5-1-1936

Subacute bacterial endocarditis

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GRANT F. MOLLRING

SENIOR THESIS

1936
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DEFINITION AND TERMINOLOGY

Subacute Bacterial Endocarditis or non-hemolytic endocarditis is an accidental infection of a heart valve, in most instances previously damaged by a rheumatic process, congenital malformation, or possibly by another cause. It is characterized by temperature found in sepsis, physical signs of valvular heart disease, evidence of embolic processes as petechial and embolic glomerular nephritis and usually a positive blood culture yielding in most cases the Streptococcus viridans. The symptoms are those of a low grade toxemia and embolic phenomena. (9)

Since first recognized as a clinical entity, distinct from the acute form in mode of onset and duration, it has received various names. At any rate there is a general uniformity of opinion among writers on the subject, in regard to the clinical and pathological findings. Libman in his discussions included such conditions as are frequently called Chronic Ulcerative Endocarditis, Chronic Malignant Endocarditis, and Endocarditis Lenta. In this paper these names must of a necessity be used interchangeably as Subacute Bacterial Endocarditis. Other names referring to the subacute form are Subacute Infective Endocarditis, Subacute Vegetative Endocarditis,
and Subacute Streptococcus Endocarditis.

The disease may be distinguished from the acute form by the insidious onset and long duration with the finding of non pus forming organisms in most instances. It is distinguished from the acute and subacute form of rheumatic endocarditis by the fact that these are still generally accepted as being non-bacterial, as well as various pathological and clinical findings to be discussed later. The forms of endocarditis, even though they may be bacterial, that occur as a terminus in infectious diseases also will not be considered. The above differentiation was first brought to attention by Sir Thomas Herder in 1920. (13)

Emanuel Libman suggested that cases of Bacterial Endocarditis be designated according to the course and infecting organism. Because the infecting organism is practically always the Streptococcus, and practically always anhemolytic strains, he designated it as Subacute Streptococcus Endocarditis. This term has not taken hold however, rather has the term Subacute Bacterial Endocarditis acquired implication that the non-hemolytic streptococcus is the infecting organism unless another, such as the influenza bacillus is definitely mentioned. (29)
HISTORY

The occurrence of endocardial vegetations was recognized more than a century ago, but only in the twentieth century has an understanding of the course and pathology of the disease been acquired.

Burroughs in 1834 was of the opinion that the vegetations were due to change in the blood, and cited several cases of ulcerations and vegetations of the heart valves. Hughes in 1839 published an article on "Fibrinous Concretions of the Heart", a condition described as humoralism, an idea which prevailed. Since the nature was thus understood they were elevated to a rank of great importance. According to Morgagni in the early part of the sixteenth century, they were first regarded as masses of coagulated fibrin. They continued to attract attention during the seventeenth century, if a firm conviction was reached it was regarded as the cause of death so no further examination was deemed necessary. Rokitansky ascribed these to a poisonous state of the blood. (9)

However it was not until 1852 that the first unmistakable record of the clinical picture was presented.
by Kirkes in his article on "The Principle Effects Resulting from Detachments of Fibrinous Deposits from the Interior of the Heart and their mixture with the Circulating Blood". (4) In 1855 Virchow suggested the connection between uterine infection and vegetations found upon heart valves in a post mortem case. (36)

In 1868 Wilkes described a case of endocarditis of a duration of six months which was complicated by pyemia, and substantiated his observations by autopsy. At this time he called attention to the fact that bacterial endocarditis as a disease had not been seriously considered in textbooks before. (4) The first record of this in a textbook was by Bramwell in his "Diseases of the Heart", in 1880. He mentioned seven cases and made mention of similar conditions. (9)

Bacteria were first demonstrated by Huberg in 1869, and by the middle of the eighties ulcerative and verrucous forms had been described. Klebs and Koster had found bacteria from both of these forms, Orth had found them only in the ulcerative form. By this time organisms were being obtained from valves with regularity so the experimental stage began in 1885 with Philopowitz and Wysokowitch who were able to produce endocarditis in rabbits by the intravenous infection of pure cultures of the organism.
The latter investigator was able to produce it with great regularity if he previously wounded the valves or endocardium of the animal by sounding the corotid. (36)

In 1883 Lanceraux gave a clear and concise description of signs and symptoms as a definite type which occurred in patients who had suffered from malaria. He thought that malaria and this disease were in some way related. However the connection was probably a coincidence due to the fact that the soldiers which he had examined had been soldiers in the tropics. About this time Rapin also recognized the disease and gave a fairly accurate description of the skin lesions, later referred to as "Osler's sign", although these observations were not published for thirty years. These were more accurately described by Hubner in 1899 and clearly recognized by Munzer in 1880.

In 1882, Leyden called attention to the disease more particularly to the "pseudomalarial type", later emphasized by Osler(1893), Dock(1895), and Coleman(1905).

Osler in 1885 in his Gulstonian lectures first called attention to the disease in its various forms and thus brought the disease to a more prominent place in front of the profession. Stem and Herschler of Gorany's clinic emphasized the protean nature of the symptoms and bought to mind the deceptive remissions and intermissions. In 1891
Franzel mentioned it in a book on heart, and in 1896 Samuel West described the first case of a type simulating splenic anemia, later noted by Parkes Weber in 1910, Osler 1912, Reisman 1918, and Auerbach 1920. In 1899 Mabel Austin described the first cases due to Bacillus influenzae. Huebner emphasized the relation of the disease to its obscure continued fever, Ebstein stressed the frequency of the condition and Harbitz published the first satisfactory description of the pathological anatomy and histology. (4)

Beginning in 1887 a series of reports by Weichselbaum, Fraenkel and Sanger, ending with Horbitz in 1899, classified various types of microorganisms (streptococcus, staphylococcus and gonococcus) which were causitive factors for the so-called malignant endocarditis. About this time they began to think of the condition as primary in the valves from a focus of infection somewhere in the body, and keeping up a continual bacteremia, or as secondary, being only a part of the general septicemia.

Krauss in 1895, Gramwitz 1900, Kueman and Lenhartz 1901, and Canon in 1903 made reports which placed the study of endocarditis with regards blood findings on a firm basis. The two last observers may be said to have contributed more material, to have placed the subject on a more logical basis, than any of the previous observers, and to have given
great stimulus to the work. (36)

However Bacterial Endocarditis as a clinical entity in the subacute form is a rather recent and new disease. Osler apparently seems to be the first to describe this form of the disease in the presentation of ten cases, of what he termed Chronic Infectious Endocarditis, at St. Bartholemew Hospital, including twenty one cases which would fall into the subacute form. In 1910 Libman discussed 43 cases of this type of the disease. (39)

Since the beginning of the century appreciation of the frequency and importance of the subject shows in the increasing number of contributions. However since the work of Osler, Herder, and Libman, the additions to the original clinical descriptions and knowledge of treatment have been negligible.
ETIOLOGY

BACTERIOLOGICAL

It seems to be a common opinion at present that the anhemolytic streptococcus or Streptococcus viridans is the exciting bacterium in the large percentage of cases. The first one to suggest an infectious origin for this condition was Verchow in 1855, who associated it with uterine infections. Attention thereafter was directed to finding bacteria in vegetations in both ulcerative and verrucous for. Weichselbaum questioned whether the verrucous form was due to microbic invasion and this view received further support from Wysokowitch and Orth. As facts then stood two general types of endocarditis were known, namely those associated with bacteria and those not. It soon became evident that among those cases of endocarditis giving definitely positive blood cultures, a certain group could be distinguished because of their subacute or chronic character. These most frequently yielded streptococcus in blood cultures. (17)

Shottmuler in 1903, was the first to draw attention to the fact that hemolytic streptococci could be isolated in subacute Infective Endocarditis. After that very little was done or written by bacteriologists in this country for several years, to bring the condition to the notice of American observers. (42)
Horder(14) in 1909-9 accurately described cases of acute and chronic infectious endocarditis of which 17 were subacute and chronic and yielded blood cultures of "saprophytic streptococcus". He showed clearly with Andrews that the type of streptococcus most often found is not the highly pathogenic one producing suppurative processes, or the equally virulent pneumococcus, but one or the other of types more closely allied to the saprophytic streptococcus of the alimentary tract. As he expressed it, "It explains the chronicity and latency, scanty or absent leukocytosis, common afebrile periods, absence of suppuration in embolic infarcts, absence of any visible forms of infection, and the enormous number of living microorganisms which may be present without causing grave symptoms.

