Rheumatic Fever: Natural History and Treatment*

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Major advances in clinical and laboratory research methods have significantly clarified the identification and natural course of rheumatic fever in the past two decades. The advances in methodology include the following:

Diagnostic Purity of Population

The label of *rheumatic fever* is now given to a population of patients more distinct and diagnostically "pure" than ever before. The Jones criteria, described in 1944 and modified in 1956 (American Heart Association, 1956), circumscribe the diagnostic boundaries of the disease, and exclude many minor illnesses that formerly were designated inappropriately as rheumatic fever. Other major illnesses that once successfully masqueraded as rheumatic fever, because they fulfilled the Jones criteria, can now be unmasked and properly identified by specific laboratory tests (such as those used for lupus erythematosus, rheumatoid arthritis, and sickle cell anemia) and by cardiac catheterization (for congenital heart disease). These diagnostic purifications improve the homogeneity and reproducibility of a population of patients with rheumatic fever, thus improving the reliability of conclusions drawn from observations of the population.

Spectrum of Post-streptococcal Inflammation

The frequent sequential testing of multiple streptococcal antibodies (a laboratory technique developed mainly in the past two decades) has demonstrated not only that acute rheumatic fever is constantly associated with Group A streptococcal infection, but also that rheumatic fever is merely an arbitrarily defined collection of events in the complex clinical spectrum of inflammation which can follow streptococcal infection. Within this spectrum, the main events used to identify rheumatic fever are arthritis, chorea, or carditis—occurring alone, in various combinations, or concomitantly with other clinical features. Because so many different combinations of events can receive a diagnosis of rheumatic fever, the clinical manifestations of the disease demonstrate many apparently disparate patterns. The differences in these clinical patterns (Massell, Fyler, and Roy, 1958; Feinstein and Spagnuolo, 1962) were responsible for much of the past confusion in assessing etiology, pathogenesis, and prognosis. Some of the unclear issues recently resolved are noted below:

Isolated Chorea

The latent interval after a streptococcal infection is usually much longer for Sydenham's chorea than for other "rheumatic" manifestations. Chorea may therefore often appear as, or after, other types of clinical rheumatic inflammation subside. Or it may occur alone, i.e., as "pure" chorea, long after the streptococcal antibody titers have receded to a level too low to permit detection of the antecedent infection.

Asymptomatic Carditis

Carditis, another type of inflammation that can occur in the post-streptococcal spectrum, is ordinarily asymptomatic if unaccompanied by significant fever or by congestive heart failure. When carditis occurs alone without symptoms created by arthritis, chorea, fever, or cardiac complications, the carditis will not be examined while it is acute because the patient will not seek medical attention; carditis can thus produce its valvular scars silently. When the scars are discovered many years later, rheumatic heart disease is said to have occurred without a "history of rheumatic fever." This type of rheumatic heart disease is undetected clinically and develops insidiously only because the patient is not examined during the acute phase of the carditis. Had the patient been symptomatic enough to seek medical attention, the signs of carditis could have been found. The failure of clinicians to find such patients early is thus a fault neither of clinicians nor patients; it is attributable to the natural behavior of the disease. When post-streptococcal inflammation produces acute carditis asymptomatically, it is clinically unexamined and hence undetected.

Severity of Symptoms and Promptness of Therapy

Although pathologists, from examination of tissue, have long known that rheumatic fever "licks at the joints and bites at the heart," the *clinical* validity of this maxim, and of its converse has only recently been demonstrated (Feinstein and Spagnuolo, 1962). The patterns of clinical behavior in rheumatic fever show that patients with severe arthritis are quite commonly free of carditis, and those with carditis severe enough to produce congestive heart failure often have no joint symptoms. This inverse relationship between the clinical severity of arthritis and carditis is a feature of natural history that creates a thera-

peutic paradox in the disease. The main reason that residual rheumatic heart disease occurs less often in patients treated soon after onset of symptoms than it does in those treated late is that most patients who seek treatment early usually do so because of arthritis. They have little or no carditis to begin with. Conversely, the late-treatment group consists predominantly of patients whose solitary carditis took a long time to produce symptoms severe enough to make the patients seek medical aid. In such patients, the cardiac damage when first found is usually too great for cure by anti-inflammatory therapy (Feinstein, Stern, and Spagnuolo, 1964b). The natural behavior of the illness, rather than the treatment, is thus responsible for many of the successes in which no heart disease is found after early therapy.

