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A STUDY OF THE ETIOLOGY OF ACUTE RHEUMATIC FEVER

BY

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INTRODUCTION

Acute rheumatic fever, also known as rheumatic fever, acute articular rheumatism, acute rheumatism and polyarthritis rheumatica is a disease, the etiology of which has not been definitely established, characterized by fever and a toxic state, and by the presence, in certain organs of the body, of small disseminated focal lesions of a proliferative type. In acute stages there is also extensive exudation in and about the joints, and sometimes in the pleura and the pericardium. Recent studies disclose widespread involvement of the visceral and peripheral blood vessels. A further characteristic is the tendency for the febrile and arthritic symptoms to disappear when the patient is given large doses of compounds of certain antipyretic drugs (quoted from Cecil - 1). In this brief description of the disease, for purposes of introduction to the etiological study, also should be mentioned the rheumatic infection of the central nervous system, chorea minor, in which appear disseminated focal lesions of nervous tissue.

Rheumatic fever is one of our most important diseases, not only because of the large number of children and young adults who are incapacitated by the painful inflammatory condition itself due to its arthritic manifestations, from which affliction the joints recover without the crippling
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effects seen in rheumatoid arthritis, but because of the cardiac involvement which almost invariably accompany the disease. This cardiac accompaniment of rheumatic fever is an important economic problem as it is the largest single cause of death in children and adolescents of school age. Also, since it occurs chiefly in school children and young adults, the cardiac disease occurs when these individuals should be economic assets rather than liabilities.

Even should the heart escape serious damage as the result of the first attack, the manifested tendency for the superimposition of another acute attack or a series of attacks on the more or less chronic cardiac sequellae, each time subjects the heart to the possibility of greater damage, and enforces economic loss during the attack and afterward as the result of rheumatic cardiac damage.

The aim of medical science is not the cure of disease, but the prevention. The prevention of any particular disease, in order to be efficient and effective, must be worked out on sound knowledge of the causes of the disease, methods of transmission and entrance into the human body. Many diseases such as typhoid, diphtheria, etc., formerly a scourge on the health of the human race, have been practically wiped out since knowledge of the underlying causes were discovered and control measures adopted,
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specific for each disease.

Rheumatic fever is such a disease, as yet not under control. However, acute rheumatism does not strike the public in spectacular epidemic form as do some of the acute infectious diseases, affecting large areas and decimating the population with high mortality rates and disabling sequellae. This disease is usually more insidious, with a case here and a case there, followed by an apparently normal recovery within a few weeks or months, but the patient with the damaged heart and the history of acute rheumatic fever is one seen all too frequently in the doctor's office.

Many able investigators have been working on the subject of the etiology of rheumatic fever for over four decades and the cause underlying this disease is still a controversial subject. In considering the etiology of a bacterial disease, it must be borne in mind that more than one factor may be at work. This is exemplified by the work of Rinehart and Mettler (2) who found that when guinea pigs, already rendered scorbutic, were injected with hemolytic streptococci, lesions apparently identical with those of human rheumatism were produced in the endocardium, myocardium and pericardium.

The search for a causal organism of the disease appears
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to be justified in view of the knowledge we have of the epidemiology of the disease. Smaller outbursts of rheumatism in urban populations, in certain families, at congested military camps, in convalescent hospitals and institutions, although rather obscure, constitute a definite chapter in the history of the disease.

In 1884 Haig Brown (3) described an often quoted outbreak at Charterhouse School when 29 boys showed all the symptoms of acute rheumatism with arthritis and carditis. These cases followed an epidemic of tonsillitis involving over 300 previously healthy boys, there being in all cases a definite time interval between the tonsillitis and the appearance of rheumatic symptoms.
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Sennertus (4) commented several centuries ago on the appearance of rheumatic fever following scarlet fever. Davis (5) in 1840 made this statement concerning the causes of rheumatic fever, "The occasional causes of this malady are few and simple and reducible to a union of two principle influences, viz. cold and moisture. Cold by its intensity or long duration is productive of the severest forms of the disease, but when moisture is added to a simply cold atmosphere, however intense, the disease is prodigiously enhanced and multiplied........I have seen drunkenness enumerated among the occasional causes. It has also been asserted that sudden acts of violence productive of contusions, lacerations and sprains are also numbered among the causes".

Haydon (6) in 1851 cared for several hundred cases of scarlet fever. 15 cases of acute rheumatic fever followed the scarlet fever after a short latent period and he considered them so closely related that he routinely gave "lemon juice" on disappearance of the rash which treatment he apparently found very effective in preventing the onset of rheumatic fever as a complication of scarlet fever.

In 1854 Dr. Hughes Wilshire (7) discussed the connection of rheumatism and scarlet fever at a medical meeting.
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as he had observed it in certain cases. In the discussion following, most of the men were of the opinion that there was no relationship but since both were inflammatory conditions involving "superoxidation" in the blood, it was not surprising that both diseases existed in the same person under peculiar and coincidental circumstances.

In 1855 Wilshire (4) observed a severe epidemic of scarlet fever in London and in a paper he took particular pains to draw attention to a particular complication of scarlet fever in this epidemic, that of rheumatic fever. With the paper he read a case history of a rheumatic fever patient which was quite a typical picture of acute articular rheumatism.

Active interest in the various aspects of the subject of rheumatic fever was given great impetus following 1876 at which time Maclagen discovered the action of salicilates on the symptoms of rheumatic fever.

In 1881 Fowler (8) noticed that a large percentage of rheumatic fever subjects had a preceding history of tonsillitis or a catarrh of the pharynx preceding the onset of symptoms by a period of time varying from a month to a few days. About 80% of Fowler's cases presented this symptom. In some cases the throat and joints were simultaneously affected. Relapses were noticed to be often
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preceded by a sore throat. Fowler believed that this sequence of events was of too frequent occurrence to be explained on the hypothesis of a merely casual connection. Fowler also noted that scarlet fever and measles, diseases which were almost invariably ushered in by severe affections of the throat, were frequently followed by the so-called rheumatic affections of the joints.

It was the early contention of Achalme (9) that the disease was due to a gram negative bacillus, this view being later disproved.

The next view was that of Singer (quoted from - 9) who claimed that the disease was an attenuated pyemia, due most frequently to the streptococcus but also the staphylococcus and other pyogenic organisms were among the causal agents. Singer's contentions were based on the bacteriological studies of post-mortem material and isolation of pyogenic cocci from the urine.

In 1892 Frankel (quoted from - 10) called attention to a paper by P. Guttman on the etiology of acute rheumatism and its complications. Guttman described a case of rheumatic fever with exudative pericarditis, complicated by kidney and muscle abscesses from which lesions Staphylococcus pyogenes flavus was isolated. He did not take any cultures from the joints and did not consider
organisms to be sole cause of rheumatic fever.

Also in 1892 Sahli (quoted from - 10) discovered Staphylococcus pyogenes citreus in the synovial membranes of the joints in a case of acute rheumatism and also in the pericardial exudate. He considered rheumatic fever to be due to a staphylococcus.

In 1893 Lance (quoted from - 12) experimentally produced rheumatic fever in rabbits with a bacillus.

In 1896 Lubarsch (quoted from - 12) reviewed a paper by Buss of Bremen who came to the conclusion that the throat and intestines are in many instances the sites of the entrance of rheumatic fever, Lubarsch's paper being on the subject of streptococci.

Triboulet and Coyon (quoted from - 11) in 1897 cultivated a diplococcus from 5 living cases of rheumatic fever and from an autopsy in one fatal case. Later in 1898 they described the production of 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 in 1897 reported 11 consecutive cases of rheumatic fever from which they had isolated a diplococcus from the blood stream.

Apert (quoted from - 11) in 1898 using the methods of Triboulet and Coyon took blood cultures from 2 cases of
chorea. One of these cultures yielded a diplococcus similar to the strains of Triboulet and Coyon.

