Rheumatic Fever in the 21st Century

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In the first half of the twentieth century, the group A streptococcus (GAS) was established as the sole etiologic agent of acute rheumatic fever (ARF). In the century’s latter half, the clinical importance of variation in the virulence of strains of GAS has become clearer. Although still obscure, the pathogenesis of ARF requires primary infection of the throat by highly virulent GAS strains. These contain very large hyaluronate capsules and M protein molecules. The latter contain epitopes that are cross-reactive with host tissues and also contain superantigenic toxic moieties. In settings where ARF has become rare, GAS pharyngitis continues to be common, although it is caused by GAS strains of relatively lower virulence. These strains, however, colonize the throat avidly and stubbornly. Molecularly distinct pyoderma strains may cause acute glomerulonephritis, but they are not rheumatogenic, even though they may secondarily colonize and infect the throat. Guidelines for the diagnosis, treatment, and prevention of GAS pharyngitis and ARF are reviewed with particular reference to the prevalence of the latter in the community.

The concept of specific rheumatogenic strains of group A streptococci (GAS) has been difficult to establish, because the actual pathogenesis of acute rheumatic fever (ARF) remains hypothetical. It required the first 6 decades of 20th century to establish firmly that pharyngeal infection with GAS alone causes all of the manifestations of acute and recurrent attacks of rheumatic fever (RF). Not all strains of GAS do so, however; more than 50 years ago, Rebecca Lancefield and others demonstrated marked variation in the virulence of GAS strains by their content of M protein and by their degree of hyaluronate encapsulation. The relevance of strain virulence to the pathogenesis of ARF is not yet appreciated by most clinicians. In the past several decades, it has become clear that the great majority of throat infections due to GAS do not cause ARF at all, but rather that the strains that do so are unusually virulent [1]. They cause ARF with an attack rate that varies with the intensity of the host’s immune response [2], which in turn is related to the virulence of the infecting strain [3].

This review considers the factors that bear most importantly on the pathogenesis of ARF and on the strategies for its diagnosis, prevention, and management. The discussion is aimed in particular at young physicians, who may have never seen a case of ARF, and some older ones, too, who have become less interested in a disease that, though they now rarely see, is still rampant in the world [4] and may reappear in their practices at any time.

ETIOLOGY AND PATHOGENESIS

Characteristics of Rheumatogenic Strains
As early as the late 1930s, it was noted that ARF was not reactivated by certain strains representing certain M protein serotypes [5]. By the 1950s, it was further reported that strains within certain M types caused acute glomerulonephritis (AGN) [6]. In the 1960s, it also became clear that the attenuated strains responsible for streptococcal pharyngitis and frequently carried in the throats of school children in the United States did not cause ARF [7]. Similarly, strains causing streptococcal pyoderma (impetigo) were shown to be different from those primarily infecting the throat; also, some pyoderma strains could also cause AGN, but not ARF [8, 9].

The characteristics of the GAS strains clearly responsible for the great ARF epidemics of World War II are well known [10]. They are very rich in M protein, heavily encapsulated by hyaluronic acid, and highly virulent in mice. They produce striking “mucoid” colonies on blood agar plates. They are tropic primarily for the throat rather than the skin, infecting the latter secondarily through wounds. More so than pyoderma strains, they evoke
strong type-specific immune responses in humans and in mice. They do not contain lipoproteinase (the serum opacity factor) usually found in skin strains. They have been distributed among but a limited number of serotypes, such as M1, -3, -5, -6, -18, -19, -24, and some others [11]. In civilian populations, however, not all strains identified within these serotypes retained a high degree of virulence, a fact that caused much confusion about the notion of the rheumatogenic potential of specific M serotypes.

There are many explanations for strain variation, but this discussion is limited to the major virulence factors. Freshly isolated virulent GAS attenuate rapidly when grown on artificial media, losing M protein and hyaluronate capsules and thus resistance to phagocytosis. Virulence is retained in vitro by repeated passage through fresh human blood or through mice, procedures by which avirulent clones are destroyed whereas virulent clones survive. During convalescence from pharyngitis, GAS strains also tend to lose their M protein and capsules [12], so that they no longer form mucoid colonies on blood agar plates but appear, rather, as opaque “pearly” colonies [13]. Nevertheless, attenuated strains may be carried stubbornly in the throat and remain transmissible, making throat carriage among school children common.

