

# A DEADLY MISDIAGNOSIS

*Is it possible to save the millions of people who die from TB?*

BY MICHAEL SPECTER

Every afternoon at about four, a slight woman named Runi slips out of the cramped, airless room that she shares with her husband and their sixteen children. She skirts the drainage ditch in front of the building, then walks toward the pile of hardened dung cakes that people in this slum on the edge of the northeastern Indian city of Patna use for fuel. Dressed in a bright-yellow sari shot with gold threads, Runi is followed by several of her children. Although she can't remember their ages, or her own, Runi must be about forty, because she dates her life from its first crucial memory: the smallpox epidemic that devastated Patna and much of surrounding Bihar province in 1974.

Runi survived that plague, and several others, but, about a year ago, after developing a persistent cough, she visited one of the private medical clinics that line the streets of Patna. There someone who called himself a doctor stuck a needle in her arm, drew a few drops of blood, examined them, and told her that she had tuberculosis. It is not an uncommon diagnosis. Tuberculosis has always been the signature disease of urban poverty, passed easily in poorly ventilated spaces. India has nearly two million new cases each year, and every day a thousand people die of the disease, the highest number in the world. Tuberculosis is also the leading cause of death among people between fifteen and forty-five—the most productive age group in any country and the key to India's prospects for continued economic growth.

For most patients, the choices are bleak. Public hospitals are so overcrowded that people are forced to rely on inaccurate tests dispensed at private labs and clinics. They are unregulated enterprises, and peddle blood tests that are responsible for tens of thousands of misdiagnoses every year. "This is deadly," L. S. Chauhan, the director

of the National TB Control Program, told me when we met in New Delhi. "But there are thousands of labs. Shut one down and the next day ten more appear."

Runi's test was indeed worthless. It determined the presence of antibodies, which show that a body's immune system has begun to respond to an infection. But most TB infections are latent: no more than ten per cent will ever cause illness. This means that ninety per cent of people with antibodies for TB in their blood don't have the disease. Runi's cough was clearly caused by something else.

Vaccines and antibiotics have long been seen as touchstones of medical progress. To stop tuberculosis, however, particularly in the developing world, an accurate diagnostic exam is needed even more. In India, China, and Africa, at least two billion people have latent infections. Yet every day thousands are told, mistakenly, that they are sick and need treatment. That's what happened to Runi. Soon after she received her diagnosis, Runi began a regimen of powerful (and toxic) drugs provided by the public-health service, and she stuck to the program for the required six months. Not long after finishing, however, she started to feel worse than she ever had before. "This is the tragedy of our TB-control program," Shamim Mannan said as we watched Runi's children play. Mannan, who is from Assam, a few hundred miles from Patna, serves as the Indian government's chief TB consultant in the region.

"Officially, she is cured," he said. "But how would we know? She took a test that showed she had the antibody for TB in her blood. So do I. So do five hundred million Indians." As Runi stooped to gather fuel for the stove, she began to cough, lightly at first and then with alarming force. Every cough sounded as if somebody had shattered a pane of glass.

"Now she really is sick," he continued, explaining that Runi's TB was no longer dormant, and that taking drugs when they are not necessary often makes them ineffective when they are. "This is what happens when tests mislead us. She will need the drugs again. If they don't work properly, she will be in real trouble. She has almost certainly infected some of her children. That makes everything harder, more expensive, more painful."

Tuberculosis strikes vulnerable people with special ferocity. Victims are seized by severe night sweats, wasted by fatigue, and punished by the blood-tinged cough that is the disease's defining symbol. In most cases, tuberculosis affects the lungs, but it can invade almost any organ of the body. When an infectious person coughs, sneezes, spits, or even shouts, he sends minute particles of sputum, or phlegm, into the air—exposing anyone nearby. For many years, the disease, which is caused by *Mycobacterium tuberculosis*, was referred to as "consumption," because without effective treatment patients often wasted away.

To fight the infection, the body's immune system forms a scar around the TB bacteria which serves as a kind of moat. Afterward, the bacteria lie dormant and cannot spread or infect others. But immune systems fail, and when that happens TB can move from the lungs to the bloodstream and then to the kidneys, the brain, and other organs. (That's why in patients with H.I.V., which ravages the cells that the body uses to defend itself, tuberculosis becomes particularly deadly.) The only way to cure the disease is with a combination of antibiotics. The treatment lasts six months because the drugs work only when the TB bacteria—which grow slowly—are dividing.

