated on foci of chronic rheumatic cardiac disease.

Syphilis.—In none of our instances of involvement of the aortic orifice was there evidence that there had been pre-existing syphilitic disease of the valves. In three cases in which syphilis of the aorta was apparent, the valves were not involved in the infective endocarditis.

Congenital malformations.—On the other hand, if one include a somewhat doubtful case already described,[76] there were two examples of affection of a bicuspid aortic orifice. In a third patient there was an anomaly of the *Septum membranosum*, which was unaffected by the acute process.

Acute pericarditis (Chart VII.), generally pyopericardium, was relatively frequent in pneumococcal endocarditis—nine of forty cases, 22·5 per cent. This is in contrast to its rarity in streptococcal endocarditis. It was purulent in six instances, fibrinous in three.

Acute myocarditis, though often not very extensive, was not infrequent—45+ per cent. of cases examined. In about half of these there were abscesses of the heart muscle.

Chronic fibroid changes were found in about 30 per cent., which is in contrast to their greater frequency in the streptococcal series, where a rheumatic history is commoner.

TABLE VIII.

Pneumococcal Endocarditis. Age Incidence.

Decades	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.	Totals.
Totals	2	0	8	6	14	7	4	0	1	42
Per cent.	4·76	0	19·04	14·28	33·33	16·66	9·51	0	2·38	

The *age incidence* (Chart II.) differs from that in rheumatic fever in that pneumococcal endocarditis appears to be a process prevalent rather later in life, one-half of the cases occurring in the fifth, sixth and seventh decades as against 30 per cent. of the streptococcal infections, where one-half occurred in the first three decades.

In our small series of forty-two pneumococcal endocarditides the malady was curiously commoner in men, 83·3 per cent., than in women, 16·6 per cent. Twenty-five, 59·5 per cent., of the series were negroes; seventeen, 40·5 per cent., were whites. These interesting figures are probably dependent on two circumstances: (1) the frequency and fatality of pulmonary infections in negroes,

and (2) the high percentage of necropsies in the series. The sentimental, religious and racial prejudices against necropsies common with many of our patients are, happily, lacking in the negro. Chart IX. shows the relatively small incidence of a history of antecedent rheumatism or chorea, 21·6 per cent. of thirty-seven cases as against 58·8 per cent. for the subacute streptococcal series.

The *portal of entry* was obvious in thirty-nine of forty-two cases, 92·8 per cent. In thirty-five, 83·3 per cent., it was clearly an acute pneumonia or bronchopneumonia. In three more it was respectively, empyema, post-operative peritonitis, septic arthritis. In three cases only, of a rather subacute character, was the portal of entry uncertain. Here the duration of the pneumococcæmia, although from the history apparently of weeks or months, was not altogether proven.

Peridental sepsis was commoner, 45·2 per cent., than in any other series save the streptococcal, but the majority of the patients were in the fifth decade of life or above.

Infection of tonsils or accessory sinuses was not very frequent—under 20 per cent.

The *manner of onset* is characteristic—in most instances a sudden rise of temperature and aggravation of the symptoms after the crisis or during the course of defervescence in pneumonia. The *course* is that of a rapidly fatal septicæmia with a high polymorphonuclear leucocytosis (Chart X.), the highest in our series, the average low count being 18,091; the average high, 30,138. Counts of under 8,000 were recorded in but seven of thirty-four cases, and counts of over 10,000 were observed in all but one of thirty-four instances in which records were made. The *fever* is high and generally continued, 77 per cent.; occasionally, 23 per cent., with intermissions. But once was the temperature moderate, in an instance pursuing a subacute course. Chilliness or actual chills are common, 43 per cent. of our series. The spleen, so often palpable in subacute streptococcal endocarditis, was felt in but 10 per cent. of our cases. *Petechiæ* were uncommon, owing, possibly, to the large proportion of negroes. Altogether, however, *embolic phenomena* were observed in more than half our series; cerebral embolism in a little over 10 per cent. *Clubbing of the fingers* was noted but twice. Focal areas of suppuration were usually found in those patients coming to necropsy, 72·5 per cent., which is in rather sharp contrast to the picture in subacute streptococcal endocarditis, 28·57 per cent.

Arthritis, generally purulent, and limited usually to a single large joint, was not uncommon.

Albuminuria was practically universal, but red blood corpuscles were found in the urinary sediment rather infrequently—in only about 14 per cent. of the cases. There was an acute nephritis in ten of thirty-seven instances, 27 per cent.

Pleurisy, apart from its regular association with pneumonia, and usually purulent, was observed in a quarter of our fatal cases.

Pneumococcal endocarditis is almost invariably a rapidly fatal process. The *duration* was of under four weeks in 88 per cent. of our series, of under two months (Chart IV.) in 95·2 per cent. But twice was the course apparently subacute. In both of these instances the estimate of the duration was based largely on the history, of which I am inclined to doubt the accuracy.

I know of no clearly proven instance of recovery, but there are few rules without exception.

The terminal event in pneumococcal endocarditis, a distinctive feature, was generally a meningitis—twenty-two, 55·0 per cent. of our series.

