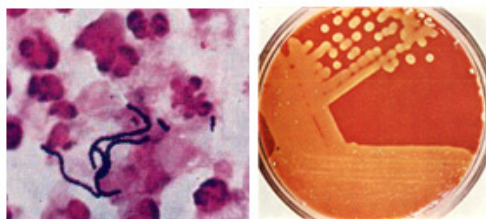


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STREPTOCOCCUS PYOGENES

Introduction

Streptococcus pyogenes (Group A streptococcus) is a Gram-positive, nonmotile, nonsporeforming coccus that occurs in chains or in pairs of cells. Individual cells are round-to-ovoid cocci, 0.6-1.0 micrometer in diameter (Figure 1). Streptococci divide in one plane and thus occur in pairs or (especially in liquid media or clinical material) in chains of varying lengths. The metabolism of *S. pyogenes* is fermentative; the organism is a catalase-negative aerotolerant anaerobe (facultative anaerobe), and requires enriched medium containing blood in order to grow. Group A streptococci typically have a capsule composed of hyaluronic acid and exhibit beta (clear) hemolysis on blood agar.



***Streptococcus pyogenes*. Left. Gram stain of *Streptococcus pyogenes* in a clinical specimen. Right. Colonies of *Streptococcus pyogenes* on blood agar exhibiting beta (clear) hemolysis.**

Group A streptococci are parasites of humans, and *Streptococcus pyogenes* is one of the most frequent pathogens of humans. It is estimated that between 5-15% of normal individuals harbor *Streptococcus pyogenes*, usually in the respiratory tract, without signs of disease. When the host defenses are compromised, or when the organism is able to exert its virulence, or when it is introduced to vulnerable tissues or hosts, an acute infection occurs.

In the last century, infections by *S. pyogenes* claimed many lives especially since the organism was the most important cause of **puerperal fever** (sepsis after childbirth). **Scarlet fever** was formerly a severe complication of streptococcal infection, but now, because of antibiotic therapy, it is little more than streptococcal **pharyngitis** accompanied by rash. Similarly, **erysipelas** (a form of cellulitis accompanied by fever and systemic toxicity) is less common today. However, there has been a recent increase in variety, severity and sequelae of *Streptococcus pyogenes* infections, and a resurgence of severe invasive infections, prompting descriptions of "flesh eating bacteria" in the news media. A complete explanation for the decline and resurgence is not known. Today, the pathogen is of major concern because of the occasional cases of rapidly progressive disease and because of the small risk of serious sequelae in untreated infections. These diseases remain a major worldwide health concern, and effort is being directed toward clarifying the risk and mechanisms of these sequelae and identifying rheumatogenic and nephritogenic strains of streptococci.

Acute *Streptococcus pyogenes* infections may present as **pharyngitis** (strep throat), **scarlet fever** (rash), **impetigo** (infection of the superficial layers of the skin) or **cellulitis** (infection of the deep layers of the skin). Invasive, toxigenic infections can result in **necrotizing fasciitis**, **myositis** and **streptococcal toxic shock syndrome**. Patients may also develop immune-mediated **post-streptococcal sequelae**, such as acute **rheumatic fever** and acute **glomerulonephritis**, following acute infections caused by *Streptococcus pyogenes*.

Bacterial Diseases

- [Protein Toxins](#)
- [Endotoxins](#)
- [Anthrax \(General Information\), \(Technical Information\)](#)
- [Botulism and Tetanus](#)
- [Chlamydia](#)
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Streptococcus pyogenes produces a wide array of **virulence factors** and a very large number of diseases. Virulence factors of Group A streptococci include: (1) **M protein**, cell-associated protein (**Protein F**) and **lipoteichoic acid** for adherence; (2) **hyaluronic acid capsule** as an immunological disguise and to inhibit phagocytosis; **M-protein** to inhibit phagocytosis (3) **invasins** such as **streptokinase**, **streptodornase** (DNase B), **hyaluronidase**, and **streptolysins**; (4) **exotoxins**, such as pyrogenic (erythrogenic) toxin which causes the rash of **scarlet fever** and systemic **toxic shock syndrome**.

