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BACTERIAL OR INFECTIVE ENDOCARDITIS

THE GIBSON LECTURES FOR 1930.

By WILLIAM S. THAYER, M.D., Hon. F.R.C.P.I.

LECTURE I.

FIRST let me thank you for the honour and the privilege you have bestowed on me in inviting me to the seat of the mother of American medicine—for such assuredly is the University of Edinburgh—to speak under a foundation established in memory of one whose talents and achievements I greatly admired, to whose rare human charm I was one of many captives.

I can see him now looking, as he always did, as if he had stepped from one of Raeburn's canvases—a charming combination of medical learning and wisdom and skill, and human understanding, tinctured by that restless sense of humour so quick to betray itself to the sympathetic glance.

Alas that we might not be listening to him to-day! One would linger longer with his memory—but time is a tyrant and I must pass directly to my subject.

Our knowledge of the nature and ætiology of that which we call rheumatic heart disease has taught us that the endocarditis, upon which so much stress was laid in the beginning, is merely one manifestation of a general process the most important feature of which, though often not the most prominent, is the cardiac disease. This cardiac disease is a general involvement of the heart in which valvular affections, acute, subacute or chronic, often, but by no means always, play a relatively important part. Indeed in the more acute and not infrequently the more chronic forms of the malady

the changes in the muscle or in the pericardium are of graver import than the sometimes more obvious endocarditis.

That the rheumatic process is infectious would seem hardly to be doubtful; that it is related to infection with certain forms of streptococci has been maintained by many in recent years.* [1, 2, 3, 4, 5]

Its characteristic gross and histological manifestations are such as might well be the immediate reaction of the human organism to the nesting of bacteria at the affected points. That this is true, however, has not yet been proven.

The arguments of Weintraud,[6] Bezançon,[7] Swift [8] and others, who believe that the lesions and symptoms of rheumatic fever, even if primarily dependent on infection with streptococci, are due to an allergic process allied to that which is observed in syphilis or in tuberculosis, are ingenious and inviting. But this point of view is still an hypothesis.

In rather sharp contrast to rheumatic heart disease is that which we call bacterial or infective or septic endocarditis, in which the focal lesions on valves, mural endocardium or in the vascular intima represent that which is the essential seat of the disease, the focus at which actual destruction of tissue may occur, so extensive as to cause death from mechanical damage to the heart or vessels; at which is kept alive the infection to which, more or less directly, death is usually due.†

Ten years ago, in connexion with a review of our experience with gonococcal endocarditis, it occurred to me that it might not be uninteresting to examine the records and such specimens as existed of acute and subacute endocarditis which had come to necropsy at the Johns Hopkins Hospital. I began by studying the records of the Pathological Laboratory and followed these back to the clinical histories with the object of gaining what information I could as to the anatomical and pathological (I use the word "pathological" in its strict sense) picture presented by endocarditis of known ætiology.

I have found these studies interesting and not without

* No attempt is made to give references to the enormous literature on the ætiology of rheumatism. References to the more important recent communications may be found, especially in the article of Swift.[8]

† This is the rule but there are exceptions, notably peracute infections, especially streptococcal and staphylococcal, in which the valvular lesions are a mere incident to an acute septicæmia associated with a lymphangitis or an erysipelas for instance or where multiple myocardial abscesses may exercise a grave early influence.

promise, and I have, I think, learned something as to the frequency and the individual features of endocarditis depending on the commoner ætiological agents.

Studies such as these are, however, never complete, and when I found it necessary to set down these lectures on paper I realised that that of which I had dreamed when I accepted

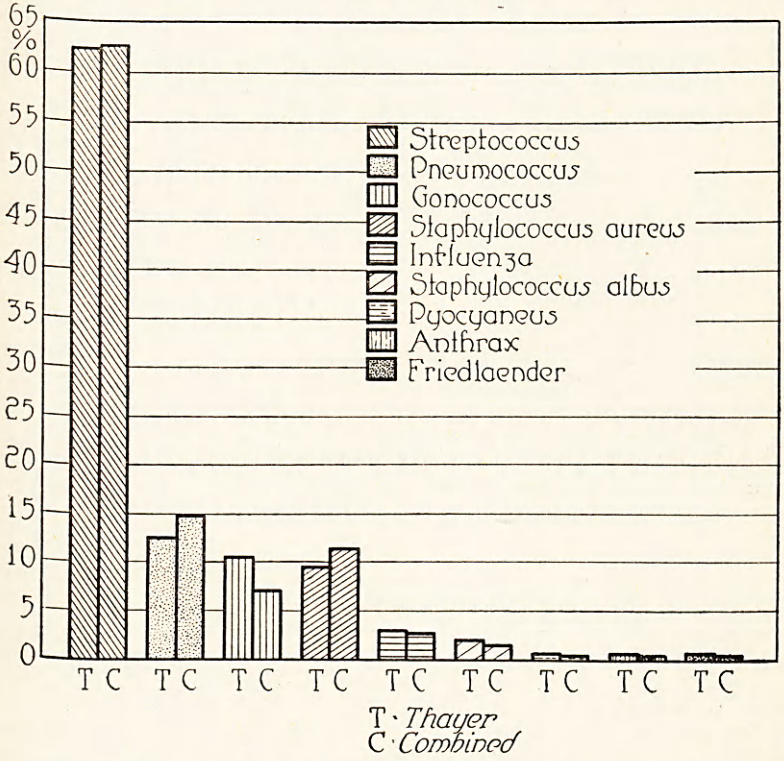

CHART I.—Bacterial or Infective Endocarditis. Relative frequency of causal agents. Thayer, 306 cases; Combined authors, 536 cases.

your invitation would have required about a year's more work by one whose capacity for work was such as was mine ten years ago.

I must therefore speak on the basis of what I have, rather than on that which I had hoped to accumulate. The series on which my studies are based represent the infective or bacterial endocarditides * of proven ætiology which have been

* For admirable summaries of the literature on subacute bacterial endocarditis the reader is referred to the articles of Debré,[9] Blumer[10] and Clawson.[11]

observed at the Johns Hopkins Hospital in forty years together with a few in my own consulting practice. Three hundred and six instances of infective endocarditis have been accumulated; these have been carefully studied clinically and, so far as possible, anatomically. In all, the infecting agent has been positively determined.

TABLE I.

Ætiological Element in 306 *Instances of Infective Endocarditis.*

Causal Agent.	Number of Cases.	Per Cent.
Streptococcus	191	62·41
Pneumococcus	38	12·41
Gonococcus	31	10·13
Staphylococcus aureus	28	9·15
B. influenzæ (Pfeiffer)	9	2·94
Staphylococcus albus	6	1·96
B. pyocyaneus	1	0·326
B. anthracis	1	0·326
B. Friedländer	1	0·326
Total	306	99·9

Adding to our series the cases collected by others,[12, 13, 14, 15, 16] we have the following table based on 538 cases.

TABLE II.

Causal Agent.	Harbitz.	Lenhartz.	Horder.	Clawson.	Cowan.	Thayer.	Total.	Per Cent.
Streptococcus	17	19	62	34	12	191	335	62·5
Pneumococcus	5	9	19	5	3	38	79	14·7
Staphylococcus aureus	8	7	7	7	3	28	60	11·2 –
Gonococcus	2	1	3	...	...	31	37	6·9 +
B. influenzæ (Pfeiffer)	...	...	5	...	...	9	14	2·6 +
Staphylococcus albus	...	1	...	...	...	6	7	1·3 +
Streptococcus and Staphylococcus	...	...	1	...	...	...	1	0·2 –
B. pyocyaneus	...	...	...	...	...	1	1	0·2 –
B. anthracis	...	...	0	...	0	1	1	0·2 –
B. Friedländer	...	...	...	...	...	1	1	0·2 –
							536	100·0

As is evident in Chart I., the correspondence between the figures is rather close save for the greater frequency of gonococcal infections in our series.

