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Streptococcal Sore Throat, Rheumatic Fever, and Glomerulonephritis

The Unsolved Riddle of Rheumatic Fever and Glomerulonephritis

Colonization of the human throat by *Streptococcus pyogenes* can lead to an acute **pharyngitis**, which usually disappears after a few days. In some people whose throats are colonized, there are no apparent signs of infection, but serum antibodies against the bacteria appear, indicating that the body recognized the colonization as an infection. Viruses also cause sore throat. In fact, most sore throats are caused by viruses, not *S. pyogenes*, but streptococcal sore throat (**strep throat**) is potentially more dangerous. Complications of a streptococcal sore throat include heart valve damage (**rheumatic heart disease**) and **acute glomerulonephritis** (kidney damage). Damage to heart and kidney are not the result of a systemic bacterial infection. The bacteria are not found in the affected organs and have been cleared from the throat before the symptoms of these secondary complications begin to appear. Thus, rheumatic heart disease and glomerulonephritis must be caused either by toxic bacterial products that enter the bloodstream or by an autoimmune response triggered by bacterial antigens. Another seemingly innocuous skin disease caused by *S. pyogenes*, **impetigo (pyoderma)** can also be followed by glomerulonephritis. Strains that cause impetigo do not cause rheumatic heart disease.

Despite decades of study, the question of how streptococcal growth in the throat or on the skin causes these sequelae is still unanswered. Given this discouraging outcome, one might be forgiven for wondering whether there is any point in continuing to study the

problem. There are two reasons for making further attempts to understand how rheumatic heart disease and glomerulonephritis develop. First, rheumatic heart disease, after nearly disappearing in some parts of the world, has now reappeared. The incidence of glomerulonephritis has remained relatively constant. Thus, the two conditions have not ceased to be a problem. A second reason is that the development of a genetic system for *S. pyogenes* (see Chapter 10) is now making it possible to determine at a more sophisticated level which features of the bacteria contribute to disease. Also, the increasing number of transgenic lines with defined immune defects may provide new animal models that will help to determine how various parts of the immune response contribute to the pathology of these diseases. At present, there is no animal model for rheumatic heart disease, a problem that will have to be solved before much progress can be made.

Streptococcal Sore Throat

S. pyogenes pharyngitis (strep throat) is acquired by inhaling aerosols from an infected person or, less commonly, by eating food contaminated with *S. pyogenes*. Strep throat is seen most commonly in school-aged children, but outbreaks also occur in institutionalized populations such as military recruits at boot camp. The symptoms are inflamed throat and tonsils, often accompanied by fever. The inflamed area of the throat or tonsils has patches of pus (fibrin, PMNs, fragments of mucosal cells and bacteria). In older children and young adults, headache and abdominal pain are also frequent symptoms. There is a seasonal pattern of strep throat cases. Most are seen in late winter through early spring.

Rheumatic Fever

Rheumatic fever (RF) occurs in less than 3% of people with strep throat and is only caused by a small subset of *S. pyogenes* strains. Symptoms begin to appear several weeks after the sore throat has subsided. Some people who develop RF may not even have noticed sore throat symptoms. The most common symptom is a migrating arthritis (i.e., pain and swelling in first one joint and then another). The migrating arthritis is self-limiting, and the pain in the affected joint subsides within a few days. In about 50% of RF cases, however, damage to heart valves also occurs (rheumatic heart disease). In some cases, heart damage is serious enough to cause death. A relatively rare complication associated with RF is **chorea**, a set of neurological symptoms including uncoordinated movement, muscular weakness, emotional instability, and facial grimacing. People who have had one episode of RF frequently have multiple recurrences. RF was one of the most common causes of death in children prior to 1950. RF was also a common cause of heart damage in military recruits during World War II. After 1950, however, the incidence of RF declined steadily, and by 1980 cases of RF in developed countries had become quite rare. Recently, a resurgence of RF has occurred in the United States, although the incidence is still far lower than it was in the pre-1950 era. Some outbreaks have occurred among school-aged children. Others have occurred at military bases. During the period when the incidence of RF declined so drastically, the incidence of strep throat did not change appreciably. The decrease in incidence of RF in developed countries is thought to be due to early diagnosis and treatment of strep throat and improved hygiene.

