of GABHS has been reported⁵ and clustering of sudden unexpected death is also well known, indeed the geographical pattern and seasonal variation of sudden unexpected death is itself suggestive of an infective process.⁶ In all our cases postmortem examination did not show a convincing cause of death and without microbiological evidence the diagnosis would have been sudden unexpected death.

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Commentary

In the 19th century Louis Pasteur identified cocci in chains in the uterus and blood of women dying from puerperal sepsis. By the 1930s, studies of illness related to *Streptococcus pyogenes* revealed a highly virulent organism capable of causing severe, often fatal invasive disease.^{1 2} It is therefore remarkable that in a trend that started before the introduction of effective antibiotics, the mortality associated with group A β haemolytic streptococcus (GABHS) has continued to decrease over the last 50 years, and bacteraemia with the organism has become a rare clinical entity.^{3 4} Today, although GABHS is among the most common pathogenic bacteria isolated from children, most paediatricians associate the organism with an acute pharyngitis or tonsillitis, rarely seeing acute suppurative disease, glomerulonephritis, or acute rheumatic fever. In this paper Sharief and colleagues report a cluster of three patients who died from overwhelming GABHS infection. Interestingly, all the cases occurred within eight weeks of each other in a small geographical area. Their paper is important in highlighting a recent change in not only the incidence of GABHS bacteraemia but also in the clinical spectrum of the disease. It now appears that the previous trend has reversed, with increasing reports of rheumatic fever and invasive infection among children in Europe and the United States.^{3–5}

These recent outbreaks have a number of similarities with those described over 50 years ago, with the majority of the patients with GABHS bacteraemia presenting with fever and sore throat, cellulitis, osteomyelitis, septic arthritis, pneumonia, meningitis, and overwhelming sepsis.^{3 6} In contrast, however, the mortality associated with the resurgent disease has been significantly lower (7–12%) than the 76% observed in the preantibiotic era.^{1 3 6} Although the disease has occurred after varicella and in association with congenital immunodeficiency or malignancy, the majority of cases have not had an underlying abnormality.

Among these new reports of severe GABHS infection there have been a number of cases of a toxic shock-like syndrome associated with the production of streptococcal toxins.^{4 5} These pyrogenic exotoxins enhance host susceptibility to endotoxin⁷ and like staphylococcal toxic shock syndrome toxins⁸ act as superantigens in their ability to expand specific T cell families and provoke cytokine release.⁵ Interestingly, it seems that this apparently new clinical entity of toxic shock-like syndrome was described over 60 years ago. In a report of an epidemic of severe scarlet fever in Yunnafu, China (1921–2), Weech identified both severe toxic and invasive septicaemic forms of the disease that were associated with throat cultures positive for haemolytic streptococci.² It is astonishing that in this epidemic, the entire population of 200 000 was affected and 50 000 deaths occurred. Therefore, if the clinical manifestations of this resurgent streptococcal disease are not new, has an old, virulent strain of GABHS re-emerged, or has a new variant developed?

To answer this question it is important to appreciate that the GABHS has a number of virulence factors. The role of pyrogenic exotoxins remains hotly debated,^{9 10} but there are many other factors including secreted proteins such as streptokinase, hyaluronidase and the haemolysins, in addition to surface proteins such as C5a peptidase, M proteins, and the immunoglobulin Fc receptor protein.⁷ Of these, the M proteins are thought to be particularly essential for the survival of GABHS within the host. These are fibrillar molecules extending from the bacterial cell surface,¹¹ which facilitate adherence to epithelial cells and inhibit effective complement mediated neutrophil phagocytosis.^{7 11 12} In a study of isolates collected between 1972 and 1988 by the Centers for Disease Control in Atlanta, Schwartz and coworkers demonstrated a significant increase in the proportion of M types 1, 3, and 18.⁴ In England, M type 1 strains have increased from 1% in 1980 to 30% of all GABHS isolates in 1987,¹³ and have largely been responsible for the dramatic increase in invasive disease in Sweden and Norway.¹⁴ Therefore GABHS strains expressing specific M proteins seem to account for the resurgence of invasive disease in both Europe and the United States.

Using multilocus enzyme electrophoresis in conjunction with M protein serotyping, Musser and coworkers have confirmed that nearly half of invasive disease episodes in Europe and the USA are caused by M type 1 and M type 3 strains, and have demonstrated that these strains are derived from closely related genetic clones, denoted ET 1 and 2 respectively.¹⁵ After analysis of isolates from the 1920s and 1930s, Musser *et al* have gone on to suggest that these clones have emerged through changes in the older strains that occurred sometime in the 1960s and 1970s, possibly driven by the low level of herd immunity.¹⁰ Restriction fragment profile studies support this hypothesis,⁹ and add to the weight of evidence suggesting that, after their

emergence, these new variants have become widely dispersed geographically. Whether these new strains originally developed through mutation or horizontal gene transfer continues to be investigated.^{9 10} However, what is clear is that these new GABHS isolates are highly adaptable in their ability to alter virulence factors in response to the environment¹² and their ability to become tolerant to penicillin.¹⁶ There is now evidence that diverse phylogenetic lineages are able to acquire the gene for exotoxin production horizontally via a bacteriophages¹⁵ and significant erythromycin resistance from plasmids.¹⁷

In conclusion the GABHS has re-emerged as the cause of a severe invasive disease that continues to have an appreciable mortality. Modern molecular techniques have been used to suggest that the organisms responsible for this change are new variants which have become widely distributed throughout the world. While vaccination seems to be the optimal strategy, at the present time, GABHS disease once recognised, should be treated aggressively.

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