/COMMENTARY

The War on Microbes: Overcoming Resistance, Enhancing Immunity

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Biotechnology, before it was even called biotechnology, can be said to have begun with the production of penicillin, which initiated the revolution in antibiotics half a century ago. Now that many of those weapons have declined in value because so many bacteria have become invulnerable to them, how can biotechnology help?

At the moment, we have a serious resistance problem. It is symbolized by the comparatively recent detection in several parts of the world of what Hans Zaehner of the University of Tübingen in Germany calls the "horror bacteria of the next few years." These are strains of *Staphylococcus aureus* that are not only resistant to methicillin (the drug of choice for many years), but also to as many as nine other antibiotics. They have also become insensitive to vancomycin—virtually the only remaining drug that has until now continued to vanquish many *S. aureus* infections.

What, then, can biotechnology offer? Zaehner and his colleague, Hans-Peter Fiedler, made some suggestion during a meeting held recently in Bath, U.K., by the Society for General Microbiology, and I would add one more. The use of cell-free screening systems for new antibiotic producers, rather than whole target organisms, is one of Zaehner and Fiedler's ideas that is surely worthy of much more active exploration than it is currently attracting.

True, there are disadvantages in replacing classical plate-diffusion tests with individual enzymes, for example. Cell-free preparations are more costly to set up, because of the need for precautions such as the elimination of proteases. The hit-rate will also be lower than the average of one antibiotic per strain achievable when screening actinomycetes with conventional techniques. Nevertheless, there could be appreciable returns from this approach. Cell-free screens would be far more sensitive, and thus revealing, than cultures of whole organisms. Among the potential revelations could be potent antibiotics not hitherto detected because they cannot penetrate the membrane of test organisms, but which could be modified so that they do gain access to the cell.

Just last year, researchers at Roche Nippon (Tokyo) reported their successful adoption of very similar tactics with the discovery of cyclothialidin (Watanabe, J., et al., *J. of Antibiotics* 47:32-36, 1994). They used an *in vitro* gyrase test to fish this antibiotic out of some 20,000 strains, and found that it had a marked effect on the enzymes from both Gram-positive and Gram-negative bacteria—superior even to the action of quinolones. When tested on whole

organisms, however, cyclothialidin appeared to be a narrow-spectrum agent with activity limited to only a few strains of *Eubacterium*. Though not itself envisaged as a new therapeutic agent, it is a promising starting structure for the development of new gyrase inhibitors.

Other proposals from Zaehner and Fiedler range from variations in culture conditions (which have been surprisingly neglected) to the screening of the many organisms that could not be grown in the past but can now be cultured.

My own suggestion regarding a biotechnological contribution to the solution of clinical problems created by multiresistant microorganisms arises from the nature of many of those infections. While some of the difficulties are created by "classical" pathogens such as *Mycobacterium tuberculosis* and *Neisseria gonorrhoeae*, advances in several different domains of medicine mean that increasing numbers of microbial invasions are of a very different sort. They occur in patients whose immune defenses have been impaired—whether by disease or, more frequently, by medical intervention such as cancer therapy.

The pathogens responsible for these hospital-based infections, in contrast to their classical counterparts, are often of low intrinsic virulence. They include various enterococci and Gram-negative rods—not inherently dangerous bacteria but nevertheless relentless opportunists able to take advantage of heightened host vulnerability. While the relative crudity of much present-day cancer chemotherapy provides conditions in which such organisms can proliferate, approaches of greater precision would not have this disadvantage.

Current studies on the cell cycle, for example, are beginning to identify potential targets for much more discriminating cancer treatments. These would not hit the bone marrow with the ferocity of many existing therapies, and would not therefore leave the patient exposed to microbial opportunists, drug-resistant or otherwise.

The same arguments apply to organ transplant recipients given immunosuppressive drugs, and to a range of other types of patient whose intensive treatment leaves them unusually exposed to infection. Extrapolating the case further, even in ordinary, nonimmunocompromised individuals, the selective boosting of the immune response may begin to rival antibiotic therapy with its well-rehearsed deficiencies. Is enhancement of the immune system the major opportunity for the medical biotechnology of the future?

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