For centuries, tuberculosis has been the source of misguided stereotypes, including the association of consumption with creativity and brilliance. "Doctors suspect that tuberculosis develops genius," a 1940 article in *Time* pointed out, "because 1) apprehension of death inspires a burning awareness of life's beauty, significance, transience, 2) the bacillus breeds restlessness and an intoxicated hypersensitiveness." Keats,

Chekhov, the Brontë sisters, and George Orwell—who was born not far from Patna, where his father managed the regional opium trade—all died of the disease.

Nonetheless, tuberculosis has always taken its most serious toll on the industrial-labor class—not on artists. The rise of industry throughout the

villages to crowded cities, slum life and tuberculosis await them. With India's urban population expected to double in the next thirty years, to seven hundred million, its cities will remain fertile ground for an infectious epidemic. Yet—no doubt owing to the fact that rich people in the West rarely get the disease—tuberculosis receives fewer re-

treatment. Compliance is essential, because stopping treatment in the middle permits the most resilient strains of the bacteria to thrive, greatly increasing the chance that they will become resistant to basic, inexpensive drugs.

Thirty-six million people have received care under the DOTS program, eight million of whom would have died



*Hospital Road in Darbhanga is home to dozens of unregulated doctors and drug wholesalers. Photograph by Lynsey Addario.*

world has been mirrored uncannily by a rise in deaths from tuberculosis. It was the leading cause of death in Europe and the United States from the eighteenth century into the twentieth. Then prosperity—rather than medicine—drove the rate of infection down. As a society becomes richer, the conditions that allow tuberculosis to flourish start to wane. Sanitation and housing improve and so does nutrition. By the nineteen-fifties, very few people in the West were dying of the disease.

In the developing world, though, tuberculosis has surged dangerously, and this year, according to the World Health Organization, there will be ten million new cases, the largest number in history. As people join the great migrations from

sources, fewer research dollars, and less attention from the global health community than either AIDS or malaria—the two other most deadly infectious diseases. TB activists don't march on Washington or chain themselves to the gates of pharmaceutical firms to demand better treatment.

Tuberculosis can be cured, but taking several antibiotics nearly every day for six months is not easy, particularly in parts of the world without running water or refrigeration. In 1994, the W.H.O. instituted a program called DOTS, which stands for "directly observed treatment, short course." DOTS requires health workers to provide medicine—and then to watch people swallow it every day until they complete their

without it. It has been a triumph by any measure. Even DOTS, though, has not been able to keep the disease from spreading. That is largely because there is no cheap, reliable test that can determine who is sick and who is not.

Blood tests, like the one Runi had, often do more harm than good. One recent study found that Indians undergo more than 1.5 million useless TB tests of this kind every year. Other approaches are almost as unreliable. Examining a person's sputum—a diagnostic procedure that was developed more than a century ago—remains the most common way to detect the infection. It is a laborious process. Technicians smear the sputum on a slide and then place the specimen under a microscope.

The instructions are comically complex. “Spread sputum on the slide using a broomstick,” a typical recipe, posted on the wall of a clinic in Patna, begins. “Allow the slide to air dry for fifteen to thirty minutes. Fix the slide by passing it over a flame from three to five times for three to four seconds each time.” If the slide isn’t held over the flame long enough, false stains will appear—suggesting that people are sick when they are not. Hold the slide too long, though, and the stain will disappear and show nothing at all. The results are accurate little more than half the time.

“You can treat a lot of people, and India has,” said Madhukar Pai, an epidemiologist at McGill University and the co-chairman of the international group that assesses new diagnostics for the Stop TB Partnership. “But if you have tests that cause misdiagnosis on a massive scale you are going to have a serious problem. And they do.”

Medicine rarely provides magic bullets, but, for the first time, a technology has been developed that might help countries like India escape the endless cycle of mistaken diagnoses and haphazard treatment. A company

called Cepheid, based in Sunnyvale, California, now makes a device, called a GeneXpert, that allows doctors to diagnose TB in under two hours—without error or doubt. “The machine is so powerful that it could help end tuberculosis,” Mannan told me. “I don’t think that is an exaggeration.”

