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 CD,+ T ceils (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-

Lung India (1996), XIV, No. 3 (P 109 - 112)

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 , Qß 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 rpoß gene in rifampian resistance, iii) mutations in rpsl 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 controversialwith 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 acheived 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,

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.

Dr. VK. Vijayan,
Cardio-Pulmonary Medicine,
TRC, ICMR, Madras 600 031.

REFERENCES

1. World Health Organisation Global Tuberculosis Programme. Tuberculosis and HIV Research : Working towards solutions. Geneva 1995; 1-23.

2. Leading article : The Global tuberculosis situation and the new control strategy of the World Health Organisation. Tubercle 1991; *72:* 1-6.

3 Raviglione MC, Snider DE and Kochi A. Global epidemiology of tuberculosis : morbidity and mortality of a Worldwide epidemic. J Am Med Assoc 1992; 273: 220-6.

4. Dolin PJ, Raviglione MC and Kochi A. Global tuberculosis incidence and mortality during 1990-2000. Bull Wld Hlth Org 1994; *72:* 213-20.

5. Dhanragir H : The changing spectrum of tuberculosis. Excerpta Medica 1995 ; 2-32.

6. World Health Organisation Press Release (WHO/22) 21 March 1996 ; 1-3.

7 Purohit SD, Gupta Rand Bhatara VK. Pulmonary tuberculosis and HIV infection in Ajmer. Lung India 1996, *14* : 113-20.

8. Mahbubani V. Trikannad V and Sainani GS. Estimation of T4/T8 ratio in patients with sarcoidosis, diffuse interstitial pulmonary fibrosis and pulmonary tuberculosrs. Lung India 1996, *14* : 121-4

9. Vidyasagar B, Venkatesh V and Ajith Kumar. Lower lung field tuberculosis. Lung India 1996 ; *71:* 125-7

10. Tuberculosis chemotherapy centre : A concurrent comparison of Home and Sanatorium treatment of pulmonary tuberculosis in South India. Bull Wld Hlth Org 1959; *21* : 51-144.

11. Tuberculosis chemotherapy centre : A concurrent comparison of intermittent (Twice-weekly) isoniazid plus streptomycin and daily isoniazid plus PAS in the domiciliary treatment of pulmonary tuberculosis. Bull Wld Hlth Org 1964; *31* : 247-71.

12 Mitchison DA Examination of sputum by smear and culture in case finding. Bulletin Int Union Against Tub 1968 ; *41:* 139-51

13. Tuberculosis Prevention Trial, Madras. Trial of BCG vaccines in south India for tuberculosis preventron. Indian J Med Res 1980 ; *72* (Suppl) : 1-74.

14. Piot MA. Outline of a District Tuberculosis Programme. lndian J Tub 1961 ; *9* : 151-6.

15. Nagpaul DR. Viswanath MK and Dwarakanath G A Socioepidemiological study of out - patients attending a city tuberculosis clinic in India to judge the place of specialized centres in a tuberculosis programme. Bull Wld Hlth Org 1970 ; *43* : 17-34.

16. Grzybowski S. Drugs are not enough. Tuber Lung Dis 1993; *74* : 145-6.

17. Stern DS, Korvick JA and Vermund SH. CD4 + lymphocyte cell enumeration for prediction of clinical course of human immunodeficiency virus disease A review. J Inf Dis 1992; *165:* 352-63.

18. Gable M. Multidrug resistant tuberculosis. Karger Gazette 1996; *60* : 6-8.

19. Medun GV and Stern DS. Pulmonary manifestations of acquired immunodeficiency syndrome. Clin Inf Dis 1992; *14* 98-113.

20. Elliott AM, Luo N, Tembo G, Halwiindi B, Steenbergen G, Machiels L, Pobee J, Nunn P, Hayes RJ and Mc Adam KPWJ. The impact of HIV on tuberculosis in Zambia. A cross - sectional study. Br Med J 1990 ; *301* : 412-5.

21. Nunn P, Kibuga D, Gathua S, Brindle R, lmalingat A, Wasunna K, Lucas S, Gilks C, Omwega M, Were J and Mc Adam K. Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. Lancet 1991, *337* : 627-30

22. Zhang Y, Nakata K, Weiden M and Rom WN. Mycobacterium tuberculosis enhances human immunodeficiency virus-1 replication by transcriptional activation at the long terminal repeat, J Clin Invest 1995; *95* : 2324-31

23. Pape JW, Jean SS, Ho JL, Hafner A and Johnson Jr WD. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. Lancet 1993; *342* : 268-72.

24 Snider DE Jr. The relationship between tuberculosis and silicosis (Editorial). Am Rev Respir Dis 1978; *118* : 455-60

25. Kaplan MH, Armstrong D and Rosen P. Tuberculosis complicating neoplastic diseases : a review of 201 cases. Cancer 1974 : *33* : 850 -8.

26. Bedall AC, Hill FGH and George RH. Hemophilia and tuberculosis. Lancet 1983 : i : 1226.

27. Rutsky EA and Rostand SG. Mycobacteriosis in patients with chronic renal failure. Arch Intern Med 1980 ; *140* : 57-61

28. Snider DE Jr. Tuberculosis and body build (Editorial). J Am Med Assoc 1987 ; *258* : 3299.

29. Snider DE Jr. Tuberculosis and gastrectomy (Editorial). Chest 1985; *87:* 414-5

30. Boucot KR, Dillon ES, Cooper DA and Meier P. Tuberculosis among diabetics. The Philadelphia Survey. Am Rev Tuberc 1952; *65* (Suppl) 1-50.

