Emerging Infections 1
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Chapter 7

The Reemergence of Severe Group A Streptococcal Disease: an Evolutionary Perspective

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Emerging infections can be defined as those diseases that have newly appeared in the population or have existed previously but are rapidly increasing in incidence or geographic range (164–167, 221). Reasons for disease emergence may include changes in the pathogen, the host, or the environment. The dynamics may be sufficiently complex that the occurrence appears inexplicable. Rates of mortality and morbidity for group A streptococcal disease have changed over the years. A dramatic decline in severe infections occurred through the middle half of this century, although the overall prevalence of colonization and infection with the organism remained the same (197). In the mid-1980s, a resurgence of severe group A streptococcal infections was recognized in developed countries worldwide. While the reasons for the emergence of many infections have been elucidated, the reason for the decrease in severity of infections due to group A streptococci in the middle part of this century and the relatively sudden resurgence of serious disease have not been explained. Is the resurgence of severe group A streptococcal disease the result of natural selection moving towards the creation of a fitter pathogen, or is it the result of a rare event(s) against a background of widespread colonization and frequent episodes of less-severe disease? In this chapter, we review changes in the epidemiology of group A streptococcal infections and describe factors associated with the fitness and virulence of the pathogen. In doing so, we also highlight the genetic diversity of group A streptococci, which, acted on by host factors, may account for periodic changes in disease severity.

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EVOLUTION AND MAINTENANCE OF VIRULENCE IN PATHOGENS

The fitness of a pathogen can be defined as its ability to multiply within a host, disseminate from that host, translocate to a new host, colonize the new host, and cause infection (139). This can be distinguished from the virulence of a pathogen, which refers to the severity of clinical illness resulting from infection. The question of whether and how the virulence of a pathogen is linked to its transmissibility and therefore to its fitness has arisen (67, 136). Virulence was previously considered an artifact of recent associations between a microorganism and its hosts; otherwise, a microorganism-host relationship would evolve towards benign coexistence. A fully evolved organism would not harm the host it needs for its survival, proliferation, and transmission. However, more recent views believe that natural selection may favor the evolution and maintenance of some level of virulence as well as commensal and symbiotic associations between microorganisms and their hosts (67, 135–137, 139, 204). Natural selection can favor strains of increased virulence if the more virulent strains have some advantage to offset the loss of transmission opportunities that result from killing or debilitating their hosts (6, 138, 139). Advantages include higher rates of transmissibility, increased resistance to host defense, and the ability to compete with other strains of the same pathogen within a single host.

There are a number of reasons why increased virulence may not always decrease transmissibility. Disease symptoms may result from pathogen multiplication in a compartment of the body other than the compartment in which transmissible organisms are produced. Disease may also occur in a dead-end host. Moreover, a strain may cause severe disease in only a small population of individuals and therefore have little impact on overall transmission.

If virulence and transmission are positively correlated for some pathogens, then the genes determining virulence may be under strong selection. Pathogens which have greater genetic variability have more potential for evolving virulent strains (67). It is now recognized that in group A streptococci such genetic variability exists as a result of intra- and intergenic recombination of virulence genes (67, 116, 123, 170, 171, 228, 247).

FITNESS OF GROUP A STREPTOCOCCI

Transmissibility of Group A Streptococci

Group A streptococci, for which humans are the major reservoir, have demonstrated their fitness by possessing characteristics which allow them to effectively multiply within and disseminate from their hosts and translocate to and colonize new hosts. The ability to transmit was documented long before the discovery of the bacterium itself (198, 199). Childbed fever was one of the most frequent causes of death among postpartum women (31, 87). Holmes in 1858 and Semmelweis in 1861 described the transmission of this disease and provided guidelines for its control (87). Transmission of group A streptococci has been demonstrated to occur in the community and in closed populations including families, colleges, the mil-

itary, nursing homes, hospitals, and day care centers (24, 44, 60, 68, 88, 96, 106, 197, 199, 213).

The skin and the mucous membranes of the respiratory tract are the primary sites of group A streptococcal colonization and infection. It has long been recognized that there are discrete populations of streptococci that have a predilection for the skin or the respiratory tract and some populations that are associated with both (5, 7, 20, 59, 114, 238). Symptomatic skin and throat infections occur in >50% of individuals after acquisition of the organism, but asymptomatic colonization is common at both sites (71, 88, 96, 109, 145, 199). In asymptomatic carriers, the organism can persist for prolonged periods, especially if it is carried in the throat (71, 78). Risk factors for pharyngitis include the age of the patient and certain serotypes (88, 96, 109). Skin infections are most likely to occur after a break in the cutaneous epithelium (71, 145).

Transmission of group A streptococci can occur as the result of direct contact with infectious secretions and/or indirectly as the result of airborne transmission or contamination of the environment or food. The method of transmission depends on whether the site of colonization or infection is the skin or the respiratory tract. Transmission to the respiratory tract requires a fairly large inoculum ($\geq 10^5$ organisms), which can be achieved only as a result of direct contact or the ingestion of contaminated food (39, 56, 69, 140, 203). Contagiousness is greatest during acute respiratory infections, whereas chronic carriers are of relatively low risk as infectious sources (86, 128). Transmission to the skin may occur by different routes. The respiratory tract does not appear to be a reservoir for autoinoculation to the skin. Ferrieri et al. (71), in a prospective study of the cutaneous acquisition of group A streptococci, clearly showed that the organism was recovered from the skin 14 and 20 days before being recovered from the nose and throat, respectively. They also demonstrated that among family members the mean interval from index to secondary skin acquisition of streptococci was 4.8 days.

Colonization of nonintact skin or of the endometrium in the postpartum patient requires a much smaller inoculum than colonization of the respiratory tract. In addition to direct contact, it can occur as a result of environmental contamination or airborne transmission (15, 85, 148, 150, 152, 157, 206, 208, 222). Group A streptococci can survive for prolonged periods in the environment (38, 203, 205). Although Rammelkamp et al. (203) reported that streptococci isolated from dust in military barracks lost their ability to cause pharyngitis, these authors did not assess the organism's ability to cause wound infections.

Fitness Determinants in Group A Streptococci

Genetic Organization and Control of Expression of Fitness Determinants

One of the original and most important fitness determinants to be discovered was the M protein. The M protein of group A streptococci was first described in 1928 by Rebecca Lancefield (131). Antibodies to M proteins identified serotypes and could also facilitate opsonophagocytosis of the corresponding isolates by phagocytic cells present in human blood. These studies formed the basis for attributing an antiphagocytic role to M protein and established this structure as a major vir-

ulence factor of group A streptococci (72, 131). More recently, analysis of the genes coding for M proteins have shown that M protein genes (*emm*) are members of a larger *emm*-like gene family and that many group A streptococci express more than one M-like protein (Mrp or Enn) and a complement-inactivating C5a peptidase (ScpA) (17–19, 35, 89, 90, 99, 183). These genes are transcribed under the positive control of the Mga regulator (multigene regulator of group A streptococcus) (26, 124, 153), a protein which has the characteristics of a response regulator of a two-component signal-transducing system (34, 188, 191). The sensory component has yet to be identified. The factors to which the Mga regulator has been found to be responsive include environmental and biological parameters, such as pH, temperature, partial CO_2 pressure, Fe^{2+} concentration, and late growth phase (151, 180, 193).