As a contrast to these instances of bacterial endocarditis I have collected from the records of the Pathological Laboratory

sixty-five consecutive examples of fatal rheumatism with acute endocarditis.*

It is rather presumptuous to take the time of an audience of British physicians in discussing rheumatic heart disease, but let us for a minute consider the picture presented by this series in contrast to that presented by my other series of bacterial endocarditides.

Sixty-five Instances of Acute Rheumatic Endocarditis with Necropsy.

The study of these records emphasizes sharply the circumstance that fatal, acute rheumatic carditis is pre-eminently a disease of early youth. Further, it bears out the truth emphasized by Carey Coombs,[18] Swift[19] and others that the rheumatic process is extremely insidious and that active and progressive changes may often be overlooked.

Sex.—The relation of the sexes differed in no way essentially from that in any series of hospital patients—60 per cent. were males; 40 per cent. were females. Among 100 consecutive cases of rheumatic fever occurring in Longcope's clinic in the years 1927 to 1929 he found the sex relations to be as fifty-one to forty-nine.

Age incidence.—Nearly three-quarters of our series (Chart II.), 72·3 per cent., came to necropsy in the first and second decades of life.

TABLE III.

Rheumatic Series. Age Incidence.

Decades	I.	II.	III.	IV.	V.	VI.	Total.
Cases	18	29	9	7	1	1	65
Per cent.	27·69	44·6	13·8	10·76	1·5	1·5	

86 per cent. in the first three. This picture, as may be seen from the chart, is in sharp contrast to that in most forms of bacterial endocarditis. While the late results of rheumatic cardiac disease are commonly seen in middle or even later adult life, the acute process and the immediate fatal results are commoner in early youth.

* The criteria necessary for determining the rheumatic character of many of the early cases of acute endocarditis were, as is set forth in my earlier publication,[17] insufficient, but in recent years our knowledge of the malady which we call rheumatism has become so much clearer that it has been easy to find thirty cases in the pathological reports of the last six years and to select a few more from older records in which, from an anatomical and clinical study, the diagnosis is clear.

Race.—Thirty-eight, 58·6 per cent. (Chart VIII.), of these patients were white; twenty-seven, 41·5 per cent., were negroes, as against seventy-eight and twenty-two for 100 consecutive cases observed in the medical clinic by Longcope, a rather striking difference dependent probably largely on the circumstance that necropsies are readily granted by the negroes, while

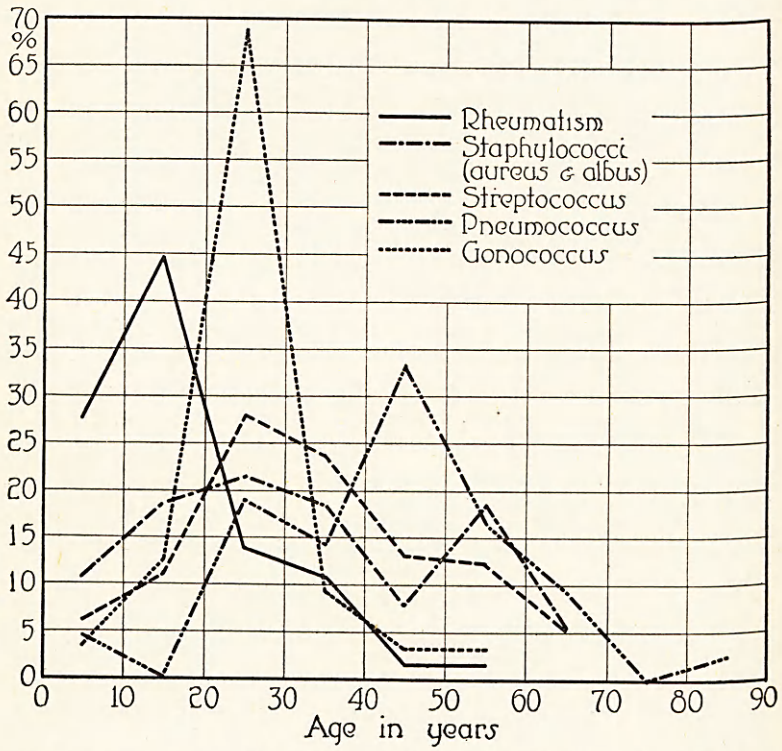

CHART II.—Acute and Subacute Endocarditis. Age incidence in various infections by decades.

they are more often refused by whites—generally by the Jewish patients who form a considerable proportion of those in the general wards.

There was a history of recognized *antecedent rheumatism* or chorea (Chart IX.) in 77·4 per cent. of sixty-two patients, but clinical or post-mortem evidence of chronic cardiac disease was present in 83 per cent. of the series. Among fourteen cases in which there was no history of antecedent rheumatism or chorea, nine, 64·28 per cent., showed at necropsy chronic rheumatic

changes. In other words acute rheumatic cardiac disease is associated, often for considerable periods, particularly in the young, with manifestations so slight as to escape notice. My own previous observations bear testimony to the importance of

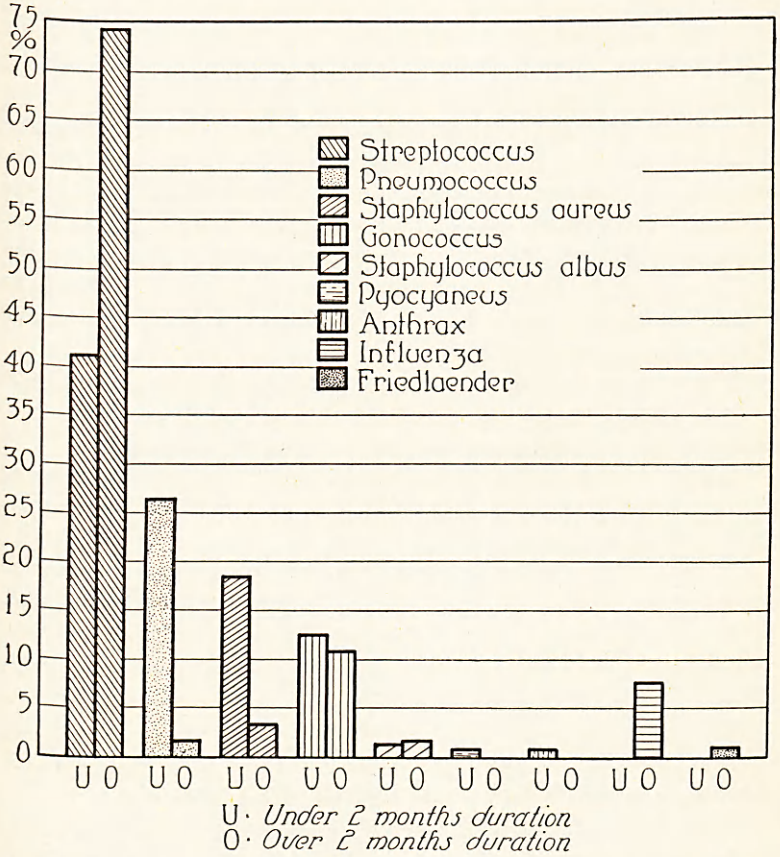

CHART III.—Bacterial or Infective Endocarditis. Relative frequency of various ætiological agents in endocarditis of under and over two months' duration.

Explanation of Chart III. This chart shows the proportional representation of each form of infection in bacterial endocarditis of under two months' and of over two months' duration. Thus, among the series of cases of under two months' duration, over 40 per cent. were due to streptococcus, etc.

unaccountable or persistent fever in association with chorea as evidence of cardiac disease.[20] *Infected tonsils* or adenoid tissue in the nasopharynx were practically universal—90 per cent. of fifty patients where notes were made on the condition of the

throat—and a considerable number of the patients, even relatively early in life, showed peridental infection. *Oral sepsis*, foci of infection in tonsils or about teeth, were found in forty-eight of fifty patients. In other words, foci of streptococcal infection were the rule.

