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Rheumatic endocarditis

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RHEUMATIC ENDOCARDITIS

Roy F. Pierson

SENIOR THESIS PRESENTED TO
THE UNIVERSITY OF NEBR.
COLLEGE OF MEDICINE
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Rheumatic Endocarditis is an inflammatory disease of the endocardium associated with Rheumatic Fever. The disease process is characterized by its indefinitely prolonged febrile course, a tendency toward relapses, arthritic and nervous manifestations, subcutaneous nodules and changes in the endocardium and myocardium which are dependent upon the extensiveness of involvement.
INTRODUCTION

Rheumatic Endocarditis and its innocent counterpart, Rheumatic Fever have been associated since Pitcairn first described this condition in 1788. Since that time they have been a most conspicuous thorn in the palm of the medical hand. For to this day, their origin has been concealed from the most discriminating minds of the profession. In spite of increasing knowledge, this condition still remains the most common cause of cardiac pathology in youth.

The purpose of this paper is to develop the history of our knowledge, and to gain insight into the incidence, etiology, pathology and possibly to learn what part treatment, specific or general, can play in the control of this disease.

Roy F. Pierson
HISTORY

It was Wells (1) a native son of South Carolina who first recorded the circumstances in which rheumatism came to be associated with the development of heart disease. According to Wells, it was Dr. David Pitcairn who was the first to point out this relationship. This worker began to be interested in, and to talk about it at St. Bartholomew's hospital as early as 1788. Jacobs (2) writes that Edward Jenner apparently recognized the connection between heart disease and rheumatism about the same time for in the records of Gloucestershire Medical society Jacobs states that Jenner delivered a report on "A disease of the heart following acute rheumatism, illustrated by dissections". Unfortunately Jenner's paper was lost. Baillie (3) appears to have been the first to give special recognition to Pitcairn's teachings. Stimulated by Pitcairn's observations and Baillie's reference Wells (1) published an account illustrated by case reports of rheumatic heart disease which leaves little doubt that he appreciated the connection between the two conditions. Later after the introduction of the method of auscultat-
ion, it became possible during the life of patients to determine whether or not the rheumatic process involved the cardiac valves. It was probably Dr. James Hope (4) who realized this possibility in 1832. Among the exciting causes of diseases of the valves he specified inflammation of the internal membranes of the heart, resulting from carditis, pericarditis, especially rheumatic fever, or from other causes.

Baillie (3), Wells (1), and Hope (4), as well as the earlier observers Pitcairn, and Jenner all realized that the heart might suffer in rheumatic fever, but it was Bouillaud, who according to Jacobs, was the first to emphasize the great frequency with which this occurred.

Once the relationship between rheumatic disease and the heart were established we find that considerable time elapsed before pathological descriptions of the lesions appeared. According to Bezamcon and Weil (5), Besnier (6) was among the first to realize the possibility of myocardial involvement in rheumatic fever, and according to Sachs (7) Hardy (8) in the same year, 1876, also made reference to this involvement. West in 1878 refers
to the myocardial involvement in his studies of forty cases of rheumatic fever. Goodhart (10) in 1879 described the involvement of the myocardium along with what he termed granular nodules of the valves in an acute case. From this observation it may be gathered that Goodhart had observed the verrucous changes on the valvular endothelium. In 1883 Cavafy (11) called attention to the obliterating endarteritis which occurred in rheumatic heart disease due to the rheumatic nodules. He noted the intimate relationship of these nodules to the vessels and that the vessels were almost obliterated by them.

Gallavardin (12) writes that Vaisse in 1885 was the first to describe interstitial lesions in the myocardium in fatal cases of rheumatic fever. According to Clawson (13) it was Romberg (14) who first made a study of the specific interstitial lesion in rheumatic myocarditis who in two fatal cases of rheumatic fever noted the presence of interstitial cellular infiltrations, among which were large cells similar to those subsequently described by Aschoff. Romberg first made these observations in 1894. Clawson (13) also gives Hirschsprung (15) the credit for being the first to give a micro-
scopic description of the subcutaneous nodule in 1881. In the same year Barlow and Warner (16) described the subcutaneous nodules as a reaction similar to that found in the valves in acute rheumatic endocarditis. They pointed out that they may be very active in the heart, and that they may also be present without giving rise to clinical symptoms.

Futcher (17) in 1895 described the subcutaneous nodules as consisting of fibrous tissue in various stages of development and the cellular elements to be made up of round cells, fibroblasts, and polymorphonuclear leukocytes. It is evident that this worker observed the valves in the process of scarring subsequent to rheumatic infection.

Poynton (18) in 1899 described interstitial foci in the myocardium which were undoubtedly aschoff bodies, however he nor any other worker of that time were aware of the specificity of these lesions, as was later pointed out by Aschoff.

Late in the nineteenth century numerous workers began to search for the etiological factor of this important disease. The earliest attempts to demonstrate the cause were directed along the lines of bacteriology, as it was thought by the
men of that time that there must certainly be a specific organism which could be isolated. It is interesting to note the number of different organisms which were isolated from rheumatic cases, this is especially interesting since we have to this day not gone far beyond these early workers in explaining the cause of this disease.

According to Poynton and Paine (19), in 1892 Frankel (20) called attention to a paper by P. Guttman upon the etiology of rheumatic fever and its complications. Guttman described an acute case of rheumatic fever from which he was able to isolate staphlococcus pyogenes flavus, from the pericardial exudate, and abscesses of the kidney but not from the joints. Guttman expressly stated that he did not believe staphlococcus to be the cause of rheumatic fever. In the same year Sahli (21) discovered the staphlococcus pyogenes citreus in the synovial membrane of the joints in a case of rheumatic fever. He was also able to isolate the organisms from the pericardial exudate. This worker in contrast to Guttman believed that staphlococcus was the cause of rheumatic infection. Netter (22) at same time was able to isolate streptococci from a case which resembled rheumatic fever clinically,
but followed an acute suppurative otitis media.

Lanz (23) in 1893 published a paper on experimental results connected with suppurative polyarthritis. From the pus of an abscess of the brain he isolated a bacillus. This bacillus on intravenous injection into a rabbit caused death in twenty three days, with a suppurative polyarthritis of the joints resulting. From these joints the bacillus could again be isolated. To this organism he gave the name bacillus pyogenes foetidus liquefaciens. A year later Maragliano (24) obtained diplococci and staphlococci from a case which commenced clinically as rheumatic fever and ended as a septicemia. This also insisted upon the relationship between rheumatic fever and suppurative affections. In the same year 1894, Chvostek (25) and Singer (26) published papers referrable to the micro-organisms which they found in the urine of patients suffering from rheumatic fever. Singer (26) found as a result of examination of the urine in 17 cases that the Staphlococcus Pyogenes Aureus was frequently present, and when present was found in considerable numbers, but grew less in number as the case clinically improved. He associated this occurrence with the rheumatic process, but
Chvostek (25) though recognizing the importance of Singer's observations doubted the validity of his conclusions.

Dana (27) in 1894 was able to isolate a diplococcus from a case of chorea following rheumatism. The organism was found in the meninges of the brain and in the spinal cord. Charrin (28) was able to isolate streptococci in cases of rheumatic fever. Sacaze (29) made an interesting observation when he suggested that some external wound often insignificant might be the site of infection in rheumatic fever. Apparently this writer had noticed the frequency with which rheumatic fever may follow some kind of injury. In 1896 Lubarsch (30) in a paper on the streptococcic group and the diseases caused by them alluded to an exhaustive paper by Buss of Bremen upon the relationship of angina faucium to rheumatic fever. Buss (31) in this paper comes to the conclusion that the throat and intestines in many instances serve as the point of entrance for the rheumatic infection.

The clinical importance of inflammation of the fauces, so called angina faucium, was early recognized as having a relationship to rheumatic heart
disease. Dr. Fowler (32) in 1880 published an account of twenty cases of rheumatism which he had observed, and all of these cases had been ushered in by attacks of tonsillitis. Cheadle (33) in 1888 again stressed the clinical importance of the relationship between the tonsils and rheumatic states in children. Achalme (34) gave new impetus in the field of bacteriology when he discovered a bacillus in the blood of patients who succumbed to rheumatic fever. Achalme's work seemed quite conclusive as he reported this organism in 9 cases. The organism resembled the anthrax bacillus and upon injection into animals failed to produce true rheumatic fever, but in many cases caused death from septicemia. Thirolix (35) in working with the same organism reported similar results. Triboulet and Coyne (36) later found the organism described by Achalme occurring along with a diplo- cocci, and were of the opinion that the diplococci occurred with the bacillus in the more severe type of cases.

Riva (37) in 1897 believed he had isolated a specific organism in eight cases of rheumatic fever. This organism varied much in size and shape when grown on different media and was both bacillary and
coccal in form. In 1899 Apert and Triboulet (38) injected rabbits with the blood from affected patients and twenty days later found thickening of the mitral valves, hypertrophy of the heart chambers and excess of clear fluid in the pericardium. In spite of the fact that there was no joint involvement this writer thought this organism to be specific and was able to recover it in eleven successive cases. Bittencourt (39) supported the researches of Achallme and Thirolix. Singer (40) gave his results upon an extensive investigation of a large number of cases and concluded that acute rheumatism was not a specific disease, but owes its origin to streptococcal and staphlococcal infection. In 1899 Kronenberg (41) expressed the belief that he doubted the relation of angina faucium to rheumatic fever, but he thought it a peculiar reaction of the joints to a series of bacterial influences.

