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The presentation of a paper treating of acute rheumatic fever is beset with numerous difficulties. First, there exists a mass of literature on the subject; an accumulation of many years, and, at present, there is no tendency toward a cessation of this accumulation. This condition immediately brings to the attention the necessity for limiting, selecting and eliminating in the mass of material available.

The second difficulty is one inherent in any discussion where the subject is one concerning which but little is known. Until the etiology of acute rheumatic fever is discovered the other phases of the disease will be but imperfectly understood and dissension will continue to be rife among medical men when considering rheumatic fever.

It is my desire here to present as comprehensive a view of the entire subject as possible under the conditions, partly from purely selfish motives. In an attempt to obtain a proper sequence and organization the disease shall be taken up in the usual manner, using the headings definition, etiology, pathology and so on.

No pretence is made at having covered most of the literature. But a very small fraction has been used in the writing of this paper.

DEFINITION

No definition will be satisfactory to all, but the following one from Osler's Principles and Practice of Medicine will probably serve as well as any other and so is hereby submitted: "An acute infection, dependent upon an unknown infective agent, and characterized by arthritis, myocarditis, and a marked tendency to inflammation of the endocardium of the valves of the heart."

ETIOLOGY

Under this heading "much has been written and but little said." The etiology of rheumatic fever has engaged the time and attention of scientists for a great many years. At present, although much progress has been made, no positive statements concerning the etiology of rheumatic fever can be made. A few of the more salient facts associated with the disease will be considered first followed by a short resumé of the theories, past and present, regarding etiology.

DISTRIBUTION AND PREVALENCE

Rheumatic fever is a disease of temperate and humid climates being rare in the tropics. It is most prevalent in the northern latitudes.

SEASON

A study of the seasonal incidence of attacks of rheumatic fever and chorea corroborated the usual impression that the disease is most common in this country during the spring months. This corresponds with the period of worst weather conditions and most frequent infection of the upper respiratory tract and is in contrast with similar studies made in England where the peak of incidence is during the late fall months, at which time cold and damp seem particularly prevalent.

AGE

In a study of the age incidence of the disease made at

the Washington University School of Medicine one hundred and fifty children were considered. In none of the cases had the primary attack occurred when the patient was under two years of age, but from the age of three years the tendency to rheumatic fever increased rapidly, a maximum of first attacks between the ages of 10 and 12 years being noted.

This study was made in the pediatrics section which naturally, did not receive patients older than 14 or 15 years, and this fact may detract from the reliability of the facts ascertained.

Of 456 cases[1] admitted to the Montreal General Hospital there were, under fifteen years, 4.38 per cent; from fifteen to twenty-five years, 46.68 per cent; from twenty-five to thirty-five years, 25.87 per cent; from thirty-five to forty-five years, 13.6 per cent; above forty-five years, 7.4 per cent.

From this we may assume that the disease is one of childhood and early adult life. Most writers give the age incidence as between ten and twelve years. This is probably true but the fact must be borne in mind that the disease is not uncommon in later life.

SEX

Considering all ages, males are affected oftener than females. Below the age of twenty the disease occurs more frequently in females. Girls between the ages of ten and fifteen are quite susceptible to the disease.

HEREDITY

This is not thought to be a factor.

EXPOSURE

Exposure to cold, wet, or a sudden change of temperature is considered a factor in determining the onset of the disease.

An attack of rheumatic fever does not confer an immunity, but, similar to pneumonia, predisposes to further attacks.

In the study made at the Washington University School[2] of Medicine the role of infection in rheumatic fever was paid particular attention. Their survey of the association of infections of the upper respiratory tract with the incidence of attacks of the disease and recurrences was made from two stand-points: (1) the number of attacks preceded by such infections, and (2) the incidence of such infections between attacks of rheumatic fever. It was found that in this group of 150 children, rheumatic fever or chorea had occurred 304 times, and definite information concerning the prodromal signs was noted in 261 instances. These are tabulated in the following table, in which it will be seen that colds and sore throats apparently precipitated 197 of the attacks-figures which confirm the general impression of the association of the acute infections of the upper respiratory tract with rheumatic fever.

Zymotic diseases and pyogenic infections preceded 36 attacks while in 28 instances an initial infection was denied. Studies of the occurrence of colds and sore throats in rheumatic subjects without reference to the acute attacks of rheumatism show the increased incidence of such infections.

Total attacks preceded by tonsilitis or sore throat.....	98
Total attacks preceded by common colds...	74
Total attacks preceded by both colds and sore throats.....	25
Total attacks preceded by other infections...	36
Total attacks preceded by no obvious infection,.....	28

The conclusions arrived at in this study were as follows:

Clinical and experimental evidence tends to show the close association of infections of the upper respiratory tract with the rheumatic syndrome.

Tonsillectomy, when followed by hygienic measures, general and local, is of value in decreasing the number of recurrences.

Care in convalescent home is of immediate benefit to the child but does not seem to lessen recurrences after the child goes home.

In a group of 90 children with constant infection in the naso-pharynx, the percentage of recurrences of rheumatic fever and chorea was paralleled by the degree of success obtained in combating the infection and improving the living conditions of the child.

Continuing the consideration of infections in the etiology of rheumatic fever it might be well to note Kaiser's work.[5] Kaiser made a study of 439 children noting particularly the relations of tonsils to acute rheumatism. In his series, a number of children who developed a severe rheumatic infection with carditis, did not have tonsillar tissue.

His analysis of 439 rheumatic children disclosed the following facts:

The most susceptible age for the first attack of rheumatism is between 8 and 14 years.

Nearly twice as many children in the community studied developed the first attack when the tonsils were still present.

Recurrent attacks of rheumatism occurred 10 per cent less often in children who had their tonsils removed after the first attack of rheumatism than in those whose tonsils were not removed.

The incidence of carditis as a complication was nearly as frequent in children who had undergone a tonsillectomy as in those who had not.

Chorea occurred as a complication with equal frequency in children operated and not operated on but the association of carditis with chorea was less in children whose tonsils had been removed.

Tonsils are the avenue of infection in many cases of rheumatism and bear a definite relationship to the disease. Their removal should be advocated in the rheumatic and potentially rheumatic child until more is known of the etiology of the disease.

Kaiser's study apparently establishes a definite relationship between tonsils and rheumatic fever and in addition proves that rheumatic fever is not necessarily the result of tonsillar infection. The tonsils are to be considered as but one of possibly many avenues of infection.

Nabarro and McDonald[4] in 1929 made a rather thorough investigation of the bacteriology of the tonsils in relation to rheumatism in children. They endeavored to isolate all the varieties of streptococci present in each tonsil so that the types could be compared. They used,in their study, fifty rheumatic tonsils from out-patients with articular rheumatism,chorea and heart conditions, all of whom had some degree of enlargement or sepsis in their tonsils. The non-rheumatic tonsils, 48 in number, were from patients with enlarged or septic tonsils, but from whom no history of any rheumatic manifestation could be elicited.

They found that streptococci isolated from rheumatic tonsils do not differ materially from those isolated from non-rheumatic tonsils and fitted in this absence of difference with the theory that there is no specific streptococcus which is the cause of the disease, but that the condition is due to a hypersensitiveness resulting from repeated small doses of toxin.

Efforts to establish a definite bacterial etiology in rheumatic fever date back many years. 5

Triboulet and Coyon, in 1897, cultivated a diplococcus from five living cases of rheumatic fever, and at autopsy on one fatal case. Later (1898) they described the production of a mitral endocarditis in rabbits by the intravenous injection of a diplococcus isolated from the blood of a patient with rheumatic fever. In another article Triboulet and Coyon reported that in 11 consecutive cases of rheumatic fever they had isolated a diplococcus from the bloodstream.

Apert in 1898, using the methods of Triboulet and Coyon, took blood cultures on two cases of chorea. One yielded a diplococcus similar to the strains recovered by these investigators. In 1899, Westphal, Wassermann and Malkoff made a bacteriologic study of a fatal case of rheumatic fever with chorea and endocarditis. A streptococcus was recovered from the blood, the brain and the heart valves. Experiments were conducted on 80 rabbits with the production of arthritis in a considerable number.

In 1900, Poynton and Paine demonstrated diplococci in eight cases of rheumatic fever. Five of the eight cases, however, were fatal, and in these five the cultures were obtained at post-mortem table. In three of the eight cases blood cultures were taken; two out of the three were positive for diplococci. In the remaining five cases, diplococci were isolated from pericardial fluid, vegetations on the heart valve or from tonsils. When injected into rabbits these diplococci produced arthritis, valvulitis and pericarditis.

Philipp, in 1903, took blood cultures on 31 cases of rheumatic fever and obtained entirely negative results. He concluded that rheumatic fever is a specific infectious disease of unknown etiology.

Loeb, in 1908, took blood cultures on 45 cases of rheumatic fever. In eight patients a streptococcus was obtained which morphologically and culturally corresponded to that described by Poynton and Paine and other workers.

In 1908 Beattie examined three cases of fatal rheumatic fever at the post mortem table. In all of them cultures from the heart's blood remained sterile. In all three cases, however, streptococci were grown from pieces of synovial membrane. These strains were identical in their cultural characteristics, and differed in no way from Poynton and Paine's "streptococcus rheumaticus".

In 1913 Rosenow reported the isolation of streptococci from the joints in seven out of eight cases of rheumatic fever. The same author, in 1914, recovered streptococci from the blood stream in four out of seven patients with rheumatic fever. Rosenow divided his streptococci into three groups, according to their effect on blood agar: 1.Those producing green; 2. Those producing slight hemolysis; 3. Those producing no perceptible change. Rosenow claimed that under certain conditions any of the three varieties could be converted one into the other. When these streptococci were injected into rabbits, they induced arthritis, endocarditis and pericarditis.