Clinical Identification of Carditis

The assessment of the noises and shadows used as evidence of carditis has markedly improved in the past two decades by recognition and removal of several older diagnostic impediments:

Reliability of the Examiner

The reliability of the clinical examiner who observes and appraises the audio-visual evidence of cardiac status has been greatly improved by use of objective, "blind," examining techniques, multiple examiners, precise descriptions, and rigorous criteria for interpretation. These improvements in the scientific performance of the clinician have been aided, and sometimes evoked, by modern methods of roentgenography and phonocardiography. As a result of these clinical and technical improvements, better methods and criteria (Feinstein et al., 1964a and c) have evolved for avoiding two types of observational error (described in the next section) that formerly created confusion in identifying the status of patients, evaluating the results of therapy, and understanding the pathogenesis of rheumatic valvular disease.

Observational Errors and their Consequences

Errors can be expected during clinical examination of the heart. Errors of commission, in which physiologic phenomena are mistakenly regarded as pathologic, often arise in making the diagnostic distinctions between: physiologic systolic murmurs loudly audible at the apex and those of mitral regurgitation; long physiologic third heart sounds and diastolic murmurs; split first sounds and presystolic murmurs; artifactual curvature of the barium esophagram and left atrial enlargement; physiologic variations in the roentgenographic cardiac silhouette and those due to cardiomegaly. As a result of such errors of commission made during an acute rheumatic attack, "carditis" initially would be diagnosed falsely and its "cure"—when the true physiologic state was eventually recognized—would later be attributed inappropriately to therapy. At a subsequent examination of a patient previously (and correctly) deemed free of carditis during the acute attack, such errors would lead to the spurious belief that rheumatic heart disease had developed insidiously.

An error of omission occurs when a pathologic phenomenon is undetected, or mistakenly regarded as physiologic. Such errors commonly arise from failure to recognize an aortic diastolic or apical presystolic murmur when it is present, particularly in situations where suspicion of the murmur is not aroused by concomitant hemodynamic or roentgenographic abnormalities. If the abnormal murmur persisted and eventually were identified correctly, rheumatic heart disease would be said to have developed insidiously in a patient believed to be free of it.

The improved modern auscultatory procedures described earlier have reduced the incidence of both types of error, and accordingly, have reduced the number of patients considered to have developed rheumatic heart disease insidiously. Recent data (Feinstein et al., 1964a, b, and c; American Heart Association, 1960) have shown that insidious rheumatic heart disease develops de novo primarily in patients who were asymptomatic and unexamined while they had acute carditis, and not in those examined during arthritis or chorea and found free of valvular involvement.

Clarification of Ancillary Tests for Carditis

Holding the belief that many noncarditic patients might later develop insidious rheumatic heart disease, clinicians had avidly searched for diagnostic aids to find evidence of the carditis that appeared to be clinically undetectable. Chief among these aids were the electrocardiogram and several laboratory tests. Although the original search for these indices of undetectable "subclinical" carditis was based on a premise that was itself not valid, the lack of validity in the existing ECG and laboratory tests for carditis has been demonstrated independently. Prolongation of the P-R interval, once regarded as a manifestation of carditis, occurs in about one-third of patients with post-streptococcal inflammation, regardless of concomitant clinical evidence of acute carditis. Moreover, in careful long-term studies (Feinstein et al., 1964a, b, and c; American Heart Association, 1960), acute P-R prolongation has been shown to have no prognostic significance. Alteration of the QT_c interval, an observation whose value was never proved initially, has now been abandoned as an index of acute rheumatic carditis. Changes in electrocardiographic T waves of young patients—particularly in III, in aVF, and in the transitional precordial V leads—were once regarded as evidence of carditis, but are now interpreted with skepticism. Because of normal variations in the anatomic position of the heart during respiration and with different phases of the cardiac cycle, and because of inconsistent placement of the external probing electrode, T-waves can vary greatly from one to another of the repeated ECG's taken in children and adolescents during a rheumatic episode. Of the various laboratory tests popularized in the past 10 years, none—despite a transient, later discredited, enthusiasm for transaminase—has convincingly been demonstrated to be a specific, reliable index of carditis. Consequently, cardiac noises and roentgenographic shadows remain the major variables that indicate carditis clinically, and the physician remains the major apparatus for assessing these variables.