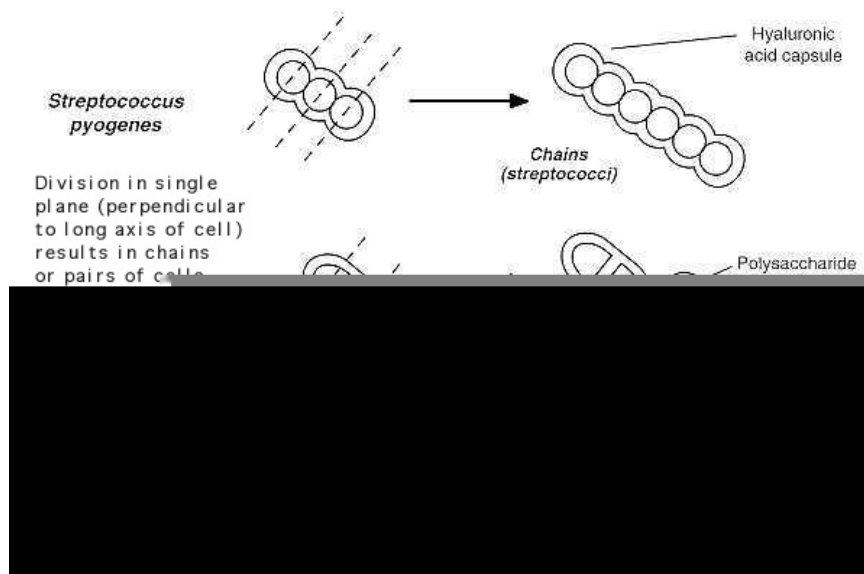


FIGURE 1. Morphology of the *Streptococcus pyogenes* and *Streptococcus pneumoniae* in comparison with staphylococci. Streptococci divide in a single plane and tend not to separate, resulting in chains or pairs of cells.

Classification of Streptococci

Hemolysis on blood agar

The type of hemolytic reaction displayed on blood agar has long been used to classify the streptococci. **Beta-hemolysis** is associated with complete lysis of red cells surrounding the colony, whereas **alpha-hemolysis** is a partial or "green" hemolysis associated with reduction of red cell hemoglobin. Nonhemolytic colonies have been termed gamma-hemolytic. Hemolysis is affected by the species and age of red cells, as well as by other properties of the base medium. **Group A streptococci are nearly always beta-hemolytic**; related Group B can manifest alpha, beta or gamma hemolysis. Most strains of *S. pneumoniae* are alpha-hemolytic but can cause β -hemolysis during anaerobic incubation. Most of the oral streptococci and enterococci are non hemolytic. The property of hemolysis is not very reliable for the absolute identification of streptococci, but it is widely used in rapid screens for identification of *S. pyogenes* and *S. pneumoniae*.

Antigenic types

The cell wall structure of Group A streptococci is among the most studied of any bacteria (Figure 2). The cell wall is composed of repeating units of N-acetylglucosamine and N-acetylmuramic acid, the standard peptidoglycan. Historically, the definitive identification of streptococci has rested on the serologic reactivity of cell wall polysaccharide antigens as originally described by Rebecca Lancefield. **Eighteen group-specific antigens (Lancefield groups) were established**. The Group A polysaccharide is a polymer of N-acetylglucosamine and rhamnose. Some group antigens are shared by more than one species.

