β Haemolytic streptococci and reactive arthritis in adults

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Abstract
There is an increasing occurrence of reactive group A β haemolytic streptococci (BHS) phenomena. This review makes a case for considering BHS in the differential diagnosis of adult reactive arthritis. This is based on (a) published reports over the past 45 years describing first attacks of rheumatic fever in adults; (b) the longstanding observation that polyarthritis is the most commonly expressed Jones major criterion in adults; (c) the broad spectrum of clinical expression of disease following streptococcal infection, with the re-emergence of the term 'poststreptococcal reactive arthritis'. The arthritis in adult rheumatic fever is characterised by sequential involvement of large weightbearing joints. Recurrent, severe, prolonged arthritis has been a prominent feature of adult poststreptococcal reactive arthritis. Carditis has been reported in 33% of adult patients with rheumatic fever. Consequently long term antibiotic prophylaxis for adults with reactive BHS phenomena should be strongly considered, and guidelines are suggested for this in individual patients. Further areas for research are discussed, particularly the interrelations between bacteria and host in disease expression, and the possibility that BHS might play a part in chronic arthritides and vasculitides.

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Streptococci are a group of Gram positive bacteria, which include some of the most common and ubiquitous of human commensals and pathogens. Streptococci are generally classified according to the type of haemolysis they produce on blood agar. The β haemolytic streptococci (BHS) are recognised by the complete lysis of red cells around colonies, the viridans streptococci produce a green colour around colonies (α haemolysis), and non-haemolytic streptococci produce no lysis. The BHS can be further subdivided into serogroups based on antigenic differences in the group-specific polysaccharide or other similar antigens present in the cell wall. These group antigens can be extracted in a soluble form and identified by precipitation with specific group antisera (Lancefield grouping). Several different groups of BHS have been identified and labelled A, B, C, etc. Rapid methods—for example, latex agglutination, are now available for the identification of the BHS commonly causing disease in man (groups A, B, C, D, F, and G).

Groups A, B, C, and G have been particularly associated with reactive and septic arthritides. Lancefield group A streptococci (synonymous with Streptococcus pyogenes) are best known in rheumatology for their association with rheumatic fever.1 Group B streptococci are most commonly associated with neonatal2 and puerperal sepsis.3 Group C and G streptococci are occasional causes of pharyngitis, skin infections and, rarely, septicemia and other serious infections.4 As the present century progressed the incidence of both sepsis due to BHS and rheumatic fever seemed to decline.5 6 This has been attributed largely to improving social conditions,7 diminishing virulence of the organisms8 and, latterly, the introduction of antibiotics.9 The decline in incidence of rheumatic fever led some to predict its eventual disappearance. Unfortunately, recent trends suggest that such beliefs were premature, and rheumatologists need to be aware of a possible resurgence of streptococci in clinical practice.

Traditionally, rheumatic fever has been associated with children of school age.10 Serious septic BHS disease has been considered to be most prevalent in patients with chronic disease or some form of underlying immunosuppression.11 These clinical reviews will consider, firstly, an apparently increasing importance of BHS in adult reactive arthritis. The second article will review BHS septic phenomena in adults who do not always have a predisposition. The emphasis in both articles is placed on the need for an awareness of these bacteria in adult rheumatology practice, points out complications that should be anticipated, and suggests areas for further research.

β Haemolytic streptococcal reactive arthritis in adults

Rheumatic fever secondary to Lancefield group A BHS constitutes the best clarified example of reactive arthritis available to us, with a clearly identified organism, increasingly understood molecular biology, and a satisfying line in secondary prevention. Rheumatic fever in children, and the biology of this disease,
have been reviewed extensively recently.⁷ ¹²–¹⁵
Reactive streptococcal disease has run the risk
of being overlooked in adults with no previous
history of childhood illness; table 1 summarises
the reasons for this. There is a strong case for
lowering the threshold for clinical vigilance for
reactive streptococcal arthritis in adults, given
that the incidence of rheumatic fever is increas-
ing again,¹² ¹⁶ ¹⁷ and a recognition that streptococci
can cause reactive arthopathies in the absence of other Jones criteria for
rheumatic fever.¹³