In the following year(1910), Shottmuller presented five cases in literature which were caused by a streptococcus of germ producing variety.(17)

In the same year Libman and Celler(28) discussed 43 cases in 36 of which blood cultures were done, 107 being done altogether. In 35 cases atypical cocci were found, and in one the influenza bacillus. The cocci found were all gram positive and were never found to have a capsule. They were either round or ovoid, or of a bacillary form, and were either in diploccus groups or in chains. They were usually
smaller than the ordinary streptococcus or pneumococcus and
grew more poorly. All produced precipitates in glucose
agar, and all were resistant to the action of bile. Libman
and Celler gave six criteria by which the organism was ident-
ified and distinguished from other forms. They appear as
follows:

1. All organisms such as streptococcus, and pneumo-
coccus are dissolved by bile.

2. Solution by bile is diagnostic of pneumococcus
and Streptococcus mucosus.

3. Absence of precipitation is against the organism
being streptococcus.

4. Fermentation of inulin to be not of pathog-
nomonic value.

5. Ring colonies are diagnostic of pneumoccus.

6. Culture characteristics.

   a. Definite, large, clear, area about a colony
is diagnostic of pneumoccus if it persists in several genera-
tions.

   b. Pneumoccus always show green.

In comparing their organisms with pneumoccus and strepto-
coccus, Libman and Celler state that they were smaller and
 grew more poorly. The real relationship to ordinary strep-
tococci was not definitely determined. At first sight they
did not appear to resemble pneumococcus even though pneum-
ococci may lose their capsules and the property of fermenting
inulin, and may acquire the property of precipitation. But pneumococci are not resistant to the action of bile. The features of Libman's Endocarditis coccus, remained constant over a long period of time.

Rosenow(34) found pneumococci in all cases. "When first isolated on broth they grew in clumps and produced diffuse turbidity slowly, upon agar slant they grew more or less tightly to the surface. The stained specimens gave diplococcus forms and chains. Chain formation as well as the property of growing in clumps in broth, and of adhering tightly to the surface of blood agar slants disappeared after culturing for a variable period. By culturing on an artificial media, all strains change gradually into typical lancelated diplococci often capsulated, growing as typical pneumococci in broth and blood agar slants. On animal inoculations this modification often occurred abruptly".

Libman(28) says,"The agglutination and opsonic studies of Rosenow do suggest relation to pneumococci but until the organisms are shown to have a definite pneumoccus character they cannot be surely classed as pneumococci."

Libman's organism showed the following cultural characteristics on patients blood. Sometimes there was a clear area which was lost on subsequent transplantations. On original plates the colonies were usually white, with or without a green opaque zone. The deeper colonies were
usually white or opaque. In subsequent cultures on blood
plates there were three types of growth; green pigment,
moist white growth, or dry almost colorless slight growth.

Thus up to this time four organisms had been de-
scribed, the Streptococcus viridans by Schottmuller, the End-
carditis coccus by Libman, the modified pneumoccus by
Rosenow, and the saprophytic streptoccus by Horder. Acc-
ording to Simons(36) "It is now well understood that the
organism which causes chronic bacterial endocarditis has
been variously named by many but these organisms are ident-
ical."

Libman succeeded in growing anhemolytic strepto-
coccus in the bulk of 95% of his cases. Geo. Ives (16)
reported forty cases with Streptococcus viridans in all, stating that many of the cultures were positive in twenty
four hours, with few exceptions in forty eight, and in a
very few not until the fourth or fifth day, no culture
being positive after the fourth day. Simons reported out
of 96 cases of the chronic form of endocarditis 92 cases
showing Streptococcus viridans and 4 the Bacillus influen-
zae.(9)

Clawson in a series of thirty cases found 32 posi-
tive blood cultures. He found Streptococcus viridans in 10,
hemolyticus in 8, staphylococci 3, pneumococcus 1. However
in all but one the organism was isolated from the heart
blood at necropsy, and it is known that the frequency of *Streptococcus hemolyticus* as an agonal invader is much more frequent than *Streptococcus viridans*.

The finding of *Streptococcus viridans* in the blood in cases of endocarditis indicates a subacute bacterial form and staphylococcus or *Streptococcus hemolyticus* generally indicates an acute form, but by no means rules out the subacute form. (5) It is also clear that *Streptococcus viridans* may give rise to an endocarditis running a rapid course. *Streptococcus viridans* in literature is the etiologic agent in the great majority of the cases, but is by no means the sole etiologic agent of Subacute Bacterial Endocarditis. (9)

A few cases of endocardial involvement with a long drawn out course properly characterized as subacute and chronic have yielded the gonococcus or the influenza bacillus. Since such a relatively small number have been dealt with, statistical analysis has probably not as yet given us the true proportion of the rarer infections. The incidence reported varies with the experience of the writer in dealing with these cases, and is safely placed at not more than 10% and is probably much less. *Streptococcus viridans* has been isolated by so many workers that it stands out as the great cause having been found in about 90% of the cases reported. (41)

The percentage of positive blood cultures as can be noted varies with different individuals and in different
countries. American authors agree in reporting a high percentage of positive cultures, British in finding a low percentage, while German writers fall into two groups, some reporting many positive others reporting only a few. It is impossible to explain these discrepancies. In some instances the diagnosis might be wrong and in many of the instances the reports are small and can not be of great statistical importance. (42)

According to White(41) the major contribution to the study of causative organisms in the disease was made by Clawson when he showed the necessity for careful preparation and standardization of media for cultivation, and when he showed the necessity for protracted study of the medium after inoculation with blood taken from veins for culture. When he showed that one or even two weeks may elapse before a clearly demonstrable growth of Streptococcus viridans will occur, he increased greatly the number of cases in which positive cultures occur.

CLINICAL

All observers agree that in order to contract Subacute Bacterial Endocarditis there must be evidence of a previously damaged valve. In the majority of instances rheumatic valve disease or some congenital defect precedes the involvement of the valves. The occurrence of previous arthritis with endocarditis determines to a certain extent at
least the location of the vegetative process of subacute Bacterial Endocarditis. It occurs very rarely on valves the seat of syphilis and the same may be said of the sclerotic valves of senescence. (31)

Between the production of the original valve lesion there is often an interval of several or many years of good health, although the infection may follow immediately subsequent to the valve lesion. To what extent the rheumatic history or preexisting valve lesion produces a predisposition to subsequent infection, or the disease in question is a problem still unsolved. (1)

Clawson (5), in examining 72 hearts of the subacute bacterial type, found that 41 (57%) showed anatomically thickening of the valves to such an extent that previous involve-was evident. As it follows, as in many cases in medicine, previous injury or excessive "wear and tear" promotes lessened resistance, and so it seems in the case of previously damaged valves predisposing to this disease. The condition is not specific of the subacute bacterial class but occurs also in the acute bacterial and rheumatic types as well. In comparing different classes it is seen that aside from the rheumatic class itself the subacute bacterial class shows the highest case incidence of a previous attack of rheumatism. In the 72 hearts examined by Clawson there was
a history of previous rheumatism in 36(50%). Previously thickened valves are probably produced by the rheumatic virus in more cases than by any other infective agent. Of 41 valves previously thickened in the 72 hearts, 27(66%) were preceded by an attack of rheumatism.

