Diagnosis, treatment and prophylaxis of acute rheumatic fever

George E. Gammel
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THE DIAGNOSIS, TREATMENT AND PROPHYLAXIS OF ACUTE RHEUMATIC FEVER

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Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

February 1, 1964

Omaha, Nebraska
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There are many publications in today's literature covering every aspect of the rheumatic fever victim. Opinion varies greatly from author to author concerning the diagnosis, treatment, and prophylaxis of this disease. Should steroids be used during the acute attack? This is perhaps the most controversial subject reviewed in this paper. On one side are very competent investigators who conclude through clinical experience, that steroids will answer the problem in the prevention of residual cardiac disease following acute rheumatic fever. Others believe steroids to be of no value in this respect, and hold that their use is contraindicated because of the many serious side reactions inherent in this drug. Has the diagnosis of acute rheumatic fever improved with the aid of advancing knowledge in both clinical and laboratory methods? There are many new and difficult tests demonstrated in the literature, and their value must be determined.

Why do the various authors use their own set of criteria when studying acute rheumatic fever? Salicylates have been used for years in the treatment of this disease. Opinions conflict as to the effects of this drug on the ultimate outcome of rheumatic fever. Again, strict bed rest is advo-
cated by many, yet temporized by others. Penicillin therapy also has been questioned. Some authors give massive initial doses, while others give only minimal amounts. There are other authors who compromise and give a dosage that ranges between the maximum and minimum. The goal of this paper is to review the important literature covering the diagnosis, treatment, and prophylaxis of acute rheumatic fever, with specific emphasis on the last ten years. In doing this, I hope to answer some of the above questions, and gain a workable understanding of the methods involved in the management of acute rheumatic fever.

Rheumatic fever is not uncommon. Holt suggests an incidence of two to three and nine tenths cases per one thousand population between the ages of five and nineteen. Feinstein and Rudsky believe that this disease is becoming milder. They point out that thirty to forty years ago such manifestations as nodules, pleuritis, pericarditis, pneumonitis, and congestive heart failure were relatively frequent. Severe epistaxis was said to be common enough to warrant special equipment for packing noses to be close at hand on rheumatic fever wards. Today the above manifestations are infrequent and mild
when they do appear. Rudak58 demonstrates statistically a decrease in the incidence of rheumatic heart disease of sixty-three per cent comparing military men examined in 1943 to a similar study undertaken in 1962. After considering the increase in correct diagnosis of this disease, he still could demonstrate a forty per cent decrease in its incidence.

Acute rheumatic fever is nearly universally accepted as being related to a previously occurring infection of group A beta hemolytic streptococcus. There are some fifty known types of this organism, each of which may produce subsequent rheumatic symptoms. These organisms are maintained in nature in the upper respiratory tract of about ten per cent apparently normal individuals. This carrier state is especially prevalent in children. The organism is transferred to the susceptible host readily by air borne droplets. Immunity may be present in the individual from previous infections. According to Mortimer and Rammelkamp53, this immunity is type specific and relatively long enduring, which may explain epidemics as an introduction of a new type of streptococcus into a community. It is estimated that the average child experiences from three to
four group A streptococcal infections per year. It has been found that following epidemics and in certain population groups, as many as three per cent of the untreated streptococcal infections are followed by rheumatic fever. It appears that the focus of this disease is on the previous streptococcal infection. Although this phase is important, Feinstein and Zagala point out from a study of one hundred eighty-three cases, that at least half of the patients who get rheumatic fever do not have a preceding sore throat to bring them to medical attention and subsequent adequate treatment.

The classical clinical symptoms of the streptococcal sore throat include dysphagia, headache, fever, beefy red throat with exudates, and cervical lymph node enlargement. Czoniczer's study indicates that the reason for the rheumatic fever episode is failure to see a physician, incorrect diagnosis made by the physician, and inadequate amounts of anti-streptococcal therapy given. They also show how the streptococcal infection can present in atypical manners giving at times only respiratory symptoms without sore throat or fever, which would be characteristic of a viral infection and lead to an incorrect diagnosis.
There are then approximately fifty per cent of the cases of rheumatic fever patients who have atypical streptococcal infections. Feinstein and Zagala calculated from their series that at least twenty-one per cent had upper respiratory infections without sore throats and that approximately thirty-three per cent had no symptoms at all. The use of the throat culture to aid in the detection of both mild and severe streptococcal infections is thought to be the most important contribution to the prevention of primary rheumatic fever. The exact method will be explained later.

Why three persons out of one hundred should contract rheumatic fever after similar infections, has been studied to some extent. It has been theorized that a constitutional predisposition may be present. Once a person has had rheumatic fever, he has as high as a fifty per cent chance of contracting the disease after a streptococcal infection. This predisposition may be either inherited or acquired. It is well known that rheumatic fever occurs most commonly among the poor. The majority of cases are found in the slum areas of regions with relatively temperate climates. Coburn points out that inadequate nutrition is part of a poor
environment. In his epidemiologic study he found that rheumatic fever children usually lack sufficient eggs in their diet, due to their cost. He noted that when families escape poverty, they increase their consumption of eggs and subsequently decrease their incidence of rheumatic fever. He concludes that supplementation of children's diets with eggs or similar nutrients may decrease rheumatic susceptibility. Holt30 suggests that the crowded conditions prevalent in slum areas concentrate susceptible persons and thereby increase the contacts with carriers and produce many respiratory infections.

Age appears to have some relationship with this disease, for those most commonly affected are between five and fifteen years of age. Relative immunity before the age of five is thought to be due to a lack of effective contacts. At five, the child starts school and is in contact with carriers of the organism. The immunity which is seen after age fifteen, according to Mortimer and Rammelkamp53, may again be due to the lack of effective contacts, as well as type-specific immunity from previous infections and possibly a decreased susceptibility to rheumatic fever.

The high familial incidence of rheumatic fever
should be emphasized. Many workers believe that susceptibility to rheumatic fever is primarily determined by inheritance. There appears to be no differences between race or sex in the incidence of this disease.

The classic time interval between the sore throat and the appearance of rheumatic fever is one to three weeks. A recent study by Feinstein and Zagala points out that sixty-one per cent of their cases demonstrates this time interval. In fifteen per cent, the rheumatic symptoms occurred simultaneously with the sore throat, and another fifteen per cent showed symptoms more than four weeks after the streptococcal infection.