EPIDEMIOLOGY OF ADULT RHEUMATIC FEVER
There is considerable evidence for a wide-
spread resurgence in the incidence of rhe-
umatic fever in the USA and Europe.¹² ¹⁶ ¹⁷
This emerged during the mid-1980s,¹⁸ but may
well be continuing into the 1990s.¹⁹ Classical
descriptions of rheumatic fever suggest that the
age of onset is typically in 6 to 14 year olds.¹⁰
Since the earliest reports of the disease,
however, adults have been well recognised as
being at risk of first time attacks.²⁰ Epidemics
among American military recruit camps were
extremely common in previous decades, so
that routine administration of benzathine penicillin was given to all American military
recruits after the second world war.²¹ ²² Two
recent outbreaks have occurred on American
military bases.²³ ²⁴ These clusters of cases
follow the traditional pattern of overcrowding
as one of the predisposing factors in rheumatic
fever.²⁵ Not all recent outbreaks in adults have
occurred in such conditions. For example, a
study of discharge summaries in hospitals in
West Virginia recorded 23 patients with rheumatic fever between 1980 and 1989, 15 of
whom were adults, and six of whom had no
previous history of an attack.²⁵ Presumably,
these were all acquired in the community and
were isolated infections as the patients all lived
in rural settings. This pattern of patients pre-
dominantly emerging from suburban or rural
middle class families has also been seen in
many of the recent epidemics in children,²⁶–²⁸
and suggests that the epidemiology of the
disease is changing in several respects.

Table 1 Reasons why rheumatic fever and streptococcal reactive arthritis may not be considered in adults

<table>
<thead>
<tr>
<th>Reason</th>
<th>Ref</th>
<th>Study</th>
<th>No of patients</th>
<th>Pattern of disease</th>
<th>Duration of arthritis (days)</th>
<th>Of arthritis in adult rheumatic fever, disease duration, non-articular musculoskeletal manifestations, and outcome</th>
</tr>
</thead>
</table>
| Low incidence of rheumatic fever (unusual for younger rheumatologists to have seen a full-blown case) |      |               |                 | Maj (97)  | 100 Maj  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  |Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  |Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  |Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | Nil  | N
emphasise the dramatically abrupt onset of the arthritis,\textsuperscript{35} 37 39 and often the marked discrepancy between the severity of the symptoms and objective physical signs.\textsuperscript{30} Teno-synovitis has been described in some of the recent series, especially overlying the wrist, hand, and ankles.\textsuperscript{23} 37 As far as I know there is only one reported case of Jaccoud’s arthritis in adult rheumatic fever.\textsuperscript{34}

Subcutaneous nodules, erythema marginatum, and chorea (the other Jones major criteria\textsuperscript{4}) are all unusual in adult rheumatic fever (0\%\textsuperscript{5}–4\%\textsuperscript{7}–9\%and 0\%–4\% respectively in the combined series\textsuperscript{25}). Carditis in older paediatric series occurred in 50\% of patients,\textsuperscript{12} and this may be even higher in recent outbreaks.\textsuperscript{18 28 41} Based on a review of 549 patients, it has been estimated that the prevalence in adults is lower at 33\%.\textsuperscript{21} The series of studies had a wide range of prevalences of carditis, varying from 15\%\textsuperscript{35} to 56\%.\textsuperscript{50} This variation might be accounted for by different definitions of carditis between studies (usually taken to include new murmurs, cardiomegaly, congestive heart failure, and pericardial friction rubs), and in the sensitivity of tests for diagnosing carditis (for example, more recent studies would have access to echocardiography, with earlier studies relying on clinical skills). It is therefore not possible to be confident about the reproducibility between studies for the prevalence of carditis. One could argue, however, that as the pathology of rheumatic fever carditis is a pancarditis the detection of any cardiac abnormality may be a pointer to inflammation at all levels of the heart.\textsuperscript{12} If 33\% represents a figure close to the truth for the prevalence of carditis, this represents the potential for significant morbidity, and suggests that careful monitoring for this manifestation is mandatory. This also has major implications for long term antibiotic prophylaxis, which is considered below. Furthermore, carditis is present in a sufficiently large minority of adults to give some value to the Jones criteria in older patients, insofar as a disease closely analogous to childhood rheumatic fever is clearly identified in some adults. The other described multisystem manifestations of group A streptococcal reactive disease are considered below.