The exact manner of rheumatic disease predisposing to subacute Infective Endocarditis is undetermined. Sometimes the bacteriology proves that the relationship is no more than a predisposition. Coombs(6) had the opinion that the infective agent concerned in rheumatic disease is the the streptococcus of Poynton and Paine which has a close descriptive resemblance to the streptococcus of Shottmuller. He believed in the capacity of rheumatic infection to produce ulceration. But, as Denman (9) says, there is no histologic evidence of a direct rheumatic origin forthcoming even when the rheumatic factor is demonstrated clinically. Both Small and Berkhang directed attention to the frequency of rabbit diseases similar to the subacute form when serologically specific anhemolytic streptococci, isolated from patients with chronic arthritis, were injected intravenously. Small called this organism streptococcus cardioarthritides which was confirmed by Swift in 1928. Rosenow has produced similar lesions by the green streptococcus but in human pathology this bacterial endocarditis is practically always secondary.
In other words bacteria are implanted on an abnormal valve and in the majority of instances the valve has been the site of an old rheumatic endocarditis. (9)

According to Sprague (37) the infection rarely attacks mitral valves which on clinical examination show evidence of mitral stenosis. As he says, Clawson (5) notes among characteristic pathological changes large vegetations on otherwise normal leaflets, or leaflets thickened from previous inflammation and involvement of the mural endocardium. Levine (18) states that, "Although mitral stenosis is the most common type of rheumatic valve disease, yet bacterial endocarditis more frequently develops in patients who have had aortic regurgitation than those who have had mitral stenosis. It is those patients who either have aortic insufficiency or have a mitral systolic murmur without evidence of mitral stenosis who are most vulnerable in this regard."

Sprague (37) says that a patient with marked mitral stenosis with a loud sharp first sound, a loud mid and late diastolic murmur and relatively slight apical systolic, is much less likely to suffer from Subacute Bacterial Endocarditis than patients with rheumatic heart disease in whom mitral regurgitation persists without development of evidence of mitral stenosis. He suggested that rigid calcified valves of chronic mitral endocarditis are less favorable ground for bacteria, being subjected to less trauma, since valves can no longer shut and so cannot strike their abnormal surfaces
against each other. It being also possible that factors responsible for healing and calcification of valves are not active in the cases which do not develop evidence of stenosis, and that the protective antigenic agents are likewise not elaborated for defense against Streptococcus Viridans. He also suggests however that some other factor is of importance because of the fact that this infection is much less common in childhood at a time when rheumatic carditis is prevalent, and affected mitral valves are not healed or calcified. As Denman (9) says Kinsella made an interesting observation later confirmed by Libman, that all of these patients show a fairly high agglutinin titer in serum against streptococcus which is producing the disease. According to Denman, "This leads us to believe that the infection is accompanied by a state of relative tissue immunity and that antibodies are concomitant in the course. Thus there is an apparent paradox of an active and usually fatal infection in a biologically immune individual." He states further that patients are discovered with a positive blood culture who do not develop later symptoms, but show a mild course and progress to apparent recovery. "All are not infectious endocarditis who show a positive blood culture even with physical evidence of an old valve injury." Swift (40) found anhemolytic streptococci in the blood stream of most individuals at some time or other. This
opinion was also expressed by Grant and by Libman. Bessler found 6% of positive blood cultures from over 100 healthy persons. (9) Swift further stated that the disease is accompanied by a state of relative tissue immunity, and that antibodies in serum under experimental conditions is concomitant in the course, and the difference between a normal person, a man sick with rheumatic fever, and an individual with subacute Bacterial Endocarditis lies in the difference in tissue response.

Lenhartz in 25 cases gave urethral injury (instrumentation), the puerperium and pneumonia as predisposing causes (36). Horder (14) in 1909 presented 150 cases which he divided into three groups; those that had rheumatic endocarditis sometime previously, those in which rheumatic endocarditis led directly to infective endocarditis and those that had no history of rheumatism. Of the 150 cases he found 72 had had the subacute type of rheumatic fever or had had chorea, 10 had scarlet fever, 2 had syphilis and 2 influenza. In 53 there was no history of preceding disease. In 118 post-mortems he found congenital defects in 8 cases. He stated that the predisposition brought about by congenital defects were probably explained by chronic thickening of the endocardium which was often found in connexion with these. He stated that such thickening may occur in valves when they are ab-
normal, such as when there are two instead of three aortic or pulmonic cusps, or around the endocardium surrounding the patency of an interventricular septum, or on the wall of the right ventricle opposite the deficient septum or against which the blood stream impinges.

Lewis and Grant (19) in 1923 presented 31 cases of postmortems on patients dying of the disease. Right or 26% presented congenitally bicuspid aortic valves. If from the total those cases are excluded in which aortic valves were only slightly effected, or escaped, then 20 cases would be left. The incidence of bicuspid valves in these was 40%. They inspected several collections of specimens and found that the bicuspid valve was quite frequent amongst them. The arrived at the conclusion that in a very appreciable number of cases the disease is determined by an antecedent local valvular defect and that neither strength nor quantity of poison entering the system nor weaknesses in the general defense of the body determined the disease. Their conclusions were that the disease is a local infection of a heart valve or valves in a body not deficient in defense, and by an organism of low virulence that not uncommonly invades the blood stream. It is only because the diseased or malformed valve offers to organisms a suitable foothold that they are able to lodge and establish themselves.
However as to how the organisms actually attain their foothold is not known. Some have thought that the coronary capillaries become involved, others thought that they lodged on some surface irregularities. Grant, Wood, and Jones in 1928 published an article which tended to point toward the possibility that "neither surface recesses in the form of pockets or crevices, nor projections in the form of connective tissue thickenings covered with endothelium can be regarded as offering bacteris a foothold on the valve."

They found that small platelet thrombi occur with greatest frequency on those valves specially liable to the disease. "These apparently not themselves the result of bacterial invasion but probably due to local secondary change in thickened valves. Such thrombi can be regarded as offering passing organisms a suitable foothold and a nidus for their establishment."

Lewis and Grant in speaking of the predisposition to the disease by congenital defects, say that the history of the disease in an individual case is one of a long drawn out struggle in which fluctuating improvements in well being of the patient often appear and in which often enough the end actually comes through such and accident as embolism, or through renal deficiency. They conclude by saying that "in by no means a negligible proportion of Subacute Bacterial
Endocarditis the facility which the organisms concerned enter the blood stream, their numbers and virulence, are not of prime importance. In this same group neither presence of local foci of infection nor weakness in the body's immunizing defenses before the organism enters the blood stream and obtains foothold in the valves, can be regarded as an important contributing cause. The determining cause is the susceptibility of the valve. The invasion by organisms is almost physiological. We suspect that this same condition may apply to all cases of Subacute Infective Endocarditis."
PATHOLOGY

The pathology of the disease is largely that resulting from embolism with congestion, toxic and inflammatory changes playing their part in the organism as a whole. The kidneys, spleen, brain, lungs, and in fact every organ in the body may be involved in this way. Since the disease is of classification one of the heart diseases, and all the manifestations of embolism arise from the heart valve vegetations, the pathology of the heart itself will only be described. The others are components of general pathology of embolism and infarction and need not be discussed in detail here.

Certain pathological aspects peculiar to the disease make it stand out clearly in contrast to other infectious diseases involving the heart. The lesion is essentially an endocarditis rarely involving the myocardium and pericardium so common in rheumatic fever, and rarely attended by exudative phenomena. Clinically this accounts for the rarity of arrhythmias, pericarditis, pleurisy, and polyarthritis in this disease, also for the rarity of electrocardiographis evidence of parenchymatous irritation of the heart as indicated in a lengthened PR interval and alterations in the QRST complex. (30)

The left side of the heart is involved much more frequently. Morrison found 80 out of 88 cases involving the left side.
This also occurs in rheumatic endocarditis and is perhaps due to greater vascularization on that side. Blumer(4) tabulates 146 cases with regards valves involved. This tabulation will be given to provide some idea as to the frequency of involvement of various valves. The following table corresponds roughly to observations made by other authors.

