Rheumatic fever: the interplay between host, genetics, and microbe

Lewis A. Conner Memorial Lecture

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ALTHOUGH the incidence of rheumatic fever has markedly decreased in this country as well as in most of the industrialized world, one need only visit any of the "developing" or third world countries to realize that this disease is still one of the major public health problems in the world. It is estimated that approximately 15 to 20 million new cases will appear each year in these countries. I personally believe that the incidence is actually higher, since many of the cases are not diagnosed at the time and only appear later as chronic rheumatic heart disease. Perhaps most important from a public health point of view is the fact that most patients do survive the acute carditis and then go on to chronic rheumatic valvular disease with all of its severe cardiologic manifestations and complications.

What is especially intriguing to the students of this disease is why the disease is changing or disappearing in many parts of the world. Although better medical conditions, the use of penicillin, and changes in socioeconomic factors have obviously contributed, the decline occurred before the widespread use of antibiotics and is changing in parts of the world where less-than-optimal medical and social conditions exist. Thus, as we shall discuss later, either there has been a subtle change in the organism's ability to cause this sequela or the host's susceptibility to the disease has changed in some manner, or a combination of both has occurred.

It is perhaps surprising that after 50 years of intensive investigation, we still do not have a clear picture of the pathogenic mechanisms involved in this disease process. There are several reasons for this dilemma. (1) The latent period between the initial streptococcal infection and the onset of the clinical and pathologic signs and symptoms of rheumatic fever severely limits prospective studies. (2) The myriad of cellular and extracellular structures and toxins associated with the streptococcal organism that may produce tissue injury (directly or indirectly) makes it difficult to decipher which structure or toxin is important in the disease process. (3) There is no suitable experimental model for studying the disease process. Nevertheless, rheumatic fever merits further study, not only for its public health implications, but more importantly, because knowledge of this disease might provide insights into other rheumatic diseases where even the causative agent (let alone etiology) is still not known.

To better understand the disease process itself, it will be necessary to review some of the salient morphologic features of the streptococcus and the host's immune response to these structures. It will also be necessary to define more clearly those streptococcal antigens that share antigenic determinants with mammalian tissue antigens. Knowledge concerning these areas of microbe-host interactions will hopefully lead to a greater understanding of the clinical and laboratory findings of the disease itself.

Streptococcal structures and cross-reactive antigens.

Each streptococcal cell is surrounded by several layers (figure 1). The M protein, seen on the outer surface as fimbria, is the most extensively studied protein antigen and will be discussed in some detail below. This antigen and the T protein serve as markers for the immunologic subclassification of group A streptococci into specific types. The next layer consists of carbohydrate and contains the specific moiety responsible for grouping of streptococci; in the case of group A, this is N-
acetylglucosamine. Beneath this is a mucoprotein layer and these three layers make up the cell wall of the streptococcus. Finally, there is the innermost layer called the protoplast membrane, a lipoprotein structure that will be discussed in further detail below. Although chemically these layers appear as discrete separate structures, a truer representation is that cell wall structures do in some manner anchor to or are intertwined with membrane structures.

From several points of view, the M proteins are among the most important of the surface antigens. There are over 80 serologic types of M protein, each of which is capable of stimulating specific protective antibodies as well as sharing a common property of being able to avoid phagocytosis by the host’s immune system. An important consideration concerning streptococcal vaccines is that a large number of the group A streptococcal types can cause rheumatic fever, a situation unlike that seen in poststreptococcal glomerulonephritis, in which only a few types appear to be responsible for the majority of cases.

Perhaps the most interesting new developments in our knowledge of the M protein moiety has been the work of Fischetti and colleagues,1 in which he has noted a marked structural homology between the M protein molecule and the muscle protein tropomyosin. Yet, antisera raised against M protein or tropomyosin do not give the same pattern of staining seen in acute rheumatic fever sera. More germane to the central theme of this presentation is the finding of Dale and Beachy2 that antibodies raised against the pepsin fragment of the type 5 M protein moiety was not only protective in the opsonic assay but also cross-reacted with sarcolemmal tissue.

