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MULTI DRUG RESISTANT TUBERCULOSIS

Tuberculosis (TB) was declared a global emergency by the World Health Organisation (WHO) on World TB Day in 1993. This unprecedented declaration was prompted predominantly by two developments; the resurgence of TB in the west from the mid 80s, where the disease had been showing a steady decline from the beginning of the century[1]; and a number of outbreaks of multi drug resistant tuberculosis (MDRTB) in the USA and in many other parts of the world, in the late 1980s and early 1990s. For much of the developing world, which bears the brunt of the global TB burden, this declaration by the WHO served the useful purpose of helping to focus attention on a much neglected disease and has helped to draw resources that were sorely needed.

Multi drug resistant tuberculosis has been a topic of growing importance in the last decade. It has figured prominently both in the medical literature and in the lay press causing great alarm all over the world. It has been described as the third epidemic, complicating the epidemics of human immunodeficiency virus (HIV) and the reemergence of TB in the West[2]. The alarm bells were set ringing by a series of outbreaks of MDRTB in hospitals, prisons and shelters for homeless persons in and around New York in the early 90s. A majority of the affected patients were HIV infected and the mortality was extremely high. Some patients were resistant to six or seven drugs[3-7].

A review by WHO of a series of 63 surveys of drug resistant TB carried out world-wide between 1985 and 1994 led to the conclusion that the new epidemic may be global[8]. Rates of primary resistance to isoniazid ranged from 0-17%; to streptomycin, 0-24%; to rifampicin, 0-3%; and to ethambutol, 0-4%. The rates of acquired resistance were isoniazid, 4-54%; streptomycin, 0-19%; rifampicin 0-15%; and ethambutol, 0-14%. The highest rates of MDRTB were from Nepal (48%), Gujarat state (India) (34%), New York city (USA) (30%), Bolivia (15%) and South Korea (15%). The WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) have subsequently established a global project of drug resistance surveillance that is based on standard epidemiological methods and quality control through an extensive network of reference laboratories in 35 countries, including India, during 1994 to 1997[9]. The prevalence of primary multi drug resistance was 1.4%. Among patients with histories of treatment for one month or more, the prevalence of resistance to any of the four first line drugs was 36%, and the prevalence of multi drug resistance was 13%. Particularly high prevalence of multi drug resistance was found in the former Soviet Union, Asia, the Dominican Republic, and Argentina. The report concludes that resistance to anti-TB drugs was found in all 35 countries and regions surveyed, suggesting again that this is a global problem.

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Drug resistance in TB is not a new phenomenon. It was recognized very soon after the introduction of effective anti-TB drugs that *Mycobacterium tuberculosis* can rapidly become resistant to the drugs used against it. Resistance to isoniazid and streptomycin was demonstrated in *M. tuberculosis* strains from patients treated in the early years of chemotherapy[10,11]. Resistance could develop to a single drug or to multiple drugs. However, the definition of multi drug resistance has undergone a change in perception over the years. In the pre-rifampicin era the term multi drug resistant tuberculosis meant disease caused by organisms that were resistant to at least two of the first line anti-TB drugs then available, usually to isoniazid and streptomycin. Today, the term is used to signify disease due to *M. tuberculosis* that is resistant to the two most effective current anti-TB drugs, isoniazid and rifampicin, with or without resistance to other drugs[12]. The difference in perception arose because, while previously isoniazid and streptomycin resistant tuberculosis could still be effectively treated with the then available drugs,especially with rifampicin and ethambutol, the outcome of treatment of isoniazid and rifampicin resistant tuberculosis is not so favourable.

Types of Drug Resistance

Drug resistance in tuberculosis may be broadly classified as primary or acquired. When drug resistance is demonstrated in a patient who has not received any anti-TB treatment in the past, it is termed as primary resistance. Acquired resistance is that which occurs in a patient who has received previous treatment. The term initial resistance is used when one is not sure whether the resistance is primary or acquired. This is a common occurrence because TB patients often conceal the history of previous treatment and sometimes patients are unaware that they have received any treatment at all. Transient drug resistance occurs in a patient who is responding to therapy just before sputum conversion, and usually occurs in the form of a few colonies, and does not warrant change of treatment. The level of primary resistance in a community is considered to reflect the quality of the control measures for tuberculosis in the past, while the level of acquired resistance is a measure of ongoing TB control measures[13]. A study carried out in South Korea illustrates this point. It showed a decline in primary drug resistance from 48% in 1980 to 2% in 1990 through improved programme efficiency. Initial drug resistance decreased at a lower rate, from 26% in 1965 to 15% in 1990[14].

Causes of Drug Resistance

Drug resistance in tuberculosis may result from the actions of the physician or the patient. A physician may contribute to the development of drug resistance by the prescription of an inadequate regimen which may be in the form of (i) an inappropriate combination of drugs; (ii) drugs for insufficient duration; and (iii) inadequate dosage of the drugs.

However, the commonest cause of acquired drug resistance, is non-adherence to the prescribed therapy by the patient. In this respect, a patient who takes the prescribed therapy regularly for sometimes and stops prematurely is less likely to develop drug resistance compared to a patient who takes drugs irregularly over a prolonged period. It is the experience of scientists at the Tuberculosis Research Centre (TRC), Chennai that most patients who relapse with tuberculosis after a complete course of treatment for the disease are likely to have sensitive organisms during their relapse[15,16] and can be retreated with the same regimen that the patient had responded to earlier.

Prevalence of Drug Resistant Tuberculosis in India

To have a clear picture of the situation in India it would be necessary to have epidemiological data covering all parts of the country over a period of time. However, this information is not available as it requires repeated surveys covering large populations, which is very expensive and logistically difficult. The data that are available are localised and from different places and cannot be compared because of differences in laboratory techniques, criteria for definition of drug resistance and patient selection. Some of the more reliable data will be reviewed here.

(i) The Indian Council of Medical Research (ICMR) conducted drug resistance studies in 1965 to 1967 in 9 cities in different geographical parts of the country. These were not surveys and did not use statistical techniques for sampling. The centres were selected more for logistic considerations than for epidemiological reasons to represent all parts of the country. Sputums from patients attending chest clinics in these nine cities were airlifted to the central laboratory located at the Tuberculosis Chemotherapy Centre, Madras (now the TRC, Chennai) where culture and drug susceptibility tests were carried out. The first study was on newly diagnosed pulmonary tuberculosis patients who had not received any

previous treatment, and the second study was on all patients, new and old. The first study showed that the level of primary drug resistance ranged from 11-20% for isoniazid, 8-20% for streptomycin and 4-11% for both drugs[17]. Overall, 20% of patients had resistance to one or more drugs ranging from 14-29% in the nine centres. The second study which reflected initial drug resistance, showed that 15-69% of patients exhibited isoniazid resistance, 12-63% streptomycin resistance and 5-58% double drug resistance[18]. Overall, 32% had resistance to one or more drugs ranging from 22-74%. This meant that one of three patients attending a chest clinic was likely to harbour drug resistant bacilli. The second study also showed that the level of initial resistance was directly proportional to the duration of previous treatment, increasing from 22% in those who had not received any previous treatment to 76% in those who had previous treatment for more than 12 months. The wide range in the level of initial drug resistance between the different centres was due to the different proportions of patients with previous treatment for different duration.

(ii) The TRC, Chennai has been conducting controlled clinical trials in chemotherapy of tuberculosis since 1956. Patients are admitted to these trials on the basis of positive sputum cultures for *M.tuberculosis*. Drug susceptibility tests are also done on all positive cultures. Hence drug resistance data are available over a 40 year period (1956 to 1997) in patients admitted to the clinical trials. In newly diagnosed patients without prior treatment, resistance to isoniazid rose from 5 to 13%, to streptomycin from 3 to 12% and to both drugs from 1-6% in this period[19]. This increase was fairly rapid up to about 1976 (3-10%), after which the increase was more gradual (10-13%) (figure). Rifampicin resistance in newly diagnosed patients was less than 1% in the period 1985-90 and about 2% in 1990-95. These figures can be considered to represent primary resistance fairly precisely because of the rigorous interrogation methods used. All patients are initially questioned in detail about previous treatment by doctors, social workers and nurses. The interrogation is repeated at the end of one month of treatment and again when drug susceptibility test results become available in those with drug resistance. These primary drug resistance figures are not very alarming and do not support the views expressed in the early years of chemotherapy, when it was predicted that drug resistance would increase to such an extent that it would jeopardise the tuberculosis control programme.

