Genetic Basis Found for Resistance to TB Drug

Of all the bacterial diseases that are developing resistance to the antibiotics used to treat them, few are more worrisome than tuberculosis, which not only can be spread by casual contact but is also often fatal. That's why a paper in last week's *Nature* sent a wave of excitement through the TB research community. In it, a team from London's Hammersmith Hospital and the Pasteur Institute in Paris describes the identification of a mutation that makes *Mycobacterium tuberculosis*, the bacterium that causes TB, resistant to isoniazid, the main drug used to treat the disease—the first time anyone had found a genetic basis for TB drug resistance. In terms of basic research, "it's a very important paper," says Joseph Bates, a bacterial geneticist from the University of Arkansas at Little Rock—and there's good reason for clinicians to sit up and take notice as well.

Although it's not yet known what proportion of drug-resistant TB cases are due to the mutation identified by the Anglo-French team—the deletion of the gene that codes for an enzyme called catalase—the discovery could be the first step in the long hike to develop new drugs to tackle isoniazid-resistant TB. The working theory is that isoniazid is toxic to *M. tuberculosis* only after it's been converted to another compound by the catalase enzyme, explains molecular biologist Douglas Young, who led the Hammersmith group. So it may be possible, he says, to design drugs to bypass this "catalase step."

The new results should also lead to improved diagnosis of drug-resistant TB. At present, it can take up to 3 months to find out whether a patient is infected with a resistant *M. tuberculosis* strain, says clinical epidemiologist Paul Nunn from the London School of Hygiene and Tropical Medicine, "by which time this patient could have infected heaven knows how many people." Stewart Cole, who heads the Pasteur arm of the Anglo-French collaboration, is already trying to develop a diagnostic test based on the polymerase chain reaction that will let clinicians find out rapidly if a sample of sputum from a TB patient contains *M. tuberculosis* with a missing or defective catalase gene.

Young says that this gene, called *kat*G, was an obvious place to start looking for mutations that confer isoniazid resistance. As early as the 1950s, researchers found that most resistant *M. tuberculosis* strains produce little or no catalase. In the current work, which started about 8 months ago, the team began by confirming that the catalase was in fact a key to the activity of the drug. The researchers first found that a highly isoniazid-resistant strain of a related bacterium, *M. smegmatis*, could be made sensitive to isoniazid by adding into its genome a stretch of *M. tuberculosis* DNA, containing *kat*G. Then they found that this gene was missing in two out of eight drug-resistant *M. tuberculosis* strains.

So if the breakthrough came so quickly after the work was under way, why have TB researchers had to wait so long to get started? The main reasons, says Young, are a dearth of funding and the reluctance of bacterial geneticists to work with an organism that grows very slowly in culture.

But now that geneticists are beginning to pay attention to *M. tuberculosis*, it shouldn't be long before other mechanisms underlying isoniazid resistance are uncovered. Indeed, molecular geneticist Bill Jacobs, from New York's Albert Einstein College of Medicine, has already mapped a second gene that also seems to be involved in resistance, and he's now working to discover this gene's function. Still, knowing how the TB bacterium resists isoniazid will be only one step toward defeating drug-resistant TB, warns Jacobs' colleague at Albert Einstein, Barry Bloom. "We have patients in New York who are resistant to eight drugs."

–Peter Aldhous

often, says Neu, a doctor will prescribe a broad spectrum antibiotic, which works against many different kinds of bacteria, when a more specific one, which acts only against staphylococcus or pneumococcus or whatever the particular problem is, will do. As he puts it: "You don't need a Cadillac when you can get away with a Volkswagen." The problem is that bacteria, even of different species, can exchange genetic material, including the genes for antibiotic resistance. So if one bacterial species becomes resistant to a broad-spectrum antibiotic, it can transfer that resistance to other bacteria as well.

Patients also have to wise up. They should always finish a treatment of antibiotics to be sure they wipe out all the infecting bacteria. The evolution of the drug-resistant TB strain has been accelerated by TB patients who failed to complete their 6- to 12-month regimen of antibiotics, says Barry Bloom of the Albert Einstein College of Medicine. And, on the other end of the spectrum, patients need to stop sharing their old antibiotics with friends and family, and pressuring their doctors to prescribe antibiotics for viral infections that are invulnerable to antibiotics, says Cohen. That's because the more exposure different bacteria get to different antimicrobials, the more likely they will evolve a new defense against it. And a 1989 report from an Institute of Medicine and the National Academy of Sciences panel calls for similar discretion in giving antibiotics to livestock.

The early identification of reservoirs of drug-resistant strains of microbes will also be critical for trying to contain the spread of the organisms. That will take global surveillance programs, some of which are already being put in place, such as the WHONET program from the Microbiology and Immunology Support Services of the World Health Organization.

Surveillance network. WHONET's goal, says its coordinator, Thomas O'Brien of Harvard Medical School, is to link a minimum of several hundred microbiology labs around the world so that information about drug-resistant strains of bacteria and viruses identified in any particular lab could be shared rapidly. "If you could see the emergence of resistance genes in bacteria early, you might be able to head off the spread early," says O'Brien, who is head of microbiology at Brigham and Women's Hospital. O'Brien is persuading doctors to join the network by providing free record-keeping software, written by his postdoc John Stelling, for keeping track of infectious diseases and drug susceptibility. Once the new recruits are dependent on the software, they mail, FAX, or hand-carry the data to O'Brien and Stelling, who then incorporate the information into their database. Although this 4-year-old computer network is operating on a shoestring budget of $3,500 a year and volunteer labor, it already has linked two dozen labs in South and Central America and a dozen in Asia, including China, says O'Brien.

Hospitals within the United States also need to improve the communication between labs, says Cohen. The CDC's current program tracks diseases—not specifically drug resistance. And state and local governments also need to restore some of the public health programs, cut during tough budget times, that used to follow up patients with TB and other drug-resistant organisms. Laments Cohen: "We're seeing a breakdown in some of our societal accomplishments. We're not preventing and controlling disease as well," he says.

In the end, a successful strategy will require a combination of all these approaches. "There's no magic bullet," sighs Jacoby. "Bugs are always figuring out ways to get around the antibiotics we throw at them. They adapt, and come roaring back."

–Ann Gibbons