Ind. J. Tub., 1990, 37, 175

TUBERCULOSIS IN INDIA, PAST, PRESENT AND FUTURE*

Wallace Fox

Introduction

It was a great honour to be invited to deliver this important oration for 1989 and I deeply regret that the change in date of the annual meeting made it impossible for me to deliver it in person, as planned. Instead, I have produced a more detailed text.

At the outset I must express my special gratitude to Dr. S.P. Pamra, Dr. D.R. Nagpaul, and to Dr. K. Chaudhuri and his colleagues in the NTI and Dr. R. Prabhakar and his colleagues in the TRC Madras who answered many questions that I put to them and made available much unpublished up to date data, and even undertook special analyses. However, the views I express are entirely my own. I hope you will consider them as constructive contributions to what I regard as a most challenging problem of a size and complexity compounded by the large and growing population, and the geographical area of India, the limited resources which can be devoted to any single problem, including health, and within its budget, to a single disease.

I intend to highlight a number of what I regard to be major aspects of tuberculosis control in India. My emphasis is on the need to improve research and evaluation, based on my background of research into the principles of chemotherapy, the role of new drugs and new approaches to their service programme application, their surveillance and evaluation and the problems of patient and physician compliance. I have had long-term collaborative programmes in both technically advanced and many developing countries of Africa, Asia and the far East, stretching back to 1952 when I joined the British Medical Research Council (BMRC). Above all, my close participation for 35 years in studies of tuberculosis in India and its problems, my contacts with many of the leading research workers, clinicians and administrators, has encouraged me to face the challenge of the above title.

I first came to India in 1955 as a member of a 3-man BMRC group asked by the WHO to advise the Indian authorities on studies relevant to the chemotherapy of tuberculosis, especially ambulatory regimens, their potential, and possible risks to the patients' close contacts. The visit led to the formation of the Tuberculosis Chemotherapy Centre, Madras. The broad background of its formation was recorded many years ago in the first report of the home and sanatorium study.[1] In amplification, after 3 weeks in India my 2 colleagues returned to the UK whilst I visited a number of cities with populations of at least 500,000 and with a sizeable sanatorium service, both basic requirements. After assessing the tuberculosis services of Bombay, Delhi, Calcutta, Madras, Bangalore, Hyderabad, Ahmedabad, Indore and Nagpur, I opted for Madras, which was soon to open with support of WHO what was then called a "training and demonstration centre". The Director of Medical Services, Madras, Dr. Sangham Lal, and his Scientific Adviser Dr. K.S. Sanjivi reacted favourably when I suggested that a chemotherapy research centre would be of much greater value, and Dr. P.V. Benjamin, the then Tuberculosis Adviser to the Indian Government said that he would approve the change if the WHO and the Indian Council of Medical Research (ICMR) agreed. Both Dr. C.S. Mani and C.G. Pandit (the 2 relevant Directors) were enthusiastic too. In this way empty premises, with X-ray equipment in the process of installation and a partially equipped bacteriological laboratory and rooms that could be adapted to patient interview and examination became available in the compound of the Madras Government's main tuberculosis clinic. I became the Unit's first Director, under secondment to the WHO, and had the task of implementing the scientific direction of the project which was the responsibility of the BMRC. This entailed establishing and training a research group and setting up an outpatient clinic and a domiciliary service from scratch as well as supervising the Tuberculosis Chemotherapy

---

* Ranbaxy Robert Koch Oration - 1989.

Abbreviations are listed on pages 209-210.

Correspondence: Prof. Wallace Fox, 28, Mount Ararat Road, Richmond, Surrey TW10 6PG, UK.

Centre's (subsequently named the Tuberculosis Research Centre) (TRC) patients in Tambaram Sanatorium just outside Madras where 100 beds had been put at our disposal. Professor D.A. Mitchison came out to Madras in 1956 for a year and built up the bacteriological and biochemical laboratory, essential for the controlled clinical trials, set up other important research studies and became a long-term consultant and collaborator. I remained in Madras for 5 years and subsequently visited annually until my retirement, but less frequently since.

In 1965, the Centre, which was originally set up as a temporary project, became a permanent unit of the ICMR, with the generous help of the Madras Government, which included making a large and valuable compound available. This enabled the ICMR to expand, and build a major laboratory unit able to undertake research in a wide variety of basic problems, with continued financial support of WHO.

In 1958, the National Tuberculosis Institute (NTI) was started in Bangalore, and was officially opened in 1960 by Pandit Nehru, the then Prime Minister. Its main objectives were 1) to formulate an applicable, acceptable and economically feasible national programme for tuberculosis, 2) to train the necessary manpower to organise and manage the programme, 3) to continue research with emphasis on operational activities to evolve the programme, 4) from the late 1970s, to monitor the National Tuberculosis Programme (NTP).

Thus, there were 2 institutes in South India 220 miles apart, Madras with the remit of the intensive study of chemotherapy and its scientific basis as well as epidemiology, for example the risk of contact infection from domiciliary therapy of index cases and the level of drug resistance in new cases of tuberculosis, and the NTI concentrating essentially on training district teams, the operational problems of programme application and on epidemiology. In between, both geographically and operationally, at Madanapalle in Andhra Pradesh was a missionary group directed by the late Dr. J. Frimodt-Moller, whose main activities were what can best be termed semi-service, supported by the ICMR. He became a close friend and a staunch supporter and admirer of the TRC, a provocative and stimulating member of its project committee, and for a number of years the independent assessor of the Centre's study radiographs, a time consuming commitment.

Soon after the WHO team leader, Dr. Halfdan Mahler, arrived in India in January 1959 to join the NTI. He, Dr. Frimodt-Moller and I agreed we three should aim to meet formally at least 3-monthly and preferably more frequently. In practice however because of the problems and pressures of establishing and running the 2 major institutions and the number of weeks in the year when one or more of us were out of the country or on leave, we only had one such formal meeting by February 1961, when Dr. Mahler returned to Geneva. Looking back over the years, I feel it is a great pity that there have not been more frequent detailed operational and tactical meetings between the staff of the 2 major institutes in addition to the eventual administrative relationships established through the 2 scientific advisory committees. A breakthrough was made when Dr. N.K. Menon who had been the first Indian Director of the Madras Centre became the Director of the NTI and Dr. S.P. Tripathy, then the TRC Director, and I went to Bangalore in 1977 specifically to discuss direct collaboration in a controlled clinical trial of short-course chemotherapy. This was readily agreed by Dr. Menon and the Bangalore participation was in the Lady Willingdon Clinic and the staff members of the 2 units worked side by side and in harmony with the clinic's staff and the research bacteriology was centred in the TRC, ensuring standardised bacteriological tests. The collaboration was a great success (Dr. P. Jagota of the NTI proved a gifted team leader with a special talent for clinical research) but unfortunately it was unexpectedly terminated, for unforeseen administrative reasons which arose in Bangalore, so that the NTI could only contribute a 2-year period of observation of its patients whereas Madras, as usual, completed a 5-year follow-up[2] which in this study was of particular importance. One of the 3 regimens studied was of only 3 months' duration, which I regard as one of the most important regimens ever studied, because of the light it shed on the striking potency of short-course chemotherapy.

(There have, of course, over the years, been other groups who, in the course of their service programme commitments, also conducted valuable investigations, clinical, operational, epidemiological and controlled trials. Those

currently active may well be in a position to make important contributions to the national programme if they evolve along the lines referred to on pages 204-205 and 208-209, that is, their research activities being integrated into an overall national plan.)

My first major conclusion is that I have no doubt that every effort must be made hereinafter to ensure that the 2 institutes (NTI & TRC) work closely together, including resuming collaborative controlled trials and other investigations. This has become even more important for a number of reasons, for example, because of the TRC's direct participation in monitoring and implementing short-course chemotherapy in 18 District Programmes (pages 182-185) and the need to improve training facilities nationally (page 208) and to monitor in special surveys important factors such as drug resistance levels nationally (pages 204-205).

Monitoring District Programmes

The roles of the National Tuberculosis Institute (NTI) and the Madras Tuberculosis Research Centre (TRC) and their interrelationship

1. *The role of the National Tuberculosis Institute (NTI)*

(*a*) The NTI formulated the National Tuberculosis Programme (NTP) and its documentation. (*b*) It produced a series of manuals for members of the District Programme Team (DPT), namely the District Tuberculosis Officer (DTO), the Treatment Organiser, the X-ray technician, the laboratory technician, and the statistical assistant, and also a manual for Peripheral Health Institutions (PHIs) as well as an introduction to District Tuberculosis Programme. Although these valuable manuals are essential for the District Programme Team, they do not cater, in a simple form, for the individual worker in the PHIs, an aspect that has in recent years been a major concern of the Tuberculosis Research Centre, Madras (see below). (*c*) The NTI Newsletter, a duplicated magazine, was introduced in May 1964 and appears quarterly. It is distributed free with a national distribution of about 700 copies including 371 district centres, 30 assistant directors of health services (tuberculosis), and a number of State TB Demonstration Centres, TB hospitals and sanatoria, State TB associations and to over 100 undergraduate and postgraduate medical institutions, and other research groups. It also has an international circulation of over 100. It publishes new and current state of knowledge articles, especially those concerned with control programmes, new concepts and research work, and answers readers' questions and summarises the performance of the NTP. Over many years, I have found it a useful forum and consider that careful thought should be given to its role and widening its scope and circulation. It covers rather different ground from other relevant publications in India such as the Indian Journal of Tuberculosis and Lung India and almost certainly has a different circulation, particularly being aimed at workers concerned with TB control and district programmes. Being free, it reaches a wide audience automatically, so the target groups should be carefully considered and the cost of improving its production and enlarging its circulation would be a valuable investment of Central Government funds. (*d*) The NTI has monitored the National Tuberculosis Programme since 1978. Of the 437 districts of India, 371 (85%) have implemented a District Tuberculosis Programme, each with a District Tuberculosis Centre (DTC). Currently, about 14,000 Peripheral Health Institutions (PHIs) in rural and semi-suburban areas function as microscopy centres, X-ray centres or referral centres. Nagpaul (1989) points out[3] that the 14,000 PHIs then participating represented only 63% of the estimated total of about 22,000 PHIs (on average 60 per district). He stresses the seriousness of the incomplete coverage and utilisation of the PHIs, which he attributes to the distance of access for the surrounding population. The PHIs report monthly to the DTC on case-finding and treatment and each DTC reports to the NTI and the latter in its turn reports to the State and Central Government. The NTI also reports back to the DTC deficiencies observed and the necessary corrective actions. Currently, 15% of the DTCs and 30% of the PHIs do not report on time, if at all, and although the DTC has the responsibility of monitoring the PHIs, by 3-monthly visits, surprisingly, only 50% are being supervised by any visits at all, a major and important deficiency in the National Programme, in addition to the 66 districts which have not implemented a District Programme at all. These are alarming observations, to say the least.