In 1899 Westphall, Wasserman, and Malkoff (quoted from 11) made a bacteriological study of a fatal case of rheumatic fever with chorea and endocarditis. A streptococcus was recovered from blood, brain, and heart valves. Experiments were conducted by inoculating 80 rabbits with the organisms, followed by the production of arthritis in a considerable number of cases.

The men most often referred to in the literature and who did a large amount of original work on the bacteriological etiology of rheumatic fever are Frederick Poynton and Alexander Paine (10). Their original article was published in 1900. Poynton and Paine demonstrated diplococci in 8 cases of rheumatic fever. 5 of the 8 were fatal cases and cultures were obtained post-mortem. The material for the cultures was obtained by a very careful technique from (1) the pericardial exudation, (2) blood from the heart, and (3) granulations from the valves. In the three living cases, blood cultures were taken and were all positive for diplococci, the blood being taken from patients suffering from an attack of acute rheumatic pericarditis. The diplococci from these cases were injected into rabbits, producing arthritis, valvulitis, and pericarditis. Strep-
tococci were occasionally seen but were not considered to be other than diplococci in chains. Strepto-diplococci were spoken of but not described. Swift and Kinsella (9) are of the opinion that these organisms, described by Poynton and Paine, are similar to Streptococcus viridans. These men believed that they had discovered the etiological agent for rheumatic fever in their diplococcus. They state that they realize the complexity of the etiology and that it is probably due to a variety of causes, but they definitely state that, as a result of their researches, they had discovered that the diplococcus which they had isolated was a cause of rheumatic fever. "Although probably not invariably present or the only cause, they are a cause."

Ten years later in another article (12) they were still convinced that their original conclusions were right in spite of criticism by other workers unable to confirm their work. Criticisms of their work and their answers in this article are briefly as follows: (1) Terminal or agonal infection criticism—some patients lived for many weeks, others were alive and working years later. (2) It was suggested that the organisms found were present as epi-phenomenon and caused only the complications— if one deprives the disease of arthritis, carditis, nodules, chor-eiform movements and pleurisy, what is to constitute rheu-
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matic fever? (3) Question about not finding the organism in all cases - they believe it always present in cases selected carefully with unlimited time and care given to the work of finding them.
PREDISPOSING CAUSES

A. Seasonal Variations:

Greenwood and Thompson (13) did an analysis of admissions to the London Hospital from 1873 to 1903 which showed that cases of rheumatic fever are most common at that period of the year during which, in England, there is usually an existence of low temperatures, viz. at the end of autumn. There is evidence of an increase in the number of rheumatic fever cases following a series of dry months. In America and on the European Continent the majority of the cases appear in the late winter and spring (quoted from - 1).

Among those who have contributed to the study of the influence of meteorological conditions on the prevalence of rheumatic fever is Sir Arthur Newsholme (14) who concludes that as a rule a heavy annual rainfall is associated with a low amount of rheumatic fever and a small amount of rainfall with an excessive number of cases of this disease. He expresses the opinion that the development of the organism is favored by a dry subsoil and it is drowned out in the wet years. He states that temperature also has an effect. The great epidemics of rheumatic fever have occurred when the mean temperature of the soil has been excessively high, i.e. over 50 degrees, and the greatest epidemics occurred when the mean
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temperature was high for over 2 to 3 successive years.

Dr. Gabbett (15) presents statistics of admissions to the London Hospital for the period from 1873 to 1881 and concludes that cases of the disease are very numerous at that period of year during which there is usually a coexistence of low temperature and heavy rainfall, viz. at the end of autumn.

Young (16) demonstrated the analogy between the geographical distribution of excessive incidence of rheumatic fever and excessive rainfall and cold in the countries of England and Wales.

B. Epidemiology:

Glover (17) made a study on a large group of aviation students who came to a camp for training in large numbers and were crowded into quarters of insufficient capacity. An epidemic of tonsillitis broke out, followed by a large number of cases of meningococcus meningitis. A study of conditions showed that a rise of tonsillitis incidence, passing the danger mark of 20%, is paralleled by a rise in the meningococcus carrier rate and when the danger mark is passed, then the case epidemic sets in. Statistics and charts showed rheumatic cases in similar number, indicating that a similar process was at work. This epidemic had nothing to do with seasons, as the epidemics
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occurred when the new group was brought together and crowded excessively. When overcrowding conditions were rectified and ventilation improved, the epidemics ceased, and during the winter season, when these epidemics were expected, they failed to occur and the carrier rate of meningococcus was almost nil, with no cases of meningitis or rheumatic fever.

C. Heredity:

There has long been an impression among physicians that the rheumatic infections tend to run in families. This impression has been confirmed by the observations of St. Lawrence (18) in New York on 100 families with children suffering from rheumatic fever, chorea, or rheumatic heart disease. He found that in 50% of these families, 2 or more individuals had had a rheumatic infection, 14.8% of 480 exposed persons in these families being infected. In 100 families of tuberculosis patients studied for comparison he found 48 families in which at least 1 additional member was affected, 14.6% of the 492 persons exposed having contracted the disease. Thus his figures show a slightly higher family incidence for the rheumatic infections than for tuberculosis.

Over a period of 2 years at the Massachusetts General Hospital, Faulkner and White (19) studied 200 families of
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patients with rheumatic fever, including 1235 persons. Physical examinations were done on 642 of these people to determine whether any were suffering or had suffered from rheumatic fever. The criteria of positive evidence of a rheumatic infection was: (1) an outspoken attack with multiple joint symptoms, (2) definite choreiform movements, or (3) definite evidence of mitral stenosis. They discovered that in 71 families or 35.5% of them, more than 1 member was affected with rheumatic fever, 8.79% of 1235 exposed persons being infected. For comparison, they investigated families of 75 persons who had no evidence of past or present rheumatic infection. These 2 groups of families belonged to the same general economic status. 474 patients in these control families were recorded. Physical examinations were done on 366. Positive evidence of rheumatic infection was found in 16% of the families and in 2.95% of the individuals. Families of rheumatic patients are more than twice as likely to have another member suffering from rheumatic fever. 3 main factors were considered as the direct or predisposing causes for the increased liability of members of rheumatic families to have rheumatic infection: (1) hereditary predisposition, (2) environmental conditions, particularly cold, dampness, and poor hygiene, and (3) direct contagion. In order to ascertain the exist-
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ence of hereditary predisposition to rheumatic fever, 29 persons having inactive rheumatic heart disease were check-
ed. Out of 97 children in this group, there was not 1 case of rheumatic fever. In contrast they found that of 322 parents of children with recent rheumatic infection, 8.9% gave positive evidence of having had rheumatic fever. Subsequent investigation showed that 8.66% of the siblings of these children were infected.

D. Social Status:

Faulkner and White (19) also made a study of the relationship of social status to the incidence of rheumatic fever and chorea. They found that the rheumatic infections are apparently less common among the so called upper classes of society. They communicated with a large number of private preparatory schools and colleges throughout the country and all attest to the rarity of rheumatic infections and heart disease in this comparatively well-to-do group.

Coburn and Pauli (3) also observed that unhygienic surroundings favored streptococci and that rheumatic fever was found much more commonly in the same surroundings.