Herry, in 1914, undertook an elaborate study of rheumatic fever based on 60 cases. Forty-three out of the sixty cases yielded positive blood cultures, in every case a diplococcus similar to that described by Poynton and Paine. Four out of five joint cultures were positive for streptococci, and seven pleural fluids all yielded streptococci. Altogether 47 of the 60 cases (78.3 per cent) yielded a streptococcus from some one of these sources. Herry found that arthritis, myocarditis and endocarditis were readily produced in rabbits by intravenous injections of these streptococci.

Swift and Kinsella, in 1917, cultured the blood from 58 cases of rheumatic fever and obtained streptococci from 7, or 12 per cent of them. The joints were cultured in 25 cases with entirely negative results. All of Swift and Kinsella's streptococci produced green on blood agar plates, but no strict biological relationship could be established between these strains by complement-fixation tests. No agglutination tests were made.

In 1925, Clawson isolated streptococci from the blood in a "relatively high percentage of cases of rheumatic fever". Altogether twenty strains of streptococci were studied. With one exception they all produced methemoglobin after a period of cultivation. The exceptional strain was a typical streptococcus hemolyticus. By injecting these streptococci into rabbits, Clawson found that lesions similar to those occurring in human rheumatic fever could be produced experimentally.

Zinsser and Yu (1928) reported the results of cultures on two cases of rheumatic fever and two cases of rheumatic carditis. In one rheumatic fever patient, intra-vitam blood cultures revealed both an alpha and a gamma strain of streptococci. The other rheumatic patient died and at autopsy an alpha streptococcus was recovered from the myocardium and pericardial fluid. Both of the patients with carditis died. Cultures from the blood of both of these patients were sterile, but post mortem cultures from the spleen in each instance yielded a streptococcus.

Suranger and Forro (1928) took blood cultures on 25 cases of "polyarthritis" and obtained green streptococci in 17, or 68 per cent, of the series.

In contrast to these positive findings is the recent study of Nye and Seegal (1929) on the bacteriology of the blood in rheumatic fever. Fifty cubic centimeters or more of blood was taken in nearly every instance. 25 cases were cultured in this way with entirely negative results.

Small and Birkhaug, whose recent studies (1927) on the etiology of rheumatic fever have attracted considerable attention, have not been particularly interested in the bacteriology of the blood and joints in rheumatic fever, but have investigated the gamma type of streptococci in relation to its presence in the throats of patients with rheumatic fever. Small's original R1 "streptococcus cardioarthritidis" was isolated from the blood, but most of his subsequent strains were obtained from the throats of rheumatic fever patients. Of Birkhaug's 27 strains of "non-methemoglobin-forming streptococci", only three were isolated fromthe blood, the remainder from tonsils, feces, etc.

In a recent study made by R.L.Cecil, E.E.Nicholls and W.J.Stainsby the following conclusions were made:

During the Spring of 1928, 29 patients with acute rheumatic fever were subjected to blood cultures of whom 9, or 31 per cent, yielded a streptococcus. During the Spring

of 1929, 31 patients with acute rheumatic fever were studied by blood cultures, of whom 26, or 83.9 per cent, yielded a streptococcus. The higher percentage of positive cultures in the 1929 series appears to have been due to improved cultural methods.

Of the 35 strains of streptococci recovered from blood culture, 33 have been classified as alpha streptococci (Streptococci viridans); one as a beta streptococcus (Streptococcus hemolyticus); and one as a gamma streptococcus (Streptococcus anhemolyticus). Some of the viridans strains produced very little green on blood agar.

Agglutination and absorption tests indicate that the strains of streptococcus viridans recovered from the blood of patients with rheumatic fever show a tendency to fall into specific biological groups.

In 7 patients with rheumatic fever who were subjected to cultures from affected joints, 5, or 71.4 per cent, yielded a streptococcus viridans. In 3 patients in whom green streptococci were recovered from both blood and joint, agglutination and absorption tests proved the identity of the strain isolated from the two sources.

These findings corroborate those of previous investigators and make it difficult to escape the conclusion that rheumatic fever is a streptococcal infection usually of the alpha or viridans type.

The pathogenesis of rheumatic fever in respect to joint lesions appears to be analogous to that of infectious arthritis and gonococcal arthritis. Bacterial allergy probably influences the clinical picture in all three conditions, but in each instance the joint manifestations are primarily dependent upon localization of bacteria in the joint, with subsequent infection.

Clawson[6], in one study, demonstrated that inflammation with a cellular reaction similar to that found in tissues in cases of human rheumatic infection could be produced by the injection of streptococci of low virulence in small doses into the myocardium and the subcutaneous tissues of rabbits. With larger doses, abcesses developed. In this study, it was not determined whether the type of reaction was influenced by existing immune or allergic reactions, since most of the animals had had injections of streptococci before.

In a subsequent study[6] (1930) experiments were carried on in an attempt to determine what part, if any, allergy or immunity played in the pathogenesis of the experimental lesions.

The lesions reported were produced by injecting streptococci in many places into the subcutaneous tissues of rabbits. The organism used was a strain isolated before death from the blood of a patient having acute rheumatic fever. This strain had been kept on blood agar medium with frequent transfers over a period of eight years.

The experiments were performed with the following three groups of animals: (1) animals that had not had injections (normal animals); (2) animals into which streptococci had been injected intravenously (immune animals); (3) animals into which in one area agar at 45° C., heavily seeded with streptococci had been injected subcutaneously (allergic or hypersensitive animals). In the normal animals, few gross lesions were

detected following the injection of either dilution (1/100 of the sediment of a broth culture of streptococci or 1/1000 of same). In the immune animals when the subcutaneous in--oculations were made before the seventh day after the immunizing inoculation, practically no lesions developed. Those animals in which the subcutaneous injections were made from the seventh to the twelfth days showed a greater frequency of lesions than did the normal animals. This was probably due to an allergic reaction. In the hypersensitive animals, gross lesions, often large abcesses, were practically always present with both the larger and smaller doses. Abcesses were much more common in the hypersensitive animals than in the normal or immune animals.

Two types of cellular reaction were noted in the nodules: (1) the exudative reaction,generally with necrosis and abcess formation, and (2) the polyblastic reaction.

The polyblastic type of microscopic cellular reaction was found in all three groups. It appears evident that this type of reaction, which is characteristic of the lesions found in patients with acute rheumatic fever, does not depend primarily on a hypersensitive stage when produced experimentally in animals. If doses sufficiently large are given, this reaction may be produced in both normal and immune animals, as well as in hypersensitive animals.

From his experiments Clawson concluded that experimental subcutaneous nodules with a polyblastic type of inflammation could be produced in normal, immune and allergic animals by regulating the dose of the injection. Such nodules were produced with much smaller doses in the hypersensitive animals.

General immunity, as indicated by a high agglutinating titer, tends to retard the development of subcutaneous nodules, except in cases in which the subcutaneous injections are made in from 7 to 12 days after the primary immunizing inoculations. In these cases, the increased nodular production is probably due to allergy.

The larger nodules in all cases, as a rule, are abcesses; hence, the greater frequency in hypersensitive animals.

The relationship between allergy and the pathogenesis of experimental rheumatoid subcutaneous nodules appears to be quantitative only.

When these experimental results and the frequency of the hypersensitive state in patients with acute rheumatic fever are considered, it becomes less difficult to understand the pathogenesis of human rheumatoid lesions.

The use of an eight year old culture in Clawson's experiments, in my opinion, somewhat discounts the value of his work. It is hardly conceivable that an organism may be kept viable for such a long period without undergoing attenuation in some form.

Practically all of the recent studies of the rheumatic diseases tend to show that streptococci are intimately concerned in their etiology. The manner in which these organisms attack in producing pathologic lesions is quite complex,and at best but imperfectly understood in our present knowledge. Small, whose work in rheumatic fever, has attracted much attention in recent years, considers three main methods of attack, anyone of which, or the combination of all, or any two of which may operate in the particular case.

These are: 1. Through the immediate effects of lodgement and growth of streptococci in the tissues.

2. Through the action of toxins distributed generally from some local focus of growth of streptococci.

3. Through the action of some other bacterial products distributed from a focal source and capable of inducing and maintaining an allergic state of the animal organism.

It appears probable that these three methods of attack seldom operate singly. The simplest combination of them may be outlined as:

(a) The effect of the toxins distributed from a primary focal source of infection in producing tissue damage at a distant point, which in turn serves as a prepared location for the secondary lodgment of the bacteria from the primary nidus of infection, or for other bacteria happening to gain entrance to and transportation in the body fluids.

(b) The effects of the allergic state of the individual in producing remote localizations of tissue damage, which predispose to the secondary localization of the bacteria from the primary focus or other bacteria transported to the site of the allergic lesion.

The three basic methods of attack were considered as follows:

1. The actual lodgment of streptococci in the tissues:-

In Small's experience with lesions in which this usually occurred, suppuration had appeared early, and the identification of streptococci by both smear and culture constituted a very commonplace bacteriologic procedure. He wonders then, why is the demonstration of streptococci such a difficult and inconstant matter in the acutely inflamed joints of rheumatic fever and in certain stages of other arthritides. Why the usual evanescent character of the acutely inflamed joints in rheumatic fever when the usual lesions in which streptococci appear heal out slowly?

These and many other considerations raise questions difficult to answer and cause one to speculate on the possibility of whether or not the streptococci at times actually recovered from the joint lesions were present locally at the beginning of the inflammatory process, as prime instigators through their immediate irritating effects, or whether they came along as opportunists to find temporary lodgment in foci of lowered resistance to streptococci.