In about one-third of the series death was due to sepsis. Among these there were four empyemas; in one an aneurysm of a sinus of Valsalva ruptured into the pericardium. In four the death was cardiac, in two depending immediately on the destructive action of the focal lesions on valves or chordæ tendineæ. In five cases the death was due directly to the acute cardiovascular changes.

Summary.—Pneumococcal endocarditis is, then, an acute and generally a rapidly fatal process occurring at all ages, but prevailing in middle and later adult life. In our series it was strikingly common among negroes. The well-defined onset usually follows an acute pneumonia. It involves, by preference, the valves of the left side of the heart and, notably, the aortic valves.

Pneumococcus affects previously healthy endocardium more frequently than does *Streptococcus* or *Bacillus influenzæ* (Pfeiffer). It shows no apparent special tendency to involve the left auricle.

The lesions are acute, ulcerative and rapidly destructive. Embolic phenomena are less frequent than in subacute endocarditis only probably because of the acuity of the malady.

The termination, almost always inside of four weeks from the first symptoms, is generally hastened by meningitis.

Gonococcal Endocarditis.

Endocarditis due to *Gonococcus* (Chart I.) occurred in thirty-two instances or 10·13 per cent. of our entire series.* This rather high percentage is due probably to two circumstances: first a keen interest in this special subject since our initial success in making a definite diagnosis intra vitam; [77,78] and secondly, because of the relatively large proportion of negroes among our patients. Venereal disease is very common among negroes in Baltimore.

Among these thirty-two cases there were eleven in which the diagnosis, made tentatively during life, was confirmed only at necropsy by the bacterioscopic demonstration of the characteristic organism in the lesions after negative cultures intra vitam or post mortem. These, save several in the influenzal group, are the only cases which have been admitted to our series of 306 without the demonstration by positive cultures of the organism intra vitam or post mortem. There were several further instances without necropsy which I feel sure were examples of gonorrhœal endocarditis. In nearly every one of these the diagnosis of gonorrhœal endocarditis was made *intra vitam* from the history, the characteristic symptoms and the negative blood cultures. In the absence of the actual demonstration of the organisms they were, however, excluded from the series. In view of this I am inclined to think that our figures do not exaggerate the frequency of gonorrhœal endocarditis—rather the contrary.

A word as to the cultivation of the organism. In the first case in which *Gonococcus* was cultivated from the blood intra vitam,[79] the colonies developed on plain agar plates and could not be transferred. The organisms were later found at necropsy. In the second instance and in most of our earlier cases gonococci were cultivated on plates consisting of about one-third blood and two-thirds agar. Later, various special media were used. At present our procedure is as previously described (p. 265) save that the tubes and plates are kept in an atmosphere of 10 per cent. CO_2.

The *anatomical lesions* in gonococcal, like those of pneumococcal, endocarditis are usually ulcerative and destructive, leading to grave deformities of the valves or to burrowing

* Case C. 51, where *Gonococcus* was overgrown by *Streptococcus viridans*, is classed in the whole series as an instance of viridans infection.

aneurysm-producing ulcers. In more chronic cases the large mulberry-like masses of vegetations may be remarkable.

From the circumstance, however, that the process is usually somewhat less acute, the clinical evidence of the development and progression of the valvular lesions is more often recognizable. Again, in contradistinction to pneumococcal endocarditis, endocarditis of Neisserian origin pursues, occasionally, a characteristic subacute course.

Distribution of the lesions.—In our seven and twenty cases with necropsy the left side of the heart alone was involved in 62·5 per cent. of the series; the right side in 22·2 per cent.; both sides in 22·2 per cent.

As in pneumococcal endocarditis (Chart VI.), the aortic valve was involved with greatest frequency—62·9 per cent. The involvement of the mitral was curiously infrequent, but 25·1 per cent., while the tricuspid and pulmonary valves each were involved in 22·2 per cent. of the series.

Seven and twenty cases with necropsy is much too small a series from which to draw conclusions; but 'tis significant that among the five instances without necropsy, two showed clinically an apparent involvement of the pulmonary valve. In one of these—a remarkable instance with recovery—there could be no doubt of the nature of the lesion. Pulmonary involvement seems to be rather characteristic of gonococcal endocarditis. This impression is strengthened by an interesting communication which I received but a few days ago from Professor Warthin of Ann Arbor. In nine subjects of gonococcal endocarditis which have come to necropsy in his laboratory, the aortic valves were involved in all; the pulmonary, in all but one.

As in pneumococcal infections (Chart V.), and in contrast to that which is true of streptococcal endocarditis, there is little evidence that chronic valvular disease predisposes to the infection. In but four (14·8 per cent.) of the twenty-seven cases coming to necropsy was there a history or evidence of pre-existing cardiac disease. These figures correspond exactly (Chart IX.) with the proportion of patients who gave a history of antecedent rheumatic fever or chorea. But even these figures are perhaps somewhat above those representing the normal prevalence of rheumatism.*

* That oral sepsis plays a part in the ætiology of streptococcal endocarditis is supported by its relative infrequency in the gonococcal series (peridental sepsis, 34·3 per cent.; tonsillar and sinus infections, 25 per cent.) as in pneumococcal endocarditis.