In 1899 Westphal, Wasserman, and Malkoff (42) published a paper entitled "On the infectious character of acute articular rheumatism and chorea". "Uber den infectiosen charakter und den zusammennhang von acutem gelenkrheumatismus und chorea. There material was obtained from a case of acute rheumatism
followed by chorea which went on to rapid death. At necropsy vegetations of the mitral valve, and a parenchymatous nephritis was found. Cultures were obtained from the heart's blood, pericardial fluid, mitral valve, spleen, and brain. Wasserman after alluding to the researches of Loffler, Michaelis, Eberth, Litten and Von Leyden, described the bacteriological results. The organism a diplococcus similar to that described by Von Leyden in rheumatic valvulitis was injected into eighty rabbits and produced fever and multiple arthritis. This organism appeared as a diplococci in the tissues but in culture grew as a streptococci. These organisms could be recovered from the exudates of animals and reproduce the disease in other animals. Litten (43) at the same time isolated a very minute streptococcus from a malignant case which was fatal in mice and guinea pigs, but lost its virulence rapidly on culture media. He was of the opinion that Westphal, Wasserman, and Malkoff probably had discovered the true excitant of acute rheumatic fever, but thought as had been previously suggested by Triboulet and Coyne that there were probably two organisms.

Poynton and Paine (19) were of the opinion
that the septic manifestations of polyarthritis, valvulitis, pericarditis, pyrexia, and sweating as seen in rheumatic fever were probably coccal in origin. The same writers isolated a diplococcus from the pericardial fluid, from blood of the heart wall, and from the throat. With this organism they were able to produce cardiac dilatation and joint manifestations in rabbits. They were of the opinion that in acute attacks of angina faucium this organism could be isolated from the throat.

From this review it at once becomes apparent that the true cause of the disease had not been definitely found. It is also noticeable that these earlier workers were in many instances quite close in many respects to what is still of considerable importance in consideration of this disease. Up until the beginning of the twentieth century it can be seen from the past review that there were no less than ten possible theories which were supposed to account for rheumatic infection. These views were briefly as follows. One view held that rheumatic fever was probably due to more than one organism possibly a staphlococcus and a streptococcus, and was septicemic in character. A second view was that there was probably a specific organism a diplococci. While a third view was that
of Achalme who believed the organism a bacillus. While a fourth view was that of a possible mixed infection of a bacillus and a coccus, but how they worked together still remained a matter of speculation. The fifth view held that there was probably no specific organism but a particular reaction of the tissues to varied infections. It can be seen that in the last quarter century we have added little to the concepts which have previously been suggested, and for that reason it seems that considerable tribute is due these keen observers of the late nineteenth century. And in the field of etiology until the causative agent is found there can be no criticism of these historical works.
INCIDENCE

The importance of rheumatic heart disease need not be emphasized. Many writers contend that rheumatic infection is the greatest single factor in producing cardiac disease. Although relatively infrequent in the tropics, the highest incidence is along our eastern shores in the New England states where 40 percent of all heart disease is rheumatic, as is 93 percent of all heart disease under twenty years of age. In half of all these cases a definite history of rheumatic fever or chorea is obtainable. The incidence of rheumatic heart disease is much higher in charity institutions than among the private patients, and is also more common among people who live under adverse conditions with poor nourishment and living quarters. (White)[44]

It is interesting to note that Strong (45) reports a higher incidence of what he calls rheumatic heart disease in cases of chorea than with rheumatic fever. He reports 40.3 percent of rheumatic heart disease in a series of 2,359 chorea cases selected from the literature, while in a series of his own cases he found 45 percent in chorea, and 38 percent with rheumatic fever. The later figure is however a bit low as compared with most figures appearing in
the literature. If one were to consider chorea as a part of the rheumatic syndrome support of this view would be available. Swift (46) was of this opinion when he stated "chorea is one of the grave manifestations of rheumatic fever". If then the heart were effected as a rule in the more serious cases Strong's statistics might easily be supported. Osler (48) in his work on chorea and choreiform affections points out the importance of chorea in the development of heart disease when he states, "The extraordinary frequency with which mitral valvulitis is met with in fatal cases is remarkable. There is no known disease in which endocarditis is so frequently found postmortem as in chorea, where it is exceptional to find the heart healthy". However Coombs (47) states that chorea usually occurs in the mildest grades of rheumatic infection. He found rheumatic heart disease in only 44 percent of chorea patients at the time of onset, as compared to 75 percent in rheumatic subjects who exhibited joint pain. Coombs (47) also found that of the cases which end fatally the percentage is little changed from those which began as rheumatic disease. In this connection it should be pointed out that rheumatic heart disease may occur without joint manifestations, and
with this in mind it at once becomes evident that
the figures of Coombs (47) might be changed. Mackie
(49) from an analysis of 393 cases of rheumatic fever
and 89 cases of chorea reported that he believed there
was no significant difference between these two types
of infection as regarding subsequent heart disease
was concerned. He reported heart involvement in 51.5
percent of his series of cases. Findlay (50) in a
series of 701 rheumatic children found rheumatic heart
disease in 50 percent of hospitalized patients with
chorea but found 75 percent in cases with rheumatic
fever. Jones and Bland (51) in a series of 518 cases
of rheumatic fever without chorea found that the in-
cidence of heart involvement was 86 percent, while
Coombs (47) pointed out that eventually 76 percent
of cases with chorea would have heart disease.

From these figures it immediately becomes
apparent that chorea frequently gives rise to the
rheumatic type of heart disease, and should there-
fore be looked upon as a part of the same disease.
This view is held by many writers, and is probably
the most widely accepted view.

Jones and Bland (51) in their series fol-
lowed the American Heart Association criteria for
diagnosis of rheumatic heart disease, but go on to state that they believe rheumatic infection may be present in the heart without any clinical manifestations. This later view is supported by the findings at autopsy, where lesions of the heart are found without an available history of rheumatic infection. If then we were able to improve our diagnostic ability a diagnosis of cardiac involvement might be possible in every case of rheumatic fever, and this is the opinion now receiving favor from many of the men working in this field.

It has long been apparent that in warmer climates rheumatic infection is less frequent. This fact is not to be overlooked, and has by many been stressed in treatment. In this connection it is interesting to note that in the studies of Stone and Vanzant (52) in Galveston, Texas they found rheumatic affections to rank fourth in importance of the four groups of heart disease in that section of the country. In a series of 915 cases, they found that only 7.3 percent were rheumatic. They compare these figures with the incidence of 22 percent from Virginia, and 45 percent from Massachusetts. White (44) points out that the incidence of mitral stenosis at autopsy was 4.68 percent at the Peter Bent Brigham Hospital in
Boston, as compared with .23 percent at the Charity Hospital in New Orleans. These figures bear out the importance of climate to the incidence of rheumatic infection, inasmuch as a person in Texas stands only one sixth as great a chance of becoming afflicted as a person living in Massachusetts.

Seegal and Seegal (53) after gathering statistics from numerous hospitals in the country between the years of 1913 and 1925 concluded that the incidence of rheumatic fever has decreased since 1918 in contrast to the period before that time. They also express the opinion that there may be a certain periodicity as regards the frequency of this disease.

Rothchild, Kugel, and Gross (54) in an important piece of work pointed out the causes of death in the various age groups. And from their work they concluded that valvular defects are not as significant as the myocardium in deaths due to cardiac failure. In their studies of 161 cases 95 showed aschoff bodies, an incidence of 89.6 percent. The remaining 11 showed activity as judged by either a fibrous pericarditis, verrucous endocarditis, acute myocarditis, or auricular lesions, but aschoff bodies could not be found. They concluded that the occurrence of heart failure in the first five decades of life
life in individuals who have valvular defect can, in the majority of instances be attributed to an active infection of the myocardium, rather than to the degree of mechanical defect. They pointed out the high grade of mechanical defects in the heart of individuals living even to the fifty and sixth decade with little or no evidence of congestive failure. They found that complete quiescence of the rheumatic myocarditis was present as early as the second decade of life. This number increased considerably in the later age periods. Circulatory failure in later decades of life in individuals with valvular defects was found in the majority of cases to be precipitated by the expected contributory causes occurring at that age, such as hypertension symptoms, or pulmonic, atherosclerosis of the coronary arteries, coronary thrombosis, myocardial degeneration and fibrosis.

The figures of Rothchild, et al, enable one to see the importance of the overwhelming infection, as compared with the mechanical defects which occur later in life.

One of the most interesting features of the rheumatic infection and the rheumatic type of heart disease is their occurrence in different members of one family. White (44) states that from
32 to 50 percent of patients with rheumatic fever, chorea, or rheumatic heart disease have near relatives with a history of similar trouble. White believes three factors are probably responsible for such family incidence: (1) inherited susceptibility to the rheumatic infection, (2) close contact, with the actual spread of exciting organisms from one throat to another, and (3) crowded or unsanitary living conditions. Christie (55) in California found a history of rheumatic heart disease in the family in 32 percent of the cases. Figures of this type in California where the incidence of the disease is low seem to be unusually significant. The figures of St. Lawrence (56) are much the same as those of Christie. St. Lawrence finding an incidence of 29 percent in a series of 100 families with 480 people, 60 percent of which were children and 40 percent adults. Of this group he found that 70 percent were not conscious of a heart disease until examined. Poynton (57) reported an incidence of 40 percent, with two or more individuals in the same family affected.

