*Kaiser Permanente Medicine 50 Years Ago:*

# Acute Rheumatic Fever in Adults

By Alvin L Sellers, MD;
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Commentary by
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***... acute rheumatic fever ... in its acute phase or in its eventual, chronic manifestation as valvular heart disease was once responsible for filling 10% of all hospital beds.***

In the 22-month period from March 1943, to January 1945, twenty patients with acute rheumatic fever have been studied and treated at the Permanente Foundation Hospital. All cases occurred among workers in the Richmond shipyards. The diagnostic criteria used were those set forth recently by Jones.[1] The major criteria for diagnosis were: 1) Active carditis, as evidenced by the development of electrocardiographic changes, cardiac enlargement, significant cardiac murmurs (grade two or louder systolic murmurs, all diastolic murmurs), congestive heart failure, or pericarditis. 2) Arthralgia. 3) Chorea. 4) Subcutaneous nodules, and 5) Recurrence of rheumatic fever. The minor manifestations include: 1) Fever. 2) Abdominal pain. 3) Precordial pain. 4) Rash. 5) Epistaxis. 6) Pulmonary findings. 7) Laboratory findings of leucocytosis, elevated erythrocyte sedimentation rate, and microcytic anemia. The minimum requirement for inclusion in this study was the presence of one major manifestation with at least two of the minor manifestations.

The age of our patients ranged from 17 to 39 years, the average age being 28.3 years. This average age is somewhat higher than those reported by Master[2] and Coburn[3] and is probably due to the more advanced average age of the population served by this hospital as compared with Navy personnel. There were 16 males and four females. This is approximately the same as the ratio of males to females in the employed population served by this hospital.

Sixteen of the patients spent the greater part of their lives in rural mid-western or southern communities. The remaining four patients were natives of California. The length of stay in the Bay area prior to the onset of rheumatic fever in the former group ranged from six months to 24 months, the average being twelve months. It is of interest that of the 16 out-of-state patients that developed acute rheumatic fever, none came from large urban centers. These facts will be alluded to later in considering the possible etiologic importance of streptococcus infection in rheumatic fever.

Eleven patients (55%) entered the hospital with a history suggestive of previous rheumatic fever in childhood or established cardiac murmurs, or both. Two of these patients had no murmurs but gave histories of migratory polyarthritis, repeated bouts of epistaxis, or previous diagnosis of "leaky heart." Three of these patients had significant established cardiac murmurs but no history suggestive of childhood rheumatic fever. Six of the patients had both significant

## Commentary

*by W Jeffrey Fessel MD, FACP, FRCP*

The accompanying report by Sellers and Levine in the 1945 *Permanente Foundation Medical Bulletin* makes for fascinating reading more than a half century after its initial publication, because we may compare what was known then with today's understanding of the disease. Also of interest is that acute rheumatic fever is a disease no longer seen in the developed countries of the Western world. Although Sellers and Levine saw approximately one new case of rheumatic fever per month, I doubt whether any reader who graduated from medical school in the past 40 years has ever seen a patient with acute rheumatic fever—yet the disease in its acute phase or in its eventual, chronic manifestation as valvular heart disease was once responsible for filling 10% of all hospital beds.

Today, as I read the reprinted article by these two researchers, I am reminded of the year 1955, when I was an intern in a hospital in England. The 45-bed medical ward for which I was responsible would have contained, at any one time, a half dozen patients with congestive heart failure caused by chronic rheumatic valvular (mostly tight mitral stenosis) heart disease. The only diuretic available at that time was a mercurial agent, which was given intravenously two or three times weekly; after a while, the patient became resistant to mercurial agents, and we had to use Southey's tubes—silver tubes of approximately 18-gauge diameter with perforations along the shaft. Four of these tubes would be inserted along the length of each edematous leg; thin latex rubber tubes were attached to the needles, and these tubes conducted the drained edema fluid to a garden bucket. That procedure could drain a gallon of edema at a time and was repeated two or three times weekly as needed.

I arrived in the United States in 1957—just in time for the prerelease of chlorothiazide, which revolutionized the treatment of congestive heart failure. Because we were given stern warnings about the dangers of overly rapid depletion of potassium, we drew blood daily to analyze electrolyte levels! The first mitral valvulotomy—considered a medical miracle—was performed in the late 1950s and resulted in deeper understanding of the pulmonary vascular changes that underlie the pulmonic hypertension seen in chronic mitral stenosis. After mitral valvulotomy became an established procedure (but before the use of valve replacement), fewer patients suffered end-stage pulmonary hypertension and right-sided heart failure from tight mitral stenosis.