THE DIAGNOSIS

More attention must be placed on the diagnosis of acute rheumatic fever because of the new and somewhat hazardous drugs which may be employed to suppress the acute manifestations, the residual valvular damage, as well as the prolonged antibiotic prophylaxis following the attack. The diagnosis may be extremely difficult, for there is no specific diagnostic, laboratory, or clinical test available to aid the physician. The disease itself complicates the picture due to the wide variability of
its manifestations. The patient may present only a chronic fever and recover without residual cardiac damage. On the other hand, he may show congestive heart failure and expire before therapy can be instituted. Feinstein's study demonstrates a twelve per cent diagnostic error in one hundred sixty-three patients referred to the hospital with a diagnosis of acute or recent rheumatic fever. He estimates that in certain rheumatic fever therapeutic groups, the original diagnosis is doubtful or incorrect in as many as ten to thirty per cent of the patients. This error is extremely important when considering the detrimental effect of steroids on an illness due to a specific infection. The infectious process would be free to advance and might threaten the life of the patient. The possible allergic or toxic reaction from penicillin, steroids, salicylates or sulfa-drugs would be a needless danger a miss-diagnosed patient would have to suffer.

The psychological problems created by a diagnosis of rheumatic fever are obstacles which prove to be very difficult for young individuals. The rheumatic subject will be forced to take a form of medication the rest of his life. He must learn to live with this label. He may, becoming overconcerned
with his heart, subsequently withdrawing from normal exercise under the watchful eye of an overbearing mother. He will also have to pay higher rates on life insurance, and be concerned with limitations imposed by the physician.

The diagnosis of rheumatic fever is based on the modified Jones criteria which is published and recommended by the American Heart Association. In 1944, Jones first published his criteria. These were modified by himself and others working in this field and published in 1955. Grossman's inquiry into the sources of error in diagnosis led to the conclusion that many of these errors could be eliminated if strict application of Jones Modified Criteria were followed.

The diagnostic features of rheumatic fever are divided into major and minor categories depending on their occurrence in this disease and other disease entities which must be differentiated from rheumatic fever. It should be pointed out that the categories have no significance as to the prognosis or severity of the acute illness. The presence of two major criteria or one major and two minor criteria indicates a high probability of active rheumatic fever, but does not absolutely prove the
### Diagnosis

**Jones Criteria (Modified)**

<table>
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<td>I. Fever</td>
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<td>II. Polyarthritis</td>
<td>II. Arthralgia</td>
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<td>III. Chorea</td>
<td>III. Prolonged P-R interval on ECG.</td>
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<td>IV. Subcutaneous nodules</td>
<td>IV. Increased ESR, WBC, or presence of C-reactive protein.</td>
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<tr>
<td>V. Erythema marginatum</td>
<td>V. Preceding beta-hemolytic streptococcal infection.</td>
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<td>VI. Previous rheumatic fever or inactive rheumatic heart disease.</td>
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Carditis is recognized when one or more of a variety of physical signs are found on examination. The presence of a cardiac murmur which is either a significant apical systolic murmur, apical mid-diastolic murmur or basal diastolic murmur, is sufficient evidence to diagnose carditis in the individual with a negative history of previous rheumatic fever. The significant apical systolic murmur is often confused with the functional apical systolic murmur which has occurred in as many as ninety percent of normal children from certain populations. Criteria for differentiation will be given later. Any murmurs which cannot be differentiated should
be watched over a period of time. This will usually allow accurate differentiation. In the individual with a previous history of rheumatic fever or rheumatic heart disease, a change in the character of a murmur under observation is evidence of active carditis. A second sign of carditis is an increasing cardiac enlargement as seen by x-ray. Pericarditis may be diagnosed in the presence of a friction rub, pericardial effusion or definite electrocardiographic evidence.

Congestive heart failure when seen in a patient under twenty-five years of age and present in the absence of other causes, is assumed to be due to rheumatic carditis until proven otherwise.

The second major criteria listed above, polyarthritis, is characterized as being migratory and manifesting subjective signs such as tenderness, heat, redness, or swelling of two or more joints. There may also be pain and limitation of the normal range of motion. It must be pointed out that arthralgia alone, without the objective signs listed above, is not enough evidence to warrant a diagnosis. Usually the larger joints, such as the ankle, knee, hip, wrist, elbow, and shoulder, are affected. There are never permanent deformities resulting
from involvement. Another differentiating characteristic is the dramatic disappearance of all signs and symptoms when salicylates are administered.

Subcutaneous nodules are seen in only two disease processes, rheumatic fever and rheumatoid arthritis. The nodules are painless and firm. The skin is freely moveable over them. They are usually seen over the extensor surface of certain joints, the most common being the elbows, knees, and wrists. They are also seen in the occipital region, or over the spinous processes of the thoracic and lumbar vertebrae. They may persist for a week to several months, and then disappear, leaving no residual manifestations. The nodules are usually present in the more severe cases of rheumatic fever.

Chorea, also known as sydenham's chorea or St. Vitus' dance, is a functional disorder of the central nervous system. This manifestation is characterized by sudden, aimless, involuntary movements, muscular weakness, and emotional instability. There are characteristic signs which may be present and will aid in the diagnosis. A spasmodic, unsustained contraction is felt when an attempt is made by the patient to grasp the examiner's hand forcefully. The choreic hand results from flexion of
the wrists and hyperextension of the metacarpophalangeal joints on extension of the arms with hands and fingers outstretched. The pronator sign may be elicited by having the child raise his arms above his head. This results in pronation of the forearms in choreic patients.

The last of the major criteria to be described is erythema marginatum, characterized as a recurrent, pink rash. The color is said to gradually fade from a sharp and sometimes scalloped edge. The rash is seen over the trunk and sometimes on the extremities, but not on the face. It is very evanescent and may come and go over a period of months or years. It is brought out by heat and migrates from place to place.

Under the minor diagnostic criteria, the first to be listed is fever. There must be a significant rise in temperature, and this must exceed the normal diurnal fluctuation. Since there is a great individual variation in normal temperature range, and because a fever does occur in many illnesses, its presence or absence cannot be weighed heavily in the differential diagnosis.