Among the earlier writers there seemed to be general agreement upon the fact that rheumatic infection was quite rare before the age of three. McIntosh and Wood (58) do not confirm this assumption
for in their studies of 24 cases over a period of years they concluded that rheumatic infection began in all before the age of three. Christie (56) in his series of 106 consecutive rheumatic children under twelve years of age found 14 children with an onset before five years of age. These figures constitute an incidence of 13.2 percent. Poynton (59) in a similar age group found 12 percent to be involved before five years of age.

While it is not so generally recognized that rheumatic infection occurs in the real young, records of large groups of patients bear out the fact that the disease is primarily one of children. McIntosh and Wood (58) were of the opinion that the greatest number of first attacks occur between the ages of five and fifteen years. Poynton (59) in a series of cases found that the average age of onset was seven years. Mackie (49) in 393 cases of all ages by dividing them into five year age groups found the highest incidence between the ages of ten and fifteen years. White (44) is of the opinion that the disease rarely begins in the first four years of life, and is especially rare before two years of age. He states that generally beginning between the fourth and eighteenth years is the highest at the seventh or
eight years, and is rarely seen to begin after twenty years. McIntosh and Wood (58) after collecting a series of 2,884 cases reported by other workers found that onset before three years of age occurred in 1.3 percent.

Value may be gathered from this information regarding the onset when it is realized that an early onset is the most likely. In this connection it is important that growing pains or other slight manifestations should not be considered lightly that a case of rheumatic infection be overlooked.

An important factor in the occurrence of rheumatic infection and rheumatic heart disease appears to be the social and economic status of the individual. White (44) states that rheumatic infection is at least one hundred times more common among the crowded poor than among the wealthier set living under better conditions. He also believes that overcrowding, exposure to cold and wet without sufficient protection, fatigue, and malnutrition are definite factors which tend to increase the incidence of rheumatic heart disease. Poynton and Schlesinger (59) point out that this however is not persistently found but that what relation social states and manner of living bears to the incidence of the disease is probably their general low-
ered resistance, and that damp and cold conditions lead to catarrhal inflammations of the upper respiratory tract and tonsils. They also suggest that like living conditions no doubt bears a relationship to the familial incidence, whether it is because the poor living conditions give rise to the disease or because they are all exposed to the same type of bacteria. It seems logical to believe that all of the above factors bear a definite relationship to the incidence of infection, for it is well known that where individual resistance is lowered disease processes can progress more favorably.

Thus far we have seen that rheumatic infection is in the majority of cases a disease of poorly nourished children, with in many instances more than one of the same family effected. It is a disease of the young, and in a great number of cases produces cripples for life. With this fact in mind it seems important from the standpoint of prognosis what a child's chances are of having cardiac involvement once rheumatic infection exists. Jones and Bland (51) in a series of 518 cases of rheumatic fever found the heart involved in 86 percent, and they were of the opinion that the more severe the attack in childhood the greater the cardiac damage. McIntosh and Wood (58)
in their smaller series of 24 cases in children under three years of age found endocarditis in 88 percent of the cases, 21 showing evidence of cardiac damage. In this connection it is interesting to note that West (60) as early as 1878 made observations regarding the cardiac involvement in relation to attacks. He found that in 44 cases of rheumatic carditis 50 percent were involved with the first attack, while with the second attack the incidence of involvement increased to 66 percent.

From these figures it can be seen that the chances of escaping cardiac injury are in the minority once a child has become infected, and that with subsequent attacks the prognosis becomes less favorable. Jones and Bland (51), and White (44) as well as others are of the definite opinion that the heart is injured in most cases even though the injury may be undetected clinically, and these workers especially stress the significance of that point.
ETIOLOGY

Since rheumatic fever was first recognized, the question of etiology has been one of considerable controversy. Many men still contend that the cause of the disease is still unknown. However, there are many factors which seem to be generally associated with the disease, and these must be given some consideration. Following the work of Poynton and Paine (19) in 1900, and even prior to that time as shown in the history, considerable work has been done in an effort to establish a definite bacterial agent as the cause of this disease. Numerous workers have found organisms in the tissues and blood streams of patients both during life and at the autopsy table, but the findings have been inconstant. Most workers who have considered a bacteria as the cause, have named some type of streptococcus as the etiological factor. However, this work has not met with universal acceptance, and seems to become less probable as time goes on.

Poynton and Paine (19) gave the name of Diplococcus Rheumaticus to a diplostreptococcus which they isolated from four pericardial exudates, two blood cultures, two valve lesions, and one angina, all from patients with acute rheumatic fever.
With this organism they were able to produce the disease in laboratory animals.

Cecil (61) by intravenous injection of Streptococcus viridans into rabbits was able to produce destructive lesions of the articular surfaces. He believed that he had demonstrated conclusively the causative agent, as he believed this organism produced similar symptoms in the human.

Swift and Kinsella (62) were of the opinion that the organism which Poynton and Paine thought was the cause of rheumatic fever, was in reality a Streptococcus viridans from their description of the organism and its cultural characteristics.

Rosenow (63) concluded from the results obtained in his works that the streptococcus was constantly undergoing changes, assuming and discarding certain affinities for definite structures. It can be seen that such a view would help to explain certain characteristics of the disease, and one could see why different parts of the body might be infected or escape unchanged.

Swift and Kinsella (62) were able to culture streptococci from the blood in only 8.3 percent of their cases. They were of the opinion that cultures from autopsy material were not sufficiently significant to be seriously considered, since pure cultures were difficult to obtain at that time.
They were therefore of the opinion that streptococci were not the primary invader but more likely secondary, since they were more commonly seen in the complicated cases. They were also unable to culture these organisms in the verrucae of the endocardium. In the positive findings which they were able to get, they found no specific type of the streptococcus group, but various members of the Streptococcus viridans. These workers also considered the possibility of the bacteria being killed off in the blood stream due to the bactericidal action of the blood.

Thalhimer (64) was unable to find any bacteria or protozoa in the verrucae of active cases of endocarditis, and therefore was opposed to the conclusion that streptococci of any type were the cause of rheumatic infection.

From their work Swift and Kinsella (62) concluded that rheumatic fever in its acute phases was not due to a bacteremia or infection of the tissues by a specific strain of streptococcus. These workers found that, the joint exudates in acute rheumatic arthritis were uniformly sterile, streptococci (non-hemolytic) were recovered in less than 10 percent of patients suffering from acute rheumatic fever, similar streptococci have been recovered from the
active endocardial lesions in only one half of the fatal cases of acute rheumatic fever, and they therefore thought it evident enough that no type of streptococcus had been constantly associated with acute rheumatic fever. However the work of Rosenow (65) did not conform with that of Swift and Kinsella, and he was able to recover streptococci from the joint exudates in 7 of 8 cases, and a year later the same worker (66) reported that he was able to recover the organisms from the blood stream in 4 of 7 cases of rheumatic fever.

In 1925 Clawson (67) isolated streptococci from the blood in a relatively high percentage of cases. His technic for blood cultures differed markedly from that of his predecessors in several aspects, 50 cc. of blood was taken, only the clot was used, and cultures were observed for one month before being discarded. Altogether twenty strains of streptococci were studied, and with one exception they all produced methemoglobin after a period of cultivation. The strain which was the exception was found to be a typical Streptococcus hemolyticus. Clawson found that when he injected these streptococci into rabbits he could produce lesions similar to those seen in human rheumatic fever. This worker also
succeeded in producing lesions in the myocardium similar to those seen in rheumatic fever by the experimental inoculation of animals with streptococci. Regarding these lesions which have been experimentally produced Small (68) in his studies of such myocardial lesions states that "exact reproduction of rheumatic fever lesions has not been accomplished." Coombs (69) and Cecil (61) were both of the opinion that they produced lesions which closely resembled the aschoff body. Cole (70), and Jackson (71) both state in their works that they were able to produce lesions in the myocardium which resembled the lesions seen in rheumatic fever. It appears that whether or not these lesions are typical depends upon the opinion of expert observers, but it is seen that in most cases writers do not say that the lesions are identical in every detail.

Small (68) working on the etiology of rheumatic infection of the joints and heart did not take blood cultures, but isolated the organisms from the throats of patients with rheumatic fever. This organism, when injected into rabbits, was seen to produce acute arthritis comparable to that seen in humans with redness, tenderness, swelling of the joints, and central nervous system excitability with choreiform movements. It was also seen that when the animals
recovered, the condition persisted in a chronic form, and in the subacute stage aschoff bodies could be seen in the myocardium. Small was quite sure that the specific type of streptococcus had been found and chose to call it the Streptococcus cardioarthritides.

Cecil, Nicholls, and Stainsby (72) in their work on the bacteriology of rheumatic fever believed that results were dependent to a great extent upon the technique of culturing. As has been seen Clawson obtained good results by special culture methods. So with Cecil it was found that in two series of cases studied in consecutive years the incidence of positive blood cultures increased from 31 percent to 83.9 percent. These workers believed that considerable significance should be attached to this point. They also pointed out that, especially in recent years, most of the organisms isolated had been of the Streptococcus variety.