31. Snider DE Jr. Jejunoileal bypass for obesity : a risk factor for tuberculosis (Editorial). Chest 1982 ; *81* : 531-2.

32. Mehra NK and Bovornkitti S. HLA and tuberculosis : a reappraisal : Asian Pac J Allergy Immunol 1986 : *4* : 49-56

33. Overfield T and Klauber MR. Prevalence of tuberculosis in Eskimos having blood group B gene. Hum Biol 1980; *52* : 87-92.

34. Yu G, Hsiech C and Peng J. Risk factors associated with the prevalence of pulmonary tuberculosis among sanitary workers in Shanghai. Tubercle 1988; *69* : 105-12.

35. Ruml D and Haelig AW. Activation of tuberculosis during prednisolone therapy. Am Rev Respir Dis 1957; *76* : 140-3.

36. Snider DE Jr. Pregnancy and tuberculosis. Chest 1984; *86* (Suppl) : 10s-13s.

37. Flick JA. Does measles really predispose to tuberculosis ? (Editorial). Am Rev Respir Dis 1976; *114:* 257-65.

38. American Thoracic Society and Centre for Disease control. Diagnostic standards and classification of tuberculosis. Am Rev Respir Dis 1990 ; *142* : 725-35.

39. Middlebrook G, Reggiardo Z and Tigertt WD. Automatable radiometric detection of growth of *Mycobacterium tuberculosis* in selective media. Am Rev Respir Dis 1977; *115* : 1066-9.

40. Shinnick TM and Good RC. Diagnostic Mycobacteriology Laboratory Practices. Clin Infect Dis 1995 ; *21* : 291-9.

41. Bothamley GH. Serological diagnosis of tuberculosis. Eur Respir J 1995 ; *8* (Suppl) : 676s-688s.

42. Somu N, Swaminathan S, Paramasivan CN, Vijayasekharan D, Chandrabhooshanam A, Vijayan VK and Prabhakar R. Value of bronchoalveolar lavage and gastric lavage in the diagnosis of pulmonary tuberculosis in children. Tuberc Lung Dis 1995 ; *76* : 295-9.

43. Iseman MD. Treatment of multidrug - resistant tuberculosis N Engl J Med 1993; *329* : 784-91.

44. Cole ST and Telenti A. Drug resistance in *Mycobacterium tuberculosis.* Eur Respir J 1995 ; *8* (Suppl 20) : 701s-713s.

45. Trivedi SS and Desai SG. Primary antituberculosis drug resistance and acquired rifampicin resistance in Gujarat, India. Tubercle 1988; *69* : 37-42.

46. Jain SK, Chopra KK, and Prasad G. Initial and acquired isoniazid and rifampicin resistance in M. tuberculosis and its implication for treatment. Ind J Tub 1992 ; *39* : 321-4.

47. Paramasivan CN, Chandrasekaran V, Santha T, Sudarsanam NM and Prabhakar R. Bacteriological investigations for short course chemotherapy under the tuberculosis programme in two districts in India. Tuber Lung Dis 1993 : *74* : 23-27.

48. Fox W. Whither short-course chemotherapy ? Br J Dis Chest 1981 ; *75* : 331-57.

49. Murray C, Dejonghe E, Chum HJ, Nyangulu DS, Salomao A and Styblo K. Cost effectiveness of chemotherapy for pulmonary tuberculosis in three sub-saharan African countries. Lancet 1991 ; *338* : 1305-8

50. Grassi C and Peona V. New drugs for tuberculosis. Eur Respir J 1995 ; *8* (Suppl 20) : 714s-718s.

51. Ad Hoc committee of the Scientific Assembly on Microbiology, Tuberculosis and Pulmonary infections. Treatment of tuberculosis and tuberculosis infection in adults and children Ciin Inf Dis 1995 ; *21* : 9-27.

52. Lancet conference : the challenge of tuberculosis Statements on global control and prevention. Lancet 1995 ; *346* : 809 - 19.

53. Fine PEM and Rodrigues LC. Modern vaccines *Mycobacterial* diseases. Lancet 1990 : *335* : 1016-20

54. Tripathy SP. The case for BCG. Ann Natl Med Sci 1983 ; *19* : 11-21.

55. Mukherjee AK. tuberculosis control programme in India : Progress and Prospects. Ind J Tub 1995 ; *42* : 75-85.

56. Grange JM : Leading article : Immunotherapy of tuberculosis Tubercle 1990 ; *71* : 237-9.

57. Stanford JL, Grange JM and Pozniak A. Is Africa Lost ? Lancet 1991 ; *338* : 557-8.

58. Balasubramanyam R, Sivasubramaniam S, Vijayan VK, Ramachandran R, Jawahar MS, Paramasivan CN, Selvakumar N and Somasundaram PR. Five year results of a 3 month and two 5 - month regimens for the treatment of smear - positive pulmonary tuberculosis in south India. Tubercle 1990 ; *71* : 253-8,

59. Sharma VK. Tuberculostatic activity of henna (Lawsonia inermis Linn.) Tubercle 1990 ; *71* : 293-5.