Glomerulonephritis

Acute glomerulonephritis can occur as the aftermath either of strep throat or impetigo. Glomerulonephritis is most commonly seen in children and young adults and is more common in males than in females. Symptoms of glomerulonephritis normally appear about 10 days after the strep throat or skin infection. Symptoms include puffy eyelids, swollen ankles, decreased urination, blood in the urine, hypertension, and other symptoms associated with kidney dysfunction. Another feature of the disease is the decrease in concentration of C3 and other complement components in blood. In young children, symptoms normally disappear of their own accord after about 3 weeks without long-term damage. In teenagers and adults, permanent kidney damage or a chronic form of glomerulonephritis can occur although this form of the disease is rare.

Endocarditis

Endocarditis is an infection of the heart valve. It is not usually listed as one of the complications of strep throat, but it could be considered to be a long-term consequence of RF because people who have heart valve damage resulting from an episode of RF are more likely to have endocarditis than normal people. Also, their heart valves can be infected by bacteria that would not be able to cause infection in a normal heart valve. The reason for the increased susceptibility of people with heart valve damage is that the damage disrupts the smooth flow of blood through the valves and produces a turbulence that allows loose clots of platelets and fibrin to form on the valve. These loose clots are called **vegetation**. Bacteria that enter the bloodstream as a result of some sort of trauma or other

Movement Disorders in Children: Yet Another Consequence of Strep Throat?*

Sydenham's chorea, a condition in which the arms and legs flail rapidly and uncontrollably, has long been known to be a rare complication of strep throat in children. Recently the possibility has been raised that some less severe types of movement disorder in children might also be complications of strep throat. These include tics of the face and neck, as well as other types of involuntary spasms often seen in children who are hyperactive or have learning disorders. The evidence that points to *S. pyogenes* as a possible cause of the movement disorders is indirect. Children with these disorders more frequently have antibodies to *S. pyogenes* than normal children, and most of them have antibodies that cross-react with human nerve tissue, a relatively uncommon type of antibody response to *S. pyogenes*. At present, the connection between movement disorders and strep throat is speculative but intriguing. The connection, if it exists, could be complicated by genetic factors that make some children more likely to develop this particular sequela of a strep throat infection. The importance of establishing whether a connection exists between strep throat and movement disorders other than chorea is that it underscores the importance of early and aggressive treatment of strep throat in children. Although it would be wrong to say that pediatricians no longer take strep throat seriously, the fact that rheumatic fever had virtually disappeared in developed countries until recently has had the effect of reducing concern about strep throat, both among physicians and parents.

*Adapted from K. A. Fackelmann. 1993. Does strep trigger movement disorders? Sci. News 144:39.

infection adhere to valve tissue. Vegetation forms around them and protects them from phagocytes. Thus bacteria that would normally be eliminated by circulating phagocytes can colonize the defective valve. Endocarditis is a serious disease that can be fatal if not treated promptly and aggressively with antibiotics. There are two types of endocarditis, acute bacterial endocarditis and subacute bacterial endocarditis. **Acute endocarditis** is characterized by rapid onset of symptoms and high fatality rate and can occur in people with normal heart valves as well as in people with damaged heart valves. It is caused by virulent bacteria such as *S. aureus*, *S. pyogenes*, and *N. gonorrhoeae*, which have the virulence factors that allow them to evade the host's immune system, colonize the valve, and damage it. **Subacute bacterial endocarditis** has a slower, more insidious onset and usually occurs only in people with damaged heart valves. It is caused by bacteria that normally would not be able to survive host defenses and can survive only in the protective vegetation that develops on damaged valves. Prominent among the bacteria that cause subacute bacterial endocarditis are α-hemolytic streptococci, a major component of the resident microflora of the mouth and throat. Although subacute endocarditis develops more slowly than acute endocarditis, it is a serious disease that can cause further heart damage and death.

Virulence Factors

A number of virulence factors of *S. pyogenes* have already been described in Chapter 10. Only those that may contribute to strep throat, rheumatic fever, and glomerulonephritis are discussed here.