Therefore, cultures of throat samples obtained from patients with sporadic GAS pharyngitis or from asymptomatic individuals yield GAS strains of varied pathogenicity. In fact, adherence of GAS to pharyngeal mucosal cells depends not on M protein alone, but also on lipoteichoic acid [14] and other surface proteins (e.g., F1) that bind to the mucosal receptor, fibronectin [15]. They act as integrins, stimulating internalization by epithelial cells [16, 17]. Once internalized, virulent strains may destroy the cell and invade deeper tissues, whereas strains of lower virulence (e.g., unencapsulated) may remain dormant within the epithelium. Like commensal organisms, they avidly colonize and tend to persist [18]. Such internalization is actually inhibited by the hyaluronate capsule [15, 19, 20, 21]. Thus, unencapsulated strains have greater tendency to colonize the throat rather than destroy and invade tissue. After a therapeutic course of penicillin, persistent clones are eradicated with difficulty. Their potential to regain virulence is at issue.

Parenthetically, the term used in some reports of “invasion” of epithelial cells as a first step in infection has caused confusion with regard to concepts of strain virulence. A more appropriate term may be “internalization” as a first step in infection. Whether the next step in infection is destruction of the cell and invasion into deeper tissues may then depend on the colonizing strain’s genetic expression of repressed virulence factors. Recent studies of the genetic regulation of the expression of the hyaluronate capsule [19, 20, 21, 22], along with other toxic substances, such as streptolysin S [23], lend further credence to the capsule’s importance as a virulence factor.

Why are rheumatogenic strains difficult to identify? In a severe epidemic of GAS pharyngitis, one strain of a given M serotype becomes prevalent and, therefore, readily identified. In such cases, attack rates of ARF can be easily calculated, but one-third or more of the patients presenting with ARF do not even remember having had an antecedent sore throat. By the time RF is diagnosed, the infecting strain is usually gone, or the persisting clones may have already attenuated so that their M type may no longer be recognizable. Therefore, confirmation of antecedent GAS infection requires demonstration of an immune response, such as an increase in antistreptolysin O titer. Moreover, new GAS strains may have been acquired during the latent period.

Patients with RF are often referred to centers (especially pediatric cardiology clinics), where in-depth studies of streptococcal strains are usually not made. Indeed, some clinical microbiology laboratories no longer make throat cultures at all, preferring to use the new rapid group A antigen diagnostic tests (RADTs) for primary diagnosis [24]. However useful they may be when the results are negative, when positive, RADTs provide no clue as to the virulence of the strain. When clinical laboratories do make throat cultures, however, colony morphology is not usually observed.

Early detection of mucoid colonies signals danger. For example, in the late 1950s, through the expertise of the late Paul Frank’s surveillance of throat cultures from naval recruits with pharyngitis at the Great Lakes Naval Training Center (Great Lakes, Illinois), the sudden appearance in this cohort of a predominant highly “mucoid” M type predicted the onset of a severe epidemic of RF [25]. In contrast, at the same base at the same time, ARF was not common among naval personnel housed in separate, nonrecruit training units.

In the 1970s, when RF was rapidly disappearing in the United States, throat cultures from symptomatic school children continued to be positive for GAS, with a frequency of 10%–20%, as had been reported for this age group in former decades. Surely, the treatment that was commonly employed could not account alone for the striking decrease in the prevalence of RF. For example, by the 1980s, few of the pharmacies that I surveyed in Boston stocked injectable benzathine penicillin G any longer, and patient compliance with the recommended full 10 days of oral penicillin therapy was quite uncommon. The disappearance of the notorious rheumatogenic M types from the school population was an observation made in Chicago school children 20 years previously [7].