Other genes which Mga directly or indirectly controls include the fibronectin-binding serum opacity factor (OF) gene (*sof*) (127, 202); *sic*, which encodes an extracellular protein (SIC) that is a streptococcal inhibitor of complement-mediated lysis (4); the gene for streptolysin S, which causes lysis of host cell membranes (124); and *speB*, which encodes streptococcal pyrogenic exotoxin B, a precursor of an extracellular cysteine protease which has several virulence mechanisms (13, 62, 97, 117, 119, 195, 216). The *mga* and *mga*-dependent genes are referred to as the *vir* regulon (41). The *mrp*, *emm*, *enn*, and *scpA* genes are located in that order on the genome immediately downstream of the *mga* gene and are referred to as the core *vir* regulon (Fig. 1) (190, 195). Those virulence factors that are not associated with the *vir* regulon include the hyaluronic acid capsule, streptolysin O,

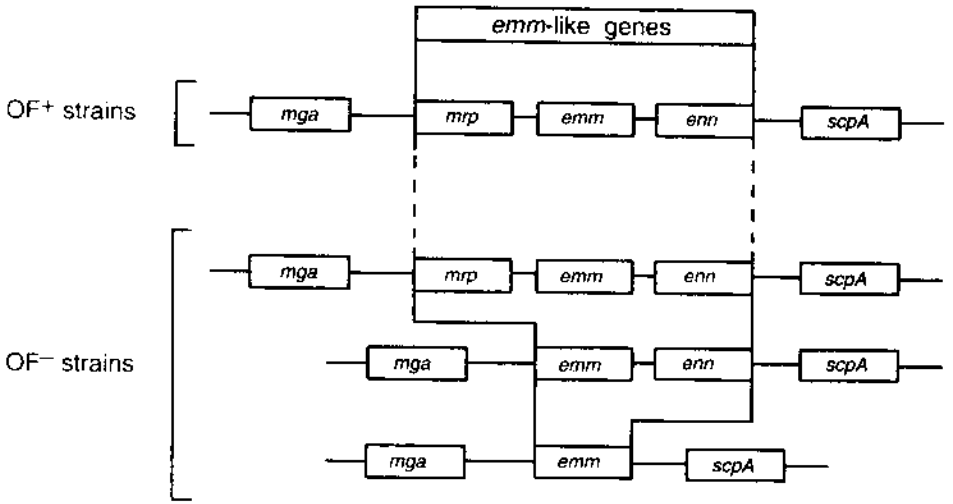

Figure 1. The *emm*-like genes of group A streptococci are located adjacent to each other at a chromosomal locus called the *vir* regulon, where they are flanked by a regulatory gene called *mga* and the *scpA* gene, which encodes a C5a peptidase. (Reprinted from *Trends in Microbiology* [123] with permission from M. A. Kehoe and Elsevier Science.)

hyaluronidase, streptokinase, a number of adhesins which facilitate colonization and invasion, and streptococcal superantigens.

Functional Classes of Fitness Determinants

A number of characteristics of group A streptococci may contribute to their fitness. These determinants can be categorized into three functional classes: adherence and colonization, invasion and replication, and avoidance of host defenses (137).

Adherence and colonization. Group A streptococcal attachment to host cells and colonization are prerequisites for streptococcal infection (Table 1). M and M-like proteins have been found to be involved in attachment of streptococci to a number of cell types (10, 27, 49, 66, 100, 232). Although M proteins are highly variable in size and sequence, their carboxy termini are all highly conserved. Much of the carboxy terminus of the M molecule is buried within the cell wall as an anchor. Adjacent to this sequence in all M proteins studied so far is the highly conserved repetitive element referred to as the C-repeat domain. This is comprised of at least two copies of the approximately 23-amino-acid C-repeat sequence separated by short, nonrepetitive spacer regions. The evolutionary conservation of this C-repeat region strongly suggests that it is important (74). The function of this region is to facilitate adherence to keratinocytes in the cutaneous epithelium and to bind factor H (73, 189).

M and M-like proteins bind membrane cofactor protein (MCP) (1, 181, 230). MCP, or CD46, is a protein found on the surface of keratinocytes. Binding of streptococci to MCP facilitates the adherence of group A streptococci to keratinocytes and their invasion through the epidermis, and it interferes with the function of MCP as a regulator of complement activation (73, 189).

The hyaluronic acid capsule has been shown to play a critical role in pharyngeal colonization and infection in mice (242). Husmann et al. (104), using a throat colonization mouse model, demonstrated that the hyaluronic acid capsule confers an important selective advantage for the survival of the bacteria in the upper respiratory tract. When a mutant containing a transposon inserted into the *hasA* gene was used, the incidence of throat colonization was significantly reduced in comparison to the incidence with the wild type.

Table 1. Possible virulence and transmissibility determinants of group A streptococci: adherence and colonization

Determinant	Characteristic(s)
M and M-like protein	Binds to membrane cofactor protein on keratinocytes and fibronectin, attaches to several host cell types
Hyaluronic acid capsule	Pharyngeal colonization
FBP54	Fibronectin and fibrinogen binding
OF	Fibronectin binding
28-kDa antigen	Fibronectin binding
Glyceraldehyde-3-phosphate dehydrogenase	Fibronectin binding
Proteins F, F2, and SfbI	Fibronectin binding
ZOP-binding pathway	Fibronectin binding

Streptococcal OF, an apoproteinase which cleaves high-density lipoprotein in sera, is produced by group A streptococci of certain M serotypes (127). The gene for OF (*sof*) is regulated by Mga and is located 15 kb from the core *vir* regulon (202). The OF molecule consists of three domains, including a domain responsible for the opacity reaction, a fibronectin-binding domain, and a cell attachment domain. OF production appears to be inversely related to the pathogenic potential of group A streptococci in that, compared to OF producers, OF nonproducers belong to serotypes more often associated with severe invasive infections (111). Strains which are OF^+ have diverged significantly from strains with OF^- serotypes. The *vir* regulon of most OF^+ strains appears to contain a triplet of *emm*-like genes in the order outlined in Fig. 1, whereas the structure varies among OF^- strains (including strains of the same M serotype), with some containing only a single *emm* gene between *mga* and *scpA* and others containing two or more *emm*-like genes (123).