Colonization of Throat and Skin

Because the mucosal membrane of the throat is protected by the washing action of saliva, bacteria that colonize the throat must be able to adhere to mucosal cells. At one time it was thought that the main adhesin of *S. pyogenes* was a fimbrial structure consisting of M protein and lipoteichoic acid (LTA). However, recent work has shown that a mutant lacking M protein adhered to epithelial cells, as well as the wild type. Thus, M protein does not function as an adhesin in the throat. It is still possible that LTA is involved in adherence, possibly in a complex with a protein other than M protein, but this possibility remains to be proved. A newly discovered streptococcal surface protein, **protein F**,

mediates adherence to pharyngeal cells and may be the main streptococcal adhesin. Protein F binds fibronectin, a protein found on pharyngeal cells and in many parts of the body. A mutant in which the gene encoding F was insertionally disrupted no longer adhered to cultured epithelial cells. Moreover, when the cloned F gene was introduced into a nonadhering gram-positive bacterium, *Enterococcus faecalis*, the *E. faecalis* strain carrying the cloned DNA was now able to adhere to pharyngeal cells. There is some recent evidence that M protein might mediate attachment to keratinocytes, a type of cell in skin. Thus, M protein could be involved in colonization of skin.

Some strains that cause RF have a thick hyaluronic acid capsule. The presence of this capsule gives bacteria growing on agar medium a wet appearance (mucoid). Hyaluronic acid is a common constituent of human tissue and is normally not immunogenic. It now appears that injection of capsular material does elicit antibody production in animals, indicating that there are important differences between this capsule and human hyaluronic acid. The capsule is antiphagocytic and could protect bacteria growing in the throat from killing by phagocytes. It may also delay recognition of the bacteria by the immune system. Whatever the level of protection afforded by the capsule, it is not sufficient to allow the bacteria to persist indefinitely because strep throat resolves without treatment. Also, nonmucoid strains can cause RF. The connection between this type of capsule and RF remains a mystery. M protein is also antiphagocytic (see Chapter 10).

Ability to Provoke an Intense Inflammatory Response

Symptoms of strep throat (swelling, pain, and pus formation) are probably due mainly to the ability of *S. pyogenes* to produce an intense inflammatory response. Two types of *S. pyogenes* products could explain this response. First, *S. pyogenes* produces a variety of hydrolytic enzymes, including hemolysins, proteases, DNases, and streptokinases. These enzymes may contribute to tissue damage, which, in turn, causes inflammation. Second, peptidoglycan fragments and teichoic acid trigger the complement cascade and elicit cytokine release. An interesting unanswered question is why some people carry *S. pyogenes* in their throats for prolonged periods without developing strep throat or its sequelae. This could be due to differences in virulence of different *S. pyogenes* strains or to immunity to *S. pyogenes*. Strains carried for a prolonged period after an infection commonly exhibit a shortened form of M protein. This could reflect a strategy for evasion of the host's immune response.

The Classical View: Rheumatic Fever and Glomerulonephritis Are Autoimmune Diseases

Rheumatic fever and glomerulonephritis are often cited as classical cases of autoimmune disease triggered by bacteria. This view of the two diseases is summarized in Figure 28-1. *S. pyogenes* colonizing the throat is continually being lysed as the host inflammatory response tries to clear the bacterial colonization. Fragments of *S. pyogenes* enter the bloodstream and provoke an antibody response. People with rheumatic fever and glomerulonephritis produce high levels of antibodies to SLO and other streptococcal antigens, including M protein. There are at least 80 M serotypes, but only a few are associated with rheumatic fever. M protein serotypes found on rheumatogenic strains have epitopes that cross-react with epitopes on cardiac myosin and **sarcolemmal membrane** proteins. Thus, T cells or antibodies that recognize these epitopes could attack heart tissue and cause an inflammatory response that damages heart valves. If rheumatic fever is an autoimmune disease, this would explain the lag of several weeks between the infection and the onset of symptoms. In people with glomerulonephritis, high levels of antibodies to streptococcal antigens interact with antigens circulating in the bloodstream, producing antibody-antigen complexes that accumulate in the kidney. Immune complexes of this sort can provoke an inflammatory response, which would attack kidney tissue and interfere with normal kidney function. Antigen-antibody complexes are visible in the glomeruli of the kidneys of people with glomerulonephritis. The decrease in C3 and other complement components seen in people with this condition also supports the hypothesis that inflammation is occurring.