Table 1. *Case-finding calculated in thousands according to type of case in the National Tuberculosis Programme, 1978-1987 (Nagpaul, 1989)*[3]

	Years									
	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987
Sputum positives	188	185	174	189	219	256	262	259	281	286
Suspect cases*	473	508	474	521	638	747	764	798	904	1000
Extra-pulmonary	61	58	56	58	66	69	77	76	95	114
Total	722	751	704	768	923	1072	1103	1133	1380	1400

*All active cases of pulmonary disease, not confirmed bacteriologically

Nagpaul[3] presents overall figures on case finding, calculated from the number of cases reported annually from the districts with a DTP, and estimates based on averages for the districts not reporting (Table 1). There are increased numbers from 1982, the first full year of the 20 point national programme, which included tuberculosis as a priority disease, but the trend is least marked for the sputum-positive patients, the most important target group. Nagpaul (1989) calculated[3] the total sputum-positive cases per 100,000 was 29 in 1978, 31 in 1982, 36 in 1983, 1984 and 1985, 37 in 1986 and 1987, and 38 in 1988.

There is evidence that over the recent decade the PHIs are making a larger contribution to case-finding (Table 2), and if this is really the case it is of considerable importance. A puzzling finding, however, is the decline in the proportion of new specimens examined that are positive for tubercle bacilli to the figure of 4.7%, which has halved since 1982. It might be that more specimens are being collected from symptomatic patients including a high proportion who are smear-negative but culture-positive (as occurred in a survey in Kenya[4,5] or of non-tuberculous conditions (possibly under the pressure of meeting set targets, a fashionable but, in my view, questionable approach in operational conditions without careful monitoring), or it may be related to less satisfactory specimens being obtained, or inefficient smear preparation or examination, or even all three. It demonstrates the importance of monitoring at a field level, and although this is a District and State responsibility, in view of the evidence that they often neglect basic tasks, the need for a representative national sample of PHIs whose case-finding is efficiently investigated is self-evident. The decline to 11.5% in the average

Table 2. *Average bacteriological workload and new positive patients found in the District Tuberculosis Centre (DTC) and the Peripheral Health Institutions (PHIs) (modified and contracted from Nagpaul, 1989)*[3]

Average	1978*			1982*			1988*		
	District tuberculosis centre	Peripheral health institutions		District tuberculosis centre	Peripheral health institutions		District tuberculosis centre	Peripheral health institutions	
		No.	% of total**		No.	% of total		No.	% of total
New outpatients sputum examined	2,859	1,575	35.5	2,895	2,690	48.2	3,359	8,489	71.6
New sputum positive cases	415	188	31.2	375	245	29.5	385	395	50.8
% of new patients positive	14.5	11.9	-	13.0	9.1	-	11.5	4.7	-

*Based on 313 districts in 1978, 353 in 1982 and 371 in 1988
**Total = amalgamated numbers for the DTC and the PHIs

proportion of positive cases in the DTCs equally requires detailed investigation.

It may be mentioned *en passant* that India has a national rule for sputum examination which is exceptional. It is that any patient with a spontaneous complaint of cough for 2 or more weeks should have sputum examined by smear for tubercle bacilli, in contrast to the widely used durations of 4 or more weeks, or a month or more. This decision was based on a careful study, but in a single district of south India in 1966.[6,7] The implications on the work load of smear examination are considerable and it would be well worth while to repeat such a survey on a wider scale across the country. If confirmed, it raises the question of whether the widely used "month" rule should not be reviewed in other countries. If, however, the "month" rule proves to be more appropriate to India the number of specimens to be examined would be reduced by at least a third. The balance between workload and case yield is an important issue to investigate and cost operationally.[4,5] It would also be a valuable opportunity to investigate the gain by doing cultures as well and also relate them to the duration of cough.

Until 1986 only conventional regimens (Table 3) have been used under the NTP for all categories of patients (Table 1). The recommendation is an 18 months' duration, with the aim that all patients should receive or collect at least a 12-month supply in this period. Currently, the great majority of patients, including all those not bacteriologically confirmed, are still recommended treatment with conventional regimens. Also, of those patients bacteriologically confirmed in districts where short-course chemotherapy has been introduced, the evidence from the TRC's 18 pilot districts is that a high proportion still do not receive short-course chemotherapy, and that they too are still on the conventional regimens (Table 5).

Table 3. *Current conventional regimens for District Programmes (1989) and the cost of a 12-month supply*

Regimen	Cost (rupees) 12-months	Number of doses 12-months
TH	73	365
PH	774	365
EH	285	365
S_2H_2	331	104
2STH/TH	273	365
2SPH/PH	857	365
2SEH/EH	450	365
2SH/S_2H_2	488	148

T = thiacetazone, H = isoniazid, P = PAS, E = ethambutol, S = streptomycin

The number preceding the drugs is the number of months of their duration

For intermittent regimens, the number of doses of drugs a week is shown by the suffix number

The aim remains an 18-month duration and supply. The increase in the number of doses and the extra cost can be calculated from Table 8.

The NTI is also monitoring the introduction of the short-course chemotherapy programme (Table 4). In addition to the 18 districts in which the TRC is involved (see below), short-course chemotherapy has been introduced into the National Programme for the treatment of smear-positive patients aged 15 or more (Table 4), *irrespective of a history of previous chemotherapy*, that is, it includes chronic failure patients. This is, however, a policy which could lead to the creation of strains resistant to rifampicin, to rifampicin plus isoniazid, and to pyrazinamide-resistant strains also, a very dangerous situation, and it is important to know if this proves to be the case, and the speed with which it occurs in the patient population. This decision was perhaps taken (1) in recognition of the difficulty of obtaining an accurate history of previous chemotherapy, especially in small peripheral health units, (2) because some patients with a history of previous chemotherapy may have been given (or taken) too little medicament for their strain of organism

Table 4. *Current (1989) short-course regimens in District Programme conditions in India*

Monitoring centre	Regimen	Cost (rupees)	Number of doses
	$2S_2H_2R_2Z_2/4H_2R_2$	240	52
NTI	2EHRZ/6EH	485	240
Bangalore	2EHRZ/6TH	345	240
	1) $2H_2R_2Z_2/4H_2R_2$	190	52
TRC	2) 2HRZ/6TH	295	240
Madras	3) 2HRZ/$4H_2R_2$	340	94

R = rifampicin, Z = pyrazinamide
Also see footnotes to Table 3.

Table 5. *Year by year comparison of the percentage of smear-positive patients put onto short-course chemotherapy in each of the 18 districts monitored by the TRC (Prabhakar, personal communication)*

District	Policy*	Percentage of patients put on short-course chemotherapy**				
		1985	1986	1987	1988	1989
North Arcot		66	61	68	55	51
Puri		88	64	79	67	68
Baroda	A	64	49	44	32	59
Thane		72	64	64	72	82
Ujjain		46	43	47	44	48
Dehra Dun		43	49	86	85	89
Karnal		36	38	31	50	73
Kanpur		26	12	18	36	30
Nagpur		16	32	33	64	53
Rajkot	B	75	59	51	53	68
Raichur		27	30	39	54	76
Sagar		44	37	79	87	91
Pondicherry		45	52	48	50	36
Vidisha		82	80	76	81	70
Aurangabad	C	39	46	48	33	76
Varanasi		58	64	62	61	81
Sabarkantha		60	60	59	70	83
West Godavari		24	30	40	44	80

* Defined on page 182

** 2 Districts had started the programme in 1983 and 8 in 1984

to have acquired drug resistance, or (3) in the hope that at least some patients, whether with primary or acquired drug resistance, would still be cured. This may still be the case, dependent on the pattern of drug resistance, the regimen of short-course chemotherapy and the patient's compliance in taking it. In my view, as a minimum, each District Tuberculosis Centre should make strenuous efforts to obtain from every patient brought under treatment an accurate history of previous chemotherapy and its details so that some information on the proportion of patients in the district who give a history of previous chemotherapy, its duration and the regimen previously received is obtained across the country. The NTI has experience of districts whose reports it regards as accurate and this group could be of special value.

The rate of admission of districts to the short-course programme has been very rapid : 1986-26, 1987-75, 1988-75, 1989-18. By October 1989, 194 districts were using short-course chemotherapy and the target set for April 1990, the end of the seventh 5-year plan, was 275 (Chaudhuri, personal communication). The three regimens of the National Programme (Table 4) can be modified to some extent. One is a fully intermittent twice-weekly regimen for 6 months. If streptomycin is not available or adverse reactions to it occur, ethambutol can be used instead. The other 2 have a 4-drug daily phase of 2 months, followed either by 6 months of thiacetazone plus isoniazid daily or, if the patient cannot tolerate the latter, ethambutol plus isoniazid. Streptomycin can be given instead of ethambutol in the first 2 months if the patient is prepared to attend daily, otherwise the patient is given a supply of oral medicament *every 15 days* in the first 2 months and then a monthly supply thereafter, to self-administer at home.

The developing countries face a dilemma. Because of the problem of initial drug resistance in many, the total absence of sensitivity tests for epidemiological surveys or patient assessment, limited culture facilities at best, and the difficulty of obtaining an accurate history of previous chemotherapy it could be argued that ideally multiple drugs, up to 5, including, wherever

possible, streptomycin and either thiacetazone or ethambutol, should be given in the initial intensive phase for all smear-positive patients. This is a paradoxical situation for countries with limited funds and so many other basic resources that need strengthening, e.g. bacteriology. It highlights the problem of the chemotherapy of tuberculosis in developing countries, the apportionment of funds to the different components of the programme and also the difficulty of deciding what are the most appropriate short-course regimens to introduce, especially because of a need to avoid producing rifampicin resistance in chronic failure patients, with drug-resistant strains already.

At a visit to the NTI which I paid with Dr. Prabhakar in November 1989 we were shown a summary assessment made by the NTI, one of its standard responsibilities. It covered 2 quarterly reports of the performance of the District Tuberculosis Programmes of a major State with about 30 Districts. The NTI assessment clearly set out deficiencies in the implementation of the programme and in its reporting, commented on case-finding and treatment, and named 6 districts where the majority of the PHIs had not been visited at all. It is also noteworthy that in the 15 districts which had reported on the staffing position, only 2 had trained DTOs *in situ* and in 5 districts the statistical assistants were not trained and in 4 more the post was vacant, these despite the training programmes of the NTI (see below). These are serious problems that can obviously greatly undermine the efficiency of the State's programme, whatever regimens are used. The value of the NTI reports is unquestionable in highlighting major deficiencies for a State prepared to take remedial action. A copy of the State report also goes to New Delhi as does a quarterly detailed summary report for all the districts of India that returned a report for the quarter in question, so that the Central Government is informed too.

