and digest pathogens — are the first to encounter *M. tb* and that the bacteria live and multiply in these macrophages. But some bacteria, such as *M. tb*, have devised ways to evade that process. "We looked at that and said, 'Well, they can't both be completely right,'" says Dr. Ernst.

Dr. Ernst and graduate student Andrea Wolf created *M. tb* tagged with a fluorescent green label to allow them to track the bacteria's progress through the body. They found that, in fact, the bacteria infect different kinds of cells and that the predominant type of cell infected changes over time. At the earliest point there is a three-way tie in the cell types infected with *M. tb*: macrophages, dendritic cells, and neutrophils (the first immune cells to arrive at a site of infection). By the third week, dendritic cells, not macrophages, are the cell type predominantly infected with *M. tb*, they reported. "That certainly calls into question the TB dogma that macrophages are the only cells that harbor *M. tb*," says Dr. Ernst. "It says TB immunity is in line with the rest of contemporary cellular immunology."

The researchers also found the bacteria in lung-draining lymph nodes, but up to 80 percent of the bacteria were once again in dendritic cells. During the first few weeks of infection, Dr. Ernst explains, a large number of infected dendritic cells carry the bacteria from the lung to the lymph nodes. It's only after the bacteria appear in these lymph nodes that T cells are activated. The T cells then have to be transported back to the lung, the main site of infection. *M. tb* takes advantage of this lost time, multiplying to overwhelming numbers. "I think that's one of the reasons TB wins," says Dr. Ernst. "It rigs the system so that by the time the T cells are recruited into the lung, there are a million bacteria."

Getting the bacteria to the lymph nodes, which has to happen before the immune response kicks into gear, appears to be the time-dependent step that slows down the whole process. Dr. Ernst says the bacteria may have evolved to survive in a part of the lung from which they can't easily be moved to the lymph nodes. Some people's bodies may be able to get around this better than others, which potentially explains why not everyone exposed to TB develops a full-blown infection. Unfortunately, even the infected cells in the lymph nodes are rather inept at inducing an adequate immune response.

Dr. Ernst's findings have sobering implications for vaccine development. If the immune system can't effectively fight the infection, vaccines designed to activate immune cells may prove powerless — at least without additional methods to foil *M. tb*'s evasive tactics. ●

05
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DOCTOR:
WILLIAM ROM

Fighting Drug-Resistant TB in New York City

BY: APOORVA MANDAVILLI

FOR A FEW WEEKS LAST SUMMER, Americans were riveted by news that Andrew Speaker, then a 31-year-old Atlanta native, may have been flying on commercial airplanes, exposing hundreds of people to a virtually untreatable type of tuberculosis (TB). They could be forgiven for having thought of TB as strictly a third-world disease. In 2006, 13,767 people in the U.S. had TB — the lowest prevalence in the country recorded since 1953 — while elsewhere 1.5 million people died of the disease.

Speaker was diagnosed in early May 2007, but against medical advice he flew to Greece for his wedding later that month. Tracked down in Rome on his honeymoon, he was told he had extensively drug-resistant tuberculosis (XDR-TB) and was asked to stay put.

Instead, he and his wife, Sarah, flew to Prague and Montreal and then drove to New York City. On May 24, officials from the Centers for Disease Control and Prevention directed Speaker to report to Bellevue Hospital, where he was served with a federal warrant that isolated him for medical evaluation, the first such federal order issued in 44 years.

Bellevue is no stranger to TB. The hospital's Chest Service, established in 1903 to treat the disease, has contributed a great deal of knowledge about its pathophysiology, clinical behavior, and treatment. In the late 1980s and early 1990s, Bellevue endured a long bout with this familiar foe, grappling with nearly 4,000 cases in New York City, many of them homeless people addicted to drugs and infected with HIV.

"I came here and I found everything was all TB and AIDS," recalls William Rom, M.D., M.P.H., director of the Chest Service. He came to NYU in 1989 after a long stint at the Rocky Mountain Center for Occupational and Environmental Health, where his primary experience had been with coal miners and asbestos workers. Dr. Rom, the Sol and Judith Bergstein Professor of Medicine and professor of environmental medicine, quickly discovered that TB treatment and care had barely changed since the 1960s, and that the available drugs were powerless against some new strains of *M.Tb*.

