

EDITORIAL

“GLOBAL EMERGENCY”

Mycobacterium tuberculosis described by Robert Koch in 1882 is the leading infectious killer of adults (1). The World Health Organisation (WHO) has estimated that there are nearly 1.7 billion individuals infected with *Mycobacterium tuberculosis* throughout the world, approximately 20 million of these are active cases and three million die each year. Eight million new cases occur each year and three million of these are infectious (2). The WHO has predicted that, if worldwide tuberculosis (TB) control programme is not improved, 90 million new cases and 30 million deaths can be expected in the decade 1990-1999 (3,4). Of the 950 million inhabitants in India, 300 million are infected with *M. tuberculosis*, 12 million have active tuberculosis, three million are infectious and half a million die each year (5). Two decades ago, the goal of industrialized countries with low prevalence of tuberculosis was the eradication or the elimination of tuberculosis. Elimination is possible, if the rate of infection is less than 1% in the general population or there is only one smear-positive case per million inhabitants. However, in many industrialized countries, the downward trend in tuberculosis rates has been either stabilized or even slightly reversed. Several factors including the closing of TB clinics, economic crisis, demographic reasons, HIV/AIDS epidemic and population migration contributed to this phenomenon. Since Robert Koch's discovery of TB bacilli in 1882, at least 200 million people especially those in the most economically productive years of life had died due to tuberculosis (6). Realizing the gravity of the problem, the WHO in 1993 declared tuberculosis as a global emergency. This has led to worldwide resurgence in research in tuberculosis. Indian scientists are also actively pursuing research in tuberculosis and this is reflected by the three articles on tuberculosis appearing in this issue of the journal (7-9).

The discovery of streptomycin purified from *Streptomyces grieseus* in 1943 by Selman A. Waksman laid the foundation of modern chemotherapy of tuberculosis. Subsequently, other anti-TB drugs such as p-amino-salicylic acid (1949), isoniazid (1952), pyrazinamide (1954) cycloserine (1955), ethambutol (1962) and rifampicin (1963) were discovered. The problem of resistant mutants due to monotherapy was overcome by the use of two or three anti-TB drugs. Indian scientists in collaboration with western scientists especially from British Medical Research Council have made significant contributions in tuberculosis. These

include the demonstration that home treatment is as good as sanatorium treatment (10), development of supervised intermittent regimens (11), the importance of bacteriology in the diagnosis of TB (12) the BCG trial in south India (13) and the formulation of nationally applicable, socially acceptable and epidemiologically effective National Tuberculosis Programme (14,15). This has been reflected in the statement: “The world owes a debt of gratitude to India for its research in the field of TB” (16).

HIV/AIDS epidemic has a devastating effect on tuberculosis. In most immuno-competent individuals, infection with *M. tuberculosis* will not lead to progressive disease, although living bacteria are not eliminated. HIV specifically infects and destroys CD₄+ T cells (17). HIV+ve individuals become susceptible both to reactivation of latent infection with *M. tuberculosis* and to rapid progression to disease following a new infection. In immunocompetent individuals infected with *M. tuberculosis*, the life time risk of developing active tuberculosis is 10%. Persons, who have prior infection with *M. tuberculosis* and acquire HIV infection later, have a risk of 10% per year of developing active tuberculosis. However, if a person with AIDS is exposed and infected with tuberculosis, he/she has a 40 % chance of developing active tuberculosis within a few months (18). Adult patients with TB and HIV infection in the initial stages present with classical post-primary disease affecting upper parts of the lungs and with cavities and necrosis. As the immuno-deficiency progresses, atypical features such as involvement of middle and lower lobes of the lungs, noncavitary disease and dissemination of the disease are encountered(19). The change from cavitary pulmonary disease to noncavitary disease is associated with a lower bacillary load. Therefore, it will be difficult to establish the diagnosis in such situation because sputum smear examination is often negative and the clinical presentations resemble the childhood tuberculosis (20). HIV+ve patients with TB respond well to treatment, but adverse drug reactions especially to thiacetazone are common (21). Even though response to treatment in HIV+ve TB patient is good, mortality is high. *M. tuberculosis* has been shown to stimulate HIV replication in macrophages through the release of cytokines (22). TB may, thus, cause acceleration of the progression of HIV disease and reduce life expectancy. Isoniazid preventive therapy has been found to be effective in preventing tuberculosis in HIV infected individuals (23). However, optimum duration and cost-

effectiveness of preventive therapy are yet to be established. Other factors, in addition to HIV/AIDS, that increase the risk of tuberculosis include silicosis (24), malignancies (25), hemophilia (26), renal failure (27), body build (28), gastrectomy (29), diabetes (30), jejuno-ileal bypass (31), certain human leucocyte antigen (HLA) types (32) certain blood groups (33), smoking (34), corticosteroid treatment (35) pregnancy or postpartum period (36) and measles (37).