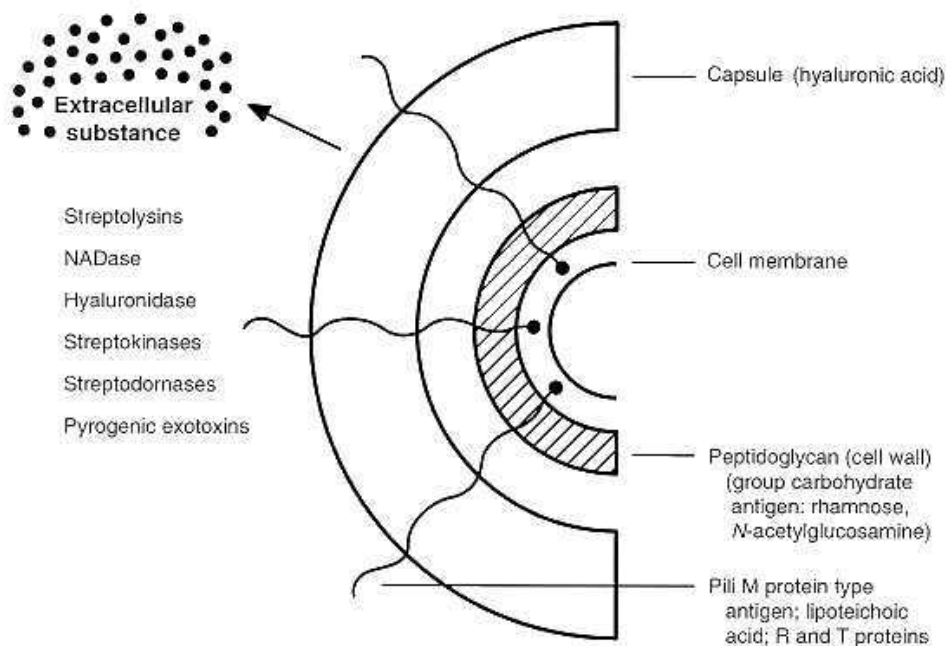


FIGURE 2. Cell surface structure of *Streptococcus pyogenes* and secreted products involved in virulence.

Pathogenesis

Streptococcus pyogenes owes its major success as a pathogen to its ability to colonize and rapidly multiply and spread in its host while evading phagocytosis and confusing the immune system. **Acute diseases** associated with *Streptococcus pyogenes* occur chiefly in the **respiratory tract, bloodstream, or the skin**. Streptococcal disease is most often a respiratory infection (pharyngitis or tonsillitis) or a skin infection (pyoderma). *S. pyogenes* is the leading cause of uncomplicated bacterial pharyngitis and tonsillitis commonly referred to a strep throat (Figure 3). *S. pyogenes* infections can also result in sinusitis, otitis, mastoiditis, pneumonia, joint or bone infections, necrotizing fasciitis and myositis, meningitis or endocarditis. *S. pyogenes* also infects the skin. Infections of the skin can be superficial (impetigo) or deep (cellulitis). Scarlet fever and streptococcal toxic shock syndrome are systemic responses to circulating bacterial toxins. Two post streptococcal sequelae (rheumatic fever following respiratory infection and glomerulonephritis following respiratory or skin infection), occur in 1-3% of untreated infections. These conditions and their pathology are not attributable to dissemination of bacteria, but to aberrant immunological reactions to Group A streptococcal antigens.

The **cell surface** of *Streptococcus pyogenes* accounts for many of the bacterium's determinants of virulence, especially those concerned with colonization and evasion of phagocytosis and host immune responses. Cell surface components include **capsular polysaccharide, peptidoglycan** and **lipoteichoic acids**, and **certain membrane proteins**, in addition to several **structural proteins** (Figure 2).

In Group A streptococci, the R and T proteins are used as epidemiologic markers and have no known role in virulence. The **M proteins** are clearly virulence factors associated with both **colonization and resistance to phagocytosis**. More than 50 types of *S. pyogenes* M proteins have been identified on the **basis of antigenic specificity**, and it is the M protein that is the major cause of antigenic shift and antigenic drift in the Group A streptococci. The streptococcal M protein, peptidoglycan, N-acetylglucosamine, and group-specific carbohydrate portions of the cell surface all have antigenic epitopes that mimic those of mammalian muscle and connective tissue. The cell surface of recently emerging (³flesh-eating²) strains of streptococci is distinctly mucoid (indicating that they are highly encapsulated) and rich in M protein. **Protein F**, thought involved in attachment to fibronectin, is presumably a nonfimbrial adhesin located on the bacterial cell surface.