The NTI has had a long-standing problem of recruitment of senior key scientific staff members. In March 1989 of 17 such posts, there were vacancies for a sociologist, a bacteriologist, 2 TB specialists, a senior statistical officer and an epidemiologist. (The sociologist's post had been vacant for 3 years). Further, over quite a period of time, some of the key posts have, of necessity, been filled by encumbents approaching retirement whose background was from other disciplines, or administration. (These posts are advertised by the Central Government and the NTI is not represented on the Central Government selection committee.) The staff shortages obviously limit the amount of field work and visiting that the NTI can undertake as well as its operational research activities and it has had to concentrate primarily on its large and important commitment to training, which is very relevant. The total number of personnel (which constitute a District Programme Team) trained up to 1989 is (*a*) medical officers 1104, (*b*) health visitors/treatment organisers 1107, (*c*) laboratory technicians 866, (*d*) radiographic technicians 771, (*e*) statistical assistants 793, (*f*) BCG technicians/team leader 361 (this category was deleted from team training for the last 10 years). The NTI does its field training not only in the Tumkur district but nearby districts of other States. The NTI currently runs regular training courses of 10-week duration twice a year including, in one of them, international candidates sponsored through WHO. It also conducts educational activities as seminar/workshops for District level and State level administrators, and professors of medicine, chest diseases, tuberculosis and community medicine, many coming from medical colleges. Undergraduate and postgraduates in medicine from nearby visit the NTI to learn about it as well as the national tuberculosis programme. Clearly, the reason a State is short of DTOs and statistical assistants lies within the State itself, not the lack of NTI training courses.

This current limitation of the activities of the NTI is a serious problem which must be overcome. Operational research and field supervision was a major activity for many years, and is essential for the evolution of the National Programme in the light of field experience. Despite the difficulties, the staff still undertake some valuable operational research projects and controlled trials, a recent example being reference(8) and related reports, and publish review articles, as well as the NTI Newsletter.

Thus, through the NTI, a framework exists to identify a number of problems and deficiencies but the patent weakness is the lack of means and an organisational structure with which to take remedial measures. There is an obvious need for the most careful consideration being given to the creation of an effective and adequately staffed

agency, with the authority to guide and assist the States in improving their District Programmes' performances.

The question arises whether, in addition to the training courses centred on the NTI, a mobile training team attached to the NTI should be established. It could visit a State which has declared a serious long-term intent and commitment to upgrading its tuberculosis control programme and run a training course for a large number of staff of all cadres, including administrators, team leaders and medical officers, treatment organisers, X-ray and laboratory technicians. Key staff from every or most districts in the State could be trained and university teaching staff too. There would thus be a concentrated effort to upgrade and improve knowledge and organisational and evaluatory skills and this might well be the most cost-effective way of training substantial numbers of the main cadres and introduce modern regimens most effectively. This approach could be supported by a well orchestrated statewide publicity campaign including the widescale use of the media and aimed at community leaders and the general public, so that a large and concerted effort could be mobilised. The health service and community's expectations and demands would also receive a stimulus and strengthening the infrastructure would be an inherent component. The team could pay further visits of shorter durations, as indicated. This would offer much wider benefits than the NTI training or retraining in Bangalore of a limited number of individuals from a number of different States. In my view, this may well be the way forward, and might be tried, in the first instance, in a single State to work out the logistics of such an approach, and move into a second State as soon as a broad *modus operandi* is established.

Since writing this section I have just received the April 1990 issue of the Indian Journal of Tuberculosis. An editorial[9] reports an important project, the "Expanded programme of Health Education and community involvement in the National Tuberculosis Programme", assisted by USAID which started in July 1987 and comes to a formal end in September 1990. The TB Association of India and the State Associations, collaborated with the Central and State Governments. The project aimed to cover 250 districts in 23 States and 2 Union Territories, a highly ambitious target! The editorial summarises errors and the lack of a proper evaluation of the components, a conclusion reached by the National Institute of Health and Family Welfare. Such projects are, in my view, operating with too small an input and for too short a time and run the risk of gradually dying out unless built into a much broader based, better supported and long-term scheme, such as I have proposed above, but full advantage should be taken of the lessons learned from this project.

2. *The role of the Tuberculosis Research Centre (TRC)*

In 1983 the TRC was asked to monitor the working of short-course chemotherapy in 18 districts, 3 groups of 6, studying 3 different *policies* (termed A, B and C) based on 3 *regimens* in order to document the applicability and acceptability of short-course regimens under field conditions. The eligible patients are sputum smear-positive patients, aged 15 years or more *with no history of previous chemotherapy for tuberculosis or for no longer than 2 months.* Three short-course regimens are being studied (Table 4). All the doses of Regimen 1, $2H_2R_2Z_2/4H_2R_2$, are administered at a health facility under direct supervision of the staff. For the daily regimen 2HRZ/6TH, Regimen 2, the patient attends every 15 days to collect a supply to self-administer at home, and Regimen 3, $2HRZ/4H_2R_2$, intermittent in the continuation phase, entails, for the first 2 months, collection by the patient every 15 days for self-administration and then twice-weekly attendance for the supervised administration. The 3 *policies* being studied are :

Policy A in which the patient is offered Regimen 1 but has a choice of Regimen 2, as an alternative.

Policy B is Regimen 2 with no alternative short-course choice.

Policy C is Regimen 3 with Regimen 2 as an alternative.

(It is currently not the policy to retreat with short-course chemotherapy if the patient relapses, a decision which will need to be considered as part of a general review of national policies and priorities.) In 1987, in the light of preliminary findings, the TRC's remit was extended to concentrate on improving the functioning and efficiency of these 18 districts' programmes and to undertake relevant field

studies. The original remit was demanding of time and this extended remit is even more so.

Table 5 shows the percentage of smear-positive patients put on short-course chemotherapy in the 18 districts monitored by the TRC. Even in 1989 the proportions are surprisingly low. This means that conventional regimens are still widely used. There are many reasons why sputum-positive patients may not be put on short-course chemotherapy. The NTI in its duplicated Guidelines for the introduction of short-course chemotherapy in the DTP lists "Living too far off, too old or sick, clinic hours not convenient, no transport facilities, travel too expensive, likely to migrate, as well as "any other reasons (not specified above)". In addition it is clear that there is not the drive or the will to make such a switch to short-course chemotherapy in many PHIs (see below). A detailed analysis of every PHI in each of the 18 districts could be very informative about the characteristics and reasons that in the same district some PHIs are and others are not involved in short-course chemotherapy after the passage of several years and despite substantial educational efforts and stimulus and interest of the TRC. The TRC has detailed computer printouts for its districts and the PHIs already, which may well be very informative on detailed analysis.

A second worrying feature is a summary of a July 1986 to June 1987 cohort analysis of short-course chemotherapy in the A, B and C Districts (Prabhakar, personal communication). This clearly demonstrates the high drop-out rate in the early months of treatment with the pilot regimens. Thus, of patients (average number in the cohort 425) in 4 Policy A districts who had elected to attend for twice-weekly supervised chemotherapy (see Table 4), 24% did not complete a total of even 1 month's treatment before terminating their chemotherapy, increasing to a total of 37% who did not complete 2 months' doses, and that in all 53% did not complete at least 80% of the due doses (a percentage widely regarded in India as the minimum therapeutically satisfactory quantity). Of 4 Policy C districts, in which patients (average number 263) who agreed to accept the regimen of daily self-administered chemotherapy for 2 months (this entailed only once a fortnight attendance to collect a drug supply) followed by twice-weekly attendance at a health facility for 4 months (Table 4) the corresponding 3 proportions were 12%, 26% and 49%. Of 13 districts (A, B and C) (average number of patients 425), the patients on the 4 A and 4 C Policies who had opted to have the daily 8 months self-administered chemotherapy (Table 4) instead of an intermittent regimen and 5 B Policy districts where it was the only regimen offered, the corresponding proportions were 18%, 28% and 48%.

Thus it is evident that a high proportion of patients in the 18 pilot district programmes do not like the current fully or partially intermittent 6-months regimens they are offered (regimen 1 and regimen 3) almost certainly because of the number of attendances entailed, and that they prefer to chose a daily 8-month regimen which entails fewer attendances, because they collect 15-day supplies to self-administer at home. Even so, there is still a high drop-out rate both early and later on with all three regimens. This is evidence that shorter duration and fewer dose regimens in themselves are not adequate, and that it is essential to improve the organisational framework and infrastructure of the programme and with them patient compliance to ensure major improvements in the therapeutic results.

A third deficiency is that in 1989 not all of the PHIs in the 18 districts had even implemented a District Tuberculosis Programme. Thus, 12 of the 18 districts had done so in 100% of the PHIs, 4 in 90-99% and 2 in only 70-79%.

A fourth deficiency is, considering the PHIs in the districts that *had* implemented the DTP, only 9 districts had introduced short-course chemotherapy in all of the PHIs, 2 in 90-99%, 4 in 70-89% and 3 in 50-69% of the PHIs.

Yet another deficiency is the average "completion rates", that is patients receiving or collecting 80% or more of the prescribed chemotherapy, for the 3 policies A, B and C, which have been studied for 4 cohorts. The cohorts are from the inception of short-course chemotherapy to October 1985, November 1985 to June 1986, July 1986 to June 1987, and July 1987 to June 1988.

The averages for the 4 cohorts for each of the 3 policies were as follows :

Policy A 46%, 57%, 51% and 54%

Policy B 48%, 42%, 52% and 48%

Policy C 52%, 46%, 52% and 51%

These figures are disappointing and a more detailed review of individual districts gives no grounds for encouragement. Thus, comparing the completion rates for cohorts 3 and 4 show for the latter an increase of 5% or above in 5 districts, a decrease of 5% or above, also in 5 districts, and a change of less than 5% in either direction in 8.

Thus, it is clear that there are a series of levels where deficiencies exist and despite the efforts and encouragement of the TRC, they remain formidable. I do not believe that these are early days and that in a few years time the situation will have improved substantially. To me this is a cause for anxiety about what will happen under the National Tuberculosis Programme where monitoring and the substantial technical, scientific and educational input of the TRC will not be forthcoming. There is no possibility of any mechanism by which a vast input of effort and expertise and enthusiasm can be mobilised for the districts already using short-course chemotherapy which by now must be over 200, or for the districts that will come in within the next few years unless a radical policy change takes place. One such radical change would be the new State approach I have suggested (pages 181-182). Unfortunately, the National 20-point Plan of 1981, which specifically included tuberculosis, led to some minor initiatives that rapidly faded, and the opportunity presented by the public endorsement of the Prime Minister, Indira Gandhi, was never energetically exploited.[10]

In November 1989 at my visit to the TRC, I interrogated in detail Dr. Prabhakar and his senior colleagues to clarify exactly how they monitored the 18 districts. Briefly, a TRC visiting team consists of a medically qualified research officer, a bacteriologist, a statistician and a social worker and Dr. Prabhakar also pays visits. Thirty five visits were made in 1988. A single field team visiting at any one time is the aim and 2 teams visiting, strains the TRC's resources. At each district visit 2 groups of local medical officers and 2 of paramedicals, both laboratory and treatment organisers, are involved in carefully planned lectures and educational seminars. This is in addition to the TRC staff visiting the DTC, discussing with its team a TRC computer print out which, as well as giving an overall summary, includes a detailed tabulation of the performance of every PHI. A visit takes, on an average, 10 days and travelling expenses are considerable since the study districts are in all parts of the country.