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murmurs and a suggestive history of previous childhood rheumatic fever.

Nine of our 20 patients (45%) had neither a history of rheumatic fever nor significant cardiac murmurs and might, therefore, represent new cases of acute rheumatic fever. It is understood that the absence of a significant past history of rheumatic fever does not mean that attacks of childhood rheumatic fever did not occur. This question has recently been discussed by Master.[2] Cohn and Lingg[4] in a study of 3125 patients with rheumatic cardiac disease followed from onset to death, state that 70 percent of patients have acquired the disease before the age of fifteen. Sixty-six percent of their patients with rheumatic cardiac disease had no recollection of previous attacks of rheumatic fever. Direct transference of these statistics and inferences drawn from them to our experience is hazardous as it appears that they were dealing with a stable population while we treated a dislocated group. It may well be that a larger number of our cases than ordinarily expected actually represent new infections.

Eleven patients (55%) were found to have had either a severe sore throat or "tonsillitis" from one to four weeks prior to the onset of symptoms of rheumatic fever. Two additional patients gave histories of upper respiratory infections two weeks prior to the onset of symptoms. Hence 13 patients (65%) gave histories of disease of the upper respiratory tract one to four weeks prior to the onset of rheumatic fever symptoms. The etiologic agents in these infections were not identified. Coburn[5] has emphasized the importance of streptococcus infections in the etiology of rheumatic fever. Indeed, he states that sensitization to antigens produced by the alpha streptococcus is the underlying factor in acute rheumatic fever. He has observed that people who come from environments poor in streptococci to congested areas rich in these organisms are very susceptible to infection. Our data lend support to this observation for, as we have seen above, 80 percent of our patients have been dislocated from rural communities to the congested environment of the Richmond-San Francisco Bay area. Coburn[3] has stated that sulfonamide administration is of no value in the prophylaxis of acute rheumatic fever once the upper respiratory infection has become established and may even precipitate acute rheumatic fever in patients that might not otherwise have suffered from the disease. Four of our patients had been given sulfonamides during their precipitating upper respiratory infection. Two of these patients had a past history of childhood rheumatic fever. In view of its inefficacy and possible danger, it would appear advisable to withhold sulfonamide therapy in upper respiratory infections, particularly in persons with a past history suggestive of rheumatic fever.

Migratory polyarthritis was an outstanding complaint in seventeen cases. All of these patients showed involvement of one or more of the major weight-bearing joints. The small joints of the hands or feet were involved in only five cases. The joints were typically involved in migratory fashion and were in most instances painful, hot and swollen. Joint symptoms subsided, as a rule, within one week after the initiation of salicylate therapy and bed rest.

Of the eleven patients who entered the hospital without cardiac murmurs, six developed significant murmurs while under observation. Five of the nine patients who entered the hospital with significant murmurs developed changes in the intensity of their murmurs or new murmurs. Thus eleven (55%) of the patients developed significant new murmurs or showed an increase in the intensity of already present murmurs while under observation.

Apical systolic murmurs were heard most commonly but aortic systolic and diastolic murmurs and mitral diastolic murmurs occurred frequently. In only two cases did murmurs disappear once they had become of significant intensity.

Sinus tachycardia occurred in 50 percent of cases and in all instances the heart rate became normal during the hospital stay.

Erythema nodosum was present on entry in two patients. It did not develop in any patient during the period of hospitalization.

Seventeen patients had temperatures over 100˚F on entry. In all cases the temperature fell to normal within one week after beginning salicylate therapy and bed rest.

Chorea, as a manifestation of rheumatic fever, is rarely seen after adolescence. Levine[6] has stated that chorea is never seen in adults over 20 years of age except in association with pregnancy. We have observed one case in our series, that of a 19-year-old female who gave no history of previous occurrence of chorea or rheumatic fever but had a grade three apical systolic murmur on entry. This young woman had one child three years old. She gave no history of prior or subsequent pregnancies.

Subcutaneous nodules were not present in any of our cases.

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Roentgenograms of the chest were taken in 17 of the 20 patients and cardiac enlargement was revealed in four. Two of these patients gave past histories of childhood rheumatic fever. None of the four patients had significant cardiac murmurs. Repeated roentgenograms taken on these four patients revealed no change in the size of the heart during hospitalization.