Multi-drug resistant (MDR) TB develops when patients don't complete the prescribed six-month course of isoniazid and rifampicin. About one in 20 new cases of TB worldwide is resistant to first-line drugs,

Dr. William Rom stands at the entrance of the Chest Service on Bellevue's 7th floor. A Bellevue security officer stands guard in the foreground.

accounting for nearly 500,000 of the 9 million new TB cases reported each year, according to the World Health Organization.

Treating these strains is even more grueling and expensive: at least four drugs taken daily for up to two years. Not surprisingly, many patients miss doses or abandon treatment entirely, putting themselves and others at risk of developing the deadlier XDR-TB. It can take weeks to identify the few drugs to which a particular strain is still sensitive. "These have to be drugs the patient has never taken before," explains Dr. Rom, "so you can be sure that they're not resistant."

Bellevue was one of only two hospitals in New York City with facilities to isolate those who failed to take their medicines regularly. Between 1993 and 1998, the city's courts allowed Bellevue and Goldwater Memorial Hospital, which closed its TB ward in 2001, to detain more than 250 patients for the duration of their treatment. Dr. Rom took the important step of modernizing Bellevue's TB facilities, outfitting the isolation rooms with HEPA air filters, negative air pressure, and UV lights to kill airborne bacteria.

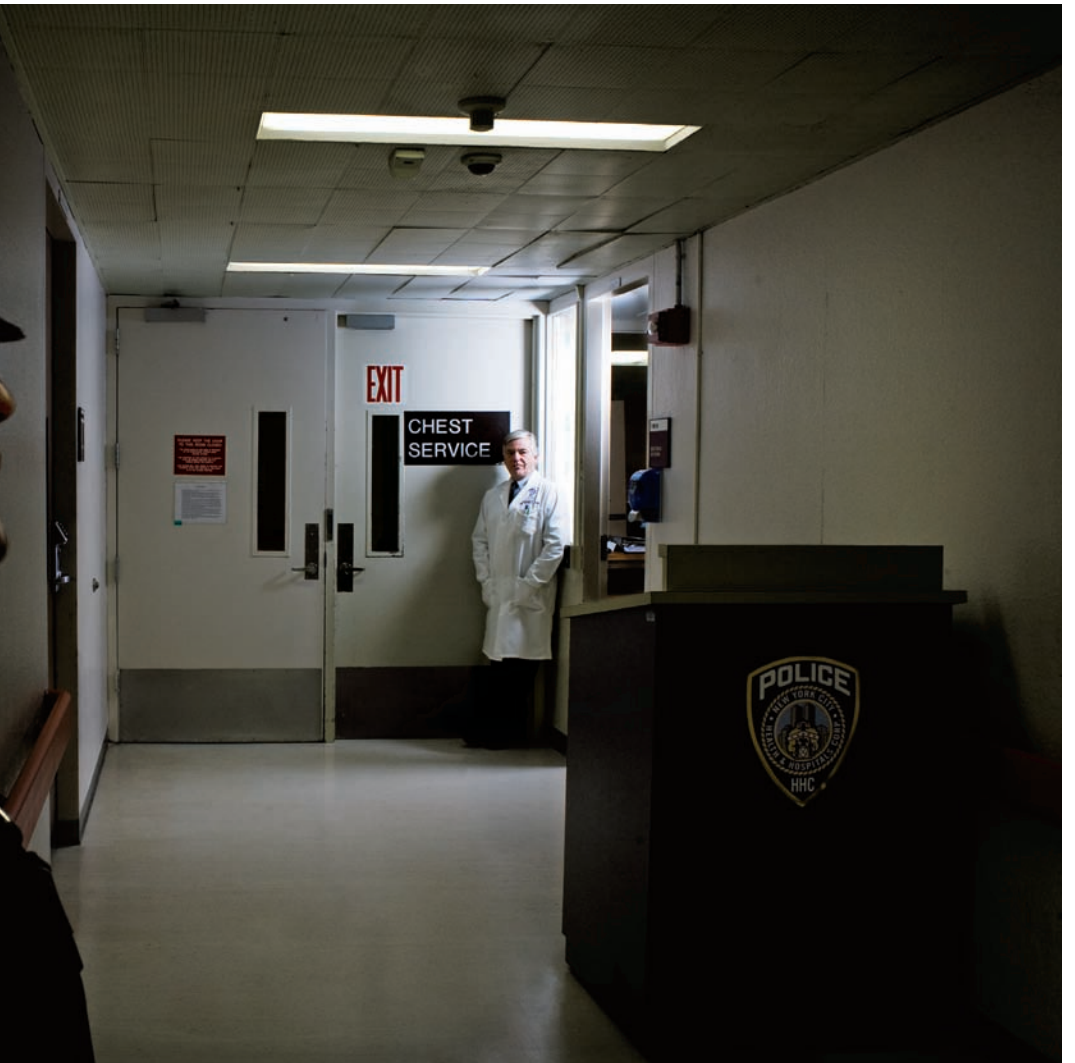
Bellevue also instituted hospital-based Directly Observed Therapy (DOT), in which patients took their TB drugs in the presence of a hospital worker. DOT is credited with turning the tide, slashing the number of cases from 3,800 in 1992 to roughly one-third that number today.