More striking yet is the circumstance that in but one instance was there involvement of the left auricular endocardium. Four times, however, the aortic intima was involved, twice alone. Once there was a mycotic aneurysm.[80]

Pericarditis (Chart VII.), as with pneumococcal infections, is commoner than in streptococcal disease, occurring in six, or 20 per cent., of thirty cases; in two of these it was purulent.

Myocardial changes, abscesses or small foci of interstitial infiltration, were found in about 40 per cent. of the series where satisfactory examination of the heart muscle was carried out.

Chronic fibroid changes were rare, as one might expect, in a group of individuals few of whom had had rheumatism and most of whom were under thirty years of age.

In the majority of those patients coming to necropsy focal suppurative processes were evident.

TABLE IX.

Gonorrhœal Endocarditis. Age Incidence.

Decades	I.	II.	III.	IV.	V.	VI.	Total.
Totals	1	4	22	3	1	1	32
Per cent.	3·12	12·5	68·75	9·37	3·12	3·12	99·99

Gonococcal endocarditis (Chart II.) stands out interestingly and sharply as a disease of the second and third decades of life, over 81 per cent. of our series. Over 68 per cent. of the patients were in the third decade; 90·6 per cent. in the second, third and fourth. This is as one might have expected. There were more men, 71·8 per cent., than women, 28·1 per cent.; negroes (Chart VIII.), 56·25 per cent., than whites, 43·75 per cent. The large proportion of negroes may be explained in part by the frequency of venereal disease among negroes in Baltimore, in part by the frequency of necropsies in the series.

The *portal of entry* must, in most instances, have been gonorrhœal urethritis, but it was by no means easy to determine the presence of gonorrhœa at the time the patient came under observation. Moreover, in many patients it was not easy to ascertain the relation in time between the onset of the endocarditis and the onset of the gonorrhœal infection. In white patients who gave a clear history this was not difficult; in negroes in whom the history is usually unreliable, it was very hard. In twelve of thirty-two cases it was reasonably clear that the cardiac complication began within five weeks after the onset

of the infection. In only three, 23 per cent., of those cases in which the times of onset of the gonorrhœa and the endocarditis were both clear, was the cardiac disease preceded by arthritis or other obvious complication of the urethritis. In five cases, 15·6 per cent., the infection followed puerperal complications. The *onset* was usually acute and associated, generally, with headache, fatigue, sudden high fever, sweating, prostration—signs of a grave general intoxication. Not infrequently there was an initial chill as in other complications of gonorrhœa.

The *course* was that of a severe acute or subacute septicæmia in which evidences of cardiac disease usually appeared under observation. The more acute instances ran a course not unlike that of pneumococcal endocarditis, ten, or over 30 per cent. of our series, passing to a fatal issue in less than a month. But nearly 70 per cent. were of longer duration. Because of this somewhat longer duration and because of the circumstance that pre-existing valvular disease is unusual, gonococcal endocarditis is rather distinguished for the frequency with which evidence of the cardiac disease develops under observation.

The *fever* is usually rather high, above 102° in 84·3 per cent. of our series, generally, 75·7 per cent. of the cases in which it could be properly followed, swinging, intermittent or remittent, and often associated with chills, 65·6 per cent. *Petechiæ*, as might be expected from the anatomical character of the lesions and the occasional subacute course, are more frequent, 31·2 per cent., than in the very acute infections such as pneumococcal endocarditis. They were observed in half of our white patients. The *spleen*, again, was more often palpable—in over 20 per cent. (21·8 per cent.).

Embolic phenomena exclusive of petechiæ were common, 68·7 per cent.—nearly as common as in subacute streptococcal infections. *Cerebral embolism* occurred in five, 15·6 per cent. of the series. *Clubbed fingers* were noted but three times in thirty-two cases. *Albuminuria* was almost universal, and acute nephritis was found in 55·5 per cent. of those coming to necropsy.

Anæmia in gonorrhœal infections is often profound and rapid in its development. There is generally well-marked polymorphonuclear leucocytosis (Chart X.), averaging in our series from 17,515 to 25,915. The single instance in which a leucocytosis was not recorded was not observed in the medical service; only one examination of the blood was made.

The issue is usually fatal, the result of the general sepsis with its accompanying anæmia and nephritis, but myocardial insufficiency (56·2 per cent. of our series) often plays a considerable part. Terminal pneumonia is not uncommon. In one of Warthin's patients death followed occlusion of the aortic orifice by a mass of large vegetations.

Happily, however, gonococcal endocarditis is not invariably fatal. Incontestable recoveries have been reported by a number of observers. [81, 82, 83, 84, 85]

Possible recoveries are recorded by G(H)urvich.[86]

I have seen two recoveries from gonococcal septicæmia of seven weeks' or more duration. In one instance [87] the existence of an endocarditis was unproven.

The other I had the good fortune to see two years ago in consultation with my friend Perry of Washington.* [88] This was a clean-cut and characteristic example of ulcerative endocarditis of the pulmonary valves. After an illness of nearly four months, recovery was complete, with, however, permanent pulmonic insufficiency.