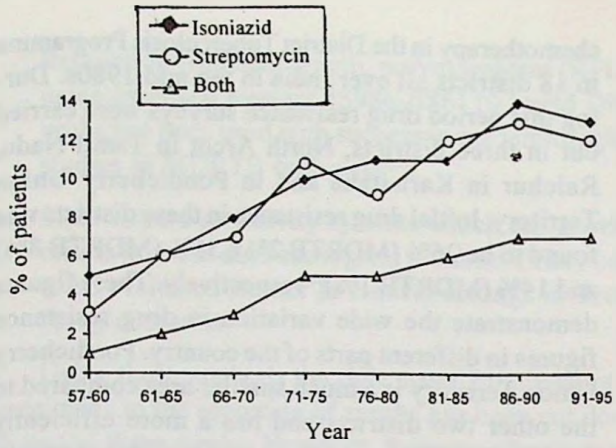

Fig. Drug resistance in newly diagnosed patients with pulmonary tuberculosis (TRC: 1957-1995)

(iii) Patients attending any treatment service, however, are a mix of new and previously treated patients. The initial drug resistance data are of more value for treatment planners. While the data from TRC are from a research institute, where patients are selected for prospective good compliance with treatment drug, resistance figures from the Institute of Thoracic Medicine, Chennai are more interesting. This institute caters to a large outpatient population and has a monthly attendance of about 150 patients of tuberculosis, old and new. Initial drug resistance to any drug in this centre has increased from 31% in 1988 to 37% in 1994 and this increase applies to all drugs, *viz.* streptomycin, isoniazid, rifampicin and ethambutol (personal communication). These data appear to suggest that drug resistance is on the increase.

(iv) In a comprehensive review of the drug resistance scenario in India, it was reported that the overall primary resistance to isoniazid ranged from 6-13%, except among the rural population of Kolar, Karnataka, with a figure of 27%, to streptomycin from 1-6% and to rifampicin from 0-2%. Acquired resistance ranged from 35-67% for isoniazid, 26-27% for streptomycin and 3-37% for rifampicin. Overall, the combined resistance to rifampicin and isoniazid was low and ranged from 0-6%[18]. In a study from Gujarat it was observed that in patients with treatment failure and relapse resistance to rifampicin increased from 3% in 1980 to 37% in 1986, and to isoniazid, from 35 to 56% over the same period[20].

(v) Data are also available on drug resistance from the TB control programme. The TRC was given the responsibility for implementing short course

chemotherapy in the District Tuberculosis Programme in 18 districts all over India in the mid 1980s. During this period drug resistance surveys were carried out in three districts, North Arcot in Tamil Nadu, Raichur in Karnataka and in Pondicherry Union Territory. Initial drug resistance in these districts was found to be 26% (MDRTB 2%), 35% (MDRTB 8%) and 14% (MDRTB 1%)[21] respectively. These figures demonstrate the wide variation in drug resistance figures in different parts of the country. Pondicherry Union Territory is a much smaller area compared to the other two districts and has a more efficiently functioning TB control programme, and these probably are the reasons for the lower level of drug resistance in this centre.

Mechanism of Drug Resistance

Drug resistance in *M.tuberculosis* occurs by random, single step, spontaneous mutation at a low but predictable frequency, in large bacterial populations. There is no convincing evidence for the role of plasmids or transposons as in other bacterial pathogens. It has been estimated that the probability of incidence of drug resistant mutants in a population of *M.tuberculosis* is depicted by the formula $P=1-(1-r)^n$, where P is the probability of incidence of drug resistant cases, r is the probability of incidence of drug resistant mutants and n is the number of bacilli in the lesion[22]. The value of r for rifampicin is 10^{-8}, that for isoniazid, streptomycin, kanamycin, ethambutol and para-aminosalicylic (PAS) acid is 10^{-6}. Thus, for isoniazid and streptomycin, there is likely to be one resistant bacillus in a population of one million sensitive bacilli. The corresponding figure for rifampicin is one in one hundred million. The probability of resistance occurring to two drugs at the same time, is the product of the probabilities of drug resistance to a single drug. For example, the probability of resistance developing to both isoniazid and rifampicin in the same bacillus is $1:10^6 \times 1:10^8$ *ie* $1:10^{14}$. Therefore, in a medium sized cavity of 2.5 cm diameter, as might be seen in a patient with open pulmonary tuberculosis, which is estimated to contain about 10^7-10^9 bacilli, there are likely to be a few bacilli resistant to isoniazid, a few bacilli resistant to rifampicin but none resistant to both drugs. This illustrates a very fundamental principle that multi drug resistant tuberculosis is an iatrogenic problem.

Genetic Basis of Drug Resistance

While, it was generally known that resistance in *M. tuberculosis* occurs due to spontaneous mutation, the exact genetic basis of this mutation has been discovered only recently. In the last seven years, there have been many dramatic discoveries in molecular biology which have greatly increased the understanding of the mechanism of drug resistance. The most important of these was by Ying Zhang of the Royal Postgraduate Medical School, London. In 1992 he and his colleagues were able to transform an isoniazid resistant strain of *M. smegmatis* by repeated splicing of DNA segments from *M. tuberculosis*, till the strain was rendered completely isoniazid sensitive[23]. The segment of DNA which was responsible for restoring drug sensitivity was also able to restore catalase-peroxidase activity. This segment has been identified as the katG gene which encodes for catalase-peroxidase activity. It is well known that many strains of *M. tuberculosis* resistant to isoniazid show reduced catalase-peroxidase activity.

However, not all resistant strains of *M. tuberculosis* are catalase-peroxidase deficient. Some strains are catalase-peroxidase positive. Thus, other mechanisms in drug resistance are also possible. Subsequently a mutation was discovered in the inhA gene, which is required for the synthesis of mycolic acid, an essential component of the bacterial cell wall, and which may be a target of activity for isoniazid in some resistant strains of *M. tuberculosis*.

In the last few years, there has been considerable progress in our understanding of the mechanisms of action and resistance to anti-tuberculosis agents. To date, there is information about 11 genes involved in resistance to all major anti-TB drugs in *M.tuberculosis*. Mutations in katG, inhA and ahpC genes are found in upto 90% of isoniazid resistant strains, rifampicin resistance is associated (> 96%) with rpoB mutations, pyrazinamide resistance with pncA mutations (72-97%), ethambutol resistance with mutations in embB (47-65%), streptomycin resistances with rrs or rpsL mutations (70%) and fluoroquinolone resistances with gyrA substitutions (75-94%). Additional genes and mechanisms may play a role, particularly in association with lower levels of resistance[24].

Transmissibility

Drug resistant strains of *M.tuberculosis* show reduced catalase-peroxidase activity, demonstrate reduced virulence in guineapigs and grow poorly in artificial media. So for many years, drug resistant *M.tuberculosis* was considered to be less infectious than drug susceptible strains. Therefore, drug resistant tuberculosis was considered to be a problem for the individual but not for the

community. However, there is now evidence to show that drug resistant bacilli are as infectious as drug susceptible ones and are capable to causing severe disease[25]. This view has been reinforced recently in the outbreaks of multi drug resistant tuberculosis in the USA, where studies have shown that contacts of patients with multi drug resistant tuberculosis were at equal risk of getting infected compared to contacts of those with drug susceptible tuberculosis.

Detection of Drug Resistance

One of the major handicaps in the management of drug resistant tuberculosis is the diagnosis. Traditional methods which include culture of the organism, identification of the cultured bacilli and drug susceptibility tests require at least 10 to 12 weeks. This leads to undue delay in the initiation of appropriate treatment and during this time the patient continues to transmit drug resistant infection in the community. There is thus a need for more rapid methods of detection of drug resistance. In this respect, some recent developments are of very great relevance.