Electrocardiographic abnormalities, other than sinus tachycardia were presented by 13 patients (65%). These included: extreme wandering of the pacemaker (two cases), A-V nodal rhythm (one case), auricular fibrillation (one case), multiple ventricular premature beats (two cases), incomplete A-V block (eight cases), incomplete A-V block with dropped beats (two cases), Wendckebach type (one case), complete A-V block (two cases), abnormally elevated ST segments (one case), and T wave changes (two cases). Auriculoventricular block of varying degree is clearly the most common electrocardiographic abnormality. The electrocardiograms in ten of the 13 patients showing the above abnormalities returned to normal during the hospital stay. Since the electrocardiographic changes are often transient, tracings must be made at frequent intervals, and it has been our practice to repeat electrocardiograms at least once a week during hospitalization.

Wendkos and Noll[7] have recently reviewed the electrocardiographic changes in 100 patients with polyarticular rheumatism and point out the value of finding electrocardiographic changes in making the differential diagnosis between rheumatoid arthritis and acute rheumatic fever. Their finding of electrocardiographic changes in 70 percent of patients with acute rheumatic fever agrees well with our experience.

The erythrocyte sedimentation rate is the most valuable single laboratory aid in judging the activity of the rheumatic process. Coburn and Kapp[8] use the sedimentation rate as a measure of the extent of inflammation in acute rheumatic fever. Every one of our twenty patients showed an elevated sedimentation on entry. The range varied from 14 millimeters to 128 millimeters per hour (Westergren method).

A white blood cell count of between 10,000 and 20,000 per cubic millimeter was found in 19 of the 20 patients. The leucocyte count returned to normal in all cases during the hospital stay.

## Treatment

The treatment of acute rheumatic fever in this hospital follows the principles outlined by Coburn.[3] Patients are put at absolute bed rest as soon as the diagnosis is made. Sodium salicylate in enteric coated tablets is given in dosage of 1.7 grams every four hours, day and night. The erythrocyte sedimentation rate and white blood cell count are determined weekly and the sodium salicylate is administered until the sedimentation rate has been normal for one week. Salicylates are then discontinued. At the end of one week without sodium salicylate the sedimentation rate is again checked and if found to be normal the patient is allowed to sit in a chair at his bedside for 15 minutes two times daily. If after one week the sedimentation rate has become abnormally rapid the patient is returned to strict bed rest and the initial treatment is resumed. If the sedimentation rate is normal after one week of sitting at the bedside, the patient is allowed bathroom privileges. If after one week of bathroom privileges the sedimentation rate remains normal, the patient's activities are increased and he is shortly released from the hospital to continue his convalescence at home. If at any time signs of active rheumatic fever return, strict bed rest and sodium salicylate therapy are reinstituted.

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High caloric, high vitamin diets are provided and supplemental vitamins are added, including 100 milligrams of ascorbic acid daily.[9]

Methyl salicylate ointment, cotton batting, splints, heat and physiotherapy are used for symptomatic treatment of joint pains and stiffness.

It is felt that some sort of occupational therapy involving minimal activity is of great value to the patient's morale during this usually protracted hospital stay.

Sodium bicarbonate was used in treatment of some of the earlier cases, but is no longer given due to its property of lowering the serum salicylate level.[10]

Hypoprothrombinemia due to salicylate therapy has been reported by Shapiro.[11] We routinely check prothrombin blood levels and have not found significant depression of the prothrombin concentration in any of our patients. Solley[12] has observed that the prothrombin levels in the blood frequently dropped after the first few days of salicylate therapy and then slowly returned to normal without the aid of vitamin K preparations and with continued salicylate administration.

Patients under treatment with ten grams of sodium salicylate daily complain of tinnitus, decreased auditory acuity, dizziness, headache, nausea, and occasionally vomiting. These symptoms are ordinarily not very troublesome and disappear with the cessation of salicylate therapy. We have not had to discontinue salicylate treatment for any of the above complaints.

## Discussion

Rheumatic fever as we have observed it in adults differs in none of its essentials from the classical rheumatic fever of childhood. The age of the patient suspected of having this disease is not of great importance when characteristic or suspicious signs and symptoms are present. The greater frequency of rheumatoid arthritis among adults, and the general feeling that acute rheumatic fever is a disease of children will lead to error and missed diagnoses unless a high index of suspicion is maintained.

The literature prior to 1941 dealt primarily with the problems of childhood rheumatic fever. However, with the mobilization of large numbers of men into the armed forces, numerous reports appeared describing outbreaks of acute rheumatic fever among army and navy personnel. Our study of rheumatic fever was stimulated in large part by these later reports, and it was found that the average age of our patients was even higher than those reported from the navy. This experience emphasizes the fact that acute rheumatic fever occurs commonly during the third and fourth decades.