The Revisionist View: Cytotoxins Play a Role

An alternative view of the cause of RF and glomerulonephritis, which is now becoming more popular, is that these conditions are caused by streptococcal toxins. The main argument against this view is the time lag between the initial infection and the development of RF (several weeks) or glomerulonephritis (10 days). Normally symptoms due to action of an exotoxin would appear within a week of the infection. Glomerulonephritis is thus considered the most likely of the two conditions to be caused by a toxin. *S. pyogenes* produces a number of proteins that could damage host organs by acting directly on them. Three toxic products of *S. pyogenes* have been advanced as candidates: **streptolysin O (SLO), streptokinase,** and streptococcal pyrogenic exotoxins (Spe; see Chapter 10). SLO is a cy-

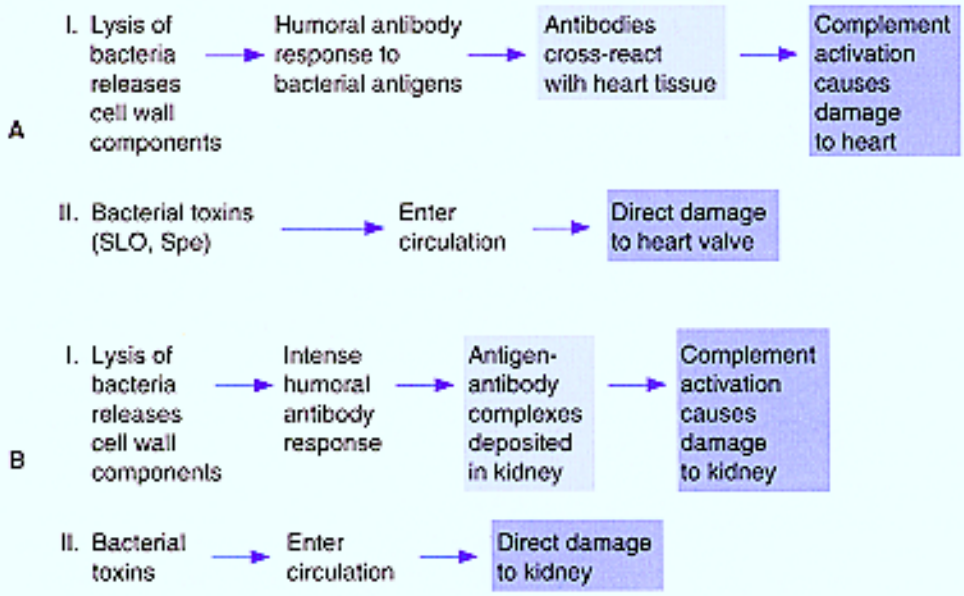

Figure 28-1 Hypotheses about the pathogenesis of RF (**A**) and acute glomerulonephritis (**B**).

totoxin with a mechanism and amino acid sequence similar to that of pneumolysin (see Chapter 27). SLO is a pore-forming toxin that lyses erythrocytes and kills a number of other cell types. In particular, SLO damages heart tissue when injected into laboratory animals. Thus, it might have a role in rheumatic heart disease. SLO is a highly immunogenic protein, and people with streptococcal infections frequently have high serum anti-SLO titers. The presence of anti-SLO antibodies indicates that SLO does enter the circulation during streptococcal infections and thus raises the question of whether enough SLO could reach the heart to have a direct toxic effect on heart valve tissue. Streptokinase is a hydrolytic enzyme that converts plasminogen into plasmin. Streptokinase from some strains of *S. pyogenes* reportedly causes the symptoms of glomerulonephritis in animals. The hypothesis that there is a connection between streptokinase and glomerulonephritis is controversial but interesting. The basis for suggesting the superantigen Spe as a possible cause of RF is that rheumatogenic strep throat strains produce Spe, whereas nonrheumatogenic strains do not. Also, Spe enhances cardiotoxicity caused by SLO when injected into animals. So far, the proponents of this hypothesis have not explained the long lag between the precipitating infection and the development of RF.

More Unanswered Questions

Two mysterious features of RF are not explained by any of the hypotheses described earlier. A person with strep throat can be treated with antibiotics as late as 9 days after the symptoms become apparent and still be protected from RF. After 9 days, toxic bacterial proteins should already be circulating in the blood, and the immune response (although it would not have reached its peak) should be well underway. A second unexplained feature of RF is connected with recurrences of the disease. Normally recurrences are due to infection with a different strain of *S. pyogenes*, but some people are reinfected by the same strain. In these people, RF symptoms take as long to develop after a reinfection as in the original episode. If symptoms are caused by an autoimmune response, they might be expected to appear much more rapidly after the second exposure. A possible explanation is that the first episode of RF actually occurs after the second (not the first) exposure to the bacteria. That is, a previous exposure primed the immune system to give the response seen as RF following a subsequent infection.