The **capsule** of *S. pyogenes* is non antigenic since it is composed of **hyaluronic acid**, which is chemically similar to that of host connective tissue. This allows the bacterium to hide its own antigens and to go unrecognized as antigenic by its host. The cytoplasmic membrane of *S. pyogenes* contains some antigens similar to those of human cardiac, skeletal, and smooth

muscle, heart valve fibroblasts, and neuronal tissues, resulting in **molecular mimicry** and a tolerant or suppressed immune response by the host.

Colonization of tissues by *S. pyogenes* is thought to result from a failure in the innate defenses (normal flora and other nonspecific defense mechanisms) which allows establishment of the bacterium at a portal of entry (often the upper respiratory tract or the skin) where the organism multiplies and causes an inflammatory purulent lesion. Some strains of streptococci show a predilection for the respiratory tract; others, for the skin. Generally, streptococcal isolates from the pharynx and respiratory tract do not cause skin infections.

There is abundant evidence that *Streptococcus pyogenes* utilizes **lipoteichoic acids** in the cell wall as adhesins. The lipoteichoic acid (LTA) is anchored to proteins on the bacterial surface, including the **M protein**. Both the M proteins and lipoteichoic acid are supported externally to the cell wall on fimbriae and appear to mediate bacterial adherence to host epithelial cells. It was been proposed that both LTA and the M protein are needed for attachment to mucosal surfaces and that this explains the role of the M protein as a determinant of virulence (Nonetheless, the M protein is a proven determinant of virulence since it inhibits phagocytic ingestion of non-opsonized streptococci.). A nonfimbrial protein (**Protein F**) has also been shown to mediate streptococcal adherence to the amino terminus of fibronectin on mucosal surfaces.

Extracellular products: invasins and exotoxins

Colonization of the upper respiratory tract and acute pharyngitis may spread to other portions of the upper or lower respiratory tracts resulting in infections of the middle ear (otitis media), sinuses (sinusitis), or lungs (pneumonia). In addition, meningitis can occur by direct extension of infection from the middle ear or sinuses to the meninges or by way of bloodstream invasion from the pulmonary focus. Bacteremia can also result in infection of bones (osteomyelitis) or joints (arthritis). During these aspects of acute disease the streptococci bring into play a variety of secretory proteins that mediate their invasion.

For the most part, streptococcal invasins and protein toxins interact with mammalian blood and tissue components in ways that kill host cells and provoke a damaging inflammatory response. The soluble extracellular growth products and toxins of *Streptococcus pyogenes* (see Figure 2), have been studied intensely. **Streptolysin S** is an oxygen-stable leukocidin; **Streptolysin O** is an oxygen-labile leukocidin. NADase is also leukotoxic. **Hyaluronidase** (the original ³spreading factor²) can digest host connective tissue hyaluronic acid as well as the organism's own capsule. Streptokinases participate in fibrin lysis. **Streptodornases A-D** possess deoxyribonuclease activity; Streptodornases B and D possess ribonuclease activity as well. Protease activity similar to that in *Staphylococcus aureus* has been shown in strains causing soft tissue necrosis or toxic shock syndrome. This large repertoire of products is important in the pathogenesis of *S. pyogenes* infections. Even so, antibodies to these products are relatively insignificant in protection of the host.

Three **pyrogenic exotoxins** (formerly known as **Erythrogenic toxin**) of *S. pyogenes* (SPEs) are recognized: types A, B, C. These toxins act as **superantigens** by a mechanism similar to those described for staphylococci. As antigens, they do not requiring processing by antigen presenting cells. Rather, they stimulate T cells by binding class II MHC molecules directly and nonspecifically. With superantigens about 20% of T cells may be stimulated (vs 1/10,000 T cells stimulated by conventional antigens) resulting in massive detrimental cytokine release. SPEs A and C are encoded by lysogenic phages; the gene for SPE B is located on the bacterial chromosome. Re-emergence in the late 1980's of these exotoxin-producing strains has been associated with a toxic shock-like syndrome similar in pathogenesis and manifestation to staphylococcal toxic shock syndrome and other forms of invasive disease associated with severe tissue destruction.