Another important cross-reaction involves the group A carbohydrate moiety N-acetylglucosamine and mammalian valvular glycoproteins.3 In a series of articles, Goldstein and his collaborators have shown that rabbit sera raised against the group A carbohydrate cross-reacts with these valvular glycoproteins and that the shared antigenic determinant is the N-acetylg glucosamine of the group A streptococcus and a similar antigen in the valvular glycoprotein material. As will be pointed out below, this cross-reaction may be quite important in the pathogenesis of valvular disease in patients with rheumatic fever.

Current work suggests that cell wall mucoprotein may be partly responsible for the chronic, remittant, nodular lesions of connective tissue after a single injection of disrupted group A streptococci.4 The injection of this material in rats does cause a chronic, relapsing arthritis and synovitis reminiscent of human rheumatoid arthritis,5 but there is little evidence to suggest that it plays a role in rheumatic fever.

The final inner layer of the streptococcal cell is a highly complex antigen lipoprotein; it contains approximately 72% protein, 25% lipid, and 2% carbohydrate by weight. This structure does not contain cell wall carbohydrates and its antigens are quite different from those in the streptococcal cell wall. Group A

FIGURE 1. Schematic drawing of the components of the streptococcal cell and its cross-reactions with various mammalian tissue components.
streptococcal membrane structures and mammalian tissues share a number of common antigenic determinants. These findings may be summarized as follows: (1) Cell membranes and extracts from group A streptococci cross-react with human glomerular basement membrane antigens.\(^6\) (2) Rabbit antisera to these streptococcal membrane structures will bind to rabbit and human muscle sarcolemmal membrane antigens (including cardiac muscle).\(^7\) They also bind to the smooth muscle of blood vessel walls but not to uterine muscle. (3) Guinea pigs immunized with a number of different types of group A streptococci developed a sensitivity indistinguishable from that produced by sensitization with allogeneic tissues.\(^8\) Antigens shared by streptococcal membrane and mammalian tissue appear to include mammalian histocompatibility antigens. Evidence is derived not only from the above-mentioned experiments of graft rejection, but also from the close biochemical similarity between mammalian histocompatibility antigens, certain structural glycoproteins, and streptococcal membrane antigens.\(^10\)

We have dealt primarily with cross-reactive antigens related to the heart or valves, but two other streptococcal mammalian tissue reactions are worthy of discussion. (1) Patients with rheumatic chorea possess an antibody that stains caudate nuclei and can be absorbed by streptococcal membrane antigens,\(^11\) indicating that streptococcal antigens share antigenic determinants with brain antigens.\(^12\) (2) Antisera bind to skin fibroblasts as well as to thymocytes.\(^13\) The latter cross-reactivity could be important in the host’s immunoregulation to streptococcal antigens.

In spite of the obvious interest in these numerous cross-reactions, a word of caution should be introduced: group A streptococci, as do tissue antigens, have immunoglobulin molecule Fc receptors on their surfaces.\(^14\) Although many of these cross-reactions are real and have included the appropriate controls, each report of streptococcal cross-reactivity should be carefully studied for the possibility that the presumed antigen-antibody reaction is not the result of nonspecific Fc receptor binding.

**Pathogenetic concepts of rheumatic fever.** Most investigators concerned with the pathogenesis of rheumatic fever now favor the concept that the disease is a result of an abnormal immune response (humoral and/or cellular) on the part of the host to a given streptococcal infection. For instance, patients with rheumatic fever have higher antibody titers to streptococcal antigens such as streptolysin O than do subjects without rheumatic fever.\(^15\) In addition, the sera of patients with acute rheumatic fever contain antibodies that react with constituents of human cardiac tissue.\(^16\)\(^17\) Antibodies are present in very low titers or are absent in uncomplicated streptococcal infections. Elevated antibody titers of antibodies to streptococcal antigens may reflect a greater antigenic challenge, although it should be emphasized that an asymptomatic streptococcal infection, so mild that the patient cannot recall the symptoms of pharyngitis, will precipitate an attack of rheumatic fever.