The early *symptoms* varied from sensations of lassitude with anorexia, moderate fever and sweating at night, with or without mild transient tenderness of joints or muscles, to the outspoken and characteristic picture of acute articular rheumatism. The *fever* varied greatly in its character. Sometimes it was moderate or even absent for considerable periods of time. Long remissions and recurrences were characteristic. Chills and chilly sensations were not recorded. *Petechiæ* were not observed. The spleen was rarely palpable. *Embolic phenomena* were observed only in instances with symptoms of myocardial insufficiency.

There was no striking *anæmia*, but, though sometimes absent, there was usually (Chart X.) a rather well-marked leucocytosis ranging generally between 10,000 and 20,000.

While albuminuria was the rule, acute nephritis was rare, and embolic *glomerulo-nephritis*, so common in vegetative endocarditis, was not observed.

It was often quite impossible to estimate the *duration* of the process, which tended to be subacute and recurrent, and in the histories given by patients mild febrile symptoms were overshadowed by those of myocardial insufficiency. Occasionally, however, the course was rapid—of but a few weeks' duration—and terminated in death from myocardial insufficiency or pericardial effusion. This was preceded by auricular fibrillation in thirteen cases (20 per cent.).

The presence of subcutaneous fibroid nodules was reported in a certain number of this series, but not with sufficient constancy or care to justify statistical consideration.

Acute fibrinous *pericarditis* was observed in nearly 60 per cent. of the series and in 26·2 per cent. more there was an adherent pericardium, so that pericardial disease, either acute or chronic, was recorded in 84·6 per cent. of the series. Serofibrinous pericarditis terminating in synechia is a striking characteristic of rheumatic heart disease—so much so as to justify the old French term "endopéricardite."

Characteristic acute, *perivascular*, *miliary nodules* (Aschoff bodies) were found in sixty of sixty-four cases in which the

Bacterial or Infective Endocarditis

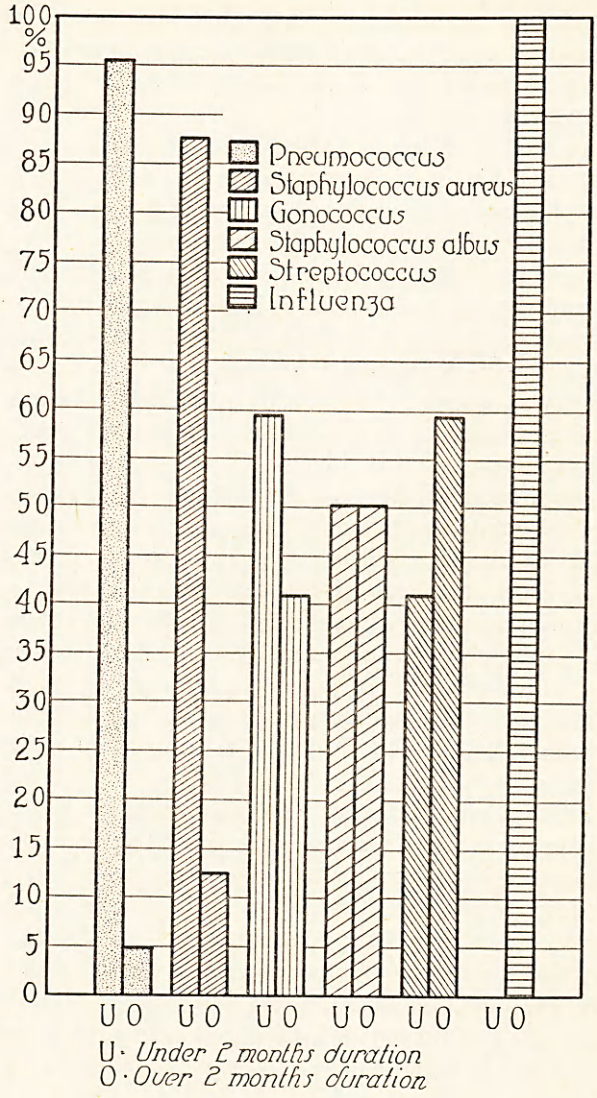

CHART IV.—Bacterial or Infective Endocarditis. Relative proportion in each series of infections with a duration of under and over two months.

Explanation of Chart IV. This chart shows the relative proportion of infections with a duration of under and over two months in each ætiological series. Thus, in the pneumococcal series, over 95 per cent. of the infections were of a rapid course, under 5 per cent., of a duration of over two months.

heart muscle was available for examination—in 93·7 per cent. of the series—and their chronic fibroid remains were observed in the remaining four. There were acute or chronic myocardial changes in every instance.

The character of the myocardial and endocardial changes of rheumatic fever is too well known to need especial note. I will emphasize, however, one important feature pointed out by MacCallum [21, 22, 23] but a few years ago, namely the frequency of acute rheumatic changes in the endocardium of the left auricle outside and above the mitral valve—changes which overlie an extensive and characteristically rheumatic inflammatory process in the auricular wall beneath. Endocardial scarring at this spot was recognized in 1869 by Lépine.[24] The essentially rheumatic character of the lesion was, I think, discovered by MacCallum in 1924.

The roughened, thickened, yellowish patch on the posterior and outer aspect of the left auricular wall just above the valve, where the endocardium is thrown into ridges and folds, is present in most instances of chronic rheumatic heart disease. The acute changes are represented by a fibrinous exudate at this seat, excited by the extensive subjacent inflammatory process. Three-quarters of our patients coming to necropsy with acute rheumatic endocarditis showed definite evidence of involvement of the left auricular endocardium, either acute or chronic.

The anatomical characteristics of the valvular lesions, gross and microscopical, the deeper valvulitis and the acute verrucose vegetations are too familiar to be entered into here. They are well described in English by Carey Coombs,[25] MacCallum,[26] Klotz,[27] von Glahn,[28, 29, 30] Pappenheimer,[29, 30] Swift [31] and others.

With the evidence which we now have we must regard rheumatic endocarditis as a reaction to minute focal necrotic changes dependent directly or indirectly on the specific infectious agent, changes generally, if not always, arising in subjacent tissues.

Anatomical distribution of the valvular lesions.—The statistics offered in this series as to the distribution of acute valvular lesions are not uninteresting. Endocarditis was observed on the left side of the heart alone in over 47 per cent. of the cases; on the right side alone in but 3 per cent.; on both sides of the heart in nearly 50 per cent. In one case the only lesions found at necropsy were the characteristic left auricular changes.

Chart VI. shows graphically the relative frequency of the valvular involvement. These figures relate only to acute changes. If, however, we include evidences of preceding attacks,

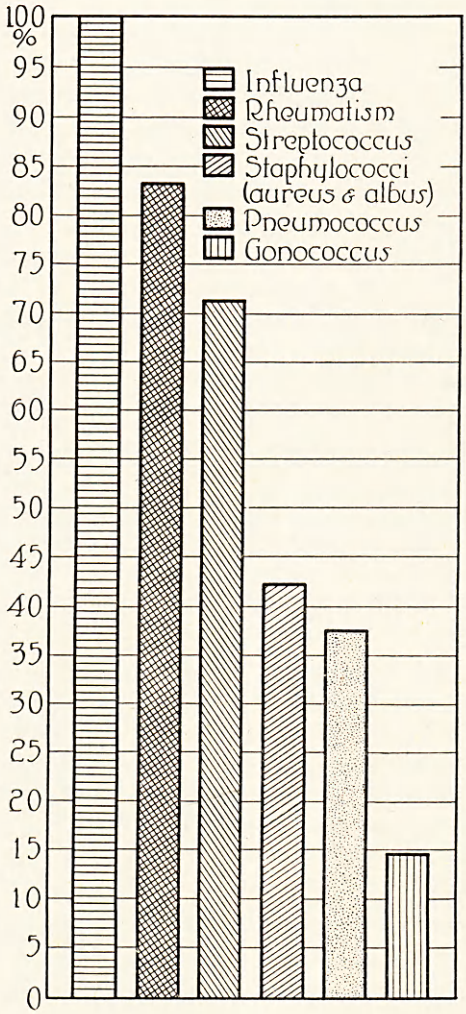

CHART V.—Bacterial or Infective Endocarditis. Relative incidence of pre-existing valvular disease.

the mitral valve was affected universally; the aortic valve was involved in 83 per cent; the tricuspid in 55·9 per cent., figures close to those of Coombs.[32] Tricuspid changes in rheumatism,

even if they be less extensive than those at the mitral and aortic orifices, are common. Pulmonic involvement is rare.