Summary.—Gonococcal endocarditis is usually an acute destructive process, generally attacking previously unaffected valves. As in pneumococcal infections, the aortic valve is involved with greatest frequency, the mitral probably next. Gonococci seem to affect the right side of the heart more frequently than streptococci and, especially, the pulmonary curtains.

* The patient, first seen by Dr Perry on 17.2.28, was a young man of 32, in good general condition, who since November 1927 had had a urethral discharge not recognized as gonorrhœa until this occasion, when positive smears were found. He had been feverish for about a week. There were no apparent complications. The physical examination of the heart was negative. A week later he had a sharp chill, the temperature rising to 105·6°. On 29.2.28 a soft systolic murmur was audible in the pulmonary area. There was a slight leucocytosis. Three days later a diastolic murmur became audible at the pulmonary area. From that time the temperature was irregular, swinging and associated with sharp chills. On 7.3.28 a pure growth of gonococci, 13 colonies to the c.c., was obtained by Dr Hunter from the blood immediately after a severe chill. When first I saw the patient, on 20.3.28, there was a soft to-and-fro systolic and diastolic murmur heard in the pulmonary area and downward towards the xiphoid process. The pulse pressure was not increased. Aortic and carotid sounds were clear. There was nothing to suggest an aortic involvement. Ten days later I saw the patient again. He was having high, intermittent fever, and had had a pulmonary infarct with resultant enfeebled respiration and friction at the left base. There was a slight systolic and a loud superficial

The infection is somewhat less acute, as a rule, than the pneumococcal, and the duration is often of several months—sometimes as much as eight or nine. Where the destructive process is not followed rapidly by a fatal issue, the vegetations may be exuberant, forming large, yellow, botyroid masses. The intoxication is usually profound; the fever, high, generally intermittent or remittent, often associated with chills. Anæmia is an early and often striking symptom; there is a pronounced leucocytosis. Because of the destructive character of the lesions, the relative frequency of a subacute course and the infrequency with which it affects the subject of previous chronic valvular disease, and because of the circumstance that its onset is usually sudden in one not previously the subject of a grave general infection, it is, probably, that form of infective endocarditis in which the actual development of the valvular lesion *intra vitam* is recognized with the greatest frequency.

The issue is generally fatal but recovery may occur.

Endocarditis due to Staphylococci. *Staphylococcus aureus.*

Staphylococcus aureus, the infecting organism in thirty-two of our series (Chart I.), is generally regarded as the commonest ætiological agent in bacterial endocarditis after *Streptococcus* and *Pneumococcus*.

Staphylococcus aureus appears to be pre-eminently a terminal invader, even in the case of endocarditis due primarily to other

diastolic murmur audible in the pulmonary area and over the right ventricle; aortic sounds, clear. Blood pressure, 103/63.

The patient was treated by repeated small blood transfusions and, on one occasion, by a transfusion from a patient convalescent from gonorrhœal arthritis. The anæmia gradually increased. There were several evident pulmonary embolisms with pain, pleural friction, signs of solidification in the lung and hæmoptysis. Throughout his course, however, the patient's appetite remained good and there was apparently no marked renal involvement. There were two treatments with an autogenous vaccine. On 22.4.28 I saw the patient again. He had just had another pulmonary embolism. Despite his attack he looked better, having had five days of normal temperature. On 29.4.28 there was again a pulmonary embolism, which, however, happily proved to be the last. The temperature fell to normal and on 30.5.28 he was discharged from the hospital in good condition, excepting a slight dullness over the lower chest in the region of his last infarction and a well-marked diastolic murmur in the pulmonary area. The patient has remained perfectly well ever since. He is now living in the Far West. In a letter, several months ago, he assured me that he was feeling perfectly well.

organisms. It was found as a terminal invader under such circumstances in five of our thirty-two cases, as well as in one more which was not included in the series. Commonly the endocarditis is but an incident in an acute pyæmia. Occasionally, however, it leads a more subacute course. The lesions are not dissimilar to those in pneumococcal and gonococcal endocarditis, but, apparently, not so acutely destructive as in the former. As the duration of the infection was short, under a month (Charts III. and IV.) in 87·5 per cent. of the series, the fresh, soft, fibrinous vegetations were sometimes rather small. In cases of longer duration the vegetations were larger; the ulcerative lesions, graver. There seems to be nothing especially distinctive about the anatomical picture save for the great frequency of multiple, small, disseminated abscesses—pyæmia.

Anatomical distribution of the lesions.—As in all forms of bacterial endocarditis, the left side of the heart alone was involved with greatest frequency (66·6 per cent.), but as in gonococcal endocarditis, the right side was more commonly affected than in streptococcal or pneumococcal disease (right side alone, 22·2 per cent.; both sides, 11·1 per cent.). The mitral valve (Chart VI.) was involved more frequently (45·7 per cent.) than the aortic (34·2 per cent.), but the tricuspid was more commonly affected than in other infections (31·4 per cent.); the pulmonary, rarely (2·8 per cent.).