In the 1980s, however, an outbreak of ARF reappeared at the San Diego Naval Base, at Fort Leonard Wood, Missouri, and among school children in several other regions of the United States, most notably in Utah and the Rocky Mountain area [26, 27]. In these regions,
...ing teams of the US Public Health Service’s Centers for Disease Control rediscovered the old mucoid, rheumatogenic strains seeded among contacts of index cases [28]. This outbreak has included >500 cases since then in the Salt Lake City area alone [29]. Moreover, in support of the probable role of reappearance of virulent GAS strains, the outbreak occurred among middle-class white children with no risk factors other than perhaps household crowding [28]. Subsequently, outbreaks of invasive GAS infection were dramatically featured by the streptococcal toxic shock syndrome and by necrotizing fasciitis (known also as Meleney’s streptococcal gangrene) [30]. These severe GAS infections spread through Europe and were reported as far away as Japan. They triggered intensive research into the phenotypic and genetic characteristics of these dangerous clones of highly invasive strains; most research focused on the erythrogenic toxins that they produced. Most were of the M1 serotype [27], but, strangely, the size of their capsules has rarely received comment.

It is obvious that identification of rheumatogenic and other specifically pathogenetic strains requires prospective studies of GAS pharyngitis by clinical investigators knowledgeable about the microbiology of GAS, its epidemiology, and its clinical sequelae. Unfortunately, in areas of the world where ARF still rages, such as the black urban centers of South Africa, a search for local rheumatogenic strains has not been systematically conducted. In populations where rampant pyoderma coexists with an extremely high coincidence of RF, such as among the aborigines of the Northern Australian Territories, and where efforts at strain identification have been made, investigators understandably have found it difficult to sort out strains found in the throat causing ARF from those causing pyoderma, when samples were taken from asymptomatic patients [31]. Pyoderma strains are notoriously transmissible from skin infections to the throat where they may persist and cause confusion with primary throat strains [8].

In Trinidad, however, where both extensive impetigo, AGN, and RF once closely coexisted, painstaking studies revealed that strains colonizing the skin, although periodically causing epidemic AGN, were not those associated with the sporadic cases of RF on the island. RF did not increase with outbreaks of AGN [32]. Seasonal variation in the mid-South climate of Memphis, Tennessee, however, permitted clear separation of the 2 diseases [9]. During the summer, patients were admitted to the University of Tennessee Medical Center (Memphis) with pyoderma and AGN, and summertime streptococcal pharyngitis was not accompanied by RF. Those with RF arrived in the late fall and winter. The pyoderma strains comprised the usual skin M and T types and were also isolated from the summertime sore throats of the studied patients. The colonies of these strains had relatively small capsules, or none. Unfortunately, precise identification of the strains causing RF was elusive, because patients arrived at the University of Tennessee Medical Center relatively late in the course of the disease and often had already received antibiotics. Moreover, they were referred from a wide geographic area of the mid-South, which frustrated efforts to investigate contacts.

The Molecular Biology and Genetics of Well-Known Rheumatogenic GAS

By 1979, the molecular structure of the M proteins of epidemic rheumatogenic strains was defined by my talented protégé and colleague, the late Edwin Beachey, and by his associates, when they cleanly separated the type-specific N-acetyl terminal peptide from the proximal piece of the M molecule [33]. The terminal type-specific epitope of the M molecule was found to be nontoxic in human skin while still antigenic in humans [34]. Since then, extensive studies of the molecular structure of M protein in Memphis by James Dale and his associates [35] has led to the production of a recombinant multivalent GAS vaccine (see the subsection about streptococcal vaccines in Primary Prophylaxis) [36].

Meanwhile, at the Rockefeller University, Vincent Fischetti and his colleagues [37] detailed the “coiled coil” structure of M protein. They further demonstrated that strains of GAS fell into 2 main molecular classes based on differences in the C repeat regions of the M molecule [38]. Class I molecules are characteristic of throat strains, whereas class II molecules, containing a much smaller and less antigenic M molecule, are associated with streptococcal pyoderma (impetigo). Indeed, an M antigen (so far unidentified) has been detected in rheumatogenic strains, and antibodies to this antigen have been found in the blood of patients with RF [39].

The M protein genes and those of hyaluronic acid, streptolysin S, C5a peptidase, erythrogenic toxins, and others have recently been identified [23] and now provide a genomic approach to characterizing GAS strains. The genes for expression and repression of the capsule have opened investigation of the conditions under which it is produced and mutations in its repressor that may affect its size and contribution to virulence [23]. Debra Bessen et al. [40] have shown that, by their distribution of M protein genes (emn) in various chromosomal patterns, GAS throat strains are clearly separate from skin strains. Other than virulence, molecular differences between rheumatogenic and nonrheumatogenic throat strains, however, are not yet clear. Are the antiphagocytic capsule and M molecule the only required rheumatogenic factors or are there other qualitative differences in strains causing RF?

