Penetrating the secrets of tuberculosis

When magic ruled human belief, a cure for tuberculosis might have been regarded as a miracle. Today's scientific faithful view two drugs, isoniazid and pyrazinamide (PZA), with almost equal wonder.

This duo has helped demote the scourge 17th-century writer John Bunyan called "the captain of all these men of death" to a curable illness. Yet today, half a century after these drugs were introduced, no one can fully describe how they work.

Driven by the emergence of resistant strains of TB, however, scientists have begun to entice the disease and its chemical assailants into yielding some of their elusive secrets. Two new reports offer insights into how the drugs work and what molecular mechanisms enable the TB bacterium, *Mycobacterium tuberculosis,* to resist them.

An estimated one-third of the world's population is infected with latent TB. Each year, 8 million people develop active cases; nearly 3 million of them die. The Centers for Disease Control and Prevention in Atlanta has counted 6,534 cases in the United States so far this year, many of them resistant to antibiotics.

Resistance is fostered by the length of treatment—typically 6 months. Many patients begin to feel better much sooner than that and stop taking their medicine. The bacterium takes advantage of such gaps in therapy to develop resistance to the drugs.

Although the authors of the reports worked separately, their research meshes well because isoniazid and PZA, while very different, have a common feature. Both drugs are harmless to the TB bacterium until they interact with its enzymes.

Clifton E. Barry III, of the National Institute of Allergy and Infectious Diseases' Rocky Mountain Laboratories in Hamilton, Mont., calls this the "Trojan Horse paradigm" for eradicating the bacterium: "You feed it something that's nontoxic, and it becomes very toxic."

The TB bacterium produces an enzyme called catalase, which activates isoniazid. When isoniazid is active, it interferes with the molecular mechanism that synthesizes mycolic acid, a fatty acid that is part of the bacterium's cell wall. This weakens the wall, leaving the cell vulnerable to corrosive, oxygen-containing molecules such as hydrogen peroxide.

Scientists knew that a TB bacterium under threat from isoniazid switches off the *KatG* gene, which codes for catalase. Catalase, however, is central to the bacterium's survival because it breaks down the highly reactive oxygen-based molecules. If the bacterium doesn't make catalase, these molecules would most likely penetrate the bacterium and destroy it. Therefore, scientists couldn't understand how the isoniazid-resistant bacterium survives without catalase.

Now, Barry and his colleagues report in the June 14 SCIENCE that TB has the makings of a back-up enzyme tucked in the inner workings of the cell. When the bacterium loses *KatG,* it compensates by turning on another gene, *ahpC,* which churns out alkyl hydroperoxidase, an enzyme that takes over where catalase leaves off.

The research also demonstrates a key characteristic of isoniazid. Rather than targeting a single enzyme, as many other antibiotics do, it interacts with two separate aspects of the TB bacterium's life cycle—the protective enzymes and the mechanism that builds the cell wall.

This makes it a provocative model for the development of new antibiotics. "We've thought of isoniazid as being somewhat old-fashioned. In fact, it is one of the most sophisticated drugs in use today," Barry says. "We think it's a prototype for a new type of drug that attacks the regulatory mechanism in bacteria."

In the June 6 NATURE MEDICINE, Ying Zhang and Angelo Scorpio of Johns Hopkins University School of Hygiene and Public Health in Baltimore report that they have identified a TB gene, *pncA,* that codes for an enzyme that converts the TB-fighting PZA into an acid lethal to the bacterium. They have also found mutations in the *pncA* gene that enable the bacterium to resist PZA.

The work promises to enable researchers to develop the first rapid test for PZA resistance. Doctors could use such a test to guide their approach to therapy, Zhang says. The test may also lead to new drugs. Although PZA is especially useful because it kills dormant organisms that isoniazid leaves unscathed, better drugs are sorely needed.

"Why do we have to treat TB for 6 months? Because the drugs currently available are not quite effective. That's because most of them attack growing forms of the cell population and not dormant forms," Zhang asserts. "Identifying factors that can attack dormant forms holds the key to more effective TB control." — *S. Sternberg*

A plan for the struggling Sierra Nevada

In a recently completed 3-year, $6.5 million study, scientists have examined the health of almost every nook and cranny of California's Sierra Nevada and declared the 400-mile-long mountain ecosystem in need of physical therapy.

Last week, the authors presented their four-volume report to Congress, which had requested the analysis. Don C. Erman of the University of California, Davis led the more than 100 scientists who worked on the study, which was organized and funded by the U.S. Forest Service.

The report outlines many problems facing the Sierra Nevada and describes an array of possible solutions, including setting up larger forest reserves and slowing development. As for protecting the range, however, it has lobbed the ball into the public's court.

"We have identified problem areas and offered some alternatives for addressing them. . . . Left unresolved is the question of whether our society has the will and the capability to correct such problems," the scientists assert.

They note that boosting investment in restoring the Sierra Nevada ecosystem—with activities such as controlling erosion, reclaiming mined areas, and thinning out stands of trees—would provide residents with jobs.

Though not calling for a ban on the controversial logging of old-growth forests, the scientists do recommend setting up larger areas of protected forests. Loggers have already cut down much of the area's most accessible pine forests, they note.

Roughly half of California's 7,000 plant species, 200 of them rare, live in the Sierra Nevada. Of the Sierra's fauna, 17 percent, or 69 species, are at risk of extinction, primarily because of habitat loss. Cattle grazing is the primary threat to native land bird populations.

The waterways "are the most altered and impaired habitats of the Sierra," the authors state. Dams have changed the flow of many streams, which are now often clogged with sediment. Non-native fish, such as trout, are thriving, while some natives, such as Chinook salmon, "are now nearly extinct from Sierran rivers." Plans to prevent further degradation must protect the healthiest waterways, restore highly degraded ones, and include all watersheds.

In the northern Sierra Nevada yearround, and during the winter in most remote areas, "air quality is some of the cleanest in the nation and even in the world," the authors assert. However, for much of the western slope, located near urban centers, visibility is "severely degraded." Strictly enforcing California's air pollution laws and staging additional controlled fires to decrease wildfires would help plants now suffering from air pollution, they say.

The report seems to be "sensitive to key issues of ecosystem management," as it discusses how all parts of a system work together, says Steward T. A. Pickett of the Institute of Ecosystem Studies in Millbrook, N.Y. He reviewed the document's eight-page summary, released along with the full report to the public this week. — *T. Adler*