Several observations support the idea that cell-mediated immunity is also important in the rheumatic process. First, the rare occurrence of the disease before 4 years of age suggests that several infections with the streptococcus are needed to sensitize the susceptible individual.\(^18\) Second, streptococcal antigens can be shown to induce delayed hypersensitivity in both animals and man.\(^19\) Finally, examination of human hearts from patients with acute rheumatic fever reveals numerous lymphocytic infiltrates, both perivascular and between muscle bundles.\(^*\)

One fascinating and, as we shall see later, perhaps explainable phenomenon is the fact that the incidence of rheumatic fever (1% to 3% of streptococcal pharyngitis cases) appears to be quite constant regardless of the area or epidemic studied. This appears to hold true even in areas such as Trinidad, where the rate of both skin and throat streptococcal infection in the population is extremely high and where periodic epidemics of large numbers of cases of glomerulonephritis occur. In spite of this high attack rate and prevalence of streptococci and their infections, the yearly attack rate of rheumatic fever remains quite constant, suggesting that there are only a limited number of people who are uniquely susceptible to this disease.

Bearing these background remarks in mind, let us now turn to the clinical manifestations of rheumatic fever and examine whether or not humoral and cellular immunity to streptococcal antigens that are cross-reactive with mammalian antigens play a role in the disease process.

**Humoral immunity**

*Carditis.* The finding that a component of the group A streptococcus has the capacity to elicit an antibody that binds to cardiac tissue led to a search for similar antibodies in the sera of patients with recent streptococcal infections and their sequelae. When the serum from a patient with acute rheumatic fever is layered over a cardiac section and stained with a fluorescein-conjugated anti-immunoglobulin G antiserum, the staining pattern bears a striking resemblance to the pattern ob-

\(^*\)Murphy GE: Personal communication.
served with rabbit antisera that have been immunized with group A streptococci (figure 2).

Examination of a number of sera (table 1) from patients with recent streptococcal infections and their sequelae revealed heart-staining antibody in most of them. However, the amount of antibody detected in individuals with rheumatic fever at the onset of their disease was strikingly different from that in patients convalescing from uncomplicated streptococcal infections. Two to 3 weeks after uncomplicated streptococcal infections, sera from the latter had little or no heart-reactive antibody, whereas sera from patients with acute rheumatic fever had antibodies detectable at a 10-fold dilution. The presence of these high titers of heart-reactive antibodies in the sera of patients with acute rheumatic fever has been an important additional diagnostic tool in cases of suspected rheumatic fever. Bright fluorescent staining of cardiac tissue at dilutions of serum greater than 1:10 is considered indicative of acute rheumatic fever. Furthermore, the absence of any significant levels of heart-reactive antibody in patients with unrelated arthritic and immunologic disorders coupled with the characteristic nuclear staining of sera from patients with lupus erythematosus has been helpful in the differential diagnosis of other rheumatic disorders. Serial studies of the sera obtained from patients with acute rheumatic fever reveal that the antibody titer declines rapidly during the first 3 to 6 months after the initial attack, then more gradually over the next 2 to 3 years. At the end of 5 years the vast majority of patients have little or no detectable antibody present in their serum unless there is an intercurrent streptococcal infection or a recurrence of rheumatic fever. When viewed in light of the clinical observations that most rheumatic recurrences occur within the first 2 years after the initial attack and are rare after 5 years, the presence of a heart-reactive antibody appears to have more than a casual relationship to the disease process.

Observations of long intervals between attacks and the appearance of heart-reactive antibody in the serum before the recurrence make it tempting to speculate that repeated streptococcal infections (perhaps with subclinical symptoms of disease) may be necessary to stimulate the production of heart-reactive antibodies. Only when the titers are sufficiently elevated does the fully developed disease complex appear. Examination of a small number of recurrences of rheumatic fever has indicated that in each case elevated heart-reactive antibody titers were present at the time of or just before the second attack (figure 3).

If this rise in heart-reactive antibody titer in the serum is related to rheumatic heart disease, then one should be able to demonstrate gamma globulin in rheumatic hearts. In fact, gamma globulin has been demonstrated to be bound to the sarcolemma of hearts from patients with rheumatic fever at the site of histologic

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TABLE 1

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>Dilutions of sera obtained in first</th>
<th>Dilutions of sera obtained at onset of rheumatic fever</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1:5</td>
<td>1:10</td>
</tr>
<tr>
<td>Scarlet fever</td>
<td>25</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Scarlet fever with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rheumatic fever</td>
<td>25</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>18</td>
<td>0a</td>
<td>0</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*aNumber of signs indicates the intensity of immunofluorescent staining of heart tissue.