Numerous other surface components of group A streptococci have been proposed as adhesins. Considerable evidence has accumulated to suggest that the organisms' ability to bind fibronectin plays an important role in their ability to adhere to epithelial cells (95). Fibronectin, a glycoprotein, can be found in a soluble form in most body fluids or in an immobilized form in association with cell surfaces or as a component of the extracellular matrix. Fibronectin has the ability to bind to a large, heterogeneous population of substrates, including integrins, collagens, fibrin, DNA, heparin, and other protein and nonprotein compounds (105). Its wide spectrum of binding activities, combined with its broad distribution in the host, makes it an attractive target as a microbial receptor. The proteins that have been implicated as fibronectin-binding adhesins in group A streptococci include the 28-kDa antigen (51), FBP54 (52), glyceraldehyde-3-phosphate dehydrogenase (186), M3 protein (211), OF (202), protein SfbI (161), protein F (81, 215), protein F2 (108), and the proteins in the ZOP-binding pathway (134).

The adhesins appear to have different functions, as evidenced by their specificity for various host cells, their variable presence in different strains, and the influence of environmental and biological factors on their expression. For example, M protein mediates adhesion to keratinocytes (182) as well as to respiratory epithelial cells (237) but not to Langerhans' cells, whereas fibronectin-binding proteins are essential for attachment to respiratory epithelial cells (92, 93, 227) and Langerhans' cells (182) but not keratinocytes (181, 186). Purified FBP54 blocks streptococcal adhesion to human buccal epithelial cells but not to HEp-2 cells, a human respiratory epithelial cell line (50).

Some adhesins are differentially regulated or modified by environmental factors (81, 134, 233). Investigators have speculated that this environmental regulation may optimize colonization and infection. In the cutaneous tissues, group A streptococci can initially colonize the surface of the skin since the aerobic environment allows expression of the appropriate adhesins. However, upon invasion of the bacterium into deeper tissues, where the environment is rich in CO_2 but poor in O_2, repression of the adhesin would facilitate bacterial dissemination (108, 233).

Invasion and replication. Group A streptococci possess characteristics that can facilitate their capacity to enter, survive in and replicate in the cells of their host (Table 2). M and M-related proteins bind to immunoglobulins in a nonimmune

Table 2. Possible virulence and transmissibility determinants of group A streptococci: invasion and replication

Determinant	Characteristics(s)
M protein	Binds to membrane cofactor protein on keratinocytes
M and M-like proteins	Nonimmune binding of immunoglobulins
Streptokinase	Converts plasminogen to plasmin
SPE B (cysteine protease)	Cleaves fibronectin and degrades vitronectin
SfbI	Binds fibronectin on epithelial cells and initiates internalization
Hyaluronic acid capsule	Invasion

fashion. The expression of immunoglobulin G (IgG)-binding properties of M and M-like proteins has been associated with the potential to invade from a cutaneous site in a mouse model and with resistance to phagocytosis (3, 77, 194, 200, 201). Among the group A streptococcal strains studied by Bessen and Fischetti, nearly all those from cases of impetigo bound IgG, suggesting that IgG-binding activity may play a critical role in establishing invasive infections from a cutaneous site (16). In a mouse skin infection model, it was found that immunoglobulin-binding protein expression by group A streptococci correlated with their ability to establish invasive cutaneous infections (201).

M and M-like proteins have also been found to possess binding properties for kininogen (9), plasmin(ogen) (14, 143), and albumin (1, 12). Ben Nasr et al. (12) demonstrated a binding region on the M protein for kininogens, which are multifunctional proteins consisting of high-molecular-weight kininogen (H-kininogen) and low-molecular-weight kininogen (L-kininogen). H-kininogen is part of the contact activation system of coagulation, which is activated upon contact with a negatively charged surface, including gram-positive and gram-negative bacteria (141). This may result in the local release of kinins, including bradykinin, which are potent proinflammatory peptides that mediate vasodilation, fever, and increased vascular permeability.

Streptokinase, which is produced by virtually all group A streptococci, is able to convert plasminogen to plasmin, a serine protease with broad specificity (142). Plasmin has been proposed as a potential agent for the degradation of extracellular matrix, and its production may contribute to the ability of group A streptococci to cause invasive infections (142). Under normal physiological conditions, free plasmin would not be readily available at the site of a streptococcal infection because of the tight regulation mediated by α_2-antiplasmin. Secretion of a bacterial plasminogen activator like streptokinase provides a source of plasmin, but the bacteria still have to compete with host regulators such as α_2-antiplasmin to capture the host protease. Group A streptococci stabilize plasmin activity not only by the binding of plasmin with the cell surface, either directly or through M proteins, but also via a second pathway dependent on plasminogen, fibrinogen, and streptokinase (14, 129, 236). In this pathway, fibrinogen binding to the bacterial cell surface provides a site for the subsequent binding of streptokinase-plasminogen complexes. This enables the organism to acquire an unregulatable surface protease that is capable

of hydrolyzing fibrin clots, in addition to providing an immobilized plasminogen activator which is not inhibited by α_2-antiplasmin (235).

There is evidence that fibronectin-binding proteins enhance the ability of some strains of group A streptococci to invade epithelial cells. Molinari et al. (161) demonstrated in vitro that the fibronectin-binding protein of group A streptococci (SfbI) was able to interact with fibronectin on HEp-2 cells and trigger internalization.

In order for organisms to multiply at the site of infection, they require nutrients essential for growth, including iron. Eichenbaum et al. (64) demonstrated that group A streptococci could not acquire iron from human transferrin and lactoferrin, suggesting that they do not produce siderophores. However, group A streptococci were able to lyse cells, which resulted in the release of intracellular iron-containing compounds, including heme, hemoglobin, myoglobin, and ferritin, and utilize them as a source of iron.

Avoidance of host defenses. *(i) Antiphagocytic properties.* Some characteristics of group A streptococci allow them to avoid host defenses (Table 3). The expression of IgG-binding properties of M and M-like proteins has been associated with resistance to phagocytosis (3, 77, 194, 200, 201). The antiphagocytic properties of M proteins have been clearly demonstrated. The molecular mechanism behind the antiphagocytic effect of M protein is not fully understood, but it has been suggested that the binding of fibrinogen to M protein could play a critical role (196, 207, 249).