In one instance fresh lesions were found on congenitally fused (bicuspid) aortic curtains.

Focal suppurative processes were not seen in the series.

Summary.—The endocarditis of rheumatism is, then, a single feature in a characteristic disease picture recognizable usually clinically and definitely anatomically. Rheumatism would appear to be a specific infection with focal manifestations, notably in joints, heart and vessels, nervous system and skin. There is a good deal to suggest its relation to infection with certain rather characteristic strains of non-hæmolytic streptococci. The definite association, however, of depots of the infectious agent at the foci of anatomical change has not been demonstrated.

Rheumatism is distinguished by the characteristic, fugitive, non-suppurative polyarthritis; by the frequency of serofibrinous pericarditis ending in adherent pericardium; by the nature and distribution of the valvular, vascular and wide-spread myocardial changes; by the apparently specific alterations in the left auricle with the involvement of the mural endocardium; by the circumstance that the non-suppurative serositides, as well as the relatively benign but chronic endocarditides, appear, in their origin, to be associated with characteristic subjacent, periarticular, subendocardial or sub-pericardial changes.

Primarily rheumatism is a disease of early youth, and especially of the first two decades, but, when once established, there is a striking tendency to chronicity through recrudescences or recurrences, often insidious, which result in the distinctive picture of chronic heart disease.

These changes, with those due to syphilis and the arteriosclerotic changes of later life, are the most important causes of myocardial insufficiency.

Bacterial, Infective or Septic Endocarditis.

There is little to suggest that rheumatic endocarditis arises other than through the development of minute foci of necrosis in the substance of valve or heart wall, as in the left auricle, with the characteristic inflammatory reaction, and later spread of the process by continuity to the superjacent endocardium. On the endocardium over such areas fibrin is deposited and the

process becomes evident as the little verrucosities along the lines of closure of the valves or as the smoother fibrinous exudate in the left auricle. The earliest changes are probably subendocardial. The process does not appear to originate on the surface.

In bacterial endocarditis, on the contrary, the earliest changes seem to take place on the surface of the endocardium itself. These appear at first as small soft vegetations packed with bacteria, usually along the lines of contact or free edges of the valves, easily brushed from the surface. At the base, in the endocardium, there is necrosis followed by a spreading inflammatory process and, according to the malignity of the infection and the resistance of the individual, a more or less rapid destruction of subjacent tissues. As the thrombi become larger and are tossed about in the blood current, implantation of the infection may follow on spots where they come in contact with the neighbouring heart wall ; again bits are readily broken off from the main mass forming emboli which lodge at distant points, resulting in the most characteristic clinical manifestations of endocarditis.

Evidence of embolism in the kidney may be merely the appearance from time to time of showers of red blood corpuscles in the urinary sediment. At other times the infarctions may be sufficiently large to result in pain and hæmaturia obvious to the naked eye. Embolism of the spleen is easily recognized by the pain and tenderness caused by the overlying peritonitis. In the skin, emboli produce manifestations all the way from tiny petechiæ, sometimes showing a white centre surrounded by a hæmorrhagic border, to larger, slightly swollen, cyanotic areas which are very tender. Small tender cyanotic spots, as was pointed out by Osler,[33] are particularly common on the pads of the fingers and toes and are remarkably characteristic of this condition. Somewhat larger patches are not uncommon on the palms of the hands and soles of the feet.[34] Tiny painful hæmorrhages under the finger nails, noted by Horder, are very characteristic. Petechiæ are frequent in the mucous membranes of the mouth, in the conjunctivæ, in the eye-grounds. Cerebral embolism with hemiplegia may occur. In lesions of the right side of the heart pulmonary embolism with acute pleural pain is not uncommon. In several of our cases it has been among the first symptoms. Embolism of large vessels may result in peripheral gangrene. Mycotic aneurysms are common.

According to the malignity of the infection the progress is acute, leading to a fatal issue within a few days—where, as a rule, the valvular lesions are but small, soft, verrucose excrescences, little larger than those seen in rheumatic fever but often softer and more ragged; or it may be subacute, lasting for many weeks or months, when the vegetations may be very large, yellow or grey, mulberry-like masses several centimetres in diameter. Commonly, in long-continued cases, there is partial organization of the vegetations with scarring and, not infrequently, calcification which results in complete or partial healing. Under such circumstances the irregular deformities of the valves are often recognizable anatomically.

More or less rapidly ulceration and a destruction of the tissues sets in at the base of the lesion, leading sometimes to aneurysms of the valves, rupture of the leaflets, ulcers burrowing into the heart or, more rarely, the great vessels, and sometimes causing aneurysms or communications between the cavities. The vegetations extend often to the cordæ tendineæ of mitral and tricuspid valves, the rupture of which is common. But the picture of so-called vegetative and ulcerative endocarditis is, after all, too familiar to call for further description.

Generally speaking bacterial endocarditides may be divided into the *acute* and *subacute*. According to the malignity of the infection and the character of the infecting agent the pathological changes and the clinical manifestations differ considerably. One can already describe with some assurance the usual clinical and anatomical picture resulting from the action of each of the commoner infectious agents.

Streptococcal Endocarditis.

By far the commonest ætiological agents are streptococci, which, as has been seen, cause over 60 per cent. of all bacterial endocarditides. The clinical picture resulting from infection with the more benign forms of *Streptococcus*—the so-called subacute vegetative endocarditis—is a striking and characteristic syndrome. But although the picture of subacute vegetative endocarditis is a sharply defined clinical entity, and although 77 per cent. of our streptococcal endocarditides were subacute in character, lasting over a month—nearly 60 per cent., as is shown in Chart IV., over two months—yet in 33 per cent. of nearly two hundred streptococcal infections *Streptococcus* was merely a terminal invader, leading, within a week

or two, to death from the general intoxication, its presence manifest anatomically only by small, soft, early vegetations or masked by already existing vegetations caused by some other organism which it had overgrown as a secondary invader.

Of the 130 instances in our series of endocarditis lasting under a month, 38·4 per cent. were of streptococcal origin.

Clinical picture associated with infection with different types of streptococcus.—As, in general, the clinical and pathological picture depends considerably on the ætiological agent, so in streptococcal endocarditis it is reasonably clear that in those instances with a duration of under a month the infecting agent is usually *β Hæmolytic streptococcus*—sixteen of our last twenty cases in which the type of streptococcus was determined—while subacute streptococcal endocarditis is dependent on infection with a milder, non-hæmolytic, usually green-growing organism (*S. viridans*), occasionally *α Hæmolytic streptococcus* (91 per cent. of 146 cases).*

With the further differentiation of streptococci made possible in recent years, it appears that in our series, as elsewhere, *Streptococcus salivarius* is the commonest infectious agent in subacute endocarditis—eleven of our last thirteen cases, the other two being dependent on *Streptococcus fæcalis.* This is interesting in connexion with the rather frequent oral sepsis in our series.