<table>
<thead>
<tr>
<th>Valve Configuration</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve only</td>
<td>58</td>
</tr>
<tr>
<td>Aortic valve only</td>
<td>16</td>
</tr>
<tr>
<td>Mitral and aortic valve</td>
<td>56</td>
</tr>
<tr>
<td>Tricuspid valve only</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonic valve only</td>
<td>4</td>
</tr>
<tr>
<td>Mitral and Tricuspid valve</td>
<td>1</td>
</tr>
<tr>
<td>Aortic and Tricuspid valve</td>
<td>3</td>
</tr>
<tr>
<td>Aortic and Pulmonic valve</td>
<td>1</td>
</tr>
<tr>
<td>Mitral, Aortic and Tricuspid</td>
<td>4</td>
</tr>
</tbody>
</table>

From the above it is seen that the mitral is involved much more frequently than the aortic, however both are involved together perhaps about the same or more frequently. In addition to the above another characteristic of this disease is the frequency of involvement of the mural endocardium of the auricle and ventricle and chordae tendinae(30) Of 150 autopsies Blumer found the mural endocardium to be involved in 55.3%. In this series the walls of the cardiac cavities, the chordae tendinae, intima of the aorta or pulmonary artery were involved either alone or in conjunction with the valvular endocardium. He emphasized the mural involvement because it is of such great frequency that its presence always suggests the subacute form of the disease. Involvement of auricular
and ventricular endocardium associated with valvulitis has been regarded as occurring only in subacute Bacterial Endocarditis. Perhaps the mural involvement is explained on the basis of duration of the process, for in the longer duration of this disease there is a greater possibility for spreading. (5)

The disease as is most commonly accepted, most commonly appears on a valve formerly the center of rheumatic involvement. The endocarditic inflammatory process of rheumatic produces a thrombus characterized by exudation of red blood cells, white blood cells, fibrin, and blood platelets. This thrombus undergoes subsequent organization producing a typical wart. Subsequent contraction of the warts results in scar formation with resulting stenosis and insufficiency of valve leaflets. With superimposed bacterial infection another acute exudate is thrown out, this time containing bacteria, and due to diminished blood supply caused by previous rheumatic damage these new vegetations become very loosely organized, and as blood rushes past the loosely organized vegetations, embolic phenomena are produced. (39) The lesions are larger than in rheumatic endocarditis, with round cell infiltration and agglutination of blood platelets. The mass is invaded by large numbers of bacteria which inhibit the spread of endothelium of the adjacent endocardium or its surface. The process then spreads by continuity. The freshly
formed portions of this vegetation consist almost entirely of bacteria. In the deeper portion they tend to diminish, fibroblasts appear and when healing, connective tissue is formed. (30)

The lesions are quite typical. As a rule there is considerable proliferation of the mitral valves. The vegetations are variously colored; greyish, pinkish, greenish. They extend upward, creeping over and involving a good part of the left auricular endocardium. They extend down along the mitral chordae tendinae being here somewhat destructive and causing ulceration and often rupture of the chordae. In aortic valves the lesions are similar but their extent is variable and are usually not characteristic. They result often in aneurysms and rupture of the valves which is less common in mitral involvement. There may be only a small vegetation on one or more, or there may be enormous green masses partially blocking the orifice. They have a tendency to spread over the endocardium and over the ventricular aspect of the aortic flap of the mitral valve and down over the chordae tendinae. At times they give a stalactite appearance. (27) The above is in contradistinction to the usual ulcerative type seen more commonly in acute cases. This seems to be connected with the more destructive nature of Streptococcus pyogenes and staphylococcus in contradistinction to Strep-
tococcus viridans and Bacillus influenzae. (36)

Clawson (5) mentions that Libman in 1920 pointed out that pericarditis was seldom found. It is infrequent in any but rheumatic hearts except when rheumatism has preceded attacks of acute or subacute bacterial endocarditis, and in such conditions rheumatic virus is generally responsible. Most authors state that myocarditis is seldom found. However Clawson in studying the myocardium in 54 hearts of the subacute bacterial type, found that there was definite indication of inflammation in 13 (24%). These showed an interstitial exudate of large or small mononuclear cells in all but two in which polymorphs were found.
SYMPTOMATOLOGY

As it appears at present Subacute Bacterial Endocarditis has several forms. The most common and most malignant form will now be discussed with regard its symptoms and signs. Later in the paper some of the other variations that have been described by several authors, especially Emanuel Libman of Mt. Sinai Hospital in New York, will be discussed.

Onset. The disease as it is commonly thought of has an onset that may be described as being insidious. Due to this fact it may take on many variations which bring it to the attention of the patient and his physician. There is no regular sequence of symptom development. As it is with any form of mild low grade chronic sepsis the first symptoms usually manifested are included in the following: Loss of weight, anorexia, chills, vertigo, headache, cough, sweats, fever, vomiting, flatulence, nausea, gastric discomfort, feeling of impending dissolution, tenderness and throbbing under the right costal margins. Embolic phenomena may first call attention to the condition; they will be discussed later. (39)

Libman(25) says that the physician should be on the lookout in every case in which fever is present and in which there is no proof that the cause is elsewhere than the valves.
It has been noted that fever is the most common symptom at the onset of the disease. Libman discusses a few of the modes of onset of the disease as he has noticed them, and these will be enumerated in outline as follows:

1. There may be fever, chills and sweats with headache and drowsy manifestations as in typhoid.

2. Malaria may be thought of because of intermittent fever and chills with perhaps an enlarged spleen making the differentiation more difficult.

3. The disease often begins with headache, malaise, general pains and nasal symptoms, as in influenza.

4. Tuberculosis may be simulated by fever cough, loss of flesh, sweats, weakness, and perhaps hemoptysis.

5. Rheumatic fever may be simulated by joint pains and fever.

6. The tender cutaneous nodes commonly present in this disease, and which may be the first manifestation, may be mistaken for paronychia.

7. Neurasthenia occasionally must be differentiated because of the onset taking the form of general weakness, loss of weight, pain in the limbs and abdomen, with depression and insomnia.

8. Renovesical symptoms as pain in the back, hematuria and bladder symptoms may be first.
9. Dyspnea, palpitation and edema may point toward myocardial insufficiency.

10. Occasionally the onset is pain in the right hypochondrium with local rigidity and tenderness.

11. Gastrointestinal symptoms as vomiting, gastric distress, loss of appetite and hyperacidity are common.

12. Occasionally the beginning is in the puerperal period with varied symptoms, at times difficult to differentiate from symptoms arising from the uterus.

The above will bring out to some extent what a varied picture may be presented to the physician as the patient comes to him. Fever, chills and sweats. The most common and the most constant symptom, fever, will be dealt with first along with the occasionally accompanying chills and sweats. Some degree of fever is present in most cases although not in all, however the latter are probably not afebrile throughout their course. The types of fever vary considerably. Occasionally there is a high continued fever which lasts a week or more and which then may change to an intermittent form possibly concurrent with the ulcerating changes in the heart valves and the dissemination of infective emboli. (14) According to Libman (25) the type which is seen most often is an irregular remittent fever. It may show increasing and decreasing waves till
103 degrees or 104 degrees is reached. A high and regular quotidian, intermittent fever is seen sometimes in the later stages. Cotton's cases(8) showed a daily rise to 100 degrees for several weeks or longer which was the rule. In a few of his cases a remittent fever to 104 degrees was noticed. In a large number, afebrile periods of one to four weeks was recorded. The latter observation has been quite been quite universally recorded but seems to have no bearing on the improvement of the cases. The temperature is apt to take a lower range or cease altogether shortly before death. According to Horder(14) this should not be taken as a good prognostic indication especially when signs of renal inadequacy intervene, as is usually the case.

