MYOSITIS, PNEUMONIA, AND "TOXIC SHOCK" SYNDROME:

WHAT'S HAPPENED TO THE GROUP A STREPTOCOCCUS?

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Streptococcus pyogenes, the group A streptococcus (GAS), remains a cause of major health problems in the developing world. For example, attack rates for acute rheumatic fever in Sri Lanka (140 cases per 100,000 per year) and India (600/100,000/yr) make this one of the most important diseases of childhood in these countries.

In the developed world, in contrast, GAS-associated diseases decreased steadily in frequency during this century, so that the incidence of ARF in Memphis, TN, for example, was only 1.8/100,000/yr in the late 1970's (Bisno, 1990). Scarlet fever, once a major cause of morbidity and mortality, had become relatively uncommon and much less severe.

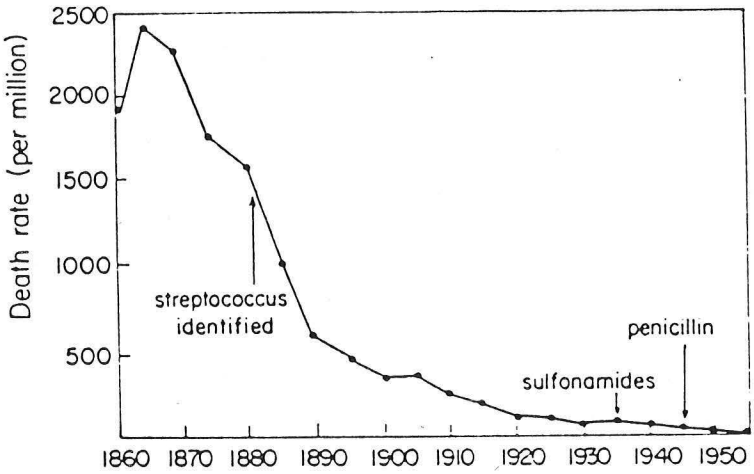

Figure from E. Kass, 1971. Mean annual death rate from scarlet fever in children under 15 years of age, England and Wales.

In the 1980's, after this long period of steady decline, the incidence of GAS diseases appeared to be increasing. Although much public awareness has followed the publicity given to the GAS-related death of Jim Henson, the creator of the Muppets, data from several sources suggest not only that GAS diseases are occurring with increasing frequency, but that exceptionally virulent organisms may be involved.

It also seemed that acute rheumatic fever might be making a comeback in the U.S., but after a flurry of reported outbreaks in the mid-1980's, its incidence seems to have declined once more. For this reason, and because there is insufficient time to deal adequately with both diseases, in this presentation I shall discuss only the rise in invasive streptococcal disease. As a worldwide problem, however, there is no doubt that rheumatic fever is far more important.

GROUP A STREPTOCOCCAL BACTEREMIA

Increases in the frequency of so-called "virulent" or "invasive" GAS disease have been reported in several locales in the U.S. and elsewhere. Documentation of this increase has come from several kinds of data. In the U.K., it is based on isolates of GAS referred to the Central Public Health Laboratory in London (Gaworzewska and Colman, 1988). Their data are summarized in the following Table.

Table 1. Isolates submitted to the London Central Public Health Laboratory, 1980-1987

Year	Total no. isolates from blood/CSF	Total no. isolates from fatal cases	Isolates from fatal cases/total (%)
1980	54	8	14.8
1981	36	5	13.8
1982	48	10	20.8
1983	36	9	25.0
1984	75	7	9.3
1985	66	14	21.2
1986	88	19	21.5
1987*	84	22	26.1

* first 6 months

Note that the laboratory received 2.5 times as many isolates from patients with invasive disease in 1986 as in 1981-1983; GAS bacteremia remained the same fraction of the total reported bacteremias during this period, however, so the increase in GAS isolates can probably be explained by improved reporting. The numbers of isolates from fatal cases/year also tripled during this interval, and the case-fatality rate (isolates from fatal cases/total blood or CSF isolates) tended to increase.

The situation in Great Britain is also illustrated by the report from Addenbrooke's Hospital, Cambridge (Francis and Warren, 1988). Seventy-one percent of the patients with GAS bacteremia were adults, and 62% were previously normal hosts. The overall case fatality rate was 48%, higher than in previous series from the U.K.

In the U.S., several centers have reported the occurrence of unusually large numbers of patients with GAS bacteremia. A single hospital in Denver reported 19 cases of GAS bacteremia in the period January - September, 1989; only 3 cases had been admitted to the same hospital in 1987 and 8 in 1988 (MMWR, Jan 12, 1990).

Group A beta-hemolytic streptococcal bacteremia cases in a hospital – Denver, Colorado, January 1987–September 1989

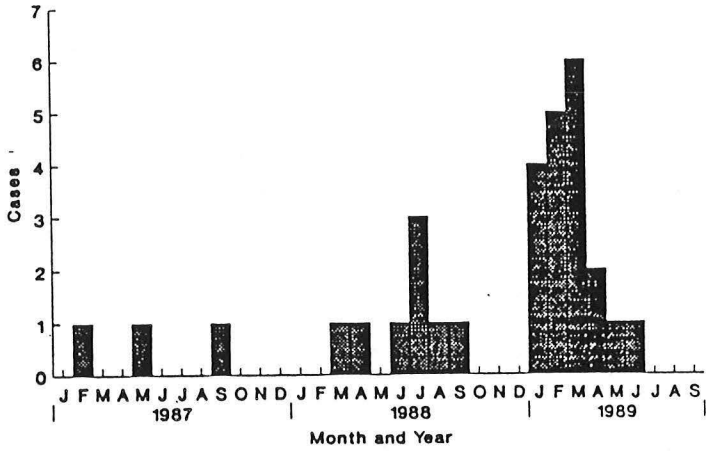

Figure from MMWR, Jan 12, 1990

Although most of the reports have described adults with GAS bacteremia, severe GAS disease also has been noted in children (Wong and Wright, 1988; Harnden and Lennon, 1988).

To find out whether an increase in GAS disease had occurred in our hospital, the Parkland Microbiology Laboratory blood culture records from 1980 - 1989 were reviewed. There were 161 cases of GAS bacteremia, or 16 per year. The number of patients per year did not increase significantly over this time period; the number of GAS bacteremias per 10,000 discharges ranged from 2.5 to 5.9 in different years. The case-fatality rate for patients with GAS bacteremia in 1987-89 was 16%, considerably lower than that reported in the studies cited above. (Thanks to Dr. Paul Southern and Mrs. Linda Jefferson, who provided the records, and to Ms. Norene Wade, who compiled them.)