Arthralgia is a second minor criteria. This is simply joint pains without objective physical
findings. This pain must be distinguished from muscle pain and a so-called normal nocturnal pain which occurs in children free disease. Arthralgia cannot be used when polyarthritis is used as a major criteria. A third minor criteria is a prolonged P-R interval of the electrocardiogram. This is non-specific and has been found in normal persons. It is present in about thirty per cent of rheumatic fever patients. Again, it cannot be used if carditis is being used as a major manifestation.

Increased erythrocytic sedimentation rate, presence of C-reactive protein, or leukocytosis are three of the most commonly used non-specific laboratory abnormalities considered in this disease. Elevation in one or more of the above tests is necessary to satisfy a minor criteria. There are many other non-specific tests, such as antistreptolysin O titer, antistreptokinase, antihyaluronidase, and deoxyribonuclease B titer, however the first three listed are the most available and inexpensive.

Evidence of preceding beta hemolytic streptococcal infection must be documented by either a positive history or an elevated or rising antistreptolysin O titer. A positive history is present if the patient had scarlet fever or a typical strepto-
coccal upper respiratory infection. The nature of this infection must be confirmed by a history of contact with other patients with typical streptococcal infection or by positive nose and throat cultures of the causative organism. A previous history of rheumatic fever documented by the same criteria as listed above, or the presence of inactive rheumatic heart disease are also used as minor diagnostic criteria.

The above major and minor manifestations must be weighted objectively by the physician. Any and every aid must be used in order to reach a correct diagnosis. There are additional systemic manifestations of this disease not listed in the above diagnostic criteria which may be used in order to provide much additional information. These include loss of weight, malaise, hyperhydrosis, pallor, anemia, and elevated sleeping pulse. Other local manifestations which sometimes are seen include epistaxes, headache, vomiting, precordial and/or abdominal pain, and erythema nodosum.

There are combinations of the above criteria that satisfy the diagnosis of acute rheumatic fever, which also may occur in the presence of other disease processes. Perhaps the weakest of all combinations
consists of polyarthritis, fever, and an elevated sedimentation rate. This combination is seen most often in rheumatoid arthritis, systemic lupus erythematosus, and sickle cell disease according to Grossman and Athreya. Various investigators find it extremely difficult to differentiate acute rheumatic fever from the above mentioned diseases, however, it is generally agreed that many of the errors can be eliminated by strict application of the modified Jones criteria. Other diseases that may be mistaken for rheumatic fever are gonococcal arthritis, subacute bacterial endocarditis, non-specific pericarditis with effusion, leukemia, serum sickness, tuberculosis, poliomyelitis, undulant fever, and septicemias, especially meningococccemia. When the above entities are suspected, appropriate tests should be performed to rule in or out the specific disease process in question.

There are many sources of error in the misdiagnosis of rheumatic fever. The first and perhaps the most common is the mistaken interpretation of arthralgia for arthritis. Again it should be stressed that there must be objective findings present in order to diagnose arthritis. A second common error is misinterpretation of the innocent functional murmur.
of the murmur of acyanotic congenital heart disease for the murmurs of rheumatic origin. According to Rudsky's work, eighteen per cent of all murmurs heard in military age individuals were of rheumatic origin. Less than three per cent were listed as due to congenital anomalies, whereas eighty per cent were believed to be functional in origin. In determining a functional murmur certain auscultatory phenomena should be kept in mind. The functional murmur is usually of grade three of six intensity or less and is short and of a mid-systolic ejection type. There is many times a significant variation of intensity and quality when the patient changes position or at different phases of respiration. The intensity of this functional murmur is increased with tachycardia and decreased after rest or relaxation. There is no significant radiation and the quality is of a vibratory nature. The functional murmur has been characterized as squeaking, buzzing, musical or soft, short, and blowing. There is no gallop rhythm or abnormal splitting of the second heart sound.

There are new and important laboratory tests being done which may prove of benefit to the physician in diagnosing certain difficult cases of
rheumatic fever. Among the acute phase reactants are serum mucoproteins and glucosamine elevations. The diphenylamine color reaction may be beneficial as well as a determination of the ratio of albumin to alpha two globulin as derived from paper electrophoretic patterns. A chondroitin sulfate tolerance test has been studied by Homma. This test measures the mucoprotein levels before and forty-eight hours after administration of a thirty per cent solution of chondroitin sulfate. Active rheumatic fever is reflected in decreasing mucoprotein levels after the chondroitin sulfate is administered. Homma suggests that therapy can safely be stopped after this has returned to normal. A normal individual would demonstrate increasing levels of mucoprotein following the chondroitin sulfate.

The fluorescent antibody test first described by Coons appears to be a very important specific test which may give definite results in difficult cases. In this test, antibodies for a specific disease are stained with a fluorescent dye. This material is then mixed with a specimen from the patient who is ill with a disease in question. If the specimen contains the germ for which the antibody is specific, there will be an antigen-antibody
reaction. The material which contained the antibody is then washed away and the specimen is placed under ultraviolet illumination. A greenish fluorescence will be seen to designate a positive test.

The diagnosis of streptococcal infections as was mentioned earlier is most important in the prevention of rheumatic fever. The common signs and symptoms were presented previously. In the absence of the common symptoms, the throat culture should demonstrate the causative agent. Pobanz\textsuperscript{51} describes a throat culture technique that achieved ninety-five per cent accuracy. He cultures the nasopharynx using a five second contact. This is plated directly on human blood agar. A disc containing bacitracin is applied, and in eighteen to twenty-four hours the plates are read for typical beta-hemolytic streptococcal colonies. He then examines a colony microscopically for characteristic gram positive cocci in odd number chains. The patients having beta-hemolytic, bacitracin-sensitive, gram-positive cocci in predominant growth were treated with intramuscular benzathine penicillin G. Pobanz suggests that bacitracin inhibition may be specific enough to omit microscopy, which would streamline the procedure greatly. He concludes that further study is in-
dicated on this point before a judgement can be made.