2. The effects of toxins of bacteria.

In the diseases caused by true toxins as, for example, diphtheria and tetanus, two facts stand out. These are: (a) The lack of tissue invasiveness of the bacteria themselves, and (b) the selective action of the toxin on certain tissues known as trophism. The local focus of infection while usually easily identified, is ordinarily a minor consideration among the pathologic lesions established by the disease. Toxin formation on the part of a bacterium does not appear to be a factor favoring the opening of tissue spaces for the general dissemination of the bacterium and may actually have the opposite effect.

Toxic products of streptococci (endotoxins) are well recognized. Among the toxin formers, those of scarlet fever and erysipelas stand out pre-eminently. These tend to disseminate their toxins from localized areas of infection. Invasion

of the organisms is for the most part limited to the regional lymph channels.

The question of a toxic product generally disseminated must be considered in rheumatic fever. The destructive and proliferative lesions in the heart and blood vessels have never been shown consistently to harbor the actual bacteria. Are these lesions the result of the action of a toxin? If so the acute exudative lesions of the joints, pericardium, and pleura may result from the same process.

Joint lesions, as peripheral, easily observed exudative lesions in rheumatic fever respond to salicylate medication. The beneficial effect of salicylate medication on the destructive and proliferative lesions of the heart is doubtful. This difference of response suggests that the mechanisms producing the two types of lesions may be different.

Small, suggesting the Streptococcus cardioarthritidis as an etiological factor in rheumatic fever, demonstrated that an antiserum against its endotoxin could be prepared. In applying the antiserum clinically in rheumatic fever, clinical detoxification of the patient and rapid improvement in heart action, as evidenced by improved valvular tones, the decrease in size of dilated hearts, and the disappearance of congestion of the liver, were more consistently observed than was a prompt clearing of the acutely inflamed joints. This difference in response of the heart and joint symptoms further suggests differences in their pathogenesis.

3. Bacterial allergy.

This is the newest and its significance least understood.

The lack of species specificity in the allergic states induced by experimental means with antigens of streptococci had led Small to make the suggestion that streptococci and perhaps pneumococci contain a highly organized common protein, which acts as a "specific allergen", regardless of its biologic origin. In considering the part which bacterial allergy plays in disease it must not be forgotten that biologic specificity of the infecting bacterium is regarded as a most important factor in lending clinical and pathologic definition to an infectious disease. This is true even within the streptococcus group as shown by the two diseases, scarlet fever and erysipelas. That patients with the arthritis of rheumatic fever and with other forms of subacute and chronic arthritis are hypersensitive to the products of streptococci is shown by the focal reactions in the joints and general reactions obtained upon the injection of minute doses of a saline extract of streptococci into such patients.

However, the allergic symptoms do not occur with significant intensity in all cases of rheumatic fever, for example, rheumatic fever in childhood without joint symptoms as contrasted with the ordinary adult type of the disease with joint symptoms and the futility of salicylates in the former as contrasted with the apparent success in the latter. Salicylates tend to offset the allergic states in experimental animals. The deduction, therefore, again appears logical that the exudative lesions in rheumatic fever are manifestations of allergy and that they are on a different basis from the destructive and proliferative cardiac lesions.

Small's studies during the past two years, in which the antiserum and antigen of Streptococcus cardioarthridis have been used in the treatment of clinical cases, have enabled him to develop a working hypothesis which may be stated as follows:

The destructive and proliferative lesions of rheumatic fever (blood vessel and cardiac lesions) are produced by a different mechanism from that causing the exudative lesions (acute arthritis).

The former types of lesions are produced by the action of a specific toxic product (endotoxin) derived from a particular streptococcus. The latter type of lesion arises because of the establishment in the patient of a condition of hypersensitiveness to a protein fraction contained in streptococci. This protein fraction is a highly specialized protein common to quite diverse immological strains of bacteria. It acts as a specific allergen because of its chemical structure and regardless of its biologic origin.

The problem in therapy of acute rheumatic fever appears to be that of complete neutralization of the toxic factor by a specific antiserum with out passively transferring to the patient hypersensitization to the protein antigen common to different streptococci. The focal reaction inthe joints following the injection of the antiserum of Streptococcus cardioarthridis in patients with acute rheumatic fever appears to be a manifestation of this passive transfer of allergy. To avoid this it would become necessary to remove from the antiserum the antibodies of the protein fraction of the streptococcus without destroying its effectiveness by the removal of any of its antitoxin content.

In closing the portion of this paper dealing with the etiology of rheumatic fever we are only able to say that from the evidence presented the etiology of the disease is associated with the streptococcus. In what particular manner it is impossible to state positively.

PATHOLOGY

The pathology of rheumatic fever is extensive. The changes occurring in the heart and vascular system have attracted the most attention, and rightfully so for it is the lesions in the above-named locations that are of serious import.

HISTORICAL [1]

The first to recognize and to emphasize the intimate relationship between rheumatic fever and affections of the heart was David Pitcairn, who made his observations while physician to the St. Bartholomew's Hospital in 1788. Baillie (1797) and Wells (1812) both refer to Pitcairn's observations. Edward Jenner apparently recognized the connection between heart disease and rheumatic fever about the same time, for in the records of the Gloucestershire Medical Society it is stated that in 1789, "Mr. Jenner favored the Society with Remarks on a Disease of the Heart following Acute Rheumatism, illustrated by Dissections". Unfortunately Jenner's paper was lost. Wells in an important memoir gave an account of fourteen cases of rheumatic heart disease treated either by himself or his colleagues (Baillie, Lister, Brodie and others) and the results of several post-mortem examinations. Baillie, Wells, and Hope realized that the heart valves could become diseased in rheumatic fever, and they and other early observers as well as their predecessors, Pitcairn and Jenner, clearly recognized the possibility that the heart could suffer in rheumatic fever, but it was Bouillaud who emphasized the great frequency with which this occurred. Among the first to record the possibility of myocardial involvement in rheumatic fever were Besnier (1876), Hardy (1876), West (1878), and Goodhard (1879) and, according to Gallavardin, Vaisse (1885) was the first to describe interstitial lesions in the myocardium in fatal cases of rheumatic fever.

The study of the specific interstitial lesions of rheumatic myocarditis begins with the observations of Romberg (1894), who in two fatal cases of rheumatic fever noted the presence of interstitial cellular infiltrations (not in nodular form), among which were large cells similar to those subsequently described by Aschoff. Poynton, in 1899, described interstitial foci in the myocardium which were undoubtedly Aschoff bodies, but neither he nor Romberg appreciated the specificity of the lesions which they reported.

The first to give a precise description of the characteristic interstitial lesions and to recognize their specific character was Aschoff (1904). Geipel published observations upon seven cases the following year. His description of the submiliary myocardial nodules agrees in the main with that of Aschoff, but he was inclined to doubt the specific nature of the lesions because he found them in a case of chronic interstitial nephritis; however, Aschoff and Tawara pointed out,a rheumatic infection could not have been excluded because adherent pericardium also was present. Since the publications of Aschoff and Geipel, a large number of investigators have described these lesions which are now known as Aschoff bodies, and pathologists are generally agreed that they are peculiar to rheumatic fever.

MYOCARDIUM

In fatal cases of rheumatic carditis, the ventricular chambers are generally found to be dilated even if death occurs afterthe first attack and the accompanying endocardial or pericardial inflammation be slight in degree. The dilation is more marked in the left side of the heart and includes the auriculoventricular rings, especially the mitral

Fisher (1896) was one of the first to recognize that mitral insufficiency in early rheumatic carditis is more often myocardial than valvular. It is difficult to prove that stretching of the aortic ring ever occurs, but there are a few clinical observations which suggest such a possibility. It is not definitely known at what stage of the rheumatic infection (in an initial attack) the hypertrophy sets in, but Coombs believes that it begins while the signs of acute carditis are subsiding. Dilatation and hypertrophy are the result of the invasion of the myocardium itself, since they develop even if the heart is not embarrassed by valvular disease or pericardial adhesions. When mechanical factors are superadded the heart undergoes further stretching and increase in weight. In a large number of cases, the naked-eye appearance of the myocardium shows no deviation from the normal. At times there may be some tigering, indicating fatty metamorphosis, and in acute cases there may be cloudy swelling.

The essential lesions are those in the interstitial tissue--the Aschoff bodies. These 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 0.1 to 0.5-0.8 mm., but in rare instances they are visible to the naked eye. In a case seen by MacCallum, there were numerous small pearly-white foci scattered especially in the muscle near the auriculoventricular ring, which proved on microscopic examination to be Aschoff bodies. The nodules are situated mainly in the subendocardial tissues, but they are also present in the subpericardial layer of the myocardium as well as in its more central portions. They are more abundant in the left ventricle, and occur especially in the basal portions; sites of predilection being the insertion of the ventricular wall into the fibrous ring of the mitral value, 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 scantiest in the papillary muscles of both ventricles, the central portion of the interventricular septum and the columnae carnae near the apex.

The specific lesions are not always found even if the presence of subcutaneous nodules or chorea, together with pericarditis and endocarditis, furnishes convincing evidence of rheumatic infection. The reported incidence varies from 32.1 per cent to 87.5 per cent. In cases of long-standing rheumatic valvular disease in which the presence of fresh vegetations reveals the existence of active infection, the nodules are less likely to be found than in cases which have proved fatal after the initial attack, or before the disease has lasted many years. The number of nodules in a given case varies within wide limits. It may be necessary to examine many blocks before any are discovered, whereas in other cases nodules are found in abundance in almost every section, and between these extremes there is every degree of variation.