(i) The BACTEC method is an automated radiometric technique, which depends on the detection of radiolabelled CO_2 as a measure of growth index for growing microorganisms. Using this system it is possible to provide drug susceptibility results for *M.tuberculosis* in three weeks[26,27]. A comparison with conventional procedures for it's ability to detect drug resistant strains shows excellent correlation[28].

ii) The luciferase phage system in which mycobacteria are infected with a phage carrying the enzyme luciferase, which is responsible for the glow of the firefly. When the infected *M.tuberculosis* carrying the enzyme is grown in culture containing the drug, to which the substrate luciferin is added, light is produced if the *M.tuberculosis* strain is resistant to the drug in the medium. If the strain is sensitive to the drug, it is killed and there is no luciferase in the system and no light is produced. Thus drug resistant strains produce light and drug susceptible strains do not[29,30]. The test is both highly sensitive and specific.

iii) Polymerase chain reaction (PCR) single stranded conformation polymorphism has made possible the rapid identification of rifampicin resistant *M.tuberculosis*[31,32]. Results are available within 24 hours. The analogous setting for isoniazid resistance is less favourable, since more than one gene may be involved in isoniazid resistance.

Restriction fragment length, polymorphism (RFLP) using insertion element IS986-/IS6110 based DNA probe has been used with success in epidemiological studies in MDRTB outbreaks[33].

iv) Slide culture sensitivity systems which can provide results in seven days show great promise[34]. They need to be evaluated further in clinical settings in developing countries.

Using these methods the time spent from receipt of specimens to the reporting of results has been cut down to two to three weeks. However, there are clearly problems in trying to apply.these new techniques in developing countries, the constraints being technological and financial. For the time being they will remain predominantly as research tools[35].

HIV and Tuberculosis

It is estimated that globally more than four million people are co-infected with HIV and TB. The HIV epidemic has had a very dramatic impact on the global epidemiology of tuberculosis in the recent past. It has been one of the major reasons for the sharp increase in the number of tuberculosis cases observed in the West from the mid-1980s, after years of declining case rates[1]. The epidemic has also caused a great increase in the number of cases of pulmonary and extra-pulmonary tuberculosis in many countries in the African continent. It is widely forecast that Asia, and South-East Asia in particular, would be the next area where the adverse impact of the HIV epidemic on the tuberculosis situation would be felt.

Tuberculosis has been shown to occur much earlier in the clinical course of HIV disease compared to other opportunistic infections. It has been estimated that only 10% of immunocompetent persons infected with tuberculosis run the risk of developing clinical disease during their lifetime, 5% in the first five years and 5% during the rest of their lifetime. HIV infection greatly accelerates this risk. The risk of developing clinical tuberculosis in a TB infected persons who is also infected with HIV is 8% per year. The HIV infected person who develops TB is likely to do so in a relatively short time after infection with TB[36].

It has also been shown that if the relative risk (RR) of developing clinical tuberculosis in a PPD positive individual is one, when there is no other underlying risk factor, the RR is 113 for someone who is also infected with HIV and 170 if he/she has AIDS. This means that an HIV infected person has 113 times greater risk and

an AIDS patient has 170 times greater risk of developing tuberculosis compared to someone who is immunocompetent.

Most of the outbreaks of multi drug resistant tuberculosis in the USA in the first half of the 1990s were in HIV infected patients. These outbreaks were characterised by extremely high mortality rates. The HIV epidemic is expected to cause an increase in the number of cases of drug resistant tuberculosis for the following reasons: (i) increase in the number of cases of tuberculosis will give rise to an increase in the number of cases with primary drug resistance; (ii) overloading of the tuberculosis treatment services because of the expected increase in the number of cases will give rise to more cases with acquired drug resistance; and (iii) immunocompromised status of HIV patients may lead to decreased efficacy of anti-tuberculosis treatment regimens, and thereby increasing the chance of acquired drug resistance[12].

Management

Multi drug resistant tuberculosis is an iatrogenic problem. Therefore the prevention of the emergence of drug resistance is of paramount importance. The best strategy to prevent the emergence of drug resistance is to prescribe standardised and well tested regimens in the proper dosage for the proper duration, and to ensure that the patient completes the full course of treatment till he or she is cured. The tendency is often to blame the patient for the development of drug resistance due to poor adherence to treatment. But it is a fact that physicians often contribute to this problem by prescribing inappropriate combination of drugs with inadequate dosage. A study on the prescribing practices of private practitioners by the Foundation for Research in Community Health (FRCH), showed that, in Mumbai, 100 practitioners prescribed a total of 80 different regimens and in Pune, 113 practitioners prescribed 90 different regimens for the treatment of tuberculosis[37]. This problem of poor prescription is not confined to the developing countries. A study in the USA that evaluated the prescribing practices of physicians in New Jersey showed that 36% of 1,230 patients were not initially treated with four or more drugs and a substantial proportion of physicians did not initially treat their TB patients according to the recommendations of the Centres for Disease Control/American Thoracic Society[38].

It has been well established that the currently advocated short course regimen of six months for the treatment of pulmonary tuberculosis, with isoniazid, rifampicin, pyrazinamide and ethambutol or streptomycin for the first two months followed by isoniazid and rifampicin for the next four months cures 94-97% of patients with resistance to isoniazid or streptomycin or to both drugs[39]. Studies at the TRC have shown that in patients with resistance to streptomycin, isoniazid, or both drugs, only 2, 8 and 17% respectively failed to respond when treated with appropriate regimens. When resistance is demonstrated to both isoniazid and rifampicin (MDRTB), however, the outlook is very different. Of 38 patients, 35 failed to respond[40].

The management of MDRTB is a challenging problem. The treatment is less effective, more toxic and much more expensive compared to the treatment of drug susceptible tuberculosis. Certain guidelines have to be borne in mind when confronted with suspected drug resistance. The first and foremost of these is to obtain from the patient an exhaustive and detailed history of previous treatment for tuberculosis. The importance of this step cannot be over emphasised. Details such as the names of drugs, the dosage, when taken for what duration and with what regularity are all important. All available prescriptions have to be perused. Patients often do not know what drugs they had been prescribed. So indirect questions might be necessary, such as did the patient take any capsules which made the urine red, any medicines that caused joint pains *etc.* Patients should be prescribed at least three drugs which the patient has not received in the past, or to which the bacilli are demonstrated to be susceptible by laboratory tests. Treatment should be supervised as far as possible, at least in the initial stages, or till the sputum becomes negative. Studies have shown that even in developed countries, there is much variation in the results from different laboratories which perform drug susceptibility tests for *M.tuberculosis*. Of more than 80 strains typed as resistant to streptomycin, isoniazid or PAS at the peripheral laboratory, only 27-49% of the strains were confirmed to be resistant when retested at the reference laboratory[41]. Incorrect results of susceptibility test can lead to unnecessary changes of drugs, decreasing the chances of cure. Judicious clinical judgement often obviates the need for drug susceptibility testing. In the clinical trials at TRC 88-92% of patients with sputum positive pulmonary tuberculosis treated with short course chemotherapy became culture negative by two months, and 90-96% by three months of treatment[42-44]. A general rule, therefore, would be to suspect drug resistance in a patient who continues to remain sputum smear positive after four months of regular treatment with an established short course chemotherapy regimen. If drug susceptibility testing is considered essential, it should be done in a laboratory with established credentials.

One important dictum in the management of tuberculosis is never to substitute a single drug to a regimen that appears to be failing as this may lead to the sequential development of resistance to the drug that are being introduced. Two or more new drugs should always be introduced. Since most drugs used in the treatment of MDRTB have adverse effects, toxicity has to be carefully monitored. Sometimes drugs may need to be withdrawn either temporarily or permanently and alternate drug substituted. Often adverse reactions can be managed with symptomatic treatment. The patient needs constant encouragement and motivation to cope with adverse reactions to drugs and to complete the full course of treatment. Ideally this should be done in hospital and it is a good policy to hospitalise patients, at least initially, to facilitate close monitoring, both for toxicity and for treatment compliance. Members of the patients family should be encouraged to participate in the patients's management by providing emotional and psychological support.

