The Once and Future Scourge

Could common anti-inflammatory drugs allow bacteria to take a deadly turn?

By LISA SEACHRIST

"Flesh-eating bug ate my face!" one British tabloid screamed last year. The story took off like wildfire, with gruesome descriptions of limbs rotting in front of people's eyes, faces melting away, and emergency amputations to save lives. From the looks of it, the United Kingdom had been struck by a menacing new bacterial threat.

But the threat wasn't new at all. The deadly bacterium turned out to be a well-known bug responsible for countless bouts of throat and skin infection. And the disease itself, necrotizing fasciitis, wasn't new either; it had simply acquired a new name.

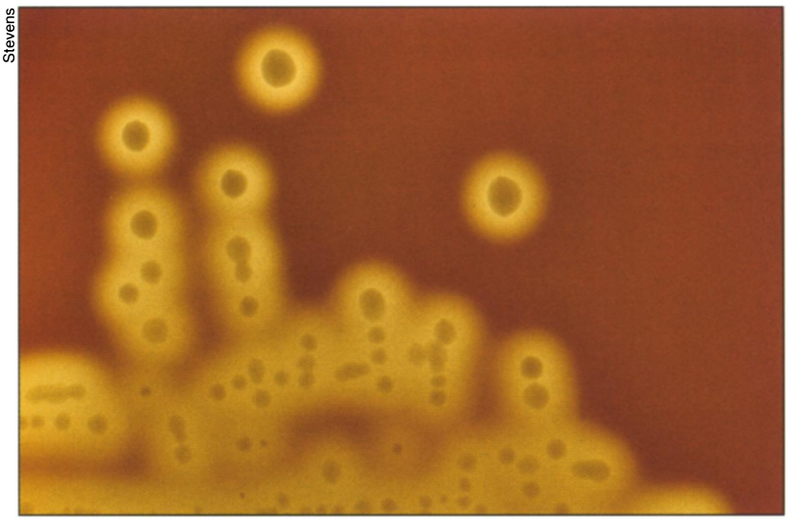
Previously known as malignant ulcer, hospital gangrene, and putrid ulcer, the disorder had shown up in hospitals, during wartime, and in nursing homes and nurseries. Sporadic accounts of fatal, runaway infections go back centuries, perhaps even to the time of Hippocrates. Most such infections arise in places with poor hygiene and among people with weakened immune systems. In modern times, the bug went quietly about its business in relative obscurity until a cluster of cases in southwest England caught the attention of the Fleet Street tabloids in the spring of 1994.

The medical community responded to the publicity by maintaining that the cluster represented an unlucky coincidence but that the underlying rate of occurrence of the disease had not changed. But no good data existed to back up the claim: Neither the British nor the U.S. government regards the disease as enough of a general threat to warrant monitoring.

In the United States, best estimates indicate that the occurrence of necrotizing fasciitis and the related toxic shock syndrome has remained stable over the past couple of years. But according to the Centers for Disease Control and Prevention (CDC) in Atlanta, the number of new toxic shock cases appeared to increase during the 1980s, from virtually none to about 2,000 per year.

"We have seen [these invasive bacterial] infections for centuries," says infectious disease specialist Dennis L. Stevens of the University of Washington School of Medicine in Seattle. "What seems to be unique now is that we are seeing a significant number of otherwise healthy individuals getting these infections."

Stevens



Group A streptococcus growing on agar containing blood. The yellow areas around the bacterial colonies result when toxins diffuse from the bacteria and destroy red blood cells in the agar.

That trend has scientists asking why the bacterium suddenly turned mean. Some maintain that the bug has become more virulent. Stevens agrees but also suggests that commonly used anti-inflammatory drugs such as ibuprofen may have played a part.

"I've been impressed [looking at] the several hundred case reports that I have studied that a significant number of individuals either took the [drugs] or were prescribed them and 24 to 36 hours later suddenly had shock and organ failure."