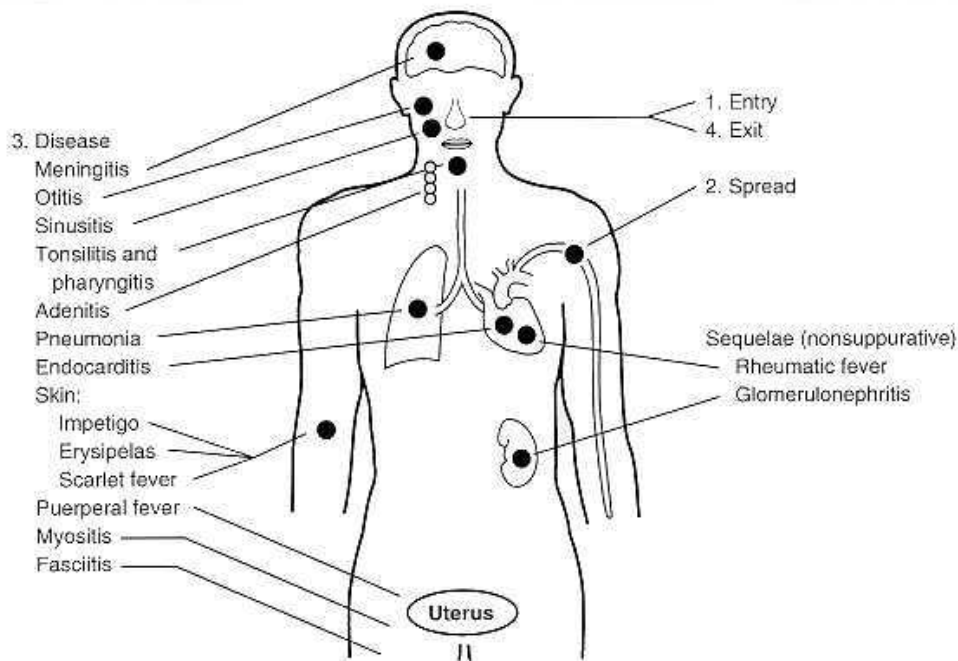


FIGURE 3. Pathogenesis of *Streptococcus pyogenes* infections.

Post streptococcal sequelae

Infection with *Streptococcus pyogenes* can give rise to serious **nonsuppurative sequelae**: acute **rheumatic fever** and acute **glomerulonephritis**. These sequelae begin 1-3 weeks after the acute illness, a latent period consistent with an immune-mediated etiology. Whether all *S. pyogenes* strains are rheumatogenic is controversial; however, clearly not all strains are nephritogenic.

Acute **rheumatic fever** is a sequel only of pharyngeal infections, but acute **glomerulonephritis** can follow infections of the pharynx or the skin. Although there is no adequate explanation for the precise pathogenesis of acute rheumatic fever, an abnormal or enhanced immune response seems essential. Also, persistence of the organism on pharyngeal tissues (i.e., the tonsils) is associated with an increased likelihood of rheumatic fever. Acute rheumatic fever can result in permanent damage to the heart valves. Less than 1% of sporadic streptococcal pharyngitis infections result in acute rheumatic fever; however, recurrences are common, and life-long antibiotic prophylaxis is recommended following a single case.

Acute glomerulonephritis results from deposition of antigen-antibody-complement complexes on the basement membrane of kidney glomeruli. The antigen may be streptococcal in origin or it may be a host tissue species with antigenic determinants similar to those of streptococcal antigen (cross-reactive epitopes for endocardium, sarcolemma, vascular smooth muscle). The incidence of acute glomerulonephritis in the United States is variable, perhaps due to cycling of nephritogenic strains, but it appears to be decreasing. Recurrences are uncommon, and prophylaxis following an initial attack is unnecessary.