The outcome of treatment of multi drug resistant tuberculosis is not very favourable. In a retrospective analysis of 171 immunocompetent patients treated over a ten year period (1973-83) at the National Jewish Hospital in Denver the overall favourable outcome was only a little over 50%[45]. All patients were treated with individually tailored regimens in which they received at lest 3 or 4 drugs which they had not received previously, or to which they were known to be susceptible. Of the 134 patients evaluated for efficacy, 65% became culture negative and 35% failed to respond. Of those who became culture negative, 14% eventually relapsed giving an overall favourable outcome in 56% of patients. Of the patients who failed, 46% died of tuberculosis.

In the Cape Province of South Africa the 5 year outcome of 240 MDRTB patients was death in 48%, cure in 33%, 15% were respiratory disabled and 13% were still bacteriology positive[46].

However, not all the reports are so grim. In a retrospective analysis reported from South Korea, of 107 patients with MDRTB treated with at least four drugs to which hey had not been exposed to before, or to which they were known to be susceptible, in 63 patients with sufficient follow up data, 52 (82.5%) responded to chemotherapy. There was no subsequent relapse among the patients who responded, and there were no tuberculosis related deaths. The authors conclude that, MDR pulmonary tuberculosis responds relatively well to carefully selected regimens. However, the mean period of follow up was only 17 months[47].

Experience of scientists of TRC, Chennai with MDRTB has been equally discouraging. In about 170 patients with MDRTB over a 12 year period (1986-1997) all but two of whom were HIV negative, only one third had a favourable outcome, and one third died. These patients were treated with regimens which included at least three or four of the following drugs: ethionamide, ethambutol, pyrazinamide, cycloserine, streptomycin or kanamycin, PAS, thioacetazone and high dose isoniazid (600 mg) with 10 mg of pyridoxine. More than one fourth of the patients defaulted mainly due to adverse reactions to the drugs, most commonly to ethionamide. In the last five years ofloxacin has been used at TRC for the treatment of these patients and the results appear to be promising, but a longer period is necessary before coming to conclusions. The fluroquinolones have marked anti mycobacterial activity and are being increasingly used to treat MDRTB. However, this class of drugs is also widely prescribed for a variety of respiratory and other infections. Caution has to be exercised as indiscriminate use will lead to the development of resistance to this class of drugs also. A report from New York indicates that this may be happening[48].

The value of the older drugs in the treatment of MDRTB today has to be emphasised. Many young patients with MDRTB have not received PAS or thioacetazone in the past and these can be used with success in such patients. So also the value of high dose isoniazid (600 mg), in patients with documented isoniazid resistance. Experience of scientists at TRC has shown that patients with MDRTB who have remained sputum positive for many years while on treatment with other drugs have converted to sputum negativity when changed to 600 mg of isoniazid and PAS as a last resort.

The duration of therapy for MDRTB has not been clearly established. The duration that has been recommended in the USA is for 18-24 months at least, or for 24 months after sputum culture converts to negative[35]. At the TRC treatment is continued for at least 12 months after sputum cultures become negative.

While the outcome for patients with MDRTB is not very favourable in immunocompetent patients, the response in HIV positive patients is even bleaker. In the outbreaks of MDRTB in and around New York city, between 1988 and 1992, predominantly in HIV infected individuals, mortality was in the order of 80% and the mean duration from diagnosis to death was 4-16 weeks.

In a study of 173 patients hospitalized from 1983 to 1993 with MDRTB, of whom 52% were known to be

HIV infected, HIV positive MDRTB patients had significantly more pulmonary and constitutional symptoms, more extrapulmonary disease, and fewer cavitary lesions on chest radiographs. Fifty five per cent of the patients in the cohort died; mortality was significantly greater for HIV positive than HIV negative (72 versus 20%) patients. The median duration of survival of MDRTB patients was 22 to 1 month. In HIV positive patients, only appropriate therapy was associated with prolonged survival[49].

In the recent past there have been a number of reports of the value of amoxycillin-clavunalic acid combination[50], interferon-γ via aerosol[51], rifabutin[52] and recombinant human interleukin 2[53] in the management of MDRTB. However, these are in small numbers of patients, and need to be evaluated in larger number of patients in well designed clinical trials.

Role of Surgery

In carefully selected patients surgery may have an important role to play in the management of MDRTB. A number of studies have demonstrated the value of resectional surgery in patients with predominantly unilateral disease, with adequate respiratory reserve and in whom chemotherapy alone had failed[54,55].

Conclusions

MDRTB is an emerging problem that many people fear would take us back into the past, to the era when tuberculosis was considered untreatable. Though there is as yet no firm evidence to indicate that MDRTB is increasing in India, it would be prudent to consider that this is likely to happen in the future. This is not very surprising since, rifampicin containing short course regimens were and are still being used in the National Tuberculosis Control Programme in which the treatment completion rates are still only around 50% and since these potent anti-TB drugs are often available over the counter without a valid prescription. Since MDRTB is a preventable problem, careful attention should be paid to the more efficient application of the existing treatment regimens in patients with tuberculous. Treatment of MDRTB should ideally be done in a hospital, at least in the initial stages and where the drugs needed to treat this condition are available. The prescription of regimens for MDRTB should be based on scientific reasoning and according to established guidelines. The WHO is advocating global tuberculosis control through the DOTS strategy. The Revised National Tuberculosis Control Programme, which is being gradually implemented in India is based on this principle. It has been shown that the administration of therapy under direct supervision will play a crucial role in helping to achieve significant reduction in the frequency of multi drug resistance[56].

There is an urgent need for research to develop drugs with anti-mycobacterial activities. Prospective controlled trials to assess the efficacy of treatment regimens for MDRTB are also required. At the beginning of the new millennium the threat of MDRTB looms large over us, and great resolve and commitment are needed to face this challenge.

References

1. Kochi, A. The global tuberculosis situation and the new control strategy of the World Health Organization. *Tubercle 72:* 1, 1991.
2. Neville, K., Bromberg, A., Bromberg, R., Bonk, S., Hanna, B.A. and Rom, W.N. The third epidemic – multi drug resistant tuberculosis. *Chest 105:* 45, 1994.
3. Centres for Disease Control and Prevention. Nosocomial transmission of multi drug resistant tuberculosis among HIV infected persons: Florida and New York, 1988-1991. *MMUR Morb Mortal Wkly Rep 40:* 585, 1991.
4. Valway, S.E., Greifinger, R., Papania, M., Kilburn, J.O., Woodley, C., DiFerdinando, G.T. and Dooley, S.W. Multi drug resistant tuberculosis in the New York State prison system, 1990-1991. *J Infect Dis 170:* 151, 1994.
5. Beck-Sague, C., Dooley, S.W., Hutton, M.D., Otten, J., Breeden, A., Crawford, J.T., Pitchenik, A.E., Woodley, C., Cauthen, G. and Jarwis, W.R. Hospital outbreak of multi drug resistant *Mycobacterium tuberculosis* infection. Factors in transmission to staff and HIV infected patients. *J Am Med Assoc 268:* 1280, 1992.
6. Fischl, M.A., Uttamchandani, R.B., Daikos, G.L., Poblete, R.B., Moreno, J.N. Reyes, R.R., Thompson, L.M., Cleary, T.J. and Lai, S.An outbreak of tuberculosis caused by multiple drug resistant tubercle bacilli among patients with HIV infection. *Ann Intern Med 117:* 177, 1992.
7. Frieden, T.R., Sterling, T., Pablos-Mendez, A., Kilburn, J.O., Cauthen, G. and Dooley, S.W. The emergence of drug reistant tuberculosis in New York city. *N Engl J Med 328:* 521, 1993.
8. Cohn, D.L., Bustreo, F. and Raviglione, M.C. Drug resistant tuberculosis : Review of the world-wide situation and the WHO/IUATLD Global Surveillance Project. International Union Against Tuberculosis and Lung Disease. *Clin Infect Dis 24(Suppl 1):* S121, 1997.
9. Pablos-Mendez, A., Biokin, N., Rieder, H.L., Bustreo, F., Cohn, D.L., Lambregts-van Weezenbeek, C.S., Kim, S.J., Chaulet, P. and Nunn, P. Global surveillance for antituberculosis drug resistance, 1994-1997. World Health Organization-International Union Against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *N Engl J Med 338:* 1641, 1998.