An editorial three months ago in the *New England Journal of Medicine* also raised the possibility that, with proper use of this device, tuberculosis—a disease that has been around since the days of the Pharaohs—could be eliminated. The cost, however, would be far too high for the Indian Ministry of Health. “Private business would have to take the lead,” Mannan said. “In the past, countries waited until they got richer and tuberculosis mostly went away. India cannot do that. The epidemic is just too big. And we are too poor.”

The GeneXpert was developed in 2002, with initial support from the Department of Defense. After the events of September 11th and the mailing of anthrax spores later that year, biological threats became a national priority. The only sure way to recognize dangerous new organisms, whether made by man or by nature, is to analyze their unique

DNA, and the GeneXpert has tested billions of pieces of mail for toxins. Its diagnostic capabilities seemed even more promising, however. In 2008, with funding from the Bill and Melinda Gates Foundation, the Foundation for Innovative New Diagnostics, and the National Institutes of Health, researchers at medical centers throughout the world began to assess the machine’s effectiveness in diagnosing tuberculosis.

Its success was striking. In a study published along with that editorial in the *Journal*, researchers reported that the GeneXpert identified more than ninety-eight per cent of active TB infections, including many that sputum smears had missed. Because the test looks for the TB bacterium itself, rather than for antibodies, latent infections don’t confuse the GeneXpert as they do blood tests. The machine costs nearly twenty-five thousand dollars and each test is about twenty dollars. Prices could plunge if similar machines were introduced and used widely.

“This is absolutely transformational technology,” Peter Small, the director of tuberculosis programs for the Gates Foundation, said. “It is a system that removes the guesswork from one of our most deadly diseases.” Unlike the sputum technique, the molecular approach is straightforward: a patient spits into a cup, and the sample is placed in a cartridge that looks much like the pods used in many espresso machines. A computer examines the sample’s DNA to see if it contains the genetic signature of TB. Results are available within hours.

The GeneXpert can even determine whether the bacteria are resistant to rifampicin, the most effective and widely used component of the four-drug cocktail commonly prescribed for TB. “People often equate sophisticated science with complexity, and this is just the opposite,” Small said. “As long as there is electricity, the tests could be carried out by unskilled workers in any village. Training them would be easy, and the potential benefits—saving billions of dollars and millions of lives—worth any effort. The question is how do we get there. I have heard people say that we should trust the government bureaucracy. But others say let’s put our faith in an unregulated collection of free agents. It’s hard to know which approach is more ludicrous.”

I put that question to Mannan, the



“Hey! Elbows off the table.”

official responsible for TB control in the Bihar region. A slight, intense man with eyes the color of wet coal, Mannan is a former Army doctor who left the service after he injured his leg jumping from an airplane. He has been frustrated by how rarely the promise of Indian medicine is realized, and by how little entrepreneurs—in one of the world's most entrepreneurial countries—are doing to help.

"We do know that private enterprise can work in India," he said. "Just look at the mobile-phone industry. And the public efforts to halt major diseases have been remarkable. But how do we get them to work together?" Nobody has an answer to that question. The interplay between public and private medicine in India is difficult to navigate, in part because the quality of private medicine varies so wildly. To demonstrate the range of medical options open to most people in Bihar, Mannan suggested that we travel to Darbhanga, about ninety miles northeast of Patna. Before we left, he said, "Everything you find in the country, the good and the bad—it is all in Darbhanga."

Even at first light, the road that leads from Patna, Bihar's capital, to Darbhanga is impossibly crowded. On the ramp of the Mahatma Gandhi Bridge, which passes over the Ganges and leads north toward Nepal, oxen jostle with motorcycles and giant trucks. On the day I made the trip, the traffic was so heavy on the bridge—at more than three and a half miles, it's one of the longest in the world—that it took an hour just to reach the lush banana plantations on the other side.