The hyaluronic acid capsule has been shown to be involved in the pathogenicity of group A streptococci; strains isolated from patients with severe streptococcal infection and rheumatic fever are most likely to exhibit a capsule (111). By use of genetically defined acapsular mutants of group A streptococci, an increase of phag-

Table 3. Possible virulence and transmissibility determinants of group A streptococci: avoidance of host defences

Determinant	Characteristic(s)
M protein	Antiphagocytic due to binding of fibrinogen, binds kininogens with release of kinins
M and M-like proteins	Binds complement regulators factor H, C4BP, and MCP
C5a peptidase	Inactivates C5a, thus retarding influx of inflammatory cells and altering pathway of dissemination
SIC	Inhibits complement-mediated lysis
SPE B	Activates IL-1β; cleaves surface proteins from group A streptococci, which block neutrophil recruitment; cleaves urokinase plasminogen activator from the surface of monocytic cells; releases kinins from H-kininogen
Hyaluronic acid capsule	Antiphagocytic
Streptolysins O and S	Destruction of tissue and immune cells
SPE A, B, C and F	Superantigen-mediated release of cytokines
Streptococcal superantigen and *S. pyogenes* mitogen	Superantigen-mediated release of cytokines

ocytized bacteria by granulocytes and a decrease in virulence to mice were reported (243, 244). For many years, it was believed that the M protein was the primary determinant of resistance to phagocytosis. However, Dale et al. (54) found that the hyaluronate capsule and M proteins are variably important in resistance to opsonization and phagocytosis, depending on the serotype.

(ii) Anticomplementary properties. The efficacy of the complement system, a nonspecific defense mechanism against microbial infection, depends largely on a set of regulatory proteins which modulate complement activation in order to enhance phagocytosis and bacterial destruction while preventing nonspecific damage to host tissues. Group A streptococci interfere with complement regulation by using M and M-like proteins to bind three of these regulatory proteins: factor H, C4b-binding protein (C4BP), and MCP (1, 181, 230). Factor H is a crucial regulator of the complement system. It functions as a cofactor for the inactivation of C3b by factor I, inhibits the formation and function of C3/C5 convertase, and contributes to inhibition of the deposition of C3b on the streptococcal surface, a critical step for phagocytosis (102, 217). As noted above, one of the functions of the C-repeat region is to bind factor H. Perez-Casal et al. (189) constructed a mutant in which the entire C-repeat domain was deleted; they showed that binding of factor H was inhibited but that the mutant strain was still protected from phagocytosis, thereby separating these two functions of the M protein.

C4BP binds to C4b, accelerates the decay of C3 convertase, and functions as a cofactor in the factor I-mediated proteolytic inactivaion of C4b. Many strains of group A streptococci bind human C4BP via the M protein family by mimicking human C4b epitopes (1, 230). MCP, a protein found on the surface of keratinocytes, is bound by group A streptococci. This not only interferes with its function as a regulator of complement activation but also facilitates the adherence of group A streptococci to keratinocytes and their invasion through the epidermis (1, 181). Åkesson et al. (4) have identified another mechanism, present in some serotypes of group A streptococci, which is able to interfere with the complement system. A novel extracellular protein, SIC, which can inhibit complement-mediated lysis is produced. Of 55 different M serotypes investigated, Åkesson et al. were able to identify it only in M1 and M57 strains.

Activation of the alternate complement pathway produces C5a, which is one of the primary mediators of chemotaxis in human tissue, attracting neutrophils to sites of infection. C5a is inactivated by removal of its C-terminal arginine residue by a serum carboxypeptidase. Group A streptococci express a C5a peptidase (ScpA), which is highly specific for C5a (43). C5a is cleaved by C5a peptidase at the neutrophil-binding site. Ji et al. (110) found that localization of mutant (*scpA* insertion and deletion) streptococci in lymph nodes and spleens of infected mice was significantly different from that of wild-type streptococci. Mutagenized streptococci were transported to lymph nodes, whereas wild-type streptococci rapidly spread to the spleen. Therefore, expression of C5a peptidase may not only retard the influx of inflammatory cells but alter the pathway of dissemination of the infecting group A streptococci.

(iii) Cysteine protease function. Of the various streptococcal pyrogenic exotoxins (SPEs), SPE B has an important role in the invasiveness of group A streptococci. The SPE B structural gene (*speB*) is found in all isolates of the species

and is presumed to be chromosomally encoded (125, 179, 209). SPE B is a cysteine protease that is released extracellularly as a zymogen which is autotruncated to form a mature protease. The cysteine protease accounts for >95% of the total protein secreted by some strains (80). There is convincing evidence that streptococcal cysteine protease is an important virulence factor in streptococcal infections (13, 62, 97, 117, 119, 195, 216, 251). Patients with low acute-phase levels of serum antibody to it are more likely to die following an invasive group A streptococcal infection than are those with high serum antibody levels (101). In addition, active and passive immunization of mice with streptococcal cysteine protease provided significant protection when the mice were challenged with group A streptococci (117). Talkington et al. (229) found a significant association between extracellular protease production and soft tissue necrosis among invasive streptococcal strains recovered from patients. In vitro, streptococcal cysteine protease cleaves biologically inactive interleukin-1B (IL-1B) precursor to produce mature, active IL-1β, a major cytokine that mediates inflammation and shock (118). Streptococcal cysteine protease degrades extracellular matrix proteins such as fibronectin and vitronectin in vitro and augments lung injury induced by products of group A streptococci in vivo (119, 216). It releases biologically active fragments of surface proteins expressed by group A streptococci, including an internal fragment of C5a peptidase which blocks the recruitment of neutrophils to the site of infection (13).

Urokinase plasminogen activator receptor is a membrane-anchored protein that promotes pericellular proteolysis and cellular migration. Cysteine protease cleaves urokinase plasminogen activator receptor from the surfaces of monocytic cells, inhibiting urokinase plasminogen activator binding on monocytic cells not only by decreasing the level of functional cell surface receptor but also by releasing a soluble form of urokinase plasminogen activator receptor that competes with the cellular receptor (251). Finally, streptococcal cysteine proteases are able to directly release biologically active kinins from H-kininogen in vitro and from kininogens present in human plasma ex vivo (97).

(iv) Cytolysins. The majority of medically relevant pathogens produce pore-forming proteins (21). Many of these toxins have been designated hemolysins because of their lytic action on erythrocytes. However, it is now recognized that their biological significance derives from their action on nucleated cells and platelets. The toxins exert detrimental local effects by destroying tissue and immune cells, thereby contributing to pathogenesis. Streptolysin O is the prototype of a large family of cholesterol-binding cytolysins that are produced by gram-positive organisms, including all group A streptococci. Streptolysin O has also been demonstrated to stimulate neutrophil adherence by eliciting the expression of a glycoprotein adherence molecule. It is postulated that during infection, such increased adherence could lead to vascular leukostasis within lung and soft tissue microvasculature (25). Streptolysin S is a potent cytolytic toxin produced by nearly all group A streptococci. The cytolytic spectrum of streptolysin S includes erythrocytes, lymphocytes, neutrophils, platelets, and other cell types (124).