Immunologic theories of pathogenesis. Consider that the antiphagocytic properties of the large molecules of M protein and hyaluronate promote the delivery of a large burden of antigens and toxins to richly lymphoidal pharyngeal tissues. Consider, also, the large amount...
of GAS antigens swallowed in the course of GAS pharyngitis and how the immune system of the gut handles or mishandles streptococcal antigens cross-reactive with host tissues. The “superantigen” portion of the M molecule containing nonspecific epitopes, to which we become progressively hypersensitized by repeated childhood GAS infections, heightens immune responses to streptococcal antigens, as is regularly observed in patients with RF. Such immunologic stress may break immune tolerance in susceptible hosts and account for the variety of cross-reactive antibodies found in synovia, skin, basal ganglia, heart valves, and so forth. [41]. Immune complexes may produce the nondestructive synovitis of the joints of patients with ARF and the reversible reactions in the basal ganglia observed in patients with Sydenham’s chorea, whereas autoimmune, cell-mediated cytotoxic reactions may destroy heart valves. The varied clinical manifestations of RF should therefore be expected, as noted in Problematic Isolated Major Manifestations.

THE RHEUMATIC HOST

Host factors are obviously important in the pathogenesis of ARF, as they are in complications of all infections. In RF, the degree to which they are acquired or genetic is unclear. Both factors may be important. No race or ethnic group, however, is intrinsically resistant or unusually susceptible to RF. Sex and age differences are, however, sometimes apparent. Sydenham’s chorea, which is equally common in both sexes before puberty, is virtually nonexistent in sexually mature male persons, and in women, it is exacerbated by pregnancy [1]. Also, a greater propensity of women to develop late-onset, tight mitral stenosis is well recognized. RF is very rare in young children before full maturation of the immune system, reaches its peak by the end of the first decade, and wanes with age thereafter. Carditis is most common and severe in the young, and arthritis is more common in adults. Rheumatic recurrences tend to be mimetic. Isolated polyarthritis, chorea, and carditis tend to recur independently, and susceptibility to all manifestations of rheumatic recurrences wanes with age. And host factors also might be expected to predispose to the chronicity of all manifestations.

RF is less concordant in identical twins (~20%) than it is in twins with other immunologic diseases, such as atopic allergy and hyperthyroidism, or in such infections as tuberculosis or poliomyelitis [1]. Search for an association with the gene products of human haplotypes, so productive in many autoimmune disorders, has not been as clear in RF [42, 43]. An increased frequency of HLA-DR4 and HLA-DR2 among white and black patients with rheumatic heart disease has been noted. Other studies have implicated DR1 and DRw6 as susceptibility factors in black South African patients with rheumatic heart disease and, recently, of DR7 and DW53 in Brazilian patients. These conflicting results have raised speculation that the observed associations might be of class II genes close to, or in linkage disequilibrium with, a putative RF-susceptibility gene [42].

Renewed interest in genetic susceptibility has been spurred by the observations of John Zabriskie and his colleagues [42] of an increased frequency of a B cell alloantigen, unrelated to MHC, found in diverse populations of individuals with RF, principally those with rheumatic heart disease. A monoclonal antibody (D8/17), prepared by immunizing mice with B cells from a patient with RF, is expressed on increased numbers of B cells in all patients with rheumatic heart disease who are of diverse ethnic origins but in only 10% of healthy individuals [44]. This antigen shows no association with or linkage to any of the known HLA haplotypes, nor does it appear to be related to B cell activation antigens [34]. Its source and pathophysiologic role remains obscure. It obviously would be of considerable importance if it turns out to be a reliable marker of susceptibility to rheumatic heart disease at birth. It has not been adequately studied in patients with ARF who have isolated polyarthritis or chorea (see the Sydenham’s chorea subsection in Problematic Isolated Major Manifestations).