The bacterium engendering such interest these days is *Streptococcus pyogenes*, or group A streptococcus. Rather than a distinct bug, group A represents a collection of strains of bacteria that vary in their ability to cause infection. Strep ordinarily lives on the skin, and approximately 5 percent of people in the United States carry the organism in their throat at any given time. While various toxins produced by the bacterial strains have been identified, it isn't clear which of the toxins, if any, prompts the bacteria to become infectious. When the bacteria take that turn, common strep throat or impetigo, a skin infection, usually results.

Occasionally, strep takes on a more destructive personality. If bacteria invade the bloodstream—for example, from the throat or a cut in the skin—strep can find its way to the subcutaneous tissue, or fascia, that surrounds muscle.

At that point, a race ensues between the body's immune system and the multiplying bacteria. Antibodies recognize foreign proteins on the bacteria and use a variety of signaling compounds, known as cytokines, to call in white blood cells; these engulf and digest the bacteria. But the bacteria manufacture a variety of toxins that help break down tissue, aiding the bacteria's spread through the fascia and into other parts of the body.

If the immune system wins, a person may develop a slight fever without ever realizing he or she had an infection. If the bacteria win, people develop necrotizing fasciitis, the ballyhooed "flesh-eating bacteria disease," or group A streptococcal toxic shock syndrome, a potentially fatal combination of shock and organ failure, with sometimes devastating results.

"It was a case of group A streptococcal

toxic shock syndrome that killed Muppets creator Jim Henson in 1990 after a bout of streptococcal pneumonia," says Stevens.

Scientists are having difficulty explaining the rise in invasive strep infections. Some dispute whether there has been any increase at all. Microbiologist Hugh Pennington of Aberdeen University in Scotland maintains that there is "no real evidence" of a rising incidence of necrotizing fasciitis in the United Kingdom. He notes that the United Kingdom escaped the increase in toxic shock syndrome cases that struck the United States in the 1980s. Pennington bets that any increase in these diseases stems from the bacteria producing more potent toxins.

Others aren't so quick to blame the bacteria.

Stevens argues that if a new and more virulent strain of streptococcus had emerged, invasive strep infections would have been far more widespread. For example, a new strain of influenza is always associated with epidemics.

He suspects that some specific factor unrelated to the bacterium is making people more susceptible. Known factors include chicken pox and trauma, but a series of anecdotal reports, beginning in the mid-1980s, has drawn attention to the link between patients suffering either necrotizing fasciitis or toxic shock syndrome and pain relievers known as nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen.

In March, researchers from the University of Otago Medical School in Dunedin, New Zealand, published in the New Zealand Medical Journal accounts of seven cases of necrotizing fasciitis, five of them associated with NSAIDs. "We have seen an increase in necrotizing fasciitis, and perhaps the very frequent use of these agents is responsible for this increase," says study author Robert Walker.

In Canada last winter, Lucien Bouchard, leader of the Quebec separatist movement, suffered what he thought was a pulled leg muscle. He took NSAIDs and later suffered a case of necrotizing fasciitis that resulted in the amputation of his leg.

The United Kingdom's National Health Service has begun to monitor cases of necrotizing fasciitis. Consulting microbiologist Michael Barnham reports that at least 10 cases have been linked to the drugs.

NSAIDs have proved invaluable for treating diseases such as rheumatoid arthritis and for relieving the aches and pains of athletic injuries. But Stevens maintains that the very mode of action that makes them so effective puts people at risk of invasive strep infections.

NSAIDs work by dampening inflammation—a vital part of the body's defenses against microbial invaders. In the October Clinical Infectious Diseases, Stevens outlines the hypothesis that NSAIDs can mask an infection and stymie the immune system.

White cells known as macrophages respond to foreign bacterial protein by producing a cytokine called tumor necrosis factor (TNF), which then circulates in the bloodstream. When TNF reaches the brainstem, it signals the brain to produce prostaglandins; the prostaglandins trigger a fever and tell the macrophages to stop producing TNF. NSAIDs block the production of prostaglandins and prevent fever, but they also fail to signal the macrophages to turn off TNF.