As has been already pointed out, an attack during this period of life may well be the patient's initial episode. A history of previous rheumatic fever is not essential to this diagnosis in adult patients.

It is thought that patients who have their initial attack of rheumatic fever after the age of 20 suffer less permanent heart damage than those who acquire their disease in childhood. We have not followed our patients long enough at the present time to be able to confirm or deny this statement. The electrocardiographic changes are typically transient. Cardiac murmurs, once they become of significant intensity, tend to remain. On the other hand, we have observed the complete disappearance of a mitral diastolic murmur which was doubtless that of relative mitral stenosis due to dilatation of the left ventricle. In another patient the Graham Steele murmur of relative pulmonic insufficiency disappeared completely.

The treatment of acute rheumatic fever is still far from satisfactory. We feel that sodium salicylate should be used as outlined above, and together with bed rest is the best treatment available at the present time. There are many patients who require two to three months of this regime to secure a satisfactory result, and there are a few who do not respond at all to intensive salicylate therapy. As Solley[12] has pointed out, it may be that the changes which occur in the endothelium of the arterioles are irreversible in these patients before treatment is initiated and that this limits or prevents any therapeutic effect.

## Summary and Conclusions

1. Twenty cases of acute rheumatic fever have been observed in adults during a twenty-two month period.
2. Acute rheumatic fever in adults does not differ in its clinical manifestation from acute rheumatic fever of childhood.
3. Nine of our patients had neither history nor signs indicative of previous attacks of rheumatic fever and might, therefore, represent new cases.
4. The therapeutic program followed at this hospital has been presented. ❖

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***Commentary*** *(continued from page 30)*

If all this seems strange from today's perspective, it is yet stranger that in those days, the medical wards were replete with patients having the consequences of severe hypertension (also virtually never seen today), for which the mainstays of treatment were *Rauwolffia* alkaloids and a diet of only rice and honey (to provide calories and no sodium)!

That Sellers and Levine saw fit to expound upon probable streptococcal involvement in the etiology of rheumatic fever—a fact today taken for granted—is interesting. I am reminded, however, that not until the mid-1950s was the streptococcal etiology of rheumatic (Sydenham's) chorea established by long-term follow-up studies that related streptococcal sore throats with the delayed onset of chorea—a delay as much as several months long. How many physicians today have ever seen a patient with rheumatic chorea? Even in those days, it was said that before the diagnosis of chorea was made, children with this condition were scolded for being fidgety. Aside from the rare Huntington's disease, chorea today is mainly a manifestation of systemic lupus erythematosus (SLE). In fact, SLE used to be exceptionally rare—I saw one case in my entire medical school experience, whereas rheumatic fever was common; today, the prevalence of these two diseases is reversed, with SLE affecting 1 in 250 black women and 1 in 1000 white women.

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At one time, *Streptococcus* was held responsible for many diseases of uncertain cause. In fact, the belief that *Streptococcus* causes rheumatoid arthritis led to development of the serologic tests now used to detect rheumatoid factor: these current serologic tests were originally developed as streptococcal agglutinin reactions. Of interest also is that rheumatoid arthritis was so named after becoming differentiated from the polyarthritis of rheumatic fever. However, so as not to make a complete nosologic break from rheumatic fever, rheumatoid arthritis was labeled "rheumatic fever-like," ie, rheumatoid. A curious fact about rheumatic fever is that it rarely affects children younger than four years of age, possibly because of either immaturity of the immune mechanisms or, more likely, lack of exposure to rheumatogenic strains of *Streptococcus*. Recognition of this pattern showed that, generally, children under age four years who had arthritis had juvenile rheumatoid arthritis and not rheumatic fever.

Sellers and Levine cite findings that assign no value to sulfonamide administration in prophylaxis of acute rheumatic fever after the upper respiratory infection becomes established. We now understand the reason for this lack of effect: the antigenic stimulus has already triggered the disease. Besides, sulfonamides are less effective antistreptococcal agents than is penicillin. Sulfonamides were introduced into medicine in 1936; in 1945, penicillin would have been available only to the armed forces and only in doses of a few thousand units. My aunt was a pathologist in those days and recalls recovering penicillin from urine so that it might be reused in other patients!

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Apical systolic murmurs were heard commonly in the series of patients described by Sellers and Levine. Not until the advent of sonocardiography did the pansystolic murmur become recognized as the physical sign of mitral regurgitation; and not until the mid-1950s was the late apical systolic murmur recognized—after prolonged follow-up studies—as the precursor of mitral regurgitation. Until then, the late apical systolic murmur was regarded as benign. Also worth remembering is that Barlow did not describe mitral valve prolapse as the click-murmur syndrome until the mid-1960s; undoubtedly, many children with mitral valve prolapse who happened to have minor joint pains or tonsillitis were misdiagnosed as having rheumatic fever.