SECONDARY PREVENTION OF RF

For prevention of rheumatic recurrences, continuous antibiotic prophylaxis is now recommended by health authorities throughout the world [4]. Monthly injections of 1.2 million units of benzathine penicillin G are the most stringent regimen. In some populations with a high prevalence of RF, however, some observers have reported that the last week of the month is not completely covered by this regimen, and they choose to administer it every 3 weeks [45, 46]. One should be sure, in any case, that the commercial formulation of the drug contains the full dose of 1.2 million units of benzathine penicillin G, and that it is not like the commonly marketed, confusing formulations, which contain smaller amounts of benzathine penicillin G mixed with shorter-acting penicillin G compounds. Where ARF is no longer prevalent, oral penicillin V, 600,000 U b.i.d., now suffices. For that matter, sulfadiazine, 0.5 g b.i.d., is also effective and inexpensive and thus useful for secondary (but not primary) prevention.

How long to continue these regimens is a matter of clinical judgment, with recognition of the major variables that affect the decision: (1) how frequently RF occurs among cohorts, (2) how recent and severe the rheumatic attack, and (3) the presence and severity of rheumatic heart disease. In a community in which RF has not appeared for many years, patients who have had polyarthritis alone and who reach adult life without rheumatic valvular disease are at lower risk (see the diagnosis of “isolated polyarthritis” below). Penicillin prophylaxis has been
safely suspended after several years of treatment when rheumatogenic streptococci have been shown to have disappeared from the community [1, 47].

Following a new GAS infection, patients with isolated polyarthritis who were observed prospectively in long-term follow-up studies developed recurrences with an attack rate greater than that of the 3% noted for first RF attacks in the military population. In a classic 5-year follow-up study that stratified recurrences by various risk factors, patients without rheumatic heart disease developed recurrences after GAS infections, with attack rates that varied from 4% in patients with a 2-tube increase in ASO titer to 36% in those with a 4-tube rise [48]. With such a relatively high propensity to recur, particularly by the challenge of more severe GAS infections, these patients with isolated polyarthritis have been considered rheumatic subjects. The recurrent attack rate was, of course, still higher in patients with polyarthritis who have rheumatic heart disease.

The risks of travel should be considered, particularly for patients with rheumatic heart disease—especially travel to so-called “undeveloped countries” in which close contact with indigenous populations may be anticipated. Problems in the diagnosis of isolated poststreptococcal polyarthritis are discussed below (see “Diagnosis”).

**PRIMARY PROPHYLAXIS**

Treatment of GAS pharyngitis is in a state of some turmoil. On the one hand, the emergence of throat flora resistant to antibiotics (gratefully, not GAS, but particularly *Streptococcus pneumoniae* and *Staphylococcus aureus*) is a consequence of overuse of antibiotics for treatment of nonbacterial respiratory infections [49]. On the other hand, fear of the return of RF has made many expert committees reluctant to compromise on the 10-day oral penicillin regimens that are required to prevent RF after rheumatogenic GAS pharyngitis [50]. Most unfortunate is the insistence by some authors that antibiotic regimens produce total eradication of GAS pharyngeal carriage, an outcome virtually impossible to achieve. Preventive antibiotic treatment of rheumatogenic GAS pharyngitis never achieved better than 90%–95% eradication of organisms from the throat. From extensive clinical observations, clones persisting after adequate therapy have limited pathogenetic potential. In order to achieve more-efficient eradication, some authors recommend that broad-acting cephalosporins or other antibiotics (e.g., clindamycin, azithromycin) replace penicillin. Some regimens are recommended for only 5 days.

In my view, these recommendations carry greater risk for emergence of resistance of vulnerable pathogenic throat flora, are more expensive, and are unnecessary. Five days of oral penicillin V, 500,000 U b.i.d., usually cures GAS pharyngitis clinically, but it will not prevent RF when the infection is due to a rheumatogenic strain. When there is no longer a threat of RF in the community, some authorities recommend that, for mild sore throats, neither diagnostic tests nor antibiotic therapy are necessary. Where RF is no longer prevalent, a negative RADT result that reliably excludes GAS may justify not prescribing antibiotics. This strategy may be the most practical and cost-effective approach to primary prevention in some regions of this country and, similarly, in those countries where ARF is no longer observed. In my own view, however, when a clinical diagnosis of GAS pharyngitis is suspected, a diagnostic test should be made, initially with an RADT and, if the results are negative, with a follow-up throat culture. If results of either are positive, a full 10 days of oral penicillin V therapy or an injection of bezathine penicillin G (when compliance is dubious or RF is still a problem in the community or region) represents the most reliable guideline for the primary prevention of RF and the intrafamilial spread of virulent strains. This view is also consistent with most current guidelines [50–52].