Clinical Course of Acute Rheumatic Fever

For reasons already cited, no single clinical pattern can be properly representative of all the ways in which rheumatic fever can appear and evolve. The patterns are composed, however, of individual clinical manifestations that often do have typical courses. Untreated rheumatic arthritis generally lasts no more than several weeks, sometimes no more than a few days, and leaves no residual defects. The knees and ankles are affected most commonly; elbows, wrists, and hips are involved less often. Although small joints of the hands and feet, and the vertebral or temporo-mandibular joints may be affected uncommonly in rheumatic fever, an alternate arthropathic condition should always be considered and ruled out when these joints are involved. The arthritis of rheumatic fever often can involve only one joint, or several joints simultaneously. The development of migratory and polyarticular arthritis, polyarticular arthritis alone, often depends upon the severity of the attack, and the promptness with which bed rest or anti-inflammatory treatment is begun.

Like arthritis, Sydenham's chorea also leaves no permanent defects, although the young patient may develop many psychologic scars from scholastic deprivation and from anxieties that the peculiar movements of the chorea may induce in him or in the people who deal with him. The duration and severity of chorea vary unpredictably in each patient, making an effective evaluation of therapy difficult. Some attacks last only a few weeks, while others last three or four months. The movements are rarely so severe as to threaten the patient's safety, and often they do not impair ambulation; most commonly the patient is able to walk but cannot write, dress, or feed himself. Erythema marginatum seldom lasts more than one or two days—sometimes only a few hours—and, like chorea, it often occurs late in a rheumatic attack. It can sometimes occur early, however, but rarely alone. Subcutaneous nodules are seen much less frequently today than in the past (the reasons for the change are unknown) and almost never occur alone without some other rheumatic manifestation.

The nodules most commonly are associated with carditis, and often with severe carditis.

If carditis occurs in a particular attack, the evidence is usually present when the acutely ill patient is first encountered in the hospital (Massell *et al.*, 1958; Feinstein and Spagnuolo, 1962). After hospitalization, a patient admitted with significant murmurs may develop additional new murmurs, rubs, changes in heart size, or congestive heart failure, but significant murmurs will seldom appear if none were present during the first two weeks of observation. In the most common situation, the patient's carditic manifestations are at their worst when he is hospitalized, and they then persist or subside during the ensuing acute course of the illness.

The belief that acute rheumatic fever was often a "polycyclic" illness has also been revised in recent years. If untreated, an episode of rheumatic fever usually follows a course of gradually declining inflammation, in which laboratory abnormalities last longer than clinical ones, except for chorea. The sedimentation rate reaches normal levels in an average of three months for patients without carditis, and in four months for those with carditis. Once a rheumatic attack has begun, anti-inflammatory treatment can suppress some of the manifestations of the inflammation, but the treatment does not repair the damage done to the heart. The attack may be followed by rebounds that represent an outlet for the inflammatory stimulus that remained dormant during the preceding suppression of inflammation (Feinstein and Spagnuolo, 1961). Post-therapeutic rebounds are one of three mechanisms by which acute rheumatic inflammation can recrudesce. A second mechanism is a recurrence of acute rheumatic fever, provoked by a new streptococcal infection. A third mechanism, still poorly understood, is present in about 5% of patients with rheumatic fever. In these patients, the acute attack is excessively prolonged or "chronic," with clinical and laboratory evidence of acute inflammation present for more than eight months in the absence of an intervening streptococcal infection. Unlike post-therapeutic rebounds, the exacerbations of inflammation in these "chronic" attacks show no temporal relationship to preceding suppressive treatment. "Chronic" attacks are most likely to occur in patients with severe cardiac damage and in those who have had many previous episodes of rheumatic fever (Taranta, Spagnuolo, and Feinstein, 1962).

Long Term Sequelae of Rheumatic Fever

Great improvements have been produced in the past two decades in epidemiologic methods for careful long-term observation of patient populations having identified attacks of rheumatic fever. Several recent large-scale studies (Feinstein *et al.*, 1964a, b, and c; American Heart Association, 1960) of rheumatic sequelae have been performed by cooperative efforts of different groups of investigators or by single institutions, and have shown the following results:

(a) Patients initially free of clinical evidence of carditis remain essentially free of it thereafter. Rheumatic heart disease remains in about 9% of patients with equivocal initial evidence of carditis.