THE TREATMENT

The goal in the treatment of acute rheumatic fever is the prevention of rheumatic heart disease. The evaluation of the therapy used by the various investigators should therefore be based entirely upon the prevention of residual cardiac involvement. This presents a formidable problem in view of the variable character of rheumatic fever. In evaluating a particular therapeutic technique, many factors must be considered. The use of the Jones modified criteria for the diagnosis of rheumatic fever is not strictly enough defined to insure complete accuracy. Since there is flexibility in the diagnostic criteria, each investigator will interpret and arrive at decisions using his own particular prejudices. Other investigators use their own modification of Jones criteria in order to fit their particular study group. There should be a distinction and subsequent separation of rheumatic fever patients with and without carditis, because of the likelihood that those without carditis will be free of damage and thus will not benefit in the therapeutic program, other than suppression of the acute phase manifestations. This appears obvious, yet many investigators
fail to make the distinction. Feinstein\textsuperscript{22} demonstrates in his study how the acute rheumatic fever patients without significant murmurs have zero to eight per cent incidence of future heart disease. When only an organic apical systolic murmur is demonstrated, the incidence of heart disease reaches twenty-six to twenty-nine per cent. Those with significant cardiomegaly and/or congestive heart failure were found to have a seventy to eighty-five per cent incidence of subsequent heart disease. Bywaters and Thomas\textsuperscript{21} felt the major factor determining the incidence of rheumatic heart disease after acute attacks, is the status of the heart at the time treatment is initiated.

Patients with a history of previous attacks of carditis should be classed separately because of their relatively poorer prognosis. The time between the onset of rheumatic fever symptoms and the institution of therapy is important, yet many times not specifically mentioned. The study groups being considered should be formed in a completely unbiased manner and should closely match each other in all aspects including the same general area of the country and same time interval from sore throat to rheumatic symptoms.
Because of these many problems, the evaluation of the various methods will be incomplete. Feinstein stresses how successful therapy depends on the final status of the heart. He concludes, that the crucial issue rests in the methods used to detect and classify cardiac damage.

In the review of the many phases in the treatment of rheumatic fever, the first to be considered is bed rest. It is theorized that keeping the patient at rest will decrease the work of the heart to a minimum and will not aggravate the diseased tissue causing excessive fibrosis and scar tissue formation. Illingworth presents the viewpoint that perhaps bed rest should be ordered and not expected. His policy is early ambulation, allowing the patient up two or three weeks after admission. In his review he finds many investigators agree, stating that greater rest is obtained by permitting more freedom for activity. They did not find early ambulation harmful but of psychological benefit. Lendrum pointed out the economic, sociological, and psychological disadvantages inherent in prolonged bed rest. Feinstein conducted a survey in 1962 and found that prolonged restriction of physical activity in rheumatic heart disease patients did not appear to
prevent or augment cardiac deterioration. He demonstrated that thirty-four per cent of a group of two hundred sixteen asymptomatic children suffering from rheumatic heart disease and subjected to physical restrictions, developed significant adverse psychological effects. In a similar group of seventy-five children who had no restrictions placed on them, only six per cent developed similar psychological problems.

The effect of penicillin on acute rheumatic fever and the possible subsequent valvular heart disease has received much attention in the past few years. Mortimer in 1959 re-introduced the concept that valvular damage may be due to direct invasion of the valvular endocardium by the streptococcus. This would represent a form of bacterial endocarditis and therapy toward the eradication of the living organism would be indicated. McCarty points out that between 1939 and 1940 bacteriological investigation by Green, Collis, Thomson, and Innes demonstrates the recovery of hemolytic streptococci from the heart valves of patients dying with rheumatic fever. This work has never been substantiated, due in part to the advent of penicillin. McCarty felt that penicillin therapy failed to alter the
course of the disease, but stated that the organism may be dormant and thus resistant to the effects of penicillin. He speculated that perhaps massive doses of cortisone could be used to reactivate the organism.

Mortimer\textsuperscript{52} went on to head a clinical trial in which forty-nine rheumatic fever patients received no antibiotics and thus served as controls. He used five hundred thousand units of sodium penicillin every four hours for the first ten days, followed by six hundred thousand units of procaine penicillin twice daily for eleven more days. Then a monthly maintenance dose of one million two hundred thousand units benzathine penicillin was given. This therapy had no effect on the acute clinical and laboratory findings, but did produce a reduction of probable statistical significance in the incidence of valvular heart disease one year later. He noted that the presence of murmur's one year after the acute attack was less in the treated group of patients than in the controls. Rammelkamp\textsuperscript{50} emphasizes the above possibility and furthers the theory by suggesting that the carditis may be due to direct invasion of the heart by the streptococcus by way of the mediastinal lymphatics. He recommends the
rheumatic fever patient receive penicillin as if
he had subacute bacterial endocarditis. McEwen recognizes the possible advantage of this technique
and suggests a compromise of one million two hundred
thousand units of benzathine penicillin G be given
three times in the first two weeks of therapy.

Salicylates have been used in the therapy of
acute rheumatic fever since 1875. In spite of this
relatively long period, its effect on the final out-
come of heart disease remains unproven. Illingworth studied this particular drug as applied to rheumatic
fever patients and concluded that the fall in temper-
ature and erythrocyte sedimentation rate was sig-
nificantly faster in those treated with salicylates
than in the controls given no specific therapy.
Other differences in this study were not of sta-
tistical significance, however, he felt that those
treated with salicylates fared somewhat better in
the follow-up examinations. Of this group fewer
developed apical diastolic murmurs and more were
apparently free from cardiac involvement at the time
of the last examination.

Alexander demonstrates how the use of sali-
cylates may be detrimental in the production of
congestive heart failure in certain cases of acute
rheumatic fever. He shows by administration of sali-
cylates during cardiac catheterisation, that the physiology of the myocardium is definitely changed. There is a significant increase in the mean cardiac output due mainly to an increase in stroke-volume. The left-ventricular work load as well as the arteriovenous oxygen difference are also increased significantly. The mechanism is not fully understood, but thought to be related to an increase in metabolic rate. Fifty cases were studied in which the blood level of salicylates reached forty milligrams per cent. Of these, nine developed some evidence of cardiac failure. He concludes that high doses of aspirin are best avoided where there is clear evidence of carditis.