While (Chart V.) in 43 per cent. there was clinical or pathological evidence of pre-existing valvular disease, there was a history (Chart IX.) of antecedent rheumatism or chorea in only one-quarter—less that half as often as in streptococcal disease.

A predilection of the infection for foci the seat of antecedent rheumatic change, so characteristic of streptococcal infections, was not notable. The left auricle was never involved.

In none of the instances with aortic lesions was there evidence of syphilis. Definite congenital abnormalities were not observed, although in one ease a dense fibrous nodule, regarded by the pathologist as evidence of a healed endocarditis uniting contiguous aortic curtains, resulted in a deformity which has been included in my summary as a possible congenital change.

As one might expect, suppurative metastases are frequent, nearly 80 per cent. of the series. There were abscesses of the

heart muscle microscopically in nearly 74 per cent.; chronic fibroid changes in a little over 20 per cent. Pericarditis (Chart VII.), always purulent, was not uncommon (23·3 per cent.).

TABLE X.

Staphylococcus Aureus. Age Incidence.

Decades	I.	II.	III.	IV.	V.	VI.	VII.	Total.
Totals	4	7	6	6	2	6	1	32
Per cent.	12·5	21·8	18·75	18·75	6·25	18·75	3·12	

Age incidence.—Aureus infections, as shown in Chart II., occurred at all ages. Although prevailing in the first four decades, there were yet seven instances in patients between 50 and 80. The sexes were equally represented.

Twenty-two (Chart VIII.), 68·7 per cent., were white; ten, 31·3 per cent., were negroes.

The *portal of entry*, as in most of the acute infections, was usually evident (67·7 per cent.), generally some acute septic process—osteomyelitis, epiphysitis, puerperal sepsis, carbuncle, etc. In one instance the infection followed directly the extraction of teeth for apical abscesses. In general, however, peridental infection was not remarkably frequent (25·8 per cent.), and infected tonsils or sinuses, so common in the streptococcal series, were not often noted (12·5 per cent.). In all of these cases the origin of the endocarditis was clearly from another source.

The *manner of onset* was usually rather sudden (64·5 per cent.), with high fever, headache, tachycardia, prostration, and the evidences of a grave general infection. The endocarditis was rarely recognizable. In eleven cases, however (35·8 per cent.), the onset was indefinite and gradual. The *fever* was usually high and continued (74 per cent.). *Chills* were uncommon—less than one-third of the series. *Petechiæ* were unusual (13·8 per cent.). As in most peracute infections, the *spleen* was generally impalpable (felt in only 12·5 per cent.). *Embolic phenomena* were observed, for the most part, in the form of disseminated abscesses, usually microscopical. Mackenzie,[89] in the description of a remarkable case of *Staphylococcus albus* endocarditis, mentions petechiæ with tiny pustular centres, "pustules with a hæmorrhagic halo," which he regards as pathognomonic of staphylococcus sepsis. *Cerebral embolism* occurred in three (10 per cent.) of thirty cases. In but four cases were there joint symptoms—twice a suppurative arthritis,

twice an arthralgia complained of a day or two before death. *Clubbed fingers* were not observed. *Albuminuria* was usually present but red corpuscles were noted in the sediment but four times. An *acute nephritis* was observed in 30·7 per cent. of the series.

Anæmia was generally moderate because of the rapidity of the course of the disease, but in several cases of longer duration it was striking, presenting the ordinary appearances of a secondary anæmia with (Chart X.) a well-marked polymorphonuclear leucocytosis. In only two instances—once in a patient in the hospital but twenty-four hours, just before death, and once in an old rheumatic heart disease with a terminal infection—was leucocytosis absent.

In one case there was a rapidly developing aplastic anæmia with a fall in the polymorphonuclear count from 80 to 40·6 per cent. in a week, the leucocytes rising from 16,400 to 42,000 per c.mm., the hæmoglobin falling from 50 to 28 per cent., and the red blood corpuscles from 2,432,000 to 1,648,000. The whole illness—the patient was the subject of an old pulmonary tuberculosis—lasted but a little over two weeks.

Duration.—Aureus endocarditis ran its course, usually within a month, and in our series was always fatal. I have seen but one possible recovery.[90] Although in four of our series the duration was of over a month—once from five to six months—staphylococci were not obtained from the circulating blood earlier than twelve days before death, and the estimate of the duration was based upon the history. However, from analogy and the observations of others[91] I am inclined to believe that, though rarely, subacute aureus endocarditis may occur. In several instances staphylococci were found at necropsy in connexion with other organisms, gonococci or streptococci, which from the history, as well as from the result of previous cultures, were clearly the exciting agents of the infection.

Death is almost invariably the result of the general sepsis, in which myocardial insufficiency may play a part.