(b) In patients with congestive heart failure or marked cardiomegaly in the acute attack, evidence of cardiac damage seldom disappears. Patients with such severe carditis are the usual source of those who die at an early age. If they survive the acute rheumatic episode, the patients with severe acute carditis often die later as a result of the remaining cardiac damage, and not necessarily because of persistent or recurrent active rheumatic inflammation.

(c) Significant murmurs later disappear in about 40% of patients who had murmurs but no cardiomegaly or decompensation during a rheumatic attack. The disappearance of murmurs is most likely to occur in patients with systolic rather than diastolic murmurs, with murmurs of one valve rather than two, and with no previous episodes of rheumatic fever.

(d) Except for a small percentage of patients incapacitated by cardiac symptoms, most rheumatic patients have no clinical impairment of cardiac function during adolescence, even though signs of major cardiac damage may be present. Restriction of scholastic or

physical activities in such asymptomatic patients appears to have no medical benefits and may create adverse psychosocial reactions (Feinstein *et al.*, 1962).

(e) Recurrences of rheumatic fever may make cardiac damage worse in patients who already have it, but do not generally bring valvular damage to patients previously free of it. In patients without previous valvular damage, a recurrence is often manifested by arthritis, chorea, or occasionally pericarditis, but seldom by persistent new valvular murmurs.

Treatment of Acute Rheumatic Fever

Although the many studies of therapy of acute rheumatic fever performed in the past decade have helped clarify the course of the disease, they have not reached uniform or consistent agreement about the value of steroid treatment. The main difficulty has been the absence of reproducibility in the different methods used to allocate patients initially into comparable sub-groups of the rheumatic spectrum, and to identify the presence and disappearance of carditis (Feinstein, 1961). At present, steroids have not been proved superior to salicylates in the routine treatment of rheumatic fever, nor has either of these agents been proved consistently more effective than no treatment. Patients without carditis usually emerge free of heart disease, and those with severe carditis usually have residual heart disease, regardless of the mode of treatment. The comparison of therapeutic agents is thus best restricted to patients with "mild" carditis, i.e., murmurs only. In such patients, current therapeutic results are inconclusive because of lack of uniformity in the identification of murmurs by different investigators.

Despite the many therapeutic controversies, certain approaches are accepted almost unanimously:

(a) A course of antimicrobial agents adequate to eradicate streptococci should be given when the diagnosis of acute rheumatic fever is established, even though throat culture and ASO titer are normal. Massive doses of antibiotics for long periods of time have not been proved more effective for therapy of rheumatic fever than an ordinary streptococcal-eradicating regimen.

(b) Patients without clinical evidence of carditis can be made comfortable by salicylates or analgesics, and do not require steroids.

(c) Chorea is a yet unsolved therapeutic enigma, with no consistent success obtained by any of the various sedatives, tranquillizers, and anti-inflammatory agents that have been tested.

(d) Steroids are unequivocally better than salicylates in a small percentage of rheumatic patients who have overwhelming decompensated carditis, and whose inflammation can not be controlled with salicylates. In these situations, the steroids do not seem to repair any of the damage left by the rheumatic fire, but save the heart from immediate acute destruction by the fire, even though the severe residual damage may lead to death a few years later.

(e) In ordinary mild carditis, steroids have no unequivocally demonstrable superiority to salicylates. The main advantage of steroids is a more rapid clinical and laboratory disappearance of certain non-cardiac inflammatory abnormalities; the main disadvantage of steroids is the frequent development of cutaneous striae (in young patients) during treatment and the common occurrence of rebounds after treatment. The rebound phenomenon after steroids can often be eliminated or minimized by giving salicylates as overlap treatment, starting on the date of reduction in steroid dosage and continuing for at least several weeks after steroids are stopped.

These clarifications in our knowledge of natural history of rheumatic fever have come from better understanding of properties of the streptococcus and of the clinical reactions it elicits in its human host. The next two decades of research should help to clarify the reasons and mechanisms for susceptibility of the host.

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