The nodules consist essentially of characteristic large cells which are arranged about a central necrotic zone in which there may be a little fibrin. The typical cell is a large polygonal element, containing one or more nuclei. The cytoplasm in hematoxylin-eosin sections, is deeply-dyed, finely granular, and basophilic. The nucleus is polymorphous and vesicular and exhibits a sharply defined nuclear membrane with one or more nucleoli, the greater part of the nucleus being clear and at times presenting, a vacuolated appearance. The multinucleated cells contain two to seven nuclei and in rare instances as many as fifteen or even twenty. The multinucleated cells differ from the Langhans giant cells of tuber-

culosis in the central arrangement of their nuclei and resemble the Dorothy Reed cells of Hodgkin's disease. Their number in the Aschoff nodules is variable; at times they are few and at other times they may comprise as many as half of the characteristic cells. Mitoses have not been seen. Intermingled with the most peripheral of the large cells and especially at the margins of the nodules are a variable number of lymphocytes, plasma cells, and a few polymorphonuclear leucocytes, including an occasional eosinophile. At times these cells, particularly the lymphocytes, may be quite numerous.

The nodules develop in the adventitia of the coronary arterioles, in the peri-adventitial tissue, or at some distance away from the vessel. Some of the nodules seem to bear no relation to vessels, but serial sections would be necessary to prove no such relationship. The nodule may approach the vessel at only one point in its circumference or may spread out in both directions until it surrounds half or even the whole of its circumference. The close proximity of the nodule to the vessel may lead to the compression of its lumen, especially when there are two nodules at opposite poles of the circumference. The interstitial tissue about the nodules is often edematous, and some of the surrounding muscle fibers may undergo degeneration.

How long it takes the nodules to develop and how long they persist is not known. Judging from the life history of the subcutaneous nodules, which are the homologues of the Aschoff bodies, we may estimate that they may last for weeks or even months. It is possible that the unknown virus of rheumatic fever is present in the nodules, producing fresh lesions from time to time and helping to perpetuate the infection in the body. As the Aschoff bodies grow older, the cells become elongated, their nuclei stain less sharply, the cytoplasm becomes acidophilic, and the cells are finally converted into a homogeneous necrotic mass. Fibroblasts grow in between the large cells, which finally disappear. It is very common to see in older lesions peri-arterial edematous foci in which a few elongated cells are embedded in the loose meshes of a fibrillary matrix. Finally the nodules are replaced by scar tissue, in which a few lymphocytes may persist for a long time. Broad parietal scars are very characteristic of the healed stage.

Aschoff and Tawara were the first to emphasize the frequent subendocardial distribution of the lesions and the possibility of resulting injury to the Purkinje system. The specific lesions are, however, rarely found in the sinoauricular node and the junctional tissues, only a few instances having been recorded. Coombs in one case found Aschoff bodies of small size at the edge of the S-A node: Geipel (1906) noted the specific lesions in the A-V bundle, and Aschoff and Tawara and Mönckelberg found the nodules in the region of the left branch of the bundle. The most extensive involvement reported occurred in the cases of Butterfield and of Naish and Kennedy. Butterfield's patient was a girl of sixteen years who developed a partial heart-block eleven days before she died. At autopsy there was a widely diffused infiltration in the heart, conspicuous in the region of the central fibrous body, and reaching its greatest intensity in the A-V node, the normal appearance of which was obscured by dense cellular infiltration with lymphocytes, leucocytes and large mononuclear cells. Throughout the remainder of the node and bundle, with the exception of the right branch, every vessel was surrounded by infiltrations, composed almost exclusively of lymphocytes. There were numerous Aschoff bodies in the myocardium and the heart valves, but there were no giant-cell lesions in the node proper.

The origin of the large cells of the Aschoff body has frequently been discussed. Some have derived the giant cells from the myocardium, but the presence of identical cells in regions where muscle is absent, e.g., the valvular or auricular endoardium, makes it difficult to accept this origin. Most observers believe that the Aschoff cells are derived either from adventitial or connective tissue cells or from endothelium.

The rheumatic virus may invade the myocardium without injuring the valves, and clinically this fact is of great importance. In other cases the endocardial or pericardial involvement may be negligible, but the degree of ventricular dilatation and the severity of the cardiac symptoms in general testify to the profound disturbance which may result from the localization of the rheumatic virus in the myocardium itself.

It is well known that the rythm of the heart may be conspicuously altered during the course of rheumatic fever. Heart block in its various stages, from slight prolongation of auriculoventricular conduction time to partial or complete dissociation is the most frequent change noted; but in addition a number of other abnormal rythms have been reported, including premature contractions, nodal rythm, auricular fibrillation and flutter, paroxysmal tachycardia and sinoauricular block. If the alterations noted in the ventricular complex of the electrocardiogram are included, there is evidence that the heart is affected in about 95 per cent of cases of rheumatic fever. Cohn and Swift believe that the changes may be explained by the presence of Aschoff bodies and perhaps of the ischemic areas consequent upon blood vessel involvement. This explanation may suffice if the specific lesions are numerous and the vascular changes marked, but it would be difficult to account for all cases in this way, inasmuch as the Aschoff bodies are so frequently inconspicuous or absent (Libman, Rothschild and Sacks).

ENDOCARDIUM

Rheumatic endocarditis is more frequent in the valves of the left side of the heart than in the right, but the incidence of tricuspid involvement is high--a fact emphasized by Libman for a good many years. In a series of eighteen cases of endocarditis with Aschoff bodies in the myocardium, Libman and Sacks discovered fresh vegetations on the tricuspid valve in 12 (66.6 per cent). Coombs noted tricuspid disease in 36.1 per cent of cases of rheumatic carditis and McCallum and Thayer in 44 per cent. The pulmonary valve is but rarely involved, only a few examples having been reported.

The appearance of the vegetations in acute rheumatic endocarditis is typical. They take the form of minute cauliflower or wart-like excrescences 1 to 2 mm. in diameter, generally of uniform size, pinkish-gray, grayish or grayish-white in color, and are situated in a row along the line of closure of the valve. Occasionally they are polypoid and somewhat larger. In rare instances, a few minute verrucae extend for a few millimeters along the chordae tendinae. The surface of the vegetations in the early stage of their development is dull and opaque, and somewhat later they present a glistening appearance. The valve leaflets may appear slighly pink and swollen. The entire line of closure of a given valve may be covered with vegetations and this is the rule in the mitral valve, but in the aortic valve and especially in the tricuspid valve, only a part of the valve may be affected (Libman). The vegetations have a rather tough consistency, being relatively difficult to crush, and they adhere with considerable tenacity to their point of attachment.

These properties explain why rheumatic vegetations do not cause embolism (Libman), the occurrence of which in rheumatic carditis is generally due to thrombosis in the left auricle.

Königer described the initial change as necrosis of the endothelium, followed by exudation of a coagulable fluid arising in the tissue lymph, with conversion of the necrotic tissue into a swollen homogeneous fibrin-like mass which soon projects above the surface and becomes a verruca by fusion with a minute thrombus which is deposited by the blood stream. According to Baehr, the thrombotic deposit consists essentially of agglutinated blood platelets, and there is early regeneration of endothelium over the vegetative nodules. While Königers histological description of the verrucae is nearly correct, evidence is accumulating which indicates that a proliferative interstitial reaction in the subendocardial tissue preceded the changes on the surface of the valve.

Swift had the unusual opportunity of studying four cases of rheumatic fever, dying within two or two and a half weeks of the onset of arthritis. In three, the attack was the first and in the fourth, death occurred during the second attack. Aschoff bodies were found in the substance of the valve and there were in addition interstitial edema and a diffuse proliferative reaction (valvulitis). These changes occurred in valves or in portions of valves which were free of verrucous deposits, suggesting that endothelial injury is not primary but secondary to the interstitial valvulitis. According to Swift, rheumatic verrucae are due to the deposition of thromi on portions of inflamed valves where the vitality of the endothelium has been impaired by repeated impacts with the contiguous valve, but he also considers it possible for small verrucae to form at a point where a submiliary nodule breaks through the endocardial surface. These findings would suggest that the virus of rheumatic fever is brought to the valve by way of intrinsic vessels, and the demonstration of blood vessels of non-inflammatory origin in a certain percentage of hearts other than those of the fetus (Kugel and Gross) shows that this method of infection is anatomically possible.

Healing of the vegetations begins at a very early stage (Libman). Blood vessels and fibroblasts invade the verrucae, which are finally cicatrized. Hyaline material may be found on the surface or within the substance of the valve for a long time after healing has occurred. The final development of mitral stenosis from a row of vegetations on the line of closure is remarkable, and a satisfactory account of the precise manner in which this occurs has never been published (Sacks). The fact that inflammation of the valves is not only an endocarditis but a valvulitis, with extension of the inflammation far beyond the region of the attachment of the vegetations, explains a great deal. It probably requires more than a single brief attack to cause serious valvular disease. That rheumatic infection tends to recur repeatedly is well known, and evidence is accumulating that this infection is frequently chronic. The manifestations of activity may not be obvious clinically: mitral stenosis of the typical rheumatic kind may reach its full development without a satisfactory history of rheumatism. It is not infrequent that active infection is discovered at postmortem examination when none was suspected during life. It is not uncommon to discover fresh verrucae on chronically diseased valves, and examination of the most thickened and deformed valves sometimes reveals deep cellular infiltration of wide extent and even Aschoff bodies. The blood vessels show intimal thickening, with narrowing of the lumen-changes which Coombs attributes to chronic inflammation.

A number of observers have reported the presence of Aschoff bodies in the auricle, but it was MacCallum who first directed attention to the frequent occurrence of a gross, coarse lesion of the endocardium of the left auricle accompanied by numerous Aschoff bodies in the lesions.

As described by MacCallum and Von Glahn, the lesion is located on the wall of the left auricle, extending upward from the root of the posterior leaflet of the mitral valve in the form of a corrugated or puckered patch or endocardial thickening, sometimes covered with a thin fibrous layer. In a few cases there were distinct projections on the auricular surface resembling vegetations. The area of involvement may be small, not exceeding 3 cm. in diameter, though usually a wider area is involved, and in rare instances the entire endocardial surface of the auricle may be affected. In the later stages of the process, the ridges and hillocks of the corrugated area flatten down and become less distinct. The thicker patches become dense and scar-like and may be infiltrated with calcium salts.