Steroids were introduced into the therapy of acute rheumatic fever in 1950 and have received much attention from a variety of investigators. It is believed that hormones exert a non-specific anti-inflammatory effect, with suppression of fibroblastic activity. This would be helpful in the treatment of acute rheumatic fever because of the suppression of the inflammatory process thought to occur in the myocardium. There are both reversible and irreversible tissue changes which occur during the natural course of the disease. If the irre-
versible changes can be modified or stopped, the ultimate outcome of heart disease will not develop, or will be modified to some extent. Wilson and Lin53,59 admit current opinion on the effect of hormone therapy in rheumatic carditis is controversial, however, fully believe that early and adequate hormone therapy is essential in acute rheumatic carditis if residual cardiac damage is to be minimized or prevented. In their clinical study, cortisone was given to fifty-five patients for seven days in a dosage of four hundred milligrams daily for four days, followed by three hundred twenty milligrams daily for the remaining three days. Hydrocortisone and corticotropin were also used in equivalent doses and given members of the hormone treated group. A control group of one hundred patients were given only symptomatic treatment with salicylates, sedation, and digitalis as needed. In the hormone treated group eighty-four per cent developed no residual cardiac enlargement or valvular lesions. The above good results were attributed to adequate hormone therapy before irreversible damage could occur.

Greenman25 and associates (1953) found hormones to be of value in the prevention of heart disease following acute rheumatic fever. They studied forty-
eight initial attacks of rheumatic carditis which were treated with cortisone for eight weeks. The dosage was three hundred milligrams per day for six weeks, followed by decreasing amounts for another two weeks. He then divided the group in relation to time of therapy after onset of the disease. Twelve children were treated within two weeks of onset. Ten of these had normal hearts at the close of the study. Sixteen of twenty-three treated between the second and sixth weeks demonstrated normal hearts. There was only one out of thirteen treated six weeks or more after onset that had a normal heart. The criteria used for the diagnosis followed the Jones criteria and were listed in each case. It is interesting to note that the murmurs disappeared within seven weeks from treatment in eighty-five per cent of those who developed normal hearts. They conclude that cortisone given in adequate amounts may prevent cardiac abnormalities if it is given within six, and especially within two, weeks of the onset of acute rheumatic fever.

Done and co-workers (1955) published their results in a controlled study on sixty-two patients with acute rheumatic fever. Twenty-eight hormone treated children were given approximately three
milligrams per pound per day of cortisone, until all laboratory and clinical evidence of rheumatic activity had disappeared. The dosage was then gradually decreased if no evidence of reactivation was present. They found that three years after discharge only six per cent of the hormone treated group had residual cardiac murmurs, whereas eighty-two per cent of those not given hormones had residual cardiac murmurs. The erythrocyte sedimentation rate returned to normal in fourteen days in the hormone treated group as compared to forty-three days required when salicylates were used. Thirteen patients on bed rest alone had normal sedimentation rates only after forty-eight days.

Markovitz and Kuttner (1955) studied the effects of intensive and prolonged steroid therapy in forty patients during their first attack of rheumatic carditis. Twenty-nine of this group received treatment within three weeks of the onset consisting of three hundred milligrams of cortisone daily for six weeks followed by a gradual decrease in dosage over the next three weeks. Of this group, twenty-four had no residual evidence of carditis. Eleven were treated after three weeks from the onset, of rheumatic fever symptoms. Of this group only two
recovered without evidence of heart disease. In their study, eleven developed serious side effects due to the steroid administration. They conclude that cortisone given early in the course of rheumatic fever in doses large enough to suppress the inflammatory reaction and for a duration that covers the natural course of the disease process, may reduce the incidence of residual heart disease. The duration of therapy ranged from nine weeks to twelve months. In 1962 the same authors reviewed the current literature and recommended short term steroid therapy, seven to ten days, for patients with clear cut or significant murmurs. Prednisone was recommended in the dosage of two to three milligrams per kilogram in four divided doses. Salicylates were thought sufficient for patients with arthritis and/or or mild carditis. Illingworth and workers (1957) compared six forms of treatment in two hundred rheumatic fever patients diagnosed by the Jones criteria. Steroids were given at high dosages (three hundred milligrams daily) for six weeks, reducing the dosage throughout the time interval. Their impression was that the cortisone treated cases fared better than all other cases in respect to
carditis. In this group more children lost organic systolic murmurs as well as diastolic murmurs. They emphasized early diagnosis and treatment as being most important in preventing future heart disease.

Dorfman[^18] (1961) did a control study on one hundred thirty-one initial attacks of acute rheumatic fever. Therapy was started eighteen days or less from onset of symptoms. The hormone treated group was given hydrocortisone, two hundred fifty milligrams daily for four days, then one hundred milligrams daily through the first eight weeks. The dosage was then decreased stepwise through the twelfth week. A second group was given aspirin, maintaining blood levels between twenty and thirty milligrams per cent. A third group was given both hormones and aspirin and the final group served as controls. Their feeling was that hydrocortisone did decrease the incidence of mitral insufficiency. They recorded only two serious complications, both duodenal ulcers, one which perforated. They recommended steroid therapy for patients who show evidence of carditis in doses equivalent to two milligrams per kilogram for nine weeks with gradual decrease in dosage after that time.
Hassell\textsuperscript{43} and his group studied five hundred eighty-three patients in first attacks of rheumatic fever. This study consisted of a group using both small and large doses of cortisone for six weeks, as well as a salicylate treated group and a large control group. They recommended steroids equivalent to cortisone in a dosage of three hundred milligrams daily for three weeks, followed by a gradual reduction of dosage over the next nine weeks, when moderate carditis is present. Moderate carditis is represented when a grade three, or louder apical pansystolic murmur without enlargement is present. Pericarditis also represents moderate carditis. They point out that as many as one half to two thirds of the patients with mild carditis showing significant pansystolic apical murmurs less than grade three or long aortic diastolic murmurs less than grade two of six, will lose their murmur within a few months to a year without specific therapy. Treatment of these persons would have to suit the individual, for the dangerous side effects of steroid therapy may out-weigh the possible beneficial advantages. Nadas\textsuperscript{55} states in his newly published book that incipient carditis is a probable indication for the use of hormones. Lockie\textsuperscript{43} believes the
Incidence of rheumatic heart disease could be lessened by adequate early steroid therapy in first attacks of rheumatic fever. Wedgwood\textsuperscript{57} makes it clear that the worth of steroids has not been proven in prevention of rheumatic heart disease, however, he does recommend and use steroids in episodes of rheumatic carditis. McEwen\textsuperscript{50} also believes that steroids probably do not affect the ultimate valvular damage in rheumatic fever, however again uses steroids in the treatment of carditis. He uses ten to fifteen milligrams of prednisone four times daily for ten days followed by a subsequent gradual reduction in dosage.