10. Medical Research Council Investigation. Streptomycin treatment of pulmonary tuberculosis. *BMJ ii:* 69, 1948.

11. Selkon, J.B. Devadatta, S., Kulkarni, K.G., Mitchison, D.A., Narayana, A.S.L., Narayanan Nair, C. and Ramachandran, K. The emergence of isoniazid reistant cultures in patients with pulmonary tuberculosis during treatment with isoniazid alone or isoniazid plus PAS. *Bull WHO 31:* 273, 1964.

12. Veen, J. Drug resistant tuberculosis: Back to sanatoria, surgery and cod liver oil? (Editorial). *Eur Respir J 8:* 1073, 1995.

13. Kochi, A., Vareldzis, B. and Styblo, K. Multi drug resistant tuberculosis and its control *Res Microbiol 144:* 104, 1993.

14. Kim, S.J. and Hong, Y.P. Drug resistance of *Mycobacterium tuberculosis* in Korea. *Tuber Lung Dis 73:* 219, 1992.

15. Santha, T., Radhakrishna, S., Ramakrishnan, C.V. and Tripathy, S.P. Retreatment of drug-sensitive relapses of pulmonary tuberculosis following chemotherapy with standard drugs. *Tubercle 57:* 177, 1976.

16. Tripathy, S.P. Relapse in tuberculosis. *Indian J Tuber 28:* 45, 1981.

17. ICMR: Prevalence of drug resistance in patients with pulmonary tuberculosis presenting for the first time with symptoms at chest clinics in India. I. Findings in urban clinics among patients giving no history of previous chemotherapy. *Indian J Med Res 56:* 1617, 1968.

18. ICMR: Prevalence of drug resistance in patients with pulmonary tuberculosis presenting for the first time with symptoms at chest clinics in India.II. Findings in urban clinics among all patients, with or without history of previous chemotherapy. *Indian J Med Res 57:* 823, 1969.

19. Paramasivan, C.N. An overview of drug resistant tuberculosis in India. *Lung India 16:* 21, 1998.

20. Trivedi, S.S. and Desai, S.C. Primary antituberculosis drug resistance and acquired rifampicin resistance in Gujarat, India. *Tubercle 69:* 37, 1988.

21. Paramassivan, C.N., Chandrasekaran, V., Santha, T., Sudarsanam, N.M. and Prabhakar, R. Bacteriological investigations for short course chemotherapy under the tuberculosis programme in two districts in India. *Tuber Lung Dis 74:* 27, 1993.

22. Shimao, T. Drug resistance in tuberculosis control. *Tubercle 68 (Suppl 2):* 5, 1987.

23. Zhang, Y., Heym, B., Allen, B., Young, D. and Cole, S. The catalase-peroxidase gene of *mycobacterium tuberculosis. Nature 358:* 591, 1992.

24. Alcaide, F. and Telenti, A. Molecular techniques in the diagnosis of drug-resistant tuberculosis. *Ann Acad Med Singapore 26:* 647, 1997.

25. Snider, D.E. Jr., Kelley, G.D., Cauthen, G.M., Thompson, N.J. and Kilburn, J.O. Infection and disease among contacts of tuberculosis cases with drug resistant and drug susceptible bacilli. *Am Rev Respir Dis 132:* 125, 1985.

26. Good, R.C. and Mastro, T.D. The modern mycobacteriology laboratory: How it can help the clinician? *Clin Chest Med 10:* 315, 1989.

27. Huebner, R.E., Good, R.C. and Tokars, J.I. Current practices in mycobacteriology: Results of a survey of state public health laboratories. *J Clin Mycobacteriol 31:* 771, 1993.

28. Snider, D.E.Jr., Good, R.C., Kilburn, J.O., Laskowski, L.F.Jr., Lusk, R.H., Marr, J.J., Reggiardo, Z. and Middlebrook, G. Rapid drug susceptibility testing of *Mycobacterium tuberculosis. Am Rev Respir Dis 123:* 402, 1981.

29. Jacobs, W.R.Jr. Barletta, R.G., Udani, R., Chan, J., Kalkut, G., Sosne, G., Kieser, T., Sarkis, G.J., Hatfull, G.F. and Blarm, B.R. Rapid assessment of drug susceptibilities of *Mycobacterium tuberculosis* by means of luciferase reporter phages. *Science 260,* 819, 1993.

30. Cooksey, R.C., Crawford, J.T., Jacobs, W.R. Jr., and Shinnick, T.M. A rapid method for screening antimicrobial agents for activities against a strain of *Mycobacterium tuberculosis* expressing firefly luciferase. *Antimicrob Agent Chemother 37:* 1348, 1993.

31. Telenti, A., Imboden, P., Marchesi, F., Lowric, D., Cole, S., Colston, M.J., Matter, L., Schopfer, K. and Bodmer, T. Detection of rifampicin-resistance mutations in *Mycobacterium tuberculosis. Lancet 341:* 647, 1993.

32. De Beenhouwer, H., Lhiang, Z., Jannes, G., Mijs, W., Machtelinckr, L., Rossau, R., Traore, H. and Portacls, F. Rapid detection of rifampicin resistance in sputum and biopsy specimens from tuberculosis patients by PCR and line probe assay. *Tuber Lung Dis 76:* 425, 1995.

33. Hermans, P.W., van Soolingen, D., Dale, J.W., Schuitema, A.R., McAdam, R.A., Catty, D. and van Embden, J.D.. Insertion element IS986 from *Mycobacterium tuberculosis:* A useful tool for diagnosis and epidemiology of tuberculosis. *J Clin Microbiol 28:* 2051, 1990.

34. Dickinson, J.M., Allen, B.W. and Mitchison, D.A. Slide culture sensitivity tests. *Tubercle 70:* 115, 1989.

35. Yew, W.W. and Chau, C.H. Drug resistant tuberculosis in the 1990s. *Eur Respir J 8:* 1184, 1995.

36. Hopewell, P.C. Impact of human immunodeficiency virus infection on the epidemiology, clinical features, management and control of tuberculosis. *Clin Inf Dis 15:* 540, 1992.

37. Uplekar, M.W. and Shepard, D.S. Treatment of tuberculosis by private general practitioners in India. *Tubercle 72:* 284, 1991.

38. Liu, Z., Shilkret, K.L. and Finelli, L. Initial drug regimens for the treatment of tuberculosis: Evaluation of physician prescribing practices in New Jersey, 1994 to 1995. *Chest 113:* 1446, 1998.

39. Mitchison, D. and Nunn, A.J. Influence of initial drug resistance on the response to short course chemotherapy of pulmonary tuberculosis. *Am Rev Respir Dis 133:* 423, 1986.

40. Mathew, R., Santha, T., Parthasarathy, R., Rajaram, K., Paramasivan, C.N., Janardhanam, B., Somasundaram, R.R. and Prabhakar, R. Response of patients with initially drug-resistant organisms to treatment with short-course chemotherapy. *Indian J Tuber 40:* 119, 1993.

41. Fox, W. The John Barnwell Lecture. Changing concepts in the chemotherapy of pulmonary tuberculosis. *Am Rev Respir Dis 97:* 767, 1968.

42. Tuberculosis Research Centre. Study of chemotherapy regimens of 5 and 7 months' duration and the role of corticosteroids in the treatment of sputum-positive patients with pulmonary tuberculosis in south India. *Tubercle 64:* 73, 1983.

43. Tuberculosis Research Centre, Madras and National Tuberculosis Institute, Bangalore. A controlled clinical trial of 3- and 5- month regimens in the treatment of sputum positive pulmonary tuberculosis in south India. *Am Rev Respir Dis 134:* 27, 1986.