Patna and Darbhanga were once important centers of civilization. Buddha found enlightenment under a bodhi tree in Bihar, twenty-five hundred years ago, and the Fortress of Maharajas still stands in Darbhanga. Today, though, the province lags behind other regions of India in every category of economic and human development. Its eighty-five million residents earn, on average, less than half what people in the rest of the country earn; plumbing and sanitation facilities are meagre. Tens of thousands of migrants pass through Darbhanga each year as they abandon their ancestral villages and seek new lives in Delhi, Mumbai, and other major cities.

The Medical College Hospital, an imposing white fortress spread over several city blocks, is the largest in the region, but the city is also home to what may well be India's most formidable collection of unregulated pharmaceutical wholesalers, a kind of medical red-light district. Virtually any drug can be purchased, in whatever quantity one desires, without a prescription. Want a thousand polio vaccines? Narcotic painkillers, cancer medication? Scarce AIDS therapies? They are all readily available in Darbhanga. But rarely at the hospital.

The tuberculosis and AIDS clinics at the Medical College Hospital are open every day from 8 A.M. to 2 P.M. By the time Mannan and I walked into the cavernous waiting room early that morning, patients packed the benches and sprawled across the floor. Most sat silently, their eyes hollow, their heads down. The sound of harsh coughing filled the air. The line for medications snaked into the courtyard, where dozens of women, many of them cradling infants in their arms, waited patiently.

Like other public hospitals in the developing world, the Medical College Hospital struggles to provide medicine for its patients. The dispensary is rudimentary: basic tuberculosis drugs are available, but not those needed to treat resistant strains, which now account for nearly twenty per cent of India's growing caseload. For people who do not respond to the first line of TB treatments, there are two choices: find money to buy medicine somewhere else or get sicker.

Since late 2009, the hospital has had one unique asset: a piece of equipment called a P.C.R., which can multiply tiny samples of DNA and analyze them. The device is not as fast as the GeneXpert, but it can examine the genetics of virtually any organism, including tuberculosis. The hospital's machine, which was purchased with money from a government research grant, has never been used. "The hospital has had this for months," Mannan said. "But nobody knows how it works." We were standing at the door of the virology lab, where the new P.C.R. Cobas TaqMan 48, made by Roche and sold for roughly fifty thousand dollars, was resting on a shelf, still wrapped in its shipping material.

How could that be? I was staring at a machine that could alter, even save, the

lives of scores of the people who were sitting nearby in the gathering heat. Mannan said nothing, though his anger was palpable. "Ask them," he said, referring to the scientists who worked in the hospital, when I tried to get him to explain. "They will tell you."

We walked down the hall to meet Ravindra Prasad, a doctor in the department of social medicine. He was an agreeable man with a round face and an easy manner. I asked why the P.C.R. machine sat imprisoned and unused.

"The chemical kit expired," he said, smiling politely. The chemicals used in the machine have a short shelf life; but I learned later that they are not hard to replace. That couldn't have been the reason. "The methods we have for diagnosing tuberculosis all function smoothly," Prasad added, as if he were reading from a prepared statement. He was referring to sputum tests, which are often inaccurate. "We follow the standard manual." Prasad offered us tea, but said nothing more about the medical needs of his patients. "It's a nice lab," Mannan said when we left. "Beautiful, actually. But if the doctors used it properly that would interfere with their private practice."

I asked what he meant.

"It is simple," he said. "If patients are treated at the hospital, they won't need to pay for anything else."

The Darbhanga medical red-light district lies just a few blocks from the main hospital. On most days, as the public clinics prepare to take their last patients, touts appear in the waiting rooms and on the hospital grounds, eager to steer people toward a private doctor on Hospital Road. More than eighty per cent of medical services in India are in private hands, and health-care costs are among the most common reasons for bankruptcy.

The touts—equal parts salesmen, psychologists, and pimps—are good at their job. If you need TB medication or a test or an X-ray, these men will get you quickly to a clinic that charges for services people are entitled to receive at no cost in public hospitals. According to Mannan, the tout receives ten per cent of any eventual fee from a referral. Rickshaw drivers get five per cent, medical assistants ten, and the referring doctor, almost always a physician based at the Med-

ical College Hospital, thirty-five per cent. That leaves forty per cent for the clinician.

Much of the time, the referring physician from the public hospital is also the private clinician who does the work. That earns him seventy-five per cent of any fee. Public salaries are not sufficient to support most doctors, so, every afternoon, many of the hospital's physicians work in these private clinics.

