/THE FIRST WORD

TB Is Back, But the Pipeline Is Empty

After the discovery of streptomycin by Selman Waksman and his colleagues at New Jersey's Rutgers University in 1944, and the subsequent development of para-aminosalicylic acid, isoniazid, and rifampin, tuberculosis' long siege finally seemed broken. In *Living in the Shadow of Death*, Sheila M. Rothman's elegant social history of tuberculosis in the U.S., the author quotes a confident E.R.N. Grigg in the *American Review of Tuberculosis*, predicting in 1958 that "... [TB] is expected to cease to be a public health problem, and before the end of this century, it may become so rare in the United States as to constitute a medical curiosity."

Although Grigg's optimism still seemed justified as recently as 1985, a survey of drug-resistant TB from the U.S. Centers for Disease Control and Prevention published last month (Bloch et al. 1994. *JAMA* **271**:665) reveals how far off the mark this prediction has fallen. In 1991, 26, 283 new cases of TB were reported, an 18% increase over cases reported in 1985. Of the 4,874 cases from the first quarter of 1991 included in this survey, nearly 14% of the patients carried *Mycobacterium tuberculosis* resistant to one or more of the drugs that had previously stopped the disease. An alarming 10% showed resistance to isoniazid and/or rifampin, two of the heaviest weapons in the TB armamentarium. The survey concluded by recommending more aggressive use of 4-drug regimens and more direct observation of patients to ensure that they continue to take their medication over the protracted (6-9 months) course of a typical treatment.

While these are appropriate and admirable goals, it seems clear that new therapeutics are needed to combat drug-resistant TB strains. But where are the new anti-TB therapeutics in the biotech pipeline? At the moment, nowhere to be seen.

There are a number of reasons for this, some cogent, others less so: (1) Our limited understanding of *M. tuberculosis* and the mechanisms of drug actions against it has made developing new drugs difficult. This has also been why (2) existing diagnostics aren't sensitive enough and current therapies lack specificity. These problems arise in part out of (3) the fact that *M. tuberculosis* is notoriously difficult to work with. It's hazardous, it's clumpy (mycolic acids on the surface of the bacterium cause it to clump; to get it to grow in a single-cell suspension, you have to grow it in detergent), and *M. tuberculosis* takes a long time to culture, making this bacterium difficult to screen compounds against. All of which leads to (4) the lack of economic incentive to go through the difficult work of developing new therapies for a relatively small (30,000 U.S.; 8,000,000 worldwide) market, and back to (5) the fact that, after 1952, and before 1985, TB, in the developed world at least, was thought to be an outgoing, not an ongoing, problem.

This no-drugs-in-the-pipeline situation could change soon. On the research side, William R. Jacobs, Jr., and his colleagues at the Albert Einstein College of Medicine in New York recently announced (Banerjee et al. 1994. *Science* **263**:227) that they have cloned a *M. tuberculosis* gene, *inhA*, which is implicated in isoniazid resistance. Although isoniazid has been used since 1952, its mechanism of action is unknown; an understanding of the genetics of the drug target should make it possible to design diagnostics and therapies against isoniazid-resistant strains. It should also be possible to look for isoniazid analogs in "easier" systems like *Escherichia coli* or *Salmonella*, analogs that might be able to bypass the resistance mechanism. Jacobs and his coworkers have also developed a method for assessing *M. tuberculosis* drug susceptibilities based on infecting it with luciferase reporter phages (Jacobs et al. 1993. *Science* **260**:819). This system could reduce the time needed to determine the bacterium's drug sensitivity from weeks to days; it may also be useful as a tool for drug screening.

Is there now an economic incentive to pick up the pace of drug research? Perhaps it is one of pure self-interest. TB is one disease that actually can spread through a large population rapidly as a result of casual contact. It has reasserted itself with alacrity. And its agents will lay siege to any part of the human herd that underestimates its tenacity.

—SUSAN HASSLER