Table 2. *S. pyogenes* bacteremia at Parkland Memorial Hospital, 1980-89

Year	Cases	Hospital Discharges	Cases/10^4 discharges
1980	8	31,645	2.5
1981	15	31,831	4.7
1982	14	32,862	4.1
1983	15	35,536	4.2
1984	18	35,526	5.1
1985	9	37,175	2.4
1986	22	34,235	6.4
1987	15	39,665	3.8
1988	21	38,817	5.4
1989	24	40,585	5.9

Longitudinal surveillance in one large community (Rochester, N.Y.; C. B. Hall, personal communication) has not revealed an increase in the frequency of streptococcal pharyngitis or scarlet fever in children over the last decade or so. The resurgence of GAS disease in this country seems to have been confined to certain geographic areas.

There have been outbreaks of GAS bacteremia in confined populations such as nursing homes. One such episode occurred at the VA Medical Center in Dallas (data courtesy J.A. Smith, M.D., and Beverly Gray, R.N.). Within a two week period in January, 1990, three patients were admitted to the hospital from the nursing home with GAS bacteremia, two from a primary skin source (cellulitis, abscess of finger) and another with pneumonia; all were hypotensive and two died. A 4th patient from the same home had pneumonia with a positive sputum culture for GAS; his blood cultures were negative. Minor skin lesions appeared to be the portal of entry of GAS in the first 2 cases. Other nursing homes have had outbreaks of GAS disease (Reid et al., 1983; Barnham and Kerby, 1981; Ruben et al., 1984); the Dallas experience is the only such outbreak described since the apparent increase in invasive GAS disease in the 1980's.

In addition to elderly persons in nursing homes, individuals who use intravenous drugs and patients with solid tumors are also predisposed to bacteremia when infected with *S. pyogenes* (Bibler and Rouan, 1986). In the early 1980's, for example, GAS was one of the principal agents of endocarditis in intravenous drug abusers in Detroit (Barg et al., 1985); in contrast to the more recent experience described above, the clinical presentation resembled that of *S. aureus* endocarditis and the outcome was usually favorable, with a case-fatality rate of only 5%.

One of the striking features of the recent reports is the fact that a significant fraction of the cases have been in **previously healthy individuals**. Relatively few cases have been reported in HIV-infected individuals (Johnson and Rand, 1990); only two of the recent PMH cases of GAS bacteremia were known to be HIV infected.

Clinical manifestations: the importance of skin and soft tissue infections

Prior to the 1980's, most patients acquired GAS bacteremia from a cutaneous lesion or inoculation site[1] (Bibler and Rouan, 1986). Most of the recently reported patients have also developed GAS bacteremia from a cutaneous primary infection, but in some the throat or lungs were the apparent site of bloodstream entry .

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[1]Bacteremia from GAS pharyngitis is thought to be unusual in the absence of suppurative complications such as jugular venous thrombophlebitis, peritonsillar abscess, etc.

Sources of GAS in patients with severe disease

	Denver (MMWR) n=19	Nottingham (Ispahani) n=40	Rocky Mountain (Stevens) n=20
Skin (cellulitis, ulcer, IVDA)	4	23	13
Respiratory tract (throat, lungs)	7	8	0
Trauma or surgery	2	1	4
Not known	6	2	7

All of the recent series have included patients with major soft tissue infections: **necrotizing fasciitis and/or myositis**[2]. These infections involve soft tissue invasion by GAS, and sheets of organisms have been seen in tissue specimens. Often the patients appeared initially to have cellulitis, but failure to respond to therapy led to further (surgical) investigation and the correct diagnosis. Streptococcal **pneumonia** has also been frequent. Only 1/3 or so of patients have an antecedent sore throat. The onset is typically abrupt, with chills, fever, cough (often with bloody sputum), and pleurisy. Although pulmonary consolidation is less common than bronchopneumonia, a third of the patients will have empyema with typically thin, serosanguineous fluid. The pleural effusions are often refractory, requiring multiple drainage attempts. Complications include mediastinitis, pericarditis, and pneumothorax.

Toxic shock-like syndrome

The reports cited above support the conclusion that there has been an increase in the incidence of invasive GAS disease in certain communities. In addition, in these places there currently appears to be a higher risk of hypotension and death associated with GAS bacteremia than in the past (Ispahani et al., 1988; Gaworzewska and Colman, 1988; Centers for Disease Control, 1990). Still more intriguing are the descriptions of patients whose GAS-induced illness has been said to resemble the staphylococcal toxic shock syndrome (STSS).

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[2] The clincal distinction between necrotizing fasciitis and myositis is difficult but important. Whereas necrotizing fasciitis usually follows local skin trauma, myositis often follows hematogenous seeding of muscle. Other features that favor myositis include rapid progression of symptoms, pain, systemic toxicity out of proportion to other clinical findings, and elevated CPK (Adams et al., 1985). Anesthesia of the skin can occur with either condition.

Staphylococcal toxic shock syndrome. Once called "staphylococcal scarlet fever," this syndrome is a multisystem, toxin-mediated illness associated with the presence of Staphylococcus aureus. There is no diagnostic laboratory test. Rather, the diagnosis is based on a clinical definition, developed by workers at the Centers for Disease Control (Reingold and Broome, 1984). The cardinal features are:

1. Fever
2. Rash: diffuse macular erythroderma; desquamation 1 to 2 weeks after onset of illness
3. Hypotension
4. Multisystem involvement - 3 or more systems
5. No other diagnosis

Although many cases have been associated with tampon use, it is important to note that numerous cases have occurred in non-menstruating individuals with surgical or other wounds, bacteremia, osteomyelitis, or other staphylococcal infections.

