4 PROCARYOTIC AND EUCARYOTIC CELLS

A Matched Team

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We can usually figure out how a machine works just by looking at it, but not so with a microbial cell. Because the primary activities of a microbial cell are chemical, not mechanical, knowing how it works means finding out how its molecules are arranged. Success in this endeavor often leads to new insights about the entire cell—and sometimes to important medical advances.

A major advance in understanding microbial structure was made in 1993 by Hiroshi Nikaido, a microbiologist at the University of California, Berkeley. Nikaido discovered how mycolic acids (long-chain fatty acids with 70 or more carbon atoms) are arranged to form a membrane surrounding *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis. Nikaido's discovery explains some of the unusual properties of *M. tuberculosis* and provides invaluable help to pharmaceutical researchers designing drugs to control the disease. New drugs are essential because the number of reported cases in the United States has been rising alarmingly since the mid-1980s, and many of these cases are caused by drug-resistant strains. Drugs that had been highly effective are useless in these cases. Tuberculosis is an even more serious problem in developing countries. The World Health Organization estimates 31 million people will die of tuberculosis in this decade, compared with 10 million deaths from AIDS.

Only *M. tuberculosis* and closely related bacteria have mycolic acids, which have long been assumed to form a waxy layer around the *M. tuberculosis* cell, giving it some of its unusual properties—slow growth rate, acid-fast staining, and resistance to many antibacterial drugs. A waxy layer would account for these properties by impeding passage of nutrients, dyes, and antibacterial drugs. Still, some nutrients and antibacterial compounds do enter the cell. How can they pass through the outer waxy layer of mycolic acids?

Nikaido used x-ray diffraction (a procedure that reveals molecular structure) to show that the mycolic acid molecules are arranged in two layers with their hydrophobic tails directed toward the space between them. The mycolic acids form a highly ordered membrane, not a disorganized waxy layer. The membrane completely surrounds the cell, but embedded proteins form water-filled pores through which nutrients and certain drugs pass slowly.

Nikaido's discovery not only helps the search for new drugs to fight tuberculosis, but it also illustrates an important principle—cellular structure and function are always related. Like a matched team of horses, one depends on the other.

Mycobacteria are protected from drugs by an outer barrier (right) that resembles the less effective outer membrane of Gram-negative bacteria (center), which Gram-positive bacteria lack.