From these observations it can be seen that the cause of rheumatic fever is not yet clear. This problem is one of the greatest interest at the present time. It is to be seen also that various forms of the streptococcus have, for a number of years, been considered as the etiological factor.
Coburn (73) has lately even suggested that Streptococcus hemolyticus is the cause of rheumatic fever.

The work of Schlesinger, et al (74) is of special interest. These workers centrifuged the pericardial fluid from active cases, and found bodies which resembled a virus. They were of the opinion that they had found the causative agent. However they also concluded that the streptococcus was of importance inasmuch as it may lower the resistance of the individual to the point where the virus can enter the body.

Jones and Bland (75) after reviewing 1200 cases came to the conclusion that streptococcus infection is only a factor in production of the disease, and that there are other factors which are also capable of producing recurrences or recrudescences, such as injuries, tonsillectomies, or typhoid vaccine. These factors may be of significance in view of the recent work of Schlesinger et al who have suggested a virus.

White (44), and Jones and Bland (75) are of the opinion that even though upper respiratory infections and tonsillitis have frequently been emphasized as factors in rheumatic fever they are not likely the only factors. White (44) states
that the place of entry of the rheumatic organism or virus is not known, but the faucial tonsils have been considered partly because their acute infection frequently ushers in acute rheumatic fever, and partly because endocarditis has been seen to follow tonsillitis without rheumatic symptoms. Jones and Bland (75) were able to show that in 75 percent of cases there was a definite history of tonsillitis.

Because of the close analogy between the sequence of events occurring in serum sickness and other frankly allergic conditions Zinsser (76), and Swift (77) were of the opinion that this was of definite importance, and sought to explain rheumatic fever upon the basis of an allergic sensitivity to some type of bacteria or virus. Swift (77) states that the allergic theory does not establish unequivocally the etiologic role of the streptococci in rheumatic fever, but that it does furnish the best explanation of how the different strains could all induce a similar clinical microscopic picture.

Irvine (78) working along the same lines as Swift and Zinsser came to the conclusion that the streptococci of the upper respiratory tract of rheumatic children are identical culturally and immunologically with those from normal children.
He was able to show that patients suffering from rheumatic fever showed marked sensitivity of the skin to filtrates from a wide group of streptococci either from rheumatic or normal subjects, and that this sensitivity is most marked in the acute stages of rheumatic fever and chorea, especially when acute carditis is not present, and is least marked when the subjects are clinically well. Irvine also thought that certain phases corresponded to certain definite phases seen in experimental allergy, and from these observations he concluded that there was a definite relationship between rheumatic fever and streptococci infections, but no particular strain was implicated.

Jones and Bland (75) were of the definite opinion from their results that there is no specific bacterial agent found in the upper respiratory tract which has been proven to be the cause of rheumatic fever. In accordance with the statement of the last workers it might be added that not only do we lack proof of an organism of the upper respiratory tract, but definite proof of any etiological factor. It might be stated that the most recent work probably favors a virus, which gains admission to the body when the resistance of the individual is lowered.
However it should be kept in mind that whether or not the tissue reactions throughout the body are due directly to a virus, or bacterial toxin, or indirectly as an allergic response has not as yet been decided.
PATHOLOGY

When rheumatic fever runs its course certain changes are to be found in the heart, and in most cases definite changes in the endocardium. When the endocardium is seen in cases which come to autopsy while in the active stages of the disease, the lesions are usually characterized by the presence of more or less continuous rows of small verrucous vegetations along the closure line of the valves. In cases which survive one or more attacks of rheumatic fever and come to autopsy in later years it is characterized by fibrous thickening and deformity of the valves. Because then of the frequency in which these lesions are found to coincide with the clinical history, and because acute rheumatism is so variable in its manifestations it has become customary in the autopsy room to apply the name of acute rheumatic endocarditis to any heart presenting these small vegetations, and the diagnosis of chronic or old rheumatic endocarditis to cases presenting the characteristic thickening or scarring. (Grant)(79)

From the standpoint of pathology it seems significant to consider the changes in the heart valves at the earliest possible time in the course to see the earliest changes. Material for such studies is not
to be found in the rheumatic heart which comes to autopsy as such, but rather in the heart which has not given rise to any symptoms. In such hearts which have come to autopsy due to accidental deaths it is possible to see changes earlier than those previously referred to as marking the active stages.

Leary (80) in studying the hearts of three patients who came to sudden death by accident found changes which he thought characteristic of rheumatic infection in its earliest phase, as well as subsequent changes. Leary found that the initial stage is one of tissue response in which there is seen what he calls palisade cells, which seem to form a palisade on the cardiac valve. Leary considers the formation of this palisade to be a complex reaction, even more so than the relatively simple mobilization of polymorphonuclear leukocytes, and histiocytes. These mobile cells when attracted to the site of injury act as individual units, even though they are massed together. This writer believed that these cells originated from fibroblasts rather than histiocytes or endothelial cells, because mobile histiocytes were still present in the palisade, and destruction of endothelial cells seemed to be taking place in toto. Leary noticed the formation of intercellular fib-
rillae as the cells of the palisade grew older, and every stage toward formation of scar tissue could be followed.

According to Leary (80) verrucae form wherever focal damage to the palisade has occurred. Where the injury is more diffuse ulcer like plaques may occur with the characteristic growth of fibroblastic cells which project at right angles to the surface. As the verrucae enlarge and healing progresses they tend to fuse and may form a continuous row along the contact edge. Old verrucae may show extensive vascularization of their centers or become converted into dense, relatively acellular masses of collagen, and healing is completed by the growth of endothelium over the surface. This author was convinced that the formation of the cell palisade, and verrucae result from injury to the surface of the valve and not from injury within. These observations are of interest since most work is seen in connection with the aschoff body with little stress placed upon the endocardial lesion. However Leary believes the endocardial lesion the most constant and grossly the most characteristic evidence of rheumatic infection. In support of this view it is interesting to note that Poynton and Paine (81) in 150 hearts of children dying from rheumatic heart disease found mitral lesions in
all but one case, while Clawson (13) in 250 cases with rheumatic endocarditis failed to find the aschoff body in 26 percent.

VonGlahn (82) in describing the lesions of the left auricle described changes in the thickened areas of the endocardium with accumulation of small mononuclear cells, many polymorphonuclear leukocytes, and a few eosinophiles. However his most striking observation was the collection of large cells generally forming a palisade along a band of hyaline material, with their nuclei perpendicular to this band. These cells were interpreted to be similar in cytology to the cells of the aschoff bodies, and concluded that they probably were modified aschoff cells their shape being determined by the laminated structure of the tissue in which they were found. VonGlahn considered these cells to be as distinctive as the aschoff cells themselves.

McEwen (83) in an extensive study to determine the origin of these cells studied scrapings from subcutaneous nodules. From his studies he preferred to give the origin of these cells as being mesenchymal elements of loose connective tissue, but states that it is possible that endothelial cells take part in their formation in some instances. He contends that
the findings in these subcutaneous nodules apply to those of the myocardium. It will be seen later that this opinion is not accepted by other men.

In view of the fact that the origin of the rheumatic granuloma cell is such a matter of controversy, a table showing the opinion of various workers taken from McEwen's work is here given. From this review it can be readily seen that no certainty has as yet been established.