The striking clinical feature of staphylococcal TSS that suggests the presence of an exotoxin is the rash. Without this finding, it is difficult to be sure that a toxin is at work, since overwhelming bacteremia can itself be associated with hypotension and multisystem failure. Most patients with severe streptococcal disease have not had a diffuse rash, and few have had desquamation. If one excludes patients who have GAS bacteremia, or deep tissue involvement, cases with **local GAS infections, negative blood cultures, hypotension, and multisystem involvement** (a working definition for toxin-mediated disease) have been reported from California (Cone et al., 1987), Massachusetts (Bartter et al., 1988), the mid-Atlantic region (Walter Reed; Dravick and Lennox, 1989), Zagreb, Yugoslavia (Begovac et al., 1990), and the intermountain area of the U.S. (Stevens et al., 1989). A probable case also occurred in a 47 year-old Dallas policeman who punctured his right forefinger during a drug raid; he developed GAS cellulitis and was hypotensive when admitted to Baylor University Medical Center in Dallas (personal communication, Dr. Cynthia Schneidler). If one includes bacteremic patients, additional cases with **local GAS infections, positive blood cultures, hypotension, and multisystem involvement** (a less restrictive definition) can be counted from these areas and also from Great Britain (Ispahani et al., 1988; Cruickshank et al., 1981), Czechoslovakia (Hribavola, 1988), and other locales, including Dallas.

The series reported by Stevens and his colleagues (Stevens et al., 1989) is particularly striking. Of the 20 patients reported from the Rocky Mountain region who had severe GAS infections from 1986 to 1988, 19 patients (95%) had shock. The overall case fatality rate was 30%. Twelve patients (60%) were bacteremic, and over half had necrotizing fasciitis or myositis. Although three-quarters of the patients had skin lesions, most had localized erythema and swelling (related to primary skin infection), one had bullous skin lesions, and none had a rash typical of scarlatina or staphylococcal toxic

shock. These patients were reported **because** their illnesses were so severe (possible selection bias), reflecting the authors' impression that this was an unusual occurrence.

Most of the patients with the "toxic-shock like" syndrome were previously normal, healthy adults. Relatively few had underlying disease or used intravenous drugs. There have been few reported cases in children (Begovac et al., 1990; Hansman and Jarvinen, 1989), although children with a similar syndrome have been seen in Dallas and elsewhere, and a large series of children with this syndrome is evidently in press.

In summary, there appears to be (1) an increase in the frequency of GAS bacteremia in certain communities around the world, (2) a higher (relative to earlier periods) risk of severe illness and death from GAS bacteremia in some of these areas, and (3) a primary or contributory role of a streptococcal toxin in some, but not all, cases.

This discussion will now turn to these questions:

1. How does *S. pyogenes* cause disease in man?

2. What has changed that might account for the increase in severe GAS disease?

3. What medical measures should be taken?

Streptococcus pyogenes, THE GROUP A STREPTOCOCCUS

Modern understanding of the streptococci rests on the fundamental discovery of Rebecca Lancefield (1933) that streptococci can be distinguished serologically according to specific carbohydrate cell wall antigens. All "group A" streptococci (GAS) thus have the same group carbohydrate. Group A streptococci have evolved specialized mechanisms for multiplying in the human host:

Colonization of the throat: adherence to epithelial cells

LIPOTEICHOIC ACIDS. These amphipathic molecules are associated noncovalently with M protein on the surface of the bacterium. They are thought to mediate the adherence of GAS to respiratory epithelium by binding to fibronectin molecules on the surfaces of epithelial cells (Beachey and Courtney, 1989). They are thus major factors in the initial (colonization) phase of infection. Subinhibitory concentrations of penicillin cause GAS to shed lipoteichoic acid from the surface; this correlates with a loss in ability to adhere to epithelial cells (Alkan and Beachey, 1978). Perhaps this contributes to the efficacy of penicillin in eradicating pharyngeal GAS colonization. Lipoteichoic acids are also potent T-cell mitogens (Beachey et al., 1979).

Local proliferation: avoid antibody recognition

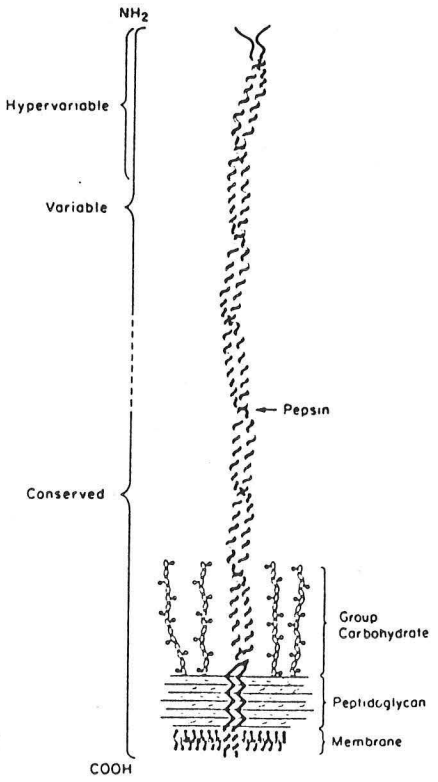
Fc RECEPTORS. GAS have surface-exposed Fc receptors. The IgA receptor has received most attention (Lindahl, 1989; Lindahl and Akerstrom, 1989); by binding the Fc end of IgA in mucosal secretions, these molecules could favor local bacterial growth. In the strains studied, the IgA receptor molecules have structural similarity to M protein and are coded for by closely linked genes (Lindahl, 1989). Fc receptor and M protein genes may be products of gene duplication (Heath and Cleary, 1989).

M-proteins and the hyaluronic acid capsule may also contribute to antibody avoidance at the mucosa (see below).

Prevent mobilization of phagocytes: destroy chemotactic factors

COMPLEMENT FACTOR 5a (C5a) PEPTIDASE. This is an acidic, high-molecular-weight (M_r = 140,000) bacterial surface protein that specifically cleaves human C5a, thereby drastically decreasing the effectiveness of C5a as a chemoattractant, delaying the recruitment of neutrophils to the site of infection. Its genetic locus is linked to the M protein gene (Chen and Cleary, 1989).

Avoidance of phagocytosis: camouflage, antigenic variation



M PROTEINS. Fibrillar proteins that extend outward from the surface of GAS, M proteins are the major means by which GAS avoid phagocytosis by neutrophils. There are over 80 different M protein types; antibodies to the M-protein are protective (i.e., facilitate phagocytosis), so immunity to GAS is said to be **type-specific**.