Some patients present chills with fever and many show fever and sweats. Some show all three. (10) Occasionally there are chills in the course of the disease due to embolism or to the onset of intercurrent disease. When frequent, the chills may have been ushered in by splenic infarction or may be due to sharp bactericidal action of the blood serum. The chills are usually followed by profuse sweating but sweating constitutes in itself a very common and often an early symptom. (25)

Blood. The secondary anemia is another finding that is
very characteristic of the disease. The anemia is progressive, and in some cases is extreme, even suggesting the blood picture of Pernicious Anemia. The hemoglobin is usually markedly lowered and the red blood count may go as low as two million. (14) The anemia is due to disturbance of erythrocytes by cocci, even though anhemolytic, and to changes in the bone marrow and its functional capacity. According to Hurxthal (15) the white count is apt to be extremely variable, and this finding may be of value in diagnosis. The majority show a leukocytosis, although there is great variability as to the amount, and at times the leukocytes may be normal. If the patient is followed along a leukopenia may be present at various times, but it is rare for this to be present continually. At any rate a marked variation in number of leukocytes may take place from day to day and often there is a sudden appearance of macrophages. These were first described by Van Neys in 1907 but their significance was not appreciated at the time. However not long after, their occurrence in this disease was recognized. As Hurxthal states, "Their presence is pathognomonic of bacterial endocarditis. The findings of one or two large mononuclear cells with an ingested red cell is strong evidence of the disease, while the presence of an increase of large mononuclears with or without vacuolization is a very suggestive and frequent finding."
To look for them the best technique is to use the lobe of the ear, rub and massage it rather vigorously until a good flush appears, then make a puncture that will give a fairly free flow of blood. It may be that this opens up small vessels so these can escape. (41) It is the opinion of Hurxthal that they may be found in over 50% of the cases. White says that they are suggestive but not pathognomonic.

The greater percentage of the remainder of the symptoms and signs are the result of emboli loosed from the vegetations on the heart valves, and as it follows, manifest themselves in every organ and system in the body, the majority being systemic rather than pulmonic because the valves on the left side of the heart are most often affected.

Cardiac. Cardiac symptoms may be said to be conspicuous by their absence as far as being of direct diagnostic value. The disease develops in a greater percentage of cases on a valve already diseased or deformed. The signs are those of the previous involvement. When there has been a previous rheumatic involvement, or when in the presence of congenital defect, or more rarely syphilitic valvular disease, with other signs of the disease, they may be of use, otherwise not, in diagnosing the endocarditis. Anomalies of the aortic valve leaflets commonly give no sign of their presence and appear to contribute to the frequency of Subacute Bacterial
Endocarditis only by furnishing a favourable site for lodgement of organisms in or upon these valves which were not previously the site of infection. In the early stages of a considerable number of cases, and even through the course some, there may be either not auscultatory signs of valve involvement or the signs which are first found may show no progressive changes. It is more common for cases to show changes in the auscultatory signs however, so the difficulty in diagnosis may not be as great in these. (40). It is however unusual for any new murmurs to develop during the course of the disease because when the mitral valve is involved there is little tendency to ulceration and the vegetations extend up on the wall of the auricle and in volve the chordae tendinae. Usually there is no tendency toward blocking of the mitral orifice. When the aortic valves are involved ulceration may occur but it is unusual. In any event any ulcerative insufficiency is compensated for by the vegetations. Although there is usually no new murmurs, the murmurs may grow louder and rougher so in following up a case if murmurs are present they should be watched and tabulated to see if any change occurs. (25)

Arythmias are rare and it may be said that the presence of auricular fibrillation is against the diagnosis.

Rothchild, Sacks and Libman (35) in a study of 123 cases of
the disease with regards the disturbance of the cardiac mechanism, found auricular fibrillation but once among the active bacterial group (109 cases), or an incidence of 1%. and in this case the rythym was normal until three days before death. In three other cases in which fibrillation was noted, and in a single instance of flutter, the endocarditis had already progressed to the bacteria free stage (this stage to be discussed later). The above findings show how rare the auricular fibrillation is in the active or bacterial phase of the disease. Also observations upon a large series of patients with fibrillation convinced them that once an arrhythmia was permanently established there is little danger that subacute Bacterial endocarditis will intervene.

All grades of delay of impulse conduction from the auricle to the ventricle have been noted, and are significant since they occur particularly when the ulcerative processes in the intraventricular septum involve the conducting system. Other changes which might be shown by the electrocardiogram are infrequent and are of no diagnostic or prognostic value (40).

The symptoms are those of myocardial insufficiency. These may be enumerated briefly but need not be discussed here. They are breathlessness on exertion or dyspnea or orthopnea, edema (feet and ankles, feet and abdomen, feet and face, feet, face and abdomen or general anasarca), palpitation, bronchitis, cough without expetoration, thoracic pain (precordial, sense
of constriction or angina like), the hypertrophy and dilatation usually occurring in the later stages.

The pulse rate is of considerable interest on account of what seems to be an accepted fact, namely that endocarditis is always associated with increased rate. Frequently however in some cases a normal rate may be seen even in the presence of fever. (15)

**Spleen.** Enlargement of the spleen is a common finding in the disease and contributes much toward the diagnosis but often leads one astray as far as the differential side goes. Clawson (5) says that splenic enlargement is the usual finding and occurs in 62% of his series of cases. Starling (37) in discussing the pathology reported enlarged spleens in 16 out of 17 autopsies. According to Clawson (5) Arnett found in 286 autopsies in cases with enlarged spleens, that enlargement of the spleen in chronic passive congestion resulting from cardiac failure is about one half as frequent as it is in the disease in question. Enlargement of the spleen in chronic valvular disease is often ascribed to venous engorgement. Cotton (8) found that the spleen was palpable in some of his cases when the venous engorgement was absent and in many with only a moderate degree of venous stasis. In a few infarction was absent, and he prefers to consider splenic enlargement in this disease as often a sign of an active infective proc-
Frequently however infarctions are present and cause severe pain and vomiting. The pain being due partly to the stretching of the peritoneum, later to perisplenitis. Pain may be felt solely in the cardiac area and at times in the left shoulder. Infarcts may be very extensive and break down or even may cause rupture. Large softening infarcts may give rise to wide fluctuation of temperature, when before the temperature may have been running a mild course, although true suppuration doesn't occur. The latter is a feature of the disease known for a long time, for pus formation does not occur in any of the lesions though it is frequent in the acute form of the disease. (25)

Even though enlargement of the spleen is common it cannot weigh against the diagnosis since a restricting factor such as previous perisplenitis often prevents the enlargement from becoming manifest. (40)

Kidney. In most cases during the course of the disease the kidneys are involved by embolism. This manifests itself in the kidney in ways extremely important for recognition of the disease. In many patients erythrocytes are a constant finding in sediment from the urine. In a lesser number of patients they occur at irregular periods in showers, but even here as a rule a careful search will reveal a very few within the intervals. Hematuria severe enough to give visible color
changes in the urine is infrequent but occurs especially with gross infarction of the kidney, and this may be signalled by pain or discomfort of abrupt onset in the kidney region. Albumin and casts are never large in amount but the casts are of several varieties. Though the kidneys usually show evidence of the disease the function as a rule is seldom reduced to the low level as in chronic glomerulonephritis except as a terminal event. Hypertension is seldom found. If the glomerular lesions are very numerous subacute hemorrhagic nephritis may occur, and at times if the cardiac lesion heals a secondary contracted kidney may be reached.

Progressive destruction of the renal units by embolism is the cause of death by uremia in certain individuals who seem to be surviving the infective process itself. Some of the glomerular lesions are indistinguishable from those of chronic glomerulonephritis, but for the most part the changes are due to embolism often with the presence of many streptococci in the glomerular loops. Vesical symptoms such as frequency, with pain and tenesmus, pain in the hypogastrium and sometimes urine retention are very common and have led to erroneous diagnoses such as abscess, tuberculosis or calculus. Marked evidences of renal insufficiency only occasionally occur and then only shortly before the patient dies. The patient usually expires from other causes before this
stage is reached.\(^{(25)}\)

The pulmonary, gastro-intestinal, bone and joint, brain and eye signs and symptoms, which as can readily be seen are mostly due to embolism and toxic manifestations, such as would be present in any embolic syndrome, will be discussed briefly. They will be discussed mainly so as to bring out in the mind a little more forcefully the problems of possible differential diagnosis, and to give a clearer idea of the many and varied manifestations of the disease.

According to Hurxthal\(^{(15)}\) respiratory signs and symptoms are present in over 25% of the cases. Libman\(^{(25)}\) states that cough is very frequent even early and at autopsy no lung changes may be found. There may be pulmonary congestion or enlarged tracheobronchial lymph nodes. There is a tendency toward bronchitis in most cases and the sputum may become hemorrhagic although hemorrhagic expectoration is not necessarily a sign of infarction and vice versa.