On microscopic examination of the more acute lesions, the lining layer of the auricle is spread apart by edema and an extensive accumulation of exudate cells of all sorts, including mononuclear cells, polymorphonuclear leucocytes, and occasionally eosinophiles. In many instances, the innermost layer of the auricle assumes a hyaline appearance over the whole patch and merges gradually into a dense film of fibrin which is deposited on an area where the endothelium has been denuded. In other cases the endothelial layer is intact. The most striking feature is the presence of numerous large Aschoff bodies which are forced into rows by arrangement of the elastic tissue lamellae so that the Aschoff bodies have a banded appearance (MacCallum). According to VonGlahn's description, the greater number of the Aschoff cells form a palisade along a band of hyaline material, their nuclei being perpendicular to the band. In some sections, the large cells are replaced by accumulations of cells with indistinct outline and compressed or distorted nuclei, together with numerous polymorphonuclear leucocytes, a few plasma cells, small round cells and eosinophiles and pale cells with vesicular nuclei which differ from the Aschoff cells in their reaction to the Unna-Papenheim stain. Von Glahn considers the masses of distorted cells and leucocytes to be as distinctive a feature as the Aschoff bodies. As healing progresses, the endocardium is invaded by capillaries and fibroblasts, the characteristic cells disappear, and finally a dense avascular scar develops, sometimes infiltrated with calcium salts.

In certain cases of mitral stenosis or insufficiency, the auricle may become tremendously dilated, assuming aneurysmal proportions. It is not easy to explain this enormous distention on the basis of mechanical factors alone, and it is possible that the underlying cause is antecedent rheumatic fever infection of the auricular wall.

PERICARDITIS

Fibrinous pericarditis is one of the most distinctive lesions of rheumatic fever. It is generally accompanied by myocarditis and endocarditis, but in a few reported cases endocarditis has been absent. Libman refers to such a case (acute pericarditis together with Aschoff nodules in the myocardium) and Geipel and Fränkel have reported cases of obliterative pericarditis accompanied by myocardial nodules but without endocarditis. The inflammation may be confined

to a localized area or areas, but in its typical form affects the entire pericardium. In the earliest stages and in mild cases, a thin layer of fibrin is exuded on the pericardial surface without serous effusion. When the fibrinous exudation is more profuse, it is beaten by the heart action into a series of ridges which run in a transverse or oblique direction or in the form of a honey-combed network. This gives the heart a characteristic shaggy appearance, which Laennec compared to the appearance produced by the rapid separation of two marble slabs thickly buttered on their opposing surfaces. The exudation of fibrin is usually accompanied by serum, which may be in either small or large amount. When the fibrin is scraped off, the serous membranes are seen to be hyperemic and often ecchymotic. Adhesions soon develop between the visceral and parietal layers which at first are very friable, but after organization occurs become firm and dense. In very severe cases, they may extend beyond the limits of the pericardium, binding the parietal pericardium to the pleura, diaphragm, mediastinum, and chest wall (adherent pericardium or mediastinopericarditis). Winkelstein reported calcification and ossification of the pericardium in a case of purulent pericarditis complicating rheumatic infection of the heart.

On microscopic examination, the freshly formed exudate is composed of fibrin, platelets, and leucocytes, together with erythrocytes. The serosal cells may become fatty and desquamate, but in many places though covered with fibrin they persist for a long time. The edematous subpericardial tissues are soon invaded by numerous capillaries and fibroblasts and exhibit a diffuse cellular reaction, with concentration of the cells about the smaller vessels. The cellular infiltrations are composed of polymorphonuclear leucocytes, lymphocytes, and a large number of mononuclear cells. The vessels frequently show endothelial swelling and proliferation, with or without thrombosis, and are often thickened as a result of the deposition of hyaline-like material or fibroids in their walls. Focal lesions in the pericardium consisting of the characteristic large cells have been noted by a number of observers. The pericardial Aschoff bodies are often quite large and are most frequently found in characteristic form during the period of organization of the pericarditis. It is evident that rheumatic pericarditis presents the same essential features as the myocarditis, if due allowance is made for the peculiar anatomical structure of the pericardial sac and the manner in which serous membranes react to injury. (Swift).

BLOOD VESSELS

Pappenheimer and Von Glahn presented histological proof of the existence of specific rheumatic lesions in the wall of the aorta in fatal cases of rheumatic fever. A number of previous observers had reported rheumatic infections of the aorta, but without carefully controlled histological examination, the only important exception being the observations of Klotz in his paper in 1912. Single or multiple aneurysms of the aorta alleged to be rheumatic have generally proved to be secondary to subacute bacterial endocarditis. The changes noted by Pappenheimer and Von Glahn are microscopic, the gross appearance of the aorta having been normal. In their first publication, these authors described the presence of Aschoff bodies or isolated Aschoff cells in the adventitia, and healed lesions in the media, consisting of compact acellular flame-shaped scars. In their second paper, they described the findings of a case in which they had

the opportunity of studying the acute stage of the medial lesions. In the outer two-thirds of the media, they noted that the nutrient arterioles were thick-walled, due in part to endothelial swelling and proliferation, and in part to cellular infiltration and perhaps edema of their walls. About these vessels were profuse collections of cells, including lymphocytes, polymorphonuclear leucocytes (which were often numerous) and Aschoff cells. It is natural that Aschoff bodies should have been found in the neighborhood of the nutrient arteries of the aorta, for these are derived from the coronary arteries. As the pulmonary artery also receives its blood supply from the coronary arteries, one would expect to find the specific lesions in the outer coats of this artery as well, though less grequently than in the aorta because of the infrequency of the Aschoff bodies in the right side of the heart.

Changes in the coronary arterioles have been described by a number of observers. According to MacCallum these changes are not very common except in the severe cases. They may result from the presence of contiguous nodules, which develop in or extend into the media, compressing the vascular lumen and disintegrating the vessel wall. In other cases, the lesions occur in vessels which bear no relation to Aschoff bodies. In the mildest form of involvement, the coronary arterioles display endothelial proliferation and sometimes intimal infiltration with round cells, with or without narrowing of the lumen. When the process is more advanced, the endarteritis is more pronounced, thrombosis may develop, and the media be involved. In some cases, there may be thrombosis without visible alteration in the vessel wall, and in others conspicuous vascular damage without thrombosis. In the most severe cases there is actual destruction of the specific elements of the vessel wall, even to the point of microaneurysmal pouching as in Geipel's case. It is chiefly the smallest arteries and less often those of medium caliber which are affected, and MacCallum has described a case in which there was destruction of portions of the walls of large coronary sinuses, with thrombus formation over these patches. In a few instances, small anemic infarcts apparently resulted from occlusion of numerous small vessels. The fate of these vascular changes has not been thoroughly investigated, but it is not uncommon to find pronounced fibrous intimal thickening in the smaller arteries in old rheumatic hearts. Krehl described this change as early as 1890, and Coombs, who also noted its occurrence, found that the artery to the A-V node frequently suffered to the point of almost complete obliteration.

Baehr and Sacks (1923) reported three cases of verrucous endocarditis accompanied by glomerulonephritis and extensive changes in the arterioles of the kidneys. The vascular lesions consisted of endothelial swelling and proliferation, cellular infiltrations with disintegration of the normal elements of the vessel and thromboses. As there were no Aschoff bodies in the heart, it was not possible to decide whether these cases were due to an unusual form of rheumatic fever or to an unknown nonrheumatic endotheliotropic virus. In another case where the Aschoff bodies were present, the smaller renal arteries were the seat of proliferative and necrotic lesions of such severity, that necrosis of the entire cortex of both kidneys resulted. In one of the kidneys a thrombus had extended from the smaller vessels into the main trunk of the renal artery with resulting infarction of the medulla as well.

Von Glahn and Pappenheimer in an extensive study

of the peripheral arteries in rheumatic fever, noted characteristic changes in a large number of vessels, including those of the lungs, aortic valve, kidney, perirenal and peri-adrenal adipose tissue, ovary, testis, pancreas, and other organs. In a series of forty-seven consecutive cases of rheumatic carditis, the changes were found in ten. The vessels involved were the smaller arteries and those of medium caliber, arterioles, and sinusoidal capillaries. The following alterations were described: exudation of fibrin into and about the vessels, destructive changes in the cellular components of the vessel wall, distinctive cellular reaction in the adjacent tissue and absence of thrombosis. There were no Aschoff bodies. The acute lesions were followed by organization, with or without the formation of new collateral channels in the intima and sometimes within the muscular layer.

Venus thrombosis, involving especially veins of the neck and the upper extremity, is an uncommon but authentic complication of rheumatic fever. In the majority of the cases reported, the symptoms of congestive failure were present and there was no definite clinical evidence of active infection when the thrombosis developed. In Sladen and Winternitz's paper on venous thrombosis in myocardial insufficiency, twenty-six of the sixty-five cases reported gave a history of rheumatic fever. In certain of the reported cases, however, the rheumatic infection was active. In one of Poynton's cases, post-mortem examination disclosed obliterative thrombosis in the superior vena cava in its upper two-thirds, both innominate, subclavian, internal and external jugular, and axillary veins and in the left inferior thyroid vein. The heart showed acute serofibrinous pericarditis, fresh vegetations on the aortic, mitral, and tricuspid valves, and focal interstitial myocarditis of the typical rheumatic type. Whether thrombosis or phlebitis is primary in these cases is difficult to say.