Summary.—Endocarditis due to *Staphylococcus aureus* is usually the accompaniment of a general sepsis associated with some focal infection such as osteomyelitis, carbuncle or puerperal sepsis. In the rapidly fatal course the cardiac involvement is often unrecognized during life, and evident at necropsy as a fresh vegetative or ulcerative lesion commonest on mitral or

aortic valves, but not infrequently on the valves of the right side, especially the tricuspid. There is little evidence to show that pre-existing rheumatic or syphilitic heart disease plays an important part in predisposing to aureus endocarditis. There is nothing notably characteristic in the manifestations of these acute infections, which occur at any period of life, run their course, usually, with high, continued fever, the special symptoms dependent on the main seat of disease, and generally terminate fatally within a few days or weeks. In cases which last several weeks, embolic phenomena and nephritis are common. Here the changes in the infected valves may reveal themselves by the appearance of previously unnoticed insufficiencies, as in pneumococcal, gonococcal and streptococcal infections. *Staphylococcus aureus*, though rarely, may give rise to subacute endocarditis.

The distinctive feature of the malady is its frequent association with multiple foci of suppuration—pyæmia. The features of staphylococcal endocarditis seem to be:—(1) the relative frequency of tricuspid involvement; (2) the acuity of its course; (3) its association with a general pyæmia.

Endocarditis due to *Staphylococcus albus*.

Endocarditis due to *Staphylococcus albus* is an occasional phenomenon. We have seen six cases, 1·96 per cent. of our series (Chart I.); 1·3 per cent. of the combined series of 538 cases. So commonly are "skin cocci" found in cultures that only instances with regard to which there can be little doubt have been accepted in the series here considered. As to but one of these, a subject dead of typhoid fever where the organisms were obtained in smears and in pure culture from an early fibrinous vegetation on a heart value, can there be any doubt as to the relation of *Staphylococcus albus* to the lesions. The other cases are unquestionable.

Twice the *course* was rapid (Charts III. and IV.), of from two to three weeks' duration; thrice it was subacute, lasting from two to four months; in the sixth instance the infection was terminal.

The lesions were rather destructive and, in cases of longer duration, large and polypoid. Once there was perforation of the tricuspid valve within two weeks of the onset. The left side of the heart was affected more commonly than the right, 66·6 per cent., but (Chart VI.), as in aureus infections, the

tricuspid was commonly involved. Mitral, aortic and tricuspid valves were affected with equal frequency, 33·3 per cent.

In none of the six cases was there history or evidence of rheumatic heart disease; in none was there mural involvement of the left auricle.

The aortic valves, in both cases in which they were affected, were the seat of old luetic changes. In none of the series was there evidence of congenital valvular disease. Mackenzie,[92] however, reports an interesting example of *Staphylococcus albus* endocarditis of the aortic orifice and at the seat of coarctation in an instance of congenital coarctation of the aorta.

Myocardial changes were observed but once—an infected infarct.

Pericarditis did not occur in the series.

Age incidence.—Two of the six patients were in the third decade of life; one each, in the succeeding four decades. Five were men; one was a woman.

The *portal of entry* was apparent in four of six cases—an old pulmonary tuberculosis; an encapsulated empyema; a paronychia; a prostatitis with catheterization. In another instance the lesion was found at necropsy in a case of typhoid fever with ulceration and hæmorrhages.

The *onset* was usually rather acute with the phenomena of a severe general infection. In four of the cases there were chills. The *fever* was irregular and intermittent in three instances; continued and high, in three. The spleen was not felt. *Petechiæ* were observed in three cases. *Embolic phenomena* were generally evident; once there was an hemiplegia. A mild arthritis was noted twice.

Albuminuria was universal; red blood corpuscles were found in the urinary sediment in four of the six instances; pyelonephritis occurred in four cases.

In the instances of longer duration there was a rather well-marked secondary *anæmia* with a pronounced polymorphonuclear leucocytosis (Chart X.). But once was a leucocytosis entirely absent—the instance of typhoid fever. While individual leucocyte counts ranged from 7000 to 44,700, the average low and high figures were 15,546 and 22,283.

In the four cases in which *Staphylococcus albus* was obtained from the circulating blood as well as at necropsy, the first positive cultures were recorded twenty, eight, seven and four days before death respectively.

On the whole, the picture was that of a subacute endocarditis of a relatively rapid course terminating as the result of general sepsis, often with pneumonia or myocardial insufficiency which, in one of our series, followed an infected infarct of the heart. In other words the course, though sometimes malignant, was that of a somewhat attenuated aureus infection.

The important point in connection with this small series is that it affords positive evidence, in common with the relatively few cases recorded in literature, that *Staphylococcus albus* may give rise to characteristic acute and, sometimes, subacute endocarditis.

Endocarditis due to *Bacillus pyocyaneus*.

The single instance of endocarditis due to infection with *B. pyocyaneus* occurred in the course of a remarkable epidemic of pyocyaneus disease with intestinal manifestations. The lesions were those of a rather acute vegetative endocarditis. The patient, a woman of 42 who died after an illness of three or four weeks presenting the features of an acute dysenteric colitis, was found, at necropsy, to be the subject of an amazing combination of maladies. There was a chronic pelvic cellulitis and an ovarian abscess, a recto-vaginal fistula, extensive ulceration of large and small intestines with perforation and acute peritonitis. There was an old pulmonary tuberculosis, acute and chronic bronchitis, bronchiectases and fibrino-purulent pleurisy. There was a double hydronephrosis with amyloid change and, as if this were not enough, the unfortunate woman was the subject of a cancer of the stomach.