The TRC has had to prepare a series of policy and instruction documents for its own staff to use so that its teams systematically cover the necessary issues at visits and obtain standardised information. Also of particular interest to me are 3 publications prepared (and revised in the light of experience) for field workers in the District Programmes, one dealing with "Treatment Aspects in a District TB Programme", a second summarising "The District Tuberculosis Programme Salient Features" and a third "Instructions to Laboratory Technicians on Sputum Microscopy". They are simple, and are still being improved (professional expertise on layout and presentation would now be advantageous) and of value as an *aide memoire* for individual field workers, and are especially necessary in the smaller institutions where the numbers of possible and actual cases of tuberculosis seen are inevitably few. Their object is very different from the detailed manuals prepared for the members of the District Tuberculosis Team by the NTI.

It is patently unnecessary for every district or State to produce its own set of simple instruction documents and the aim should, in my view, be to produce a model set primarily by the collaborative efforts of the TRC and the NTI, since both have direct and overlapping national responsibilities. They too should seek advice from a limited number of knowledgeable critics from other parts of the country to broaden the input of experience. Where there are local conditions in individual States or districts which require modifications to the model set, these can, of course, be introduced locally. Ideally, they would be discussed with the NTI/TRC team to see if they are really necessary, and, if of general interest, can be reported in the NTI Newsletter. It is important to consider the use on a substantial scale of improved simple manuals and, in particular, to evaluate under field conditions what they achieve, before they are introduced nationally.

I have urged the TRC to publish its approach to supervisory visits to districts, explaining its procedures and also to document the cost in time, effort and finance of such visits, with the current objectives, or if the objectives were limited to monitoring activities or operational research. Obviously, there are financial and staff constraints on such visits and this is why it is

important that they be costed. With 437 districts in India the primary aim must be to raise the *average* standard as rapidly and economically as possible, not just to concentrate on producing a limited number of outstandingly efficient districts. These will emerge in any case, when a district team, especially its leader, is of high quality and receives full support from the State Director of Medical and Health Services.

It is clear that if every DTO and his trained colleagues were paragons of efficiency, energy and enthusiasm, the TRC's role at a field level could be limited to operational research and epidemiological and sociological studies, but this is not the case and, realistically, is unlikely ever to be so. The NTI's role would also be much easier to perform if every district reported to it, and did so punctually, providing all the stipulated information, and the PHIs were visited regularly by the DTOs, as is intended in the National Programme.

The NTI regards the information on short-course chemotherapy it currently receives as unsatisfactory. In part, this is because the district statistical assistants have not been trained in the preparation of the new reports and currently the details required are complicated for the PHIs to complete (Chaudhuri, personal communication). The reporting instructions and forms adopted by the TRC and the NTI also had differences which have created problems for both groups and these are in the process of being ironed out. The TRC has the great advantage of a well trained statistical assistant from its own staff, working in 16 of its 18 pilot districts. A similar NTI appointment (and so responsible to the NTI) for each district should be considered, and tried out on a pilot scale.

It will also be appreciated that a sudden switch from conventional chemotherapy, even in a district programme, and much more so in a whole State, is not possible because, in addition to the provision of the new drugs and adequate instructions on their use and introduction, the staff and patients, the administration and community leaders all have to understand and accept the new policy. Inevitably, conventional chemotherapy regimens remain among the list of options for smear-positive pulmonary disease, and are to be used, according to current policy, for all smear-negative disease. The attraction of conventional duration regimens to the patients, especially if oral, when monthly supplies are given from the outset, is the fewer attendances they need to make.

I predicted in 1983[10] that the introduction of short-course chemotherapy in India would inevitably mean that data would need to be collected for both conventional and short-course regimens for a number of years, and the additional recording and its complexity would put extra responsibility and strain on staff at every level, and especially in the district programmes and this is indeed the case. When short-course (6-month) chemotherapy was declared the National Policy in Algeria it took 3 years to introduce despite a population of approximately only 20 million, and adequate funds to purchase all the necessary drugs for the new national short-course regimen from the outset. In Tanzania, a country with a slightly larger population, despite a declaration of a National Commitment to Tuberculosis Control in the mid-1970s (and other advantages), and the implementation of the programme by the International Union Against Tuberculosis from 1978 and several years building up a framework based on standard duration chemotherapy, it still took (Styblo, personal communication) 4 years to introduce short-course chemotherapy to all 20 Regions of the country.

It is now essential to review what information is being collected about district programmes both by the NTI and the TRC and whether it is in the best form and whether indeed it is all necessary. It may be possible to design reporting forms with one section with information which must be provided by every district and on a second section information which, though not obligatory, would be valuable. Further, the issue arises on the relative emphasis in data collection to be given to bacteriologically confirmed and unconfirmed cases, as well as to short-course and conventional chemotherapy, and new and retreatment cases.

There is now an urgent need for a detailed analysis of the data collected by the TRC with a full presentation of the findings and as full an explanation of them as possible and an assessment of their implications. Careful consideration needs to be given to the question of which of the regimens currently studied should be persevered with. My own view is that the evidence of unacceptability on a wide scale in District Programmes is already clear for the fully

supervised intermittent regimen. What is not clear is for what section of the patients it is suitable. Has it, for example, been acceptable in the urban areas, suburban areas, and in areas close to PHIs? Are there any other identifiable factors that are associated with improved or impaired cooperation? The TRC may well have answers to the important issues from the data already collected. The TRC's annual reports and the publication of conference presentations give interesting yet tantalizing tabulations. Inevitably the tables and text are inadequate to give a balanced and interpretable picture of the achievements and failures of District Programmes and how best to proceed with or modify the approaches.

Tables 3 and 4 show the cost and the number of doses in each regimen, whether conventional or short-course. I think of these regimens in terms of the number of "units of patient compliance" each regimen requires if the patient is to receive every dose. For example, the units of compliance for a fully self-administered daily oral regimen are a small number of attendances to collect drug supplies, but a large number of doses for the patient to swallow to complete the course. In contrast, at the other extreme, for a fully supervised intermittent regimen the number of attendances is relatively high, but the number of doses, all taken under full supervision is small. This approach helps us to see current and new regimens in terms that are relevant both to the patient's convenience (and so compliance) and the workload of the treatment services.

Among the 18 pilot districts under the TRC are 2, namely, North Arcot and Pondicherry, geographically convenient to Madras, in which the TRC has been monitoring the programme intensively, including (1) the efficiency of the equipment, radiographic and microscopy, (2) the bacteriology, pre-treatment, at the end of chemotherapy, and at follow-up, and (3) undertaking operational and sociological studies.

On the laboratory side it obtains pre-treatment smears, cultures and sensitivity tests, which latter need to be related to the history of previous chemotherapy and to failure during chemotherapy and bacteriological relapse when these events occur, and the drug sensitivity of the strains at the time, as well as to the regimen the patient received. Thus, it is collecting invaluable information on the levels of drug resistance in the patients on presentation for treatment, and changes in the levels over a period of time and on the emergence of drug resistance in individual patients. Again, a detailed analysis and a full presentation and discussion of the findings is urgently required.

Clearly, these 2 districts might be quite unrepresentative of the situation around the country, and there is a need for a network of centres able to monitor drug resistance along similar lines (pages 204, 205).

Operational studies by the NTI and TRC

The TRC, like the NTI, has also undertaken in its recent remit operational studies relevant to District Programmes. For example, it has studied the use of the address cards system in North Arcot District to see whether it is successful in obtaining accurate patient addresses in small towns and villages, as it was in large towns of Tamil Nadu.[11] It has also studied policies of motivation in 2 different treatment centres under field conditions, an extension of an approach that had previously been studied in the TRC patients,[12] as well as by the NTI in the Bangalore area.[13] Like the NTI it has also studied patient awareness of symptoms and their utilisation of the available resources of primary health care under District Programme conditions, studies that can produce surprising and unexpected information. For example, in Hong Kong a collaborative survey with the BMRC conclusively demonstrated the need for better education of the general public[14] about tuberculosis and the existence of a free Government service. Two subsequent surveys[15] showed how difficult it is to run a *successful* case-finding campaign using the mass media (television, the newspapers and posters), as assessed by studying whether the number of symptomatics attending and cases of tuberculosis diagnosed before, during and after the publicity campaigns were increased.

Fully Supervised Intermittent Chemotherapy

I have, for well over 20 years, advocated the importance *in urban areas of India* of organising fully supervised intermittent chemotherapy in a way convenient to the patient so as to improve compliance. I suggested that the administration of each dose should be near the patient's home or place of work or en route between them, whichever was most convenient for the individual patient as in studies in Czechoslovakia[16] and

Britain.[17] Fully supervised intermittency, especially in short-course regimens is now receiving emphasis both in the Indian National Programme as well as in the TRC's Pilot Districts and so I intend to repeat yet again largely verbatim but also with some expansion what I wrote in 1984, using the same data I had obtained for the year 1983 for Madras City.[10]

In 1983, the possible sources of supervised chemotherapy in Madras City were (and still are) numerous. Madras City had a population of 3.3 million and a geographical area of 169 sq km. The Madras Corporation had 69 dispensaries as well as 40 maternal and child welfare clinics with enough space and facilities to organise with safety fully supervised intermittent chemotherapy for tuberculosis, and, if need be, to give streptomycin injections. There were 14 State hospitals, 4 Central Government hospitals and 10 dispensaries, 2 Employees' State Insurance hospitals and 31 dispensaries, 20 voluntary organisations (including missionary hospitals), 20 Service Clubs clinics, including Rotary and Lions, 15 Jain Medical Relief centres, and some 3,000 general practitioners.

