New Clue to the Cause of Toxic Shock

Acquisition of viral DNA by Staphylococcus aureus *may enable this bacterium to produce toxins that cause the symptoms of toxic shock*

Although the bacterium *Staphylococcus aureus* has been strongly linked to toxic shock syndrome and is presumably its cause, the connection has not solved all the problems concerning the origin of this disease. For example, the explanation for the sharp increase in incidence a few years ago is unclear. Also puzzling is the reason that only some strains of this common bacterium produce the characteristic symptoms of toxic shock, which include fever, lowered blood pressure, vomiting, diarrhea, and a rash in which the skin peels.

In this issue of *Science* (p. 316), a group of investigators from Rockefeller University report results that may shed some light on these issues. Steven Schutzer, Vincent Fischetti, and John Zabriskie have found that almost all strains of *S. aureus* isolated from toxic shock patients carry a latent form of a bacterial virus that is only rarely detected in strains isolated from controls. They suggest that acquisition of the viral material may lead to the production of toxins that produce toxic shock symptoms. William Ledger of New York Hospital–Cornell Medical Center says of the work, "It could explain why this organism appeared and why we see the type of symptomology that we see."

There are strong precedents for the situation now proposed for toxic shock. The symptoms of scarlet fever, which is caused by *Streptococcus pyogenes*, and of diphtheria, which is caused by *Corynebacterium diphtheriae*, are elicited by toxins produced by the bacteria. In both cases, only those strains of bacteria that carry bacterial viruses—bacteriophages—produce the toxins.

Bacteriophages have two ways in which to parasitize their hosts. They may multiply rapidly after entering the cells, thus leading to cell death. Or the viral DNA may become integrated into the bacterial genome. In that event, the cells continue to live, transmitting the viral genome to their progeny. It is this second mode of parasitism, called lysogeny, that is seen in the pathogenic strains of *S. pyogenes* and *C. diphtheriae*. The viral DNA's either carry genes that code for the toxin proteins or the integration of the DNA may activate bacterial genes that were previously repressed.

Zabriskie, who was one of the pioneers of the work on *S. pyogenes* in the early 1960's, notes that the symptoms of toxic shock closely resemble those of scarlet fever. He says, "Staph with a similar property could act in exactly the same way as the strep. Schutzer picked up the notebook of 1962 and applied it to 1982."

Schutzer, Fischetti, and Zabriskie obtained 12 strains of *S. aureus* that had been isolated from toxic shock patients and 18 strains from individuals who did not have the disease. Under certain conditions bacteria that have undergone lysogeny can be made to release the bacteriophage in the virulently infectious form, which can be detected by its ability to kill susceptible cells. The investigators found that 11 of the 12 toxic shock–associated strains of *S. aureus* released infectious virus, whereas only one of the 18 control strains did. The investigators also showed that bacteriophage isolated from two toxic shock–associated strains could enter into a lysogenic relationship with a laboratory strain of the bacterium, a potential mode of transmission of toxin-generating capabilities among bacteria.

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Although these findings, taken in conjunction with the precedents established by the work on scarlet fever and diphtheria, provide circumstantial evidence that lysogeny of *S. aureus* is necessary for the initiation of the pathological events of toxic shock, they do not prove it. "What we really have is a very strong association between lysogeny and toxic shock strains," Zabriskie says. "The next question is, are they causally related?"

It is still necessary to show that lysogeny of *S. aureus* results in the production of toxins that can elicit toxic shock symptoms in experimental animals. Two groups, those of Merlin Bergdoll at the University of Wisconsin and Patrick Schlievert of the University of Minnesota, have previously identified toxins that are produced by *S. aureus* strains from toxic shock patients, but not by most control strains. An obvious next step is to determine whether these or other toxins are produced as a result of lysogeny of the bacterium.

Trials are also under way at Rockefeller to find out whether the acquisition of bacteriophage DNA is associated with toxicity in experimental animals. Preliminary evidence suggests that it is.

Development of a new strain of *S. aureus* carrying a bacteriophage might account for the upsurge in toxic shock cases that began in 1980. "Toxic shock is not new to the extent that it was never seen before," Ledger says. "But it is new in terms of numbers." Between 1970 and the end of 1982, the Centers for Disease Control (CDC) received notice of 1925 cases; 75 percent of them were reported in the 3-year period ending in 1982. The cases have tended to cluster in a four- or five-state area, including Utah and the states of the upper Midwest. This type of patchy distribution is further supportive evidence of the involvement of a new bacterial strain.

Another factor that has been advanced by several investigators to explain the increased incidence of toxic shock is the use of tampons, particularly those of very high absorbancy. About 85 percent of the cases reported to the CDC occurred in menstruating women who were using tampons at the time the disease developed. The connection, if any, between lysogeny of *S. aureus* and tampon use is unclear. However, as Ledger points out, "tampon use may be a factor that increases the risk, but it doesn't explain the total thing."

In any event, the hypothesis that lysogeny of certain strains of *S. aureus* may be the ultimate cause of toxic shock has a major advantage: it is easily testable. Answers should not be long in coming.—**JEAN L. MARX**