E. Geographic Relationship:

Coburn and Pauli (3) in studies of hemolytic streptococcus ecology and geographic relationship, especially as
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related to rheumatic fever, have pointed out the relationship between the distribution of acute rheumatic fever and the distribution of upper respiratory diseases. Rheumatic fever occurs very frequently in the North Temperate Zone, but is very rare in the Tropics. This fact has caused the theory of dampness and cold as the underlying pathogenic factors. A study of these workers shows close relationship between upper respiratory infection, climate, and rheumatic fever. The influence of climate on the streptococcus is evident from certain aspects of scarlet fever in relation to its geographical distribution. Scarlet fever is unknown in Puerto Rico, yet the inhabitants get it if they go to New York City, statistics showing a high incidence of such cases. An example of climatic influences is found in two tropical cities which are geographically located about 60 miles apart. The one city, Sao Paulo, which is located high in the mountains has many outbreaks of scarlet fever cases, while Santos, near the seashore, with a typical climate of the tropics, rarely has a case. Further study in New York City from statistics and graphs show an increase of hemolytic streptococci in the throat flora preceding rheumatic outbursts in the spring and late winter. This study was made from a case series of 165 patients. A study of 148 patients
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who had previously had an attack of rheumatic fever were studied with respect to the throat flora, with the following results:

1. Patients who were free from all morbid upper respiratory infections seemed in all cases clinically quiescent.

2. Those who were suffering from recrudescences gave a history of contracting a pharyngitis before the recrudescent attack and cultures of the throat flora showed hemolytic streptococci during the period of infection.

Milan and Smillie (20) made extensive bacteriological studies of colds on an isolated tropical island (St. Johns, U. S. Virgin Islands, West Indies). Hemolytic streptococci were rarely found in this study. Streptococcus pyogenes was harbored by only 3% of the people of this island and when found, only few in number.

F. Age Relationship:

It is usually stated, according to Swift (quoted from - 1), that the majority of cases occur within the first 3 decades of life. Although the disease is occasionally found in the very young, it begins to appear more frequently at 4 or 5 years. From this time on, the relative incidence varies according to the class of patients seen by any given
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observer. It is however quite generally agreed that the height of the curve is at an age period of from 9 to 12 years. The importance of the rheumatic infection later in life, however, is significant as shown by Pappenheimer and Von Glahn's tables, showing 45% of their fatal cases occurred in patients over 30 years of age. Brooks and O'Regan (21) observed that rheumatic fever tended to occur during periods of life demanding greatest physical activity, with statistics as follows: first decade - 50 cases; second decade - 140 cases; third decade - 210 cases; fourth decade - 171 cases; fifth decade - 88 cases; sixth decade - 26 cases; seventh decade - 9 cases; eighth decade - 6 cases. These statistics based on 700 cases from Bellvue Hospital, all consecutively selected.

G. Sex Factor:

This is a factor which is believed by some to be a matter of importance, but Brooks and O'Regan (21) state that males as a class are more exposed to conditions which invite infections. Their statistics show an incidence of 443 males to 257 females. Cecil (1) however, contradicts this with the statement, "While polyarthritis is seen more often in men than in women, if we include all manifestations of the disease, females are affected more often than males. This is especially illustrated by the greater frequency of
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mitral stenosis among women".
ASSOCIATION WITH UPPER RESPIRATORY INFECTION

It has long been noted by observers of the disease that attacks of polyarthritis are associated with preceding attacks of upper respiratory disease such as acute pharyngitis, tonsillitis, scarlet fever, etc. Sennertus (4) early noted the association of scarlet fever with the disease as a clinical entity, as did Haydon (6) and Wilshire (4 and 7). In 1881 Fowler (8) made observations on the association of a preceding history of tonsillitis or a catarrh of the pharynx in about 80% of his cases and believed that this sequence of events was too frequent to be of accidental occurrence and believed that this had some connection with the etiology of the disease. Haig Brown (quoted from - 3) recognized a symptom free interval between tonsillitis and the onset of acute rheumatic fever.

Bland and Jones (22) have recently made observations similar to those of Fowler (8) in 1881. They note, "Frequent association between tonsillitis and upper respiratory infection and subsequent rheumatic fever has been observed and commented on by many students of the disease. It is generally agreed that this relationship between the preceding infection and subsequent acute rheumatism is too consistent to be merely a chance occurrence". This important phase has been commented on by Coburn, Schlesinger, Collis, Sheldon, Boas, Schwartz, Hiller, and Graef. The percent-
ASSOCIATION WITH UPPER RESPIRATORY INFECTION

Age of instances of rheumatic fever preceded by upper respiratory infection may be as high as 75%. Not only does this hold for the initial appearance of the disease, but also for recrudescences and recurrences.

Coburn and Pauli (3) have also noted the association of hemolytic streptococcus infection of the throat and the recrudescences of acute rheumatic infection. Bland and Jones (22) have noted that recurrent polyarthritis has been found following infections other than tonsillitis, viz. scarlet fever, pneumonia, otitis media, measles, eryseptilas. Appendectomy was related in 10 cases to subsequent attacks of rheumatic fever, tonsillectomy, joint injuries, operations, etc.

Coburn (23) makes the comment that severe attacks of rheumatic fever are generally preceded by mild hemolytic streptococcus pharyngitis. These organisms disappear from the mucosal surface, they can be demonstrated in submucosa, tonsils, or sinuses.

In Bradley's (24) series of 550 cases, he studies the relationship of upper respiratory infection to the pathogenesis of rheumatic fever. He has considered the linkage of hemolytic streptococcus to rheumatic fever occurrence. The nature of this link is unknown, but Bradley has examined 1 element of it, that of the naso-pharyngeal episodes
ASSOCIATION WITH UPPER RESPIRATORY INFECTION

preceding acute rheumatism. 124 persons were examined in their homes. 19 suffered from hemolytic streptococcus naso-pharyngitis attack. 5 of the 19 developed chorea, pallor, and heart murmurs. The remaining 14 had previously had frank rheumatism and 6 of these relapsed after this naso-pharyngeal episode. 12 non-streptococcal episodes failed to initiate relapse of rheumatic fever when 9 out of the 12 were known rheumatic subjects. Relapses of rheumatic fever followed Streptococcus pyogenes infection in 43% of known rheumatic cases, while no relapses occurred in 31 rheumatics who had no such infection.

Brooks and O'Regan (21) mention the prodromal symptoms as tonsillitis, pharyngitis, simple sore throat, and sinus infections; in short, catarrhal disease of the upper respiratory passages. Adenitis is mentioned as a frequent introductory sign. These observations based on 700 cases from Bellevue Hospital.

Glover (17), who studied upper respiratory infections, carriers of meningococcus meningitis, subsequent meningitis, and rheumatic fever among overcrowded aviation students, showed that the incidence of rheumatic fever was closely associated with the upper respiratory epidemics and subsequent meningitis. These epidemics were prevalent during the weeks following the entrance of the students
ASSOCIATION WITH UPPER RESPIRATORY INFECTION

into training, and was not related to seasons. With the establishment of ventilation and better hygienic conditions, such as wider spacing between the beds, there were no further epidemics even during the winter season when epidemics of upper respiratory infections and rheumatic fever were expected. There was a drop in the meningococcus carrier rate to almost nil, with no cases of meningitis or rheumatic fever.

Rosenow (25) noted in his experiments with various strains of streptococci on rabbits, guinea pigs, white rats, and dogs, with a strain of streptococcus, which he describes as being less virulent than Streptococcus hemolyticus and more virulent than Streptococcus viridans, that cold played an important role in the success of the experiments, and exposure to cold after the injections increased the percentage and degree of joint involvement.
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The theory that rheumatic fever is a streptococcal infection has received considerable support from the demonstration, in the sera of patients with these diseases, of specific streptococcal immune bodies. Tunnicliff(26) performed agglutination reactions with the sera of 12 rheumatic fever patients against strains of Diplococcus rheumaticus and Streptococcus pyogenes, and demonstrated agglutinins in small amounts in 7 instances. Swift and Kinsella(9) failed to find any streptococcal agglutinins in the sera of 5 patients with rheumatic fever against streptococci which they had recovered from their respective blood cultures, but Clawson(27), working with strains of Streptococcus viridans, isolated from cases of rheumatic fever, found agglutinins in 4 out of the 5 sera examined. Clawson's strains of streptococci, when tested by agglutination reactions, apparently were divided into two groups. The large group represented a homologous strain. Another group would not agglutinate with sera except with their homologous strains. This group is considered a heterogenous group.