If it were possible for the purpose of full supervision of tuberculosis chemotherapy, to break down in Madras City the artificial administrative divisions between the units under the Corporation, State, Central Government, Employees' State Insurance Scheme and the various voluntary agencies, then it could be made much more convenient for patients to attend nearby facilities for supervised chemotherapy. Recommendations have been made in editorials in the Indian Journal of Tuberculosis in 1981[18,19] that general practitioners too could be involved in the programme and, provided they keep suitable records, should have free X-ray and bacteriological facilities as well as free antituberculosis drug supplies. It does seem to me that the medical profession should really make strenuous efforts to set up in one or more cities, both large and small (why not including Madras?) an organisation that cuts across artificial administrative barriers between different agencies. If this were achieved it could lead to a substantial proportion of patients in urban India being conveniently and more effectively treated in this way. (The overall management would remain the responsibility of those with the necessary skills and facilities.) There is no doubt that the effectiveness of intermittent regimens, both of conventional duration and short-course, depends on their acceptance by the patients, which in its turn depends on the efficiency and flexibility of the organisation of such regimens. There is no inherent reason why the same approach might not be tried in small towns. In fact, an appropriate and flexible exploration of what proportion of patients could have convenient access to intermittent chemotherapy in a District Programme has yet to be undertaken. The detailed analysis of the accumulated data obtained by the TRC might, in fact, give pointers for further exploration. Also, it must always be remembered that if an efficient primary health care network does come into existence this might radically influence the situation.

Stead and his colleagues in the USA[20] successfully used short-course chemotherapy *unsupervised* twice-weekly intermittent for most of its duration and in subsequent studies, but this depends on patient self-administration, and lacks the assurance provided by full supervision of every dose of intermittent chemotherapy.

Finally, the importance of voluntary agencies interfacing with official agencies cannot be overstressed and this again is an area where concerted efforts are necessary. The need to educate and involve the general practitioners who represent such a large sector of the tuberculosis treatment services and are often the first point of contact with the patient is another important priority. The TB Association of India had done this on an inevitably limited scale because of financial constraints (Pamra, personal communication), but what is needed is a national implementable plan. The involvement and goodwill of practitioners of indigenous systems of medicine could also make a valuable contribution, and they must not be overlooked or dismissed without searching consideration of their role in the community and what contribution they might make to the National Tuberculosis Programme.

New Approaches to Patient Compliance

(A) Background

Obtaining continued patient compliance in long-term therapy for tuberculosis after the rapid disappearance of their symptoms and early return to their normal state of health is a universal

problem. In 1956 we developed in the then Tuberculosis Chemotherapy Centre, Madras, a coordinated approach to patients under ambulatory domiciliary treatment for pulmonary tuberculosis. This included (1) the involvement of the family as well as the patient during the pre-treatment diagnosis and assessment period, (2) frequently repeating during therapy the need to take the medicaments regularly and emphasizing the family's or a neighbour's role in supervision, (3) a policy of restricting the medication to antituberculosis chemotherapy whenever possible, (4) surprise visits to the home to (*a*) check the patient's stock of pills and (*b*) to collect a urine specimen to test for antituberculosis drugs, and (5) taking speedy absconder action if a patient failed to attend when due.* It was, in fact, the continuing problems of patient compliance despite their urban domicile, which led us to explore fully supervised intermittent chemotherapy in Madras which I had already come to realise by 1958 might be an alternative approach in urban conditions and for which evidence of possible effectiveness subsequently arose from studies in the Centre of the serum profiles in patients on isoniazid.[21] The *in vitro* and *in vivo* studies of Mitchison and his colleagues have explained the underlying mechanisms and the role and limitations of individual drugs.[22] Two further advantages of intermittent chemotherapy were the reduction in drug costs (an important issue) and the reduced risk of drug toxicity, provided appropriate dose sizes and rhythms were used. I had always visualised full supervision as organisable in urban areas for patients with reasonably convenient access to the treatment services and it was in fact the preferred regimen by both patients and staff in a programme involving all new patients in a large area of Czechoslovakia with substantial urban *and rural* populations set up as a collaborative investigation between the BMRC and Dr Polansky's group.[16] Nevertheless I had not regarded full supervision as suitable for rural areas in developing countries except for patients near to treatment facilities, or until an effective primary health care infrastructure had been set up or existed (as was virtually the way supervision was organised in the Czechoslovakian study) and administrative problems such as whether peripheral health staff could distribute or supervise antituberculosis chemotherapy were resolved. For this reason I had regarded daily self-administered chemotherapy as the only practicable policy for *widescale* rural use in India, supervised wherever possible by the family or by local responsible community members. The position has, however, changed and I present in section C a further suggestion which I regard as being of substantial potential importance, not least because it opens up new fields of laboratory research *in vitro* and *in vivo* and in controlled trials in patients, but, in due course, hopefully, in operational studies under service programme conditions also.

I should add that it was the patient compliance problem which had led us in the BMRC to explore both short-course chemotherapy and then intermittency combined with short-course chemotherapy studying regimens based on isoniazid and rifampicin. Also, pyrazinamide was reintroduced into primary chemotherapy in the very first study which was conducted with our collaborators in East Africa.[23,24] This was a study of 4 daily 6-month regimens, streptomycin plus isoniazid, streptomycin plus isoniazid plus rifampicin, streptomycin plus isoniazid plus pyrazinamide, streptomycin plus isoniazid plus thiacetazone, compared with, as a control, a standard 12-month regimen of streptomycin, thiacetazone and isoniazid for 2 months followed by thiacetazone plus isoniazid. The culture negativity rate at 2 months was significantly higher for the rifampicin and pyrazinamide regimens than for the thiacetazone and 2-drug 6-month regimens, and the relapse rates were also strikingly lower, 3% and 8% respectively, compared with 22% for the thiacetazone and 29% for the 2-drug combination (the latter difference being statistically non-significant).

(B) New formulations in the field of leprosy and tuberculosis

Leprosy

In recent years, stimulated by the

* For every patient admitted to treatment a full list of addresses was obtained, namely 1) the patient's home address, 2) the addresses of his relatives and friends in Madras city, and 3) how often he visited them, 4) if employed, the place of work, 5) if children were at school, its address, 6) the address of his native place. If a patient failed to attend and the home was locked and the neighbours did not know where the patient or the family was, a systematic approach to the above alternatives was made until the patient was traced. (Adequate transport and devoted trained home visitors for this purpose were available.)

developments with the contraceptive pill, an increasing number of medicaments are packed commercially in "bubble" or "calendar" packs with a day's, week's, fortnight's or month's supply. In the field of leprosy this approach has also been adopted in large-scale pilot investigations. Four-week calendar packs have been produced for paucibacillary and for multibacillary (Fig. 1) patients using WHO drug and dosage recommendations, in Danish International Development Agency-assisted projects in 4 hyperendemic districts in India, namely in Orissa, in Tamil Nadu, and 2 in Madhya Pradesh. In the Philippines a project supported by the Sasakawa Memorial Health Foundation and WHO has been implemented since 1985 and recently in Thailand the government has introduced blister packs in a few provinces with both specialised and semi-integrated leprosy control programmes. The leprosy mission of South Africa has in Transkei produced low technology packs which have been used successfully for several years.[25] Such preparations lend themselves to important operational studies designed to assess whether, and, if so, how much greater cooperation is obtained by using the packs compared with dispensing the same duration drug supply in the standard way. Even though urine testing[26] and surprise checks of the calendar pack would be very suitable measures of compliance, I am unaware of any publication reporting attempts to assess the benefit from the use of the packs. Such an approach is important in its own right, but is also necessary to measure other strategies aimed to improve further, by whatever means, the regularity achieved by the use of calendar packs.

Tuberculosis

Turning to tuberculosis, in the Philippines the use of short-course chemotherapy in the National Tuberculosis Programme was adopted nation-wide in August 1986 for sputum-positive patients, or those with a lung cavity, after 2 negative smears. Valeza and McDougall (1990) have reported in a letter in the Lancet[27] that in the Philippines, between September 1986 and September 1989, over a quarter of a million patients had a 6-month regimen as two calendar blister pack preparations. First, one of rifampicin, isoniazid and pyrazinamide daily, was given for 2

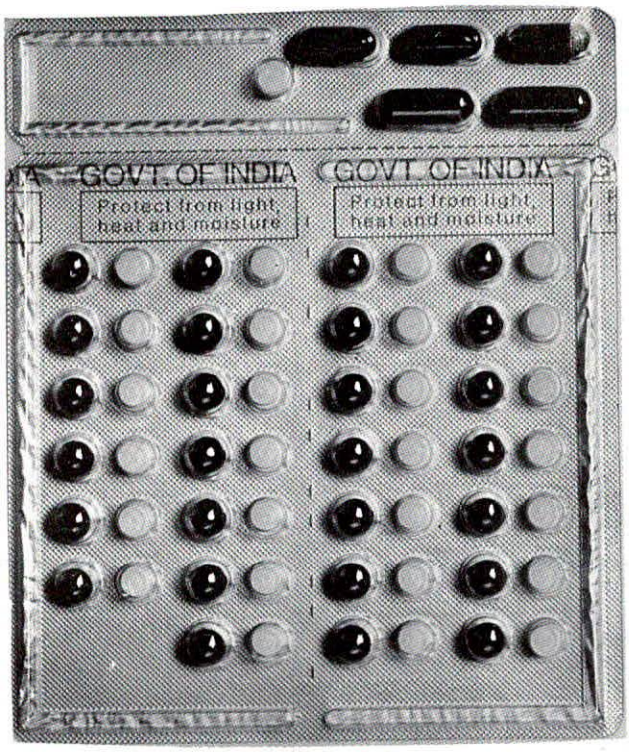

Fig. 1. A 4 weeks' calendar pack for multibacillary leprosy, as used in the Indian pilot project. The first dose (supervised) is rifampicin 600 mg, clofazimine 300 mg and dapsone 300 mg. The 27 self-administered daily doses are clofazimine 50 mg and dapsone 100 mg (Pharmanova, a division of Scanpharm A/S, Copenhagen, Denmark).

months. A week's supply was provided in a single pack (Fig. 2), but the dimensions are quite considerable (15 cm by 10 cm). This was followed by much smaller weekly calendar packs of isoniazid and rifampicin daily in the continuation phase of the next 4 months. There is no cohort analysis and the data they present do not enable a clear picture of what gain has resulted from the use of the calendar packs, but it is reported to have proved highly acceptable, both to patients and staff, as an improved approach. They also state "the pace of implementation has outstripped objective assessments of their value, notably in improving compliance". (A committee on the National Consensus on Tuberculosis in the Philippines representing the Lung Centre of the Philippines and the Quezon Institute, both Governmental, has recommended the addition of a fourth drug due to the high incidence of resistant cases locally. The Department of Health has not yet expressed its official view). More recently a blister pack preparation containing ethambutol in addition to the other 3 medicaments for the first 2 months is being marketed in the Philippines (Lederle SCC Kit). Because of the bulk, each blister pack contains a day's supply, a move away from the calendar presentation. Ciba-Geigy are also marketing in a number of countries individual daily blister strips with 2 tablets of rifampicin plus isoniazid, each containing 300 mg of rifampicin and 150 mg of isoniazid, and either 3 or 4 scored tablets of pyrazinamide, each of 500 mg, that is the 3 vital drugs for the first 2 months of bacteriologically confirmed pulmonary tuberculosis.

