NOWHERE HAVE THE POWER—and the limitations—of antimicrobial agents been more clearly revealed than in the control of rheumatic heart disease. On the one hand, we have an organism which in the test tube is exquisitely and uniformly sensitive to penicillin. And we can point with pride to the remarkable prophylactic record of antimicrobials in reducing the frequency of rheumatic recurrences. On the other hand, we must be cautious in attributing our currently favorable position exclusively or even primarily to the use of antimicrobials. A close examination of the statistics reveals that the rheumatic fever problem was declining before these agents were available. The reasons for the beginning decline before the antibiotic era are obscure—possibly due to socioeconomic improvements such as changes in housing or even in nutrition. Since the reasons for this are obscure we must be guarded in our optimism that this trend will continue forever downward. Above all, we must not become mesmerized into believing that antibiotics are the final answer to the rheumatic fever problem, that all we have to do is improve our delivery of health care—spread enough penicillin widely and judiciously—and the disease will disappear completely and permanently.

We still have problems. Even with throat cultures, we have problems in identifying and differentiating streptococcal infections. Despite uniform in vitro sensitivity, we still see and are puzzled by failures in eradicating streptococci from patients who have received "adequate" or repeated penicillin treatment. There is a continuing significant prevalence of streptococcal infections and their complications in the United States. In the many developing countries of this world and among the poor of our own country, rheumatic fever persists as a major cause of heart disease. Lurking behind this is the possibility that the group A streptococci may some day suddenly develop an in vitro resistance to penicillin.

For these reasons it is important that we not only intensify our efforts to apply existing knowledge but continue to devote a significant proportion of our energies and resources to understanding the pathogenesis of rheumatic heart disease and to developing alternative approaches to its control.

Dr. T. Duckett Jones, whose contributions to this field we honor by this lecture series, put it this way: "The exact incidence of the disease, or the decrease in incidence or in severity, seems of less importance than the need to gain further knowledge of how and why human beings develop rheumatic fever . . . So long as surgeons find mitral stenosis requiring valvulotomy, or children and young adults continue to die of rheumatic fever and rheumatic heart disease, the problem exists. Rheumatic fever is and will remain with us until new knowledge and better preventive or therapeutic agents become available."

**Requirements for Development of Rheumatic Fever**

For more years than most of us would like to admit, the basic skeleton of the sequence of events leading to the development of rheumatic heart
disease has been clear. Although intensive research has impressively expanded our knowledge of the biology of the group A streptococcus, and in recent years has revealed a bewildering and fascinating plethora of cross-reactions between streptococcal antigens and various mammalian tissues, we still have difficulties in fitting all of the pieces together in an all-embracing and workable concept of the pathogenesis of rheumatic heart disease.

From a critical review of the evidence, one can single out a few absolute requirements for the development of acute rheumatic fever (table 1). First, the presence of a group A streptococcus. Second, a streptococcal antibody response, probably indicative that actual recent infection has occurred. Third, treatment studies indicate the necessity for the persistence of the organism in order for this complication to occur. Fourth, the infection must be located in the upper respiratory tract.

**Importance of Site of Infection**

Textbooks and investigators have paid insufficient attention to the necessity for the infection to occur in the throat in order for heart disease to develop. This article will review the possible explanations for attraction of group A streptococci to the pharynx and the various bacteriologic, immunologic, and host factors that may contribute to the development of heart disease following infection at this location.

In recent years our laboratory has focused on the problems of streptococcal infections of the skin and their complications. While these studies have been of intrinsic interest, their most useful purpose may have been to sharpen our appreciation of the importance of the site of infection in the development of rheumatic fever.

For many years there have been casual retrospective observations suggesting that rheumatic fever does not follow streptococcal infection of the skin. The lack of carefully documented prospective studies and the ambiguity of the role of the streptococcus in the etiology of impetigo left considerable doubts about the validity of these observations.

Recent prospective studies in our laboratory and studies in other laboratories have dispelled these doubts. Although cultures of impetiginous lesions often contain a mixture of gram positive organisms, the streptococcus is the primary agent and the staphylococcus is a secondary invader in these mixed lesions. As in infections of the throat, the streptococcus in impetigo is in a high percentage of instances a group A streptococcus. Earlier difficulties in the M typing of impetiginous streptococci had suggested that they may be lacking or poor in M production and therefore relatively avirulent. It is now clear that these strains do produce M protein but have been impossible to M type because they represent previously undescribed M types for which no typing sera were available. The relative infrequency of demonstration of an elevated antistreptolysin O titer in impetigo has raised questions about the streptococcal etiology or the intensity of the inflammatory response, but as we shall see subsequently, patients with streptococcal impetigo often show a strong antibody response to other streptococcal antigens.

Lastly, the occurrence in some populations of repeated streptococcal infections of the skin due to a variety of types should provide an excellent situation for the development of rheumatic fever and yet rheumatic fever does not occur.