**Streptococcal vaccines.** We will probably not eradicate RF from the world without a GAS vaccine. James Dale and associates have prepared a recombinant multivalent vaccine composed of the end-to-end combination of the type-specific epitopes representing some of the most common M serotypes in which rheumatogenic strains are usually found [36]. Trials of efficacy in humans are currently underway. Oral immunization with similar vaccines also seems promising, because an M type-specific IgA response to this route of immunization has been well demonstrated. In view of how much M antigen is swallowed in the course of a GAS sore throat, the oral route for production of protective IgA may be the most effective one. And in light of the number of M serotypes (>90), we must focus on those known to contain strains of greatest pathogenetic potential.

**Diagnosis.** In his Harvey lecture at the end of the eighteenth century, William Cheadle proposed that each major manifestation of ARF represented part of a single larger syndrome [1, 53]. In the 1940s, T. Duckett Jones adopted these manifestations as criteria to serve as a guide to diagnosis, noting that they “occurred together with a frequency that far exceeded chance.” The criteria became particularly useful in clinical investigation to insure admission to clinical studies of clear-cut cases of ARF. The major manifestations are polyarthritis, carditis, and chorea, and, less frequently but no less characteristically, subcutaneous nodules and erythema marginatum. In the 1960s, when antistreptolysin O and other GAS antibody titers generally became available to clinical laboratories, a committee of the American Heart Association revised the Jones criteria, suggesting that the criteria, particularly those for polyarthritis, could be strengthened by including evidence of antecedent GAS infection.
Some limitations were emphasized—circumstances in which a diagnosis of ARF may be made without strict adherence to the Jones criteria, which are, after all, but general guidelines. For example, in contrast to arthritis, chorea, which is the latest of the major manifestations after the antecedent infection to appear, may present without any other major or minor features of RF—so-called “pure chorea.” Also, isolated acute carditis may first come to medical attention several months into or after the rheumatic attack. By then, antibody titers may have decreased to normal levels and the minor manifestations of systemic inflammation (fever, erythrocyte sedimentation rate, C reactive protein, etc.) may have abated.

Most patients with recurrent RF fulfill the Jones criteria, but in some patients, the diagnosis of a recurrence is less obvious [51]. For example, when rheumatic valvular disease preexists, clear recognition of a new bout of carditis requires evidence of fresh cardiac injury, such as pericarditis, acute cardiac enlargement, and/or congestive heart failure, or a newly detected murmur from a valve not previously affected. The Jones criteria, therefore, apply more readily to initial attacks, and more diagnostic latitude is sometimes needed to interpret recurrent carditis in patients with preexisting rheumatic heart disease. The steps in the evolution of the modification of the Jones criteria have been reviewed recently in detail [53].

PROBLEMATIC ISOLATED MAJOR MANIFESTATIONS

Isolated polyarthritis. Where ARF is uncommon, the diagnosis of isolated polyarthritis is problematic because of the large differential diagnosis [51]. Polyarthritis is, however, recognizable early in the rheumatic attack when streptococcal antibodies are at peak elevation. Therefore, the absence of significant increase in GAS antibodies at the onset of polyarthritis is a useful negative predictor of the diagnosis of ARF, and it suggests a reactive arthritis due to another infection, such as rubella, Lyme disease, the enteric organisms causing Reiter’s disease, ankylosing spondylitis, and so forth.