The indisputable advantages of the blister packs are that they are easier to dispense than separate medicaments, make it easy for the patient to know the dosage of each drug to take daily, and provided the appropriate plastic is used for the pack, the medicaments are protected against hot and humid tropical climates, and the increase in cost of this type of formulation (estimated at 5% in the Phillipine study)[27] is small, but might be more (up to 15% has been quoted) for less expensive regimens. However, it is clearly important to study, by both surprise checks of the calendar pack and excretion of the drugs in the urine, whether patient compliance in ingesting the daily dose is improved. These are in addition to the patient remaining on treatment as measured by the regularity and punctuality of attendance to collect supplies, and what proportion of patients do so for the full duration of treatment and for those who drop out

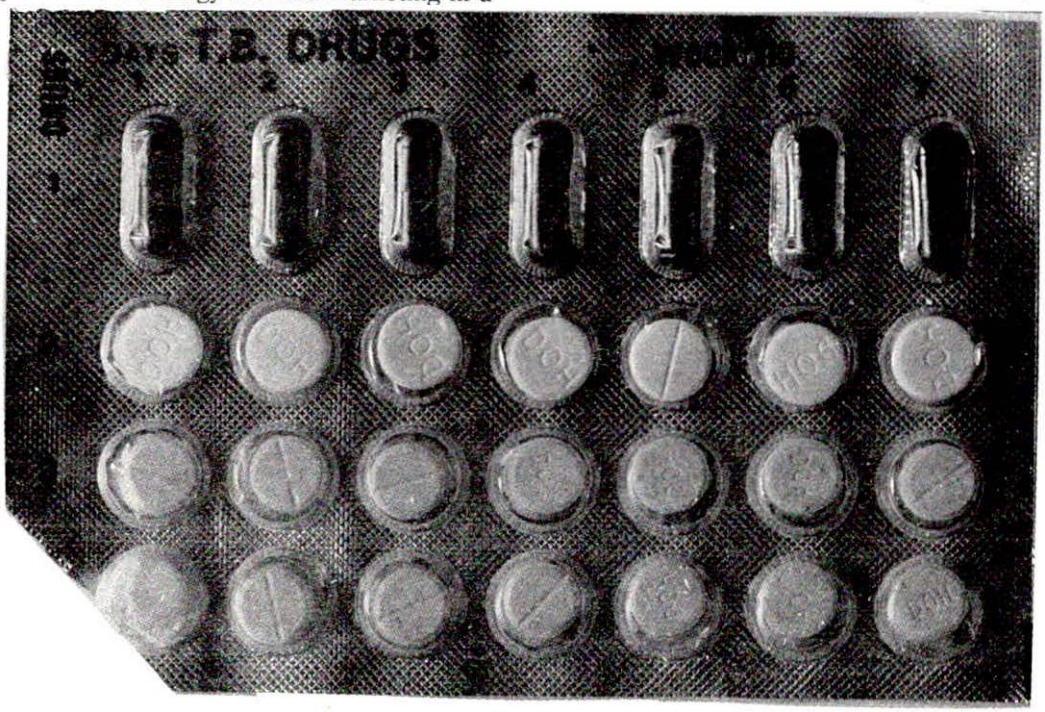

Fig. 2. Weekly calendar pack in 2 month intensive phase of short-course chemotherapy for tuberculosis in the Philippines. A daily dose is rifampicin 450 mg, isoniazid 300 mg and pyrazinamide 1000 mg and is self-administered by the patient at home.[27]

prematurely the reason why. Also, what are the therapeutic results in the latter as compared with the outcome in the patients who complete the course? The real proof of therapeutic benefit is fewer failures during treatment and a lower relapse rate when compared with dispensing the same medicaments in ordinary containers (in the developing countries often an envelope or wrapped in a piece of newspaper). It is relevant that therapeutic benefits are much easier to measure in patients with pulmonary tuberculosis than in leprosy, because clear-cut bacteriological culture assessments can be made during treatment as well as bacteriological relapse after stopping, which, if it occurs, usually does so within the first year or two of follow up.

(C) Converting an intermittent regimen into a daily regimen–a research problem

In the light of these experiences with drug packs, an important research approach which I now wish to suggest is the possibility of converting a fully supervised intermittent regimen to what, from the patient's point of view, would be a daily regimen. This could be achieved by using calendar packs for 1, 2 or 4-week periods, but ensuring that every day the patient has at least one pill to take. Table 6 illustrates research daily calendar pack options, as alternatives to a fully supervised intermittent regimen of ethambutol, isoniazid, rifampicin, and pyrazinamide given 3 times a week for 2 months followed by rifampicin and isoniazid, also fully supervised, twice a week for 4 months (a month is usually a lunar month in clinical practice). The 3-times weekly regimen could be spread over a 6-day period in the way illustrated in the table giving rifampicin plus ethambutol one day and isoniazid plus pyrazinamide on the next in a calendar pack for the patient to self-administer at home. There is good evidence that both 2-drug combinations achieve a high level of effectiveness. Isoniazid and pyrazinamide was compared with isoniazid and PAS in the era when 2-drug combinations were used and was at least as effective as the latter.[28,29,30] Rifampicin plus ethambutol as retreatment for failure patients in Hong Kong was surprisingly effective (ranging from 79% to 87% success rates) when given, daily, twice a week and even once a week, or once a week after a 1-month daily phase.[31,32] Sunday could either be a placebo (P) day or an extra dose of isoniazid could be given.

Table 6. *Converting a supervised intermittent regimen to a daily regimen in calendar pack form* A Research Approach*

	First 2 months		Next 4 months	
Day of week	Fully supervised dosage	Unsupervised calendar packs	Fully supervised dosage	Unsupervised calendar packs
Mon	EHRZ**	RE	RH	RH or RH
Tue		HZ		P H
Wed	EHRZ	RE		P H
Thur		HZ	RH	RH RH
Fri	EHRZ	RE		P H
Sat		HZ		P H
Sun		P or H		P H

*The essential first step is to study every dose of both types of regimen given under full supervision (ref 35 and pages 191-192)

**For definitions see footnotes to Tables 3 and 4

P = Placebo

In the continuation phase, instead of twice-weekly fully supervised rifampicin plus isoniazid there are daily blister pack options (Table 6). Thus the twice-weekly regimen could remain unchanged and on the rest of the days the patient could receive a placebo (P) tablet or alternatively an extra dose of isoniazid. There are a number of other regimens given intermittently throughout, or daily initially and then intermittent, but the principle proposed would still apply. The evidence from India is that currently patient compliance with all the regimens so far tried under District Programme conditions is disappointing as in so many developing countries, and for India fully intermittent regimens in rural areas. Hence the need for a radical change of approach, which the calendar format would offer if impeccably conducted research shows it to be justified. It is unlikely that sociological enquiries and the study of non-cooperative or failure patients are going to solve the problem in tuberculosis since it applies to all long-term therapy of any disease and very often short-term therapy too, as well as to prophylaxis.[33] Much has been published since then, including books on the subject,[34] but the basic general problem remains.

(D) The role of the Tuberculosis Research Centre (TRC) in exploring (C) above

Professor Mitchison and I had discussions

several years ago with our Madras colleagues about the need for a study of an intermittent regimen compared with the same drugs presented in pairs to make a daily regimen. The Centre undertook a pilot study of the daily regimen approach, which has provided evidence to justify a carefully conducted controlled clinical trial along the lines discussed in (C) above. The claims for calendar pack preparations from workers in the field of leprosy, including India itself, provide further justification for converting an intermittent to a daily regimen as I suggest in section (C), as well as the recent report on tuberculosis from the Philippines.[27] The *essential* first step is to obtain accurate information of effectiveness and toxicity of the 2 approaches under strictly controlled trial conditions *when every dose of both regimens is fully supervised.*[35] This will establish whether a substantial scale field trial of a calendar pack preparation should be launched, again with a proper evaluation of patient compliance. The target is an effective, less toxic, cheaper, more acceptable and more easily dispensed regimen, protected from the environmental temperature and humidity when in the patient's charge. Such a study under strict supervision of every dose of both regimens, which is an essential feature of the study design, will start shortly in the TRC and its sub-centre in Madurai. It is only such a study that can establish whether the regimens in this form merit, in due course, comparative field trials using calendar pack preparations. Such field trials too, *if and when this stage proves justifiable,* will need very careful design, planning and execution, if the findings are to carry conviction. I do not advocate this approach being used in routine clinical practice for it is an hypothesis to be carefully tested first.

(E) The underlying mechanisms

This is a complicated issue and I have no pretensions to being a laboratory scientist, so I write from my own viewpoint. In the early days of chemotherapy it was regarded as essential to maintain continuous minimal inhibitory concentrations of each medicament throughout the 24 hours. For this reason the administration of the drugs was in divided doses, 4 times a day being a common rhythm in the early days for PAS.[36,37] An important step forward was made from two observations in the late 1950s and early 1960s in Madras. First, that patient non-compliance was not solely a problem of bulky PAS (a view strongly held in WHO circles at that time) but that it applied equally to isoniazid and, indeed, to placebo also.[38] Secondly, 400 mg of isoniazid a day was more effective when given alone to patients with smear-positive cavitary disease in one dose than when given in 2 doses of 200 mg.[39] This was so even though all the patients on the divided dose, whether rapid or slow inactivators of isoniazid, had a continuous level of serum isoniazid above the minimal inhibitory concentration of the drug, which was not the case with the single 400 mg dose a day.[21] Obviously one dose a day makes less demands on patient compliance and family supervision than 2 doses a day.

Another view which was held in the early days of chemotherapy was that it was essential to give the drugs in combined chemotherapy together, in order that each drug protected the other or others from the emergence of drug resistance. Indeed, there was a period in the 1950s and early 1960s of strong advocacy of studying the serum level 6 hours after a dose of drug and relate this to the ability of dilutions of the serum to kill the individual patient's tubercle bacilli (the specific serum antimycobacterial activity test) not only to isoniazid and streptomycin but other drugs, including PAS, kanamycin, viomycin, thiacetazone, cycloserine and pyrazinamide.[40] The National Jewish Hospital, Denver, Volumes of the period, e.g. Volume 21,[41] make fascinating reading, and the stimulating work of Gardner Middlebrook (an outstanding figure), William Russell Jr, William Dye, Irving Kass, Sidney Dressler, Maurice Cohn and their colleagues and its scale in a single group reminds us of an era (and of the earlier pioneers) when there was great worldwide interest in tuberculosis chemotherapy and the underlying mechanisms, new drugs and their optimum clinical use. This is in sharp contrast to the current era when the pharmaceutical industry is loath to bring promising new antituberculosis drugs to the state of clinical trial, although they are badly needed for the third world countries. (The technically advanced countries too would be beneficiaries of their study in the third world countries, as has happened for many years with ambulatory chemotherapy and standard duration, intermittent and short-course regimens).[42]

Questions of additive or synergistic activity

and antagonism between drugs arise. The construction of isobolograms, standard practice for nontuberculous antibacterials have been studied for non-tuberculous mycobacteria.[43,44] Appropriate animal experimentation is obviously important.