On the posterior leaflet of a mitral valve were a few minute vegetations and, on the free edge of the anterior leaflet, a clump of larger, fresh, fibrinous masses. The mitral vegetations, peritoneum, intestinal ulcers and ovarian abscess yielded pure growths of *B. pyocyaneus*. From the spleen and kidney *B. coli* was recovered. Bacterioscopically, in the vegetations both short, thick and long, slender bacilli were seen. Lenhartz,[93] in his article on septic disease, mentions *B. pyocyaneus* as an occasional cause of endocarditis.

Endocarditis due to *B. anthracis*.

The instance of anthrax infection[94] occurred in a man of 59 who had been handling hides. The endocarditis, small, fresh lesions along the free edge of mitral and aortic cusps,

was unrecognized *intra vitam.* The case was carefully studied. Cultures *intra vitam* and from the vegetations, blood and organs post mortem were pure.

Endocarditis due to *B. mucosus capulatus.*

The one example of endocarditis due to infection with Friedländer's bacillus was a typical subacute endocarditis of three months' duration, with involvement of the tricuspid valve, frequent pulmonary embolisms and a terminal empyema.*

Among many other agents which may cause infective endocarditis, one may mention *Meningococcus*,[95, 96] *B. abortus*,[97, 98] which may, apparently, give rise to a subacute endocarditis, *B. coli*—with regard to the primary infectivity of which I feel somewhat doubtful—*B. typhosus* and others.

Differential Diagnosis.

Endocarditis in acute malignant septicæmias due to *β Hæmolytic streptococcus*, such as those associated with an ascending lymphangitis following a wound or a puerperal infection or an osteomyelitis or an erysipelas, or in like staphylococcal infections, or in a pneumococcal septicæmia which passes rapidly into a meningitis, can, generally, only be surmised.

In pneumonia, however, where, during apparent convalescence, there is a sudden sharp rise of temperature with tachycardia and the reappearance or aggravation of the septicæmia, one should always suspect a cardiac complication.

The same is true in gonococcal infections, where a sudden

* The patient was a man of 32. There was no history of previous cardiac disease. The portal of entry was obscure and the onset sudden, with pain in the left chest and chills, symptoms rather suggesting that he may have had a pulmonary infarction. This was followed by intermittent and remittent fever (97° to 102°), lassitude, anorexia, dyspnœa, cough and, eventually, œdema of the extremities. Entering the hospital three weeks before death, the heart was found to be enlarged transversely. There was auricular fibrillation. There was a systolic murmur, loudest over the lower sternum, and, on one occasion, a murmur was described in diastole. There was no accentuation of the second pulmonic sound. There was a terminal empyema. After death, which occurred at the end of an illness of three months' duration, subacute fibrinous vegetations were found on the free edge of a congenitally malformed tricuspid valve with extension to one of the chordæ tendineæ. Cultures from the circulating blood thirteen days before death were negative. On two occasions later, three days and one day, respectively, before death, cultures revealed pure growths of Friedländer's bacillus. At necropsy, unfortunately, cultures were not taken.

exacerbation of fever occurs without other apparent complication. And in both pneumococcal and gonococcal infections, owing to the usual absence of previous valvular disease, the fresh endocarditis soon makes itself apparent, if the course be not too acute, by the modification of the heart sounds.

In endocarditis of a more subacute character the condition is usually recognized or suspected by the careful observer. He who has an opportunity properly to study his patients is rarely surprised by the discovery of an infective endocarditis at necropsy.

Streptococcal endocarditis affects, usually, foci the seat of chronic rheumatic affection, and it is precisely with rheumatic heart disease that streptococcal endocarditis is often confused.

Rheumatism is protean in its manifestations. Arthritis may be lacking. The fever and sometimes the leucocytosis may be slight. In both rheumatism and streptococcal endocarditis the onset may be rather indefinite and insidious, the fever moderate, irregular or hectic, the leucocytosis slight. In streptococcal endocarditis, however, the fatigue and prostration of the patient is often out of proportion to his fever and general manifestations. A peculiar grey, *café-au-lait* complexion, enlargement of the spleen, anorexia, gastro-intestinal symptoms, anæmia, especially splenic enlargement, are important and suggestive symptoms. Embolism, especially Osler's phenomena in the extremities, in a patient in whom the signs of general cardiac involvement are not sufficient to justify the expectation of intracardiac thrombi, is a very important sign. The repeated culture from the circulation of non-hæmolytic streptococci in any appreciable numbers, especially if there be no other obvious focus from which they might come, is usually enough to confirm the diagnosis.

On the other hand occasional growths of like streptococci may be obtained in rheumatism and, in patients under twenty years of age, one must realize that it is rash to make a positive diagnosis on blood cultures alone. The frequency of embolic phenomena in myocardial insufficiency with auricular fibrillation should be remembered, but auricular fibrillation, as has been pointed out, is curiously infrequent in subacute streptococcal endocarditis. In chronic rheumatic endocarditis, however, in the absence of auricular fibrillation, I have seen extensive thrombi on the auricular wall, associated with multiple embolisms, and the frequency of embolic phenomena in occlusion of the terminal

branches of the coronaries and resultant mural thrombi in the left ventricle is familiar.