Small(28) demonstrated agglutinins for the so called Streptococcus cardioarthritis in the sera of 31 patients. Identification was based on agglutination with rabbit serum prepared by sensitizing rabbits to original strains of Strep-
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tococcus cardioarthritis, giving a titer of 1:2,000. He also experimented with the preparation and use of antiserum for use in rheumatic fever. Rabbits were sensitized to Streptococcus cardioarthritis until they gave a titer of 1:20,000. Patients suffering from chorea and polyarthritis were given 20 cc of the serum and the symptoms terminated by crisis. In a series of 9 cases, similar results were obtained. These patients received the full effect of the serum in about 3 days, with loss of choreiform movements, if present, loss of swelling of joints, and return of mobility of joints.

By means of agglutinations and absorption tests, Cecil, Nicholls, and Stainsby(11) showed that the strains of streptococci recovered from the blood of patients with rheumatic fever showed a tendency to fall into specific biologic groups. In this series of experiments on 60 patients with definite fever and joint manifestations, cross agglutinations were made with 16 sera from rabbits immunized against 16 strains of streptococcus. The 16 immune sera were tested for agglutinins against each of 35 strains of streptococcus recovered from patients with rheumatic fever. The results indicate that these bacteria tend to fall into the above mentioned biological groups. An interesting feature of the agglutination tests was the close biolog-
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ic relationship between the streptococci isolated from blood and joints of the same patients.

In a later publication Nicholls and Stainsby(29) made a more detailed report on the streptococcal agglutinins in rheumatic fever and showed that these agglutinins were present in the joints as well as in the sera of rheumatic patients.

Coburn and Pauli(3) have recently claimed that the agglutination and complement fixation reactions of sera from patients with acute rheumatic fever point to streptococci. Furthermore, precipitin tests indicate that, at the time of the attack, patients developed in their blood specific precipitins to the protein fractions of the hemolytic streptococcus.

Coburn and Pauli(30), in checking the immunological changes occurring in rheumatic subjects between subsidence of the local infection and development of rheumatism, examined sera for the presence of antibodies to hemolytic streptococci. Four types of reaction were used:

1. In 150 healthy rheumatic subjects, only 2 were found to have precipitins for hemolytic streptococci protein fractions.

2. In 50 healthy nurses entering training-- no precipitins.
3. In patients with lobar pneumonia the formation of precipitins to hemolytic streptococci was slight, definite but not persistent.

4. In 20 patients, during acute stages and convalescence from scarlet fever or erysipelas, there was marked precipitin formed in 1 individual. She was a member of a rheumatic family and developed rheumatic carditis.

5. In the sera of 20 nurses who contracted hemolytic streptococcal throat infections in the spring, precipitins were not detected during the acute illness but appeared four weeks later in most cases in slight concentrations. In 4 instances appearance was marked and 3 developed rheumatic fever. In sera of the individuals with acute rheumatic fever the concentration of precipitins became more marked as activity of the process heightened.

Finally these authors demonstrated that at the onset of rheumatic fever there occurs in each instance a rise in antistreptolysin as strong evidence of infection by hemolytic streptococci.

Todd(31) observed that antihemolysin was not formed in animals immunized to Kleb–Loeffler bacillus, pneumococcus, hemolytic staphylococcus, non-hemolytic streptococcus, or
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other infectious agents, but only in animals immunized to hemolytic streptococcus.

Coburn and Pauli (30) in an article on the development of antistreptolysin, present the following information. In normal individuals in good health, the titer of antistreptolysin is of such a degree that .01 cc of serum neutralizes 2½ minimal hemolytic doses of yeast extract streptolysin. The antistreptolysin titer of convalescent patients convalescing from other diseases is approximately normal. The antistreptolysin titer during the acute stage of illness with hemolytic streptococcus is also approximately normal. In patients convalescing from hemolytic streptococcus infection, the neutralizing dose is approximately .005 cc. In each rheumatic subject, during the attack following the hemolytic streptococcus pharyngitis, the neutralizing dose is approximately .005 cc. In patients with rheumatic fever denying previous upper respiratory infection, the neutralizing dose is approximately .005 cc. The antistreptolysin titer remains normal in the rheumatic subject during the first two phases (active infection of upper respiratory tract and following quiescent period) and rises precipitously just before the onset of rheumatic manifestations.

Finally, the presence of antistreptolysin titer to
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such minimal hemolytic doses of yeast extract streptolysin is considered a specific indication of infection with hemolytic streptococcus. The constant finding of this high titer of antistreptolysin in serum of patients with rheumatic fever is strong evidence that the rheumatic attack has been initiated by hemolytic streptococcus.

In a recent article by Coburn (23), the following facts are presented with reference to the general significance of antistreptolysin production:

1. A rise in antistreptolysin titer is generally accepted as evidence of a recent infection with hemolytic streptococcus. Persistence of a high titer suggests continued antigenic activity of organisms or their derivatives.

2. Possible significance of antistreptolysin response in rheumatic fever:
   a. In a group of rheumatic subjects infected with a single strain of hemolytic streptococcus, those that developed an antistreptolysin response developed acute rheumatic fever, while those who failed to make this response escaped the attack.
   b. A rheumatic fever subject who con-
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tracts a series of streptococcus infections, develops acute rheumatic fever only when the infection is followed by a rise in antistreptolysin titer.

Coburn and Pauli (32) collected 40 strains of streptoccci from 38 patients who had had at least one previous attack of rheumatic fever. These patients were symptom free at least six months and contracted a pharyngitis with hemolytic streptococci predominating the throat flora. One half of these developed a recrudescent attack of rheumatic fever. It was possible to obtain blood serum just before or just at the onset of the attack of pharyngitis which was used to study the change in antistreptolysin titer with progress of the disease, in 25 of the cases. In the E strains which were toxin producers, the antistreptolysin increase was great. This group was the effective group which initiated 19 recrudescent cases of rheumatic fever in the 38 cases described above. Those strains which failed to produce skin toxins and did not give rise to development of high titers of antistreptolysin were ineffective in activating the rheumatic process.
BACTERIAL THEORIES

A. Diplococci:

Triboulet and Coyon (quoted from Cecil - ll) in 1897 cultivated a diplococcus from 5 living cases of rheumatic fever and at autopsy in 1 fatal case. Later in 1898 they described the production of mitral endocarditis in rabbits by the intravenous injection of a diplococcus isolated from the blood of a patient with rheumatic fever. In another series, Triboulet and Coyon collected 11 consecutive cases of rheumatic fever from which they had isolated a diplococcus from the blood stream.

Apert in 1898 (quoted from Cecil - ll), using the methods of Triboulet and Coyon, took blood cultures on 2 cases of chorea. 7 yielded diplococci similar to strains of Triboulet and Coyon.

Poynton and Paine (10), in a series of 5 cases of rheumatic fever at autopsy and 3 living subjects, obtained by a very careful technique, (1) Pericardial exudation, (2) Blood from the heart, (3) Granulations from the valves, (4) Blood from living subjects during an attack of acute rheumatic pericarditis, and (5) Exudation from inflamed tonsils. In cultures of this material, diplococci were found in every case. Streptococci were occasionally seen, but were not considered to be other than diplococci in chains. Strepto-diplococci were mentioned but not des-
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dcribed. When injected into rabbits, these diplococci produced arthritis, valvulitis, and pericarditis. Swift and Kinsella (9) later thought that this diplococcus was similar to Streptococcus viridans.

Herry in 1914 (quoted from Cecil - 11), undertook an elaborate study of rheumatic fever based on 60 cases. 43 out of the 60 yielded positive blood cultures and in every case they were able to isolate a diplococcus similar to that described by Poynton and Paine. Streptococci were also found.

Rosenow (33) in his work has been able to obtain 3 types of cocci, 1 of which was a diplococcus. The cases from which the diplococci were isolated were those with more or less muscle involvement. The organisms produced a slight but hazy hemolysis on blood agar plates. Injected into animals, the organism produced arthritis, endocarditis, pericarditis, myositis, and a most pronounced myocarditis. Rosenow showed, however, that each of his three cocci could be readily converted into the other type by culture methods which will be discussed later.