Steroids are a potentially dangerous drug causing many and varied side effects. Massell\textsuperscript{48} thinks that not all patients with rheumatic carditis should be given steroids. He points out the severe side effects and states that this must be weighed carefully. Perhaps the most common side effects are weight gain, moon face, buffalo hump, hirsutism, acne, and skin striae. The skin striae are especially important when developing on the legs of a young girl, for scars will persist after the steroids are withdrawn. Adrenal insufficiency may follow steroid therapy with associated sodium and fluid retention and po-
basium excretion. There may be hyperglycemia, glycosuria, hypertension, psychosis, convulsion, and myopathy of the leg muscles. Osteoporosis with secondary compression fractures of the spine is not uncommon. Peptic ulcer with perforation or gastrointestinal bleeding is quite common. The development and unhindered spread of infection should always be remembered and inhibited with adequate and proper antibiotics. Gamma globulin may be used when exposure to a virus has taken place.

In the evaluation of steroids in the treatment of rheumatic fever, we have so far seen only the investigators that have found beneficial results using them. Next in order is a review of the major works of the past ten years that find no advantage in the use of hormones and consider their side effects dangerous enough not to use them. Perhaps the largest and most impressive is the United Kingdom and United States joint report\(^5\) (1955). Ninety-seven rheumatic fever patients were studied and subsequently divided into three groups. The first group received ACTH in a dosage of eighty units reduced over a six week period. The second group received cortisone, three hundred milligrams initially followed by gradual reduction over six weeks and
the third group received aspirin for six weeks. Follow-up examinations were done one year after therapy. At the end of one year there were no significant differences between the three treatment groups in relation to the status of the heart. The acute manifestations were controlled faster in the steroid treated groups; however this was balanced by a greater tendency for the acute manifestations to reappear after treatment was terminated. A Combined Rheumatic Fever Study Group\textsuperscript{13} studied twenty-nine patients during their first attack of rheumatic fever. They were treated with prednisone, sixty milligrams daily for three weeks gradually reduced over the next nine weeks. Twenty-eight similar patients were treated with acetylsalicylic acid, fifty milligrams per pound daily for nine weeks. There was no evidence of a significant reduction in the incidence of residual rheumatic heart disease after comparing the two groups. The risk involved in giving large doses of steroids for twelve weeks was considered unwarranted.

Johnson and Ferencz\textsuperscript{27} (1953) studied one hundred eighty patients, one hundred treated with cortisone for twenty-one to twenty-eight days, and
## STEROID THERAPY IN ACUTE RHEUMATIC FEVER

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Number in study</th>
<th>Cardiac involvement defined</th>
<th>Control</th>
<th>Conclusion, Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenman et al. (1953)</td>
<td>48</td>
<td>yes</td>
<td>no</td>
<td>benefit seen</td>
</tr>
<tr>
<td>Johnson et al. (1953)</td>
<td>130</td>
<td>yes (graded)</td>
<td>yes</td>
<td>no benefit after three years</td>
</tr>
<tr>
<td>Markowitz et al. (1955)</td>
<td>40</td>
<td>carditis only</td>
<td>no</td>
<td>benefit seen</td>
</tr>
<tr>
<td>Dumb et al. (1955)</td>
<td>30</td>
<td>yes</td>
<td>yes</td>
<td>benefit after three years</td>
</tr>
<tr>
<td>Illingworth (1957)</td>
<td>200</td>
<td>yes-listed</td>
<td>yes</td>
<td>benefit after nine years</td>
</tr>
<tr>
<td>Wilson et al. (1959)</td>
<td>47</td>
<td>yes-carditis only</td>
<td>no</td>
<td>benefit seen</td>
</tr>
<tr>
<td>Combined Study Group (1960)</td>
<td>57</td>
<td>yes-carditis in all cases</td>
<td>yes</td>
<td>no benefit after three years</td>
</tr>
<tr>
<td>UK and US Joint Report (1960)</td>
<td>445</td>
<td>yes-graded to severity</td>
<td>yes</td>
<td>no benefit after five years</td>
</tr>
<tr>
<td>Dorfman et al. (1961)</td>
<td>131</td>
<td>yes-carditis</td>
<td>yes</td>
<td>benefit at end of one year</td>
</tr>
<tr>
<td>Massell et al. (1961)</td>
<td>583</td>
<td>yes</td>
<td>yes</td>
<td>benefit seen</td>
</tr>
<tr>
<td>Sywaters et al. (1962)</td>
<td>49</td>
<td>yes-graded to severity</td>
<td>yes</td>
<td>no benefit after five years</td>
</tr>
</tbody>
</table>

A comparison of various clinical trials using steroids in the treatment of acute rheumatic fever.
eighty treated before cortisone came into use. Their data indicates that no significant difference is present in the incidence of heart disease after the acute rheumatic fever attack in the cortisone and precortisone series. Bywaters and Thomas (1962) compare three groups of rheumatic fever patients. They were treated by bed rest alone, six weeks of AUTC, cortisone, or salicylates and twelve weeks of cortisone or salicylates respectively. No differences were noted between any of the treatment groups in the development or disappearance of significant murmurs during the hospital stay or at a five-year follow-up examination. They conclude that there is as yet no evidence that steroids are of value in reducing the severity of residual heart disease.

THE PREVENTION

The prevention of rheumatic fever has perhaps shown the most outstanding advances in actual proven benefits than any phase previously reviewed. Acute rheumatic fever is thought to be associated with a streptococcal infection. Today we have specific drugs that destroy or inhibit this organism. If they are used properly, many of the rheumatic heart disease patients could be eliminated and many more protected from further valvular damage by recurrent
rheumatic fever episodes.