(v) Superantigens. Group A streptococci secrete a variety of biologically active proteins, including certain ones that are collectively referred to as superantigens because of their profound effects on the immune system (115). The normal function

of major histocompatibility complex (MHC) class II molecules is to present peptide antigens to T cells. The MHC class II molecule is used by superantigens as a specific cellular receptor (Fig. 2), and the complex of an MHC class II molecule and a superantigen stimulates a substantially larger number of T cells than does an antigen-specific response. In addition, superantigens stimulate lymphocytes expressing distinct T-cell antigen receptor (TCR) Vβ subsets. The effects of bacterial superantigens may cause an acute response, such as shock, or a chronic autoimmune-related response. The acute response to superantigens is mediated mainly by the release of proinflammatory cytokines, such as interferon-γ, IL-6, and tumor necrosis factor α (Fig. 3) (125). These cytokines are produced primarily by cells that express the CD4 cell surface molecule and have a T helper type 1 (T_H1) profile.

In group A streptococci there are six known superantigens: SPE A, B, and C; SPE F (mitogenic factor); streptococcal superantigen; and *Streptococcus pyogenes* mitogen. There are also others that have not yet been identified (13, 118, 119, 125, 162, 174, 239, 257). The SPEs share many biological properties, including fever induction and the ability to enhance susceptibility to endotoxic shock. SPE A has been shown to be expressed at approximately fourfold-higher levels in cells grown

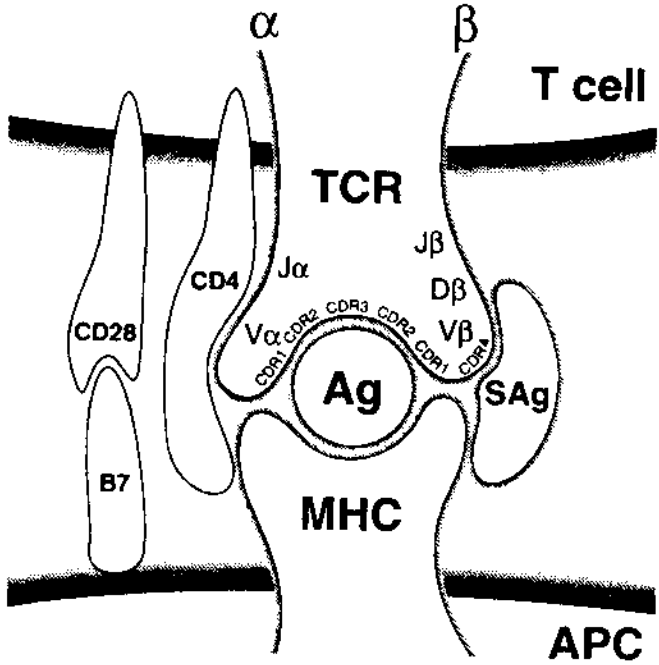

Figure 2. Bridging of T cells and antigen-presenting cells. A schematic model of a superantigen (SAg) interaction with a TCR and an MHC class II molecule is shown. APC, antigen-presenting cell; Ag, antigen. (Reprinted from *Clinical Microbiology Reviews* [125] with permission from M. Kotb and the American Society for Microbiology.)

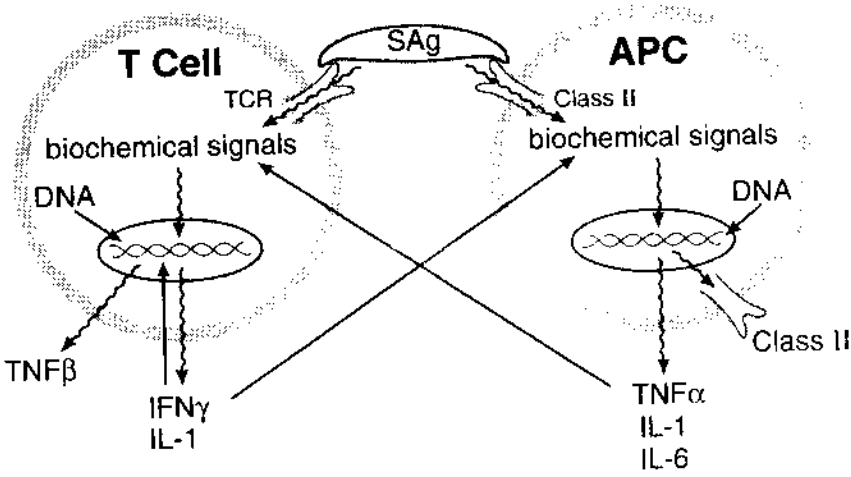

Figure 3. Interplay between T-cell- and antigen-presenting cell (APC)-derived cytokines and induction of an inflammatory cytokine cascade by superantigens. IFN, interferon; SAg, superantigen; TNF, tumor necrosis factor. (Reprinted from *Clinical Microbiology Reviews* [125] with permission from M. Kotb and the American Society for Microbiology.)

at 37°C than in cells grown at 26°C, suggesting that toxin production may be turned on once infection in the soft tissue or bloodstream is established (255).

There is both in vitro and in vivo evidence to support the notion that an infecting group A streptococcal superantigen(s) stimulates T cells to produce excessive amounts of proinflammatory cytokines that are instrumental in the pathogenesis of streptococcal toxic shock syndrome (STSS) (253). Several studies have demonstrated in vitro that group A streptococcal superantigens are mitogenic and elicit production of substantial amounts of cytokines (162, 169, 178, 179, 209). In vivo, it has been demonstrated that transgenic mice with T cells expressing TCRs specific for the superantigen tested were highly susceptible to superantigens, unlike nontransgenic mice (258). Miethke et al. (158) presented in vivo evidence that toxic shock syndrome due to staphylococcal TSST-1 superantigens required the presence of T cells, that the cytokine burst was due to TSST-1-stimulated T cells, and that TNF was the key factor in the pathogenesis of shock.

It is well established that under certain conditions, exposure of T cells to superantigens can result in either proliferation, anergy, or apoptosis of superantigen-responsive T cells (125). A consistent pattern of Vβ expansion or depletion in the peripheral blood of patients with severe group A streptococcal infection leaves the footprints of a superantigen. Choi et al. (37) demonstrated preferential elevation of Vβ2 T cells in patients with staphylococcal TSS. Watanabe-Ohnishi et al. (239) found depletion of specific Vβ-bearing T cells in patients with severe group A streptococcal infections. The pattern of deletion was different from that of any known streptococcal superantigen but similar from patient to patient, suggesting a novel superantigen in STSS. Administration of polyspecific intravenous Ig (IVIG)

can block in vitro T-cell activation by staphylococcal and streptococcal superantigens (108, 176). Several published case reports have show an apparent correlation between IVIG administration in the setting of STSS and clinical improvement (9, 130, 172, 187, 223). There is also in vivo evidence that the neutralization of mitogenic activity of the infecting strain by IVIG is due to antibodies provided by the IVIG (177).

