

DOCTOR:
JOEL ERNST

New Insights into an Old Foe: TB

BY: APOORVA
MANDAVILLI

Joel Ernst, M.D., holds up a petri dish filled with recombinant *E. coli* bacteria.

WHITE PLAGUE. KING'S EVIL. WASTING disease. Phthisis. Consumption. Tuberculosis (TB) is an old disease with many names and guises. But it wasn't until last year that scientists discovered how old this ancient scourge really is. Egyptian mummies, skeletal remains, and genetic analysis had all suggested that TB had been around for at least a few thousand years. But in a block of rock mined from a quarry in western Turkey, anthropologists discovered the fossil of a young male dating back some 500,000 years and infected, unexpectedly, with tuberculosis. They announced in December 2007 that the young man had lesions on the inside of his skull, the imprint of brain membranes inflamed with TB — proof that the disease has been ravaging humans for much longer than anyone had ever suspected.

An estimated 2 billion people — nearly one-third of the world's population — are thought to harbor *Mycobacterium tuberculosis* (*M. tb*), the bacterium that causes TB. It grows slowly, lurking in the lungs for years, and outwits the body's immune system, in part by waiting for the host's defenses to weaken. In most people, that opportunity never arises, and they show no symptoms of the disease. But once *M. tb*

takes hold, it literally consumes the body from within, eating through lung tissues and the blood vessels that run through it. Every time someone with a full-blown infection speaks, sings, coughs, or sneezes, the bacteria expelled linger in the air for hours, ready to invade the next victim

This is why TB has so often been a disease of the poor, because it is at its most deadly in overcrowded, unsanitary conditions. In 2006, TB infected 9.2 million people worldwide, claiming the lives of 1.5 million, most in the developing world. In some parts of South Africa, as many as 70 percent of those with TB are also infected with HIV, because TB is opportunistic.

Most bacteria or viruses that attack the body elicit a robust immune response within a few days. For TB, the earliest detectable response takes weeks, by which time the bacteria have multiplied to nearly 100,000 times their initial number.

"What are you doing in the meantime?" asks Dr. Joel Ernst, chief of the Division of Infectious Diseases. "Nothing — getting sick. The immune system is not doing a very good job of handling the infection."

Last year, Dr. Ernst's team refuted immunology dogma by showing that, although the lungs are the primary site of TB infection, a full immune response requires that the bacteria first be transported to lymph nodes between the lungs, and that *M. tb* manages to establish a chronic infection, in part by interfering with this process. That may seem like basic information that should have already been known about such a familiar enemy, but TB is now largely limited to developing countries.

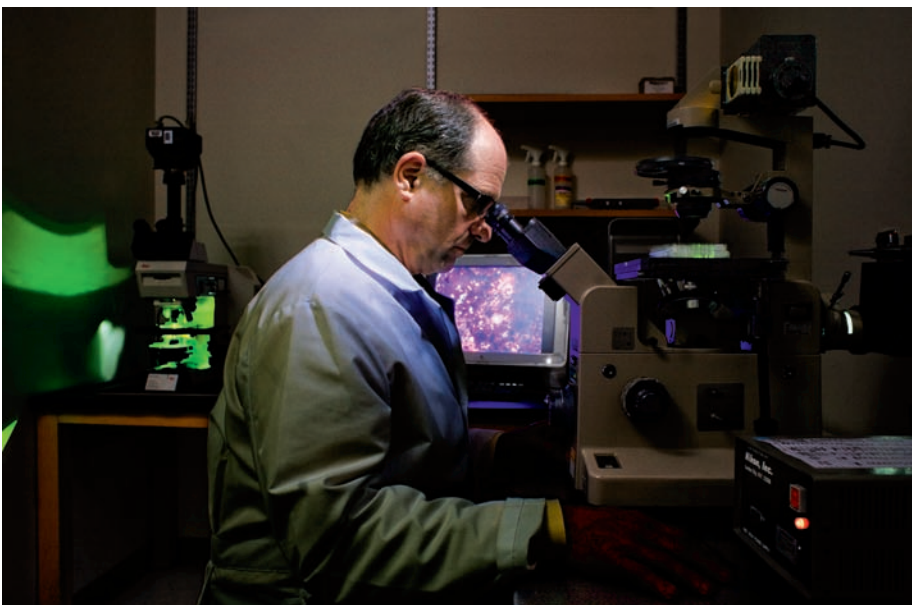
The standard treatment for TB has not changed since the 1960s: several toxic drugs taken every day for six months. The available vaccine, BCG, is only partially effective, and the most commonly used diagnostic test is 100 years old.

But in the past 15 years, research on TB has enjoyed a renaissance. Following a frightening epidemic in New York City in the 1990s, the NIH — and, in particular, scientists in New York — began paying closer attention to the disease. Several new drugs and vaccines are now in the pipeline, and researchers are working on tests that can diagnose TB more easily.

Until recently, "the disease was in poor countries and the technology was in rich countries," says Suman Laal, Ph.D., associate professor of pathology and microbiology. "Now there's this realization that either you stamp it out everywhere or you stamp it out nowhere."

Dr. Ernst, the Jeffrey Bergstein Professor of Medicine and professor of microbiology and pathology, became interested in TB in the mid-1980s. At the time, the NIH funded only a handful of TB projects. Many of the cases in New York were resistant to the available drugs, underscoring the urgency for clinical research on new treatments and basic research to understand the progression of the disease. Dr. Ernst soon won grants to study why the body's carefully constructed defenses are no match for *M. tb*.

It has long been thought that when a virus or a bacterium infects the body, the first response is from dendritic cells, gatekeepers that initiate the immune response, dispatching T cells on a search-and-destroy mission. But researchers suspected that the body marshaled another kind of initial response to TB. They had believed that in the lungs, macrophages — cells that usually engulf





NYU
Medical
Center

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.

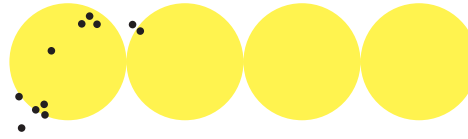
Dr. Ernst’s findings have sobering implications for vaccine development. If the immune system can’t effectively fight the infection, vaccines designed to activate immune cells may prove powerless — at least without additional methods to foil *M. tb*’s evasive tactics. ●

05

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.

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,

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



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.