THE past two decades have seen a remarkable decline in acute rheumatic fever (ARF) in North America and Western Europe and, indeed, in almost every area of the world where improved economic conditions have led to good housing, diminished crowding, and control of the spread of streptococcal infections. This decline, despite the still frequent appearance of streptococcal pharyngeal strains in most populations, justifies some speculation as to whether or not group A streptococcal strains have undergone qualitative as well as quantitative changes that might have affected their rheumatogenic potential.

I have used the term "rheumatogenic" streptococci advisedly to raise again an old issue which, in my opinion, needs close re-examination. Strong evidence that there are nephritogenic and nonnephritogenic strains of group A streptococci has accumulated rapidly since the concept was first clearly documented by Rammelkamp and his associates. The notion that there might be, similarly, rheumatogenic and nonrheumatogenic strains of group A streptococci seemed to be dispelled by the Warren Air Force Base studies during the period of 1949-51.1

Factors Affecting the Attack Rate of Acute Rheumatic Fever

Rammelkamp and his colleagues1 firmly established that, in epidemics in closed populations, cases of exudative pharyngitis due to group A streptococci were followed by an approximate 3% attack rate of ARF. In their studies, this was true regardless of the M-protein serotype of the infecting group A strain. Virtually the same attack rate of ARF was observed in untreated cases of pharyngitis due to M types 5, 14, and 24, respectively (table 1).

Subsequent variations and attack rates of ARF following sporadic pharyngitis in civilian populations have been attributed more to quantitative factors in the severity or virulence of the infection rather than to qualitative differences in the nature of the infecting strains.2 For example, in our studies in Chicago with the late Alan C. Siegel and with Dr. Eloise Johnson there seemed to be a quantitative threshold of streptococcal pharyngitis beyond which acute rheumatic fever did not occur.3 During a 12-year period (1956-68) 886 patients with untreated, non-exudative uncomplicated pharyngitis associated with positive cultures for beta hemolytic streptococci were followed closely and did not develop either ARF or acute glomerulonephritis (AGN). In 709 (80%) of these selected patients, the streptococci were group A and in 275 (39%) of the group A infections an increase in antistreptolysin O titer was demonstrated (Siegel AC, Johnson EE, Stolleran GH: Unpublished data). Therefore, although the majority of these infections might represent viral disease with pharyngeal carriage of streptococci coincidentally, in at least several hundred patients streptococcal infection could not be excluded. The streptococcal strains isolated in these cases of simple sore throat, however, often could not be typed.
as M with available conventional anti-M typing sera. Furthermore, those strains that were M typable appeared to have relatively little M protein as judged by a variety of methods.

### Are There Nonrheumatogenic Group A Streptococci?

Although quantitative variation in the virulence of streptococcal disease is undoubtedly of considerable importance to the pathogenesis of acute rheumatic fever, recent studies of AGN caused by skin infecting strains of group A streptococci raise the question as to whether or not "nephritogenicity" and "rheumatogenicity" may be completely independent properties of group A streptococci, if not actually mutually exclusive.

There is currently need, therefore, to focus sharply upon the evidence which raises the possibility of antigenic differences between strains that can cause either rheumatic fever or acute glomerulonephritis, and, if such there be, strains that cause both or neither sequel(s)!

### Clinical Experience

It is an old observation that ARF and AGN rarely, if ever, occur in the same patient at the same time. When arthritis, carditis, and nephritis are found together, it has become axiomatic to seek a diffuse vascular disease, such as polyarteritis or systemic lupus erythematosus, as the likely cause. One could argue that attack rates of ARF and AGN, repectively, following streptococcal infections are sufficiently low so that their simultaneous occurrence is likely to be quite rare on the basis of statistical probability. ARF has occurred, however, in some epidemics of streptococcal sore throat with attack rates as high as 21%, and AGN has occurred with still higher attack rates. One might expect, therefore, that of large numbers of cases of either disease recorded during a severe epidemic, a few cases of the second simultaneous poststreptococcal complication should have been observed. Such simultaneous streptococcal sequelae have not been a feature of the reported experience of studies of large numbers of patients with either disease.

A second clinical observation relevant to this discussion concerns the route of infection that may differentiate rheumatogenic from nephritogenic strains. ARF seems to be almost always, if not exclusively, a complication of a pharyngeal infection. It is not a complication of pyoderma. AGN occurs after either skin or pharyngeal infection. Nephritogenic skin strains of streptococci often parasitize the throat. The best known rheumatogenic pharyngeal strains do not seem to parasitize the skin.

### Epidemiologic Evidence for Nephritogenic and Non-nephritogenic Pharyngeal Strains

It is abundantly clear that strains of some M serotypes do not cause acute glomerulonephritis despite their capacity to produce rheumatic fever. Rammelkamp and his associates, reviewing 2,366 untreated young adult males with exudative streptococcal pharyngitis, failed to observe any instances of AGN following large numbers of infections with strains of M serotypes 1, 5, 6, 14, 18, and 24.