Treatment and Prevention

Strep throat is a self-limiting infection, but it is important to treat strep throat cases with antibiotics to prevent development of RF and acute glomerulonephritis. Only about a quarter of *S. pyogenes* strains cause RF or glomerulonephritis, and not all people who are colonized with these strains develop the complications, but because of the potential seriousness of these complications, it is desirable to use antibiotics to treat any case of strep throat even though only a minority of cases would actually lead to complications. In outbreaks of streptococcal sore throat, prophylactic antibiotic therapy should help to limit the spread of the bacteria.

However, this approach is not invariably successful. In a recent outbreak among military recruits at a Marine Corps base, prophylactic administration of penicillin did not stem the outbreak. The reason for this failure is not clear because in other cases prophylactic treatment was successful in stopping an outbreak.

Although it is important to treat streptococcal sore throat with antibiotics, it is also important not to use antibiotics unnecessarily. Because most sore throats are caused by viruses, which are not affected by antibacterial antibiotics and do not cause RF or glomerulonephritis, a definite diagnosis of streptococcal sore throat should be made before antibiotics are prescribed. Many clinicians (especially older ones) remain convinced of their ability to diagnose strep throat on the basis of symptoms alone, despite numerous clinical studies that have demonstrated conclusively that diagnosis on the basis of symptoms is unreliable. A simple and reliable type of diagnostic test is to inoculate a blood agar plate with a throat swab, incubate overnight at 37°C and check for β-hemolytic colonies. There are also several rapid identification tests on the market based on serological tests for group A streptococcal antigens. These tests are specific for *S. pyogenes* but are not very sensitive. Thus, although they are more rapid than the blood agar plate method, they give a high percentage of false negatives. A person with strep throat is treated with penicillin. So far, strains of *S. pyogenes* have remained uniformly susceptible to penicillin. Penicillin allergic individuals are treated with erythromycin. A person who develops RF must usually take antibiotics for long periods to prevent a recurrence of infection leading to repeated episodes of heart damage.

Endocarditis is a serious, potentially life-threatening infection that must be treated promptly with antibiotics. Because so many types of bacteria can cause endocarditis, choice of the appropriate antibiotic can be problematic. Dentists have been advised to give penicillin prophylactically to any patients having dental surgery who have a history of rheumatic heart disease. The rationale for this treatment is that penicillin would kill bacteria escaping into the bloodstream from the mouth (because oral streptococci are uniformly susceptible to penicillin) and thus reduce the chance that the bacteria would colonize damaged heart valves. This seemed like a reasonable strategy, but a recent retrospective comparison of dental patients with a history of RF who did or did not receive antibiotic prophylaxis prior to oral surgery found no difference in the incidence of endocarditis. Apparently, the recommended antibiotic regimen is not working, but it is not clear why.

SELECTED READINGS

Bisno, A. L. 1991. Group A streptococcal infections and acute rheumatic fever. N. Engl. J. Med. **325**:783–788.

Caparon, M. G., D. S. Stephens, A. Olsen, and J. R. Scott. 1991. Role of M protein in adherence of group A streptococci. Infect. Immun. **59**:1811–1817.

Hall, G., S. A. Hedstrom, A. Heimdahl, and C. E. Nord. 1993. Prophylactic administration of penicillins for endocarditis does not reduce the incidence of postextraction bacteremia. Clin. Infect. Dis. **17**:188–194.

Hanski, E., P. A. Horwitz, and M. G. Caparon. 1992. Expression of protein F, the fibronectin-binding protein of *Streptococcus pyogenes* JRS4, in heterologous streptococcal and enterococcal strains promotes their adherence to respiratory epithelial cells. Infect. Immun. **60**:5119–5125.

Hultgren, S. J., S. Abraham, M. Caparon, P. Falk, J. W. St. Gemme, and S. Normark. 1993. Pilus and nonpilus bacterial adhesins: Assembly and function in cell recognition. Cell **73**:887-901.

Schlievert, P. M. 1993. Role of superantigens in disease. J. Infect. Dis. **167**:997–1002.

SUMMARY

1. Streptococcal sore throat, caused by *S. pyogenes*, can be followed by three serious complications: rheumatic heart disease (heart valve damage), chorea (neurological damage), and glomerulonephritis (kidney damage). Strep throat is usually acquired by inhaling aerosols and is most common in school-aged children and in crowded populations such as military recruits. The symptoms vary somewhat with age, but inflamed throat and tonsils with patches of pus and fever are typical. Most cases occur in late winter to early spring.

