

Carlos Fioravanti / Brazil

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Cover

Mortal drama

A new strain of bacteria, resistance and medication, poverty and interaction with Aids worsen the tuberculosis picture

Carlos Fioravanti

Last month two studies were released worldwide showing the dramatic situation of one of mankind's most feared diseases – tuberculosis (or TB). One of them describes the new strain of the main species of TB-causing bacteria, the *Mycobacterium tuberculosis* bacillus, which presents a loss of genome 1.5 times greater than the biggest loss ever found in any other of the six species of TB *Mycobacterium*. Still, it has survived, strengthened its capacity to elude the body's defense cells and become responsible for one out of very three cases of TB identified in Rio de Janeiro. Infection by this strain, called RD-Rio because it was discovered there, is linked to greater weight loss, more blood in the sputum and more lung perforations. The other work, with laboratories from nine countries, shows that this strain predominates over hundreds of others in the United States, Central America and Africa. This month a third article should be published showing that this same variety causes one third of the TB also identified in the city of Belo Horizonte.

“Our hypothesis is that this strain may go undetected and spread more easily because it has lost part of the genes that cause the production of the proteins that would denounce it to the host organism, but apparently it isn't more resistant to treatment with antibiotics than the others,” says Luiz Cláudio Lazzarini de Oliveira, a professor from the Federal University of Rio de Janeiro (UFRJ), who

returned to Brazil last month after three years at Cornell University in the United States. The studies he was involved in show not only one of the mechanisms whereby the TB bacteria survives and gains strength, but also one's inability to deal with a disease that, when it does not kill, turns life into a stream of anguish and pain governed by the shadow of death, as Manuel Bandeira, a poet from Pernambuco, portrayed in the letters and poems that illustrate this report. *Mycobacterium tuberculosis* attacks the lungs of 9 million people every year worldwide, killing one person every 15 seconds.

TB, which was fought up to ten years ago with publicity campaigns and compulsory examinations to enter school or any employment, got out of control because of the epidemic of AIDS, which makes the body more sensitive to opportunistic micro-organisms of the *M. tuberculosis* varieties that resist one or more medications, and because of a lack of drugs more effective than the current ones. "We haven't had any new drug against TB in the last 45 years," laments Marcus Vinícius Nora de Souza, a researcher from the Drug Technology Institute (Far-Manguinhos) in Rio de Janeiro. Once again regarded as one of the worst threats to humankind, as it was in the late 19th century, TB is advancing in the wake of the lack of combined action among research centers, companies and public authorities. Afrânio Kritski from UFRJ coordinated an analysis of scientific publications on TB in Brazil from 1986 to 2006 and found there is a gulf between basic research and applied research (making the search for new medication difficult) and scant participation of companies, besides the mainly bureaucratic difficulty of carrying out the clinical trials that might lead to new treatment. According to Kritski, this work, published at the end of last year in a special edition on TB of *Revista de Saúde Pública* (the Public Health Journal), "signals where we are going as a nation." "We have a lot of papers and little that is applicable," he says. The Brazilian Network for Research and Fighting Tuberculosis (*Rede TB*) sprang up five years ago with the aim of bringing teams from various areas together, avoiding fragmented views, to stop a disease that spreads through the air; however results to date have been essentially academic. "To control TB we must work together."

Opportunistic infection

In one of the centers of the State Department of Health of São Paulo that deals with patients with sexually transmitted diseases, Leda Fátima Jamal struggles to increase the speed with which TB is diagnosed among those who are especially susceptible: carriers of the HIV virus that causes Aids. In another article in the journal *Revista de Saúde Pública*, Leda and Fábio Moherdau, from the National TB Program, say that the interaction between the two diseases is jeopardizing the government's TB detection and treatment targets. "When the defense system of the body of a person with Aids is very weakened," observes Leda, "TB may not manifest itself in an obvious way." Examining the sputum can easily lead to negative results and create a doubt that can only be solved with another type of test, a bacterial culture, whose results take a month. To complicate matters further, one of the most used antibiotics, rifampicine, may reduce the action of the anti-retroviral drugs of the Aids treatment.