Misdiagnosing acute rheumatic fever with carditis had serious consequences. As is emphasized in the article by Sellers and Levine, absolute bedrest was important for preventing major cardiac damage and meant use of bedpans and spoon feeding for the first week; thereafter, the regimen was gradually relaxed until normal activities were allowed—usually six weeks later. Patients were allowed to sit out of bed for 15 minutes twice daily only after the erythrocyte sedimentation rate (ESR) had been normal for one week—an event which might not happen for three or four weeks. If the ESR again became fast, the patient was returned to absolute bed rest. (One of my tasks as a house officer on the rheumatic fever wards was to draw blood from each of the 15 or 20 patients once weekly and to set up the ESR in Westergren tubes. We did this by mouth-pipetting; hepatitis viruses and HIV were unknown.) Absolute bedrest was the prescribed regimen not only for the carditis of rheumatic fever

but also for acute myocardial infarction with the result that as many patients died from pulmonary embolism as from the myocardial infarction. An interesting observation—one which has never been adequately explained—is that pulmonary embolism was rare in the children with acute rheumatic carditis and also in patients treated with bed rest for active pulmonary tuberculosis. A revolutionary announcement came about 25 years ago: Patients who have had heart attacks can safely be discharged from the hospital after three weeks. Equally revolutionary was the subsequent announcement that these patients may leave the hospital after only seven days; and discharge after only two days is now proposed for some patients with myocardial infarct. We may imagine the outrage that such suggestions might have provoked in earlier years! Some children with rheumatic carditis were in the hospital for six months because the ESR might not yet have become normal. Sellers and Levine indicate that "some sort of occupational therapy involving minimal activity is of great value to the patient's morale during this usually protracted hospital stay." The occupational therapist taught basket weaving, sewing, and simple activities that helped pass the time; much later, the occupational therapist's focus shifted to physical therapy for the upper limbs.

The statement of Sellers and Levine that "rheumatic fever as we have observed it in adults differs in none of its essentials from the classical rheumatic fever of childhood" would not have been made ten years after these authors' article appeared. In fact, although the cardiac manifestation in adults is usually slight, effects on joints are much more severe and long-lasting. Indeed, as is said proverbially, rheumatic fever in children "licks the joints and bites the heart," whereas in adults it "licks the heart and bites the joints."

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For this issue of *The Permanente Journal*, I was asked to provide both a Commentary on the paper by Sellers and Levine and an update on the subject of rheumatic fever. I have given a personal perspective with some reminiscences that might interest younger physicians; however, little update is available, because the disease is now virtually unseen in the United States. (Rheumatic fever is still seen in Latin America.) We understand the immunologic basis of the carditis, which results from cross-antigenicity between epitopes in the streptococcal cell wall and cardiac myocytes. We also understand why rheumatic fever was rarely accompanied by poststreptococcal nephritis: The nephritogenic strain of *Streptococcus* has cross-antigenicity with glomerular epitopes but not with epitopes in the cardiac myocyte; and the *Streptococcus* responsible for rheumatic fever has cross-antigenicity with epitopes on cardiac myocytes but not with glomerular epitopes. Treatment today would differ substantially from that offered in 1945, when the mainstays of treatment were strict bed rest for carditis and use of salicylates for inflammation. Although an international study done in the 1950s showed no benefit of cortisone over salicylate treatment, the dosages of cortisone used (ie, 60 mg daily, tapered over six weeks) would today be regarded as inadequate, and carditis would be treated with high dosages (60 to 120 mg daily) of prednisone. Death from acute rheumatic pancarditis (endocarditis with valvulitis plus myocarditis plus pericarditis) should be rare, and chronic valve disease should be less likely to occur. Fortunately, today's rarity of rheumatic carditis means that we will not have the opportunity to conduct a clinical trial of TNF-$\alpha$ antagonists in patients with rheumatic carditis, although I suspect this treatment might be beneficial because part of the myocardial damage could be mediated by cytokines. Rheumatic chorea is certainly mediated by cytokines, because no neuropathologic changes are associated with Sydenham's chorea.

In conclusion, rereading Sellers and Levine's article reminds us of a scourge that is, fortunately, no longer with us, at least in the developed world. Their work also allows us to reflect on the undreamed-of advances made since those days toward our understanding of both disease pathogenesis and therapeutics. ❖

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