44. Tuberculosis Research Centre. A controlled clinical trial of oral short-course regimens in the treatment of sputum-positive pulmonary tuberculosis. *Int J Tuber Lung Dis 1:* 509, 1997.

45. Goble, M., Iseman, M.D., Madson, L.A., Waite, D., Ackerson, L., and Horsburg, C.R.Jr. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and streptomycin. *N Engl J Med 328:* 527, 1993.

46. Schaaf, H.S., Botha, P., Beyers, N., Gie, R.P., Vermeulen, H.A., Groenewald, P., Coetzee, G.J. and Donal, P.R. The 5-year outcome of multi drug resistant tuberculosis patients in the Cape Province of South Africa. *Trop Med Int Health 1:* 718, 1996.

47. Park, S.K., Kim, C.T. and Song, S.D. Outcome of chemotherapy in 107 patilents with pulmonary tuberculosis resistant to isoniazid and rifampicin. *Int J Tuber Lung Dis 2:* 877, 1998.

48. Sullivan, E.A., Kreiswirth, B.N., Palumbo, L., Kapur, V., Mussr, J.M., Ebrahimzadeh, A. and Frieden, T.R. Emergence of fluoroquinolone-resistant tuberculosis in New York city. *Lancet 345:* 1148, 1995.

49. Park, M., Davis, A.L., Schluger, N., Cohen, H. and Rom, W.N. Outcome of MDRTB patients, 1983-1993. Prolonged survival with appropriate therapy. *Am J Respir Crit Care Med 153:* 317, 1996.

50. Iwanaga, T., Yokota, K., Kishikawa, R., Ikeda, T., Tsurutani, H., Hirose, T. and Nishima, S. The combination of amoxicillin-clavulanic acid and ofloxacin in the treatment of multi drug resistant *Mycobacterium tuberculosis. Kekkaku 72:* 9, 1997.

51. Condos, R., Rom, W.N. and Schluger, N.W. Treatment of multi drug resistant pulmonary tuberculosis with interferon via aerosol. *Lancet 349:* 1513, 1997.

52. Lee, C.N., Lin, T.P., Chang, M.F., Jimenez, M.V., Dolfi, L. and Olliaro, P. Rifabutin as salvage therapy for cases of chronic multi drug resistant pulmonary tuberculosis in Taiwan. *J Chemother 8:* 137, 1996.

53. Johnson, B.J., Bekker, L.G., Rickman, R., Brown, S., Lesse, M., Ress, S., Wilcon, P., Steyn, L. and Kaplan, G. rhulL-2 adjunctive therapy in multi drug resistant tuberculosis: A comparison of two treatment regimens and placebo. *Tuber Lung Dis 78:* 195, 1997.

54. Kir, A., Tahaoglu, K., Okur, E. and Hatipoglu, T. Role of surgery in multi drug reistant tuberculosis: Results of 27 cases. *Eur J Cardiothorac Surg 4:* 531, 1997.

55. Pomerantz, M. and Brown J.M. Surgery in the treatment of multi drug resistant tuberculosis. *Clin Chest Med 18:* 123, 1997.

56. Weis, S.E., Slocum, P.C., Blais, F.X., King, B., Nunn, M., Matney, G.B., Gomez, E. and Foresman, B.H. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *N Engl J Med 330:* 1179, 1994.

This article has been contributed by Dr. M.S. Jawahar, Dy. Director, Tuberculosis Research Centre, Chennai.

ICMR AWARDS & PRIZES 1996

The Indian Council of Medical Research has awarded the following prizes and awards to various Indian scientists for their outstanding research work in various fields of biomedical sciences.

Basanti Devi Amir Chand Prize, 1997

Dr. Kamala Krishnaswamy Director National Institute of Nutrition Hyderabad	Diet and cancer
and	
Dr. M.Gourie-Devi Director and Vice-Chancellor National Institute of Mental Health & Neurosciences Bangalore	Neuroepidemiology

Dr.P.N.Raju Oration Award for Research in Orthopaedics, 1996

Dr.O.N.Nagi
Professor and Head
Department of Orthopaedics
Postgraduate Institute of
Medical Education and Research
Chandigarh

Bone grafting – New techniques

Sandoz Oration Award for Research in Cancer, 1996

Dr.B.B.Yeole
Deputy Director
Bombay Cancer Registry
Indian Cancer Society
Mumbai

Cancer epidemiology

and

Dr.Ranju Ralhan
Additional Professor
Department of Biochemistry
All India Institute of Medical Sciences
New Delhi

Tumour suppressor genes

Dr.Y.S.Narayana Rao Oration Award for Research in Microbiology, 1996

Dr. Gita Satpathy
Additional Professor (Microbiology)
Dr.Rajendra Prasad Centre for
Ophthalmic Sciences
All India Institute of Medical Sciences
New Delhi

Chlamydial infections

Dr. Kamala Menon Medical Research Award for Research in Internal Medicine, 1996

Dr.Dipika Mohanty
Director
Institute of Immunohaematology
Mumbai

Molecular basis, diagnosis, pathophysiology, and management of bleeding disorders

Kshanika Oration Award for Women Scientists, 1996

Dr. Asha Mathur
Professor and Head
Department of Microbiology
K.G.Medical College
Lucknow

Role of chemotactic cytokine in JE virus infection

Dr.M.K.Seshadri Prize for Practice of Community Medicine, 1996

Dr.Umesh Kapil
Additional Professor
Human Nutrition Unit
All India Institute of Medical Sciences
New Delhi

Community medicine and maternal and child health

JALMA Trust Fund Oration Award for Research in Leprosy, 1996

Dr.N.K.Mehra
Professor and Head
Department of Histocompatibility and Immunogenetics
All India Institute of Medical Sciences
New Delhi

Molecular basis of susceptibility to leprosy : HLA studies

ICMR Prize for Biomedical Research for Scientists belonging to Underprivileged Communities, 1996

Dr.R.K.Kale
Associate Professor
School of Life Sciences
Jawaharlal Nehru University
New Delhi

Radiation/Cancer biology

ICMR Prize for Biomedical Research in Underdeveloped Areas, 1996

Dr. Neeru Singh
Deputy Director
Malaria Research Centre Field Station, Mandla
Medical College Campus
Jabalpur

Malaria

BGRC Silver JubileeOration Award for Research in Haematolgoy/ Immunohaematolgoy, 1996

Dr.Roshan Colah
Assistant Director
Institute of Immunohaematology
Mumbai

Molecular genetics and prevention of major haemoglobinopathies in India

and

Dr.K.Madhavan Nair
Senior Research officer
National Institute of Nutrition
Hyderabad

Nutritional haematology

M.O.T.Iyengar Memorial Award for Research in Malaria, Filariasis, Plague or Medical Entomology, 1996

Dr.T.Adak
Assistant Director
Malaria Research Centre
Delhi

Diagnostic tools for identification of malaria vectors

Prof. B.K.Aikat Oration Award for Research in Tropical Diseases, 1996

Dr.Neeloo Singh
Scientist
Division of Biochemistry
Central Drug Research Institute
Lucknow

Molecular parasitology of leishmaniasis

Amrut Mody Unichem Prize for Research in Neurology, 1996

Dr.Atul Goel
Associate Professor
Department of Neurosurgery
Seth G.S.Medical College
Mumbai

Cranio-vertebral and spinal stability

Amrut Mody Unichem Prize for Research in Chest Diseases, 1996

Dr.S.K.Sharma
Professor
Department of Medicine
All India Institute of Medical Sciences
New Delhi

Granulomatous lung disorders

Lala Ram Chand Kandhari Award for Research in Dermatology and Sexually Transmitted Diseases, 1996

Dr.V.K.Sharma
Additional Professor
Departmentof Dermatology
Postgraduate Institute of
Medical Education and Research
Chandigarh

Clinical, immunological and therapeutic studies on alopecia areata

Prof. Surindar Mohan Marwah Award for Research in Geriatrics, 1996

Dr.Kalluri Subba Rao
Professor and Head
Department of Biochemistry
University of Hyderabad
Hyderabad