ARTHRITIS

The joints most frequently affected are those of the knees, ankles, shoulders, wrists, elbows and hips, but less commonly any of the other joints may be involved, including the vertebral, sternoclavicular, phalangeal, and temporomaxillary articulations and possibly even those of the larynx. On exposing the joint, the synovial membranes are found swollen, hyperemic and sometime ecchymotic, and there is even more edema of the periarticular tissues. The fluid in the synovial cavity, which is rarely more than moderate in amount, is albuminous and somewhat turbid but not purulent and contains a few fibrin flakes.

Fahr examined the joint capsule of the knee, including the quadriceps tendon and the synovial membrane in sixteen cases at post-mortem and found changes in nine. He noted proliferation of the fixed cells of the synovia and towards the lumen of the cavity the proliferation zone was bounded by a broad layer of necrotic tissue. Swift excised bits of joint tissue from patients during the first week of an acute attack and found focal lesions of the synovia, focal necrosis of the capsule, thrombosis of the smaller arteries and endothelial and perivascular reactions comparable with the changes in the heart and subcutaneous nodules. Fahr and Coombs also saw structures in the deeper layers which they considered homologous to the Aschoff bodies.

Swift emphasized the presence of two types of

response on the part of the body to the virus of rheumatic fever, the one exudative and the other proliferative, and these are well illustrated by the joint changes. The exudative reaction causes the exudation of serum into the periarticular tissues and of serum, fibrin, and cells into the synovial cavity. The proliferative reaction results in the development of granulomatous formations resembling Aschoff bodies in the deeper structures. Salicylates cause a disappearance of the exudative reactions, but not of the proliferative lesions, the persistence of which indicates that the rheumatic infection is not eradicated by the action of the drug. (Swift)

SUBCUTANEOUS NODULES

Hillier described these nodules in 1868 and Jaccoud gave an accurate account of them in 1871, but Meynet (1878) was first to recognize their connection with rheumatic fever. Their higher incidence in the more virulent forms of infection is one of the reasons given for their having been found more often in England than in this country, but Brenneman is of the opinion that careful and systematic search will reveal the nodules with unsuspected frequency in this country. Pathologists are generally agreed upon the fundamental histopathological similarity between the subcutaneous nodules and the Aschoff bodies.

The subcutaneous nodules vary in size from 1 to 2mm. to 1 to 2cm., and are rather firm (generally painless) structures, situated under the skin over bony prominences and attached to fasciae, aponeuroses, tendons, or periosteum. Sites of predilection are the back of the elbow, the malleoli, over the patella, the dorsal surfaces of the hands and feet, the scalp and the spines of the vertebrae. They vary in number from one or two to a hundred or more; their average number in cases in which they are easily found being five to ten.

In the early stages, the nodules have a grayish, translucent gelatinous appearance, and on cut section show in the more central portions minute yellowish opacities. The opaque areas are composed of irregular strands of homogeneous, necrotic tissue in which there may be some fibrin, and surrounding these areas there is a mantle of large mononuclear and multinucleated polygonal branching cells which are similar to the Aschoff cells in the myocardial nodules. The rest of the node is composed of a highly vascularized and often edematous mass of tissue which is made up of fibroblasts, epitheloid cells, a variable number of round cells, and polymorphonuclear leucocytes, including eosinophiles. Almost all the blood vessels show endothelial proliferation, sometimes to obliteration, and a few may show thromi. According to Swift the larger nodes are conglomerates of submiliary nodules. The nodules generally appear suddenly and after a few days disappear; in some cases they persist for weeks or months. The rapid disappearance of the nodule must occur by absorption of the necrotic material and fibrin with subsequent conversion of the nodule into scar tissue (MacCallum). The deposition of calcium salts in the nodules occurs occasionally, and even cartilage and bone formation has been reported.

CHOREA

Sydenham differentiated the disease which is now known as chorea minor or Sydenham's chorea in 1686, but the relationship of this affection to rheumatic fever was not recognized until the nineteenth century. Among the first to comment on this connection was Bright (1839), who stated that rheumatism was distinctly mentioned as

one of the exciting causes of chorea as early as 1802. The presence of Aschoff bodies in the myocardium in fatal cases of chorea testifies to the rheumatic nature of the cardiac complications.

Examination of the brain and its investing membranes in chorea has revealed the presence of a diffuse encephalitis or meningoencephalitis, the main lesions being in and about the smaller blood vessels. The most conspicuous lesions are frequently those in the region of the corpus striatum, injury to which is said to initiate choreiform movements; but Wilson has called into question the theory of the exclusive striatal origin of chorea. According to Wilson, choreiform movements are produced by an afferent disorder of regulation attributable to lesions in the cerebello-mesencephalo-thalamo cortical path. What ever the required localization, the lesions of chorea are sufficiently wide spread to include these areas as well.

With the naked eye, the changes are not obvious, hyperemia being the most frequent of the gross findings. Microscopically, the lesions are widely disseminated and consist of engorgement of the blood vessels, thromboses in numerous small arteries and veins with occasional proliferation and fatty infiltration of the endothelium, small areas of softening from vascular occlusion, serous exudation and small round cell infiltration about the small blood vessels and certain changes in the glia and nerve cells. Similar changes are found in the piaarachnoid in some cases. The absence of typical Aschoff bodies may be due to the peculiar histological structure of the brain, and the vascular and perivascular lesions are very similar to rheumatic lesions elsewhere in the body.

PLEURA AND LUNGS

Fibrinous pleurisy is a common complication of rheumatic carditis. Left side involvement, probably because of nearness of the pericardium, is more frequent but bilateral involvement is not unusual. The incidence of pleurisy in rheumatic fever varies from 2 to 20 per cent, and from 5 to 10 per cent in the majority of statistics. The inflammation may be fibrinous only or accompanied by a serous effusion, generally moderate in amount and seldom requiring paracentesis. The acute inflammation is followed by organization of the fibrinous exudate, and adhesions between the visceral and parietal pleura soon develop.

Bronchopneumonia and lobar pneumonia can complicate rheumatic fever; but the question of the existence of a specific rheumatic pneumonia has frequently been discussed.

KIDNEYS

Acute nephritis is uncommon. Various authors give the occurrence as 0.5 to 1.5 per cent.

Reference has been made, earlier in this paper, to the occurrence of vascular lesions in the kidney.

SKIN AND OTHER ORGANS

Many skin lesions are said to occur, namely, purpura, erythema multiforme, nodosum, papulatum, gyratum, figuratum, urticatum and annulare. Analysis of the re-

ported cases indicates that extensive skin eruptions in rheumatic fever are not common, but do occur. Bass reported erythema marginatum and erythema multiforme respectively in two cases of rheumatic fever in which Aschoff bodies were found in the heart. Erythema nodosum has been seen a few times. Lehndorff and Leiner consider erythema annulare to be typical of rheumatic endocarditis.

Inflammatory changes have been noted in striated muscles and Von Glahn and Pappenheimer reported the finding of Aschoff bodies in the diaphragm in one case.

TREATMENT

A study of the therapeusis of acute rheumatic fever discloses a situation existent similar to that encountered in the study of the etiology of this disease. As usual, when we find many types of treatment advocated, none presents sufficient efficacy to even approach a point considered satisfactory.

That the mechanism, by which beneficial results are obtained through utilization of known methods of treatment, is but dimly understood is a rather disconcerting fact.

In the literature one may find innumerable remedies advanced for the treatment of rheumatic fever; some seeming plausible, most of them lacking sufficient basis to merit consideration. In this paper I feel that it is advisable to consider only those methods of treatment which, by laboratory and clinical research, have been proven to be of value. To enter into a lengthy discussion of each of the many modes and theories that have been put forth would add but little value and would make tedious reading.

At present there seems to be three forms of treatment recognized as definitely established procedures, or as having possible beneficial results. These are as follows:

1. Rest, with salicylates in the acute endocarditic (exudative) and pancarditic (proliferative) stage, followed by prolonged rest with nourishing food, fresh air, and sunshine, in the subacute or more or less latent stage.

2. Rest with antistreptococcus serum in the acute stage followed by prolonged rest, nourishing food, fresh air, sunshine and vaccines in the subacute stages.

3. Intravenous desensitization or immunization with suitable antigenic substances-building up the immunity so that the liability to renewed infection will be lessened, or if new infection occurs, the reactivity of the tissue will approximate that of immunity without hypersensitiveness.

Salicylate therapy has been, for many years, the most effective and reliable treatment for rheumatic fever and remains so at the present time.

Salicylic acid was introduced into medical use as a substitute for carbolic acid. Buss[16] in 1875 discovered the antipyretic properties of the salicylates but Stricker and Maclagan in 1876 were the first to note their remarkable action in rheumatic fever. After their introduction in 1876 the salicylates rapidly came into general use in the treatment of rheumatic fever and the situation has remained unaltered to the present time. As the years have passed most of the various salts of salicylic acid have enjoyed a period of popularity, first one and then another being advanced as the most efficient form of salicylate. The sodium salt became the most common form of administration and is today considered the most satisfactory and efficient salicylate preparation.

The manner in which the salicylates accomplish their beneficial results is not known. There is no appreciable effect on the circulatory or respiratory systems.[17] There is a dilatation of the skins vessels following administration of salicylates which accounts for the antipyretic properties of the drug.

The salicylic preparations produce a slightly augmented flow of bile, apparently from some specific action on the liver cells. In its passage through the tissues salicylic acid modifies the metabolism, as is shown by an increase of 10-12 per cent in the nitrogen and sulphur of the urine. This indicates a consider-

ably augmented decomposition of the proteins of the body, but whether it is accompanied by increased oxidation is unknown. A still more notable increase of the uric acid excreted has been observed, different authors estimating it at 30-45 and even 100 per cent. This occurs also in animals and persons on a purine-free diet; the uric acid escapes through the kidney more easily, and the percentage in the blood falls as that of the urine rises.