Host defenses

S. pyogenes is usually an **exogenous secondary invader** following viral disease or disturbances in the normal bacterial flora. In the normal human the skin is an effective barrier against invasive streptococci, and nonspecific defense mechanisms prevent the bacteria from penetrating beyond the superficial epithelium of the upper respiratory tract. These mechanisms include mucociliary movement, coughing, sneezing and epiglottal reflexes. The **host phagocytic system** is a second line of defense against streptococcal invasion. Organisms can be opsonized by activation of the classical or alternate complement pathway and by anti-streptococcal antibodies in the serum. *S. pyogenes* is rapidly killed following phagocytosis enhanced by specific antibody. The bacteria do not produce catalase or significant amounts of superoxide dismutase to inactivate the oxygen metabolites (hydrogen peroxide, superoxide) produced by the oxygen-dependent mechanisms of the phagocyte. Therefore, they are quickly killed after engulfment by phagocytes.

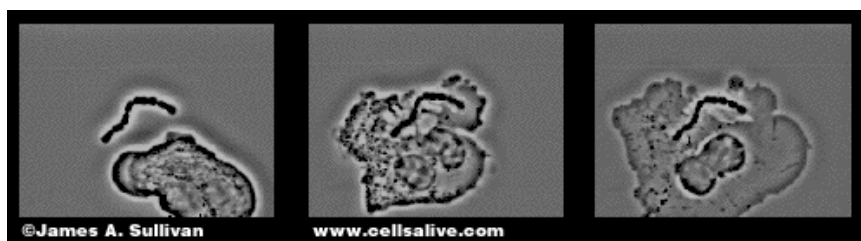


FIGURE 4. Phagocytosis of *Streptococcus pyogenes* by a macrophage.

The hyaluronic acid capsule, of course, allows the organism to evade opsonization. The capsule is also an antigenic disguise that hides bacterial antigens and is non antigenic to the host. Actually, the hyaluronic acid outer surface of *S. pyogenes* is weakly antigenic, but it does not result in stimulation of protective immunity. The only protective immunity that results from infection by Group A streptococcus comes from the development of type-specific antibody to the M protein of the fimbriae, which protrude from the cell wall through the capsular structure. This antibody, which follows respiratory and skin infections, is persistent. Presumably, protective levels of specific IgA is produced in the respiratory secretions while protective levels of IgG are formed in the serum. Sometimes, intervention of an infection with effective antibiotic treatment precludes the development of this persistent antibody. This accounts, in part, for recurring infections in an individual by the same streptococcal strain. Antibody to the erythrogenic toxin involved in scarlet fever is also long lasting.

The occurrence of cross-reactive antigens in *S. pyogenes* and various mammalian tissues possibly explains the autoimmune responses that develop following some infections. The antibody mediated immune (AMI) response (i.e., level of serum antibody) is higher in patients with rheumatic fever than in patients with uncomplicated pharyngitis. In addition, cell-mediated immunity (CMI) seems to play a role in the pathology of acute rheumatic fever.

Treatment and prevention

Penicillin is still uniformly effective in treatment of Group A streptococcal disease. It is important to identify and treat Group A streptococcal infections in order to prevent sequelae. No effective vaccine has been produced.

Table 1. Summary of virulence determinants of *Streptococcus pyogenes*

Adherence (colonization) surface macromolecules

M-protein

Lipoteichoic acid

Protein F

Enhancement of spread in tissues

Hyaluronidase hydrolyses hyaluronic acid, part of the ground substance in host tissues.

Proteases

Evasion of phagocytosis

Capsule: hyaluronic acid is produced.

C5a peptidase: C5a enhances chemotaxis of phagocytes .

M protein is a fibrillar surface protein. Its distal end bears a negative charge that interferes with phagocytosis. Mutations during the course of infection alter the structure of M proteins, rendering some antibodies ineffective. Strains that persist in carriers frequently exhibit altered M proteins.