Biochemical and molecular basis of aging,

AWARDS/ PRIZES FOR YOUNG SCIENTISTS

Shakuntala Amir Chand Prizes, 1996

Dr.Sunil Pradhan
Associate Professor
Department of Neurology
Sanjay Gandhi Postgraduate Institute of
Medical Sciences
Lucknow

Clinical neurophysiology

Dr.Vedantam Rajshekar
Professor of Neurosurgery
Department of Neurological Sciences
Christian Medical College
Vellore

Computerised tomographic stereotactic surgery

Dr.Ashim Ghatak
Scientist E-1
Division of Clinical and Experimental Medicine
Central Drug Research Institute
Lucklnow

Cardiovascular medicine

Dr.Poonam Kakkar
Scientist E-1
Ecotoxicology Section
Industrial Toxicology Research Centre
Lucknow

Studies on oxidative stress

Raja Ravi Sher Singh of Kalsia Memorial Award for Research in Cancer, 1996

Dr.B.M.Biswal
Senior Research Associate
Department of Radiation Oncology
Institute Rotary Cancer Hospital
All India Institute of Medical Sciences
New Delhi

Clinical research in cancer

Tilak Venkoba Rao Award for Research in Psychological Medicine, 1996

Dr.R.K.Chaddha
Associate Professor
Institute of Human Behaviour and Allied Sciences
Delhi

Somatisation in psychiatry

DR.T.Ramachandra Rao Award for Research in Medical Entomolgoy, 1996

Dr.B.N.Nagpal
Senior Research Officer
Malaria Research Centre
Delhi

Anophelines in India

Dr. Dharamvir Datta Memorial Oration Award for Research in Liver Diseases, 1996

Dr.R.K.Dhiman
Assistant Professor
Department of Hepatology
Postgraduate Institute of
Medical Education and Research
Chandigarh

Endoscopic ultrasonography in portal hypertension

Prof. B.C. Srivastava Foundation Award for Research in Community Medicine, 1996

Dr.K.K.Ganguly Senior Research Officer ICMR Headquarters New Delhi	Sociocultural and epidemiological aspects of opium use

Major General Saheb Singh Sokhey Award for Research in Communicable Diseases, 1996

Dr.Samiran Panda 5/3, Snuff Mill Street Belghoria Calcutta	Clinical epidemiology of HIV disease in Manipur

DR.H.B.Dingley Memorial Award for Research in Paediatrics, 1996

Dr.Shally Awasthi Associate Professor Department of Paediatrics K.G.Medical College Lucknow	Effect of air pollution on respiratory disease in preschool children

ICMR NEWS

The following meetings of various technical groups/ committees of the Council were held:

Meetings of the Scientific Advisory Committees (SACs) of the ICMR Institutes/Centres:

SAC of the Institute of Immunohaematology, Mumbai	October 6-7, 1999
SAC of the Vector Control Research Centre, Pondicherry	October 25, 1999
SAC of the National Institute of Virology, Pune	November 14-15, 1999
SAC of the Malaria Research Centre, Delhi	November 26, 1999

Meetings of the Scientific Advisory Group (SAG)/Task Forces (TFs)/Expert Groups (EGs)/Project Review Committees (PRCs)/Project Advisory Committee (PAC):

TF on New Initiatives in Genome Research	September 25, 1999 (at New Delhi)
EG on Copper IUDs	September 27, 1999 (at Mumbai)
PAC on Clinical Trials with ICRC Vaccine for Leprosy	October 5, 1999 (at New Delhi)
ICMR's Ethical Committee on Human Research	October 9, 1999 (at New Delhi)
TF on Pancreatic Diseases	October 9, 1999 (at Chandigarh)
EG on Hypertension amongst Youth	October 18, 1999 (at New Delhi)
PRC on Cardiovascular Diseases, Ophthalmology and Anaesthesia	October 21,1999 (at New Delhi)
TF on Human Genetics	October 22, 1999 (at New Delhi)
PRC on Gastroenterology, Experimental Medicine, Urology, Oral Health and Oncology	October 25, 1999 (at New Delhi)
PRC on Biochemistry and Cellular and Molecular Biology	November 8, 1999 (at New Delhi)
TF on Childhood Asthma	November 12, 1999 (at Chandigarh)
Expert Committee on Handigodu Disease	November 15-17, 1999 (at Sagar Taluk of Shimoga District in Karnataka)
SAG of the Division of Reproductive Health and Nutrition	November 18-19, 1999 (at New Delhi)
EG on BCG Vaccine	November 27, 1999 (at New Delhi)

Participation of ICMR Scientists in Scientific Events:

Dr. Veena Shatrugna, Asstt. Director, National Institute of Nutrition (NIN), Hyderabad, participated in the second International Congress on Women, Work and Health at Rio de Janeiro (September 19-22, 1999).

Dr. N. Raghuramulu, Dy. Director (Sr. Grade), NIN, Hyderabad, participated in the International Conference on Chemistry and Biology of Vitamin D Analogs at Rhode Island, USA (September 26-28, 1999).

Dr. J.M. Deshpande, Director, Enterovirus Research Centre, Mumbai, participated in the fifth meeting of the WHO Global Polio Laboratory Network at Geneva (September 29 - October 1, 1999).

Dr. C.N. Paramasivan, Dy. Director (Sr. Grade), Tuberculosis Research Centre, Chennai, participated in TB Laboratories Modular Course at Addis Ababa (October 2-17, 1999).

Dr. Vas Dev, Sr. Research Officer and Officer-in-Charge, Malaria Research Centre (MRC) Field Station, Sonapur, participated in the second International Conference on Insecticide Treated Nets at Dar es Salaam (October 11-14, 1999).

Dr. B.N. Nagpal, Sr. Research Officer, MRC, Delhi, participated in a workshop on How to Grow and Use Neem at Mbita Point, Kenya (October 14-19, 1999).

Dr. Lalit Kant, Sr. Dy. Director-General and Dr. Mukesh Kumar, Sr. Research Officer, visited Vietnam under the Indo-Vietnam Joint Committee Programme on Science and Technology for Joint Collaboration on Medical Research (October 13-20, 1999).

Dr. Neeru Singh, Dy. Director and Officer-in-Charge, MRC Field Station, Mandla, participated in the WHO Intercountry Consultations on Adverse Effects of Developmental Projects on Mosquito-borne Diseases at Bangkok (October 18-22, 1999). She also participated in the WHO Informal Consultation on Malaria Diagnostics at Geneva (October 25-27, 1999).

Dr. U. Sengupta, Director, Central JALMA Institute for Leprosy, Agra and Dr. M.D. Gupte, Director, Institute of Epidemiology, Chennai, participated in a workshop on Future of Leprosy Research in the Post-genome Era at Bethesda (November 21-22, 1999).

ICMR AIDED SYMPOSIA/SEMINARS/WORKSHOPS/COURSES/CONFERENCES

Symposium/Seminar/Workshop/ Course/Conference	Date & Place	Contact Address
I Conference of the Council of Behavioural Scientists	October 2-3, 1999; (at Agra)	Dr. S. Qamra, Organising Secretary of the Conference, Central JALMA Institute for Leprosy, Agra-282001.
National Symposium and Update on Problem Areas in Diagnostic Oncopathology	October 8-10, 1999; (at Sevagram)	Dr. N. Gangane, Organising Secretary of the Symposium, Department of Pathology, Mahatma Gandhi Institute of Medical Sciences, Seyagram, Wardha-442102.
IV Postgradute Course on Endocrine Surgery and International Workshop on Endocrine Telesurgery	October 25-29, 1999; (at Lucknow)	Dr. S.K. Mishra, Course Convener, Department of Endocrine Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow-226014.
India Consensus Development Workshop on Standards of Care in HIV Disease	October 28-30, 1999; (at Chennai)	Dr. Suniti Solomon, Organising Secretary of the Workshop, YRG Care, T.Nagar, Chennai-600017.
International Workshop on Challenges to Scientists to Preserve the Mother Earth in the Next Millennium	October 28-30, 1999; (at Pondicherry)	Prof. T.R.C. Sinha, General Secretary, National Environmental Science Academy, 206, Rajtower-I, Alakananda Community Centre, New Delhi-110019.
X All India Congress of Cytolgoy and Genetics	October 29-31, 1999; (at Kalyani)	Prof. G.K. Manna, Secretary Convener, AICCG, B-10/250, Kalyani-741235.
III National Conference of the Indian Association of Cardiovascular and Thoracic Anaesthesiologists	November 12-14, 1999; (at New Delhi)	Dr. Nita Saxena, Prof. and Head, Department of Cardiac Anaesthesia, Cardiothoracic Centre, All India Institute of Medical Sciences, New Delhi-110029.