*bThese sera were obtained during active disease.
damage (figure 4). Knowledge concerning the nature and specificity of this immunoglobulin will be crucial to our further understanding of the role these antibodies play in the pathologic process.

With respect to valvulitis, the sera of a number of patients with rheumatic fever and rheumatic heart disease have been shown to contain antibodies that bind to N-acetylglucosamine, the carbohydrate specific to the group A streptococcus. Patients with valvular disease have higher titers of this antibody than patients without valvular disease, and these antibodies persist for years after the initial attack. In contrast, in patients without valvular disease, the titers decline rapidly after the initial rheumatic insult. Persistence of high titers in patients with rheumatic valvular disease may be related to the slow and sustained release of valvular cross-reactive glycoproteins, thus perpetrating the valvular damage. It remains to be seen whether the presence of these antibodies is specific to patients with rheumatic disease or whether they also occur in patients with advancing arteriosclerotic heart disease and other forms of nonrheumatic heart disease.

**Arthritis.** Swelling of the major joints has always been one of the major features of rheumatic fever. Yet even this manifestation appears to vary from area to area. It has been our own experience in Trinidad, as well as that of other investigators, that incipient carditis without arthritis is often the major clinical manifestation of the disease in tropical areas of the world. Analysis of the synovial fluid in well-documented cases of rheumatic fever with arthritis generally reveals a decrease of the complement components C1q, C3, and C4, indicating their consumption by immune complexes in the joint fluid.

More recently, we have noted the presence of high levels of circulating immune complexes in the sera of patients with acute rheumatic fever, which persists for several months after the acute attack. Friedman et al. from our laboratory have isolated these complexes and raised antibodies to them in rabbits. The anticomplex antibody gives a reaction against extracellular products of a rheumatogenic strain, which is distinctly different from that seen with rabbit sera raised against nephritis complexes. These results also demonstrate that circulating complexes in patients with acute rheu-

FIGURE 3. Heart-reactive antibody titers and laboratory data obtained from a patient with rheumatic fever who had two well-documented acute attacks 11 years apart. Note the disappearance of the heart-reactive antibody during years 2 to 5 and its reappearance during years 6 to 10 after streptolysin-O (ASO) evidence of two intercurrent streptococcal infections secondary to breaks in penicillin prophylaxis. High titers of heart-reactive antibody appeared with the second attack. CRP = C-reactive protein.

FIGURE 4. Immunofluorescent photomicrograph depicting deposits of human IgGbound to the blood vessel and surrounding myofibers in a frozen section of cardiac tissue obtained during surgery from a patient with rheumatic fever. Sections of the same area revealed an inflammatory process consistent with an Aschoff lesion.
rheumatic fever do indeed contain streptococcal antigens within the complex. However, the nature of the antigens and their relationship to the disease complex remain unknown.

Another mechanism for the observed synovitis in rheumatic fever could be antibodies to streptococcal antigens that bind to the smooth muscle of blood vessel walls. Thus one might envisage a vasculitis of the vessels secondary to streptococcal antibodies cross-reactive with smooth muscle cells of vessel walls, perhaps augmented by the circulating immune complexes in the sera of these patients. The fact that host immunoglobulins have been noted in the blood vessel wall in these patients makes this concept attractive but still unproved.

Chorea. This clinical syndrome has always been an enigma as a frequent late manifestation of rheumatic fever. However, recent data have demonstrated that sera of patients with Sydenham's chorea contain an antibody that binds to the cytoplasm of caudate nuclei in the thalamic and subthalamic areas of the brain. This antibody correlates quite well with the clinical course of the disease. The “streptococcal connection” has been firmly established by the observation that streptococcal group A membranes completely abolished the immunofluorescent staining whereas other streptococcal antigens did not. Unpublished data by our group also revealed that this antibody was also present in spinal fluid in five well-documented cases of acute rheumatic chorea.

Cellular immunity. The question of whether hypersensitivity to hemolytic streptococci and their products may play a role in the pathogenesis of the nonsuppurative sequelae has been the subject of investigation for many years. Using skin tests as an index of delayed sensitivity to streptococcal products, several investigators have agreed that hypersensitivity to streptococci and their products is a common occurrence in man and increases in intensity with the age of the individual tested. These reactions were also more intense in subjects with rheumatic disease than in control subjects; the greatest number of positive reactions were obtained with autogenous streptococci, suggesting type-specificity to the reaction. Repeated streptococcal infections and exposure to their products may be vital to the disease process, in view of the rarity of rheumatic fever before age 3 to 4 years.