Studies at the Naval Medical Research Unit No. 4 at Great Lakes, Illinois, during a period of several years also revealed large epidemics of streptococcal pharyngitis due to certain M serotypes (notably types 1, 3, 5, 19, and 24) which did not appear to produce AGN, although prospective studies in untreated patients were not made. Such strains could be considered, therefore, either nonnephritogenic or certainly of very low nephritogenicity.
It is not implied that all strains containing the above M antigens are necessarily non-nephritogenic. From time to time sporadic cases of AGN have been reported which seem to be associated with strains representing some of these M serotypes. The observations simply point out the low or absent nephritogenicity of the specific epidemic strains studied.

**Epidemiologic Evidence for Nephritogenic Skin Strains**

During the past few years several studies have made it clear that the strains producing streptococcal pyoderma belong to a whole population of previously unrecognized M-protein serotypes which have patterns of cross reactions with antisera to T antigens that are quite different from those of the conventional strains that have produced epidemic pharyngitis in previous studies.8-12 Since Rammelkamp and his colleagues and Stetson’s group13 called attention to the frequent association of pharyngeal strains of M types 12 and 14 with nephritis, an epidemic of AGN in Minnesota,14, 15 was found by Wannamaker and colleagues to be due to a strain (Red Lake) subsequently designated a new M protein, type 49.16 Maxted and his colleagues17 showed subsequently the wide geographical distribution of this strain which was actually more commonly found as a cause of pyoderma than of pharyngitis. Indeed, the difficulty of M typing of pyoderma strains had been pointed out by Parker and his associates as early as 1955.8 These workers demonstrated, however, that when skin strains were typed with agglutinating sera against surface T antigens, they showed patterns of cross reactions that were characteristic (table 2).

Since then, several studies of AGN due to streptococcal pyoderma (table 2) have revealed the existence of hitherto unrecognized M types—types 52, 53, and 54 at Cass Lake, Minnesota,11 55,18 57, and 589 in Trinidad, 5619 in Memphis, Tennessee, and 59 to 61 in Birmingham, Alabama.20

In studies of patients with endemic pyoderma-nephritis in Memphis, many of the above M types have been identified as well as a large number of strains which seem to contain M proteins on the basis of their resistance to phagocytosis in human blood but which have not been classified as yet and are presumably new M types.19 A sample of our Memphis strains from patients with pharyngitis shows that of 115 tested for resistance of phagocytosis, 41% grew well in fresh human blood, indicating the presence of M protein in considerable amounts.21

It appears, therefore, that in most parts of the world where AGN is still endemic and epidemic, most cases of AGN are associated with impetiginous skin lesions. It should be emphasized that the property of nephritogenicity is not necessarily constant in all skin strains. Whereas pyoderma occurs in many populations as a constant endemic disease, AGN fluctuates episodically, presumably when a strain that has a strong nephritogenic potential becomes prevalent. The epidemiology of AGN in tropical island populations, such as Trinidad, has been well described by Poon-King and associates.22 Approximately

---

**Table 2**

M-Antigens Recently Found Among Group A Streptococci Isolated from Pyoderma Patients

<table>
<thead>
<tr>
<th>T patterns</th>
<th>M-types</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/13/B3264</td>
<td>52 and 53</td>
<td>Red and Cass Lakes11</td>
</tr>
<tr>
<td>15/17/19/23/47</td>
<td>54</td>
<td>&quot; &quot; &quot; &quot; &quot;</td>
</tr>
<tr>
<td>8/25/Imp 19</td>
<td>55 and 57, 58</td>
<td>Trinidadb, 18</td>
</tr>
<tr>
<td>28, 3/13/B3264</td>
<td>56</td>
<td>Memphis19</td>
</tr>
<tr>
<td>(14), 25/Imp 19</td>
<td>59</td>
<td>Birmingham10, 20</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>&quot; &quot;</td>
</tr>
<tr>
<td>(9), 11</td>
<td>61</td>
<td>&quot; &quot;</td>
</tr>
</tbody>
</table>

*Circulation, Volume XLIII, June 1971*
rheumatic fever is virtually absent. In the fall, when school begins, pyoderma and acute nephritis decline rapidly and acute rheumatic fever appears within a month or two\(^2\) (fig. 2). The low incidence of ARF in our Memphis City Hospital outpatient population during the hot months when acute pharyngitis was associated with positive cultures for the group A streptococcus appears quite prevalent as shown in figure 3. Study of 1,746 throat cultures on patients with sore throat in this population shows that beta hemolytic streptococci were present in 30% of cases of sore throat, and that the beta hemolytic streptococci in 66% (343) of the 521 cultures in these cases were in group A. The low M typability (13%) with the conventional M typing antigens available to us prompted further studies of the identity of these strains by T agglutination methods. Forty-three per cent of T-type strains fell into patterns generally associated with skin infections.