HISTORY OF SEVERE GROUP A STREPTOCOCCAL DISEASE

Severe group A streptococcal infections have long been recognized, and the history of group A streptococcal disease has been characterized by periodic changes in severity. Streptococcal infections were recognized by Greek physicians in the fifth century B.C. Sydenham described the disease as "febris scarlatina" as early as 1664 (120). This description clearly differentiated this disease from measles and other rashes, which allowed outbreaks of scarlet fever to be documented throughout the world.

History of Severe Group A Streptococcal Disease to 1900

The most severe forms of streptococcal disease were well known long before the discovery of the bacterium. Hippocrates recorded epidemic erysipelas and clinical descriptions of a disease that we would clinically refer to today as necrotizing fasciitis (58, 70, 120).

In Loudon's review of the history of necrotizing fasciitis, he notes that even though the term was only first introduced in the 1950s by Wilson (250), historical descriptions of the disease are so consistent that its origins can be traced with confidence. Synonyms of necrotizing fasciitis included malignant ulcer, gangrenous ulcer, putrid ulcer, phagedena ("eating away"), and hospital gangrene (144). Although several different pathogens may cause necrotizing fasciitis, only group A streptococci have been associated with secondary transmission and changing epidemiology (23, 121, 144). The characteristic features of the disease were the extreme rapidity with which it progressed, destroying subcutaneous tissue in a matter of hours; the severity of the pain; the fact that it often occurred in the site of a trivial scratch or wound; and the way it attacked the young, healthy, and strong as often as individuals debilitated by injury or illness. Those characteristics are similar to those of group A streptococcal necrotizing fasciitis described in more recent times (29, 46, 47, 53, 57, 61, 62, 84, 144, 154, 159, 184, 185, 224, 241, 252, 256).

In their historical review, Katz and Morens (120) focused on scarlet fever as a possible indicator of streptococcal disease. Recognizing the limitations of their data, they concluded that there were at least three epidemiologic phases for scarlet fever. In the first phase (ancient times until the late 1700s), scarlet fever was either endemic or occurred in relatively benign outbreaks separated by long intervals. In the second phase (1825 to 1885), scarlet fever suddenly began to recur in cyclic and often highly fatal urban epidemics. Where previously no mortality had been associated with scarlet fever, fatal epidemics were reported in Paris, Dublin, London, and New York. Geographic clusters of severe cases were reported in large cities,

with case fatality rates that reached or exceeded 30% in some series in the United States and Europe. Katz and Morens (120) considered whether an apparent increase in severity might result merely from better reporting of cases. However, examples such as data from Oslo (1863 to 1878) (Fig. 4) showed a clear dissociation of incidence and case fatality rates, suggesting the cocirculation of both highly virulent and less virulent strains. In the third phase (1885 to the present), scarlet fever became a milder disease in developed countries (126).

History of Group A Streptococcal Disease after 1900

In the United States, during the middle part of this century, there was a further dramatic decline in the occurrence and mortality of scarlet fever (87, 197). This occurred without an associated decrease in pharyngitis due to group A streptococci and with continuing severe infections and their sequelae in developing countries (112, 254).This decline in severity began in the 1930s, before the advent of antibiotics for the treatment of streptococcal disease, and continued through the 1970s (113).

By the late part of this century, there also had been a dramatic decline in the mortality associated with bacteremic group A streptococcal disease. The mortality had declined from 72% in the preantibiotic era to 7 to 27% (22, 55, 63, 91, 122, 173, 231). However, in the early 1980s, reports began to describe increased mortality due to group A streptococcal bacteremia (35 to 48%), and anecdotal reports emphasized cases of rapid death in bacteremic patients presenting with shock (53,

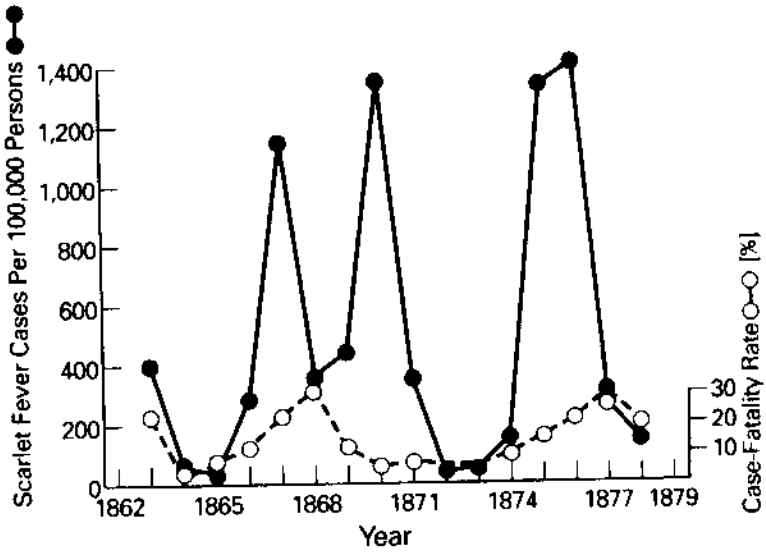

Figure 4. Reported cases of scarlet fever per 100,000 persons and scarlet fever case fatality rates in Oslo, Norway, from 1863 to 1878. (Reprinted from the *Journal of Infectious Diseases* [126] with permission from R. M. Krause and the University of Chicago Press.)

55, 76, 83). By the mid-1980s, reports described an increase in invasive group A streptococcal infections and an illness similar in severity to scarlet fever in the preantibiotic era, which was designated STSS and is often associated with specific M types (30, 45, 79, 98, 103, 107, 147, 214, 226).

In addition to the increase in invasive and severe invasive streptococcal disease, there were increased reports of necrotizing fasciitis (33, 46, 57, 121, 224). The first well-documented report of streptococcal necrotizing fasciitis was that by Meleney in the 1920s (it is not to be confused with Meleney's synergistic gangrene, a disease due to *Staphylococcus aureus* and microaerophilic streptococci) (155, 156). He described 20 cases of hemolytic streptococcal gangrene in which the only or predominant organism was a hemolytic streptococcus. In only one case was an anaerobic organism also isolated. After that, only isolated cases were reported between the 1950s and early 1970s (8, 11, 48, 82, 168, 225, 240, 248, 250). By the 1980s, reports of group A streptococcal necrotizing fasciitis with or without STSS began to appear in the literature (46, 47, 56, 65, 121, 132, 147, 184, 224, 241). Kaul et al. (121) reported on 77 cases of streptococcal necrotizing fasciitis gleaned from a prospective, population-based surveillance study of invasive group A streptococcal infections in Ontario, Canada. From 1992 to 1995, the annual incidence of necrotizing fasciitis increased fourfold from 0.85 per million people to 3.5 per million ($P < 0.001$).