From an anatomical standpoint streptococcal endocarditis affects the left side of the heart in the great majority of instances (78·7 per cent. of our series). The right side alone was involved in but 5 per cent. of ninety-nine cases with necropsy. In this particular streptococcal infections stand with rheumatic

* Only twice in this series did *β Hæmolytic streptococcus* appear to be the agent. One case was a characteristic subacute vegetative endocarditis of eight months' duration in which cultures had been negative up to the day of death, when abundant colonies of *β Hæmolytic streptococcus* were obtained from the blood during life as well as from blood and vegetations at necropsy. It is hard to believe that the organism here was not a terminal invader. The other was again a characteristic subacute endocarditis in which *β Hæmolytic streptococci* were cultivated on three occasions in the course of eight days—1, 5, 11 colonies to the c.c. respectively. Then after an interval of sixteen days the organism cultivated was *α Hæmolytic streptococcus* which was recovered from the blood six times during forty-five days—20 to 150 colonies per c.c.—and, at necropsy, from the vegetations. In some earlier cases in the series the classification of the organism was not satisfactory.

endocarditis (3 per cent.), in contrast to the other forms of bacterial endocarditis, in which the right side alone was involved more frequently (17 per cent.).

TABLE IV.

Distribution of the Lesions according to the Cavities of the Heart.

	Left Side.	Right Side.	Both Sides.	Total.
	Per Cent.	Per Cent.	Per Cent.	
Streptococcus . . .	78 (78·7)	5 (5+)	16 (16·1)	99
Other Bacterial Endocarditides.				
	Per Cent.	Per Cent.	Per Cent.	
Pneumococcus . . .	30 (81+)	3 (8·1)	4 (10·8+)	37
Staphylococcus aureus . .	18 (66·6)	6 (22·2)	3 (11·1)	27
,, albus . .	4 (66·6)	2 (33·3)	0	6
Gonococcus	17 (62·9)	6 (22·2)	4 (14·8)	27
B. influenzæ (Pfeiffer) . .	4 (57·1)	1 (14·3−)	2 (28·5)	7
B. pyocyaneus . . .	1	...	...	1
B. anthracis . . .	1	...	...	1
B. Friedländer . . .	...	1	...	1
	75 (70+)	19 (17·7)	13 (12·1)	107

The mitral valve is the seat of election of streptococcal infections, as indicated on Chart VI. (80·8 per cent. of the series);* the aortic next (48·5 per cent.); the tricuspid next (17·17 per cent.); the pulmonary in but 8 per cent. In this respect again the distribution resembles that of rheumatic endocarditis.

It has long been known[40] that bacterial endocarditis is especially common on valves and in localities in the heart the seat of chronic change or of congenital malformation. This, while perhaps true of all forms of bacterial endocarditis, is notably true of streptococcal infections, especially of those with the more benign types of the organism. In our complete series there was evidence, clinically or pathologically or both, of *pre-existing valvular disease* in 58 per cent. of the acute and in 71·2 per cent. of the subacute infections.

In subacute streptococcal endocarditis coming to necropsy, there was evidence of pre-existing valvular disease in 81·1

* But one must not forget the remarkable experience of Coombs,[35] Cotton,[36] Starling,[37] Morawitz[38] and Horder[39] as to the greater frequency of aortic involvement in patients who had done severe service in the War.

per cent. of the cases, almost exactly the experience of Horder.[41] These figures (Chart VI.) are in striking contrast to those observed in the other forms of bacterial endocarditis save in the influenzal series.

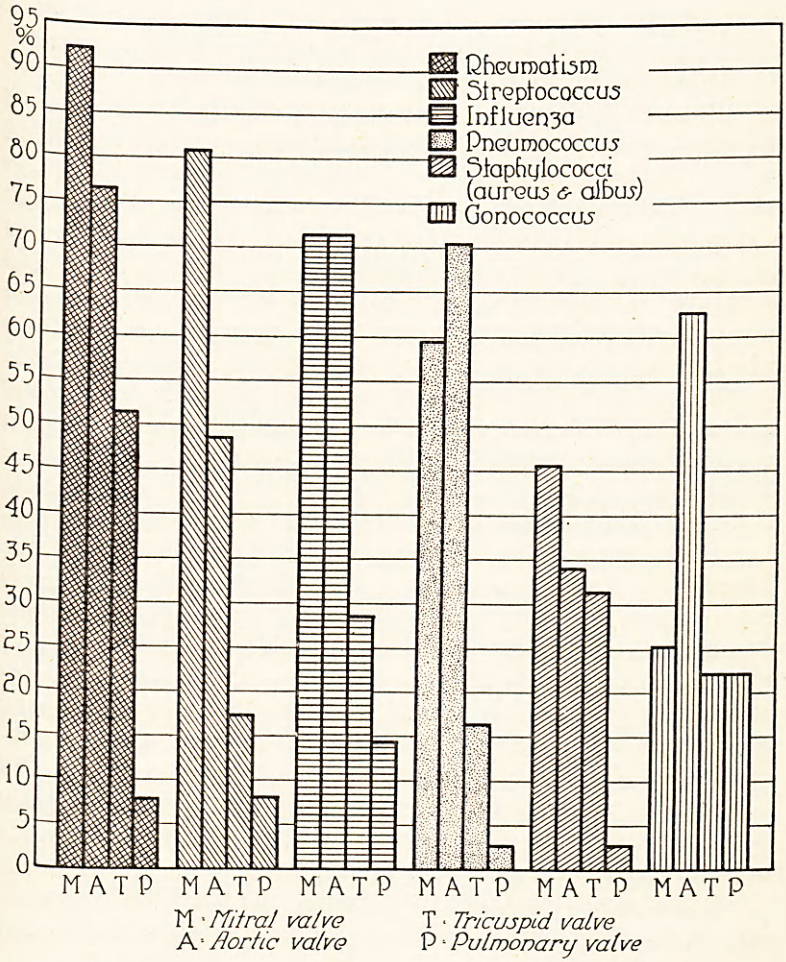

CHART VI.—Acute and Subacute Endocarditis. Proportional involvement of individual valves.

But while it is clear that chronic valvular disease of rheumatic origin predisposes to secondary streptococcal infection, this is not true of syphilis, so common a cause of aortic disease.

In sixty-three instances of streptococcal endocarditis involving the aortic valves, there was but one where the lesions were situated on a focus clearly the seat of *luetic change.*

In two more cases where syphilis of the aorta was evident, it is *possible* that the valves may have been the seat of a previous luetic affection, though there was nothing anatomically or clinically to indicate that this was the case.

Lewis and Grant,[42] among thirty-one unselected cases of subacute streptococcal endocarditis of the aortic valves, found evidences of *congenital malformation*—bicuspid conditions—in 26 per cent. Abbot[43] found eighteen instances of bacterial endocarditis in forty-four hearts with bicuspid aortic cusps (45 per cent.). Among our ninety-nine instances of acute and subacute endocarditis coming to necropsy, there were five in which aortic lesions were situated on a bicuspid valve; one in which a congenital pulmonary stenosis was the seat of the lesion; one in which the lesion involved a possible congenital defect of the pulmonary valve and extended upwards through a patent *Ductus Botalli* into the aorta. Assuming that these bicuspid valves were evidence of a congenital defect, which, in one instance, was believed not to be the case by the pathologists, we have found congenital lesions at the seat of the affection in 7 per cent. of this series. In three of these there was reasonably good evidence of the existence of chronic rheumatic valvular disease as well. There was one further instance of subacute viridans aortitis with complete recovery in which the lesion must have been at the seat of an aortic coarctation. Among sixty-five instances of streptococcal endocarditis involving the aortic valves, five, 7·7 per cent., showed evidence of a bicuspid formation.* I cannot help fancying that the proportion of congenital lesions in Lewis and Grant's original series is exceptionally high.