When GAS antibodies are increased, however, the diagnosis of ARF remains presumptive, requiring months of close observation, because such elevations may have been only coincidental GAS infections that were not causally related [1, 51, 55]. Chronicity of the arthritis, its recurrence in the absence of a new GAS pharyngeal infection, joint deformity, or the appearance of rheumatoid factor or DNA antibodies, et cetera, may eventually reveal it to be caused by a different disease (e.g., rheumatoid arthritis, systemic lupus, polyarteritis). Although typically migratory, many authorities have observed some patients with the polyarthritis of RF that was not initially characterized “migratory” but, rather, “additive,” and furthermore, who relapsed once or twice after 6-week courses of antirheumatic therapy (more often with corticosteroids than with nonsteroidal anti-inflammatory drugs [NSAIDs]) [56]. In prospective studies of acute rheumatic attacks that occur in the absence of a new GAS infection, relapses of RF have been noted as late as 5 weeks after completion of 6 weeks of antirheumatic therapy. And some patients do not respond brilliantly to salicylates, requiring corticosteroids instead. Nonetheless, these cases finally heal without deformity. In a few patients, rheumatic heart disease has been noted years later.

Poststreptococcal reactive arthritis (PSRA). What is at issue is whether to recognize PSRA as a separate disease from the polyarthritis clearly associated with RF [57, 58]. The characteristics of PSRA that are not typical of ARF are persistence of arthritis for several months, nonmigratory polyarthritis, poor response to NSAIDs, and, in adults, an apparent predilection for female patients. Thus, some authors claim that PSRA does not meet published Jones criteria and should therefore be excluded [43]. Brief textbook descriptions of the typical polyarthritis of RF, however, such as those described in the Jones guidelines as “almost always migratory” and “lasting 4 weeks,” are helpful guidelines, but they are not necessarily a mandatory requirement for the diagnosis of ARF. Indeed, Jones criteria have been “required” only in rigorous clinical trials to assure homogeneity of patient cohorts.

Although a different etiology of polyarthritis may be inadvertently included, some authorities prefer to retain patients with so-called PSRA on antibiotic prophylaxis, but for a modified duration, with the exact time dependent on other variables, particularly the prevalence of RF in the community. Moreover, some patients with PSRA developed rheumatic valvular disease after several years of follow-up—indeed, in some reports, the rates were as high as 7% in children with PSRA [43]. Although the numbers of the reported cases of so-called PSRA are still rather few and not always similarly defined, they deserve further study.

Eventually, the immunologic and host factors deciding the development of the major manifestations of RF, their severity, and their chronicity may warrant separate etiologic classifications other than their coexistence, as noted by T. Duckett Jones, “with a frequency exceeding chance” [51, 53]. Meanwhile, in my opinion, they still warrant the same prophylactic management currently advised for patients with the isolated typical polyarthritis of RF.

Sydenham’s chorea. Sydenham’s chorea, similarly, may occur as an isolated manifestation, and frequently recurs following new streptococcal pharyngitis. After puberty, it is almost entirely limited to women. Like polyarthritis, it is most often evanescent—over in a few weeks—but occasionally, it may be stubborn and persist for many months. The pathogenesis of chorea, which is similar to the synovitis of polyarthritis, seems to be associated with immune complex dis-
ease produced by nondestructive antoan-
tibodies localized to the basal ganglia and
striatal system of the brain [59, 60]. Se-
vere chorea seems to respond occasion-
ally to treatment with iv IgG [61]. It
seems to be closely related to the so-
called PANDAs (postinfectious autoim-
mune neurological diseases). These in-
clude tics, Tourette’s syndrome, and
obsessive-compulsive behavior, all of
which have been observed in some pa-
tients during or after an attack of rheu-
matic chorea [60].

Of course, patients with PANDA that
did not express choreiform movement
and were not previously referred to RF
centers were more often referred to pe-
diatric neurologists. PANDAs are now
known to be often associated with ant-
tecedent GAS infection [62]. If studies in
progress reveal them to be preventable by
antistreptococcal prophylaxis, they might
well be included, like PSRA, as variable
features of the syndrome of ARF, not-
withstanding the fact that, as in chorea,
other autoimmune disease (e.g., systemic
lupus erythematosus) may occasionally
cause them. A possible association of
PANDAs with rheumatic heart disease,
such as seen in long-term follow-up of
patients with chorea, should also be care-
fully studied.

Carditis. Rheumatic carditis is vir-
tually always associated with the mur-
murs of valvulitis [1, 51]. Isolated myo-
carditis or pericarditis without valvulitis
is rarely, if ever, due to RF. Thus, the
finding of valvular involvement is critical
and is aided by noninvasive imaging
methods.