**Peculiarities of Streptococcal Impetigo**

Now let us examine some of the peculiarities of streptococcal impetigo and how these may relate to the failure of rheumatic fever to develop. First, in human volunteers it is possible to produce pharyngitis by simply placing group A streptococci in the nasopharynx. To produce cutaneous infections it is necessary to traumatize the skin and even with trauma one cannot produce these infections with consistency. Secondly, with streptococcal impetigo the initial lesion is vesicular. We never see vesicular lesions in streptococcal pharyngitis although we know that the mucous membranes of the oropharynx are able to react in this manner in response to certain viral agents. Impetiginous lesions are essentially painless whereas pain is often a prominent feature in streptococcal pharyngitis. Of considerable interest—and with perhaps greater implications as to the pathogenesis of rheumatic fever—is the fact that the serotypes of streptococci associated with impetigo are different from those associated with rheumatic fever.

### Table 1

<table>
<thead>
<tr>
<th>Sine Qua Non for ARF</th>
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<tr>
<td>1. Group A streptococcus</td>
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<tr>
<td>2. Antibody response</td>
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<tr>
<td>3. Persistence of organism</td>
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<tr>
<td>4. Upper respiratory tract site</td>
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ARF = acute rheumatic fever.
commonly associated with infection of the upper respiratory tract.\textsuperscript{12, 22}

The serotypes of streptococci associated with impetigo often have complicated and peculiar T-agglutination patterns, as originally pointed out by Parker and his coworkers\textsuperscript{29} in England. Most of these streptococci have been assigned high numbers in the M typing scheme since they have only recently been worked out. The numbers assigned to the most recently described new M types, most of which are associated with impetigo, can now be extended into the 60's.

The tendency for streptococcal impetigo to be more common in young children\textsuperscript{12} does not explain the failure of rheumatic fever to appear after infection at this site. Impetigo does occur in older children, and infancy is no absolute barrier to the development of rheumatic fever. The fact that impetigo is to a large extent a summer disease\textsuperscript{22} cannot explain the total absence of rheumatic fever following this cutaneous infection. Studies at Warren Air Force Base indicate that the attack rate of acute rheumatic fever following streptococcal infection in the summer does not differ from that following streptococcal infection in the winter.\textsuperscript{20}

Impetigo seems to be a disease predominantly of warmer climates,\textsuperscript{22} yet we have become increasingly aware of the prevalence of rheumatic heart disease in tropical\textsuperscript{31, 32} as well as temperate climates. Lastly, the streptococcal serotypes associated with impetigo are found in the upper respiratory tract, but their appearance at this site is delayed and rarely results in clinical signs of infection.\textsuperscript{20}

A series of careful longitudinal studies in our laboratory conducted by Drs. Ferrieri and Dajani\textsuperscript{20, 21} have traced quite clearly the path of migration of gram positive cocci associated with impetigo. Group A streptococci appear first on the normal skin where they can be isolated for an average period of eight days before lesions of impetigo which harbor streptococci of the same serologic type develop. These same streptococci are not found in the upper respiratory tract until two to three weeks after the development of skin lesions. Staphylococci follow a different route, appearing first in the upper respiratory tract, then on the normal skin, and finally in skin lesions.

Continuing with the peculiarities of streptococcal impetigo, we recognize that though it is now well established that group A streptococci can be found on the normal skin of children,\textsuperscript{17, 22} the existence of a true carrier state is questionable since it is not known whether these isolations mean repeated deposition with limited survival or prolonged viability and multiplication on the normal skin.\textsuperscript{13}

Experiments with human adult volunteers would suggest that streptococci are rapidly killed when implanted on the normal skin, probably due to the presence in sebum of unsaturated fatty acids which are bactericidal for group A streptococci.\textsuperscript{12} The importance of these lipids in the pathogenesis of streptococcal impetigo in children is unclear.

Moreover, the role of type specific immunity in protection against streptococcal infection of the skin is uncertain, both from epidemiologic evidence and from experimental impetigo in animals.\textsuperscript{12}

**Selective Antibody Responses in Impetigo**

Since immunologic concepts play a leading role in our theories of the pathogenesis of rheumatic fever, the selective antibody response following streptococcal impetigo is of special interest.\textsuperscript{12, 18, 22} Studies are now available from several different laboratories describing skin infections due to a variety of serologic types.\textsuperscript{18, 19, 24} These studies all agree that the antistreptolysin O response is feeble whereas the response to other antigens, specifically DNase B and hyaluronidase, is vigorous.