Clawson (27), although a champion for the alpha group of streptococci, reported that most of his strains when first isolated were diplococci. They differed from
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gonococci and meningococci in that the individual cocci were elongated in the long axis of the chain. They have a tendency to be lance shaped and in this way resemble the pneumococcus. They differ from the pneumococcus in not being bile soluble, not fermenting inulin, and in not being capsule producers. "It cannot be said that these strains never grow out into chains, but the marked tendency is for them to appear as diplococci".

B. Hemolytic Streptococcus:

The role played by the hemolytic streptococcus in the etiology of rheumatic fever is a very puzzling one. It has been found so rarely in joint cultures, blood cultures, etc., in cases of rheumatic fever, that it seems safe to conclude that it does not act as a direct contaminating agent in the pathology of these structures. Cecil (11) reports one case out of a series of 60 cases in which the blood cultures yielded a hemolytic streptococcus. Clawson (27) in a large series of cases from which he obtained a large percentage of positive blood cultures containing streptococci, found only 1 strain of hemolytic streptococci. 1 strain of typical beta hemolytic streptococci was found at autopsy in the pericardial exudate of a child dying during an attack of rheumatic fever. Rosenow (25) reported the isolation of streptococci from the joints
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in 7 out of 8 cases of acute rheumatic fever. None of these strains, however, were hemolytic, but by animal passage and other methods, 3 of the strains from acute rheumatism have been converted into typical hemolytic streptococci.

On the other hand, however, the consistent findings of streptococcus pharyngitis and upper respiratory infections preceding the acute rheumatic attacks, coupled with immunological findings, etc., during the course of the disease, gives strong indication that in some manner the hemolytic streptococcus plays an important role in the etiology of acute rheumatic fever.

Coburn (23) found that there was close relationship between the presence of hemolytic streptococci in the throat and the onset of rheumatic fever, as severe attacks of rheumatic fever are generally preceded by this condition. Most rheumatic fever patients are Dick negative, indicating that they have developed neutralizing antibodies to the erythrogenic toxin. Increases in antistreptolysin titer and precipitins to M substance are regularly developed during attacks of acute rheumatism. It appears that toxin and streptolysin are released at the onset of the infection, whereas M substance and nucleoproteins are released after the disintegration of the bacterial cells.
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In addition to these, well recognized antibodies and antifibrolysin are found in the blood of patients with acute rheumatic fever. Observers are agreed that these are responses to hemolytic streptococcus infection.

Coburn and Pauli (32) made a study of 38 cases who had at least one previous attack of rheumatic fever, with at least 6 months of complete freedom from the symptoms. These cases under study contracted a pharyngitis with hemolytic streptococci dominating the throat flora. One half of these developed a recrudescent attack of rheumatic fever with an accompanying rise in antistreptolysin titer which has been discussed in another section.

Coburn and Pauli (34) conducted studies of throat flora on a large number of individuals at the Presbyterian Hospital Nurses Training School and among rheumatic fever subjects to determine the nature of the organisms associated with outbreaks of rheumatic fever. Hemolytic streptococci in most cases appeared in the throat from 1 to 5 weeks before the onset of the rheumatic attack. These organisms have been investigated with the usual types of bacteriological tests and in addition have been classified serologically. The results have demonstrated that the organisms were not of single type, but fell into 6 antigenic groups. The majority of the freshly isolated
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strains were strong toxin producers. The organisms producing the strongest toxin were cultures from the patients who developed extremely intense rheumatism.

In a series of patients, Bradley (24) found 19 who were suffering from streptococcal pharyngitis. 5 of this number eventually developed chorea, pallor, and heart murmurs and of the remaining 14, all of whom had had a previous attack of rheumatic fever, 6 suffered a recurrence after the attack of streptococcal pharyngitis. 12 non-streptococcal cases of pharyngitis failed to initiate a relapse of rheumatism when 9 out of the 12 were known rheumatic subjects.

C. Streptococcus Viridans:

For more than 30 years, it has been suspected that rheumatic fever was a streptococcal infection and evidence in favor of this theory accumulates from year to year (35). Starting with Poynton and Paine (10) in 1900, various investigators have succeeded in cultivating streptococci, usually of the viridans type, from the blood stream and the joints of patients with rheumatic fever (35).

Rosenow (33) found Streptococcus viridans in his cultures of blood and joints of patients suffering from rheumatic fever, which, when injected into animals, produced a non-destructive arthritis, pericarditis, and endocarditis.
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Herry (quoted from - 11) in 1914 undertook an elaborate study of rheumatic fever based on 60 cases. 43 out of the 60 cases yielded streptococci which were green producers on blood agar. Hitchcock and Swift (36) obtained strains of streptococci from patients suffering with rheumatic fever, some from patients suffering from conditions unrelated to rheumatic fever. They found Streptococcus viridans was the only strain isolated from patients suffering from active rheumatism, saprophytic strains being devoid of the capacity to produce rheumatic fever.

Clawson's (27) strains, when first isolated, were diplococci. They differ from gonocci and meningocci in that the individual cocci are elongated in the long axis of the chain. They have a tendency to be lance shaped and in this way resemble the pneumococcus. They differ in not being bile soluble, not fermenting inulin, and in not being capsule producers. It cannot be said that these strains never grow out into chains, but the marked tendency is for them to appear as diplococci. When first isolated, they do not produce green on a blood agar plate the first 24 hours. This seemed to be a uniform characteristic. All of the inactive strains from rheumatic fever cases, after a period of culture, became producers of green on blood agar. Clawson concludes from his work, and that of
others, on the basis of morphological, cultural, and immunological characteristics, that the group cannot be considered a specific one, but that it represents a heterogeneous group, generally green producers, of low virulence.

Although Swift and Kinsella (9) failed to obtain as high a percentage of positive blood cultures (from 8 - 10%) in their 143 cases, yet they believe that if it can be proven that the streptococcus is the etiological agent of rheumatic fever, it will be one of the members of the viridans group. All of the organisms found by these workers produced green on a blood agar plate. They state in their article that they believe the streptococci described by earlier workers corresponds to what is now known as streptococcus viridans, but as these men gave no attention to hemolytic properties, it is impossible to correlate absolutely their results with those of later workers.

Suranyi and Forrio (quoted from - 1) took blood cultures on 25 cases of polyarthritis and obtained green producing streptococcus in 17 or 68% of the series. The blood was first hemolyzed and the sediment cultured in broth tubes.

Cecil, Nicholls, and Stainsby (11) have recently reported the isolation of streptococci from the blood and
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joints in a high percentage of patients with rheumatic fever. They conclude that rheumatic fever is probably a streptococcal infection, usually of the viridans type, although indifferent or even hemolytic streptococci may occasionally act as the exciting agent. Cultures were taken, during the febrile stage before salycilates were administered, from 60 patients with definite fever and joint manifestations. In 29 cases in 1928, 9 or 31% were positive with a gram positive micrococcus. 31 cases in 1929 showed 26 or 83.9% yielding a micrococcus in pure culture, all having the morphological characteristics of the alpha of viridans type. There was 1 exception which was a hemolytic streptococcus.

D. Indifferent Streptococci:

It has been recently proposed by Small and Birkhaug (quoted from - 37) that indifferent streptococci, which are those not producing green or causing hemolysis on blood agar, must be considered as an etiological factor. That the indifferent streptococci were not completely apathogenic was suggested by the observations of Kinsella (37), who recovered them in 4 instances in the blood stream of patients suffering from subacute bacterial endocarditis.

Serological study of a large number of strains of in-
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different streptococci has revealed the existence of a
large homogenous group to which the designation type I
has been applied. It is recognized that the members of
type I are not necessarily identical and that further sub-
divisions into subtypes may be possible. All strains of
type I ferment inulin and salicin. The remaining strains
belong to type X. They are distinguished by their failure
to react strongly with type I serum.