Microscopic examination of sputum smears for AFB devised by Robert Koch more than a century ago continues to be the most important diagnostic test in tuberculosis (38). Even though *M. tuberculosis* culture is the gold standard for the diagnosis, it is time consuming and expensive and is not practicable for routine management of patients. Radiometric method such as BACTEC system, though provides rapid results (average, 9 days) is also expensive and cannot be applicable in our country, except in a few referral centres (39). The new diagnostic tests (40) that are being evaluated include improved AFB detection by immunomagnetic separation strategy, detection of mycobacterial components (tuberculo-stearic acid, 2-eicosanol etc.), signal amplification methods (branched DNA signal amplification, Q β signal amplification and reporter phage systems) and target amplification methods (polymerase chain reaction (PCR) amplification, RNA amplification, strand displacement amplification and ligase chain reaction amplification). A serological test that aids in the diagnosis of smear negative and extrapulmonary tuberculosis is not currently available (41). Childhood pulmonary tuberculosis is managed clinically because of the absence of a reliable diagnostic test. We had demonstrated that gastric lavage was better than bronchoalveolar lavage for bacteriologic diagnosis of childhood pulmonary tuberculosis (42).

The emergence of multidrug resistant (MDR) strains due to careless TB treatment practices, is a real threat to TB control programme (43). The diagnosis of MDR-TB in an individual is a virtual death sentence. MDR-TB is defined as resistance of *M. tuberculosis* to the antimicrobial activity of more than one of any anti-TB drugs. Currently, MDR-TB is synonymous with resistance to the two most effective anti-TB drugs, viz: isoniazid and rifampicin. Molecular basis of drug resistance in TB includes the following features: i) deletion or mutation of the Kat G gene or modification of inh A gene in isoniazid resistance, ii) mutations in rpo β gene in rifampian resistance, iii) mutations in rps1 or rrs genes in streptomycin resistance and iv) mutations in gyr A or gyr B genes in fluoroquinolone resistance (44). There is a suggestion that MDR-TB is increasing in India (45-47).

The availability of drugs with high bactericidal activity and with capacity to inhibit the development of resistance has made it possible to evolve potent short course chemotherapy regimens for treatment of tuberculosis (48). Short course chemotherapy of six months duration has been found to be more cost-effective than 12-18 months of treatment (49). When MDR-TB is suspected, it is important to use four or five agents to ensure that patients receive at least two drugs to which organisms are likely to be sensitive (43). Resurgence of tuberculosis has focussed attention on the development of new anti-TB drugs that include rifamycin derivatives, fluoroquinolones, clofazimine, combination of betalactam antibiotics and beta-lactamase inhibitors and new macrolides (50,51). The role of BCG vaccination in controlling TB is controversial with trials reporting efficacy rates between 0% and 80% (52,513). However, vaccination of newborns with BCG is recommended, as there are evidences that BCG provides reasonable levels of protection against childhood forms of TB and against leprosy (53,54).

The Worldwide resurgence in tuberculosis has prompted the WHO and many nations to evolve new strategies to control tuberculosis. A Revised National Tuberculosis Programme (RNTP) is being pilot tested in selected cities and states in India (55). The RNTP envisages introduction of short course chemotherapy and administration of anti-TB drugs under supervision by a health worker during intensive phase of treatment and this is termed as DOTS (Directly Observed Treatment, Short-course). It is expected that RNTP should achieve a cure rate of 85% of infectious detected cases and a detection rate of 70% of all infectious cases. A wellknit monitoring system will be an integral part of the revised strategy. Even though the World Bank is expected to finance the project, it has not spelt out how supervision of each patient can be achieved in a country like Ours without taking into consideration the local situations.

As patient adherence to treatment is one of the key factors for successful management of TB patients, intensive research is needed to reduce the duration of treatment to one or three months using newer drugs or immunotherapy (56,57). It had been previously shown that three months treatment with potent anti-TB drugs had achieved bacteriological conversion at the end of treatment in virtually all patients, but the relapse rate was high (58). Other important research needs in TB include improvement of the diagnosis of sputum smear negative adult and childhood pulmonary tuberculosis, impact of HIV infection on tuberculosis, role of preventive treatment in different high risk situations especially HIV/TB, involvement of private medical sector in TB control,

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reason why Only some people infected with *M. tuberculosis* develop disease and some treated successfully develop relapse, development of new vaccines, role of mycobacteria in other chronic granulomatous diseases (eg. sarcoidosis), understanding the molecular basis of resistance mechanisms to anti-TB drugs, new drug targets and development of new drugs especially from ayurvedic system of medicine (59).

Even though medical profession is trying hard to achieve control of TB, it can be a reality only if there is strong political will and support for the control programme.



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