![Antibody Response by Site of Infection](image)

**Figure 1** Differences between antibody responses following infection at different sites. ASO = Antistreptolysin O.
The initial studies from our own laboratory\textsuperscript{18} in this area are summarized in fig. 1. With antistreptolysin O (ASO) we see a relatively poor response in skin infections as contrasted with a good response in throat infections, whereas with anti-DNase B we see a strong antibody response regardless of the site of infection. For two reasons it seemed unlikely to us that this difference in ASO response was due to a difference in the capacity of the infecting strains to produce streptolysin O. First, most of the strains in this outbreak were of a single type, type 49. Second, we could demonstrate no significant differences in \textit{in vitro} production of streptolysin O among strains isolated from the two sites. Our conclusion was that the site \textit{per se} was the important determinant in the antibody response.

**Serologic Types in Acute Nephritis**

Even though streptococcal impetigo does not result in acute rheumatic fever, it commonly results in acute nephritis following infection with specific nethritogenic types.\textsuperscript{22} It is of interest to note however that the specific streptococcal types leading to nephritis are different in the case of skin infections than they are in the case of throat infections.\textsuperscript{12, 22} The classic type leading to nephritis following infection of the throat is, of course, M type 12; that following infection of the skin is M type 49. The other types associated with nephritis are also different depending on the site of the preceding infection (table 2).

**Factors Attracting Streptococci to the Throat**

What are the factors that attract group A streptococci to the throat? We know relatively little about the determinants which result in localization at this site. However, recent studies by Swanson and his collaborators\textsuperscript{34} have indicated that the M protein of group A streptococci is located on fimbriae projecting from the surface of the organism. Further studies by Ellen and Gibbons\textsuperscript{35} have suggested that adherence of group A streptococci to oral epithelial cells is dependent upon the presence of these M protein-containing fimbriae. Figure 2 (upper left panel) shows M positive streptococci with fimbriae on their surfaces. Avirulent strains which lack these M protein-containing fimbriae (upper right, fig. 2) do not adhere to epithelial cells. Thus, M protein, which we have long known to play a role in resistance to phagocytosis, also appears to facilitate sticking to epithelial surfaces (lower panel, fig. 2) and may, by this mechanism, resist the removal of the organism by bathing secretions.

**Local Factors in Pathogenesis of Rheumatic Fever**

What are some of the local factors that might conceivably be important determinants in the pathogenesis of acute rheumatic fever? First, anatomic factors may play a role. For a number of years it has been postulated that lymphatic connections between the pharyngeal tissues and the heart may be a direct route for living streptococci, L-forms, or streptococcal products to pass from one site to another. As figure 3 from the recent Russian literature shows,\textsuperscript{36} some impressive connections between the tonsils and the heart have been demonstrated by injection of lymphatic channels in cadavers. However, direct evidence that streptococci or their products actually travel this route is not available.

The differences in serologic types of group A streptococci which infect the skin and those which infect the throat\textsuperscript{12, 22, 37} may be a valuable lead which should be carefully scrutinized. However, studies to date have not revealed any consistent differences in these strains which seem to relate to the pathogenesis of rheumatic fever.

The existence of a definite carrier state in the throat—and its possible absence on the skin—may also be a significant factor since antibiotic treatment studies have associated persistence of the organism with development of rheumatic complications.\textsuperscript{11}

Secretory factors may be important. Glynn and Holborow\textsuperscript{38} have postulated a role for salivary haptenes in the pathogenesis of rheumatic fever. The possibility that IgA, an important protein component of secretions of the upper respiratory tract, may play a role has not been explored. If one is intrigued by the possibility that rheumatic fever may be caused by a combined insult resulting from both viral and bacterial infection, as has been postulated by Birch et al.,\textsuperscript{39} it is of interest to note that the viruses commonly causing infection of the upper respiratory tract are often different from those causing infection of the skin.

<table>
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<th>Table 2</th>
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<td>Nephritogenic types of streptococci</td>
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<tr>
<td>Classic</td>
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<tr>
<td>Other</td>
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Local Inhibitors of Streptolysin O

Finally, the possibility that the cutaneous environment may provide important inhibitors of biologically active components of group A streptococci needs to be carefully examined. For example, cholesterol and other sterols are known to bind streptolysin O irreversibly and to inhibit both its hemolytic activity and its toxicity.\textsuperscript{46, 41} Cholesterol is a major component of the epidermal lipids, especially in children.\textsuperscript{42} We have to consider the possibility that the sterols in the skin may be binding to the streptolysin O produced at this site, thereby inhibiting not only its biologic activity but also its antigenicity. Indeed, Dr. Edward Kaplan in our laboratory has recently demonstrated that lipid extracts of rabbit skin contain a potent inhibitor of the hemolytic activity of streptolysin O.\textsuperscript{43} As shown in figure 4, Dr. Kaplan also found that these lipid extracts of skin also inhibit the antigenicity of this streptococcal product.\textsuperscript{43} Rabbits were injected...
intravenously with sublethal doses of streptolysin O with and without skin lipids. Rabbits receiving mixtures of streptolysin O and skin lipids showed significant depression in antibody response when compared with rabbits injected with streptolysin O and saline.