It has been seen that streptococcal endocarditis in general, but especially subacute infections, occur usually at the seat of

* Among 210 necropsies on subjects dead of infective endocarditis, there were eleven in which an affected focus was the seat of congenital change, 5·2 per cent. Among 126 cases in which the aortic valves were affected, there was a congenital change in seven, 5·55 per cent. There was one obvious infection at the seat of a coarctation of the aorta in a patient who recovered. I see that Miller[44] doubts the correctness of this diagnosis. I can only say that had he seen the patient his doubts would have departed. In one instance there were congenital peculiarities in tricuspid and mitral valves which were not affected.

a chronic rheumatic valvular lesion. This is true also of *mural endocarditis*, which is strikingly frequent (88·4 per cent. of our subacute cases). Common on chordæ tendineæ, papillary muscles, the wall of the left ventricle and sometimes on the aortic intima, whither it spreads by contact, it is found especially and with great frequency (50 per cent. of our cases) on the wall of the left auricle and precisely on the patch of chronic rheumatic endocarditis. This localisation, so characteristic of subacute vegetative endocarditis, is characteristic precisely because of the tendency of the infection to become implanted on old rheumatic foci which offer a favourable nidus for its development. The demonstration by Grant, Wood and Jones[45] that small platelet thrombi are not infrequent on the surface of cardiac valves, especially in the localities at which streptococcal endocarditis is common, and that they are commoner on valves the seat of chronic, rheumatic and congenital changes, affords a reasonable basis for their hypothesis that these thrombi offer a suitable foothold for streptococci which may from time to time gain access to the circulation. When one considers the frequency with which, in transient acute febrile attacks, streptococci may be cultivated from the circulating blood, the force of this suggestion may be appreciated.

The subacute course of many streptococcal infections is associated with large vegetations which often show all stages—on the one hand of healing, leading to marked deformities, and, on the other, of progression with great destruction of tissue. Gangrene of the extremities (two in our last eighty-two cases), mycotic aneurysms at distant points (seven among our last eighty-two cases), and indeed any phenomenon which one might expect from the dissemination of infected emboli, may be observed.

There is little characteristic about the *myocardial changes* met with in streptococcal endocarditis. *Acute* myocarditis was observed in about half our series. Apart from the characteristic submiliary, perivascular Aschoff bodies, found in eight instances in which the bacterial endocarditis was engrafted as a terminal infection on a rheumatic heart disease, and an equal number of cases in which miliary abscesses were found microscopically, the changes consisted of small areas of focal, usually perivascular, infiltration with round cells and leucocytes, which were not very extensive and about which there seemed little specific.

Chronic fibrous changes are commoner, as one might expect in view of the frequency of antecedent rheumatic heart disease.

Pericarditis.—In Chart VII. is set forth the striking rarity of pericarditis in streptococcal endocarditis, a point of considerable diagnostic significance. In the subacute series pericarditis was observed in but 5·8 per cent.

Age incidence.—While occurring at all ages, streptococcal endocarditis (Chart II.) is commonest in early and middle adult life.

TABLE V.

Streptococcal Endocarditis. Incidence according to Age.

Decades	I.	II.	III.	IV.	V.	VI.	VII.	Total.
Totals	12	22	55	47	26	24	10	196
Per cent.	6·12	11·22	28·06	23·98	13·26	12·24	5·10	

Sex.—The distribution between the sexes was about that of the ordinary hospital representation—men, 111 (56·63 per cent.); women, 85 (43·36 per cent.).

Race.—(Chart VIII.). The same was true as to race—whites, 152 (77·5 per cent.); negroes, 44 (22·4 per cent.).

Duration.—As has been mentioned already, fifty, 33⅓ per cent. of the series, ran a rapid course terminating within a month; sixty-one (Chart IV.), 40·66 per cent., ran their course within two months.

TABLE VI.

Table showing the Duration of 100 *Cases of Subacute Streptococcal Endocarditis followed to their Termination.*

Duration.	Cases with Necropsy.	Cases without Necropsy.	Recovered.	Total.
1 to 2 months	9	2	0	11
2 „ 3 „	5	2	0	7
3 „ 4 „	14	0	2	16
4 „ 5 „	12	2	2	16
5 „ 6 „	8	3	0	11
6 „ 7 „	8	2	0	10
7 „ 8 „	3	1	0	4
8 „ 9 „	4	2	0	6
9 „ 10 „	5	0	0	5
10 „ 11 „	1	1	0	2
11 „ 12 „	2	0	0	2
Over 12 months	7	1	0	8
?	2	0	0	2
Total	80	16	4	100

Thirty-seven of 100 instances of subacute endocarditis followed to the end lasted over six months; eight, apparently over a year.

The *portal of entry* of the infection was reasonably clear in two-thirds of malignant acute infections of under a month's

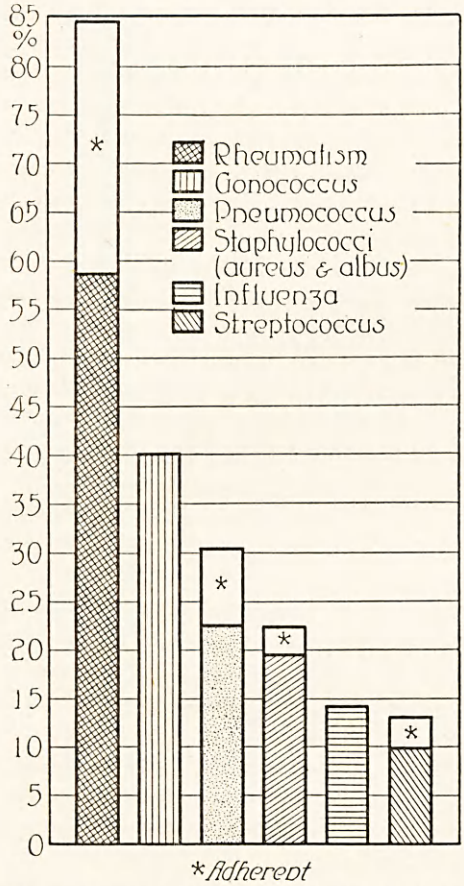

CHART VII.—Acute and Subacute Endocarditis. Relative incidence of pericarditis.

duration—in other words, those depending for the most part on *β Hæmolytic streptococcus.* These were acute focal lesions in various parts of the body—puerperal sepsis, infected wounds, acute genito-urinary infections, empyemata, erysipelas, trauma, etc. Here the manner of onset was usually acute and the course that of an intense septicæmia.

In *subacute endocarditis*, however, where the onset is so often insidious, the portal of entry was apparent only in 27+ per cent. of our series. The onset seemed especially common in connexion with acute pharyngeal and upper respiratory infections, tonsillitis and sinusitis, and pelvic infections.

Among eighty-four instances in which no other portal of entry was apparent, and in which notes as to the condition of the teeth were made, in fifty-four there was peridental sepsis, while in ninety-one cases, in which notes were also made as to the condition of tonsils and sinuses, as many as three-quarters showed evidence of oral sepsis. In thirteen further patients the onset of the malady followed, directly, a tonsillitis or a sinusitis (ten instances) or the extraction of teeth the seat of focal infection (three). The figures as to the teeth are interesting when the relative youth of the patients in the series is considered.

Course and clinical history.—The course of the *more acute infections*, due in great part to *β Hæmolytic streptococcus*, is rapid and varies according to the nature of the original process which usually dominates the picture, which is generally that of an intense septicæmia with high, continued fever. The endocarditis is often undeterminable clinically. Nevertheless petechiæ and embolic phenomena were observed in a quarter of our cases. The *leucocytosis* is generally higher than in the more subacute endocarditis. *Pericarditis*, which is remarkably infrequent in subacute streptococcal endocarditis, was somewhat commoner in the acute series—five of forty-five cases, 11·1 per cent.