<table>
<thead>
<tr>
<th>Date</th>
<th>Subcutaneous Nodules</th>
<th>Date</th>
<th>Myocardial Nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>1878</td>
<td>Bang, conn. tissue cells</td>
<td>1904</td>
<td>Aschoff, leuocytoid elements</td>
</tr>
<tr>
<td>1883</td>
<td>Cavafy, lymphoid cells</td>
<td>1905</td>
<td>Geipel, conn. tissue cells</td>
</tr>
<tr>
<td>1883</td>
<td>Carvasy, young conn. tissue</td>
<td>1906</td>
<td>Aschoff, Tawara, lymphocytoid elements,</td>
</tr>
<tr>
<td></td>
<td>cells</td>
<td>1904</td>
<td>and conn. tissue cells</td>
</tr>
<tr>
<td>1887</td>
<td>Gilly, embryonic conn. tissue</td>
<td>1906</td>
<td>Geipel, conn. tissue cells</td>
</tr>
<tr>
<td>1889</td>
<td>Cheadle, conn. tissue cells</td>
<td>1907</td>
<td>Coombs, conn. tissue cells</td>
</tr>
<tr>
<td>1895</td>
<td>Futcher, fibroblasts</td>
<td>1908</td>
<td>Saigo, epitheliod and muscle cells</td>
</tr>
<tr>
<td>1904</td>
<td>Wick, epitheliod cells</td>
<td>1909</td>
<td>Bracht, Wachter, Conn. tissue cells</td>
</tr>
<tr>
<td>1912</td>
<td>Frank, conn. tissue cells</td>
<td>1910</td>
<td>Roy, conn. tissue cells, mononuclear</td>
</tr>
<tr>
<td>1913</td>
<td>Voelcker, conn. tissue cells</td>
<td>1911</td>
<td>wandering cells</td>
</tr>
<tr>
<td>1914</td>
<td>Tilp, endothelial cells</td>
<td>1911</td>
<td>Coombs, endothelial, or conn. tissue</td>
</tr>
<tr>
<td>1914</td>
<td>Patella, lymphatic endothelial</td>
<td>1911</td>
<td>cells</td>
</tr>
<tr>
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<td>Fahr, conn. tissue cells</td>
<td>1912</td>
<td>Gallavardin, epitheliod cells</td>
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<td>1919</td>
<td>Jacki, polyblasts</td>
<td>1913</td>
<td>Fraenkel, adventitial conn. tissue cells</td>
</tr>
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<td>1923</td>
<td>Perkins, endotheliod cells</td>
<td>1913</td>
<td>Huzella, conn. tissue cells</td>
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<tr>
<td></td>
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<td>1914</td>
<td>Huzella, muscle cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1917</td>
<td>Langmann, endothelial or mononuclear</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>wandering cells</td>
</tr>
</tbody>
</table>
The appearance of the vegetations found in acute rheumatic endocarditis according to numerous workers are characteristic of that disease and typical. (64), (47), (84), (17). Thalhimer (64) gives the appearance of these minute beaded vegetations in which he found them to be composed entirely of an organizing hyaline thrombus. The connective tissue immediately beneath the endocardium furnishes fibroblasts through which the thrombus becomes organized. This area of actively growing connective tissue cells has all the characteristics of growing connective tissue elsewhere. More plasma is present between these cells than is
found elsewhere in the valve. About the base of the thrombus and at times the tissue throughout shows an inflammatory process, with an infiltration of mononuclear leukocytes, occasional plasma cells, and polymorphonuclear leukocytes. The endothelium on either side of the thrombus where it arises from the endocardium shows a condition of active growth, apparently an attempt to grow over the thrombus. Thalhimer (64) states that the verrucae in acute stages are infrequently covered with endothelium. Libman (85) contended that the endothelium rapidly grows over the thrombus, and usually covered it. VonGlahn (82) states that the endothelium frequently is intact over the site of the thrombus, indicating that this is not always the case. Thalhimer (64) was of the opinion that these lesions were so superficial that their origin must be endothelial or subendothelial.

There seems to be general agreement as to the appearance of the vegetations which appear on the heart valves from the descriptions given by different workers. However it seems that one must consider if possible what part the aschoff body plays in the superficial changes seen along the edge of the valves.

Boyd (86) states that the aschoff body
is not always to be found in cases of rheumatic carditis. He is supported in this assumption by Sachs (7) who collected figures from the literature and found the incidence to vary from 32 to 87 percent. Boyd (86) is of the opinion that a failure to demonstrate the aschoff body does not exclude a diagnosis of rheumatic carditis. It will be seen later that many writers contend that the aschoff body is the specific lesion in rheumatic carditis. Boyd (86) and Grant (79) are both of the opinion that in the wall of the auricle are to be found lesions which are as characteristic as the aschoff body. VonGlahn (82) was also of the opinion that these lesions constituted a picture as prominent and distinctive as the aschoff body.

Boyd (86) suggests that the term endocarditis is a mistake and that valvulitis is a much better term to be used. He believes that the pathology is chiefly that of the deeper structures since they by microscopic examination are much more injured than the epithelium. Coombs (87) seems to confirm the findings of Boyd when he states that the nodule begins in the depths of the valve, spreading to the surface, and finally "pointing" through the proliferating vascularized endothelium. Boyd (86) calls
attention to the increased vascularity of the valves, indicating new blood vessel formation from those previously existing. He goes on to describe the changes which he prefers to refer to as a valvulitis by stating that around the newly formed vessels typical nodules with aschoff bodies may be seen with diffuse cellular infiltration. These cells are chiefly lymphocytes, but in the more acute cases polymorphs are seen in increased numbers. Edema is a marked feature accounting for the swelling of the valve. The proliferation of fibroblasts is one of the chief changes to be noted which later are to produce scarring. These changes to Boyd indicate a valvulitis rather than an endocarditis. However he points out that the endocardium does not escape injury, and that the endothelial cells first proliferate and then degenerate, while on the valve edges where trauma is most severe the endothelium suffers most, becomes necrotic and is thrown off. Then from the circulating blood, fibrin, and platelets are deposited upon the necrosed surface, thus forming the vegetations. This inflammatory mass is then invaded by vessels becomes organized, and in time becomes covered with endothelium.

Coombs (88) calls attention to the distribution of the aschoff bodies in relation to the coronary
vessels, when he states that the relationship may be so close that the impression is that of a periarteritis nodosa. Cavafy (11) as early as 1883 pointed to the obliterating arteritis seen in connection with rheumatic nodules. Boyd (86) thinks that certain significance should be attached to this point, since the mitral valve being the most vascular is most frequently damaged. Kugel and Gross (89) have by injection methods shown that the mitral valve is the most vascular. They have also shown that the valvular intrinsic blood supply is not uniform in all valves, and that with age the valves become relative less vascular. These findings to Kugel and Gross suggested the possibility of the valve being infected through its intrinsic blood supply. It will be seen later that this view is also held by other men.

Coombs (88) in describing the changes seen in the heart valves states that in all cases of acute rheumatic endocarditis the dominant feature of the histological picture is the presence of certain cells which are almost certainly the outcome of proliferative activity in the local tissues. These cells are identical with those seen in rheumatic myocarditis. They are larger than ordinary fibroblasts which they resemble in shape. These large cells are gathered to-
gether into groups or tracts into which other cells enter scarcely at all. In cases of destructive or malignant endocarditis groups of such cells are not seen. Their destruction of the valve is of two kinds, first they may lie in nodules in deeper parts of the valve, or even in the center of one of the chordae tendinae. In these nodules which are especially plentiful in valves vascularized by previous inflammation there is often a central area of slightly granular material staining well with eosin inclosed within a ring of these cells. Secondly they may form layers along the surface of the valve without dropping deeply into its substance; such layers correspond to patches of fibrin deposited on the surface of the valve.

These nodules referred to above appear to express the inflammatory reaction provoked locally by the impact of the rheumatic micro organisms, or whatever agent is responsible, borne into the wall by the coronary arteries. The histology of these nodules is the same whether they are intermuscular or subendocardial. When a nodule arises under the endocardium certain changes follow in the neighboring area of serous membrane. Coombs (88) was able this change completely in his series. First there is a localized patch of edema formed just beneath the endothel-
ium. Lymphocytes appear in the patch, and the building of new capillaries is soon visible. At the same time the endocardium is liable to become detached, this leaves an ulcerated surface through which a few lymphocytes escape, while upon it fibrin is heaped up, and is sometimes separated from the endocardial surface by a layer of leukocytes, chiefly polymorphonuclears. This leukocytic covering is more apt to be found in ventricular recess than on the valves probably because the greater stagnation of blood favors it. Stems of newly formed capillaries may grow into this fibrous mass from their endocardial roots, but the presence of fibrin is not essential for their formation.

Swift (90) in discussing the histopathology of the endocardial lesions states that even in the young lesions there is seen in the substance of the heart valve under the endocardium distinct evidence of inflammation not exudative but proliferative in nature. He is certain that characteristic lesions occur in the mural endocardial without primary injury to the endothelium. He therefore believed that the primary injury occurred in the valve substance rather than on its surface.

Swift (91) in his work a year later reported the findings in four different cases which died within
two, and two and one half weeks of the appearance of
the arthritis; in three it was the first attack, in
one it was the second. In the first no verrucae were
were detected macroscopically, but many typical sub-
miliary nodules were found in the valves and adjacent
chordae. Numerous areas of perivascular inflammation
were present throughout a thickened valve; and occas-
ionally definite endarteritis was discernable in the
smaller vessels. The entire valve was swollen, but
only in one small area of the endocardium was there
evidence of necrosis or verrucae formation. The
second case showed similar vascular changes and areas
of focal inflammation throughout the valvular tissue.
A few typical submiliary nodules and slightly larger
flat verrucae formation in one small area. In the
third patient the fatal issue occurred during tonsil-
lectomy on the nineteenth day when it was felt he had
entirely recovered from the acute disease. A small
verruca was found at only one place on the aortic
valve, but in the substance of the valve there was
distinct evidence of mild interstitial inflammation.
The death of the fourth patient occurred on the four-
teenth day of the second attack of the disease. Gross-
ly no vegetations were seen on any of the valves, but
microscopically there were many foci of intense in-
-48-
filtration with polymorphonuclear leukocytes, lymphocytes, and a few large endothelial cells. In a few small areas there was desquamation of the valvular endothelium and very slight deposit of fibrin which was interpreted as early evidence of verrucae formation.

Swift (90) also made observations concerning the valvular blood vessels, and states that not infrequently there will be seen partial or complete closing of the lumina with thrombi that have already been formed as a result of injury to the vessel wall. He noted also that the blood vessels might be constricted by aschoff bodies in the perivascular space compressing one segment of the wall against another. Or when two or more submiliary nodules come to lie one on each side of a vessel the edema often present in such foci is sufficient to produce a constricting ring. Endarteritis with swelling and proliferation of the endothelium as well as of the other intimal cells was not infrequently seen in the smaller branches of the coronary arteries.

From Swift's findings it can be seen that interference with the circulation must lead immediately to disturbed nutrition of the muscle tissue and of the impulse conducting fibers supplied by the involved
vessels. Bedside study and electrocardiographic investigation in a series of Swift's patients indicated that the myocardium or conduction system was disturbed in 95 percent of the cases. While Swift conceives of this disturbed function being due to a toxic condition, he rather believes that there is a direct relation between the histopathological lesions found post mortem and the disturbed myocardial function found during life.