### The Syndrome of ‘Poststreptococcal Reactive Arthritis’

As a consequence of the low prevalence of carditis, and the rarity of other Jones major criteria in adults, the term ‘poststreptococcal arthritis’ was first coined in 1959\textsuperscript{42} in recognition of the fact that streptococcal reactive disease was possible in adults, but in many ways distinct from the disease in children. With the re-emergence of streptococci as an important cause of reactive arthritis, and several reminders of the broad expression of streptococcal reactive disease, this term has reappeared in recent reports on children in the slightly modified form of ‘poststreptococcal reactive arthritis’ (PSRA).\textsuperscript{43 45} Most cases have been reported in children, and their clinical features have been reviewed recently.\textsuperscript{13} Over the past few years a small number of adult case reports have emerged.\textsuperscript{46–48}

An overview of the descriptions of these cases suggests that a number of clinical features may be useful in discriminating between rheumatic fever and PSRA. Apart from lacking other Jones criteria, the suggested distinctions between PSRA and rheumatic fever are (a) an onset within 10 days following a streptococcal infection, as opposed to the average 21 days classically described for rheumatic fever\textsuperscript{10}; (b) prolonged or recurrent arthritis and arthralgias (usually lasting around two months\textsuperscript{13}), as compared with the fleeting migratory arthritis described in rheumatic fever, where individual joint attacks last one to five days, with resolution of all arthritis in three weeks\textsuperscript{12}; (c) the dramatic response of rheumatic fever carditis and arthralgias to aspirin is not evident in PSRA.\textsuperscript{13}

Some further interesting features emerge from a detailed scrutiny of the handful of adult cases that have been described to date. Recurrent severe arthritis has been a feature of most cases.\textsuperscript{46–48} In two patients investigated cryoglobulins were present, and skin rashes with testicular swelling and pain in one,\textsuperscript{48} emphasising the multisystem nature of this condition for some patients (considered further below). A further patient was HLA-B27 positive with recurrent sacroiliac pain a prominent feature.\textsuperscript{46} An adult with rheumatic fever, HLA-B27 positivity, and prominent sacroiliac and lower back pain, with dactylitis and calcaneal erosions has also been described.\textsuperscript{49}

The concept of PSRA as a distinct syndrome is rendered vulnerable by the observation that some children with this label went on to develop rheumatic fever,\textsuperscript{45} and that outbreaks of rheumatic fever have occurred simultaneously with PSRA.\textsuperscript{13} If adult cases of streptococcal disease fit more neatly into the PSRA category, this may simply be a reflection of the low prevalence of carditis and other Jones major criteria in adult rheumatic fever.\textsuperscript{21} Some of the cases labelled as PSRA probably fulfil the criteria for rheumatic fever, having arthritis as a major criterion, and fever and a raised erythrocyte sedimentation rate as two minor criteria.

Whether it will continue to be useful to differentiate between rheumatic fever and
PRSA will require further longitudinal studies, but at present it is of value, if only to emphasise the broad spectrum of poststreptococcal manifestations, without having to believe that these phenomena are necessarily biologically distinct. Differences in the clinical picture may have more to do with the host than the bacteria, insofar as there is a genetic predisposition to rheumatic fever, raising the possibility that the host immune response may be the primary determinant as to whether a patient develops rheumatic fever or PSRA. Alternatively, it may be the age of the patient which is the most important determinant of disease expression, so that, for example, the incidence and severity of carditis appear to diminish with age.

GROUP G STREPTOCOCCI AND REACTIVE ARTHRITIS

To complicate the situation further, reactive arthropathies may not be confined to group A streptococci but may also be a feature of Lancefield group G infections. There are two reports of prolonged sterile polyarthritides in patients with group G streptococcal septicemia, and we recently reported on a patient with group G streptococcal pharyngitis in the absence of septicemia who developed a reactive polyarthritides and adductor enthesis. Group G streptococci have cell wall antigens that cross react with group A, and both produce streptolysin, so that the anti-streptolysin O (ASO) titre can be diagnostically useful for both groups. Antigenic mimicry has been invoked to explain the associations of group A streptococci (such as the M-18 virulence protein) with arthritis. Group G streptococci can occasionally produce proteins which are cross reactive with M proteins, so that there may be a molecular basis for considering that group G streptococci can initiate reactive arthritis.