Recent studies on M protein structure have found that the proteins have three general structural regions (Figure and summary from Fischetti et al, 1988):

The **COOH-terminus** of the protein anchors the M protein to the streptococcal cell wall and membrane. The amino acid sequence of this region is conserved among strains of different M types and is also very similar to that of certain other gram-positive bacterial surface proteins (e.g., protein A of Staphylococcus aureus, certain FcR proteins of GAS).

The central "rod" is a long **alpha helical coiled coil** comprised of a series of heptad amino acid repeats. The length of the rod can vary considerably, probably because of recombination events that occur within the long stretches of DNA repeats.

The **N-terminus** of the protein is an 11-amino acid nonhelical domain that differs from one M protein to another; it is termed the "hypervariable" region of the molecule. Antibodies to this domain are M protein-specific and are protective (promote opsonophagocytosis)(Beachey et al., 1988). Fischetti has proposed that "the central rod domain [of the protein] may function as a shaft to position the N-terminal domain away from the cell surface." (Fischetti et al, 1988).

Antigenic variation allows the GAS to avoid opsonization unless the host has specific anti-M antibody. The mechanism by which M protein resists opsonization by complement is not understood, but an interesting clue is the recent finding that M proteins bind fibrinogen. The fibrinogen-binding site is evidently in the N-terminal half of the M protein molecule but not in the outermost domain, since type-specific antibodies can bind to the M protein in the presence of bound fibrinogen (Ryc et al., 1989; Poirier et al., 1989). The bound fibrinogen appears to impede complement deposition on the streptococcal surface (Poirier et al., 1989). Clindamycin, which in subinhibitory concentrations denudes the surface "fuzz" on streptococci, promotes phagocytosis by increasing the deposition of C3 on the surface (Gemmell et al., 1981).

S. pyogenes thus may avoid phagocytosis by two mechanisms, both of which are carried out by the M protein: by antigenic variation and by coating itself with a host molecule (fibrinogen) that makes it "look" like self. Another camouflage molecule is the **hyaluronic acid capsule**; strains that produce lots of this material have a mucoid colonial morphology and are said to be more virulent than non-mucoid strains.

M protein typing of GAS has been a very useful epidemiologic tool, as specific M types have been associated with different post-streptococcal sequelae. By M typing, one can define nephritogenic and rheumatogenic strains of *S. pyogenes*, for example; interestingly, rheumatogenic strains share certain epitopes in the C-terminal region of their epitopes (Bessen, 1989). Certain M types have been found in association with skin infections ("skin strains"), others with throat infections ("throat strains"), etc. This information is useful background for considering the associations of particular M types with the recent cases.

A virulence regulon?

Many bacteria are now known to regulate the synthesis of key molecules coordinately in response to environmental stimuli (Miller et al., 1989). For pathogenic

bacteria, this often involves the coordinate regulation of genes that encode for molecules ("virulence" factors) that favor bacterial growth in the host animal. There are sensor molecules that transmit an environmental stimulus (e.g., change in osmolarity) to regulator/receiver molecules that in turn regulate the transcription of one or more target genes. Together the genes are said to comprise a virulence regulon. This appears to be a common mechanism whereby bacteria, e.g. *Vibrio cholerae*, adapt to living in different environments. Evidence that GAS may have a similar capability has recently come from the finding that the antiphagocytic M protein and the antichemotactic C5a peptidase are coordinately controlled and undergo simultaneous phase variation. The genes that encode these proteins are evidently closely linked and are downstream from a putative virR locus (Simpson et al., 1990; Caparon and Scott, 1989).

Spread in tissue: extracellular enzymes

STREPTOKINASE. All F.C.A.s have heard about streptokinase, currently one of the better remedies for acute coronary thrombosis. All GAS produce streptokinase, though the genes for doing so differ somewhat from strain to strain (Huang et al., 1989). The enzyme, which activates plasminogen, is thought to facilitate the spread of GAS through tissue and to contribute to the serosanguineous quality of streptococcal pus. The streptokinase of certain strains is said to play a major role in the pathogenesis of post-streptococcal nephritis (Johnston and Zabriskie, 1986).

DNASE b. This enzyme may also contribute to the thinning of pus, as it degrades DNA released by white cells, etc. More certain is its role in serodiagnosis: antibodies to DNAse b can be a valuable method for retrospective diagnosis of streptococcal disease (not specific for group A, however).

Exotoxins: cytolytic toxins

The best known property of *S. pyogenes* is its pattern of hemolysis on blood agar: almost all GAS are beta-hemolytic, producing a clear zone of hemolysis in the agar below surface colonies.

Hemolysis of erythrocytes in agar illustrates an important property of GAS, the secretion of enzymes and other molecules into the environment. Hemolysis is produced primarily by streptolysin S, but streptolysin O is the better cytotoxin, having the ability to kill myocardial and other cells (see review by Wannamaker, 1983). Streptolysin O is inactivated by cholesterol and other sterols; inactivation by sterols in the skin is said to account for the absence of anti-streptolysin O antibody response to GAS skin infections in many individuals. Streptolysin O is produced by other beta-hemolytic streptococci, including groups C and G, so a high ASO titer is not diagnostic of group A disease.

The pyrogenic exotoxins (erythrogenic toxins); scarlet fever

Scarlet fever is a systemic reaction to a toxin produced by GAS. The characteristic rash is a diffuse erythroderma that has a sandpaper-like quality to the palpating finger (according to Christie [1974], it is a "fine flush or erythema, [with] raised red specks, or puncta, on top of it: punctate erythema"). Circumoral pallor, Pastia's lines (petechiae in skin folds in the antecubital fossa, popliteal fossa), strawberry tongue[3] and fever are other typical features. Desquamation occurs days to weeks after the onset of the rash.

Isolates of GAS usually produce one or more streptococcal pyrogenic exotoxins (SPEs), and isolates from cases of scarlet fever usually produce type A. When injected into experimental animals, SPEs elicit (1) fever, (2) enhancement of lethal shock (synergism with gram-negative endotoxin), (3) hepatic and myocardial damage, (4) increases in T cell numbers (T-cell mitogenicity). SPE-A is evidently more toxic in rabbits than SPE-C (Lee and Schlievert, 1989). SPE-A and staphylococcal enterotoxins B and C1 were shown recently to induce TNF production in rabbits (Fast et al., 1989). These responses to SPEs do not require prior sensitization to the SPE.

