Drug-resistant TB may bring epidemic

Research opportunities are opening up for the long-neglected study of *mycobacterium tuberculosis*, a disease of poverty that is once again on the rise. TB is back.

Mycobacterium tuberculosis (*M. tb.*), a scourge that industrialized nations thought had been eradicated, is resurgent, a fresh reminder that mankind has yet to conquer the bacterial world. Even though TB has infected one-third of the people on this planet, and kills three million every year, it had been thought that there was an armamentarium of antibiotics large and powerful enough to kill any form of the tubercle bacillus that came along.

But within the past three or four years, public health officials have reported an increased incidence of TB mutants resistant to one or more antibiotics. The record is a mutant that is resistant to eleven drugs. In New York City, where the emerging crisis is at its worst, among hospitalized patients in November 1991, 46 per cent of TB isolates were resistant to one or more antibiotics. And therein lies the spectre of an epidemic.

Poverty, homelessness and crowding, which are endemic in New York, Los Angeles and other urban areas, are a new breeding ground for the tubercle bacillus in developed countries, just as has always been the case in the poorer countries of the world where TB is, even today, a major cause of disease and death. The spread of the human immunodeficiency virus (HIV), with its capacity to incapacitate the immune system, has simply added to the host range for TB which is spreading quickly among people with AIDS.

As Barry Bloom, a Howard Hughes Medical Institute investigator at the Albert Einstein College of Medicine in the Bronx observes, "we didn't really know before just how important the link between immune deficiency and TB is". Now we do. And AIDS activists are at the forefront of pressure for new money for treatment and research.

Last week, a committee of the US House of Representatives, chaired by Ted Weiss (Democrat, New York), held hearings to assess the damage caused so far by resurgent TB and to predict the future. It was not an optimistic occasion.

The public health challenge is formidable. Because TB was a major cause of death in Western countries early in this century, a good deal is known about the epidemiology and pathology of the disease. Physicians know, for instance, that TB can be effectively treated in patients who consistently take their medicine for the 6–18 months it can take to destroy all vestiges of *M. tb.* The problem is maintaining therapy in homeless people, drug addicts and others caught in poverty.

The crisis of drug-resistant TB arises because of increasing numbers of people who begin treatment but lapse after a few weeks, allowing the bacillus to evolve protective mutations against antibiotics. Public health authorities told the Weiss committee that the epidemic can be stopped only by a small army of nurses and aides who could go out into the community day after day to stand by while patients take their TB pills. In New York City, where the resurgence of TB appears to be most serious, there are only seven such people to monitor more than 25,000 patients.

The challenge of TB to basic science is no less daunting. In the late 1960s, when TB appeared to be under control, public health programmes were dismantled and TB faded from view. Understandably, it never reached the top of the research agenda in molecular biology during the 1970s and 1980s when diseases such as cancer and then AIDS received the bulk of research funding and attention.

So it is regrettable but no surprise that, from a molecular point of view, the story of *M. tb.* is one of unanswered questions. Furthermore, the pool of researchers in the field is small, as is federal funding. Even in the light of the lurking epidemic, the TB budget at the US National Institutes of Health (NIH) is only $5.2 million.

The tubercle bacillus has an unusual waxy coat made of up what one investigator describes as "a whole mess of lipids" whose structure and function have yet to be elucidated. Unlike many organisms that multiply rapidly (*Escherichia coli*, for instance), the tubercle bacillus replicates only once every 24 hours. Whereas an *E. coli* colony will form on a plate in about eight hours, *M. tb.* takes about a month to form a colony. Why? It is possible that its slow growth is related to the bacillus's two ribosomal RNA genes, but no one knows that for certain and, in any case, no mechanism of gene regulation is understood.

People have guessed at the mechanisms by which antibiotics effectively kill nonresistant TB strains. Isoniazid, a mainline anti-TB drug, is thought to block synthesis of mycolic acid in the cell wall. Interference with RNA polymerase is offered as the mechanism by which Rifampin kills the bacillus, but this explanation has not been fully elaborated at a molecular level.

The need for fundamental research on the tubercle bacillus is impeded not only by limited money but also by genuine risk. Unlike the AIDS virus which, lethal though it is, is difficult to contract, people working with TB are all too aware that the bacillus is transmitted by air. At least four physicians in New York are dying of multiple drug-resistant TB. The upshot is that P-3 containment facilities will be absolutely essential. Bloom has a new one, thanks to the Hughes Medical Institute, which built it at a cost of approximately $180,000. And the US Centers for Disease Control (CDC) are equipped to handle the bacillus, as are a few other laboratories, more are needed.

Testifying before the House committee, CDC director William L. Roper reported progress in the rapid diagnosis of TB, which currently takes 2–8 weeks, but new tests are still only prototypes. DNA amplification techniques that can detect the bacillus in sputum within 48 hours are being tested, and diagnosis with high-performance liquid chromatography within just four hours has been demonstrated in CDC's research laboratories. Studies to identify linkages between TB strains using restriction fragment length polymorphism (RFLP) techniques are also taking place (more than 500 strains from 29 TB clusters have been identified during the past nine months). And CDC, in collaboration with pharmaceutical companies, are screening for new anti-TB drugs.

The real opportunity in this public health crisis is in basic science, where there is plenty of room for young scientists with training in molecular genetics and related fields and where, perhaps, there may be more money. The Human Genome Project, which initially excluded pathogenic organisms, is now funding analysis of *M. tb.*, and its mycobacterial relative, *M. leprae*. The goal is to sequence the entire genome within three to five years, enabling researchers then to identify all the proteins, enzymes, antigens and drug targets in these lethal organisms. But it is likely to be a long haul.

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