Clinical implications

REACTIVE ARTHROPATHIES

There are a number of clinical implications that arise from these observations. The first is to be aware of the possibility that group A, and probably group G, streptococci may cause reactive arthropathies in adults. At present it is not possible to estimate the incidence of rheumatic fever or PSRA in adults in the United Kingdom, as it is unlikely that this explanation for a monarthrisis or polyarthritis is considered in all presenting patients, even when they are seen by specialists. Further work is needed on the epidemiology of these conditions in adults. This must start with a recognition of the possibility of streptococcal reactive disease in adults presenting with arthritis. The history in adults with a recent onset of arthritis must include an inquiry about symptoms of pharyngitis, though this will only be positive in 60% of patients with rheumatic fever or PSRA. Likewise, a throat swab may only grow streptococci in around 29–37% and, conversely, some patients are persistent streptococcal carriers. Evidence for a recent streptococcal infection must therefore largely be obtained by serological testing. Caution is necessary in relying solely on a single raised ASO titre. After a previous infection a proportion of patients develop a prolonged raised ASO titre, so that at most an increased titre suggests previous infection, but which may be in the distant past and irrelevant to the current problem. In contrast, only about 80–90% of patients with rheumatic fever develop a raised ASO titre, so that there is considerable room for false negatives. The diagnostic accuracy can be improved in two ways. Firstly, demonstrating increasing ASO titres two to four weeks apart, and in particular an increase in titre of two or more dilutions, is considered diagnostic. Secondly, other antibody tests can be performed which would indicate a recent streptococcal infection. In a study of 88 patients with rheumatic fever, 78% had a raised ASO titre, 90% had a raised ASO titre or antihyaluronidase, and 95% had a raised ASO titre or antihyaluronidase or antistreptokinase. Anti-DNAase B is also available in some laboratories, and is positive in a similar proportion to the ASO titre in patients with rheumatic fever.

EXTRA-ARTICULAR MANIFESTATIONS

The second major clinical implication is to be aware of the extra-articular manifestations of rheumatic fever and PSRA once a diagnosis of recent streptococcal infection and arthritis or arthralgia have been substantiated. Table 4 lists those manifestations that have been described in adults and attempts to estimate broadly the prevalence of these disorders from published reports, given that different units of measurement are often used in different studies, and that the absence of a description of a manifestation may represent 'false negatives' in some cases. Many younger rheumatologists will never have seen a full-blown case of rheumatic fever, and it is therefore worth pointing out both the classically described Jones criteria and some of the more unusual recently described manifestations in adults, and re-emphasising the broad spectrum of poststreptococcal disease manifestations.

MANAGEMENT

The third area for clinical concern is that of management. The vast majority of the adults that have been described with rheumatic fever and PSRA have had a self limiting condition that has responded to conservative treatment, albeit with the need for short term treatment with steroids in some cases. Permanent joint damage and severe multisystem disease is rare. A review of 489 adult patients with rheumatic fever, however, estimated mortality at 1.2%. The last published death in these series was in 1966, so that better management or a decline in the severity of the disease might suggest that death would be most unusual today. Management of the acute case therefore resides in
eradicating the organism, treatment with non-steroidal anti-inflammatory drugs or short term treatment with steroids for the articular and extra-articular manifestations, and vigilance for potentially life threatening complications.

An interesting question that has yet to be resolved is whether or not these patients should receive prophylactic penicillin as has been advocated for rheumatic fever. Some of the children with PSRA went on to develop rheumatic fever or recurrent PSRA and it has therefore been argued that these children should be treated as patients with rheumatic fever with long term prophylaxis. Whether the same applies to adults requires further longitudinal research. Recurrent severe arthritis, however, has been a feature of some of the handful of adult cases of PSRA that have been described (see above). Although this can be extremely painful and disabling, it is not in itself life threatening. The much more compelling argument for long term prophylaxis is the possibility of carditis, which may affect as many as 33% of adult patients with rheumatic fever. This argument is based on three observations: (a) the risk of rheumatic fever after an episode of acute streptococcal pharyngitis is much greater in patients who have already had a previous attack than in the general population; (b) patients who have had previous rheumatic carditis are at greatest risk for further cardiac damage with recurrences; (c) the overall risk of cardiac disease increases with the number of recurrences in all rheumatic patients.