Well-trained doctors are not the only people working on Hospital Road, however. Officially, a doctor needs a license to practice medicine in India. In fact, though, there are no mechanisms to verify the validity of licenses or to punish people who break the law. It is not rare for "doctors" to lack medical training completely.

We arrived as darkness began to fall; hundreds of people, having finished the workday, crowded the rutted streets. There were dozens of drug shops, with names like Raj Medical Agency, Krishna Scientific and Surgical Works, and Zar Whole Sale Drugs—often illuminated by a single bulb. The streets of the medical red-light district are filled with "specialists." Mannan and I wandered into a back alley where two men asked after our health with more solicitousness than was necessary. I asked what they were offering, and one of them let out a loud cackle.

"Let me show you," he said, and led us to a small room with several chairs, a table, and three refrigerators. The man said that his name was Pranay, and he offered a variety of blood tests, for liver function, kidney function, H.I.V., and several other standard diagnostics, all at reasonable prices. Wholesalers make their money through volume sales, not high prices. "We get twenty-five to thirty referrals a day," he told me.

The stall next door could have been an exhibit in a science museum: it contained an ancient X-ray machine, held together with duct tape and baling wire. The owner had just finished taking chest slides for a middle-aged man. He didn't offer any of the customary lead shields or other protections against possible radiation leaks—and that machine certainly leaked. "It's

safe," the man said. "They are X-rays."

He told us that he ran about fifteen to twenty chest X-rays a day; he charges a hundred rupees for each, or a little more than two dollars. His services were also available for broken bones and other routine problems. I asked how he had acquired his equipment and where he had learned to use it. He told us that he had taken the X-ray machine from a hospital in Bihar that was about to throw it away. The idea of training made him laugh. "Did you see 'Slumdog Millionaire'?" he said. "Before this, I was a chai wallah"—a man who serves tea—"just like that kid."



It was time to return to Patna; driving late at night on the roads of rural India is a risky business. Before we left, though, Mannan insisted that we make one more stop, at another clinic nearby. The place was essentially an open concrete garage; against one wall stood a small table with hot plates on which patients could heat rice. The room was full, and more than a dozen people stood on the street, waiting to get in. "This is the best TB clinic in town," a pharmacist who owned the shop next door explained.

The head of the clinic, Dr. P. M. Srivastav, works at Medical College Hospital, and we had spoken with him earlier. At night, for a hundred and thirty rupees, Srivastav will see anyone who waits in line. He doesn't test for tuberculosis at his clinic, and said that he refers people he suspects of having the disease to the hospital. He does, however, earn a fee from every patient he sees, including those he sends back to the hospital for free treatment. "Now do you understand why that machine is wrapped in plastic?" Mannan asked.

As we were about to leave, a large car pulled up at the front door. Srivastav climbed out of the back seat, looked at us with surprise, and smiled sheepishly. Before I had a chance to ask a question, he was gone, safely tucked away in his private office.

The uncertainties and dangers of diagnosis remain the greatest obstacle to successful TB treatment, in India and throughout the developing world. For that to change, investments from

international aid organizations and from private companies will be necessary. That may seem unlikely, but it has happened before, most notably with AIDS drugs. In the nineteen-eighties, when AZT became the first effective treatment for H.I.V., the annual cost for each patient was ten thousand dollars. People in the West, who were rich or lucky enough to have good insurance, could afford it. In countries that struggle to provide basic immunizations against diseases like measles, though, AIDS treatments were a fantasy. Then various groups, including the Clinton Foundation, the Gates Foundation, and the Global Fund to Fight AIDS, Tuberculosis and Malaria, joined together to push for lower prices. Generic manufacturers, led by Cipla, the Mumbai-based pharmaceutical giant, began to churn out highly effective medicine at a small fraction of what it cost in the United States. Political pressure mounted, officials of the World Health Organization joined the call for cheaper AIDS medications, and today the governments of poor countries like India can buy those drugs for an annual price of less than a hundred dollars per patient. These drugs are normally distributed in bulk, through international AIDS organizations.