A simple view, which may well be largely correct, is that each bactericidal drug will eliminate dividing bacilli drug-sensitive to it if it is given separately and that it is only doubly resistant strains that might multiply when a 2-drug combination is given, but that even when given together, doubly-resistant strains are less likely to respond to a 2-drug combination than a fully sensitive strain or a strain resistant to one drug. This was the basis for the view that the addition of extra drugs at the start of chemotherapy was desirable when there was any likelihood that initial drug resistance might be present. We must also remember that the patient's host resistance is a "drug" and can be a very powerful one as testified by extensive healed and calcified pulmonary tuberculosis lesions that had never been diagnosed, much less treated, in the pre-chemotherapy era. Mitchison[45] has emphasised that in the prevention of drug resistance the early bactericidal activity of drugs and the sterilising capacity of drugs must be considered separately. The overall evidence is that important features in the construction of effective regimens include (1) the drugs given, (2) the total quantity of each drug a week, and (3) the interval between doses. The aim is, in fact, to use each drug in its optimal way taking into consideration its pharmacokinetic characteristics, its type of antibacterial effect and its toxicity.

There is also much evidence of the lesser need for potent combinations in the continuation phase, and that intermittency, even at a frequency of once a week, with rifampicin and isoniazid, is an effective continuation regimen[46] (in the rural areas of Hong Kong, rifampicin, isoniazid, streptomycin and ethambutol.[47]) Indeed there is now a possibility that other rifamycins might well be effective at longer intervals than weekly in the continuation phase.[48]

Drug Combinations and the Bioavailability of Rifampicin

Combined preparations of antituberculosis drugs have been widely used since soon after the introduction of isoniazid in 1952. Combinations of isoniazid with PAS, thiacetazone, ethambutol and rifampicin have been marketed on the grounds that (1) it is more convenient for the patient to take isoniazid and a companion drug together rather than separately, and (2) monotherapy, especially with isoniazid alone with its greater risk of the emergence of isoniazid resistance, is avoided. Isoniazid monotherapy was a tempting choice for patients because of its small bulk, when compared with, for example, 10 grams of bitter PAS sodium. However, a special problem has arisen about the bioavailability of rifampicin and the quality control of combined preparations containing rifampicin.

Fixed combinations of isoniazid and rifampicin have been widely used for many years. More recently, a fixed combination of rifampicin, isoniazid and pyrazinamide developed by Lepetit is now marketed in the UK by Merrel Dow. Similar preparations are available in other technically advanced countries too. Since the late 1970s, my BMRC colleagues, Professor Mitchison, Dr Gordon Ellard, and I were closely involved in the design of 2 such combined formulations by Lepetit : one was for daily regimens (Rifater 2* which contained 50 mg isoniazid, 120 mg rifampicin and 300 mg pyrazinamide per tablet). The other was for intermittent chemotherapy which required different proportions of the 3 drugs (Rifater 3, which contained 125 mg isoniazid, 100 mg rifampicin and 375 mg pyrazinamide per tablet). Early unpublished studies conducted by Professor Acocella and his Lepetit colleagues showed that serum levels of isoniazid, rifampicin and pyrazinamide after giving them in 3 combined Lepetit preparations (Rifater 1, 2 and 3) were closely similar to those achieved when the same quantities of the 3 drugs were given to volunteers as separate formulations in cross-over design studies in Italy. In a further Lepetit preparation (Rifater 4), unbeknown to the firm's research group the pharmaceutical section had altered the order in which the 3 drugs were mixed. The consequence was a striking and alarming reduction in the absorption of rifampicin in the bioavailability studies (Acocella, personal communication).

* The first formulation (Rifater 1) was never taken to clinical trial because of the low dosage of pyrazinamide it provided.

In my view the only safe policy currently is, therefore, to avoid the use of fixed triple combinations of rifampicin, isoniazid and pyrazinamide unless their origin is from sources with impeccable reputation and quality control, and with unquestionably *"demonstrated bioavailability"* as emphasised by Pamra,[58] Reichmann[61] and the above (1988) editorial.[59] This is especially important in the many developing countries which, like India, already have high levels of initial drug resistance to isoniazid and to streptomycin. If such a policy is not followed there will be a high risk of using preparations with a poor bioavailability of rifampicin which could have disastrous consequences both for the individual patient and the national programme for it could lead to a high failure rate with short-course chemotherapy and eventually much more resistance to isoniazid, to rifampicin, and isoniazid plus rifampicin. In this connection the responsibility that many countries have accepted under the WHO certification scheme for drugs to be exported are highly relevant.[62] Now the onus must clearly be for the manufacturers to provide adequate batch data for all triple combinations before they are marketed even in the country of origin, an issue that clearly falls within the WHO ambit and which applies, on current evidence, to all production in every country, and possibly the double combination too.

I now, however, view the situation from a different and important point of view which I consider calls into question the alertness and awareness of the pharmaceutical industry in relation to quality control exercised over the production of rifampicin–containing combinations, certainly the triple formulation, and possibly even the combination of isoniazid and rifampicin as marketed in the developing countries, which is also a most worrying aspect.

In the investigations of Ellard *et al.*[49] of the 2 Rifater formulations referred to above, not only were plasma levels of rifampicin, isoniazid and pyrazinamide estimated, but also the urinary excretion of the 3 drugs and their principal metabolites. Both sets of measurements indicated the excellent bioavailability of each of the 3 drugs in the 2 combined formulations. These findings clearly confirm the evidence previously obtained over a decade ago by a group working in Ciba-Geigy in Basle. Brechbuhler and his colleagues[63] published in 1978, that the renal elimination of rifampicin plus desacetyl rifampicin provides a reliable and much more convenient method of assessing rifampicin bioavailability than estimating areas under plasma concentration curves.

The similarity in the results obtained in these 2 studies are noteworthy. Brechbuhler et al.[63] extracted rifampicin and desacetyl rifampicin into toluene and measured the absorption of the extract at 478 nm. In this way they showed that after giving doses of 600 mg rifampicin in their standard formulation, some 13% of the dose was excreted in the urine within 24 hours. Ellard et al.[49] used the colorimetric method[64] of Sunahara and Nakawgawa (1972), in which rifampicin and desacetyl rifampicin are extracted from urine into an equal volume of isoamyl alcohol and the absorption of the extract measured at 475 nm. They recovered 15% of the dose of the standard formulation and 14% of the 2 Rifater combined formulations in the urine within the same time period. Furthermore, the more detailed kinetic studies of Brechbuhler et al.[63] suggest that rifampicin bioavailability studies could probably be conducted using urine collected just over the first 8 hours following dosage, since 78% of the total urinary excretion occurs during this time.

A further valuable precaution would, of course, be to confirm the completeness of the urine collections using the simple colorimetric alkaline picrate method.

These urinary methods are clearly both much easier and cheaper to organise and undertake than the invasive and much more technically demanding serum assays. They fall well within the scope of at least some laboratories in many developing countries, and, of special importance, the National Drug Supervisory laboratory as well as the State level reference laboratory in a country such as India. Thus, drug regulatory bodies can, in fact, exercise effective quality control. They can also insist that the manufacturer checks each batch, a practice already common in the field of vaccine production.[62]

Cross-over studies can therefore readily be designed to compare the bioavailability of rifampicin in combined formulations with that in standard formulations of the same rifampicin alone. Aliquots of urine samples can now be used

to test the ability of selected laboratories in developing countries to perform the urine assay accurately with other aliquots being assayed in reference laboratories in technically advanced countries. Parallel serum/plasma samples can also be obtained in selected studies for testing abroad to confirm the urinary bioavailability conclusions.

It would be valuable to know what batch quality control the pharmaceutical firms in the technically advanced countries who are marketing the triple combination have been using in the past as well as currently, and I hope that this information will be forthcoming because it may provide further guidance.

In my view, there should be a meeting of the WHO and its expert advisers with representatives of some major pharmaceutical firms marketing the triple combination, so that what might be regarded as "a case study" of the manufacture and marketing of the triple combination can be undertaken. This would review quality control, past and current, and what procedures should be followed in future, and how best to organise further parallel studies of urinary excretion and serum levels, which might well need to involve the WHO. The WHO could inform Governments of the recommendations reached. Such a review should also include the manufacture of preparations of isoniazid and rifampicin which might well be a major problem too. I have been informed from a reliable pharmaceutical source that experience shows that there are significantly more batch problems with the manufacture of rifampicin and isoniazid than with rifampicin alone (Acocella[56] had found that 1 of 3 double combinations was deficient in the bioavailability of the rifampicin) and it is likely that the same happens when a third drug is added, in this case, pyrazinamide.

Antituberculosis Drugs in India

There are a number of important aspects of antituberculosis drugs in India which have to be considered. Their national availability, cost and quality, and the regimens used and their availability and acceptability to the patients, are all of great importance.

1. Bulk supplies of antituberculosis drugs

In 1983 the Adviser (Drugs) to the Government of India gave me information on the metric tonnes of each antituberculosis drug available in India for the year 1982-83 as well as the licensed capacity (that is the maximum quantity which can be made available either by manufacture in India or importation) and the amount imported. These figures, required for the Merck Oration[10] were, as I had been warned, not easy to come by, nor was permission to publish them. From these data I calculated the number of patients who could be treated daily for a year as a convenient measure for comparisons from year to year related to the number of new patients diagnosed.

The bulk supplies of antituberculosis drugs available in India annually from 1982 to 1986 are informative (Table 7). Unfortunately, the 1982-83 figures are the only official Government figures. The rest of the figures are from unofficial sources, but I have been advised that there is no reason to doubt their reliability. They show that adequate quantities of isoniazid were available with a drop in 1985-86, a year when isoniazid was unavailable in many Government treatment centres because the producers, who were mostly the smaller firms with limited resources, could not make a profit if they supplied it at the price the Government had fixed.[65] There were adequate stocks in the local markets at a higher cost, yet Government units had no option but to give the patients prescriptions for them to purchase this essential medicament themselves! Unfortunately, such shortages still occur and Prabhakar (personal communication) recently (1989) encountered an isoniazid shortage in a district in one of the major States. This re-emphasises the importance of satisfactory drug manufacturing and importing policies, ordering, stocking, and distribution system throughout every State, including all the PHIs involved in the programme.