While waiting for firmer guidelines, I suggest that the following factors should be considered in determining which adults require long term antibiotic prophylaxis. The first should be taken as absolute, with the others becoming progressively more relative and tailored to the circumstances of individual patients: (a) those who develop carditis (new murmur, cardomegaly, congestive heart failure, and pericardial friction rubs) during an attack of rheumatic fever; (b) those with PSRA and mitral valve disease or aortic incompetence, even if it is difficult to substantiate the temporal relation between these murmurs and the reactive arthritis (these murmurs may represent previous attacks of rheumatic fever); (c) those with a single severe extra-articular attack of PSRA—for example, vasculitis, meningitis, septic arthritis (these murmurs may represent previous attacks of rheumatic fever); (d) those with more than one attack of disabling reactive arthritis or enthesitis, leading to a prolonged stay in hospital or loss of work; (e) those with a first degree relative with a history of rheumatic fever in whom the other considerations listed above are not clear cut.

Recommendations on the details of antibiotic prophylaxis have been reviewed elsewhere.

**INTERFERENCE BETWEEN CLINICAL AND LABORATORY RESEARCH**

The interface between clinical and laboratory research can be considered under three key questions: (a) what features of the bacteria predispose subjects to rheumatic fever and PSRA; (b) which human host factors are important in disease expression; (c) can BHS cause chronic inflammatory connective tissue disease?

**What features of the bacteria predispose subjects to rheumatic fever and PSRA?**

It has been known for 50 years that not all strains of group A streptococci that cause sore throat also cause rheumatic fever. Furthermore, the intensity or virulence of infection affects the attack rate of rheumatic fever. These observations can be tied together by demonstrating that only certain M serotypes (most recently, 1, 3, 5, 6, and 18, and, previously, the additional 14, 19, 24, 27, and 29 types) predispose to rheumatic fever, that structurally these serotypes are markedly different from non-rheumatogenic M serotypes containing epitopes which are cross
reactive with cardiac sarcolemmal membrane,\textsuperscript{71} myosin,\textsuperscript{72} \textsuperscript{73} cartilage and synovium\textsuperscript{74} and, finally, that these M types belong to heavily encapsulated bacteria, which are the most virulent, most resistant to phagocytosis, and strongly immunogenic.\textsuperscript{97} \textsuperscript{75} \textsuperscript{76} An increasing awareness of the possible association between streptococci and adult reactive arthropathies will enable M serotyping of isolated streptococci, to determine which types are important in adult rheumatic fever, and whether these differ from those associated with PSRA, thus potentially giving biological respectability to the clinical differentiation.

\textbf{Which human host factors are important in disease expression?}

Patients who develop rheumatic fever have abnormal humoral and cellular responses to streptococcal antigens. For example, serum from patients with rheumatic fever contains heart reactive antibodies which persist for two to three years after the infection,\textsuperscript{77} \textsuperscript{78} and lymphocytes from these patients show increased responsiveness to streptococcal antigens.\textsuperscript{79} These differences between patients prone and resistant to rheumatic fever are partially genetically determined. The most impressive association to date has been with a B cell antigen designated 883, with a relative risk of 12 times for contracting rheumatic fever in those patients with the marker as compared with those without, and present in patients with rheumatic fever from a large number of different countries.\textsuperscript{80} A monoclonal antibody, D8/17, has been isolated from immunisations of rheumatic fever B alloantigens into mice, which identifies a B cell antigen present in 90–100\% of patients with rheumatic fever,\textsuperscript{81} as compared with 10–15\% of healthy controls. This marker is also present on a high percentage of rheumatic fever B cells, indicating an abnormal expansion of D8/17 positive B cells in rheumatic fever.\textsuperscript{82} Associations with HLA-DR alleles have been described, but are weaker than those for the B cell alloantigen, and vary from group to group.\textsuperscript{82} \textsuperscript{83} This raises the possibility that genes linked to HLA-DR, but probably not the HLA-DR locus itself, may have a role in predisposing to rheumatic fever. These observations raise interesting questions in the context of adult rheumatic fever and PSRA. Do patients who develop clinically significant rheumatic fever in adult life differ genetically or in terms of their immune response from the paediatric patients? Do patients who develop a reactive arthropathy in the absence of other features of rheumatic fever differ genetically from those who contract full-blown rheumatic fever?