A similar effort will be required to lower the cost of diagnosing tuberculosis. There will also have to be a transformation in how TB medicine is regulated. That may seem like an insurmountable barrier, but, with the proper incentives, the system could work. Again, one can look to the history with AIDS medicines for a model. Because Cipla and other Indian pharmaceutical companies are frequently inspected by international regulators—such as the U.S. Food and Drug Administration—governments are willing to buy their products. That's one reason that Indian firms have become the most important manufacturers of generic AIDS medicines in the world.

Any company that sells molecular diagnostics would need the same sort of oversight. But producing cheap, internationally acceptable versions of the GeneXpert would surely lead to great profits.

"You have to keep in mind that India has many terrible doctors," Mad-

hukar Pai told me. "But it also has some of the best private medicine available." I saw that in Darbhanga, where, in addition to the shoddy purveyors of the medical red-light district, I visited the Geeta Molecular Diagnostic Lab, a new private facility not far from the center of town. There I was greeted by a team of researchers, all in starched lab coats, including Deepak K. Prasad, a geneticist and the director of the laboratory. He led us on a tour: there were separate sections for gene detection, gene amplification, and histological analysis. Geeta Diagnostics had two P.C.R. machines and other, similarly advanced diagnostic tools. Few facilities in New York are better equipped. Patients sat on cream-colored couches reading magazines and sipping tea.

"The genetic approach to diagnosis is really where medicine is going," Prasad told us. The company, which is two years old, offers tests for heart disease, several types of cancer, thyroid disease, H.I.V., and tuberculosis, among other disorders. The TB test costs fifteen hundred rupees—a little more than thirty dollars. The lab does between fifty and seventy-five each week, and its doctors are paid well enough so that they don't need to work at second jobs.

"You can call it expensive, but you have to look at the eventual costs, not the initial price of a single test or one piece of machinery," Prasad said. That would be difficult to dispute. Thirty dollars may be a lot of money for most Indians; but treating drug-resistant strains of tuberculosis costs thousands of dollars and places a terrible burden on the country, not to mention on the people who are sick. In fact, treatment and deaths caused by TB in India cost more than three billion dollars in lost productivity each year.

The power of machines like the GeneXpert has already become evident at Mumbai's Hinduja Hospital, a private institution that has been using one for three years. Mumbai has one of the worst TB problems in India, particularly with drug-resistant cases. Yet at Hinduja the machine has made it possible for doctors to diagnose and treat patients before they are able to spread the disease. "There has always been a pretty standard approach to

using fancy medical technology," Camilla Rodrigues, who runs the microbiology department, told me when I visited. "You develop it in the West and use it there. Eventually, it trickles down to the poor countries." Rodrigues pointed out that, with tuberculosis, the pattern makes no sense. The GeneXpert was invented in the West, but India and Africa need it much more urgently. "Every time we make a correct diagnosis, we save not one life but many," she said, waving in the direction of the boxy metal-and-Plexiglas machine sitting in a corner of the lab. "And with this machine we make correct diagnoses in two hours."

Rodrigues has been working with tuberculosis for two decades. "When I started, it seemed hopeless," she said as we sat in her office, which is adjacent to a busy lab filled with graduate students, most of whom are focussing on TB.

"You would ask people why we are not doing more to stop this terrible, crippling epidemic, and the answer was usually a shrug," she continued. Rodrigues has cavernous eyes and long dark hair pulled back in a bun. She speaks frankly but somehow conveys a buoyant sense of optimism. "For so long tuberculosis has been a part of life here. In the past, if you said you have the disease people would hardly flinch. Can you imagine going to a neighbor in New York and saying you have tuberculosis? People would shriek."

Lately, though, Rodrigues has begun to sense a shift away from the habitual fatalism that has defined the Indian approach to public health. "Sometimes I go to Churchgate Station," she continued. "It is the busiest train station in the city, maybe in the country. I go at rush hour. You cannot move or breathe or think. You cannot walk or talk. It is the perfect place to spread tuberculosis.

"But it is also the perfect place to stop it," she said. "I walk around that platform and I look at people and I say to myself, Which of you are sick? We need to know. And, finally, after more than a century we can know. At this point, it is just a matter of will." ♦

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Michael Specter takes readers' questions, and narrates a slide show of photos from Bihar.