From the findings of Coombs (88), and Swift (90) it can clearly be seen that there is a definite relationship between the aschoff bodies and the changes which are seen on the endocardium. It has previously been stated that it is not always possible to demonstrate these lesions, but Coombs (88) is of the opinion that this is due to improper search.

White (44) states the typical lesion which was first described by Aschoff and Tawara in 1904 is probably at this time the best criterion of active rheumatic states. Clawson and Bell (85) considered the rheumatic nodule to be specific and found the lesion 21 of 24 cases. Gross, Antopol, and Sachs (92) were able to demonstrate aschoff bodies in 90 percent of 40 hearts. While Thalhimer (64) also believed the aschoff body specific, and was able to
demonstrate them in all cases.

Although some debate exists as to the specificity of these rheumatic nodules some attention must be given to the details of these lesions. Swift (90) has pointed out that there are two main types of lesion in rheumatism, the one proliferative, and the other exudative. It is the proliferative lesion in which we are most interested. The later lesion occurring in the joints and pericardium according to Boyd (86) is merely incidental.

Numerous workers have written of the typical appearance of the aschoff body, but space does not permit repetition of these works. Gross, and Ehrlich(93) are of the opinion that the aschoff body as it occurs in the heart should be considered apart from lesions occurring elsewhere. This preference is based upon the fact that even in the heart the structure of the aschoff body varies with its location. In respect to McEwen's (83) work they point out that even though it is of considerable importance one cannot make the basic assumption that one is here dealing with a process identical with that occurring in the heart even though the same etiological factors are at work. They go on to state that certainly the subcutaneous nodule represents a different histological appearance, and
therefore no doubt lacks the specificity of the nodule when seen in the heart. Gross and Ehrlich point out that the subendocardial, left auricular endocardial, and perivascular lesions occur in a compressed form which modifies the topography of evolutionary stages. They therefore thought that the aschoff body could best be studied in its evolutionary phases in the looser interstitial tissue of the myocardial bundles where it achieves its most important characteristics unhampered by fibro-elastic tissue.

According to Gross and Ehrlich (93) the aschoff body very early in its development invariably discloses a swelling of the interstitial collagen fibers as the most conspicuous phenomena. The lesion shows swelling and fusion of the fibers with development of intense eosinophilic properties. The ground substance swells, takes the picric acid stain with Van Geisen's method and stains with fibrin methods. On the other hand argentophilic fibrils are preserved. With resolution of the inflammatory process these newly acquired staining properties disappear. Even at these very early stages two distinct types of lesions are recognizable. One type apparently arising in those areas where the collagen occurs in the form of
relatively large compact masses maintains for some time this dense collagenic structure and eventually gives rise to what they term the coronal aschoff body. The other type arises in the looser connective tissue where the collagen strands occur as more or less isolated fibers. This type eventually gives rise to the reticular type of aschoff body. Simultaneously with the swelling of the collagen there is a local accumulation of small round cells with spherical nuclei, extremely inconspicuous cytoplasm. The origin of these cells is uncertain and are therefore called "mesenchymal cells" in order to avoid further controversy. Already in this stage Pap's stain discloses argyrophilic fibrils in close proximity to the proliferating mesenchymal cells, as well as along the swollen collagen fibers in the reticular form. Up to this point the lesion cannot safely be considered specific for rheumatic fever, but additional phenomena take place in the aschoff body from this point on which when taken as a whole present a picture that is apparently not seen in any condition where rheumatic fever can be ruled out. It is for that reason that Gross and Ehrlich believe these lesions to be specific.

With the further changes which make the aschoff body specific development may take place.
along several different lines. The topography of these lesions as a whole as well as the relation of the cells to the collagen framework, is apparently determined by the density and configuration of the tissue in which they lie. Thus the endocardial and subendocardial aschoff bodies are represented by compressed somewhat elongated lesions which tend to assume the form referred to as the mosaic type.

Gross and Ehrlich (93) point out that contrary to what is found in the literature, these lesions rarely if ever show a fibrin constituent, and the aschoff body does not influence any elastic tissue present at the site of the lesion. These writers go on to state that all stages of aschoff bodies may show a mantle of polymorphonuclear leukocytes, eosinophiles, lymphocytes, plasma cells, and fibroblasts. These non specific constituents are generally found around the young nodules so frequently seen in the myocardium of children. On the other hand a variety of lesions which present no specific characteristics may also be found. These may vary from interstitial edema with relatively few wandering cells to large collections of leukocytes, particularly eosinophilic, and even abscess formation.

Gross and Ehrlich (93) also noted that
dissolution of the aschoff bodies is not infrequently encountered. This is usually preceded by disappearance of nuclear chromatin, with nuclear ghosts in the form of more or less empty vesicles. Damage to the myocardium adjacent to the aschoff bodies may be relatively mild, but at times considerable destruction may take place. The neighboring myocardial cells may appear hypertrophied, at times vacuolated and may show complete dissolution and replacement by enormous scars.

Gross and Ehrlich, (93) and MacCallum (94) point out that even though the aschoff body is essentially submiliary and visible only microscopically, the extensive scarring of adjoining muscle, as well as fusion of neighboring aschoff bodies may produce lesions which are macroscopically visible.

Sachs (7) in describing the aschoff body states that these structures are rounded, globular, fusiform, or spindle shaped inflammatory nodules located in the interstitial tissue in close relation as a rule to the coronary arterioles. They are usually of microscopic dimensions ranging in size from 1 mm. to .5 mm., but in rare instances may reach sufficiently large sizes being detectable by the naked eye as pointed out by MacCallum.

Sachs (7) states that the left ventricle is
the more abundantly affected, especially its basal portions, sites of predilection being the insertion of the ventricular wall into the fibrous ring of the mitral valve, the myocardium near the origin of the aorta, the apex close to the septum, and the interventricular septum near the base. In the right ventricle, they are most likely to be found in the muscle bordering on the fibrous ring giving origin to the tricuspid flaps. They are least frequent in the papillary muscles of both ventricles, the central portion of the interventricular septum and the columnae cornaeae near the apex. Since this work of Sachs (7) the relative frequency of aschoff bodies in different sites has been shown by more detailed studies.

Gross et al (92) in attempting to standardize procedures for microscopic studies of the rheumatic heart found that in using their methods aschoff bodies were found in 90 percent of forty hearts showing acute verrucous endocarditis, and in 15 percent of thirty nine hearts showing chronic valvular disease. When they failed to find these lesions in their routine procedure for block taking, blocks from other portions of the heart also failed to show aschoff bodies. From these results it can be assumed that these workers have shown the most common sites for the
aschoff bodies. The following chart shows their results from thirty nine cases, all showing aschoff bodies.


<table>
<thead>
<tr>
<th>Sites</th>
<th>Aschoff bodies</th>
<th>Scarring</th>
<th>Arteriosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Auricle (L.A.)</td>
<td>10</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Mitral Posterior (M.P.)</td>
<td>32</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>Posterior Papillary muscle, left (P.P.M.)</td>
<td>22</td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td>Aorta, Aortic valve, and Mitral valve (A.M.V.)</td>
<td>9</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>Tricuspid valve, and septum (T.V.)</td>
<td>32</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Pulmonary artery, and valve (P.A.V.)</td>
<td>19</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

Boyd (86), MacCallum (94), VonGlahn (82), and Clawson and Bell (84) all have called attention to the fact that the endocardium of the auricle is subjected to the same changes as seen elsewhere in the heart. Clawson and Bell (84) found the auricle involved in 40 percent of cases, while VonGlahn (82) found the auricle involved in nine of thirty one cases. Boyd (86) was of the opinion that these auricular lesions were as characteristic as the aschoff body or the endocardial verruca.
From these studies we may conclude that the heart is involved in most cases of rheumatic fever, typical changes are seen in the endocardium which are dependent upon valvular injury, and the aschoff body specific for rheumatic infection is demonstrable in a high percentage of cases with proper sectioning methods.
SYMPTOMS AND DIAGNOSIS

The importance of making a diagnosis of endocarditis is very evident, however it is in many instances exceedingly difficult to make. It is not the heart which gives the warning of the disease, for rheumatic fever may run its course and the heart be injured without giving any warning whatsoever. Thus Cohn and Swift (95) contend that it is difficult to say in what cases the heart will become involved, and what cases will escape. So far there has been no method by which can be judged the possible involvement of the heart. Some authors believe that the heart is involved more or less in all cases. It has been previously pointed out that many workers have found cardiac involvement in over 80 percent of their cases.

Cohn and Swift (95) point out that even with affection of the valves there is no sure criterion by which to make a diagnosis, and years may pass before the condition becomes apparent. Importance is added to this disease since it is primarily a disease of the young, and early diagnosis and care are certainly not to be overlooked. Rothbart (96) says that it is a generally accepted fact that rheumatic endocarditis is one of the manifestations of rheumatic fever, and is found in 1 to 3 percent of the school children in
the larger centers. Past experience has taught us that rheumatism in children may manifest itself in a number of different forms. Rothbart (96) believes that growing pains, arthritis, and chorea, with or without heart involvement represent rheumatic states, but there may be other manifestations more vague. He goes on to point out that growing pains are often regarded to lightly, and that normal growth does not cause pain. Rheumatic pains should in all cases be differentiated as they are not related to exercise, occur most commonly at night but may occur at any time. In case of doubt a child should be treated until proven well.