Ironically, the city's epidemic afforded doctors the opportunity to apply advanced technology to an age-old disease.

Dr. Rom and his colleagues quickly became TB experts, leading rigorous studies on the epidemiology of the disease and the treatment of drug-resistant strains. Of the 173 patients with MDR-TB admitted by Bellevue between 1983 and 1994, 72 percent were cured with second-line drugs. In those also infected with HIV, however, the cure rate was only 20 percent.

More recently, researchers have made inroads into understanding the immune system's response to *M. tb*, the effectiveness of linelazid and aerosolized interferon-gamma on XDR-TB patients, and the interaction between HIV and TB.

After only 72 hours at Bellevue, Andrew Speaker was flown to National Jewish Medical Center in Denver. His diagnosis, based on tests conducted there and at Bellevue, was later downgraded to MDR-TB. The city he left behind is home to nearly 1,300 people infected with TB, and Bellevue sees more than its fair share, including some with MDR-TB. "TB is a disease of poverty and immigrants," says Dr. Rom. "There's plenty of both in New York City." ●



06

RESEARCHER:
SUMAN LAAL

Hope Grows for Faster TB Test

TO CONFIRM THAT YOU have TB, the doctor will ask you to cough up at least a teaspoonful of phlegm, or sputum. You'll have to come back to the hospital twice more to provide samples, and technicians will painstakingly culture the slow-growing bacteria from the sputum. A few weeks after that third visit — by which point you may have exposed others — the doctor should be able to tell you whether you have TB.

This crude sputum diagnostic test is 100 years old. "The situation is fairly horrendous," says Dr. Suman Laal, Ph.D., associate professor of pathology and mircrobiology.

There are a few expensive alternatives: fluorescent microscopy, automated culture systems, and tests for the bacterial DNA. But 90 percent of the disease is concentrated in the poorest parts of the world, where these options are not feasible.

Clinically, TB symptoms can be difficult to distinguish from those of other bacterial or fungal infections, pneumonia, or certain tumors. Diagnosis with X-rays is subjective and all but useless in people who are HIV-positive, and a commonly used skin test gives false positives in anyone who has been immunized with the BCG vaccine or has been infected with the TB bug's bacterial cousins.

The ideal test for TB would be fast, cheap, and would deliver a simple Yes or No answer — much like a dipstick pregnancy test. But developing a test like that has proved challenging.

The DNA of the bacterium that causes TB twists and coils into a structure that was difficult to unravel with old-fashioned sequencing techniques. In 1998, when researchers finally decoded its enormous genome, they found that some 500 of the bacteria's 4,000 genes belonged to a previously unknown genetic family.

Applying what they've since learned about the bacterium's proteins, several teams are trying to develop simple TB tests. Dr. Laal and other researchers across the U.S. and in India have been working to develop a urine- or serum-based test that would detect one or more of the bacterium's proteins, even in someone infected with HIV. Her quest has taken Dr. Laal back to her native India at least once every year. The country has sizable epidemics of both TB and HIV.

The combination of proteins made by the bacteria change as the infection progresses, so researchers have tried to find ones that are expressed throughout the course of the disease. From a promising list of 12 proteins, they found two in particular that signal active TB infection well before symptoms become obvious and irrespective of HIV infection.

Researchers are now trying to identify a small piece of each protein that would be cheaper and easier to produce en masse. "I think we're pretty close to having a set of peptides that can replace the smear test," says Dr. Laal. ●