Echocardiography (EC) and Doppler
methods. Most cases of rheumatic car-
ditis are not severe enough to be symp-
tomatic, and the diagnosis of isolated car-
ditis has previously depended on
auscultation alone [53, 54, 63, 64]. Ap-
proximately 80% or more of the cases of
mitral regurgitation detected by EC are
also readily diagnosed by the auscultation
of experienced clinicians. The remaining
“subauscultatory” cases are those with
the mildest degree of mitral or aortic re-
gurgitation. If, indeed, they are rheu-
matic in origin, >80% of these valvular
lesions are likely to heal without scarring
(see “Treatment,” below); however, the
sensitivity of EC may detect degrees of
valvular regurgitation within physiologic
range, and not functionally significant,
especially in children and in very thin,
active individuals with highly elastic valve
leaflets and rings.

Although EC, particularly accompa-
 nied by Doppler studies, offers greater
sensitivity and specificity for the assess-
ment of valvular regurgitation, it need
not be considered essential for the di-
agnosis of RF by experienced primary
care physicians, especially in settings
where the disease is common and med-
ical resources are limited [51, 53]. None-
theless, cardiologists proficient in echo-
Doppler technology now use this method
routinely to distinguish abnormal from
physiologic valve leaks more sensitively
and accurately than by auscultation alone.
Despite the relatively good prog-
nosis of “silent” rheumatic mitral regur-
gitation, EC does, indeed, provide an ac-
curate assessment of the presence and
severity of valvulitis, especially in an era
when cardiac auscultation has been
taught less extensively and is used with
less confidence by young clinicians. In
any case, it is doubtful that a diagnostic
tool that is as powerful as EC will be
neglected in the assessment of valvular
disease wherever the instrument is avail-
able and certainly where its expense may
not be too great a concern. In my view,
whether or not subauscultatory mitral re-
gurgitation can be accepted as the sole
criterion of carditis in the absence of
other major manifestations of RF re-
 mains at issue and is certainly dependent
on the experience of the examining car-
diologist, not only with the technique of
EC, but also with the diagnostic criteria
of RF [53, 63, 64]. Whether the Jones
criteria should be modified to incorpo-
rate these techniques is being debated
with differences of opinion tempered by
considerations of availability and cost-
benefit of EC to developing countries,
since outcomes of the treatment and
management of such minimal valvular
inflammation may not differ signifi-
cantly, whether they are detected or not
(see “Therapy”) [53].

RIGHT VENTRICULAR
ENDOMYOCARDIAL BIOPSY
(EB)

When the characteristic murmurs of
rheumatic carditis are detected early in
the course of a rheumatic attack and are
associated with other major and minor
manifestations of RF, such as arthritis
and fever, the yield of useful additional
clinical information from EB has been
low. Its diagnostic sensitivity in 1 rela-
tively large study was only 27% [65]. EB
has, however, confirmed the presence of
underlying carditis in unexplained con-
gestive heart failure of acute onset in
some patients with preexisting rheumatic
heart disease and elevated antistreptoly-
sin titers, which suggest a rheumatic re-
currence. In patients with chronic rheu-
matic heart disease, however, EB does not
appear to provide additional diagnostic
information. In my opinion, in patients
with rheumatic carditis, EB should be
limited to clinical investigation.

Treatment. Treatment has not
changed much in recent decades [1]. Be-
cause valvar scarring is suspected to be
the result of cytotoxic cellular autoim-
munity, anti-TNF drugs that seem to de-
lay or reduce joint destruction in patients
with rheumatoid synovitis possibly might
reduce valvular scarring in patients with
rheumatic carditis. There is no longer
much argument, though, that cortico-
estroids, however symptomatically ben-
eficial, do not prevent valvular damage [1].
The new COX-2–inhibiting NSAIDs may
be welcome to reduce the adverse gas-
trointestinal effects of large doses of as-
pirin, although, for 4- to 6-week thera-
peutic courses, such side effects have not
been a great problem, especially in chil-
References

29. Veasy LG, Hill HR. Immunologic and clinical correlations in rheumatic fever and rheu-