Two innovations of team from the Infectious Diseases Center (NDI) of the Federal University of Espírito Santo (Ufes) may help in the struggle to detect TB earlier. The first is a double filtration method for sputum that raises the sensitivity of the fastest and cheapest method for detecting TB from 70% to 90%. The second is an adaptation of the low cost Ogawa culture method for use on a greater scale in the diagnosis of TB. "The five city administrations of the Vitória Metropolitan Region adopted the sputum culture for all patients suspected of having the disease as standard procedure," says Reynaldo Dietze, NDI coordinator. "The percentage of cases detected rose by 25%."

Governments, companies and international foundations spent US\$ 413 million in 2006 in the search for new TB diagnoses, medication or vaccines, but there is still nothing on the horizon. One of the difficulties, explains Dietze, who is part of an international clinical research network, is that people with TB who take part in the trials must be monitored for two years after the six-month treatment to check whether the disease will re-appear. In Brazil there are also molecules with an action against *M. tuberculosis*, such as the IQG 607 compound from a laboratory in the Catholic Pontifical University of Rio Grande do Sul (PUC-RGS) that is linked to the

Rede TB, but for many reasons its development is progressing slowly. In an article published in *Médecine Tropicale*, Pascal Millet, from the University of Bordeaux 2, considers the sluggishness of public institutions, governments and companies in developing and testing new drugs that might halt the global expansion of the world's neglected diseases as "hypocrisy, indifference or lack of coordination."

Danger lurks around the corner

New drugs would be welcome for halting the bacteria that cause common TB as well as the strains that are resistant to one or more drugs, thus requiring stronger treatment with an uncertain outcome. The 'unconquerables' have already taken over in the world, especially in China, India and the Russian Federation, which account for 60% of the 300,000 new cases of multi-resistant TB already identified. These are also advancing toward Brazil: since 2000, almost two thousand cases of TB resistant to rifampicin and isoniazid, the two drugs most often used against the disease, have appeared. "We have multi-resistant bacilli because we create them through wrong or interrupted treatment," comments Fernando Fiuza de Melo, director of the Clemente Ferreira Institute, a pioneering medical center in São Paulo that detects an average of three new cases of TB a day.

Sometimes the multi-resistant bacteria are lurking right around the corner. Joycenea Mendes, from UFRJ, headed a team that examined 63 people with TB in October and December 2002, and found eight of them with strains resistant to one or more drugs; they lived in one of the 12 poor communities of the so-called Manguinhos Complex, alongside the Oswaldo Cruz Foundation where the laboratory analyses were conducted. This is a rate of multi-resistant TB similar to that of Mozambique and one of the highest in Brazil. According to Draurio Barreira, general coordinator of the Ministry of Health's national TB control program, based on the preliminary data from the second national survey of information about resistance to TB treatment, Brazil's resistance levels are still lower than the international standards, possibly because treatment is free and the drug doses prescribed are bigger than in other countries. The final results of the analysis of almost 10,000 samples are likely to come out in August this year.

The bacillus identified by German bacteriologist Robert Koch on March 24, 1882 has developed even more dangerous varieties, the extra-multi-resistant strains. Capable of surviving any drug, have already infected almost 30,000 people in the world and are frightening the inhabitants of certain countries, such as South Africa. "The extra-multi-resistant strain hasn't arrived in Brazil yet," says Barreira. Tereza Cristina Scatena Villa, a professor from the Ribeirão Preto School of Nursing the University of São Paulo (USP), warns us: "It will get here." Several studies show that the multi-resistant varieties precede the appearance of the extra-multi-resistant strains, particularly in countries with precarious medical assistance in which the antibiotics suitable under such circumstances may not be available. The old battle between the human species and Koch's bacillus is unlikely to end soon. Barreira took over the national TB control program in October last year and promptly began the battle to establish a consensus on how to deal with this problem. At the end of this month, each working sub-group of the advisory committee that he reactivated with representatives from universities and government officers, must present their proposals for decentralizing care (almost half the new cases appear in hospitals rather than healthcare centers), and expanding access to diagnosis (the same test carried out in one day in some states may take up to two weeks in others) and to the treatment that often only begins when the person infected with Koch's bacillus is coughing up blood and has already lost a lot of weight.