An individual's susceptibility to scarlet fever can be determined by injecting a small amount of SPE intracutaneously. In susceptible individuals, the SPE elicits an erythematous, edematous reaction within 24 hours; antitoxin prevents this reaction. The Dicks (1922), who originated this test (the "Dick test"), thought that the SPE produced the reaction directly, via a primary toxic effect. Subsequent workers have argued that skin reactions to SPEs may require prior exposure to SPEs and involve delayed hypersensitivity responses (Schlievert, 1979). The evidence may be summarized as follows:

(1) In surveys of military recruits, positive Dick tests (skin reaction, = susceptibility) were more common in individuals from geographical areas with a high incidence of GAS infections (Rantz et al., 1946).

(2) Scarlet fever does not occur in infants; it usually is observed only after repeated streptococcal infections.

(3) In rabbits, SPEs do not elicit skin reactions unless the animals have been presensitized to the same (homologous) or other (heterologous) SPEs. Moreover, animals presensitized to other antigens (such as PPD) show enhanced skin reactions when given the antigen plus SPE; antiserum to the SPE neutralizes the enhancement. Cross-reactions between different SPEs suggest that there are common determinants in the molecules. (Schlievert et al., 1979). It appears that

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[3]"The tongue is covered with white fur through which project red papillae, but in the next day or two the fur disappears leaving the tongue stripped and studded with the enlarged papillae. These are referred to as the white and red strawberry tongue of scarlet fever..."(Christie, 1974)

scarlet fever occurs when a previously sensitized individual is exposed to SPE-A (less frequently B, or C); the SPE enhances skin reactivity to other streptococcal antigens (see discussion by Wannamaker, 1983).

Favoring the idea that SPEs produce scarlet fever by a direct action on cells is the ability to cause the rash to blanch by administering antitoxin intradermally (the Schultz-Charlton test), and the observation that in some communities, the age of peak incidence of scarlet fever is younger than that for streptococcal pharyngitis (Dr. C. B. Hall, Rochester, N.Y., personal communication).

Summary: SPEs directly induce shock, lethality, enhanced susceptibility to endotoxin, T-cell division, etc.. The cutaneous reaction to the SPEs, in contrast, may require prior sensitization (a delayed hypersensitivity reaction); the evidence for this is controversial. Kim and Watson proposed that the toxins have two structural regions, one that elicits the direct reactions and another that elicits the DH skin reaction. This is a reasonable working hypothesis but the issue is by no means settled.

The SPEs are produced only by group A streptococci (Schlievert, 1979); the SPE genes are encoded on bacteriophages and can be transferred from strain to strain. Recent studies also suggest that the bacteriophage may pick up the SPE gene from *S. pyogenes* (Johnson et al., 1986).

The disappearance of scarlet fever from the U.S. has been attributed to a decrease in the prevalence GAS strains that produce SPE-A (Lee and Schlievert, 1989), and it is generally held that SPE-A has been responsible for most cases of scarlet fever in this country. On the other hand, only 45% of GAS isolates from cases of scarlet fever around the world were found to contain the gene for SPE-A when studied recently by Ferretti's group (Yu and Ferretti, 1989). In Great Britain, isolates from patients with scarlet fever have produced SPE-B and /or SPE-C, not SPE-A.

STAPHYLOCOCCAL AND STREPTOCOCCAL TOXINS

Most cases of menstrual toxic shock syndrome have been associated with S. aureus isolates that produce toxic shock syndrome toxin-1 (TSST-1). In contrast, isolates from non-menstrual cases are usually TSST-1 negative; in one recent series, two-thirds of these isolates produced staphylococcal enterotoxin B (Schlievert, 1986).

Toxin	Source	Host Reaction
Enterotoxins A,B,C,D,E	S. aureus	vomiting, GI (toxic shock)
Exfoliating toxins	S. aureus	Scalded Skin
TSS toxin (TSST-1)	S. aureus	Toxic Shock
Pyrogenic exotoxins A,B,C	S. pyogenes	Scarlet Fever

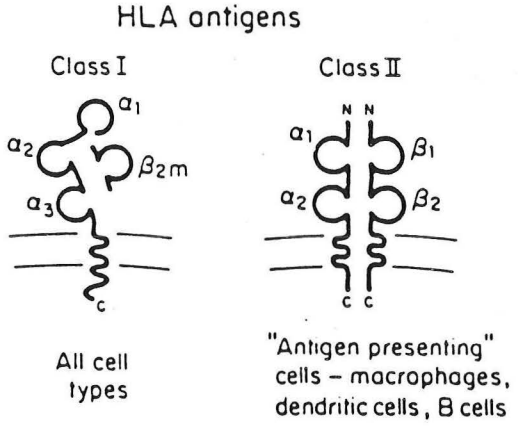
It is now appreciated that the scarlet fever and staphylococcal TSS toxins are closely related. Moreover, these toxins have major structural similarity to the other staphylococcal toxins, the enterotoxins and exfoliating toxins.

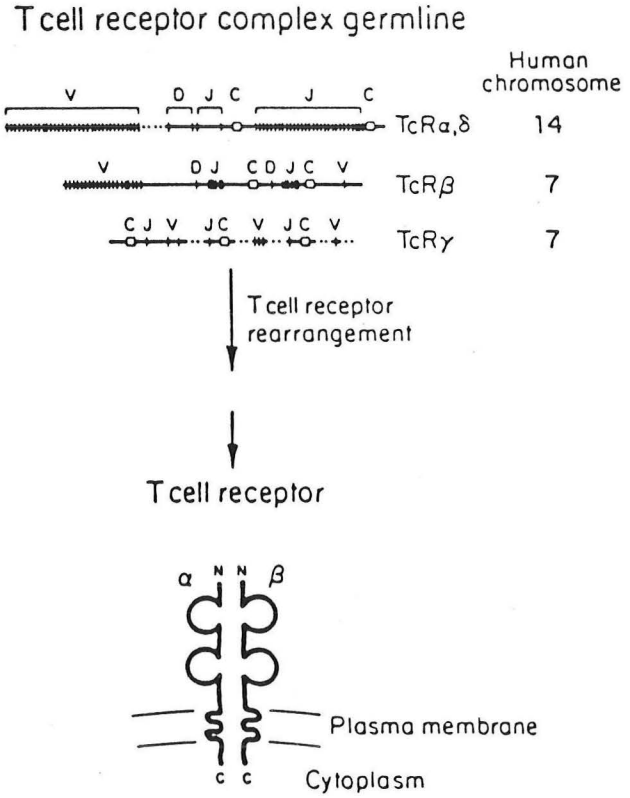
Although these toxins can be distinguished from one another (molecular size, antigenicity, biological properties), they have striking amino acid sequence similarity (Marrack and Kappler, 1990). TSST-1 has the least similarity to the others.