Small and Birkhaug (quoted from -11) had their in-
terest in the indifferent, or gamma streptococcus, first
aroused by the recovery of such an organism from the blood
stream of a patient with rheumatic fever. Small called
his organism the Streptococcus cardioarthritis. Small (28)
catalogued strains of Streptococcus cardioarthritis isolat-
ed from a series of 31 patients. Identification of these
strains was based on agglutination with rabbit serum pre-
pared by sensitizing rabbits to the original strain of
Streptococcus cardioarthritis, giving a titer of 1:2,000.
A remarkable constancy of fermentation reactions among
these strains was reported. They were non-hemolytic, non-
motile, facultative anaerobes with an optimum growth at
37°C. There was no methemoglobin formed, no green or dirty
brown on a blood agar plate. Birkhaug (39) referred to
his strain as a non-methemoglobin forming streptococcus.
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He describes the organism, in addition to the previous statement, as an inulin fermenting, bile insoluble, toxigenic, gram positive streptococcus, regularly isolated from tonsillar crypts, blood cultures, heart vegetations, feces, and urine of persons with rheumatic fever. Culturally, toxigenically, and serologically, the non-methemoglobin forming streptococci constitute a closely related group of micro-organisms, distinguishable biologically from groups of Streptococcus viridans and Streptococcus hemolyticus. Studies were made concerning the production of soluble toxins by these different groups with the following results: 1. 98 strains of hemolytic streptococci produced no demonstrable toxin. 2. 249 strains of Streptococcus viridans showed that 4.7% were toxin producers. 3. Among 68 strains of non-methemoglobin forming streptococci, 72% were found to produce a soluble toxic filtrate.

Experimental injection intra-articularly and intramuscularly of large doses of the soluble toxic filtrate of the non-methemoglobin forming streptococcus produced a typical clinical picture of polyarthritis of the rheumatic type without suppuration or injury to the articular surfaces. There was also produced, by the injection of the toxic filtrate, acute bacterial endocarditis, myocarditis,
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and massive vegetations on the heart valves.

The evidence presented by these investigators in favor of the indifferent streptococci as the exciting agent in rheumatic fever was based, not so much on the recovery of the organisms from the blood stream, joints, and other lesions of rheumatic fever, as it was on the frequent cultivation of the gamma streptococcus from the tonsils, throat, and teeth of these patients.

Cecil, Nicholls, and Stainsby (11), although concluding that rheumatic fever is probably a streptococcal infection and plays a much more important role than the indifferent group, admit that the indifferent streptococci may occasionally act as the exciting agent.

Nye and Seegal (40) made cultures from 25 cases of rheumatic fever, using the combined methods of Clawson, Small, and Birkhaug, in which they used 50cc or more of blood. Throat, urine, and stool cultures were also made. The results of the above experiments were as follows:

1. No streptococci of any kind from the blood cultures.
2. Throat cultures from non-rheumatic patients were 22% positive for gamma streptococci.
3. Throat cultures from rheumatic fever patients were 20% positive for gamma streptococci.
4. These non-hemolytic streptococci, which are morphologically and culturally identical with Small's and
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Birkhaug's strains, have all failed to show any noteworthy degree of homogeneity. 5. Representative strains of these streptococci have proven to be relatively non-pathogenic for rabbits following intravenous injection. 6. These organisms, with a few exceptions, have failed to produce soluble skin reacting toxins comparable to Birkhaug's standard test toxin. 7. The foregoing facts seem to invalidate the assumption that any of these non-hemolytic (gamma) streptococci play a specific role in the etiology of rheumatic fever.

Hitchcock (37) has recently verified the work of Nye and Seegal by showing that indifferent streptococci are as frequent inhabitants of the throats of non-rheumatic individuals as in those suffering from acute rheumatic fever.

E. Transmutation Theory:

Rosenow (25) in 1913 reported the isolation of streptococci from joints in 7 out of 8 cases of acute rheumatic fever in early stages. Blood cultures were made in 7 cases and gave positive results in 2 of these. Cultures of the tonsils yielded similar organisms in 2 cases. Experiments on rabbits, guinea pigs, white rats, and dogs show cultures of organisms of relatively low virulence, more virulent than Streptococcus viridans and less than Streptococcus hemolyticus. Multiple, non-suppurative arthritis, endo-
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carditis, pericarditis, myocarditis, have been obtained repeatedly in the same animal. Strains from the tonsil at the height of the attack gave the same results as those from the joints. By animal passage, and other means, 3 of the strains from acute rheumatism have been converted into typical hemolytic streptococcus on 1 hand, and pneumococci on the other. During 1 of the transition stages, the strain (from a joint) lost its affinity for pericardium, endocardium, and articular tissues, but acquired a pronounced affinity for myocardium, skeletal muscles, and kidney, producing non-suppurative myocarditis, myositis, and acute nephritis. In a later work (33), Rosenow obtained 3 types of cocci from the joints of cases suffering from acute rheumatic fever, each of which could be converted into the other quite readily by using low oxygen pressure during culture, and animal passage. 2 of these types, 1 of which was a long chain producer, and the other a micrococcus, and were originally isolated from the joints of patients during an acute attack, produced green on blood agar, and when injected into animals, produced a non-destructive arthritis, pericarditis, and endocarditis. The long chain organisms were described by Rosenow as being larger and more uniform in size than those of Streptococcus viridans. The third type was a diplococcus and was originally from cases with
more or less muscular involvement in their attacks. This group, when cultured on blood agar, produced a slight, but more or less hazy, hemolysis. When injected into animals, it produced arthritis, endocarditis, pericarditis, myositis, and a most pronounced myocarditis. In addition to these strains, 21 strains of hemolytic streptococci were isolated from a wide range of sources including erysepylas, scarlet fever, puerperal sepsis, arthritis, cow's milk, etc. These organisms were all in one way or another converted into Streptococcus viridans.

The above strains, as well as those of rheumatic fever, have been converted into pneumococci, which conversion has been found to be complete in every way and confirmed by every test known, by morphology, capsule presence, solubility in bile, in NaCl solution, specific immunity response, as manifested by production of opsonin, and agglutination by antipneumococcus and antistreptococcus serum.

Callow (41) working on the bacteriology of blood in rheumatic fever, found streptococci or pleomorphic bacilli in 70% of patients with rheumatic fever, and was able to show that the pleomorphic bacilli transmuted to streptococci.

F. Negative Results:

Nye and Seegal (40) took blood cultures from 25 cases
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of rheumatic fever using the combined methods of Clawson, Small, and Birkhaug, using 50 cc or more of blood, but failed to find streptococci of any kind. Beattie (42) made cultures from the heart's blood in 3 cases of fatal rheumatic fever at the autopsy table. All of these cultures remained sterile. One culture, made from a joint in the same series of cases, also remained sterile. However, in these 3 cases he was able to grow a non-hemolytic streptococcus from pieces of synovial membrane. When these were innoculated into rabbits, he was able to obtain one animal in which appeared a typical picture of infection, with blood and the joint exudate giving sterile cultures.

Swift and Kinsella (9), in a series of 143 cases from whom they made blood and joint cultures, taken from a few hours to a few days after the appearance, and before any salycilates were taken, although obtaining from 8 to 10% of positive blood cultures, found all joint cultures to be sterile. The work of these men was checked with that of Rosenow and they did not believe that their lack of positive cultures was due to technical errors, such as the stage of the arthritis, or faults of the culture media.

Wilson and Edmond (43) recently reported their results of blood cultures obtained from 67 children suffering with rheumatic disease. In 46% of the cases, positive cul-
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tures were obtained. The organisms were either streptococci or pleomorphic bacilli. However, in a control series of 78 children not suffering from rheumatic fever, 33% of the blood cultures were positive, the organisms being streptococci or pleomorphic bacilli. The authors, in view of the positive findings in the control series, conclude that those organisms recovered from the blood of children with rheumatic disease did not appear to be of primary etiologic significance.