As a result, "patients mask their clinical symptoms with the NSAIDs and prevent a proper diagnosis," argues Stevens. Furthermore, overproduction of TNF allows the bacteria to spread more easily and contributes to shock and organ failure.

Stevens suggests, for example, that at the time Lucien Bouchard pulled a muscle, he may also have had strep circulating in his bloodstream. When he damaged the muscle, blood leaked into the injured area and the bacteria took hold. NSAIDs lessened his pain but did nothing to combat the mounting infection and may have lessened Bouchard's own ability to fight the infection.

An interesting "ecological" link between NSAIDs and invasive strep infection occurred last year in the form of an increase in cases of necrotizing fasciitis among children infected with chicken pox. Benjamin Schwartz of the CDC points out that the increase coincides with the introduction of suspensions of ibuprofen for pediatric use. Parents might give their children the medication to calm fever, pain, and itching associated with chicken pox, but in so doing make it easier for bacteria from the skin to enter the body via the disease's open sores.

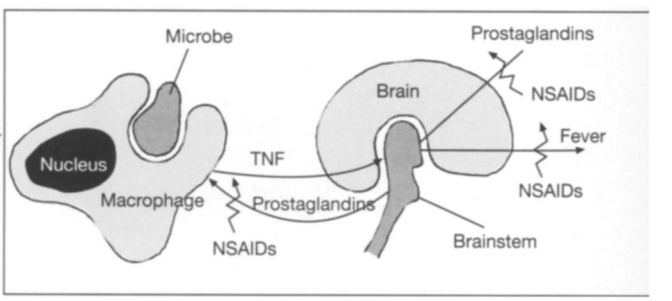
Schwartz notes, however, that "the war in Bosnia also coincides with the increase in invasive strep infections following chicken pox, and certainly there is no reason to believe they are linked in any way."

Establishing that NSAIDs increase susceptibility to invasive strep infections requires more than these tenuous suggestions. Schwartz emphasizes that all of the associations so far come from analyses of individual cases and not from controlled studies. Pennington points out that NSAIDs have become some of the most widely used drugs worldwide, yet toxic shock syndrome and necrotizing fasciitis remain relatively rare. Any link between the two may "simply reflect the large numbers of people who take the drugs," he notes.

Conducting a study that matches patients who develop invasive infection with those who suffer only strep throat or impetigo remains the only way to truly determine whether a link exists. Such an endeavor, Pennington maintains, will be tremendously difficult and costly.

Although evidence of a link remains scanty, Schwartz believes that the widespread use of drugs with a proven ability to dampen the immune system makes such a study worthwhile. In addition, Stevens is developing an experimental model to test his theory directly.

In the meantime, Stevens and Walker argue against the use of NSAIDs when a bacterial infection may be the root of the problem. Stevens notes that people who have "increasingly severe muscle pain accompanied by fever and chills should see their doctor." And they should not take NSAIDs until they've received antibiotics to treat the bacterial infection or have been otherwise assured of the absence of such an infection.



Tumor necrosis factor (TNF), produced by macrophages when they encounter bacteria, circulates through the blood to the brainstem. The brainstem then generates prostaglandins to induce fever and stop TNF production. NSAIDs prevent prostaglandin formation and stop fever but don't interfere with TNF, which may be involved in shock and organ failure.

"Once these group A strep infections are established and patients are in shock, 30 to 70 percent will die and many will lose extremeties," says Stevens. "Our best efforts can only be aimed at earlier diagnosis and prevention. Not using NSAIDs when strep infection is possible is the best advice I can give."

The researchers agree that, in general, NSAIDs pose no dangers and that they remain vital treatment tools. But because they reduce fever, they can mask underlying bacterial infections.

The tip-off to these dangerous but extraordinarily rare invasive strep infections, Walker reiterates, is severe pain disproportionate to any injury. Despite the utility of NSAIDs, Walker cautions weekend athletes to take the drugs with care. "These drugs are used because of their profound effects on the immune system," says Walker. "They're not just some innocuous candy-lollies." □