SPEs: superantigens?

A molecular mechanism to account for the ability of these staphylococcal and streptococcal toxins to elicit toxic responses has recently been proposed (White et al., 1989; Marrack and Kappler, 1990). The mechanism, like many recently discovered mechanisms whereby microbial products elicit host responses, involves molecular mimicry.

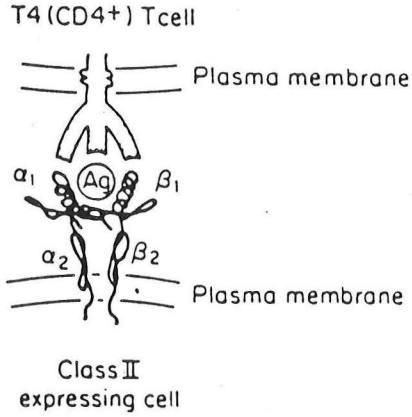
Background. Protein antigens are processed by antigen-presenting cells (e.g., macrophages), which "present" them to T cells by inserting the peptide into a molecular pocket formed by the components of the class II major histocompatibility complex. T cells (CD_4+) of appropriate specificity recognize the peptide-class II complex via the T cell receptor (TCR); in concert with CD3, the TCR so engaged triggers T cell division and other responses, including cytokine release.





Drawings from Wilson, 1990.

Certain molecules have attracted interest because they are capable of forming complexes that are recognized by large numbers of T cells (Marrick and Kappler, 1990). These molecules ("superantigens"), in combination with class II molecules, form ligands that are recognized by virtually all T cells that have a particular kind of TCR structure. The TCR is comprised of two protein subunits, α and ß. Each of these consists of constant and variable regions, like immunoglobulins. The variable regions, which account for diversity in antigen recognition, are known as Vα, Jα, Vß, Dß, and Jß. Specific variable elements, defined by their reactivity to monoclonal antibodies, can be identified on individual T cells. **Superantigens**, when presented in combination with class II molecules, are recognized by T cells bearing TCRs that have particular **Vß** structures, regardless of their other specificities for antigen. A large percentage of the T cells in an animal can become involved. Mice produce **endogenous** superantigens known as **mls** (minor lymphocyte stimulating antigens); these seem to cause the deletion, in the thymus, of all prospective T cells bearing Vßs with which they react. This is said to be an important mechanism for **clonal deletion** of T cells that recognize self antigens. Similar endogenous superantigens have not been identified in man.



Drawings from Wilson, 1990.

Another class of superantigen includes the staphylococcal enterotoxins and their relatives, including TSST-1 and the SPEs. These proteins have quite similar protein sequences and they share a common region, about two-thirds of the way through the protein, that is very similar to a sequence that is found at the COOH-terminal end of human and mouse **invariant chain**. Invariant chain is a peptide that is associated with nascent class II molecules; it is thought to prevent occupancy of the (antigen-presenting) pocket by peptides produced endogenously by the cell, then to dissociate from the class II molecule as it reaches the surface of the cell, allowing peptides (such as those derived from invading microbes) to occupy the groove. Neither invariant chain nor superantigens are thought to occupy the groove themselves, however.

Hypothesis: **SPEs and the staphylococcal exotoxins link class II molecules to TCRs that have particular Vß structures, eliciting T cell division and cytokine release. Shock and other pathologic changes then result.**

Evidence: mice which lack T cells are not affected by staphylococcal enterotoxin B, unlike their normal littermates which have T cells. Mice engineered to lack the Vßs that react with certain toxins are unaffected by those toxins. During toxic shock in man, the percentage of peripheral T cells bearing the Vß with which the toxic shock-associated toxin reacts, Vß2, rises to as much as 50% (normal = less than 10%)(cited by Marrack and Kappler, 1990).

Implication: the staphylococcal and streptococcal toxins thus may produce disease because they are able to bind to (link) specific structures on T cells and antigen-presenting cells. Since their structure mimics that of invariant chain or endogenous superantigens, this is an example of **molecular mimicry** as a pathogenetic mechanism. Production of the toxins may be advantageous to the GAS for other, unknown reasons (foster growth at mucosal surfaces, spread in populations, etc), since the ability to elicit shock and death of the host, per se, is unlikely to favor multiplication and spread of the streptococci. Since the toxin gene is borne by a bacteriophage, it is also possible that the production of toxin is an incidental activity that has no particular survival advantage for the bacteria--perhaps other phage-encoded genes confer some unknown property that favors survival or spread of lysogenized streptococci. It is also intriguing to wonder if the phage might have acquired the SPE gene from the host genome in the distant past.

Problems: this mechanism is most attractive as an explanation for toxic shock syndrome. It accounts less satisfactorily for the principal clinical response to the staphylococcal enterotoxins, nausea and vomiting. In fact, patients who experience staphylococcal enterotoxin poisoning do not usually have fever, much less shock. Since in staphylococcal food poisoning the organism (or the heat-stable toxin) is introduced into the gut, perhaps its primary action is in the GI tract, with little toxin absorbed to interact with circulating T cells, etc. The toxin might also have much higher affinity for CNS targets than for T cells. The connection between this mechanism for T cell activation and the rash of scarlet fever and TSS is also uncertain. Reconciliation of the clinical illnesses associated with these toxins and their ability to act as superantigens awaits further study. Interestingly, a streptococcal M protein has also been reported to behave as a superantigen (Tomai, 1990).

STREPTOCOCCAL TOXIC SHOCK SYNDROME?

As noted above, staphylococcal TSS is a multisystem illness that has several characteristic features: fever; diffuse erythroderma, with eventual desquamation; hypotension; and evidence for multisystem involvement. Bacteremia is not necessary; the toxin is released from a localized site of infection, absorbed into the blood, and spreads hematogenously.