2. Symptoms of rheumatic fever begin to appear several weeks after the throat infection has subsided and sometimes occur in people with no recollection of a symptomatic sore throat. The most common symptom is a self-limiting, migrating arthritis, but heart valve damage also occurs in about 50% of cases. A less common symptom, chorea, is due to neurological damage. These symptoms are not due to bacterial infection of the affected organs but to some direct or indirect effect of circulating bacterial products. The incidence of RF declined between 1950 and the late 1980s, and had become quite rare in developed countries. During recent years, however, there have been a number of outbreaks

of RF in schoolchildren and military recruits. The reason for the resurgence is probably the return of strains able to cause the condition. Rheumatic fever incidence has remained a problem in developing countries, which did not experience the decline seen in developed countries.

3. Acute glomerulonephritis may occur after streptococcal sore throat or skin infections. It is most common in boys. The symptoms are due to kidney dysfunction caused by inflammation. The incidence of glomerulonephritis, unlike that of RF, has remained relatively constant throughout the century.

4. Increased risk of endocarditis (infection of the heart valves) could be viewed a long-term complication of rheumatic heart disease. Valve damage sustained during an attack of rheumatic heart disease causes a turbulence in blood flow that favors formation of loose clots of platelets and fibrin (vegetations) on the valves. Bacteria that would normally be killed by blood phagocytes can grow in the vegetations where they are protected from phagocytes. Subacute bacterial endocarditis occurs primarily in people with damaged heart valves.

5. Adherence of *S. pyogenes* to the epithelial cells of the throat appears to be mediated by a fibronectin-binding protein, protein F, but there could be other adhesins that contribute. M protein is not involved in adherence to pharyngeal cells, as was once thought to be the case, but could be important in colonizing skin. M protein is also antiphagocytic. Some rheumatogenic strains have a hyaluronic acid capsule that may protect them from phagocytosis and delay recognition of the bacteria by the immune system. These defenses are not sufficient to prevent the inflammatory response from clearing the bacterial infection of the throat, usually within a matter of days. *S. pyogenes* products cause an intense inflammatory response. Products that may contribute to inflammation include a variety of hydrolytic enzymes that cause tissue damage, and cell wall fragments that activate the complement cascade and trigger the release of cytokines. *S. pyogenes* produces several cytotoxins. One of these, streptolysin O (SLO), is related to pneumolysin and is also a pore-forming toxin. SLO lyses erythrocytes and kills a number of other cell types, including heart cells. SLO is highly immunogenic, and anti-SLO antibodies are seen in the serum of people recovering from strep throat. Another toxin is Spe, a superantigen.

7. There are two competing hypotheses about the cause of RF and glomerulonephritis. The best-established one is that both conditions are examples of autoimmune disease. In the case of RF, epitopes on M protein cross-react with epitopes on heart tissue, and this might trigger an attack on the heart by the immune system. In the case of glomerulonephritis, high concentrations of antigen-antibody complexes form and are deposited in the kidney, where they may provoke an inflammatory response that damages the kidney. The alternative hypothesis is that streptococcal toxins such as SLO or Spe damage heart and kidney directly. The main argument against the toxin hypothesis is the long lag time between the bacterial infection that precipitated the complications and the development of symptoms.

8. Strep throat is self-limiting, but it must be treated with antibiotics (penicillin or erythromycin) to prevent development of complications. Patients who develop RF are usually given long-term penicillin therapy to prevent reinfection. Endocarditis must also be treated with antibiotics.

QUESTIONS

1. Symptoms associated with damage to heart valves are seen in both RF and bacterial endocarditis. How do the two conditions differ?

2. Summarize the arguments that RF and glomerulonephritis are autoimmune diseases brought on by a bacterial infection.

3. How would you settle the controversy over whether an autoimmune response to bacterial antigens or direct action of toxic products of *S. pyogenes* are responsible for the symptoms of RF and glomerulonephritis?

4. Should a vaccine against *S. pyogenes* be developed? What characteristics would such a vaccine have to have?

5. Compare and contrast the virulence factors of *S. pneumoniae* with the virulence factors of *S. pyogenes* that are covered in this chapter.

6. Compare and contrast rheumatic fever/rheumatic heart disease with invasive *S. pyogenes* disease (see Chapter 10) and with diphtheria (see Chapter 9).