

Old wine in new bottle

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Tuberculosis is still the most important infectious disease in third world countries in terms of numbers of death and economic losses. In India about eight million people suffer from active pulmonary tuberculosis, of which 25% are infectious cases. Nearly two million fresh cases are reported every year, thus making India the country with the largest number of tuberculosis patients.

With the advent of potent antitubercular drugs like streptomycin, isoniazid and rifampicin, the disease was eradicated in the western countries and Japan by the end of the first half of this century, and hence research on tuberculosis and the organism which causes the disease, *Mycobacterium tuberculosis* was no longer fashionable there. It is only recently with the advent of AIDS in these countries and the lowered resistance of AIDS patients that tuberculosis has staged a comeback there and a number of schools have started work on *M. tuberculosis*.

The problem of tuberculosis in India is complicated by the fact that a high incidence of the disease is resistant to currently available drugs. This problem has now appeared in the western countries and research is under way there to tackle it. At the Indian Institute of Science, Bangalore, however, research has been going on since 1957 to study the biochemical and genetic basis of drug resistance in tuberculosis.

Among the currently available anti-tubercular drugs, one of the most potent is isoniazid or INH. INH has the peculiar property of only inhibiting the growth of mycobacteria, but not of

other bacteria, which are, however, inhibited by the rest of the known anti-tubercular drugs. The mechanism of action of isoniazid has, therefore, been of considerable interest to mycobacteriologists.

In 1975 Gayatri Devi *et al.*¹ showed the role of the enzyme peroxidase in *M. tuberculosis* in the action of isoniazid. They isolated from the organism a purified protein with three activities—peroxidase, catalase and Y-enzyme. In one-step isoniazid-resistant mutants of the organism, all the three activities, disappeared. They, therefore, postulated that 'a single mutation from isoniazid sensitivity to isoniazid resistance in *M. tuberculosis* leads to the loss of catalase, peroxidase and Y-enzyme activities'. Ramakrishnan suggested² that in isoniazid-sensitive strains the drug is converted by this protein (with all the three activities) in the presence of nicotinamide adenine di-nucleotide to a toxic compound which inhibits the growth of *M. tuberculosis*, and gave a tentative structure of this compound.

Gopinathan³ used fast-growing saprophytic species of mycobacteria, *M. smegmatis* and presented genetic evidence to support the conclusion of Gayatri Devi *et al.* arrived at by biochemical studies. By using a transducing mycobacteriophage I3 (ref. 4), he showed that development of INH resistance by transduction led to a simultaneous loss of catalase, peroxidase and Y-enzyme activities. Conversely, the transduction of drug sensitivity to a resistant cell resulted in a concomitant gain of all the three activities.

Zhang *et al.*⁵ have now cloned the gene encoding the catalase-peroxidase activities from *M. tuberculosis* and partially sequenced it. They then transformed an INH-resistant strain of *M. smegmatis* with this gene (kat-G) and found that the strain had become INH-sensitive. In addition, *E. coli*, which is naturally resistant to INH, could be made INH-sensitive by transformation with katG from *M. tuberculosis*. Deletion of katG from the chromosome of two out of three INH-resistant strains of *M. tuberculosis* from patients confirmed that katG and the catalase-peroxidase enzyme codes are responsible for the INH sensitivity of *M. tuberculosis*.

The rediscovery of catalase-peroxidase enzyme as the target of INH action has been considered sufficiently significant to merit reporting in the popular press like *Time*⁶ and *New York Times*.

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3. Gopinathan, K. P., *Curr. Sci.*, 1981, 50, 216.
4. Sundar Raj, C. V. and Ramakrishnan, T., *Nature*, 1970, 228, 280.
5. Zhang, Y., Heym, B., Allen, B., Young, D. and Cole, S., *Nature*, 1992, 358, 591.
6. *Time*, No. 34, August 24, 1992, p. 13.

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