Whereas some cases of streptococcal TS-like syndrome share these features, including absence of bacteremia, most have not had the desquamating, diffuse erythroderma or strawberry tongue, and GAS bacteremia and soft tissue or deep tissue infection have been common. The following table summarizes the features of TSS, Scarlet Fever, and severe streptococcal disease with "TSS."

	Staphylococcal toxic shock syndrome	Scarlet Fever	Severe streptococcal disease
Rash	diffuse	scarlatiniform	variable, none
Desquamation	common	common	uncommon
Hypotension	++++	+/-	++++
Bacteremia	-/+	-	+++
Tissue Invasion	-	-	++

The streptococcal cases are heterogeneous. A simplified categorization might be:

1. Invasive disease, without a SPE-mediated component; bacteremia, often with myositis and/or fasciitis

2. SPE-mediated disease ("streptococcal toxic shock"); cellulitis or other local infection, without bacteremia or deep tissue invasion.

3. Invasive disease with toxin-mediated manifestations; combines features of 1. and 2.

Most of the patients reported from Great Britain would fall into the first category, whereas most of those from the U.S. would be in the 2nd and 3rd. Interestingly, many cases of severe streptococcal disease reported in this country (category 3) seem superficially to resemble the entity once known as "septic scarlet fever", which usually occurred in children with streptococcal pharyngitis. Christie described this condition as follows:

"In these cases the local throat lesion is severe. There is much peritonsillar invasion, sometimes with perforation of the pillars of the fauces and early invasion of the middle ear with purulent otitis media or mastoiditis, and often spread of the organisms to the cervical lymph nodes with great swelling and often suppuration. The rash in these cases is often atypical, and consists of scattered blotches of erythema or macules, especially around the joints. The danger to the patient is from septic complications rather than from toxaemia. Penicillin would doubtless be invaluable, but **I have not seen such a case in the penicillin era.**" (Christie, 1974)

In the largely adult patients with severe, invasive streptococcal disease the portal of streptococcal entry has usually been a break in the skin, rather than tonsillitis, but the local and distant invasive (septic) complications seem quite similar to those described for septic scarlet fever. Another streptococcal disease with a similar pathogenesis would be puerperal sepsis; instead of septic invasion of tonsils, middle ear, and mastoids (septic scarlet fever from tonsillitis), or of muscle, fascia, and soft tissue ("toxic strep" from a cutaneous or i.v. source), puerperal sepsis may include endometritis, salpingitis, pelvic cellulitis, and septic thrombophlebitis.

It is interesting that in septic scarlet fever the rash is described as "atypical," since most of the recently described patients with severe GAS disease have not had a diffuse rash, and a minority has eventually desquamated.

In arguing that the recent cases have not fit with the descriptions of septic scarlet fever, Dr. Ben Schwartz (C.D.C.) points out that myositis and fasciitis were not described in the literature on this form of scarlet fever. He maintains that the recent cases of severe disease are a different, new process.

An important clinical implication of this discussion is that, unlike typical patients with staphylococcal toxic shock or classical (mild) scarlet fever, patients with the severe streptococcal syndrome must be followed very closely to detect **tissue invasive local and metastatic septic complications.** The other two syndromes are toxin-mediated, this one is only partially so. Relatively few patients have had a pure, toxin-mediated "toxic shock" syndrome due to GAS.

WHAT HAS HAPPENED TO *S. PYOGENES*?

1. M types 1 and 3 have often been associated with severe disease.

In the series cited above from Great Britain (Gaworzewska and Colman, 1988), the percentage of isolates that was either M1 or M3 increased during the 1980's: These are M types that have been associated with rheumatic fever outbreaks in the past (Bessen et al., 1989) but they had been infrequently noted in surveillance done prior to the recent experience.

Year	Total no. isolates from blood/CSF	No. isolates of M type 1	3	% M1 + M3
1980	54	11	11	40
1981	36	5	2	20
1982	48	6	4	21
1983	36	4	5	25
1984	75	12	7	26
1985	66	24	11	52
1986	88	35	15	57
1987*	84	54	7	72

* first 6 months

Equally striking was their observation that **90% of the isolates from fatal cases were these M types.**

In the Rocky Mountain series, 6 of 10 blood isolates tested were M types 1 or 3 (Stevens et al., 1989), whereas 6 of 8 blood isolates from the Denver patients were these M types (CDC, 1990). Most of the isolates from the other reported cases have not been typed. In a study of over 5,000 isolates submitted to CDC for typing, Schwartz et al. (1989) found that 7.7% and 8.6% of the isolates from sporadic cases and time/space clusters, respectively, in 1972-79 were M types 1 or 3. In 1980-88, in contrast, 14.9% (sporadic) and 18.4% (cluster) isolates were these M types, again supporting the idea that cases associated with M types 1 and 3 have increased in frequency. The isolate from Jim Henson's blood was M type 1.

The association of these M types with the occurrence of severe illness in distant locales suggests that M types 1 and 3 may be markers for a virulent clone of *S. pyogenes*. This not the whole story, however, since other M types can be associated with severe disease. In particular, M-nontypable T11/12 strains have been associated with the toxic syndrome (interestingly, the strains from the patients at the Dallas VAH were M-nontypable, T11/12). In Britain, the prominence of M type 1 seems to have faded, as in 1989 only 3 of 26 isolates from fatal infections were type 1--the remainder were types 3 (7 isolates) and others (16 isolates, 8 types)(G. Colman, personal communication).

It is hard to fit these data into a unitary hypothesis that would account for the occurrence of clusters of severe GAS disease. In addition, one cannot predict that the responsible strain(s) will persist. Perhaps the M types are markers for other molecules (gene products) that are the true "virulence" factors; perhaps these genes are phage-encoded, and therefore transmissible between different M types of GAS; perhaps different kinds of clonal analysis will discover the key gene products. A major research effort is currently underway.

2. Streptococcal pyrogenic exotoxin A has reappeared in the U.S. (but not in Britain)

Whereas isolates that made SPE-A were rarely encounted in the U.S. during the 1960's and 1970's, 8 of 10 isolates from the Rocky Mountain series produced this toxin. Interestingly, none of the isolates tested by Gaworzewska and Hallas (1989) in Britain made this toxin in vitro, including 32 M type 1 and 5 M type 3 strains, whereas exotoxins B and C were commonly found. Since the U.S. and British isolates were all from patients with severe disease, SPE-A is evidently not required for *S. pyogenes* to produce hypotension, etc. In fact, SPE-B has also been associated with a substantial fraction of the cases of severe disease reported in the U.S.