Salicylate circulates in the blood as the sodium salt; most of it is carried in the plasma, but some passes into the corpuscles; it does not accumulate in the joints more than elsewhere. It is found in practically all secretions and organs of the body; the brain is said to contain less than most of the other organs, averaging perhaps a third as much as is found in the muscles, blood or spleen. About three-fourths of that ingested is excreted by the kidneys, for the most part unchanged, in smaller amount in a combination with glycine, which is known as salicyluric acid, and which is strictly analogous to hippuric acid. It appears in the urine within an hour of administration by mouth and is all eliminated in forty-eight hours. It has been found in the milk, perspiration and bile, but does not appear to be excreted into the stomach nor is any found in the feces. About 20 per cent or more is completely destroyed in the tissues, and this fraction is higher in rheumatic fever than in normal persons; thus the actual concentration in the blood and urine may be lower in rheumatic fever.

Under salicylate treatment the pain, swelling and redness in the joints rapidly lessen, the temperature often falls, and the disease makes less demands on the strength and courage of the patient. Whether it acts on the unknown cause of the disease or not, is unknown. Hanzlik claims that it is purely symptomatic treatment and that salicylate may be substituted by a mixture of other antipyretic and analgesic remedies. I do not believe that the clinical experiences bear out Hanzlik's ideas. It is a much discussed question whether the salicylate treatment reduces the liability to endocarditis and pericarditis. Some clinicians claim it increases the incidence of these complications, while others claim it reduces it; others that it does not influence either way. The more general view is, probably, that the cardiac affections are less often met with and are less severe under salicylate medication, and very often it is continued in small quantities even after the heart is undoubtedly involved in the disease. Levy and Turner have shown that the salicylates favorably influence the conduction mechanism of the heart in acute rheumatic fever. In this disease the auriculo-ventricular conduction time may be considerably prolonged but under the salicylates it is brought back to normal. The explanation may be that the salicylates lessen edematous infiltration in the region of the bundle with a resulting shortening of conduction time. Studies concerning the effect of salicylates on the heart complications will be considered later in this paper.

Salicylates sometimes fail in rheumatic fever, as quinine does in malaria, and they sometimes act more satisfactorily in one joint than in another. Relapses occur even during the continuous treatment with ordinarily adequate amounts of salicylate. Large doses of sodium salicylate (15-30 grs.) repeated every two to three hours are necessary in some cases at first, the quantity being reduced as the symptoms abate. A convenient rule for sodium salicylate dosage in rheumatic fever is to give a grain per day per pound of body weight. After the acute stage the drug should be continued in smaller doses, 10 grains three times daily, for several weeks or months. Children tolerate salicylates well and may take relatively larger doses than could ordinarily be given when calculated according to their age. Alkaline carbonates are usually given along with the salicylate, on the ground that they lessen the gastric action by preventing the formation of the irritant salicylic acid.

In other acute constitutional diseases accompanied by fever, even when the joints are involved, salicylate has no such specific action as in acute rheumatic fever. In gonorrhoeal arthritis and in the various forms of disease which are roughly classified as rheumatic- chronic rheumatism, arthritis, neuralgia, myalgia, salicylate is usually of little service, so that some special relation seems to exist between the salicylate and the cause of rheumatic fever.

Salicylate in some cases promotes the absorption of effusions into the serous membranes, such as the pleura, and also subretinal effusion. How this is affected is unknown, but it is hardly probably that the slight diuretic action of the drug is responsible for it.

The chief object in treating a case of rheumatic fever should be to bring the patient through the attack with an undamaged heart or with as little injury as possible.[1] Rest is essential and should be begun at once and continued as long as necessary. The joints are extremely tender so the bed should be smooth and soft. The patient should wear a flannel nightgown and blankets should be used rather than sheets on account of the sweating and to prevent chilling.

As to diet, Eliot[16] obtained good results with a strict milk diet. At present an easily assimiable diet of sufficient calories, with fluids freely, is considered satisfactory.

Local treatment may be used but is not considered of much value.

The salicylate treatment has been considered. It is interesting to note that salacin was the form in which Maclagan introduced salicylates in 1876.

It is claimed by some that the alkaline treatment decreases the heart complications and shortened the disease. This treatment consisted of giving potassium acetate and citrate in doses of 15 grains each every three hours until the urine became alkaline and then often enough to keep it so. At present alkali is usually given in the form of sodium bicarbonate administered with the sodium salicylate.

The maintenance of good nutrition and growth is of great importance in preventing relapses and in avoiding heart complications during convalescence from rheumatic fever.

Lukens and Stroud[18] emphasize strongly the persistence of an active carditis in rheumatic fever patients for at least 3 to 5 years, as evidenced by careful temperature determinations and physical examinations. They consider maintenance of nutrition as the most important therapeutic measure in the infection.

The above men quote H.F.Swift: "Assisting a patient to overcome his infection by increasing his general nutrition has been shown to be one of the most important therapeutic measures in tuberculosis. Maintaining or increasing a typhoid fever patient's weight has been shown to shorten convalescence from that disease. In our experience the maintenance of nutrition is one of the most important therapeutic measures in rheumatic fever..... This brings us directly to what I regard as probably the most important phase of treatment of rheumatic fever; namely the length of time it is necessary to keep the patient quiet. Briefly, it can be stated that this should be as long as signs of infection persist."

No treatment has been found to be very satisfactory in the prevention of the cardiac complications. At the

Children's Heart Hospital[19] in Philadelphia, rest with salicylates in the acute stage, followed by prolonged rest with nourishing food, fresh air, and sunshine in the subacute stage, was the type of treatment used exclusively.

A follow-up study was made in the Spring of 1928 which included all discharges from the hospital from July 2, 1922 to June 23, 1928. In these six years only one child died at the hospital. Of 272 children discharged in the six years, follow-up information was obtained from 182 children, 57 being dead on July 1, 1928 and 27 not found. There were 144, or 53 per cent., of the children who were attending school or working at the time of the follow-up. There were 44, or 16 per cent., who were unable to attend school. 57 or 21 per cent., had died and 27, or 10 per cent, the worker could not locate.

The age range of these children was from 5 to 15 and approximately equally divided as to sex.

158, or 58 per cent., of the 272 were under satisfactory medical supervision at the time of the follow-up and 30 children were not. The series represented children with heart disease of all degrees of seriousness.

From this study, the results of the treatment being considered good, we see that, at the best, our therapy of the heart complications of rheumatic fever, are not good.

In September, 1930, Leech[20] reported a controlled clinical study on the value of salicylates in the prevention of rheumatic manifestations in children.

Sixty-seven children with potential heart disease and inactive rheumatic heart disease were given daily rations of 20 grains of acetylsalicylic acid for a six months' period. A control group of 79 children with similar potential and acquired rheumatic heart lesions was used. There were fewer recurrences of chorea in the experimental group. The control children did not do as well as the experimental in the matter of gain in body weight, improvement in heart rate, general bodily comfort and actual physical capacity as judged by the functional classification based on ability to carry on normal activities without discomfort.

No evidence of any effect of the drug on the slowly progressive development of mitral stenosis was seen, nor did they expect to. The number of rheumatic recurrences was too small and the time too short to allow accumulation of evidence in regard to any possible effect of the medicine in preventing endocarditis as a sequelae of chorea or other rheumatic manifestation, but Leech did speculate as to the reason for a moderate preponderance of diminutions and disappearances of cardiac murmurs among the patients receiving the salicylate rations.

Improvement in bodily comfort seemed to play a part in allowing a more satisfactory gain in body weight. It was strikingly evident that normal gain in body weight was an accompaniment of general well being. Practically without exception the children with recurrences of chorea lost weight previous to the recurrence or gained but slightly. Often these children were subject to more or less troublesome joint and muscle pains and general discomfort. The acetylsalicylic acid seemed to be the factor which enabled some of the children to gain weight. It was found that a child who was gaining weight normally was not apt to develop chorea. By increasing the physical comfort of the child and by making it easier for him to gain weight there seemed to be an indirect effect of the drug which resulted in fewer attacks of chorea.

Leech's study would tend to show that there is an advantage in giving a daily ration of salicylate to children

who are actual or potential instances of rheumatic heart disease.

As we come to a consideration of the treatment of rheumatic fever with serums and vaccines we are forced to confine ourselves chiefly to the work of J.C.Small of Philadelphia.

It was in January, 1927, that Small [9] described a new species of streptococcus isolated from cultures of the blood and of the pharyngeal exudate in cases of rheumatic fever, under the name Streptococcus cardioarthritidis. (Small's work has been noted previously in a section of this paper but for the sake of clarity the repitition is allowed.) By March, 1928, he had prepared the anti-serum of Streptococcus cardioarthritidis in both cattle and horses. The bovine anti-serum had an advantage over the equine in that it produced but very mild symptoms of serum sickness.

The anti-serums produced at this time had to be used in amounts varying from 25 c.c. to 200 c.c. in bringing about clinical responses. Later the equine anti-serum was concentrated by the globulin precipitation method and a dosage of but 10 to 20 c.c. required.

In the use of the serum it was found necessary to guard against two contingencies--hypersensitiveness to the serum of the species employed in its preparation and local reactions of a specific nature arising from the local inflammatory reaction of immunity upon union of antigen and antibody in the diseased tissues. The first named it was possible to avoid by intradermal tests, and the latter by the broken dose method of administering the serum and by injecting it subcutaneously or intra-muscularly. It was found that not more than 5 c.c. of the concentrated anti-serum should be injected as the first treatment. Another 5 c.c. was given after 8 to 12 hours and if necessary 5 to 10 c.c. injected after another 18 to 24 hours.