Loeb (44) attempted to cultivate the suspected organism from 45 cases, all of which were clinically typical of acute rheumatic fever. Patients who had passed the acute febrile stage were rejected. Of the 45 examined, 35 gave no cultures at any stage. Of the remaining 11 cases, cultures were obtained from the blood in 10 cases and the remaining case showed a positive culture from the knee joint.
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Small (28) and Birkhaug (39) believed that the etiologic basis of rheumatic fever was that of specific streptococci elaborating specific toxins. These men, in their experiments with non-methemoglobin forming streptococci, which have been discussed in another section, examined the toxin producing properties of these strains, which were isolated from patients having acute rheumatic fever, and obtained from tonsillar crypts, blood cultures, heart vegetations, and feces. Birkhaug, in comparing these strains with other types of streptococci, found that, in 98 strains of hemolytic streptococci isolated from variously selected sources, there was no toxin demonstrated. In a series of 247 strains of Streptococcus viridans, 4.7% were toxin producers. However, 68 strains of non-methemoglobin producing streptococci were found to produce a soluble toxic filtrate. These soluble, toxic, filtrates were injected into rabbits in large doses and produced a typical clinical picture of a polyarthritis of the rheumatic type without suppuration or injury to the articular surfaces.

Birkhaug (Quoted from -35), following the work of the Dicks on scarlet fever, prepared a toxic filtrate, which he employed in skin reactions to indicate susceptibility to scarlet fever.

Small (28) prepared an antiserum by sensitizing rab-
bits to his original strain of Streptococcus cardioarthritis to a titer of 1:20,000. Patients were given this serum during the febrile stage of a rheumatic attack. In a series of 9 cases, all were improved by the serum but two, who were found to be erroneous diagnoses. The full effect of this toxin neutralizing serum was obtained in about three days, with loss of choreiform movements, and subsidence of swelling. The effects occurred by crisis.

Coburn and Pauli (32), in discussing the bacterial identity and general characteristics of organisms isolated from throats in an upper respiratory epidemic at the Pellham Home, which was followed by an outbreak of rheumatic fever among the inmates, discovered that these hemolytic streptococci, which they believed to be the underlying etiological factor responsible for the rheumatic outbreak, were strong toxin producers. They also noted that the organisms which produced the most powerful toxins were cultures from the patients who developed extremely intense cases of acute rheumatic fever subsequent to the nasopharyngeal episode. Further experimentation showed that about 70% of these toxins were neutralized by a monovalent streptococcus antiserum.

Meyer (Quoted from 44), unsuccessful in 30 cases to get positive blood cultures, concluded that the disease
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was either an intoxication from the bacteria which remained localized in the throat, or that the organisms entered the blood and were there rapidly destroyed.
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It is difficult to explain the frequent absence of bacteria from even the most acute lesions, especially since they can be found in such large numbers in other bacterial diseases of the heart. The doctrine of allergy or tissue hypersensitivity has been invoked, by Swift and Zinsser in particular, to explain this discrepancy (45). The similarity of the joints in rheumatic fever to the acute joints of serum disease has also been a stimulating factor in formulating the theories of the factor of allergy in the etiology of the disease (1).

Swift and Derick (46) have shown that repeated slight infections with streptococci, or a single chronic infection, may induce, when produced in rabbits, a heightened sensitivity to the organism or its products. Thus injection of the killed organisms into the skin, or their instillation into the conjunctival sac of such an animal, produces a local reaction of the tuberculin type, while intravenous injection may cause general symptoms or even rapid death. The same inoculations into normal, unsensitized animals produce no effects. An attempt to explain this mechanism as a stage in the production of immunity has been offered, suggesting that is a manifestation of a defense mechanism. Any fresh contact of the sensitized animal with the micro-organism provokes an exaggerated
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tissue response leading to the destruction of the invading organisms. A perversion of this normally defensive mechanism has been suggested as the rheumatic response to streptococcal infection. The tissues have acquired a capacity to react violently to the most minute doses of the antigen, which may either be the streptococci, or the autolytic products of the streptococci, discharged from some chronic focus, the reaction being manifested by an extreme degree of edema. Boyd(47) suggests, concerning the two types of lesions of rheumatic fever, that the proliferative type, the rheumatic nodule, is due to implantation of bacteria, while the exudative, or edematous lesion is a manifestation of allergy. He goes on to say that the recurring attacks or rheumatic fever may be merely the appearance of exudative features in persons long subject to the proliferative form of lesion. The bacterial conception of allergy demands the presence of a chronic focus of infection in the body.

Swift (1) states that focal infections, such as tonsillitis or sinusitis, have been long considered as the sites from which bacteria were fed into the blood stream. Boyd mentions the teeth as a probable focus. Swift further states that, while foci may have the role of feeding bacteria into the blood stream, he considers them as areas
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from which the whole body is sensitized. Also the majority of patients with rheumatic fever show skin hypersensitivity to streptococcal filtrates or to certain bacterial fractions. They also show tuberculin like response to intravenous injections of streptococcal vaccines or nucleoproteins. Some individuals who have never had rheumatic fever also show similar reactions, but several studies indicate that a higher proportion of rheumatic fever patients react.

Klinge (Quoted from 35) has reported wide-spread focal lesions following repeated intra-articular injections of horse serum into rabbits previously sensitized to this particular protein. Klinge contends that the lesions produced in his rabbits have many points of resemblance to those found in rheumatic fever, and he believes that this peculiar type of lesion is the result of repeated shocks to hypersensitive tissue with foreign protein.

Working on the theory that the symptoms in rheumatic fever were allergic manifestations from some chronic focus of infection, a number of investigators have studied skin reactions in rheumatic fever. Derick and Fulton (48) recently found that 88% of rheumatic children between 6 and 10 years of age gave positive skin reactions to hemolytic streptococcus nucleo-protein, compared with 12% among non-
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rheumatic controls of the same age.

Coburn and Pauli (3) have found that patients with rheumatic fever furnish the highest proportion of reactors to a similar hemolytic streptococcus nucleo-protein. Jones (Quoted from -35) found 96% of positive skin reactions among 130 rheumatic children at some period of the disease, and reports that spontaneous recovery was usually accompanied by increasing reaction to this filtrate.

Myers, Keefer and Oppel (45) carried out skin tests with the nucleo-protein of the Streptococcus hemolyticus on patients with rheumatic fever and obtained the following results: Of the 40 patients tested who had rheumatic fever, 77% gave positive reactions, and in 32% the reactions were marked. In skin tests on 20 patients with respiratory infections due to the hemolytic streptococcus, 95% were positive, of which 35% were marked. In a control group of 207 cases, 44% gave a positive reaction, but in only 12% was the reaction marked. From these observations the authors concluded that the presence of strongly positive skin reactions in patients with rheumatic fever indicated that these patients might be highly allergic to the products of the hemolytic streptococcus.

Bland and Jones(22) noted that there was a reactivation of a low grade rheumatic fever as a result of...
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apeutic injection of T.A.B. vaccine. Zinsser, Swift, and others had also noted its analogy to the sequence of events occurring in serum sickness and other frankly allergic conditions.

Faber (49) made some remarkable discoveries along this line in producing experimental arthritis in rabbits. He noted that when very virulent strains of organisms were used, arthritis was produced after the first injection and that the joint smears were usually positive. He further noted that if a less virulent streptococcus was used, no joint lesion was demonstrable after the first injection. However, a second injection was followed by a very definite arthritis. "In other words" says this worker, "The development of arthritis in these cases is conditioned probably upon some anterior process set up in the joint".