It may be due to a congestion of the lung plus a general hemorrhagic tendency. Infarction of the lung is not frequent and when it occurs it is usually the same as that occurring in valvular disease, although vegetations may reach the lung from right sided heart lesions or occasionally from the left side due to an open foramen ovale or ductus arteriosus. As
Hurxthal says, even though the majority of vegetations are on the left side there may be small emboli not producing gross infarction but plugging the smaller nutrient bronchial vessels thereby setting up sufficient local disturbance to give rise in part to the frequency of pulmonic signs not explainable on any other basis. Pleural effusion may occur secondary to pneumonia or infarction and there may be pulmonary edema during the course of the disease, but when this occurs it is more usually near death.

**Gastro-intestinal.** Abdominal pain and general gastrointestinal symptoms are conspicuous in some cases. There is often disturbance after eating, pressure in the epigastrium, anorexia, nausea and vomiting, or symptoms generally like hyperchlorhydria. The symptoms may lead one to suspect malignant disease. Gastro-intestinal symptoms may of course be produced reflexly from congestion of the liver or infarction of the spleen or kidney. There are often unexplainable pains in the epigastrium and these may occur in severe form early in the disease. Herder(13) found that 17% of a large series of his patients had abdominal pain. When present it was usually in the upper Quadrant. The liver is often enlarged due to toxemia and congestion. If the enlargement is marked there may be tenderness and occasionally if is very marked and rigidity is present. Jaundice however is unusual. Pains are also produced from involvement of the larger abdominal
organs and embolic aneurysms in the mesenteric vessels. (25) Pains without assignable cause may occur anywhere and Herder believes such pains may be due to small omental hemorrhages. **Joints** Swelling of the joints or periarticular structures is not infrequent. Patients often complain of arthritic or periarthritic pains, although these are all milder than in rheumatic fever. Lenhartz has described many of the pains as being "more or less marked rheumatic pains located less in the joints and more in the muscular attachments nearby, or in the periosteum of the long bones." (25) Redness is not unusually found with the swellings and pain. The edema itself may be slightly marked early but it is much more frequent and in greater evidence later. It is usually soft and is due partly to anemia and partly to cardiac weakness as explained by Libman. General edema may occur more commonly due to anemia than nephritis. Herder (14) states that the involvement of periarticular structures is probably embolic because they lack the symmetry characteristic of true rheumatic joints and there is less tendency to synovial effusion, focal edema and discoloration common in the overlying skin. At any rate the edema and pain are probably not the result of inflammation as is seen in rheumatic fever. Failure to bring about relief of symptoms with salicylates in acute arthritis associated with rheumatic heart should lead one to suspect bacterial endocarditis.
Bones Libman(25) stresses the tender sternum in pointing toward diagnosis of the disease in some patients. He says that this does not occur in all, and when it does occur is apt to be late. He also brought out that there are many causes of this symptom but when it is found and there is no definite cause discernible the examiner should think of subacute bacterial endocarditis. He states that it is best to tap the upper part and then the lower part with the same force to elicit tenderness, and that it is best not to use pressure. As a possible cause he suggests active regeneration of the bone marrow. However, severe pains and tenderness may be located in any of the bones, and as was mentioned before Lenhardt suggested that the source was located in the periosteum.

Cerebral Cerebral symptoms are quite common. Early in the course there may be vertigo in the morning or after exertion. Headache, irritability, and insomnia are common. Near the end of the disease the patient is apt to develop delirium, stupor, and coma. There may be extensive hemorrhages into the brain or into the ventricle and subarachnoid spaces which are due in the main to rupture of embolic aneurysms. Cerebral embolism is very frequent and various forms of paresis or paralysis have been described.(25)

Eye The eye findings are of much value in the diagnosis of the disease at times. Most commonly they occur as petechial hemorrhages in the fundus or small hemorrhages. In contrast to rheumatic endocarditis, iritis, or iridocyclitis are very rare.
Amblyopia or central scotoma due to embolism may occur and if the eye muscles blood supply is involved strabismus occurs. (25) Falconer(10) published 15 cases in which he found five who had optic neuritis accompanied in four by recurrent retinal hemorrhages. In these both eyes were effected but there was no failure of vision in any. He states that to exclude retinal hemorrhage the fundus has to be repeatedly examined, as they come and go and leave no trace of their presence. In discussing the value of the above indifferent- tial diagnosis Falconer brings out that their main value lies in the hint they give that the condition is more serious than that at first sight may be apparent.

One of the main set of symptoms and signs, and perhaps the most important as far as calling the attention of the patient as well as the physician to the disease, and assisting greatly in the clinical diagnosis, remains to be dealt with. It is this set of symptoms and signs manifest- ing themselves in the cutaneous system and small digits of which we are speaking. It consists of petechiae, Osler's nodes, splinter hemorrhages, tender fingers and toes and clubbing of the fingers. These have been discussed in detail by many authors especially Cotton, Blumer, Libman, Osler, and others and are commonly recognized as being of quite notable diagnostic value.

Petechiae petechiae in Libman's series occur in over 80% of the cases. They vary in amount and are apt to come out in crops lasting several days and then disappearing
leaving a yellowish stain. They should be looked for daily because they disappear so fast. They are a dull red color at first and later small hemorrhages with a yellowish pin point center. When first appearing they are dull red in color are never palpable and do not fade on pressure. (8) It is important to examine particularly the conjunctival mucous membrane of the upper and lower lid, the supraclavicular and lateral cervical regions, the buccal mucous membrane and the fundus of the eye. If the lid is squeezed they will stand out sharply against the anemic conjunctival mucosa. When looking for them on the buccal mucous membrane caution must be exercised in not mistaking traumatic lesions for petechiae, especially near the labial commissure, because many people bite here producing small hemorrhages. Petechiae in cerebrospinal meningitis are like these but are more apt to be bluish. Also splashes of hemorrhage in the conjunctival mucous membrane unaccompanied by general purpura occurs more often in cerebrospinal meningitis. When the petechiae have white centers they are best for diagnosis because they are then definitely embolic and not purpuric in nature. Elevation does not occur in Subacute Bacterial Endocarditis. It is pathognomonic of staphylococcus infection, especially aureus, and they are then really miliary abscesses surrounded by a zone of hemorrhage. (16)

It was thought by many of the earlier writers, and
some of the later ones, that the petechiae are embolic; however Lewis and Harmer (20) in 1926 showed that the petechiae may be artificially produced in a case of subacute bacterial endocarditis by increasing the venous pressure. By using a blood pressure cuff and thus distending the veins but not occluding the arteries they found that in normal subjects to produce petechiae a pressure of at least 90 millimeters of mercury from within or an equivalent or greater suction (usually -130) from without for a space of 3 minutes was necessary. The petechiae were pinpoint size or a little larger and appeared in the superficial layers of the skin. In contradistinction however, a pressure of but 60-70 millimeters similarly applied and maintained in cases of subacute bacterial endocarditis produced similar petechiae. They decided that two factors probably acted together in determining the rupture, namely a lowered tone of the vessels whereby they fail to resist distention, and undue fragility of the vessel wall. They found that the pressure required was unusually low in the disease in question and always low when spontaneous hemorrhages are occurring. It is Hurxthol’s (15) opinion that this would seem to indicate that a good many lesions are simply purpuric and therefore are not especially indicative of endocarditis. He thinks that by far the most reliable sign is the conjunctival petechiae.
Osler's Nodes. These are very important diagnostic signs of the disease as Blumer says. They were first described by Huebner in 1899 as a transitory swelling with pain in the finger pads and reddening of the skin of localized parts of the finger similar to erythema multiforme. Neinzer in 1900 described a painful spot on the thumb of one of his patients. Rapin in 1903 speaks of what he calls "taches rosées" on the fingers and speaks of painful indurated spots on the body "like flea Bites". Osler however was the first to pay particular attention to them. He described them as follows: "The nodes appear at intervals as small swollen areas, some the size of petechiae and others as large as 1.5 cm. in diameter. They are raised, red and with a whitish spot in the center. They may pass away in a few hours, but usually last one day or longer. The most common site is on the tip of the finger which may be slightly swollen. They also occur in the pads of the fingers and the skin of the lower part of the arm. In one case they occurred in the skin of the flank. They are never hemorrhagic. Sometimes they are of a vivid pink hue with a slightly opaque center. Libman found other forms as erythematous areas without nodule formation, which may cover the whole toe pad or be pinpoint. Some of the larger ones being paler, and in them can be seen darker erythematous lesions the size of a pinpoint. No matter how small they are always tender when recent. Also he encountered anemic areas in the skin usually
accompanied by nodule formation, and these were also tender. A whole terminal phalanx of a hand or foot may be anemic, swollen and tender, or a dusky red or purplish, swollen and tender. Sometimes there was an anemic nodule surrounded by a delicate area of hyperemia. A week may elapse before all the tenderness has disappeared. Most lesions disappear within 3-4 days. They may often change from a red to a bluish color and may leave a light brownish stain behind them. Blumer(3) states that there is discrepancy in the frequency of observation of these nodes. There is less about it in the German literature than in the French. His experience is that if the lesion is looked for, it can be observed, or if the history is asked for, it can be obtained in approximately 40% of the patients. It is not pathognomonic of the subacute form but in the vast majority is suggestive of this form of the disease.