The course of *subacute streptococcal endocarditis* is remarkably characteristic. The *onset* is generally insidious, with loss of energy, fatigue, noticed towards the end of the day, the relation of which to a slight rise of temperature may pass quite unnoticed for some time. Indefinite muscular pains or tenderness in the regions of joints (52·4 per cent. of our series) are often among the early symptoms. The *fever*, once discovered, is generally moderate, irregular, intermittent or remittent, but persistent or recurrent after short intermissions. A moderate, steadily increasing *chloranæmia* of the secondary type sets in early. At first there may be few revealing symptoms, but the presence of an old rheumatic endocarditis should always arouse one's suspicion, especially if the spleen be palpable (52·7 per cent. of our series). Sometimes the fever, with its accompanying chilliness in the afternoon and sweating at night, becomes,

early, a pronounced feature, and cultivation from the blood of non-hæmolytic streptococci or *Streptococcus mitis* renders the diagnosis probable. But the cultivation, even on several occasions, of non-hæmolytic streptococci from the circulating

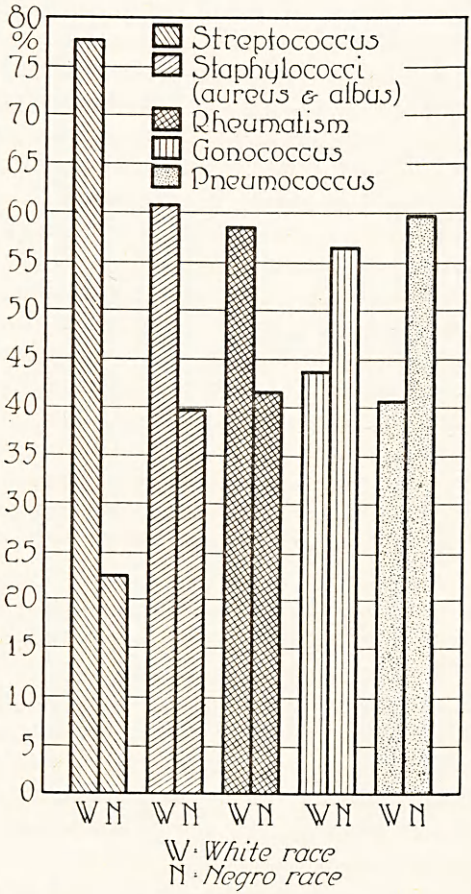

CHART VIII.—Acute and Subacute Endocarditis. Proportional distribution ætiologically between white and negro races.

blood is not enough in itself to justify a diagnosis of subacute, vegetative endocarditis. Transient bacteræmia in infections with the milder forms of *Streptococcus* is very common. We have observed it often in the Johns Hopkins Hospital, and under a variety of circumstances. In rheumatic fever it is not at all uncommon. Twice within the last two years I have seen,

in consultation, instances of rheumatism in which, during a period of three months, several cultures of *Streptococcus viridans* were obtained from the circulating blood by competent and reliable bacteriologists. Each of the patients were young men—one aged 18; one, 13. Each had been ill several months with persistent, intermittent fever following a pharyngitis in one; in the other an upper respiratory infection. In both there had been moderate muscular and articular pains without swelling or redness. In both there was a leucocytosis as high as 20,000. In neither was the spleen palpable. In neither were there embolic phenomena or red blood corpuscles in the urine. In neither was the anæmia very pronounced. Both showed evidence of chronic valvular disease. In one, at the time at which I saw him, there was a serofibrinous pericarditis which influenced me strongly in my diagnosis. In both of these patients three cultures of non-hæmolytic streptococci had been obtained within a period of several months. In both the history and the general appearance seemed to us to justify the diagnosis of rheumatism, and in both a complete recovery followed after an illness of about four months. In such cases a differential diagnosis is exceedingly difficult and can be arrived at only by the careful weighing of all the evidence.

But even in true vegetative endocarditis it may be some time before the revealing cultures are obtained, and the diagnosis may remain uncertain for considerable periods. Particularly suggestive is the progressive *anæmia*, which is generally more striking than in rheumatism, and the appearance of *embolic phenomena*, which are very common (74·3 per cent. of our series). Embolic phenomena are, of course, frequent in myocardial insufficiency from other causes where intracardiac thrombi are common, notably with auricular fibrillation or after cardiac infarctions; but in most instances of subacute streptococcal endocarditis evidence of myocardial insufficiency is not striking at first, and auricular fibrillation is notably rare—5 per cent of our series (four cases of old rheumatic heart disease, one of syphilis).

Certain phenomena which have usually been regarded as embolic but may well, in some instances at least, be due to endothelial proliferation in capillaries or precapillary arterioles—a true endovasculitis as Merklen and Wolf[46] and others [47, 48] point out—are characteristic. I refer to the suddenly appearing small,

painful, slightly swollen, cyanotic areas in the balls of fingers or toes (*Osler's phenomenon*), the little hæmorrhages under the finger nails (Horder), or the larger and tender cutaneous or subcutaneous areas especially common in the extremities but present elsewhere as well. Sudden pain and tenderness in the splenic area, which is very frequent, and the intermittent presence of blood corpuscles in the urine (sixty-nine, 47·5 per cent. of 143 cases) are suggestive. In view of recent studies, many of the

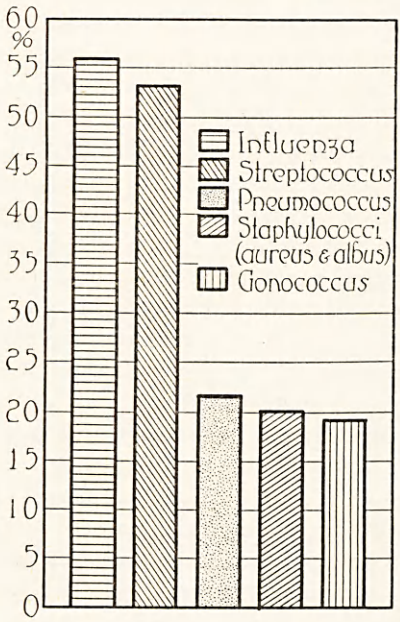

CHART IX.—Bacterial or Infective Endocarditis. Relative incidence of history of antecedent rheumatic fever or chorea.

phenomena regarded as of purely embolic origin may turn out to be focal reactions to a spreading infection or, as some would have it, the result of sensitization to the existing infection. Cerebral embolisms resulting in nervous manifestations, meningeal or mental phenomena,[49, 50, 51] hallucinations, delusions, maniacal delirium are not uncommon and are sometimes seen early in the course of the disease. Horder[52] has seen the introduction of the malady by choreiform symptoms. In one of my own cases the patient consulted me because of manifestations suggestive of multiple sclerosis. Occlusion of

larger cerebral vessels or, more rarely, rupture of mycotic aneurysms, with hemiplegia, is distressingly common—forty-five, 31 per cent., of 145 cases in our series; thirty-seven, 37·3 per cent., of ninety-nine cases followed to a termination. In instances of longer duration a moderate degree of clubbing of the fingers [53, 54, 55, 56] is common (44·1 per cent. of our series).

Albuminuria is almost invariably present. With the increasing anæmia and the recurring embolic phenomena the characteristic embolic glomerulo-nephritis described by Horder,[57] Löhlein,[58] Baehr[59] and others generally becomes evident—61·5 per cent of fifty-two cases coming to necropsy; 74 per cent. of our last series of twenty-seven cases.

Beside an increasing chloranæmia of the secondary type there is usually a leucocytosis. This may, at times, be quite absent, while, on the other hand, it may be rather high. Counts as low as 2600 and as high as 53,500 were recorded in our series. Chart X. sets forth a comparison between the average low count, 9606, and the average high, 15,455, with like figures in other forms of endocarditis. Morphologically the picture is as in any other secondary anæmia save for the occasional appearance, especially at periods when the phenomena of what have usually been regarded as peripheral embolisms are present, of monocytes and large *endothelial phagocytes*.[60, 61, 62, 63, 64] Their presence is probably the result of a long-continued sepsis. I have seen like cells in the blood of grave malarial fever.