Also, reports of group A streptococcal myositis/myonecrosis either alone (61, 154, 256) or included with cases of necrotizing fasciitis began to appear (29, 33, 46, 57, 62, 84, 130, 159, 168, 224, 252). Before 1986, primary group A streptococcal gangrenous myositis was infrequently reported (2, 8, 168). Typically, in these cases, the skin and fascia were minimally involved. In Meleney's report, he clearly described the gangrenous involvement of the subcutaneous tissue, secondary involvement of the overlying skin, and sparing of muscles and tendons (155). Muscle involvement typically has been described as a posttraumatic soft tissue infection or as a localized abscess typically associated with a favorable prognosis (149, 163, 220).

Current Status of Group A Streptococcal Disease

The ability to classify severe invasive streptococcal infections is important for development of surveillance programs and to ensure that studies of clinical outcome, epidemiology, and pathogenesis can be compared. Are STSS, necrotizing fasciitis, and myositis/myonecrosis a continuum of the same disease process, or do they have different pathogenic mechanisms? Clinically, it appears that STSS is a separate entity from necrotizing fasciitis and myositis/myonecrosis. Studies done in Great Britain and Sweden, which reported increases in severe group A streptococcal infection, did not report the concomitant presence of necrotizing fasciitis (45, 79, 226). Martin and Høiby (147), in their report of an increase in incidence and severity of group A streptococcal disease due primarily to M1 strains, reported only a small number of cases of necrotizing fasciitis. Hoge et al. (98) carried out a retrospective survey of the medical records from all 10 hospitals in Pima County, Ariz., to identify sterile-site isolates of group A streptococci between April 1985

and March 1990. They found significant changes in the clinical spectrum of invasive infections, with an increase in patients with clinical features of STSS during the last three years of the study. Necrotizing fasciitis was not associated with shock or any of the other clinical features of STSS, suggesting that fasciitis was not a component of the syndrome. Kaul et al. (121) found that only 36 of 77 cases of group A streptococcal necrotizing fasciitis were associated with the presence of STSS. In surveillance data from Ontario, Canada, multiorgan failure is as commonly associated with pneumonia (30%) as with necrotizing fasciitis (29%; $P = 0.90$).

Several authors have speculated that necrotizing fasciitis differs clinically from necrotizing myositis (2, 155, 256), overlap syndromes have been reported in some case series, and most recent studies have not clearly differentiated the two conditions (29, 33, 61, 62).

GENETIC DIVERSITY AND THE EVOLUTION OF GROUP A STREPTOCOCCI

Horizontal Gene Transfer in Group A Streptococci

It seems reasonable to assume that an organism's ability to evolve virulence factors relates to mechanisms that allow increased genetic variation (67). M proteins from different group A streptococcal strains are highly variable in both length and sequence, and this variability is reflected by the recognition of over 80 different M protein serotypes (72). The *emm* and *emm*-like genes of the *vir* regulon encode proteins with highly variable amino-terminal regions, with the *emm* genes having a much larger number of distinct alleles (123). The allelic variation appears to have arisen from the accumulation of base substitutions and short deletions or insertions (94, 245, 246). Evidence now suggests that, in addition to vertical sequence divergence, horizontal transfer of *emm*-like genes among strains has occurred (19, 192, 247). It is thought that such horizontal gene transfer has played a major role in the evolution of the *emm*-like genes. Using sequence analysis, several investigators have demonstrated that there are identical alleles of *emm* or *enn* genes in unrelated group A streptococci and that there are divergent *emm* or *enn* genes in strains that are indistinguishable by multilocus enzyme electrophoresis (245, 246). Horizontal transfer of DNA between streptococcal species could explain the finding of *emm* gene homology between group A and G streptococci as well as the recent appearance of a previously undescribed form of severe group G streptococcal disease in dogs (160).

As pointed out by Kehoe et al. (123), the realization that horizontal gene transfer is occurring in group A streptococci has important implications regarding our understanding of the evolution of these pathogens. Horizontal gene transfer has resulted in *emm*-like genes and *vir* regulons with mosaic structures. Such an ability to recombine, in conjunction with strong selective pressures, can accelerate the evolution of functional diversity.

Current Strains of Invasive Group A Streptococci

The increase in invasive and severe invasive disease in the mid-1980s was reported almost simultaneously from several countries on different continents and

usually was due to a predominant M type. The public health laboratories in Great Britain (45, 79) reported an increase in bacteremic isolates in Great Britain in 1987. Of the 55 deaths reported, 33 were due to M1/T1. In Sweden, during the winter of 1988–1989, there was an increase in the incidence of bacteremia illness due to group A streptococci (Fig. 5) (226). The peak was due to M1/T1 infections and was associated with an increased case fatality rate (33% versus 15% for other M/T types). Similar observations were made in Norway by Martin and Høiby (147) and in New Zealand by Martin and Single (Fig. 6) (146).

The increase in invasive and severe invasive disease in North America was due in part to the introduction of one or more serotypes, most frequently M1/T1 and M3/T3. Schwartz et al. (214) analyzed clinical and microbiological data from isolates sent to the Centers for Disease Control streptococcal reference laboratory between 1972 and 1988. They found that the proportion of M types 1, 3, and 18 increased significantly during the study period. These M types were more likely to be invasive, to cause fatal infection, and to occur in a cluster of infection than were other types. These findings suggested that changes in the epidemiology of group A streptococcal disease may be the result of changes in the distribution of particularly virulent M types causing infection rather than a global increase in the severity of all group A streptococcal infections. In the report by Kaul et al. (121) on streptococcal necrotizing fasciitis in Ontario, the most common streptococcal serotypes were M1 (35%) and M3 (25%). The proportion of M3 strains increased during the study period (44% of 1995 isolates compared with 16% in 1992 to 1994; $P = 0.01$).

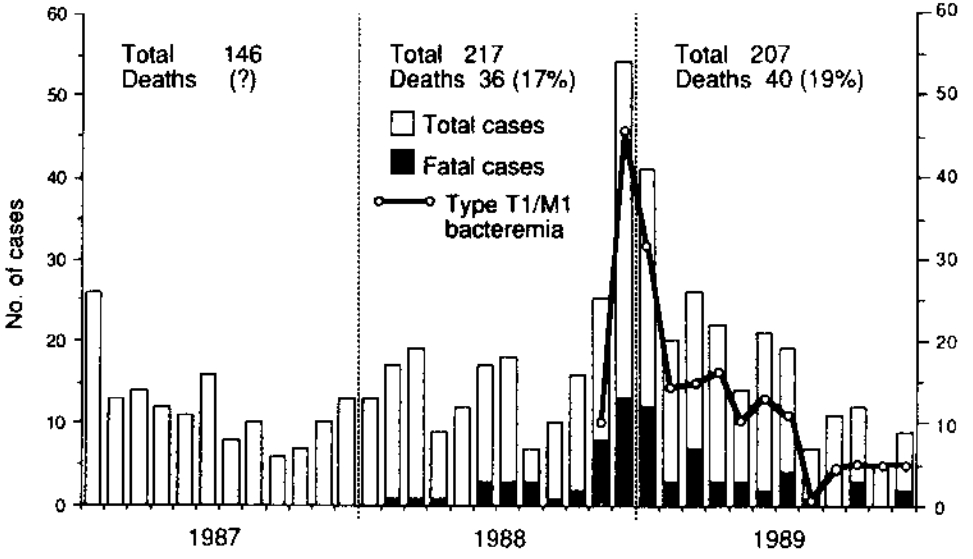

Figure 5. Monthly incidences of group A streptococcal bacteremia in Sweden, 1987 to 1989. (Reprinted from the *Journal of Infectious Diseases* [226] with permission from A. Strömberg and the University of Chicago Press.)

