Experts Dissect Last Layer of Anthrax Toxin

By NICHOLAS WADE

Scientists have worked out the exact three-dimensional structure of the edema factor, the last of three components in the deadly toxin produced by the anthrax bacterium. The knowledge should help in understanding how the edema factor works and in devising drugs to block it.

The structures of the other two, known as lethal factor and protective antigen, have already been worked out by the same technique, known as X-ray crystallography, an arduous way of visualizing structures too small to be picked up by light.

With the three toxin components deciphered, biologists are beginning to understand the extraordinary cunning with which the anthrax bacterium first stifles the body's immune system by blocking the signals that coordinate its usual defense against bacterial invasion.

The structure of the edema factor, so called because it causes swelling, was worked out by Chester L. Drum of the University of Chicago, working with Dr. Wei-Jen Tang, also at the university, and Dr. Andrew Bohm of Tufts University. They describe their work in the current issue of the journal Nature.

Anthrax spends most of its time as an invisible spore, lurking in soil. When a spore is inhaled by a grazing animal, or slips through a break in the skin, it is swiftly engulfed by a macrophage, a type of cell that patrols the body surfaces for invaders.

The anthrax spores, however, are specialized to destroy their captors. They germinate into bacteria, burst out into the bloodstream, and flood the body with their three toxins. Protective antigen, so named before its true role was understood, serves as the attack vehicle for the other two toxins. The protective antigen proteins assemble in clusters of seven, forming a barrel-shaped structure with a docking site for either edema factor or lethal factor, the other two members of the toxic troika.

The toxin-laden barrels seek and enter many kinds of cell, but macrophages again seem to be their principal target. Mr. Drum and his colleagues have found that the edema factor, which is harmless while inside the bacterium, is activated as soon as it bumps into a common component of cells known as calmodulin. It grabs both ends of the calmodulin, changing shape as it does so. The activated edema factor is able to generate a small messenger chemical widely used within cells, synthesizing it a thousand times as fast as the cell itself does.

The messenger, known as cyclic AMP, quickly reaches abnormally high levels, which derange the macrophages and block them from performing their usual role of sending out cytokines to alert the immune system to a bacterial invasion.

Lethal factor, the other anthrax toxin, also inhibits cytokine production, though through a different mechanism. "The bacterium is stifling the immune response completely, so that the body doesn't know it is being infected," said Dr. Robert C. Liddington of the Burnham Institute in Torrey Pines, Calif. Dr. Liddington worked out the structure of lethal factor last year.

Experts are uncertain how anthrax delivers its coup de grâce. One idea is that the macrophages are suddenly killed, releasing a flood of pent-up cytokines. The cytokines, which cause a useful inflammatory response in small doses, are lethal en masse. Vessels leak, blood pressure drops, organs fail and the victim dies from septic shock.

But another anthrax expert, Dr. John Collier of Harvard Medical School, said it was not yet clear that the macrophages produced cytokines, and that anthrax might kill by some other means.

With the victim's death, the immune system is immobilized. The anthrax bacteria are free to grow and devour the body's nutrients until they run out of food. Their lethal orgy ended, they turn back into spores and wait patiently to repeat the cycle.

Dr. Drum said it took him nearly four years to work out the structure of the edema factor, a protein he said some ancestral anthrax bacterium may have hijacked from an animal cell many millennia ago.

Knowledge of the exact structure of the three toxins should speed the search for new drugs, which are likely to be used in combination with antibiotics. Dr. Liddington said drugs against lethal factor might be ready to test in 18 months.

Activating a Toxin

Edema factor, an anthrax toxin, changes shape when it reacts with a common cell protein. The shape change activates the toxin, and it deranges the cell's internal signaling process.

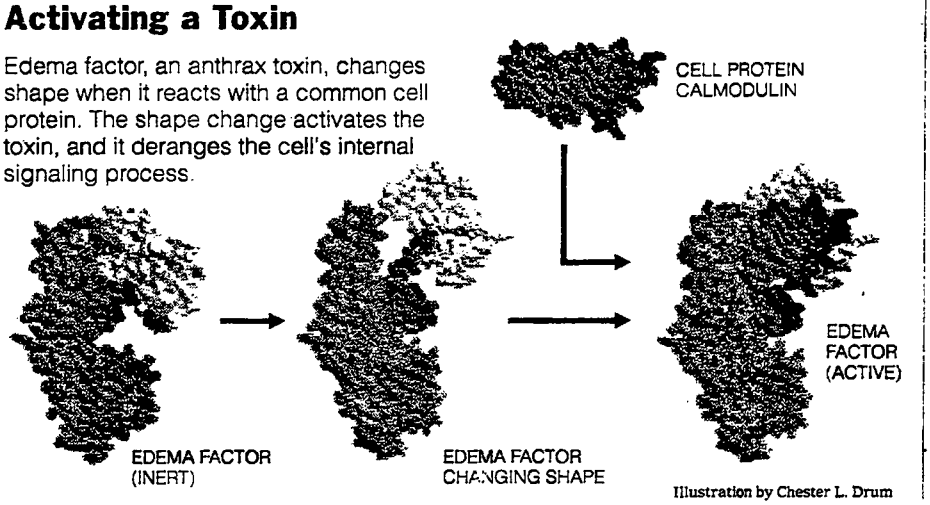

Illustration by Chester L. Drum

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