With the progress of the illness the peculiar grey, *café-au-lait* colour which Libman first pointed out becomes very striking. The anæmia generally becomes rather pronounced and is distressingly rebellious to treatment.

Cardiac lesions are usually evident at the outset because of the frequency of chronic rheumatic heart disease, but changes and progression in these lesions may be apparent. Occasionally, in the early stages of the disease, before the onset of recognizable embolic phenomena, the diagnosis may remain uncertain in the absence of clinical evidence of a valvular lesion. Usually, however, these signs appear rather early. *Myocardial insufficiency* is not, as a rule, a striking symptom; it was notable in less than a quarter, twenty-three of ninety-nine cases, followed to the end.

Death was usually the result of sepsis and nephritis. Occasionally it was sudden. Once, in an instance without

necropsy, it occurred in the midst of an anginoid attack; once from an embolism of a coronary artery.*

Terminal *bronchopneumonia* is frequent — 20 per cent. of our series.

Apart from the two cases which I believe to have been rheumatism, I have seen but three apparent recoveries from

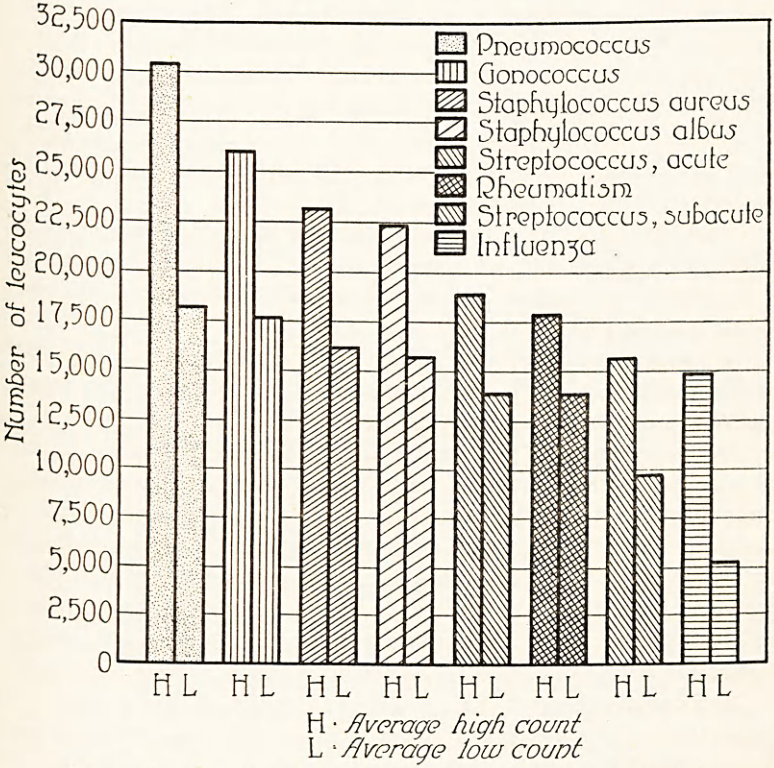

CHART X.—Acute and Subacute Rheumatic and Bacterial Endocarditis. Average leucocyte counts—high and low.

subacute streptococcal endocarditis. In the first of these,[65] where the history was not entirely satisfactory from a diagnostic

* This happened early in the course of the illness. The patient was a coloured man of 40 who was brought to the hospital moribund. At necropsy fresh fibrinous lesions showing *Streptococcus mitis* in pure culture were found on the pulmonic valve and on a plaque of syphilitic aortitis just opposite the mouth of the left coronary artery. A part of this latter thrombus had broken loose and plugged the left coronary. In another the death, though not immediate, was rather sudden, following an embolism of the mesenteric artery.

standpoint, the duration was from three to four months. The second was a typical example of subacute infection with *Streptococcus viridans*, with a duration of four months and intermittent fever, anæmia, albuminuria, red blood corpuscles in the urinary sediment, leucocytosis, in a coloured woman of 40 with coarctation of the aorta. There were no gross embolisms but the picture was quite characteristic, and *Streptococcus viridans* was obtained from the circulation in abundant pure cultures five times during five weeks. There was no apparent local focus of infection save peridental sepsis. The symptoms were wholly characteristic and there was no doubt in our minds that the lesion was at the seat of the aortic coarctation. She recovered entirely and remains in good health.

The third instance was that of a woman of 38 who passed through a characteristic course without, however, any grave embolic phenomena. The duration of the illness was about three months.*

I have never seen recovery from subacute streptococcal endocarditis in a patient from whom there had been persistent grave and repeated embolisms.

I have recently observed a fourth patient who passed through a wholly characteristic attack of what appeared to be subacute vegetative endocarditis with multiple emboli, intermittent fever, splenic enlargement, infarction of the spleen and kidney, with apparent recovery after three months. Here, however, we failed to cultivate the organism, although the clinical picture was such as to render the diagnosis strongly probable. The patient probably came to us during the course of her convalescence. Libman [66] has described like cases. As positive cultures were not obtained from the blood, I have not been willing to include this case in our series. It is unusual not to be able to demonstrate the bacteria, if proper care is taken.

* In this patient, although the evidence of cardiac involvement seemed clear and although the course of the illness with anorexia, loss of weight, anæmia, splenic enlargement, intermittent and remittent fever, and *Streptococcus viridans* septicæmia seemed quite characteristic, recovery was followed by a pelvic peritonitis of which there were no signs during the course of her illness and from which several months later, on operation, no growths were obtained on culture. The first recognized symptoms of fever had followed a gynæcological examination which had revealed nothing but a cervical polyp and an endocervicitis. I have seen the patient since and, while there is no further cardiac enlargement, the systolic murmur at the mitral area is persistent and indicative, I think, of an organic lesion.

There is one point in connexion with diagnosis on which too much emphasis cannot be laid, namely the length of time over which it is necessary to study the plates or tubes before discarding them as negative. Non-hæmolytic streptococci are sometimes very slow-growing organisms. Cultures should be taken, if possible, at the height of a febrile period and followed for a full three weeks. I have seen abundant pure cultures apparent first on the eighth and thirteenth days respectively.*

The average duration of the disease, as has been said, was over five months, and in eight cases the malady lasted over a year.

Summary.—Streptococcal endocarditis is, then, by far the commonest of the bacterial endocarditides. The clinical and pathological manifestations vary according to the character of the infecting organism.

(1) Infections due to *β Hæmolytic streptococcus* usually run a rapid course with high, continued fever and the phenomena of a malignant septicæmia. Endocardial lesions are often small, fibrinous villosities along the lines of closure or at the free border of mitral or aortic valves. They are generally unrecognized during life. Occasionally, however, *β Hæmolytic streptococcus* seems to give rise to a more subacute process resembling that occurring in infections with the more attenuated streptococci.

(2) The milder forms of streptococcus—non-hæmolytic, the group spoken of as *Streptococcus viridans*, including *α Hæmolytic streptococcus* (*Streptococcus mitis*), and, notably, *Streptococcus salivarius* and *Streptococcus fæcalis*—give rise to the characteristic picture of subacute vegetative endocarditis—*Endocarditis lenta.*

* The following is the procedure followed by Amoss (personal communication) in the Biological Division of Professor Longcope's Clinic:—For making the ordinary cultures 20 c.c. of blood is taken from a vein and mixed with 100 c.c. of plain dextrose agar. From this four plates are made, each of 2 c.c. of blood in 10 c.c. of agar. The remaining 12 c.c. is mixed with beef infusion broth. If growths do not appear and there is reason to suspect a streptococcal infection, 20 c.c. of citrated blood is laked in 100 c.c. distilled water. This is centrifugalized, the supernatant fluid is poured off, and the sediment is distributed in four deep tubes of dextrose, ascitic fluid agar. These are sealed and incubated. They should be followed for at least three weeks. Growths have been evident first only on the thirteenth day; growths from glands have appeared first as late as the eighteenth day.

(*To be continued*)