During the past 5 years our group has been reexploring this question of cellular reactivity to streptococcal antigens in patients with known sequelae of streptococcal infections, namely rheumatic fever and post-streptococcal glomerulonephritis. This has been a unique opportunity for us since, in Trinidad, both diseases occur simultaneously in the same age group and there is no seasonal variation in the occurrence of the two diseases. Our results, obtained with two techniques of measuring cellular reactivity to streptococcal antigens in vitro, indicate that patients with acute rheumatic fever have increased cellular response compared with control subjects and that this reactivity is primarily to membranes of those streptococcal strains commonly associated with rheumatic fever in Trinidad (figure 5). This reaction persists for at least 2 years after the initial attack. Since this reactivity was not seen in patients with acute poststreptococcal glomerulonephritis (data not shown), a specific reactivity to these antigens in patients with rheumatic fever is suggested. The exact nature of the antigen(s) responsible for the observed reactivity is unknown at present.

Although these results strongly suggest that there is a heightened response to streptococcal antigens in patients with rheumatic fever, the exact role these sensitized cells play in this disease process remains unknown. The present finding that there is abnormal cellular response to membrane antigens, coupled with previous reports of an abnormal humoral response to the streptococcal membrane, could argue strongly for a crucial role of this cell structure in the pathogenesis of rheumatic fever. The cross-reactive properties of these antigens might result in autosensitization to tissue antigens with cytotoxic effects in the host tissues. This concept is consistent with the histologic findings of a large number of lymphocytic cells in and near the pathologic cardiac lesions of rheumatic fever. More recently, Raizada et al. have also shown that the majority of the lymphocytes present in these pathologic lesions are of the T\(_1\) helper subset of lymphocytes.

Although most investigators believe that cellular immunity plays an important role in the pathology of the disease process, there are actually very few reports demonstrating a cytopathic effect of these sensitized cells. Experimentally, Yang et al. were able to show that lymphocytes obtained from guinea pigs sensitized to group A streptococcal membrane streptococcus (and not to group A cell walls or group C membranes) were cytotoxic for guinea pig embryonic heart cell monolayers. A crucial and important point in these studies was their observation that guinea pig sera containing heart-reactive antibody did not enhance the cytotoxicity, indicating that the observed cytotoxicity was an antibody-independent, cell-mediated reaction.

Only Hutto et al. in a small number of cases have demonstrated that mononuclear cell populations ob-

**CIRCULATION**
tained from patients with rheumatic fever were indeed cytotoxic for human heart cell monolayers. However, Gaurishanker and Agarwal\textsuperscript{34} have noted that lymphocytes obtained from patients with acute rheumatic fever exhibited heightened reactions to both streptococcal antigens and heart tissue, indicating that cells sensitized to both streptococcal and tissue antigens are present in these patients.

Genetics. No discussion of rheumatic fever would be complete without a reference to the possibility that individuals with rheumatic fever are perhaps genetically programmed to respond abnormally to a streptococcal infection. A little more than ninety years ago it was pointed out that rheumatic fever occurred frequently in more than one member of an affected family.\textsuperscript{35} Since that time many investigators have postulated that there is an inherited susceptibility to rheumatic fever, but neither the mode of inheritance nor the methods of its expression have been delineated satisfactorily. Observations in 56 patients with rheumatic fever and their respective twins suggested that genetic factors, if operative, had limited penetrance, since only three of 16 pairs of monozygotic twins were concordant for rheumatic fever.\textsuperscript{36} Other studies have concentrated on the presence or absence of selected blood groups and the secretor status of subjects with rheumatic disease in an effort to identify a susceptible genotype.\textsuperscript{34}

Although our efforts to find an association with either the HLA-A or B loci were unsuccessful,\textsuperscript{37} recent results\textsuperscript{38} lend strong support to the existence of a genetic marker in patients with rheumatic fever. By means of a serum containing a B cell alloantigen called 883\textsuperscript{+}, a positive reaction was found in approximately 72% of all patients with rheumatic fever from both New York and Bogota, Colombia, suggesting that this genetic marker was worldwide in its distribution. Screening against a panel of known HLA-ABC and Dr specificities also indicated that this marker was not associated with any of the known HLA haplotypes.