The primary prevention of acute rheumatic fever has been dealt with earlier in this paper. Again, the diagnosis of streptococcal infections can be made clinically in many cases and an adequate dose of penicillin given. The American Heart Association recommends that treatment be started immediately when the streptococcal infection is first suspected. Effective blood levels of penicillin should be maintained for a period of ten days to insure adequate therapy. Intramuscular administration is recommended, however, the oral route may be used if full cooperation by the patient can be guaranteed. In known rheumatic heart disease patients, only the parenteral penicillin should be used and in maximum doses. The intramuscular penicillin dosage for children is six hundred thousand to nine hundred thousand units of benzathine penicillin G one time or three hundred thousand units of procaine penicillin with aluminum monostearate in oil every third day for three doses. The recommended adult dosage schedule is nine hundred thousand to one million two hundred thousand units of benzathine penicillin G one time or six hundred thousand units of procaine penicillin every three days for three doses. Oral penicillin must be taken
for ten full days even if symptoms disappear before this. The dosage for both children and adults is two hundred thousand to two hundred fifty thousand units three times a day for ten days. For individuals who are sensitive to penicillin other broad spectrum antibiotics, such as erythromycin and the tetracyclines, can be used. They are thought probably to be as effective as oral penicillin. Again, an adequate dose must be given for ten full days.

Morris5 and associates (1956) studied the effect of sulfadiazine on two hundred ninety-one patients hospitalized with exudative pharyngitis or tonsillitis. This therapy did not eradicate the streptococcus from the throats as determined by throat cultures and thus did not prevent rheumatic fever. Catanzaro's10 group studied five thousand one hundred ninety-eight airmen who received antibiotics or sulfadiazine for similar strep throats. It was found that the attack rate for rheumatic fever was not reduced appreciably in patients where the organism persisted in spite of therapy. Again, sulfadiazine had little effect on the carrier rate and appeared to prolong the latent period in cases developing rheumatic fever.

The main problem in the primary prevention of
rheumatic fever is the subclinical streptococcal infections which have minimal or no antecedent symptoms. This group of infections represents only a minority of the total cases as pointed out by Grossman and Stamler in their study of one hundred ten cases of rheumatic fever. They estimated that about eighty-four per cent of their cases of rheumatic fever could have been prevented if the correct diagnosis were made by the physician and subsequent adequate therapy given. They feel that better education is necessary in order to bring the child with a streptococcal infection into the physician for adequate penicillin therapy.

Secondary prevention of rheumatic fever refers to diagnosed rheumatic fever individuals. As noted earlier, the rheumatic subject is much more prone to develop acute rheumatic fever after a streptococcal infection than the non-rheumatic subject. It is for this reason that the American Heart Association recommends prophylaxis for all patients who have well documented histories of rheumatic fever or chorea or who show definite evidence of rheumatic heart disease. Exceptions may be made in adults without heart disease who have had no rheumatic attacks for many years, however, this rule must be
applied to the individual and the proper steps taken. Prophylaxis should be started as soon as the diagnosis of rheumatic fever is made, and continued indefinitely. The Heart Association recommends benzathine penicillin G intramuscularly in a dosage of one million two hundred thousand units once a month as first choice in the long range prophylaxis of rheumatic fever. Second choice is oral sulfadiazine, five tenths to one gram once a day. Oral penicillin in dosages of two hundred thousand to two hundred fifty thousand units once or twice a day is also recommended, the latter dosage probably being the more effective. Feinstein and DiKassa (1959) did a controlled study comparing the above three techniques. The incidence of streptococcal infections was determined by laboratory studies of the antistreptolysin O titer, antistreptokinase, and antihyaluronidase. In the benzathine penicillin group, a seven and three tenths per cent incidence of streptococcal infections was found. In the sulfadiazine and oral penicillin groups a twenty-one and one tenth per cent and twenty and seven tenths per cent incidence was found respectively. The problem of missed oral dosages was considered and evaluated by interview and counting the returned pills. When
only those patients with good records of dependability were used, intramuscular penicillin was found to be better still in preventing streptococcal infections than the other two methods. The recurrence rate of rheumatic fever per patient year was three tenths per cent, one and nine tenths per cent, and five per cent in the intramuscular penicillin, sulfadiazine and oral penicillin groups respectively. Wood71,72 did a similar study in 1953 using four hundred seven rheumatic fever subjects. His results were similar, showing the intramuscular penicillin group fared better in respect to streptococcal infections and rheumatic fever recurrences than the oral penicillin or sulfadiazine groups. The sulfadiazine treated group fared a little better than the penicillin treated group.

Other groups of investigators studied the possibility of intermittent penicillin administration. Kohn40 and co-workers treated forty rheumatic patients with one hundred thousand unit tablets of penicillin four times daily for seven days, once a month. They compared this group to others receiving no medications. There was a significant reduction in the number of recurrences during the three year study. Lim and Wilson42 in 1960, gave one hundred three
rheumatic patients adequate penicillin therapy at
the onset of respiratory illnesses. They compared
this group to one hundred ten similar patients
receiving continuous oral penicillin prophylaxis.
They found no significant difference in the recurrence
rate of active carditis between the two groups when
the interval from the last attack was considered.
They saw no advantage of continuous oral penicillin
prophylaxis over adequate penicillin therapy when
indicated provided the patient could be placed under
close medical supervision.

Markowitz and Hemphill44 point out an eleven
per cent incidence of toxic reactions seen in a
group of sixty-four children receiving a sulfonamide
preparation as compared to a two and five tenths
per cent incidence of similar side effects seen
in eighty-two patients receiving a two hundred
thousand unit tablet of benzathine penicillin G
daily. They found no difference in relation to
rheumatic fever recurrences, but favored the peni-
cillin because of the lower incidence of toxic side
reactions. The chief toxic reactions of the sul-
onamides are skin eruptions and leukopenia. If a
morbiliform rash is seen while using a sulfa
preparation, the drug can be continued if caution
is used. If urticaria or a scarlatiniform rash is seen associated with a sore throat or fever, the drug should be discontinued. A leukopenia below four thousand and polymuclear neutrophile count of below thirty-five per cent requires discontinuence of medications because of the possibility of agranulocytosis. For this reason a weekly white count is recommended by the American Heart Association for the first two months of therapy. The toxic reactions seen with penicillin are urticaria, angio-neurotic edema, and reactions similar to serum sickness. Once these reactions are seen, the drug should be discontinued and an appropriate substitute started immediately.