In this series of experiments, joint cultures or smears were usually negative. In other experiments, endotoxin was extracted and injected into a joint, followed 8 to 15 days later by intravenous injection of living organisms, which procedure produced a definite arthritis in the joint originally treated. This preparatory or sensitizing process is purely a specific one it seems, as a different organism for the two injections produces no effect or at least in some cases a very doubtful one as worked out by Faber's
experiment. An analogy is suggested by this worker between the development of arthritis in rabbits after repeated intravenous injections and the development of the primary lesion in human acute rheumatic fever.

Zinsser and Yu (50) sensitized guinea pigs to hemolytic streptococci and more especially to pneumococcus autolysates. They were tested for sensitiveness by inoculations both into the skin and one knee joint, under the proper control. Inflammatory reactions of the joint were obtained which were in general proportionate to the degree of sensitization indicated by the skin tests. Pathological examination of such joints showed heavy exudates into the joints, into the joint capsule, and into the adjacent tissues. There was no necrosis, and all the tissues were intact or separated by elements of exudate.

These experimenters believe that the fact that non-hemolytic streptococci are particularly common in rheumatic fever could be explained by the consideration that the biologic balance of invasiveness and resistance established between human beings and these organisms is of such a nature as to be likely, more than most other organisms, to lead to the establishment of foci.

They state, "Evidence seems to point toward the conclusion that the allergic state is a part of the immun-
oologic mechanism, and in its first stages, before anti-
bodies have been accumulated to any extent in the circul-
ation, the phenomenon is mainly cellular, expressing its-
self in an extraordinary irritability of the cells to con-
tact with the antigen." They conclude, "A coordination
of the observations in these cases with experimentation
on bacterial allergy seems to us to lend added support to
the point of view that focal infection, with consequent
sensitization of the body, is in keeping with the many
otherwise contradictory experimental and clinical observ-
ations that have been made on this disease, and tend to
lend added weight to the view that the allergic theory is
a reasonable one as applied to the causation of many of
the manifestations of rheumatic fever."
Although the possibility of a virus having something to do with the causation of rheumatic fever had been considered by several investigators, it was not until 1935, when Schlesinger, Signy, and Amies published their work on the virus as an etiological factor in rheumatic fever that any support was given to this hypothesis. In earlier work the attempt had been made to infect animals with materials from rheumatic patients, but convincing evidence was not obtained. Recent advances in the study of viruses, particularly the use of the high speed centrifuge in obtaining deposits of elementary bodies from virus infected material, and the examination of these particles with respect to their morphological characteristics and serological reactions (51). The technique employed was essentially that used by Ledingham (52) and Amies (53) in their studies on the viruses in vaccinia and fowl pox.

Schlesinger, Signy, and Paine (54) suggested that the infection with hemolytic streptococci, by producing a condition of increased tissue susceptibility, enabled an as yet undiscovered causal agent to enter the body or allowed some agent already lying latent in the body to assume active characteristics.

By preparing high speed centrifuged exudates, it was hoped that this agent would be deposited in the sediment
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so obtained. The pericardial fluid of cadavers, within 12 hours of death, was used for the experiment. Dark field examinations revealed particles of uniform size which, in the light of experiences with other virus diseases, appeared closely to resemble elementary bodies. In 7 cases of pericarditis, 6 were positive for these bodies. There were pleural exudates in 5 out of the 7 cases in which 1 was positive for the "elementary bodies". In the control series in which 8 pericardial exudates and 2 pleural exudates from non-rheumatic conditions were examined, no bodies of uniform size and refractility were seen at all.

Agglutination for elementary bodies was demonstrated by Ledingham in 1931 in vaccinia and fowl pox and later in varicella and zoster by Paschen and Amies in 1933 with specific antisera (quoted from 52). These agglutinations have been performed on 36 patients, all of which had well established rheumatic cardiac involvement. Patients used were acute, convalescent, and quiescent cases. The highest titers were in patients in whom the rheumatic process had been active for a long period. The sera of quiescent patients failed to agglutinate these suspensions. Negative reactions were obtained from normal persons or those suffering from non-rheumatic infections.

Miller (55), in a series of attempts to transmit a
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virus from patients with rheumatic fever in acute stages, inoculated 27 rabbits and 14 guinea pigs with either whole blood, serum, joint fluid, pleural fluid, throat washings, or suspensions of tonsil tissue, the latter 2 being passed through a Berkefeld filter. Subsequent transfer inoculations were employed using healthy animals. The animals of the first series were used to obtain inoculation material whether they showed disease or not. This set of experiments produced only 2 animals presenting an acute non-bacterial arthritis. In about one-half the rabbits and two-thirds of the guinea pigs, myocardial lesions were found which were thought to resemble Aschoff bodies. Control animals had these lesions in about the same percentage and it was concluded that such lesions were normal in these animals in a certain percent of cases.

One of the most recent works published on the subject of a virus as the possible causal factor in acute rheumatic fever is that of Eagles, Evans, Fisher, and Keith (51). Suspensions were prepared from patients suffering with rheumatic fever. The material suspected of harboring the virus was obtained from the following sources:

A. Pericardial and pleural exudates:

The material from the pericardium was usually obtain-
VIRUS

ed post-mortem, while the pleural exudates were usually obtained during life. A suspension was prepared by a preliminary spinning of from 3,000 to 4,000 revolutions per minute. The supernatant fluid was then subjected to centrifuging at 14,000 revolutions per minute for 1 hour. This was the technique employed on all specimens. In most cases the material obtained was sterile with respect to organisms.

The suspensions from these sources showed the typical bluish opalescence, by illumination, observed in suspensions of known virus particles.

B. Joint fluids:

Exudates were obtained from the joints at the height of inflammatory reactions and maximum effusion. Due to the viscid consistency of the substance obtained, a special technique was necessary to properly centrifuge this material, but, when worked out, positive results were obtained. Both of the above sets of results were confirmed by positive agglutination reactions between the suspensions and sera from rheumatic fever patients.

C. Other sources:

Suspensions from blood, urine, cerebro-spinal fluid, subcutaneous nodules, and ascitic fluid contained relatively few of the particles and were not suitable for agglutin-
VIRUS

ation tests.

D. Control material:

Pericardial and pleural fluids were obtained from cases of tuberculosis, cancer, cardiac failure, without a history of rheumatic fever, and infections of known bacterial etiology. Joint fluids were obtained from cases suffering from simple traumatic injury and non-rheumatic conditions, as tuberculosis and osteomyelitis. Synovial membranes from knee joints with torn semilunar cartilages were examined.

Material obtained from infectious sources showed small particles in the suspensions, which were believed to be cell granulations and products of cellular disintegration. Simple transudates from the pleura and pericardium yielded only very minute amounts of centrifuged material, which was not in the least comparable in amount with the pathological exudates. There were no deposits obtained from normal joint fluid.
SUMMARY

The amount of work done on the etiology of rheumatic fever has been tremendous and the results present a great variety of ideas, some of them quite convincing and many of doubtful significance.

There are many able investigators who still believe that the disease is caused by a streptococcus. Even though there is much evidence to the contrary, it can not be denied that there is a very close relationship between this organism and the disease. Whether this relationship is a direct or a predisposing factor is still the subject of controversy. Studies of outbreaks of rheumatic fever and large numbers of cases indicate that predisposing causes, such as upper respiratory infections of certain types, heredity, environmental conditions, and the presence of epidemics, are very important in the etiology of the disease.

The idea that rheumatism is an allergic manifestation to the protein fractions of organisms occupying foci of infection the body has gained considerable favor among numerous investigators and their work with experimental animals and observations of clinical similarities between acute rheumatism and serum sickness seems very convincing. However, since the field of allergy is still filled with puzzling features, this idea has its limitations.
SUMMARY

The most recent idea to be advanced is that rheumatic fever is a virus disease, the onset preceded by predisposing factors, such as those mentioned above, or others including trauma and post-operative rheumatism. The work and results of Schlesinger, associates, and others on virus as a factor, although very recent, sounds very plausible. This work, like all the others, is still one of controversial nature, and the final outcome of this study is still in the future.
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