In doubtful cases in the young the appearance of a sero-fibrinous pericarditis is suggestive evidence of rheumatism. Its infrequency in subacute streptococcal endocarditis has been pointed out.

This is not the place to enter into an elaborate discussion of the differential diagnosis of subacute streptococcal endocarditis. From subacute endocarditis due to the bacillus of Pfeiffer, *Gonococcus*, *Staphylococcus* or the other less frequent ætiological agents, it can be distinguished only by the cultivation of the organisms from the blood. In the early stages of the observation of a suspected case, one hunts always for hidden foci of infection in all parts of the body. Cholecystitis, pyelitis, cystitis, peridental or sinus infections, abscesses in various parts of the body may, of course, give rise to like irregular, intermittent fever with the signs of a latent infection. Hepatic abscess, especially amœbic abscesses of the liver, in an individual who, by chance, has an old rheumatic valvular disease of the heart may be very confusing. Progressive cardiac changes, persistent cultivation of the exciting agent from the blood, and embolic phenomena alone make the diagnosis probable.

In a patient with afebrile gonorrhœa, sudden chills and intermittent fever without other obvious complication should always suggest the possibility of cardiac involvement. As such patients are rarely the victims of chronic heart disease, time confirms or disproves one's suspicions. In hospital patients in whom a proper history is not obtainable, an infective endocarditis in which confirming blood cultures are not obtained on repeated effort is always suggestive of a gonococcal infection. *Gonococcus* is notably difficult to cultivate from the circulation, and in a surprisingly large proportion of such cases gonococci are found in the valvular vegetations. An infective endocarditis in an individual between 18 and 30, appearing under observation, with characteristic manifestations and negative blood cultures, especially if care have been taken in the bacteriological methods, should always suggest a gonococcal endocarditis.

Prognosis.

The study of this series of cases suggests, I think, that there is a distinct individuality, pathologically and clinically, in the phenomena resulting from endocarditis dependent on different infectious agents.

There are also differences from a prognostic standpoint. It is hard to reach a definite conclusion as to the prognosis in the more acute and malignant infections, where endocarditis is but an incident unrecognizable clinically. Recovery is occasional even in acute septicæmias of the utmost apparent gravity. Who can say in how many of these there may have been an early endocarditis?

Recovery from acute pneumococcal or staphylococcal endocarditis I have never recognized.

On the other hand the prognosis in gonococcal endocarditis, even with grave symptoms, is not necessarily fatal.

The gravity of the prognosis in subacute endocarditis is well known. This seems to depend mainly on the character and seat of the lesion—unvascularized thrombi which protect the culture from the action of body fluids, at a seat where they are inaccessible to surgical approach and cannot be immobilized. The organisms themselves are relatively benign and easily disposed of when once they are in the blood; it is the nest which must be reached.

Nature, through vascularization and organization, sometimes does the work. Clinically, we are relatively helpless.

Treatment.

In acute streptococcal infections the apparently good results which have been obtained from sera elaborated against certain strains such as those commonly associated with scarlet fever and erysipelas give reason to hope that the future may hold something in store. In infections with *Meningococcus* antisera may be tried. The same may be said of infections with *Pneumococcus I.*—but by the time an endocarditis has set in the outlook is usually hopeless. In gonococcal infections transfusions may be tried with the blood of one who has recently recovered from a febrile complication of gonorrhœa—as in Perry's case—if such a blood be available.

The essentials of treatment of any infective endocarditis, acute or chronic, remain as ever: rest, absolute, in bed and the protection of the patient from every care. Fresh air, a nourishing diet, and, especially, general massage, which is too often neglected, are important. On the success of the efforts of the physician to keep the patient cheerfully occupied mentally the life of the latter may depend. Where the anæmia is marked, frequent transfusions may be very beneficial.

The most important principle in the treatment of infective endocarditis is *nil nocere.* The use of intravenous arsenicals and mercurials and other so-called internal antiseptics is irrational and sometimes dangerous. I have seen ulcerative colitis after mercurochrome; death has followed the use of gentian-violet. Since the article of Capps[99] I have been in the habit of using arsenic in the form of cacodylate of sodium subcutaneously. Used with care it is harmless. I do not know what influence it has had. The three probable recoveries that I have seen, as well as the two instances which I believe to have been rheumatic fever, which I have reported, were treated in this way.

At the present moment it is through scrupulous general care of the individual that the best results are to be accomplished.

GENTLEMEN,—You have been very patient. I thank you. Something over two hundred years ago a wise compatriot of ours—for two hundred years ago we were compatriots in fact as well as in spirit—ended a volume entitled *Manuductio ad Ministerium* (*Directions for a Candidate of the Ministry*), with these wise words with which I also shall conclude: "'Tis a Trespass upon the *Rules of Prudence* never to know, *when to have done.* Wherefore, *I have done.*"

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