Barreira remembers that the incidence rates of notified TB in Brazil fell by an average of 1.8% a year during the 1980s and continued stable in the early 1990s. They continued to drop, by an average of 2.8% a year, even when Aids appeared on the scene. "The bacillus that causes TB is not gaining, but to have 5,000 deaths a year caused by a curable disease is unacceptable," he worries. In parallel with sizeable scientific progress, the previously so-called white plague, so named because of the extreme paleness of those afflicted by it, is still spreading. Because of the shortcomings of medical care and the negligence of possible carriers of *M. tuberculosis*, who prefer to attribute their persistent cough to their smoking habits, every year the diagnosis reaches the hands of almost 100,000 Brazilians at an advanced stage, when the bacillus has possibly infected other people. Before

getting treatment, a sick person may contaminate ten people, of whom one will develop the sickness years later, generally after undergoing circumstances that lead to strong physical or emotional wear and tear or that weaken the body's defenses.

Treatment is cheap, free and if properly complied with, effective: in two or three weeks the most noticeable symptoms, i.e., continuous coughing and weight loss, disappear. The problem is that on average 12% of people, mainly the poor, abandon the treatment. Curing this disease imposes sacrifices, such as abstaining from alcohol for some six to nine months and taking, on a daily basis, different combinations of drugs that may cause nausea, asthma and loss of balance as they fight the billions of *M. tuberculosis* reproducing, circulating or latent in the body. Although more common among the poor, the bacillus has invaded other territories. "Doctors normally hide the fact that they have had TB," says Lucia Penna, a professor from the University of the State of Rio de Janeiro (Uerj). Years ago, while working in a hospital, she caught TB and felt the stigma and social isolation experienced by anyone who has the disease. However, the measles, hepatitis and pneumonia viruses are much more voracious when it comes to infecting people than the TB bacillus, recalls Fiuza de Melo. He himself has had TB twice, once in the pleura, the membrane that protects the lungs, and once in the pancreas.

An anonymous letter

"If family doctors and community agents participated more," suggests Lucia Penna, "the diagnosis would be much faster and treatment would be monitored closely, with the guarantee of a cure." Fiuza de Melo proposes hierarchized decentralization: each health center must detect and monitor new cases to be treated at units with better trained teams. For Melo, it is also important to look for and treat asymptomatic carriers. "Those who transmit the disease the most are not the sick but stronger individuals who cough more and expel drier particles of sputum with bacilli."

"It's possible to control TB provided there is political commitment at all government levels, from the minister to the municipal health secretaries," says Tereza Villa, one of the coordinators of a national survey into supervised treatment

(the sick have to take the drugs in front of a health professional). Even a poor state like Paraíba responded well to the introduction of this form of treatment: the incidence of TB fell, but later, when the administration and the working teams in some towns changed, it began rising again.

Barreira considers the moment favorable to strong action against the white plague. Together with dengue fever, malaria and Hansen's disease, TB is now a priority of the current federal administration. Since last year, Barreira has had an added US\$27 million from the Global Fund against Tuberculosis, to be used over the next five years in expanding supervised treatment, early and joint diagnosis with Aids, and the participation of society. Another gain is the possibility of using this extra money quickly. Barreira says that only a short while ago, because of the laws that govern the spending of public money, the purchase of an incubator for the diagnosis of TB in Rio took almost one year.

Perhaps it is hard to change history and habits quickly. When two doctors who are TB experts meet, they themselves say that three working proposals are put forward. "We're very good at diagnosing problems, but we get lost when we try to solve them," notes Dietze. Souza, from Fiocruz, warns that if the current inertia persists, "we run the risk of returning to the early 20th century, when there was no effective treatment and sick people were put in sanatoriums to breathe pure air and to rest." Initially the sanatoriums were distant, because they were built to make the cities healthy. Around 1908, Dr. Clemente Ferreira received an anonymous letter threatening him with death if he installed a TB sanatorium in São Paulo. Ferreira kept the letter and carried on regardless.