Felter (97) writing on the diagnosis of rheumatic heart disease states that it is certainly not always easily done at the onset, but when there is sudden onset of high fever, with swollen, red, and painful joints the diagnosis is self evident. However he states that any of the following signs and symptoms may indicate the less spectacular onset of rheumatic fever; fatigue; loss of weight; pallor; anorexia; epistaxis; irregular pain, such as growing pain, abdominal pain, and precordial pain in 10 to 15 percent; sweats; fever; sore throat; tonsillitis; tachycardia; leukocytosis; murmurs; a prolonged P-R
interval in about 20 percent of the electrocardiograms; hypertrophy of the heart by percussion; chorea; lesser heart damage; erythema nodosum; rheumatic nodules; pericardial friction rub; and joint symptoms. Felter believes that any patient particularly a young patient with acute infection and fever, without localizing signs should be expected of having rheumatic fever, especially since 10 percent of rheumatic heart cases give no history of rheumatic fever.

Rothbart (96) contends that until we have further information regarding the relationship of chorea and rheumatic infection we should consider chorea as rheumatic and direct treatment toward prevention of cardiac complications. This relationship has previously been referred to under incidence, but it may be here added that Jones and Bland (51) in a more recent study of 482 cases of "pure chorea" followed over a period of eight years, observed that the incidence of rheumatic heart disease was only 3 percent, but 73 percent where rheumatic fever subsequently developed. To these workers a case of so called pure chorea was one in which there was no other clinical signs aside from the choreiform movements. This point seems important, because while the incidence of rheumatic heart disease is low in pure chorea, it
is relatively high where rheumatic fever subsequently develops, and the two conditions seem to be definitely associated.

Rothbart (96) stresses the importance of differentiating chorea from habit spasm, tic, and other nervous disorders, diagnosis depends upon the insidious onset of purposeless arrhythmic coarse movements of the body, tremor of the tongue, dysarthria, and ataxia of the extremities.

Sutton and Dodge (99) in their work on the treatment of rheumatic carditis used the following signs and symptoms as evidence of active carditis: (1) Fever, (2) tachycardia, (3) change in quality of the heart sounds, (4) presystolic gallop sounds, (5) development of new murmurs, (6) change in the quality of the murmur present, especially the presence of a high pitched, shrill musical quality in the apical systolic murmur, (sometimes described as the "sea gull" quality), (7) change rhythm (heart block or loss of sinus arrhythmia), (8) electrocardiographic changes chiefly prolongation of the P-R and QRS intervals, and (9) the presence of subcutaneous nodules. These workers did not depend upon the presence of all of the above findings, but considered a case active when two or more of the signs or symptoms were present in
a given case.

According to White (44) the symptoms found in rheumatic heart disease are dependent upon certain factors; (1) the activity of the rheumatic infection, (2) obstruction to the circulation resulting from the specific lesions, and (3) heart failure which may come as the result of overwhelming acute or subacute myocarditis, or chronic valvular disease, or disturbed heart rhythm, or of two or even all of these conditions combined. However it has been seen that the many persons with chronic rheumatic heart disease have no symptoms at all and live active lives without difficulty, but of greater importance than structural defect is the determination or absence of activity. White points out that a low grade rheumatic infection may run for months or years in a child showing only a slight elevation of temperature at intervals, or daily, and is quite common in children as compared with virulent polyarthritis which is relatively rare in children and more apt to occur in the adult. The older the individual the more the joints suffer and the less the heart; the younger the subject the more the heart and the less the joints.

Symptoms referable to the heart when acutely invaded are somewhat rare. Regarding such symptoms
White (44) states that there may be precordial pain, somewhat sharp, rarely angina pectoris, occurring usually in subacute or chronic valvular disease with marked aortic regurgitation, and probably dependent on insufficient coronary supply due not only to a low diastolic blood pressure, but also to a storm of vasoconstriction involving the coronary arteries with a resulting transient hypertension in sensitive individuals. It is also this writer's contention that disturbances in rhythm such as premature beats or paroxysmal tachycardia, giving rise to palpitation, are due to the effort syndrome that accompanies any infection. Dyspnea also is usually due to the effort syndrome but sometimes arises from an acute pericarditis, or from cardiac dilation and failure accompanying an overwhelming acute myocarditis especially in early childhood.

Boyd (86) states the different murmurs give the signs and symptoms of lesions of the endocardium. Since the mitral valve is the one most commonly effect ed the principal murmurs are those heard over the mitral area, both systolic and presystolic. The systolic murmur of mitral regurgitation is due to dilation of the auriculo-ventricular ring with myocardial failure rather than to scarring of the valve
and chordae tendinae as previously thought. The pre-
systolic murmur is valvular in origin, and is due to
stiffening and sclerosing of the valves. There is
then a tendency for the auricle to be effected, weak-
en, and a clot form in the backwater which may give
rise to an embolus. Aortic regurgitation is only one
third as common as mitral and is to be attributed to
the sclerosing and shortening of the cusps rather than
myocardial weakness. A tricuspid systolic murmur is
due to the enormous widening of the ring which occurs
when the valve is itself effected by the endocarditic
changes, the sclerotic changes are comparatively
slight. In rare instances stenosis may occur. An
accentuated pulmonary second sound, so common an acco-
herence of mitral incompetence is due in part to
the resistance encountered in the pulmonary circulation.
In part it is to be attributed to the fact that the
enlarged left heart peels the lung away from the pul-
monary artery so that the root of that vessel comes
in contact with the chest wall.

Martin (100) states that even though the
vast majority of patients suffering from acute rheuma-
tatic fever have an associated heart involvement, this
fact may be readily overlooked. He is of the opinion
that there are few characteristic symptoms during
the acute stage, and practically no symptoms as far as the endocardium is concerned. Pain over the precordial area, tachycardia out of proportion to the temperature and persisting as the temperature falls, continued low grade temperature after the acute joint symptoms have subsided, changes in the quality of the heart sounds, the appearance of changes in rhythm especially auricular fibrillation, or partial block, should all suggest cardiac involvement. When a case is under prolonged observation, the appearance of a murmur not present before or the increase in the mitral systolic murmur previously noted, is according to Martin of importance. He calls attention to the fact that most of these signs and symptoms have their origin in the myocardium rather than the endocardium, and goes on to say that in any case of acute rheumatic fever, no matter how mild, endocarditis and myocarditis should be assumed to exist until satisfactorily disproven, and if in doubt the patient should be treated as if the condition was known to exist.

Bach and Hill (101) after observing the sedimentation of the erythrocytes in rheumatic fever state that the clinical diagnosis may be difficult, and is dependent upon the elucidation of rather indefinite symptoms and signs. It is also important
after a diagnosis has been made to determine whether a case is quiescent or active so that the proper treatment might be instituted. There are certain investigations which are of value in making or substantiating the diagnosis of the disease and are of assistance in following its course. Among these the weight, temperature and pulse rate, the blood leukocyte count, the electrocardiographic findings, and the erythrocyte sedimentation rate are of real interest. These men in following juvenile cases during the rheumatic disease process concluded that, when the clinical picture is that of juvenile rheumatism in the active phase the blood sedimentation rate is definitely raised. When it is that of quiescent rheumatism or rheumatic heart disease unassociated with clinical signs of activity the rate approaches normal limits. These workers set the normal limits at 10 mm. for the first hour, and 20 mm. for the second hour. They found that in cases clinically active the rate varies from 136 mm. to 30 mm. the first hour, and from 136 mm. to 60 mm. the second hour. In the inactive cases the rate was found to range from 9 mm. to 3 mm. during the first hour, and from 20 mm. to 5 mm. during the second hour. White (44) is also in favor of this test as he believes that the sedimentation rate is usually in-
creased in proportion to the activity of the disease, and may be the only evidence which exists of a long drawn out low grade infection.

The prolongation of the P-R interval has by many become recognized in the diagnosis of rheumatic heart disease. Martin (100), Jones and Bland (75), Sutton and Dodge (99), Cohn and Swift (95), and Rothbart (96) all have stressed the importance of the electrocardiogram in the diagnosis and treatment of rheumatic heart involvement. The later writer states that at least 80 percent and possibly more of all cases with rheumatic infection have some heart involvement arising during a first or subsequent attack. Early cardiac disease can be missed by the usual bedside studies and may only be detected by special studies such as the electrocardiogram. He contends that to disregard the fleeting pains and wait for more definite clinical evidence of rheumatic heart disease is to wait too long.

Schott (102) in a special article upon the value of the electrocardiogram points out that in mild cases of rheumatic heart disease changes may be seen with no other signs of cardiac involvement. These changes may disappear as the disease subsides, but are definite evidence that the heart has been involv-
ed, and should make prolonged rest in bed imperative. The main change in the electrocardiogram is a disturbance in conduction through the specific system of the heart due to toxic damage of the conduction system. The most frequent manifestation of heart involvement according to this writer is a lengthening of the P-R interval from .2 seconds to .3 or .4 seconds or even more. There may however be evidence of dropped beats.