Leukocidins are proteins secreted by the streptococci that kill phagocytes.

Defense against host immune responses

Antigenic disguise and tolerance provided by hyaluronic acid capsule

Antigenic variation. Antibody against M protein (antigen) is the only effective protective antibody, but there are more than 50 different M types, and subsequent infections may occur with a different M serotype.

Production of toxins and other systemic effects

Toxic shock: Exotoxin is superantigen that binds directly to MHC II (without being processed) and binds abnormally to the T cell receptor of many (up to 20% of) T cells. Exaggerated production of cytokines causes the signs of shock: fever, rash, low blood pressure. aberrant interaction between toxin, macrophage, and T cells.

Induction of circulating, cross-reactive antibodies

Some of the antibodies produced during infection by certain strains of streptococci cross-react with certain host tissues. These antibodies can indirectly damage host tissues, even after the organisms have been cleared, and cause autoimmune complications.

Table 2. Summary of diseases caused by *Streptococcus pyogenes*

Suppurative conditions (active infections associated with pus) occur in the throat, skin, and systemically.

Throat

Streptococcal pharyngitis is acquired by inhaling aerosols emitted by infected individuals. The symptoms reflect the inflammatory events at the site of infection. A few (1-3%) people develop rheumatic fever weeks after the infection has cleared.

Skin

Impetigo involves the infection of epidermal layers of skin. Pre-pubertal children are the most susceptible. Cellulitis occurs when the infection spreads subcutaneous tissues. Erysipelas is the infection of the dermis. About 5% of patients will develop more disseminated disease. Necrotizing fasciitis involves infection of the fascia and may proceed rapidly to underlying muscle.

Systemic

Scarlet fever is caused by production of erythrogenic toxin by a few strains of the organism.

Toxic shock is caused by a few strains that produce a toxic shock-like toxin.

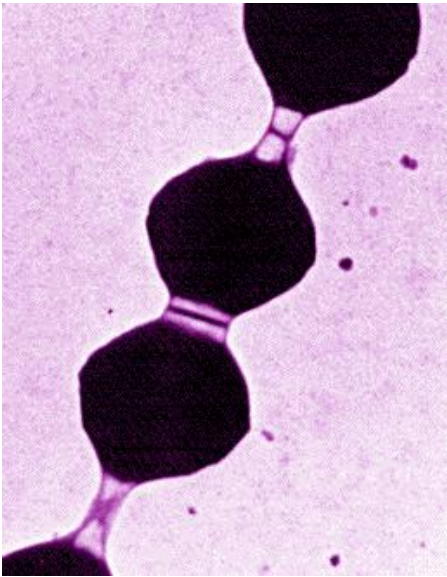
Non-suppurative Sequelae

Some of the antibodies produced during the above infections cross-react with certain host tissues. These can indirectly damage host tissues, even after the organisms have been cleared, and cause non suppurative complications.

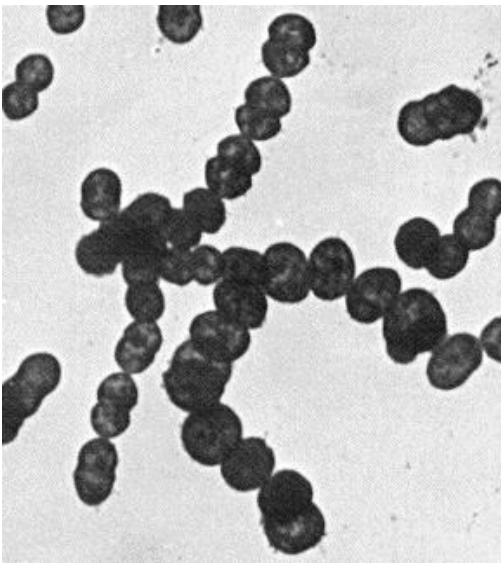
Rheumatic fever. M protein cross reacts with sarcolemma. Antibodies cross-react with heart tissue, fix complement, and cause damage.