These findings suggested that many strains of streptococci isolated from sore throat patients at our institution are a reflection of the large reservoir of streptococcal pyoderma present in the study population. It is still not
clear whether such strains are actually causing significant streptococcal pharyngitis or are simply associated by throat carriage with extensive summertime viral pharyngitis. From the immunologic studies, however, at least a third of these sore throats appear to be associated with streptococcal antibody increases, although the magnitude of the antibody response is not great.21

The hypothesis of nonrheumatogenicity of skin strains may explain the situation we have observed in Memphis. During the summer nonrheumatogenic skin streptococci are predominant in our population. Many colonize throats, some perhaps cause true pharyngitis, but either due to lack of virulence in the throat or lack of some crucial antigen or toxin, they are unable to cause ARF. During the fall and winter, small focal epidemics due to other throat strains that have moved in may be the cause of sporadic cases of ARF that we observe. If this is true, we should be able to observe a change in M and T serotypes from skin strains to throat strains during the fall. So far we have not been able to document this. Perhaps the small foci of rheumatogenic throat strains are diluted by the large reservoir of skin strains present in our population. Our current task is to seek out and identify these hypothetical foci of rheumatogenic strains, if indeed they occur, by prompt and careful throat culturing of index cases of ARF and of all of their close contacts. Such studies are in progress.

Do Skin Strains Cause Recurrent Acute Rheumatic Fever?

An additional indirect but important line of evidence for the nonrheumatogenicity of pharyngeal infection by skin streptococci may be sought in observations of their effect upon rheumatic subjects. As you may recall, the attack rate of rheumatic fever may be extremely high in patients who have had previous rheumatic attacks, particularly if they have rheumatic heart disease, have had their rheumatic attacks in recent years, and have an infection associated with a vigorous immune response.

For the past 6 years in Memphis we have been studying the effect of discontinuing chemoprophylaxis in rheumatic subjects at lowest risk for recurrences. More recently, we have begun a protocol by which prophylaxis is interrupted during the months from May to September and then resumed in the fall. This protocol was adopted because of the impression of many observers that rheumatic recurrences in the Memphis area were extremely rare during the warm season. Our data on the high frequency of pharyngeal isolation of streptococci from sore throats in the summer months surprised us. They have caused us to look carefully, however, at the immunologic responses (antistreptolysin O and other streptococcal antibody titers) of our rheumatic subjects during this season. So far, our data consist of too few confirmed immunologic responses to calculate a significant attack rate because we have observed only 228 rheumatic patient-years and have documented only 31 immunologically significant infections. Most of these infections occurred during the warm months and in several cases skin strains were isolated from the patients' throats. A low or absent attack rate of recurrent rheumatic fever
in this population following infection with skin strains would provide further support for the notion of nonrheumatogenic streptococci.

In conclusion, both the clinical epidemiologic and the microbiologic evidence seem to focus on different strains of streptococci which appear to be capable of producing either one or the other streptococcal sequel. Perhaps there are strains that can do both or neither. A clearly established potential for a given strain as nephritogenic or nonnephritogenic, and as rheumatogenic or nonrheumatogenic, would be of great value. Placed side by side, the unique antigens of each might be compared and their affinity for cross reactions with the glomerulus or with the heart might be tested. Should no distinctions be possible, the route of infection and its quantitative aspects might, after all, be the determinants of the elusive pathogenesis of AGN and ARF.

The chance to test many of the hypotheses raised in this discussion no doubt awaits those with the best prepared minds, particularly when rampant poverty in many parts of the world make ARF and AGN diseases still available for study.

References


2. **Stolleraman GH**: Factors determining the attack rate of rheumatic fever. JAMA 177: 823, 1961

3. **Siegel AC, Johnson EE, Stolleraman GH**: Controlled studies of streptococcal pharyngitis in a pediatric population. I. Factors related to the attack rate of rheumatic fever. New Eng J Med 265: 559, 1961

4. **Stolleraman GH, Siegel AC, Johnson EE**: Variable epidemiology of streptococcal disease and the changing pattern of rheumatic fever. Mod Conc Cardiovasc Dis 34: 45, 1965


7. **Frank PF, Stolleraman GH, Miller LF**: Protection of a military population from rheumatic fever. JAMA 193: 775, 1965

8. **Parker MT, Tomlinson AJH, Williams REO**: Impetigo contagiosa: The association of certain types of *Staphylococcus aureus* and *Streptococcus pyogenes* with superficial skin infections. J Hyg 53: 458, 1955


*Circulation, Volume XLIII, June 1971.*


Rheumatogenic and Nephritogenic Streptococci
GENE H. STOLLERMAN

Circulation. 1971;43:915-921
doi: 10.1161/01.CIR.43.6.915

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/43/6/915.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/