Unfortunately, just at the time when important questions concerning the nature and role of this antigenic marker to the disease process were being asked, the supply of this particular alloantisemur became exhausted and attempts to find another multiparous serum with similar characteristics were unsuccessful. In an effort to remedy this situation, we have spent the past 2 years making hybridoma antibodies to the B cell alloantigen originally recognized by the 883\textsuperscript{+} serum. Our results to date have been quite successful (table 2). Clone 83S19.23 identified (with one exception) all patients originally described as 883\textsuperscript{+} by the multiparous alloantisemur. In addition, clone 256S10 identified five of the seven patients with rheumatic fever originally defined as 883\textsuperscript{−} by the human alloantisemur. Thus the use of the two monoclonal antibodies has permitted us to correctly identify approximately

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Stimulation of mononuclear cell populations obtained from patients with rheumatic disease and control subjects to type 41 and type 55 streptococcal cell wall and membrane antigens. Note the prolonged heightened reactivity to type 41 antigens (left) when compared with the lack of reactivity to the type 55 antigens (right).}
\end{figure}
92% of all patients with rheumatic fever. A preliminary survey of the frequency of the marker 83S19.23 in patients with rheumatic fever from different geographic areas is depicted in table 3. As can be seen, the presence of this antigen on the surface of B cells is remarkably constant irrespective of the rheumatic fever population studied, suggesting a worldwide distribution for the antigen. As noted, this marker is present in approximately 20% of the normal population, making this group of individuals at high risk of contracting the disease. Since studies of attack rates of rheumatic fever rarely exceed 5% in a given population, factors such as the virulence of the infection, the sensitivity state of the susceptible individual, and the host’s response to the infection at the time must also contribute to the actual development of the disease in the susceptible individual. Thus, although the susceptible group of individuals is 20% of the normal population, it is the combination of genetics, the sensitized state and the virulence of the organism that combines to produce the actual disease.

Whether or not this antigen is present on other cells or acts as a streptococcal antigen receptor is not known at present. Nor are we sure of the exact role the B cell marker plays in the production of the pathologic damage seen in patients with rheumatic fever. However, the presence of a genetic marker that indicates a high risk factor of contracting the disease and that can be identified at birth has broad implications for public health.

Conclusions. Although current evidence strongly implicates an immunologic mechanism in the pathophysiology of rheumatic fever, the details of the manner in which the disease process develops are by no means clear. The evidence to date strongly indicates that there is an abnormal immune response in patients with rheumatic disease to streptococcal antigens, in particular a humoral and cell-mediated response to cell membrane antigens of group A streptococcus. These antigens are known to be cross-reactive with heart and other muscle tissue antigens. The relationship between a B cell alloantigen and susceptibility to rheumatic fever suggests that abnormal reactivity to streptococcal antigens may be genetically determined on the basis of something analogous to immune response genes linked to histocompatibility genes.

Although we still do not know the exact role this genetic marker plays in the disease process, the ability to identify a group of individuals at risk has broad implications for public health. For example, in third world countries where budgets for health programs are limited, treatment of high-risk individuals for prevention of rheumatic fever and as priority candidates for any contemplated vaccine would be a priority. In addition, if the evidence accrues that only high-risk individuals actually get rheumatic fever, one might change the length of penicillin therapy for streptococcal infections for those individuals not bearing the B cell alloantigens. It should be emphasized that these studies have not been carried out yet, so that the present regimen of treatment of all patients with streptococcal infections is still advised.

Thus our working concept of the pathogenic mechanisms operative in rheumatic fever is as follows: Exposure in a susceptible individual to infection with group A streptococcus gives rise to an exaggerated humoral and cellular response to those streptococcal antigens cross-reactive with human cardiac and muscle tissue. This reaction could be augmented or abetted by the

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**TABLE 2**

Comparison of the original 883+ rheumatic patients with patients identified by hybridoma clones 19.23 and 256S-104