Thus we have seen that the diagnosis of rheumatic heart disease is difficult at times even though there may be enumerable symptoms, and that it is only by careful persistent studies, with the aid of all laboratory procedures, that the more difficult cases shall be recognized if at all.
TREATMENT

The treatment of rheumatic endocarditis is indeed a great problem. The work which has been done in attempting to discover adequate therapeutic measures to cope with this disease process has been tremendous, but thus far we have little which has been definitely proven to be of value.

Martin (100) states that the treatment of acute rheumatic endocarditis can be summed up in one word, rest. He goes on to state that drugs except to alleviate pain and promote rest have no field. The patient should be kept at rest until all evidence of active infection has subsided, as decided by laboratory methods, and return to activity should be in a most gradual manner. The complete subsidence of temperature, return of pulse rate to normal, the restoration of the blood picture to normal, and a normal sedimentation rate, should take place before any activity is considered.

Felter (97) states that having made a diagnosis of rheumatic fever we must do all in our power to protect our patient from heart damage. Prolonged rest in hygienic surroundings is of greatest importance. A cure is not to be expected from salicylates although they increase the comfort and produce rest.
He states that we must expect functional murmurs because they are common, and watch for changes as we know they may be long in forthcoming. Felter (97) states that the average period in bed at the Good Samaritan Hospital is four months, although it may in some instances be two years. Not until the rectal temperature stays below 100 degrees, the patient is gaining weight, the white blood count is under 10,000, and the sedimentation test normal is it safe to let the patient out of bed. Regarding the value of the sedimentation rate as an indication of disease activity it might be well to state that this laboratory procedure seems to have definite value. Bach and Hill (101), Felter (97), Martin (100), Jones and Bland (51) and others have pointed out that this test is perhaps our best criterion by which to judge activity of rheumatic infection. They believe that any child with an elevated erythrocyte sedimentation rate should be kept in bed until it becomes normal, and if the sedimentation rate is persistently low there is little damage in allowing the child to resume a normal life.

Felter (97) points out that when the patient can be allowed to be up, he is to be allowed one hour out of bed each day for the first week, two hours the
second week, and increasing an hour each day weekly for the next six weeks. This rule of course does not hold if there is a recurrence of symptoms. Every attempt should be made to save an injured heart, and there is no better way than by diminishing the load which the heart has to carry to the minimum. This writer stresses the point of early diagnosis of heart failure as it should be caught in the presumptive stage. He divides heart failure into two stages; first that of waning reserve, and second the stage of actual signs of circulatory embarrassment and breakdown.

Rothbart (96) stresses the point of using digitalis when cardiac insufficiency becomes evident. He believes it has no pharmacological basis for being assumed harmful in carditis. He thinks the electrocardiogram should be used at intervals during the process of digitalization. Oxygen has a definite place when cyanosis is evident according to this writer, and when there is decompensation the semi-fowlers position may be of definite value. Rothbart states that in the treatment of rheumatic endocarditis with cardiac failure, next to digitalis, the most important treatment is sedation. The barbiturates or codein may be used, but if not effective morphine is definitely indicated because of its
mental and physical relaxation. Edema is combated by purgation, diuresis, and dehydration. Acetyl salicylic acid is of value for joint pain, but has no effect upon the heart.

Rinehart and Mettier (103) were able to produce in laboratory animals pathological changes similar to those seen in rheumatic fever by a diet deficient in vitamin C, and from their work concluded that the disease was a deficiency disease. They have therefore suggested the use of vitamin C in the treatment of rheumatic heart disease. This type of treatment, although there are some who prescribe to it, has not as yet met with approval to any great extent. Along this line however it has been seen that a good nutritious diet, high in carbohydrates, and all the different vitamins is of definite importance during the convalescent stages of rheumatic infection.

Anemia may complicate the picture in cases of rheumatic infection, and Rothbart (96) contends that liver and iron in adequate doses are indicated in such cases. The use of frequent small blood transfusions also has a definite place in the treatment of such cases. Glucose, as 20 percent 15 to 20 cc. by vein each day or every other day may also be given in the hope of increasing the nourishment of the

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heart. Rothbart believes that the effects from this procedure are difficult to evaluate but at least are harmless. He also points out that thus far the use of vaccines and sera have not been accepted, and that results from their use have been disappointing. It is interesting to note in this connection that Coburn (104) and his associates seem to have definitely shown that on the basis of rheumatic fever being a sensitivity to a streptococcus that the use of vaccines and sera may only serve to increase the sensitivity or susceptibility of the tissues to further rheumatic infection even though the antistreptolysin in the blood is increased. It has also been shown by Coburn (104), Jones and Bland (75), and others, that the use of sera or vaccines may be of no therapeutic value, but may even serve to aggravate the disease.

Much discussion still exists regarding the value of removal of the tonsils in cases which are effected by rheumatic fever. Concerning this question Rothbart (96) states that he believes bad tonsils should be removed, but the removal of tonsils indiscriminately is to be condemned. He also points out that such removal of tonsils has not decreased the incidence of reinfection, since the frequency of
remissions in tonsillectomized patients is just as great as in the non-tonsillectomized. However he goes on to state that the clinical improvement following removal is so marked that it seems to be justified in every case. If the heart is yet unaffected it does seem to lessen the incidence of cardiac involvement. The optimum time according to Rothbart is during convalescence after an afebrile period. During this afebrile period there should be absolute clinical inactivity determined by laboratory methods. The patient should also be given salicylates for two weeks following operation. To early surgical intervention may precipitate an acute flare up, and in some instances result in death.

Starling (105) believed that early removal of the tonsils was indicated, and based his assumption upon the belief that the tonsils served as a portal of entry for the infecting organisms. He emphasized the importance of enlarged lymph nodes as a criterion for infected tonsils. Poynton (106) regarded tonsillectomy as a valuable prophylactic measure in rheumatic cases. Miller (107) made an exhaustive study of rheumatism in tonsillectomized children and his final conclusions led him to believe that the operation was a harmless proceeding.
in that it was rarely followed by any immediate recurrence of rheumatism, and he further observed that cases of rheumatic carditis in which convalescence had been duly protracted frequently made rapid improvement following the removal of septic tonsils. He however believed that the tonsil is only one of the many problems which must be considered in the treatment of rheumatic carditis. Smith (108) contends that in spite of conflicting opinion that the general consensus of opinion favors operative interference if there is definite evidence of tonsillar infection, and if the tonsillar glands are obviously involved. He therefore believes that it is an acknowledged fact that rheumatic manifestations and cardiac lesions are likely to be relatively mild in tonsillectomized children.

Since its first recognition the practitioner has searched for a cure for rheumatic endocarditis. Thus far there has been no therapeutic measure which seemed adequate to cope with this disease condition and its devastating effects. However within the past few years men working in the field of fever therapy have suggested that the use of artificial hyperpyrexia has a definite value in the treatment of rheumatic carditis.
induced fever had a distinct advantage, because of the uniformity at which the temperature could be controlled. They also pointed out that the patient could be administered fluids and chlorides by mouth during treatment. They concluded that advanced rheumatic endocarditis was not contraindicated in proper controlled fever therapy. Aside from the factors pointed out by these workers against the use of typhoid vaccine, it is seen that Jones and Bland (51) have pointed out the fact that the use of vaccine may produce a reactivation of the process while there seems to be no such danger with the use of the mechanical induced fever.

More recently Dunn and Simmons (111) have reported the results with 15 cases of acute rheumatic fever treated by the use of the Kettering Hypertherm, 12 of the fifteen cases being selected from 172 arthritic patients at the University of Nebraska fever department, and 3 cases from the University of Colorado. Of the 15 cases studied 3 were complicated by chorea. Thirteen of the patients became symptom free the use of fever therapy. Of the entire group three had relapses. These writers are of the opinion that fever therapy produces definite symptomatic relief, and probably shortens the length of the attack.
In 1933 Sutton and Dodge (109) reviewed the literature pertaining to fever therapy in the treatment of chorea. They at that time reported satisfactory results in 150 cases treated with triple typhoid vaccine, and believed that the course was definitely shortened. In 1935 these workers (99) continued their studies by using radiant energy and concluded at that time that fever therapy, by radiant energy or by typhoid vaccine, had no harmful effect upon the heart. In fact they had noticed that there was considerable improvement in the clinical picture following the use of fever. It must be remembered that previous to this time that fever therapy when complicated by cardiac pathology was considered a bit dangerous.

Barnacle et al (110) a year later reported 13 cases of chorea treated by the Kettering Hypertherm with recovery in all cases. Of these 13 cases 5 had definite rheumatic carditis, and all were considered cured. They were of the belief that the shock following the injection of triple typhoid vaccine as shown by chills, vomiting, severe headache, extremely high fever, and marked prostration, is a serious contraindication when there is already a badly damaged heart. They believed mechanical
These writers are hopeful that fever therapy will be valuable in reducing the number of subclinical cases in the future.

As we have seen, the results presented in favor of fever therapy in the treatment of rheumatic endocarditis are very striking. It seems probable that here is a therapeutic measure which is definitely worth consideration as in time its value may be correctly established. However it must be granted that results seem to be definitely encouraging, and in the future, we can expect further valuable developments in this phase of treatment of rheumatic endocarditis. As in all fields of medicine, further strides will be sure to come forth.


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