While the significance of these findings is uncertain, for some time it has been known that the risk of developing rheumatic fever is related to the magnitude of the immunologic response. Although a similar relationship has been shown with several different streptococcal antigens, the most extensive data concern the antibody response to streptolysin O. For both initial and recurrent attacks, the risk of developing rheumatic fever after group A streptococcal pharyngitis increases with an increase in the ASO response. Thus, in modifying the antigenic response to streptolysin O, skin lipids may influence the risk of developing this complication.

We must also consider that skin lipids may have a more direct effect. In addition to its hemolytic properties, streptolysin O is toxic for a variety of
CHAIN THAT LINKS THE HEART TO THROAT

Figure 4

Inhibition of antistreptolysin O response by lipid extracts of skin. SO = streptolysin O. Antistreptolysin O in Todd units.

other cells. Of special interest to the cardiologist is the finding that streptolysin O is a potent cardiotoxic agent. As little as 50μg injected into a rabbit results in complete disorganization of the cardiac cycle and death in cardiac standstill within a few minutes after injection. In the isolated perfused heart, irreversible disturbances of the conduction system have been demonstrated. More recently, Halbert and his coworkers have shown that streptolysin O has a toxic effect on isolated pulsating mammalian heart cells. On the panel on the left of figure 5 are shown intact actively pulsating heart cells. As shown in the panel on the right, within three minutes after exposure to streptolysin O, these cells stop beating and develop blebs. All of these toxic manifestations of streptolysin O are inhibited by cholesterol.

Cholesterol as it is circulating in the blood is in a bound form and does not inhibit streptolysin O. Even hypercholesteremic sera do not inhibit so that there may be something special about the state of cholesterol in the tissues which allows it to be inhibitory.

In recent years cholesterol has received such a hostile reception in cardiology circles that it is probably heresy to suggest that in some situations it may have a salutary effect. Perhaps it is time that someone puts in a good word for cholesterol.


Figure 5

Changes in mammalian myocardial cells produced by streptolysin O. 1a = normal cells; 1b = cells exposed to streptolysin O.

Circulation, Volume XLVIII, July 1973
In this regard it is of interest to recall the studies of Coburn\(^4\) of some years ago in which he thought that a factor in egg yolk was protective against rheumatic fever. It would be ironic indeed if our efforts to manipulate the diet, which are now being extended into the pediatric age group, would result in a population less susceptible to atherosclerosis but more susceptible to rheumatic fever.

**Summary and Conclusions**

To summarize, it is certain that cholesterol inhibits the hemolytic activity and the cardiotoxicity of streptolysin O and it is probable that it inhibits its antigenicity as well. Lipid extracts of skin containing cholesterol appear to inhibit both the hemolytic activity and the antigenicity of streptolysin O. Whether they inhibit its cardiotoxicity is unknown but it would seem likely that they may.

With the overriding dominance of immunologic theories, it has not been fashionable in recent years to consider that rheumatic fever may develop from a direct toxic effect of a streptococcal product. Yet none of the antibodies described to date—cross-reacting or otherwise—has been shown to have a cytotoxic effect on previously undamaged cells and for this as well as other reasons one cannot determine whether they are the cart or the horse. It is certainly possible that damage by a streptococcal toxin such as streptolysin O is necessary to initiate the rheumatic process, with cross-reacting antibodies or other factors contributing to its full development. And it is intriguing that this toxin may be inhibited when infection occurs at a particular site.

Obviously, the studies presented today are just a beginning, and much more work needs to be done to test the various hypotheses which have been mentioned.

One of the most serious handicaps to studies of the pathogenesis of rheumatic fever is the lack of a satisfactory laboratory model. With the notable exception of Glaser et al.,\(^48\) few investigators have considered the site of infection in attempting to develop animal models, but it would seem important that experimental pathologists pay more attention to this aspect of the problem.

Another question which needs better documentation is whether other kinds of streptococcal skin infections such as erysipelas and infected burns, which may involve deeper tissues, and whether infection at other nonpharyngeal sites such as infection of the genitourinary tract, also fail to result in rheumatic fever.

In conclusion, one of the most peculiar, constant, and neglected facets of the pathogenesis of rheumatic fever is the necessity that the initiating infection take place in the upper respiratory tract. In this analysis, I have used studies on streptococcal infections of the skin as a foil, exploring some of the local factors which might be significant determinants in the development of this complication. Critical examination of the accumulated data would suggest that the location of infection is equally as important as the infecting agent in the pathogenesis of rheumatic heart disease. For this reason, the site of infection deserves renewed attention by clinicians and investigators interested in rheumatic fever and its etiology.

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CHAIN THAT LINKS THE HEART TO THROAT


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