Where the emboli lodge in the deeper vessels of the fingers and toes, Osler's nodes do not develop. Blumer(3) observed a number who complained of localized pain or tenderness in one or more of the fingers and toes. There was pain on pressure but no swelling nor redness. It was his assumption that this was due to enlodgement of deep emboli and this was substantiated in some by simultaneous occurrence of obvious peripheral emboli. He thought that this was probably similar to tender toes which sometimes occur in typhoid fever.
Splinter Hemorrhages. In two of 48 cases Blumer(3) observed hemorrhagic lesions under the nails. Examination showed linear hemorrhages beneath the nails four to five millimeters in length and several millimeters removed from the nail's growing edge.

Clubbed fingers. Clubbing of the fingers is the last important sign to be discussed in the general symptomatology of the disease. It has been generally stated that clubbing is usually associated with pulmonary lesions particularly with bronchiectasis or else with congenital cardiac lesions. Its significance in Subacute Bacterial Endocarditis was not noted for sometime. The English school of clinicians were probably the first to appreciate the frequency of clubbing in this disease. Cotton(7) states that they occur in 70% of the cases. He states that the ends of the fingers appear swollen and rounded. The nails are convex and there is an increase of connective tissue at the base of the nails or on the palmar surface of the finger tips, or a lateral widening of the pulp of the finger. There are not necessarily signs of local venous stasis giving a reddish or cyanosed appearance as in clubbed fingers associated with congenital heart disease. The finger tips in some are distinctly pale, in others the color is in no way different from the normal healthy skin. In some the changes in the finger tips are associated with hard and scaly hands, fray-
ed nails or nailbed or other signs of local injury. Cotton emphasizes the frequency of clubbing in association with an enlarged heart and states that they are not seen, or at least are seen relatively infrequently in cases without signs of cardiac enlargement. He found clubbing of the fingers in 63 of 788 cases of structural disease of the heart, and of these 44 were in Subacute Infective Endocarditis. He says that "In cases of structural disease occurring amongst adults, clubbing of the fingers is usually associated with Subacute Infective Endocarditis. Although clubbing is not to be regarded as conclusive evidence of infection it is nevertheless one of the most valuable signs we possess in determining the correct diagnosis."
"When one observes for a period of time a heart lesion accompanied by fever of irregular remittent type with loss of weight, joint pains, myalgia, progressive anemia of the secondary type, anorexia, leukocytosis to a moderate degree, and all the characteristics of a mild or moderate septicemia, repeated blood cultures should be made and in 90% of the cases the organism will be found."(43)

Moore(29) states that the recognition in early or pre-embolic stage is seldom easy, usually difficult, and often impossible. As Libman has well pointed out, its early manifestations often mimic other diseases referable to an organ which has been involved and the underlying systemic disorder not infrequently foes for a long time unrecognized, particularly when the patient seeks the advice of a specialist relative to the offending organ. Unnecessary instrumental procedures and misdirected surgery can often be avoided by proper interpretation of phenomena occurring early in the disease. Although embolic phenomena, including petechiae and tender cutaneous nodes should constantly be looked for they are not infrequently absent. Of even more importance early in the illness are the "septic" manifestations, such as continued chills and fever occurring in a patient who has a heart murmur. The relatively mild clin-
ical course for many months with freedom from severe complicating symptoms is not unusual. (2)

A positive blood culture is usually relied on to provide a correct diagnosis, but clinical symptoms of course must be used when for some reason or other, as faulty technique, bacteria free stage etc., cause a negative result. In rare instances even a positive blood culture does not mean endocarditis, and if endocarditis is present it may or may not be the type under consideration. (16) According to Musser (31) and generally substantiated by authors such as Libman, Horder etc., the most definite positive substantiative finding is the occurrence of embolic phenomena.

Most important in the differential diagnosis, as enumerated by Blumer (4), are influenza, malaria, typhoid, malta fever, pulmonary and renal tuberculosis, thrombophlebitis, purpura, hemorrhagica, pernicious anemia, splenic anemia, recurrent rheumatic endocarditis, infections arthritis, pyelitis, cholecystitis, and obscure pus collections such as osteomyelitis, empyema and liver abscess. There is also at times a close simulation of active rheumatic endocarditis. It has been shown by Clawson (5) that a positive blood culture of Streptococcus viridans can be obtained from both types and one frequently finds so-called rheumatic skin nodules in patients with rheumatic endocarditis. Clawson states that the important factor in differentialiation are embolic manifestations.
VARIous FORMS OF THE DISEASE DESCRIBED, WITH PROGNOSIS AND MANNER OF TERMINATION

In addition to the typical form of the disease, generally followed in describing the symptomatology, other forms have been mentioned in the literature especially by Emanuel Libman. Libman observed over 800 cases in a period of twenty-five years and since then has stopped counting them. He regarded the prognosis at first as entirely hopeless as has almost everyone else, however it is his opinion that the outlook depends on the type of case. Libman (23) divides the disease into four main forms:

1. Active bacterial form.
2. Bacteria free stage.
3. Transitional forms.
4. Mild forms.
5. Recurrent forms.

Active bacterial form. This form of the disease, or the type usually recognized, runs a course of 4-18 months and is characterized by fairly marked temperature elevation, positive blood culture and usually embolic phenomena. This type as mentioned above was discussed under the symptomatology of the disease. In Libman's first 150 cases he had four complete recoveries, but since then has observ-
ed a number of other instances. Altogether he has observed 10 complete recoveries.

The cause of death in this type is most commonly exhaustion. The myocardial weakness which may be present is usually of the type due to fever, anemia and general weakness. At times, particularly if mitral stenosis is present, death may occur suddenly, preceded or not by hemoptysis due to pulmonary infarction or by a sharp attack of pulmonary edema. Embolism of coronary artery is a rare terminal event but of a cerebral vessel quite a frequent one. The patient may be carried off by gangrene due to embolism of a peripheral vessel. Other causes are polynuclear meningitis, subarachnoid and intraventricular hemorrhage which are due at times to rupture of embolic aneurysms, rupture of such aneurysms situated elsewhere in the body, hyperpyrexia and uremia. The last mentioned is uncommon in cases still active compared to those in the bacteria free stage.

Complicating pneumonia or intercurrent or preexisting disease may carry off the patient. In some cases a combination of various cause. Of cases recovered completely from the attack some have remained free from the infection also some pass into the bacteria free stage and succumb after some weeks or months.