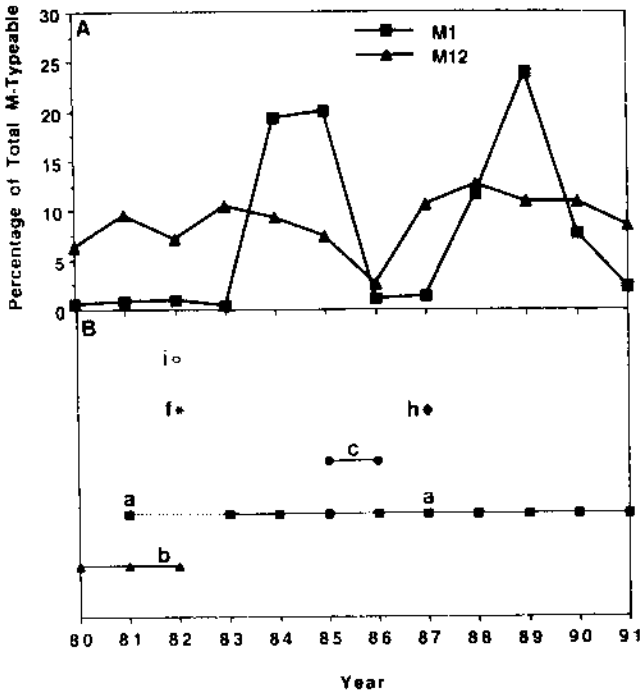

Figure 6. (A) Temporal distribution of New Zealand M type 1 and 12 isolates as percentages of all M typeable isolates by year. (B) Years in which each RFLP type was found among New Zealand isolates. (Reprinted from the *Journal of Infectious Diseases* [346] with permission from D. R. Martin and the University of Chicago Press.)

Recent studies that have taken into account the population genetic structure of group A streptococci have revealed that there is considerable genetic diversity within the species (123, 171, 219, 247). This means that previous epidemiological studies which have relied on serotyping systems may be insufficiently sensitive with regard to the relationship among strains. Techniques that use genetic analysis have provided evidence that the resurgence may be due not only to the emergence of one or two M types but to specific clones within an M type. Cleary et al. (40) characterized M1 strains isolated from cases of uncomplicated pharyngitis and systemic infections before 1992 and identified a unique clonal variant of serotype M1, termed M1inv$^+$ for M type 1 invasive phenotype positive, that was found significantly more frequently in patients with serious disease. Ninety-one percent of M1 strains from cases of serious infection had a common restriction fragment length polymorphism (RFLP), contained the *speA* gene, and carried the T12 bacteriophage (210). In addition, M1inv$^+$ replaced M1inv as a cause of uncomplicated disease after 1988 (210). In population-based surveillance in Ontario, typing of a sample of M1 strains associated with invasive infections between 1992 and 1996 revealed that all were of the M1inv$^+$ strain. LaPenta et al. (133), using a lung carcinoma

epithelial cell line, found that M1inv$^+$ strains internalized significantly more efficiently then either M1inv$^-$ or M12 strains.

Musser et al. (170) analyzed 108 isolates of group A streptococci from patients with invasive and severe invasive disease. Using multilocus enzyme electrophoresis, they found considerable genetic diversity. Within this genetically diverse population, more than two-thirds of the cases of streptococcal toxic shock syndrome were caused by strains of two related clones, designated ET1 and ET2. Among the 115 isolates of ET1, nine RFLP patterns were found, although most (87%) were either RFLP type 1a or 1k. In New Zealand, the dominant strain until 1983 (RFLP type 1b) was replaced by RFLP type 1a, which was subsequently responsible for the majority of M1 infections (146). Between 1980 and 1990, two distinct waves of invasive disease episodes were caused by strains of RFLP pattern 1a (Fig. 6).

Despite the association with a specific M1 clone, investigators have also ascribed cases of severe invasive disease to other serotypes or other M1 clones (28, 29, 56, 57, 75, 168). Other diverse M types, and even nontypeable strains, are becoming increasingly important. Norgren et al. (175) genetically analyzed M1 strains of group A streptococci isolated from patients with and without complicated infections. They found genetic diversity among isolates and could find no association between any single clone and a specific clinical condition. Carapetis et al. (28) conducted a 12-year review of all cases of group A streptococcal bacteremia at a children's hospital in Melbourne, Australia, from 1982 through 1993. They found that during the latter part of the study the severity of disease increased significantly. During the study period, M1 isolates were equally distributed. However, molecular typing also identified a genetically distinct strain that was virulent and M nontypeable. Chaussee et al. (32) characterized isolates of group A streptococci obtained during the 1980s and 1990s from patients with a variety of clinical manifestations, including necrotizing fasciitis and STSS. They found considerable genetic and phenotypic heterogeneity among isolates from recent cases of severe infection.

Severe disease caused by strains other then the M1 clone may be caused by those strains that have acquired a virulence gene(s) by horizontal transfer. The findings of both genetic and phenotypic homo- and heterogeneity add support to the notion that virulence is multifactorial and able to be mobilized between strains of group A streptococci and possibly even between other streptococcal groups (36, 42, 212, 218, 234).

CONCLUSIONS

Historically, the occurrence of severe group A streptococcal infections has varied. Although there was a decline of severe disease during the 20th century, such illness still existed, and these infections, caused by diverse serotypes, may have represented the baseline of severe illness upon which recent increases have been superimposed. Given the wide array of virulence factors, these periodic changes may have resulted from similar or different mechanisms affecting the fitness of the pathogen. The current increase in severe disease, particularly STSS and necrotizing fasciitis, is most likely related to changes in serotype distribution, production of toxins, and/or other factors. This may represent an evolutionary change toward

greater organism virulence but more likely reflects the introduction of a virulent clone into immunologically naïve populations. As immunity to these virulence factors increases, virulence will be lost. We believe that this resurgence of more severe group A streptococcal disease does not represent the natural selection of a more virulent clone that will predominate but rather that as population immunity increases we will once again return to periods of waxing and waning of group A streptococcal disease severity.

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