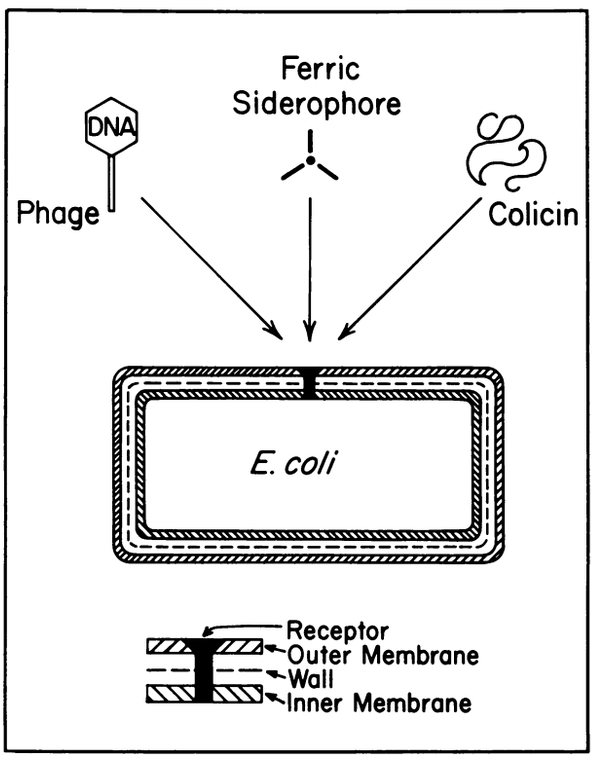
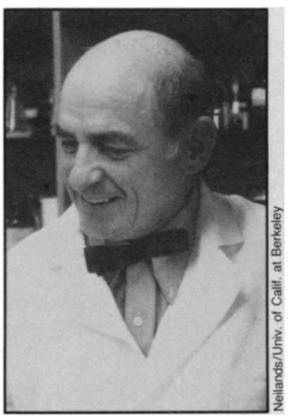
Bacterial Blitz: Storming the Achilles Pore

A miniature war at the cell surface ends in capture of the essential iron receptor

BY JANET L. HOPSON





Neilands and the logistics of iron pore warfare. Bacterial viruses (phages), bacterial antibiotics (colicin) and iron-carriers (siderophores) vie for entrance at the iron pore. The victor determines the fate of the host cell.

This is one type of germ warfare humankind is only watching from the sidelines. The biochemist who discovered it calls it "CBW," colicin-bacteriophage warfare. That researcher plans, someday, to get off the sidelines and to play both ends against the middle in this minute struggle at the surface of bacterial cells. If the strategy works, it may enable him and his colleagues to design better weapons against intransigent human germs.

This natural germ warfare story started about 20 years ago when biochemist J. B. Neilands of the University of California at Berkeley discovered "siderophores." These are ferric iron transporting compounds produced by bacteria such as *Escherichia coli* and *Salmonella typhimuriam* and fungi such as *Aspergillus, Penicillium* and *Ustilago.*

Ferric iron (oxidation state +3) is an essential nutrient for bacteria as well as higher animals. *E. coli* and other single-celled organisms have evolved an ingenious system using siderophores to ensure that a supply of ferric iron is always on hand for oxygen delivery, energy utilization and DNA synthesis: When ferric grows scarce in the surrounding environment, *E. coli* produces siderophore molecules called enterobactin and spews them out through "iron pores" in the cell wall. Enterobactin molecules capture ferric iron and diffuse back into the cell through what Neilands calls the "Achilles pores." When ferric is plentiful, siderophore production stops.

These iron pores render the bacterium vulnerable to attack by its enemies, colicin and bacteriophage—hence the name Achilles pores. Bacteriophages are viruses that only infect bacteria, and colicins are natural antibiotics produced by bacteria to kill competing bacterial species. Phages and colicins have themselves evolved an ingenious survival mechanism: They enter the target cell quite neatly by commandeering its essential iron pores. Thus three biochemical units—iron transporters, bacterial viruses and bacterial antiobiotics—all do battle for the same entry site on the bacterial cell wall.

Neilands and his students have studied this warfare intensively during the past two years. They recently reported a new twist to the American Chemical Society meeting in New York. *E. coli,* not to be outdone by killer colicin proteins or lethal viruses, protects itself with its own siderophores and the iron they deliver. When the environment is iron-rich, Neiland hypothesizes, *E. coli* stops producing siderophores and iron pores. "B" group colicins and phages T1, T5 and $\phi 80$ thus have a much harder time gaining entrance. The cell is therefore protected, indirectly, by the presence of iron. When the environment is iron-poor, on the other hand, the cell creates more vulnerable iron receptor pores as it sends out siderophores. But these molecules, Neilands found, fight off colicins and phages to deliver both ferric and protection.

Siderophore-colicin-phage competition was the second of only three such systems found in nature. Another worker showed that certain colicins and phages compete for the vitamin B_{12} receptor. A third group has discovered competition at the *E. coli* maltose receptor, since Neilands's work.

Understanding the skirmish at the iron pore and at other nutrient receptor sites may help biochemists design more specific, effective antibiotic systems.

"There must be iron uptake mechanisms in every cell," Neilands says. "We might be able to create antibiotics, for instance, designed to attack the cell at the iron receptor. Or perhaps," he says, "we could 'engineer' bacteriophage or siderophore molecules to carry bacteriocidal drugs into the iron pore. Both of these approaches would be specific and targeted, rather than broad spectrum and random like some current antibiotics and chemotherapeutic agents." Neilands's group currently is studying and comparing the structures of the "landing gear" of the competing molecules, to learn more about binding and insertion mechanisms.

Although Neilands himself calls the competition "warfare," it sometimes worries him, he says. "One must wonder whether the Pentagon—and I use that here as a conspicuous symbol—will point to this as the 'brutality of nature' and as a rationale for human brutality. As scientists, we provide the basic information which can be used by government for destructive purposes. I don't feel," he says, "that our responsibilities end at publication. We stand at the wellspring and open the top, and we must oversee the floods we generate."

In this particular case, he says, medical applications lie sufficiently far in the future that predictions of illicit uses are probably unproductive. He will, instead, Neilands says, devote his time to "humanizing his profession" and bringing it to the public sector. □