CHAPTER - 1
INTRODUCTION
1. INTRODUCTION

India is the endemic home of several infectious diseases amongst which tuberculosis occupies prominent position. Poverty, malnutrition, insanitary environmental conditions, lack of potable drinking water supply are the gifts of decadal persistence of an insensitive administration. According to WHO report, tuberculosis remains a widespread disease in developing countries, and even in a number of technically advanced countries, it often causes more deaths than all other notifiable disease combined together (Arata Kochi, 2001). Available data suggest that there are 1700 million people, or one third of the world’s population are, or have been infected with Mycobacterium tuberculosis. The overall proportion of infected people is similar in the industrialized and developing nation. However, 80% of infected persons in industrialized countries are aged 50 years or more while 75% of those in developing country are less than 50 years old. This is the result of difference in past and current levels of transmission of the infection (Arata Kochi, 2001).

The members of the genus *Mycobacterium* are important pathogens for man and animals. They are responsible for two most dreaded disease in the history of mankind namely tuberculosis and leprosy. These two major mycobacterial diseases are caused by *M. tuberculosis* and *M. leprae* respectively. Several other species of *Mycobacteria* are
pathogenic to man, animals and birds as well (Gange, 1980; Mitchell and Rees, 1983).

Both tuberculosis and leprosy continue to be major public health problems in India. The infections due to Mycobacteria are further increasing with the rise in cases suffering from acquired immunodeficiency syndrome (AIDS) (WHO, 1991).

Since the advent of streptomycin in 1949 (Waksman, 1949) Sulphones in 1943 (Faget et al., 1943, Cochrane et al., 1949) against leprosy, the effective chemotherapy has been the mainstay in treating the sufferers of these diseases and is also considered important in blocking the transmission to the susceptible individuals.

1.1 Anti-tubercular drugs

During the last five decades, several groups of drugs active against M. tuberculosis have been developed. In 1950s to 1960s, Streptomycin, Isoniazid (INH). Para-aminosalicylic acid (PAS) were the commonly used primary antitubercular drugs (Zetterberg, 1949; Winder, 1964; Brock, 1966; Youatt, 1969). Later several other drugs like Rifampicin, Ethionamide, Ethambutol, Pyrazinamide were established as active compounds against tuberculosis and in various combinations are commonly used for the treatment of human tuberculosis (McClune et al., 1956; Rist, 1960. Karlson, 1961, Thomas et al. 1961; Riva and Silvestri. 1972; Ji et al, 1986).

1.2 DRUGS EFFECTIVE AGAINST ATYPICAL ENVIRONMENTAL MYCOBACTERIA

The infections due to environmental mycobacteria have been becoming increasing important. Most of these infections are due to M. kansasii, M. avium, M. scrofulaceum, M. szulgai, M. fortuitum, M. chelonei, etc. (Chapmar 1977; Wolonsky, 1979; Shield, 1983; Yamamoto, 2000). Although some susceptible strains among these non tuberculous mycobacteria to conventional anti-tubercular compounds such as INH, Streptomycin, PAS, Rifampicin, Quinolones etc. have been
reported (Chapman, 1977; Wolinsky, 1979; Leysen et al., 1989; Gillespie, S.H., et al., 2001), a large number of these *Mycobacteria* tend to be resistant to commonly used ant-tubercular drugs.

### 1.3 Drug Resistance in Tuberculosis

1988; Iseman et al, 1990; Jain, 1992), (x)Ethionamide, Ioxyl Amithiozone (Rist, 1960; Lefford, 1969) and (xi) Clofazimine (Morrison, 1972) have been reported. Even resistance to a newer compound like ofloxacin has been observed (Leysen et al, 1989).

1.4 Drug resistance in other Mycobacterial diseases

One of the prominent features that first called attention to any atypical Mycobacteria was the resistance of most of these strains to the common conventional anti-mycobacterial drugs such as INH, Streptomycin and PAS etc (Chapman, 1977). Natural and acquired resistance to conventional and unconventional agents in various Mycobacteria has been reported. The important reports are:

I. Strains of M. kansasii resistant to INH, PAS, Streptomycin and Ansamycin including Rifampicin have been reported (Hedgecock and Blumenthal. 1965; Wayne et al, 1968; Woodley et al. 1972, Chapman. 1977; Payton, M. and Pinter, K., 1999).

III. Several *M. intracellulare* strains resistant to INH, PAS, Streptomycin, Rifampicin, Ethambutol and Beta-lactams have been observed (Schwabacher, 1957; Honza *et al.*, 1966; Tsukamura, 1972; Capman, 1977; David, 1981; rastogi *et al.*, 1981; finch, 1986; Hoffner and Svenson, 1991).


V. *M. szulgai* strains resistant to INH and PAS have been reported by Capman (1977) and Wolinsky (1979) and including rifampicin has been reported (Nakayama, S., et al, 2000).

VI. Several investigators have observed resistance to Amikacin and Ciprofloxacin among the strains of *M. foruitum* complex. (Hawkins and McClean, 1966; Gangadharan and candler, 1977; Wallace *et al.*, 1990).

VII. Strains of *M. marinum* resistant to INH, PAS, Rifampicin and Beta Lactams have been reported (Adams *et al* 1970; Van Dyke and Lake 1975; Wolinsky 1979; and Finch 1986).
VIII. Several strains of *M. xenopi* resistant to INH, PAS and Beta lactams have been demonstrated (Boisvert, 1965; Engback *et al.*, 1967; Finch, 1986).

IX. Resistance to INH among strains of *M. ulcerans* has been reported (Finegold and Martin, 1982).

X. Several strains of *M. segmatic* resistant to INH have been demonstrated (Payton. M. *et al.*, 1999; Raynaud. C. *et al.*, 1999)