\textbf{Can BHS cause chronic inflammatory connective tissue disease?}

There are a number of interesting analogies between the changing epidemiology of rheumatic fever over this century and changes in the occurrence and expression of rheumatoid arthritis (RA). Until the 1980s rheumatic fever was not only declining in incidence\textsuperscript{9} but also in severity, so that the prevalences of carditis, nodules, chorea, and erythema marginatum were all decreasing in those patients with rheumatic fever.\textsuperscript{56} Similar changes seem to be taking place in RA, with not only declining incidence\textsuperscript{86} \textsuperscript{87} but also a decreasing occurrence of seropositivity, erosions, and nodules.\textsuperscript{88} This raises the possibility that the triggering factor(s) responsible for initiating this chronic inflammatory disease obeys similar biological rules to those set for group A streptococci. There are a number of clinical observations that raise the possibility that BHS reactive phenomena may not only be useful in disease models in chronic inflammatory arthritis in certain strains of inbred rodents but may also have a role in human chronic rheumatic and connective tissue diseases: (a) recurrent inflammatory arthropathies in adults and children with streptococcal reactive disease; (b) the irreversible inflammatory damage caused to some tissues such as cardiac tissues; (c) the devastating multisystem nature of post-streptococcal disease in some case reports\textsuperscript{89}; (d) the possibility that BHS may be important in childhood polyarteritis nodosa.\textsuperscript{10}

There is recent laboratory evidence to support these possibilities. Antibodies directed against group A streptococcal M proteins cross react with antigens on the surface of chondrocytes, cartilage, and synovium.\textsuperscript{74} Patients with RA have increased levels of antibodies directed against the group A streptococcal cell wall peptidoglycan/polysaccharide (SCW PG-PSP) complex.\textsuperscript{89} Antibodies directed against galactosyl IgG, the proportion of which is raised in RA,\textsuperscript{90} cross react with group A SCW PG-PSP.\textsuperscript{91} Antibodies to mycobacterial heat shock protein are raised in RA,\textsuperscript{92} \textsuperscript{93} and these seem to correlate with the level of galactosyl IgG.\textsuperscript{94} Heat shock proteins are highly conserved between species, and it is known that streptococci produce very similar molecules, which might evoke an immune response.\textsuperscript{95} A further study has suggested a high level of association between positivity for anti-perinuclear factor and antibodies directed against SCW PG-PSP complex in 55 patients with juvenile chronic arthritis, suggesting antigenic similarity between SCW PG-PSP and the perinuclear antigen.\textsuperscript{96} This was particularly marked in the adult pattern seropositive polyarticular juvenile chronic arthritis, with lower prevalences of these antibodies in other categories of juvenile chronic arthritis.\textsuperscript{97} These potential examples of 'molecular mimicry' between self antigens and a commonly occurring pathogen may be of theoretical importance in initiating or driving chronic inflammatory disease, though much more work is needed in these areas. BHS may break immune tolerance in predisposed hosts by indirect actions. When the type-specific component of the large M molecule is split off by peptic digestion the remaining non-type-specific component can induce intense cytotoxicity by binding directly with polyclonal T cell receptors, leading to polyclonal
T cell activation, and thus acting as a "superantigen". This superantigen effect might enhance any autoimmune to cross reactive antigens.

Conclusions and recommendations

1 Reactive streptococcal phenomena are increasing. These disorders can occur in adults, where polyarthritis is the chief manifestation. The incidence is unknown, partly as a consequence of the diagnosis not being considered.

2 Immunological research in this area must start on the firm foundation of reliable and valid case definition. Substantiation of recent streptococcal infection should rest on changing ASO titres (or other antistreptococcal antibodies) two to four weeks apart.

3 There is a wide variety of clinical expression of adult streptococcal reactive disease. In the clinical situation, even when recent streptococcal infection cannot be fully substantiated, an adult presenting with an abrupt onset of additive or migratory polyarthritis needs urine analysis for protein, careful cardiovascular examination for an electrocardiographic low threshold for requesting echocardiography.

4 All isolated group A and G streptococci in reactive arthropathies should be M typed to determine the nature of the responsible strains, and whether similar types are responsible for childhood and adult rheumatic fever and PSRA.

5 Further genetic studies and longitudinal studies need to determine whether it is useful to distinguish between rheumatic fever and PSRA.

6 If we are at the start of a reactive BHS epidemic, and musculoskeletal manifestations may be prominent expressions of disease in adults, it is necessary for rheumatologists to remain vigilant and report any streptococcal reactive arthritis to their national public health laboratories.

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Beta haemolytic streptococci and reactive arthritis in adults.

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