By March, 1928, Small had data on the action of the anti-serum of Streptococcus cardio-arthritidis in 251 patients, 121 of whom were treated in the special rheumatic fever wards of the Philadelphia General Hospital. He was able to obtain prompt beneficial effects following its use in chorea and in acute rheumatic fever. The effects occurred with regularity and were observed in the acute arthritis, the endocarditis, the myocarditis, the pericarditis, the pleuritis, the pneumonitis, and the subcutaneous nodules of rheumatic fever. In chorea the purposeless twitchings subsided promptly and usually disappeared within a week after the administration of the serum.

The protection conferred by the anti-serum was estimated to last from four to five weeks judging from the few relapses which occurred early in the work. This period of time is in accordance with the length of the period of passive immunity conferred by the other therapeutic anti-sera.

In advocating the serum therapy Small cites a number of observations [62] as tending to prove the specificity of the Streptococcus cardioarthritidis in rheumatic fever. He claims the Streptococcus cardioarthritidis is a species of streptococcus showing distinctive cultural characteristics and one which may be easily identified immunologically. While not recoverable from the blood stream in rheumatic fever patients in most instances, Small has recovered it in three typical active cases of the disease.

Individuals subject to recurrent attacks of grave rheumatic fever demonstrate an extreme susceptibility to minute doses of the vaccine prepared from it as manifested by

general reactions, in which arthritic pains and stiffness, general malaise, anorexia, fever, precordial pain, cardiac arhythmias, and muscular twitchings, are very evident.

The opsonins for the microorganism have been worked out. The titer of its opsonins in the sera of patients has been found to parallel the clinical condition of the patient, so much so, that they have come to regard it as a useful indication in determining dosage of the antiserum and as a valuable prognostic sign. The opsonins regularly rise during the favorable course of the disease regardless of the type of treatment, and persist at a high level during convalescence and following recovery.

Two eight-bed wards in the Philadelphia General Hospital have been given over to the study of rheumatic fever since April, 1927. Small and his co-workers made observations on 70 patients in these wards between April 1927 and October, 1927.

In this, their early experience with the antiserum, they endeavored to administer the anti-serum as soon as possible after the patient was admitted and a diagnosis made. The serum dosage was from 25 to 200 c.c., depending on the severity of the case. The serum was administered intra-muscularly. No salicylates were given, but sufficient codeine and morphine was given to keep the patient comfortable. They attempted, at this time, to give at one injection the amount of serum thought necessary, but frequently a second injection was required. As noted earlier in this paper Small changed his mode of administration later in his work.

Observing that relapses occurred from 4 to 5 weeks after the administration of the anti-serum, Small began the practice of developing active immunity within this period, by means of the administration of Streptococcus cardioarthritidis vaccine in small, carefully regulated amounts at 5 day intervals. In many instances active immunization was started soon after the administration of the anti-serum. The vaccine was followed by such severe reactions that Small discontinued its use in favor of soluble products of the micro-organisms which he termed soluble antigen. It was a normal saline extract of the bacteria and was used in two dilutions--a 1:10,000 and a 1:1000 dilution. The initial dose of the 1:10,000 dilution was not greater than .1 c.c. subcutaneously. The 1:1000 dilution was reserved for follow-up treatment after a course of the more dilute product, or for patients who had recently received adequate amounts of the anti-serum.

There appeared to be no contra-indication to an attempt to build active immunity during the existence of a period of transferred immunity. Since this practice was started Small reports that no relapses have occurred.

Small suggests that there is a quantitative neutralization of the toxemia with the anti-serum and an incomplete detoxification in the case of the salicylates. He feels that this idea, if confirmed, would leave a significant place for salicylates in the treatment of rheumatic fever, in that they would be used to reduce the toxemia thereby decreasing the amount of antiserum needed to complete quantitative neutralization.

He considers the development of a specific vaccine, for use in treatment and prophylaxis, of prime importance.

In the face of Small's encouraging reports it might be well to consider the results obtained by other men using similar methods of treatment.

The lack of efficacy of known remedial agents in the therapy of rheumatic fever is sufficient reason for the serious consideration of new therapeutic agents which exhibit even the slightest merit.

The, thus far, most effective treatment of rheumatic fever, namely salicylates, is, in most instances, not capable of preventing the disease from proceeding on to the production of serious and often fatal lesions. In view of these facts Small's claims for his serum assumed great importance.

To substantiate or disprove Small's claims C.N. Hitchcock, McEwen, Currier and W.F. Swift[23] in October of 1930 investigated the effects of antistreptococcus serum upon the course of the disease.

Taking into consideration the possibility that many types of streptococci may act in the causation of the disease in subjects peculiarly hypersensitive, they attempted to determine whether different antistreptococci serums might not have similar therapeutic effects.

Accordingly, in a series of cases exhibiting various rheumatic manifestations, they used three types of antistreptococcal serum, viz., a commercial polyvalent serum, a sample serum supplied by Small, and a serum prepared by the inoculation of a heifer with a green-producing streptococcus isolated from a subcutaneous nodule. None of these cases gave unequivocal results to show that the serum had produced any benefit, on the other hand, undesirable reactions following its use were noted in 21 of the 60 cases. Success of ever mild degree could be claimed in only 6 of 20 cases which were properly controlled, and in none of these was the improvement more than that following simple bed rest. From this study Hitchcock and his associates concluded that no justification for a general adoption of antistreptococci serum in the therapy of rheumatic fever existed. We cannot place too much emphasis on their report, however, as the number of cases studied was quite small.

The therapy of rheumatic fever by means of salicylates, serums, vaccines, rest and nutrition have been discussed in this paper. There now remains one aspect of the treatment of rheumatic fever which, in view of the present great interest in it, I believe should be considered here, namely, tonsillectomy.

The part the tonsil plays in rheumatic fever, whether to remove or not to remove, if removed at what time--these problems have been the center of warm debates in recent years.

Rober and Finland,[24] in a rather exhaustive study of all cases of rheumatic fever admitted to the Boston City Hospital between Jan. 1, 1924, and Dec. 31, 1928, came to the conclusion that tonsillectomy was a safe therapeutic measure and presented evidence that the operation could be performed during the active stage of the disease without harm to the patient. Their study included 165 patients.

In a study of 204 cases of classical rheumatic polyarthritis reported by von Costa[25] in Nov. 1930, the conclusion is that operative treatment of focal infection in acute polyarthritis may have a favorable influence on lingering cases, but has no value as a prophylactic measure against the recurrences of the disease.

The monumental work of Kaiser on the results of tonsillectomy appear to offer us the most thorough and reliable information along this line.

His recent report[26] discloses that his study was made on 3000 children of high school age. One half of the children had tonsil enucleation at the age of 5 or 6 years. They were examined at that time; their complaints and records of infections previous to operation were recorded. The recent examination of the children furnished similar data for the ten year period subsequent to operation. The other half of the group were children in whom tonsillectomy was recommended 10 years ago, but not done. They were examined exactly as the other group and served as controls in the survey. A survey similar to this was made on 2400 children 3 years after the removal of tonsils.

Kaiser divided the rheumatic manifestations into chorea, growing pains, rheumatic fever, and rheumatic carditis. Chorea occurred with equal frequency in the two groups previous to operation, but over the ten year period twice as often in the operative group-1.6 per cent as against 0.8 per cent in the controls. In another survey made on rheumatic manifestations in a much larger group of children, it was found that chorea occurred as often in children who had been operated on as in children who had not. The disease did not seem to be favorably influenced by removal of the tonsils, except that less carditis was associated with chorea occurring in tonsillectomized children. Growing pains, which are now generally conceded to be a mild rheumatic manifestation, were reported in about 3 per cent of the children in both groups before removal of tonsils. The attacks were more common in both groups during the school age, occurring in 7.8 per cent of the operative group and in 9 per cent of the control group. Rheumatic fever had existed in about 1 per cent of the children of both groups before operation. During the ten year period 52 children, or 2.3 per cent, suffered from this disease, while among the control children 76, or 3.5 per cent had the complaint. This shows a lessened incidence of rheumatic fever in the tonsillectomized children of about 1.3 per cent. This reduction is in the primary attacks of rheumatic fever only, for other studies show that recurrent attacks of rheumatic fever are not influenced by tonsillectomy. Rheumatic carditis was found in more children of the operative group before operation but in spite of that was somewhat less common among the children who had been operated on, over the ten year period, the rate being 1.17 per cent as compared with 1.3 per cent among the children not operated on. The lessened incidence of growing pains, rheumatic fever and rheumatic carditis is probably due to the lessened incidence of sore throat in tonsillectomized children. The most significant fact brought out in the study, as it pertains to rheumatic fever, is that removal of the tonsils offers no better than a 33 per cent escape from a primary attack of rheumatic fever, and no obvious protection if tonsillectomy is performed after the first attack.

Judging from Kaiser's report it seems to me that the sensible course to follow in the matter is careful examination and attention as regards the tonsils, with removal if they are found to be infected. If they are not infected the operation is not justified, for there is no decrease in the incidence of recurrent attacks of rheumatic fever and no improvement in the patient's condition. I believe the expense and inconvenience of the operation are unjustified in the absence of tonsil infection, but are justified and should be freely indulged in the presence of infection in the tonsils.

In a recent study[27] of 413 children the conclusion arrived at, was that routine removal of the tonsils for prevention of rheumatic fever was not based on conclusive data.

The great importance of preventing rheumatic fever, in children is seen, when we note[28] that it is estimated that four-fifths of the heart disease in children is the result of rheumatic fever. This, aside from other results of rheumatic fever,[29] is sufficient reason for further work in

connection with the disease.

The methods of treatment which have been proven to be of merit have been discussed. Other methods of various types, for example, irradiation,[30] might be discussed, but I do not feel that they are of sufficient importance to merit our attention.

I have made an effort to limit this paper to the most authentic and important features of the disease discussed, and to emphasize those features in the body of the paper. For this reason a summary is deemed an unnecessary repetition and is accordingly omitted.

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