Glomerulonephritis. Antigen-antibody complexes may be deposited in kidney, fix complement, and damage glomeruli. Only a few M-types are nephritogenic.

Gallery of electron micrographs of *Streptococcus pyogenes* from The Laboratory of Pathogenesis and Immunology at Rockefeller University, the home of research on *Streptococcus pyogenes*.



Dividing streptococci (12,000X)



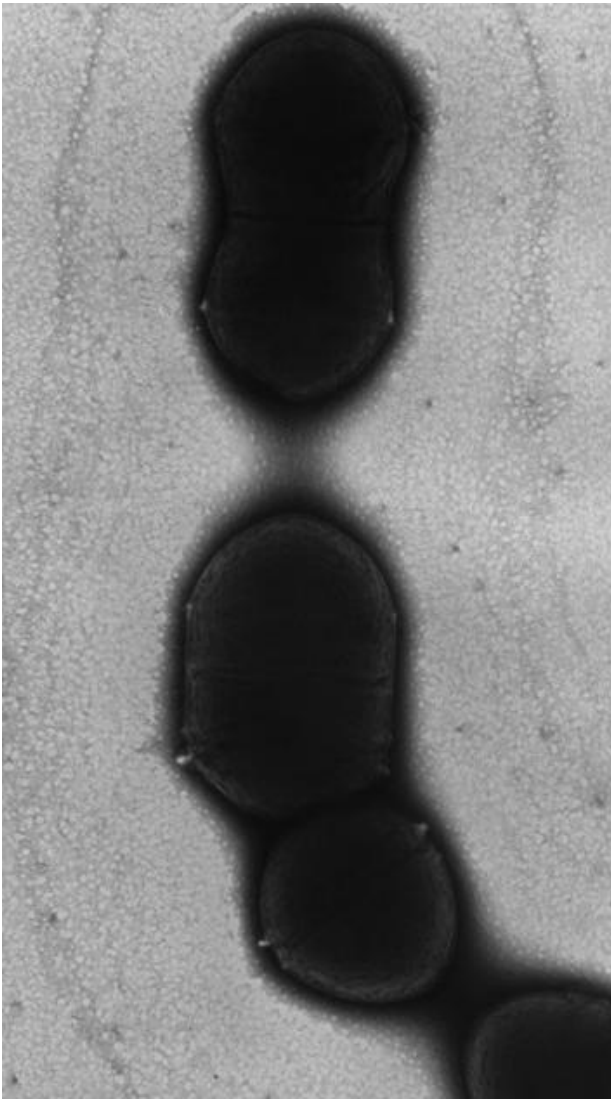
(6,500X)

Critical point dried whole group A streptococci (*Streptococcus pyogenes*) viewed directly by transmission electron microscopy (TEM). Chains of streptococci are clearly evident. To remove cell surface proteins, cells were treated with trypsin prior to preparation and mounting. Strain: D471; M-type 6.



(20,000X)

Electron micrograph of an ultra-thin section of a chain of group A streptococci. The cell surface fibrils, consisting primarily of M protein, are clearly evident. The bacterial cell wall, to which the fibrils are attached, is also clearly seen as the light staining region between the fibrils and the dark staining cell interior. Incipient cell division is also indicated by the nascent septum formation (seen as an indentation of the cell wall) near the cell equator. The streptococcal cell diameter is equal to approximately one micron.



(28,000X)

Negative staining of group A streptococci viewed by TEM. The "halo" around the chain of cells (approximately equal in thickness to the cell diameter) is the remnants of the capsule that may be found surrounding the exterior of certain strains of group A streptococci. The septa between pairs of dividing cells may also be seen.



(70,000X)

High magnification electron micrograph of an ultra-thin section of a group A streptococcus sibling pair. At this magnification, especially in the cell on the left, the cell wall and cell surface fibrils, consisting primarily of M protein, are well defined. Interdigitation of these fibrils

between neighboring cells of different chains is also in plain view. Strain: C126/21/1; M-type 43.