The different disease categories discussed above might be accounted for as follows:

1. Invasive disease (the M1 or M3 clone; M nontypable too)

2. Toxin-mediated disease (pyrogenic exotoxin A [less commonly, B or C])

3. Invasive disease with toxin-mediated manifestations (both)

In this classification, most patients in Great Britain would seem to have invasive disease, whereas 1/2 - 3/4 of the patients in the U.S. would have invasive disease with toxin-mediated manifestations, and 1/5 or so would have the toxin-mediated disease. As suggested by Dr. Schwartz, the intriguing, unusual feature of the disease in the 1980's has been the predilection of the strains to produce myositis and fasciitis; the basis for this is unknown.

ANTIMICROBIAL THERAPY

Penicillin G remains the drug of choice for *S. pyogenes*. It should be used in high doses (18 - 24 MU/day, or 3 - 4 MU q4h) in patients with severe soft tissue infections or presumed sepsis. One potential problem with penicillin G therapy was noted soon after the drug was introduced. H. Eagle reported in 1952 that penicillin G was unable to kill *S. pyogenes* when bacterial growth had reached high density in tissue. He felt that the ineffectiveness of penicillin was due to the much slower growth of the streptococci when they reached high concentrations in tissues. Stevens et al. (1988) have recently confirmed Eagle's observation using a model of *S. pyogenes* myositis in the mouse. They found that penicillin was effective only if it was given before the mice were inoculated with a high inoculum (3.5×10^9 organisms) of *S. pyogenes*. With any delay in administration, penicillin was ineffective. In contrast, clindamycin was substantially more effective, producing survival in 80% of the animals even when given 6 hours after the inoculation.

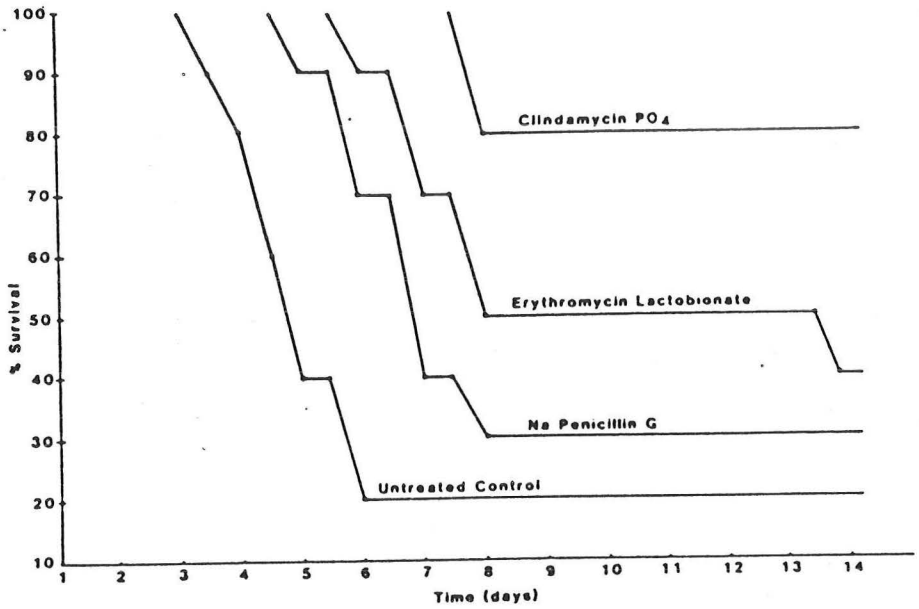


Figure from Stevens et al., 1988. Groups of 10 mice received 3.5 x 10^9 GAS intramuscularly. "Antibiotics were administered 6 h after initiation of infection and were continued every 4 h for a total of 4 doses. Animals were observed for 14 d, and the percent survival was calculated."

With many gram-positive bacteria, clindamycin is not affected by inoculum size, whereas the efficacy of penicillin G is very inoculum-dependent (penicillin requires cell wall synthesis to kill; clindamycin inhibits protein synthesis). Clindamycin also inhibits M protein synthesis and denudes the surface of the bacterium of the "fuzz" that is evident using electron microscopy. This is associated with greater complement binding and opsonization for phagocytosis (Gemmell et al., 1981).

No clinical trials have compared penicillin G and clindamycin in patients with severe streptococcal disease. For the moment, penicillin should remain the drug of choice, although its poor performance in myositis, necrotizing fasciitis, etc. may encourage the use (probably in combination) of clindamycin. Trimethoprim-sulfamethoxazole is not effective therapy and should not be used when GAS is suspected.

CONCLUSIONS

There has been an increase in the frequency and severity of group A streptococcal disease in certain places, while most communities seem to have been unaffected. Most of the cases have been reported in adults, who have often been previously healthy; cases in children have also been described. Bacteremia has usually followed infection or inoculation at a cutaneous site. Some patients have had multisystem derangements that appear to have been entirely toxin-mediated, yet more commonly the severely ill patients have been bacteremic; in the absence of some obvious toxin-mediated effect, such as a

rash, it is hard to assess the relative contributions of exotoxins and other bacterial and host factors in the pathogenesis of shock and multisystem failure in these patients.

Streptococcal bacteremia and tissue invasion can probably produce multisystem organ failure in the absence of a toxin; the association of certain M types with many of the cases may reflect the emergence of a particularly virulent clone of GAS. On the other hand, the isolation of SPE-A producing GAS from many of the cases suggests that this toxin may play some role in pathogenesis, probably contributory rather than primary in most cases. Other SPEs may also be important. The tendency for patients to develop myositis and fasciitis is unexplained.

There is no evidence that currently practiced management of streptococcal pharyngitis or skin infections should be altered. On the other hand, the recent reports of rapidly developing cellulitis and sepsis in some individuals reinforce the importance of prompt antimicrobial (and, when indicated, surgical) therapy of streptococcal skin lesions. Management of patients with GAS sepsis should include aggressive efforts to discover and treat soft tissue (muscle, fascia) invasion. When patients with GAS disease are hospitalized, measures should be taken to prevent nosocomial spread of GAS to patients and personnel. Penicillin G remains the antibiotic of choice for severe disease, although in patients with severe invasive disease its efficacy has been questioned.

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