Symposium/Seminar/Workshop/ Course/Conference	Date & Place	Contact Address
XIX Annual Convention of Neonatology Forum	November 18-19, 1999; (at Bangalore)	Dr. P.P. Maiya, Organising Secretary of the Convention, Agadi Hospital, Bangalore-560027.
Symposium on Microbial Infections of the Central Nervous System	November 20, 1999; (at Chandigarh)	Dr. Nancy Malla, Organising Secretary, XXIII National Congress of IAMM, Department of Parasitology, Postgraduate Institute of Medical Education and Research, Chandigarh-160012.
XXXII Annual Meeting of Nutrition Society of India	November 25-26, 1999; (at Coimbatore)	Dr. Usha Chandrasekhar, Convener and Organising Secretary of the Meeting, Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore-641043.
National Conference on Challenges in HIV/AIDS in the Next Millennium	November 25-27, 1999: (at New Delhi)	Dr. Ashutosh Biswas, Organising Secretary, Department of Medicine, All India Institute of Medical Sciences, New Delhi-110029.
National Symposium on Advances and Applications of Animal Sciences for Human Welfare and I Zoological Congress of Eastern India	November 25-28, 1999; (at Darjeeling)	Dr. J. Pal, Head, Department of Zoology, University of North Bengal, Siliguri, Darjeeling-734430.
International Conference on Man, Environment and Nature	November 26-28, 1999; (at Calcutta)	Prof. Sunirmal Chanda, Convener of the Conference, Centre for Study of Man and Environment, Parivesh Kendra, CK-11, Sector-2, Salt Lake City, Calcutta-700091.
XXIII All India Cell Biology Conference	November 27-29, 1999; (at Hyderabad)	Dr. Lalji Sngh, Convener of XXIII AICBC, Centre for Cellular and Molecular Biology, Hyderabad-500007.
XXIV National Conference and International CME of Indian Society of Blood Transfusion and Immuno-haematolgoy	November 27-30, 1999; (at Lucknow)	Dr. N. Chaudhury, Organising Secretary, ISBTI 1999, Department of Transfusion Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow-226014.
International Symposium on Chemotherapy: Problem and Perspectives in 21st Century	November 28-29, 1999; (at Lucknow)	Dr. R.C. Saxena, Head, Department of Pharmacology, K.G. Medical College, Lucknow-226003.
XI Annual Conference of the Physiological Society of India	November 28-30, 1999; (at Delhi)	Prof. M. Fahim, Head, Department of Physiology, Vallabhbhai Patel Chest Institute, Delhi-110007.
International Congress on Frontiers in Pharmacology and Therapeutics in 21st Century	December 1-4, 1999; (at New Delhi)	Prof. S.K. Gupta, Secretary General of ICPT-21, Department of Pharmacology, All India Institute of Medical Sciences, New Delhi-110029.
Symposia on (i) Impact of Statistics in Biomedical Research; and (ii) Recent Advances in Statistical Methods and Challenges for the New Millennium	December 2-4, 1999; (at Bangalore)	Dr. D.K. Subbakrishna, Organising Secretary of the Annual Conference of ISMS, Department of Biostatistics, National Institute of Mental Health and Neurosciences, Bangalore-560029.
Workshop on the Role of Nitric Oxide Gas in the Treatment of High Altitude Pulmonary Edema and Adult Respiration Distress Syndrome	December 4, 1999; (at Pune)	Dr. W. Selvamurthy, Director, Defence Institute of Physiology and Allied Sciences, Delhi-110054.
Indo-European Seminar-cum-Workshop on Advances in Human Cytogenetics	December 6-9, 1999; (at Lucknow)	Dr. S.S. Agarwal, Head, Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow-226014.
XXXI Annual Conference of the Society of Nuclear Medicine	December 8-11, 1999; (at Madurai)	Dr. Y.N.I. Anand, Organising Secretary of the Conference, Department of Imaging Science, Meenakshi Mission Hospital and Research Centre, Madurai-625107.

Symposium/Seminar/Workshop/ Course/Conference	Date & Place	Contact Address
International Symposium on Cancer Control in Developing Countries	December 10, 1999; (at Calcutta)	Dr. Urmi Sen, Organising Secretary of the Symposium, Chittaranjan National Cancer Institute, Calcutta-700026.
XV Asia Pacific Cancer Conference	December 12-15, 1999; (at Chennai)	Dr. T. Rajkumar, Secretary General, The XV APCC Secretariat, Cancer Institute (WIA), Chennai-600036.
II International Conference on Contaminants in the Soil Environment in Australasia - Pacific Region	December 12-17, 1999: (at New Delhi)	Dr. Rajendra Prasad, Organising Secretary of the Conference, Council of Scientific and Industrial Research, Rafi Marg, New Delhi-110001.
International Conference on Medical Diagnostic Techniques and Procedures	December 15-17, 1999; (at Chennai)	Dr. Megha Singh, Organising Secretary, ICMDTP, Department of Applied Mechanics, Indian Institute of Technology, Chennai-600036.
III International Symposium on Cognition, Education and Mental Health	December 16-19, 1999; (at Varanasi)	Dr. C.B. Dwivedi, Organising Secretary of the Symposium, Department of Psychology, Banaras Hindu University, Varanasi-221005.
LXVIII Annual Meeting of Society of Biological Chemists (India) and Symposium on Current Trends in Biology	December 27-29, 1999; (at Bangalore)	Dr. Sandhya S. Visweswariah, Organising Secretary, 68th SBC(I) Meeting, Indian Institute of Science, Bangalore-560012.
XVIII National Symposium on Reproductive Biology and Comparative Endocrinology	December 27-29, 1999; (at Chennai)	Dr. R. Moses Inbaraj, Organising Secretary, 18th SRBCE, Department of Zoology, Madras Christian College, Chennai-600059.
XLIII All India Congress of Obstetrics and Gynaecology	December 27-30, 1999; (at Lucknow)	Dr. Vinita Das, Organising Secretary of the Congress, Department of Obstetrics and Gynaecology, K.G. Medical College, Lucknow-226003.
LXXXVII Session of the Indian Science Congress	January 3-7, 2000; (at Pune)	Dr. Bhushan, Patwrdhan, Local Organising Secretary, Indian Science Congress-2000, University of Pune, Pune-411007.
Workshop on Gene Amplification Techniques in Disease Diagnosis and National Conference of Laboratory Medicine	January 21-25, 2000; (at New Delhi)	Dr. Sarman Singh, Organising Secretary of the Conference, Department of Laboratory Medicine, All India Institute of Medical Sciences, New Delhi-110029.
V World Conference on Injury Prevention and Control	March 5-8, 2000; (at New Delhi)	Prof. Dinesh Mohan, Secretary General (FIWOCO), Transportation Research and Injury Prevention Programme, Indian Institute of Technology, New Delhi-110016.

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Reproductive Biology

At the Institute for Research in Reproduction, Mumbai:

- Training Course on Cytological Detection of Reproductive Tract Infections (December 13-17, 1999).

Nutrition

At the National Institute of Nutrition, Hyderabad:

- Postgraduate Certificate Course in Nutrition (December 1, 1999-February 28, 2000).

Biomedical Statistics

At the National Institute of Epidemiology, Chennai:

- Training Course in Field Epidemiology (November, 1999).

Haematology

At the Institute of Immunohaematology, Mumbai:

- Training Course in Advanced Haematology and Immuno-haematology (October 11-29, 1999).

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