Bacteria free stage. This type has especially been des-
cribed by Libman (27). He described 21 cases in 1912-1913. This type refers to patients who usually present valvular defects and certain symptoms due to a previous attack of the disease and is usually not clinically recognized. Blood cultures remain sterile in this type except for rare transitory bacteremia, and at postmortem the vegetations even when stained by special methods show few or no bacteria. When the number of bacteria is small or when they are absent the patient is going over into the bacteria free stage and the lesions will be found to be healing. The characteristic endocardial lesions will be found but they will have undergone healing with fibrosis, hyalinization and calcification, no longer containing bacteria in spreads and sections. Negative culture alone do not establish this diagnosis for in some cases the blood cultures are persistently negative and myriads of bacteria are discovered on endocardial vegetations at autopsy. Such cases are merely in the active stage in which bacteria can not be cultured. (35)

Embolism is quite common in this type also, for even when the lesions are bacteria free and even when they undergone fibrosis and calcification pieces may break off and plug the vessels. The cases are essentially afebrile as far as the endocarditis is concerned for there are no bacteria on the surface of the lesions to be thrown into the
blood current keeping up fever and other toxic manifestations. However fever may be produced by marked anemia, large infarctions or complicating febrile conditions.

There is usually a valvular defect and also one or more of the following manifestations in varying combinations: A peculiar dark pigmentation of the face, renal insufficiency due to subacute or chronic glomerulonephritis, marked anemia, splenomegaly and embolism. In 1922 Libman and Sacks found that uremia due to subacute or chronic glomerulonephritis was present in one third of these cases in which endocardial lesions had entirely healed. The part played by myocardial insufficiency is striking and is a much more marked feature than it is in cases in the active bacterial stage. According to Libman(23), "While the damage done to the heart muscle during the bacterial stage is no doubt a factor, it is probable that just as much or more significance is to be attached to additional strain upon it because of the increase in preexisting valvular defects brought about in the process of healing." Practically always there is moderate splenic enlargement and tenderness of the lower sternum occurs very often. Petechiae and Osler's nodes may appear, but less frequently and in much smaller numbers than in cases in the active stage. Osler's nodes according to Libman occur in 50% of the active bact-
terial type but in 21 bacteria free cases reported by him they occurred in only 3.

**Mild cases.** Libman (23) says that since patients with a positive blood culture may make a complete recovery without clinical residua, and since patients are found in the bacteria free stage giving no history of the active stage, one must take for granted the existence of cases in which the patient has suffered from an unrecognized endocardial infection and has recovered without any clinical residua or sequelae. Such patients might remain well indefinitely except for consequences of previously existing valvular defects, modified or not by attacks of Subacute Bacterial Endocarditis of valvular changes produced by the latter.

Although the bacteria free stage is characterized by healing of endocardial lesions and by absence of bacteria in sections, the healing is only in the pathological sense. They are not cured but succumb to mischief done to the heart valves, myocardium, hematopoietic system or kidneys during the active or bacterial stage, or to embolism or intercurrent infection. Libman states that bacteria free stages may last at least as long as two and one half years, and it is quite probable that they may last much longer. (23)

**Mild cases.** Oille, Graham and Detweiler and Salus of Prague have reported cases of what they term mild cases of the disease.
Oille, Graham and Detweiler(32) described 23 cases of a subfebrile condition in 1915 and published a further report in 1924. In all of these cases by means of the Rosenow technique, anhemolytic streptocci were found in the blood. Of five of the cases in which 2-4 blood cultures were made, 3 showed positive cultures at time intervals of 3-4 months and all recovered from the infection. When a further report was made in 1924 by the same authors 3 could not be traced and the remaining 20 were living, 4 being in good health while 14 were fairly well and able to carry out their daily occupations. One was gradually losing weight and strength. In 1920 Salus of Prague reported from the clinic of Kunke 18 cases in all of which an organism corresponding to Streptococcus viridans being isolated, all recovered.

As appears before in this paper it was shown that a few organisms may enter from time to time under normal conditions and a transient bacteremia is not uncommon with many infections, but according to Oille no lesion other than endocarditis produces clinical signs and symptoms such as were found in their series of cases i.e. Fatigue weakness, shortness of breath palpitation, precordial pain, moderate anemia, fleeting pain in joints or muscles, gastrointestinal disturbance, restlessness, irritability, depression, crying spells and mild fever although none showed progressive anemia and emaciation, chills or signs
of emboli. Where a bacteremia persists for months as was found in three in which repeated blood cultures were done and the clinical course and signs were similar in the remaining cases, according to them it is fair to consider that the bacteremia in them also persisted for months.

Libman(23)says that Capps, Biggs, Major, Smith and others have described similar cases sporadically. He says that such a mild infection may occur in an individual who presents no evidence of a previous attack of the disease, and who may or may not be the subject of an old valvular infection. He thinks that we will most likely find such mild forms as recurrences in patients who have suffered an attack of the disease of a more severe type, and who have made a complete recovery. The rectal temperature may or may not go over 99.6 degrees for weeks at a time. It may reach 101 and rarely 102 degrees. The patients are often up and about and take part in daily affairs. Marked embolic features are not likely to be encountered. If anemia is present it may or may not be marked. When marked it is of assistance in diagnosis, as are also splenic involvement and development under observation of clubbed fingers. Also important to look for is tenderness in the lower sternum, white centered petechie, Osler's nodes and meningismus. All of the cases that he recognized have recovered. The duration is essentially short, occasionally as short as three weeks.
but may last for quite a long time.

Recurrent forms. In 1923 it was first mentioned by Libman (22) that recurrence of infection could take place. He observed the following forms.

1. An attack of infection, a period of good health, a second attack followed by good health.

2. Same as one but the second attack fatal.

3. An attack of infection, symptoms of the bacteria free stage, followed by a second attack with fatal outcome.

4. Symptoms of the bacteria stage followed by an attack of the active disease with fatal issue.

5. Same as three with recovery from the active infection, the symptoms of the bacteria free stage persisting.

In other words patients may suffer from two attacks and recover, or die, or a patient may come under observation afebrile in the bacteria free stage, develop a fresh infection and recover or die.

In hearts obtained from cases of this disease examples of recurrence are surprisingly common. Not infrequently lesions of old healed attacks are found, accompanied by one of active infection, or an old healed attack and a healing attack. The presence of macrophages in the blood in a case in the bacteria free stage, in which they were previously absent, may be of help in establishing diag-
nosis of recurrence. Occasionally the recurrence may be suspected if all manifestations of active infection are at hand, but at the same time the patient may have a peculiar deep brown color of the face which occurs in the bacteria free stage but not in the active stage. There is evidence that repetition of infection may be due to an invasion from focal infection. Recurrence may also be caused by invasion of blood by bacteria deposited in various tissues during the previous attack. (23)

The prognosis of the disease in general would need consideration of many other factors such as types and extent of preexisting valvular and myocardial disease, influences of other diseases that might be present, and terminating infections. Also mixed infection of the valves and the relationship with rheumatic fever, and to take up in detail the effect of disease on various body organs.

In closing, a description by Moore(29) will be given which aptly describes the terrible disease and brings out more forcefully its general unfavorable prognosis and the woeful lack of knowledge as to its treatment. His discussion follows: "Days, weeks and months pass by, every day with its morning of hope and its evening of depression. The fatigue, fever and anorexia continue-moments, days and even weeks of apparent improvement and elation are fatally dispelled by ever recurring aggravation of
of first one then another symptom, and slowly and surely the patient loses ground. The anemia increases. Evidence of myocardial insufficiency are added to symptoms of chronic sepsis. The complexion assumes the peculiar earthen color. With advancing renal changes the anorexia becomes more obstinate and is often associated with nausea and vomiting. Edema of the face and dependent parts sets in. Profoundly enfeebled with pale anxious face, puffy transparent eyelids, inert waxy bulbous fingers, the patient is harassed by dyspnea, depending in part on myocardial weakness, by the anemia, by the nephritis, in part on sepsis, associated with constantly recurring painful cutaneous or splenic emboli and persistent nausea. The least movement exhausts him, the nightly sweats awaken him. He is so tired! The attention of the nurse annoy him, and so often to crown his ills a sudden hemiplegia with flaccid arm and leg and drooping mouth, open eye etc. comes. Finally with wrinkled forehead and troubled face he sinks into a troubled sleep and breathes his last, a victim of chronic sepsis, myocardial weakness, terminal pneumonia, or embolism or all."

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Omaha, '36
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