<table>
<thead>
<tr>
<th>Subjects</th>
<th>883+ a</th>
<th>19.23 b</th>
<th>256-104 c</th>
<th>Both clones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic (n = 24)</td>
<td>18/24  (75%)</td>
<td>17/24 (71%)</td>
<td>5/7 (71%)</td>
<td>22/24 (92%)</td>
</tr>
<tr>
<td>Normal (n = 24)</td>
<td>4/24  (16%)</td>
<td>5/24 (20%)</td>
<td>5/24 (20%)</td>
<td>ND</td>
</tr>
</tbody>
</table>

a Assays were carried out by both immunofluorescence and cytotoxicity techniques.
b Original multiparous 883+ serum used by Patarroyo.
c Hybridoma clone isolated from animals immunized with B cells from 883+ rheumatic subjects.
d Hybridoma clone isolated from animals immunized with B cells from 883+ rheumatic subjects.

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**TABLE 3**

Comparison of the frequency of reactivity in rheumatic and non-rheumatic individuals from various geographic areas with monoclonal antibody 83S19.23

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No. of patients positive/total</th>
<th>% frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Delhi and Chandigarh</td>
<td>13/22</td>
<td>59.1</td>
</tr>
<tr>
<td>New Mexico</td>
<td>30/39</td>
<td>76.9</td>
</tr>
<tr>
<td>New York</td>
<td>17/23</td>
<td>74.0</td>
</tr>
<tr>
<td>Nonrheumatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Delhi and Chandigarh</td>
<td>3/18</td>
<td>16.6</td>
</tr>
<tr>
<td>New Mexico</td>
<td>5/30</td>
<td>16.6</td>
</tr>
<tr>
<td>New York</td>
<td>4/22</td>
<td>18.0</td>
</tr>
</tbody>
</table>
uncovering of buried cross-reactive determinants in the host, perhaps as a result of a direct toxic effect on the tissues during the early stages of the infection (i.e., the latent period). At a critical level of the exaggerated response, tolerance to the host’s “self” antigens is broken. There is a direct attack on the host’s tissues by cells sensitized to streptococcal antigens that are cross-reactive with heart, brain, or smooth muscle tissues. Experimental data would suggest that circulating heart-reactive antibody does not play a role in the cytotoxic effects. Data confirming these findings in the case of human patients is still unproved.

Turning to the question of the arthritic manifestations of the disease, circulating complexes contain streptococcal antigen and antibody with perhaps a particular affinity for synovial receptors could account for this clinical manifestation of the disease. However, one cannot forget that antibodies that bind to smooth muscle cells of blood vessel walls are also potentially capable of causing a generalized vasculitis with subsequent effects on joints, myocardium, skin, and even mesenteric structures in the patient.

It is clear that further work needs to be done to more clearly delineate the relative roles of cellular and humoral immunity, as well as the role of the genetic markers in rheumatic fever. Since there is an abnormal cellular and humoral response to streptococcal antigens in these patients, and since only group A streptococci contain the cross-reactive antigens, the concept of a streptococcus-induced “autoimmune” process operating in rheumatic fever is attractive.

To return finally to the question of why the pattern and incidence of rheumatic fever are changing in many parts of the world, including third world countries, any deviation in this host-microbial circle could affect the rheumatic fever cycle. A decrease in the organism’s virulence or potential to exhibit cross-reactive antigens would obviously affect the incidence of disease. One can speculate that smaller families, decreased spread of a virulent strain, and better medical care could change the type of streptococcus present in the community. Moreover, if fewer genetically susceptible individuals carrying the 883" marker are present in the population, this might have a strong impact on the relative number of new cases in the community. It is my belief that a subtle change in the socioeconomic environment, possibly related to dietary changes and ingestion of greater amounts of meat, might be one of the key factors in the changing incidence of this disease. For example, in those countries where meat or meat products (possibly capable of eliciting cross-reactive antibodies) are consumed, the incidence of rheumatic fever will be low as a result of the protective blocking effects of these antibodies. The converse will occur in those countries whose poorer economic status would not generally include the consumption of meat by its inhabitants. Although this is pure speculation, it may prove to be one of the most important factors in the lower prevalence of rheumatic fever. Yet it would be foolhardy to ignore the many other factors (better nutrition, health care delivery systems, smaller families, etc.) that could markedly influence the microbe-host interaction. The disease still presents a challenge that will require the continuing efforts of clinicians, epidemiologists, and basic researchers if we are to completely understand this fascinating and as yet unsolved microbe-host interaction.

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