DISCUSSION

In reviewing the literature covering the diagnosis, treatment, and prophylaxis of acute rheumatic fever, much was gained in understanding the approach toward a patient showing symptoms of acute rheumatic fever. The importance of following Jones criteria was emphasized. The criteria have been modified by Jones and others associated with the American Heart Association as new concepts evolved. It should be pointed out that fulfillment of the criteria does not necessarily prove a diagnosis of rheumatic
fever, but aids the physician in making a final decision. Every factor must be taken into consideration and reviewed by the physician who must be aware of the great number of ways rheumatic fever may present. Every effort should be made to make the diagnosis before starting therapy because of the many dangerous drugs used today in treating this disease. A diagnosis of rheumatic fever will remain with the individual the rest of his life causing problems not only through the question of continuous prophylaxis, but also through job opportunities and insurance buying.

Acute rheumatic fever is usually preceded by a group A beta-hemolytic streptococcal infection; The recognition of this infection as pharyngitis and/or tonsillitis, with swift adequate penicillin therapy, would aid greatly in reducing the over-all incidence of rheumatic heart disease. Because the streptococcal infection may manifest with completely atypical symptoms, the diagnostic throat culture should be made available to out state physicians, which would again help reduce rheumatic fever occurrences. An upper respiratory infection due to streptococcal organisms is best treated with either six hundred thousand to one million two hundred
thousand units of benzathine penicillin G one time
or oral penicillin, two hundred fifty thousand units
four times daily for ten days.

The treatment of rheumatic fever is perhaps
the most controversial phase of this complicated
disease. Bed rest, penicillin, and salicylates are
accepted by most authorities as useful in the acute
attack. The amount or quantity to be used during
an acute episode has received much attention. Some
use minimal amounts while others use large quantities.
Steroids have been used experimentally for more than
ten years. Definite beneficial results were achieved
by some only to be refuted by others, because of
gross defects in certain phases of their clinical
trials. Various other authors corrected these de-
fects and still derived benefit from the cortico-
steroid. Other large studies have been undertaken
using many physicians in different geographical
areas. They demonstrate no significant benefit in
reducing the incidence of subsequent cardiac damage.

The following is a program of treatment which
I believe to be acceptable in the treatment of acute
rheumatic fever. A patient so diagnosed should be
placed at bed rest while the disease is active.
Ambulation can begin when the patient is asymptomatic.
and there is no evidence of progression of the cardiac manifestations as determined by laboratory and clinical data. A gradual return to full activities is then indicated for most cases, however, this must be suited to the individual's capacities. A suitable nutritious diet should be ordered and good nursing care received.

It should be assured that group A beta-hemolytic streptococci are present in the patient's throat, even if all cultures are negative, and suitable penicillin therapy undertaken as outlined above. At the conclusion of the ten days of treatment, continuous prophylaxis should be started and maintained indefinitely.

Complications of this acute phase of the illness, such as congestive heart failure or atrial fibrillation, should be treated as necessary. Other less common complications such as pneumonitis, acute nephritis, erythema nodosum, and chorea are usually self limited and treated symptomatically.

In patients which show no evidence of carditis, aspirin is the drug of choice. Relief of extra-cardiac symptoms is usually achieved within twenty-four hours. A dose reaching subtoxic levels should be used in order to achieve maximum benefit. A
dosage of forty milligrams per pound in four divided
doses will usually accomplish this. Another method
requires administering six tenths grams of aspirin
every hour until tinnitus, nausea, or vomiting is
noted. Subtract one gram from the total amount
used and give this in four divided doses daily,
beginning twelve hours after toxic symptoms clear.
This dosage should be continued for ten weeks.
The amount is then gradually decreased over an ad-
ditional two weeks. This process protects against
rebound phenomena to some extent.

Patients with mild carditis, meaning systolic
apical murmurs less than grade three of six, or
diastolic aortic murmurs less than grade two of
six, can receive either aspirin or steroids. The
final decision must depend on a thorough evaluation
of the individual's total disease. A majority of
these murmurs are lost without therapy. The ad-
vantages must be weighed against the risk of unde-
sirable effects which are seen with steroid therapy.

Where moderate to severe carditis is present,
one of the corticosteroids is the drug of choice.
Prednisone, sixty milligrams daily or dexamethasone,
six milligrams daily should be given in divided doses
and continued for three weeks. This is followed by
a stepwise reduction in dosage over the next nine weeks. If symptoms return, the preceding dosage level should be given and maintained for several days before starting the reduced dosages again.

The benefits of secondary prevention of acute rheumatic fever have been proven by many investigators. If adequate amounts of penicillin are taken continuously by the individual, he can expect practically no subsequent acute attacks. Resistance to penicillin by streptococcal organisms has not been found away from the hospital. Benzathine penicillin G, given intramuscular in a dosage of one million two hundred thousand units once a month is probably the best treatment procedure available. If the oral route is desired, sulfadiazine, five tenths to one gram once a day can be given. This is an effective, safe, and fairly inexpensive drug. Oral penicillin, two hundred thousand to two hundred fifty thousand units once or twice a day can be given and is practically equal in effectiveness. This drug produces fewer toxic reactions and is tolerated well by the cooperative child.

SUMMARY AND CONCLUSION

The recent literature covering the diagnosis, treatment, and prophylaxis of acute rheumatic fever
revised.

A fairly accurate diagnosis of acute rheumatic fever can be made in most cases if the modified Jones criteria is followed.

The treatment of acute rheumatic fever has received much controversial coverage.

Bed rest, salicylates, and penicillin are usually accepted as drugs of choice for this disease.

Steroids are thought to be indicated by many authors and contraindicated by others.

Primary prevention of acute rheumatic fever requires prompt and adequate treatment of all streptococcal infections.

Secondary prevention entails continuous penicillin or sulfadiazine therapy for the duration of the patient's life.
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