It is clear from Table 7 that nationally PAS has a very minor role, that the use of thiacetazone is declining, whereas in contrast the use of ethambutol has increased substantially. In this respect a view has grown up over the years in India that thiacetazone is frequently toxic and unacceptable to the patients, although no evidence that I am aware of has been produced to confirm that the level and severity of adverse reactions is particularly high or that divided doses, as recommended, does not usually resolve indigestion. Ethambutol has been widely advocated, advertised and accepted as a safe

Table 7. *Antituberculosis drugs in India (metric tonnes)*

Drug	Licensed* capacity (1.4.83)+	Total available				Number of patients who could be treated daily for a year	
		1982-83+	1983-84	1984-85	1985-86	1982-83	1985-86
Isoniazid	433	199	152	205	113	1,817,000	1,031,000
PAS and salts	1,090	288	217	119	107	79,000	29,000
Thiacetazone	153	49	38	47	18.25++	895,000	333,000
Ethambutol	121	123	207	269	295++	421,000	1,010,000
Pyrazinamide**	3	17	34	14.5	52++	31,000	94,000
Rifampicin**	0	25	75	67	71	152,000	429,000
Streptomycin	490	247	248	235	188	902,000	686,000

*Licensed capacity = maximum quantity of drug which can be manufactured or imported
+These figures were provided by the Adviser (Drugs) to the Government of India
**All imported
++Figures for year calculated from supply in first 10 months.

substitute. However, it may cause irreversible ocular damage which, although uncommon when appropriate dosages are used, is still a risk. In many developing countries, including India, ocular lesions with impaired vision are particularly common in the general population. The widespread use of ethambutol under field conditions with supervision by relatively untrained paramedical staff with little access to skilled medical staff might well prove hazardous. Because of the increasing use in district programmes in developing countries, this risk must not be overlooked and special care in young children, the elderly and in impaired renal function, is necessary. Publications from India[66,67] warn caution, and consideration should be given to organising studies to establish what risk exists in District Programme conditions.

The use of pyrazinamide is increasing and this is likely to continue as the switch to short-course chemotherapy increases because it is one of the 3 major drugs in this type of regimen. The use of streptomycin shows evidence of decline, and this too is likely to continue because limitations of cadres of staff permitted to give streptomycin injections and the advent of AIDS (not the only risk) raises further cause for concern about injections under field conditions.

How much more valuable the information in Table 7 would be if it contained the official Government annual figures and was fully up to date. The Tuberculosis Association of India[65] was also unable to obtain the official Government figures on a regular basis (Pamra, personal communication).

In my view the information on licensed capacity and quantity of each drug should not only be made freely available but should be published annually in the appropriate respiratory diseases journals, in addition to the Indian Journal of Tuberculosis and the NTI Newsletter so that the medical profession can discuss and decide if they are appropriate. In considering the quantities it is also important to know about exportation. Indeed, steps should be taken to obtain and publish the *official* figures from 1982-83 up to 1989, as soon as possible, so that we can get up to date and also check whether the figures from 1984-86 in Table 7 are accurate, and also take into account the influence of exportation. If there are good reasons why export figures need to be kept confidential at a Governmental level, then the publication of the annual supply of each drug available in India should be reported. In 1987[68] it was reported that exports of bulk drugs and formulations were worth over Rs. 217 crores and that the Indian pharmaceutical industry is one of the most diversified and integrated industries in the entire third world.

This is a period when the regimens used in India are changing year by year and from State to State and are likely to do so for many years to

come, as short-course regimens are progressively introduced and modified in the light of further knowledge of their efficacy and of service programme experience.

2. The number of doses of drugs in a regimen

Rather than consider the number of patients that could be treated daily for a year, as above, it is more realistic, with the introduction of short-course regimens, to consider the quantity of each drug likely to be given to a patient in an effective regimen, and then calculate how many patients could be treated with that regimen from the bulk supplies available.

For example, there are a number of highly effective 6-month daily regimens containing rifampicin throughout that require 180 doses. We know, however, that 60 doses of rifampicin is an important quantity which might be given in several very effective ways, for example daily for 2 months, 3 times weekly for over 4 months, and twice-weekly (only 52 doses) for 6 months. The bulk supply of rifampicin available for the year 1985-86, if none was exported and its use was restricted to tuberculosis (it is also used in leprosy and other infections), would be enough to provide 60 doses for more than 2½ million patients receiving 450 mg doses and just under 2 million on 600 mg doses! On the basis of information provided by Dr SK Noordeen of WHO of the therapy policies in India, I have calculated that in 1986 it is likely that the quantity of rifampicin used for the treatment of 300,000 leprosy patients, of whom I have assumed one third were multibacillary and two thirds paucibacillary, was 4 metric tons. These requirements for leprosy reduce the above calculation in Table 7 by 100,000 patients on 600 mg. Thus, the leprosy programme was a minor consumer of rifampicin. Although the quantity now used has increased substantially with intensification of the treatment programme with regimens that include rifampicin, leprosy remains a minor consumer compared with the rifampicin production.

It is of particular interest to consider pyrazinamide because its *only* use is as an antituberculosis drug, important because of its unique sterilising role.[10] It is given as a maximum of 60 doses when it is prescribed daily for 2 months, a widely used duration and rhythm, even in the technically advanced countries. In the service programme in Hong Kong it is currently given 3 times a week for 4 months (an exceptional duration but still less than 60 doses) in a fully supervised 6-month intermittent regimen. In District Programme conditions in India it is being given either as 60 daily doses or twice a week for the first 2 months (16-17 doses) for smear-positive patients, and is currently being studied in Madras in a controlled clinical trial, given 3 times a week for 3 months (39 doses). The 52 tonnes bulk supply in 1985-86, if none had been exported, would provide enough pyrazinamide to give 60 doses to nearly 600,000 patients, or a twice-weekly supervised dose for 2 months to over 2 million patients. I might add, *en passant*, that a small proportion of the metric tons are of morphazinamide, although in a detailed review of the literature a few years ago I could find no evidence whatsoever to justify its use instead of pyrazinamide. The claim of lesser toxicity is misleading since it is less active than pyrazinamide. In my view its use should be stopped.

Since the regimens that contain rifampicin and/or pyrazinamide which are recommended for the National Programme are those in Table 4 monitored by the NTI, it is clear that there were apparently very large supplies of both of the drugs in India. The impression these figures in Table 7 give is of an excess of at least some drugs rather than a shortage. This again underlines the need to know what the Indian consumption actually is.

3. The cost of individual drugs currently used in District Programmes

The latest cost of doses of individual drugs is a basic figure, for from it the cost of any regimen can be calculated. By far the cheapest drugs (Table 8) are isoniazid and thiacetazone. The substitution of ethambutol, which is 7 times as expensive as thiacetazone, as a companion drug to isoniazid results in a fourfold increase in price of ethambutol plus isoniazid as compared with thiacetazone plus isoniazid, and PAS produces a tenfold increase in price. If rifampicin is the companion drug, the average cost of a dose of isoniazid plus rifampicin is no more than of isoniazid plus PAS, and in practice rifampicin is given for a much shorter period of time and many fewer doses are given. Pyrazinamide, expensive in

Table 8. *Cost per dose of antituberculosis drugs in Madras (April 1989)*

Drug and dose	Price per dose (rupees)
Isoniazid 300 mg	0.11
Thiacetazone 150 mg	0.09
Streptomycin 0.75 g	2.76
Sodium PAS 10 g	2.01
Ethambutol 800 mg	0.67
Pyrazinamide 1000 mg	1.65
Pyrazinamide 1500 mg	2.37
Pyrazinamide 2000 mg	3.30
Rifampicin 450 mg	1.86
Rifampicin 600 mg	2.48

individual doses, is given as a maximum number of 60 doses. Streptomycin is the most expensive individual drug with the added cost of the injection, the restriction to individuals authorised to give them and the increasing concern about the transmission of infections.

It must be added that drug costs in India do fluctuate rapidly, some increasing and others decreasing, so the cost of regimens must be calculated annually.[68] Hence also the desirability of bulk purchase arrangements for as long a period in advance as can be negotiated, especially those purchased from abroad.[10]

(4) Who pays for antituberculosis drugs?

The Planning Commission of the Central Government ("Hindu" 6.7.83) turned down the recommendation of a Health Ministry Task Force that it should provide all the antituberculosis drugs required for the National Tuberculosis Programme free. Instead, it is adhering to the policy of providing 50% of the drugs supplied to the State Government clinics and to other schemes shared equally by the Central and State Governments. Again, I wish to repeat my view[10] that the medical profession must make a concerted and sustained effort to have this decision reversed. In addition to the psychological effect of the Central Government showing its commitment to giving priority to Tuberculosis Control as recommended in the National 20-point Plan, the provision of 100% of the necessary antituberculosis drugs would remove the shortages because of States underbudgeting for tuberculosis drugs on financial grounds, in relation to their own health priorities.

(5) Quality control of antituberculosis drugs

There are a limited number of antituberculosis drugs relevant to district programmes in India (Table 8) and it is important that their quality is monitored. This is no easy task in a country, which, in addition to major manufacturers (or as in the case of rifampicin and pyrazinamide, of imported powder) has a very large number of small firms preparing medicaments in what, in pharmaceutical terms, can only be regarded as unsatisfactory conditions, with, at best, suspect quality control, if any at all.[65,68] The method of packaging for hot humid conditions, of storage by the distributors and their outlets, and the sale or use of drugs that have passed their expiry dates, are also relevant, especially in rural areas. The question arises whether the sources of reliable antituberculosis drugs should not be reviewed and monitored to the satisfaction of an expert group, so that order is brought into what is, to say the least, a difficult and confused situation. General practitioners who represent a major sector of the prescribers of antituberculosis therapy must also be kept informed of the need to adhere to high quality formulations, and be given guidance as to which they are. They should advise their patients about reliable stockists, and this is particularly important in District Programmes and in rural areas.

It is relevant that the TRC keeps a careful check on the quality of drugs which it uses in controlled clinical trials to be sure of their potency and this is a wise precaution. It has also conducted a study which showed that the rifampicin, isoniazid and pyrazinamide used in the North Arcot district programme conditions remained potent when stored for up to 30 months in circumstances far from favourable, although not fully documented (GS Sarma, personal communication), a study that could well be repeated in areas of high temperature, high humidity, or both. The aim, however, should be to ensure refrigerated storage whenever possible, be it bulk supplies in a Central or State Government store or the stock of a peripheral dispensary or pharmacies where general practitioners' patients may take their prescriptions.

Pre-treatment Drug Resistance

A knowledge of the level of primary drug

resistance (that is resistance of strains in newly diagnosed patients who have had no previous chemotherapy) or of initial drug resistance, which includes in addition (1) not only such patients, but (2) patients who have unknowingly received antituberculosis chemotherapy, for a chronic cough without adequate investigations, and were not informed what their medicaments were, (3) or had knowingly had previous chemotherapy and concealed the fact for fear that they would not be retreated. In developing countries representative surveys to monitor the levels of drug resistance in newly diagnosed patients are of importance, especially to isoniazid, and now, above all, to rifampicin, especially if they have a large private sector, as in India, and rifampicin is also being used on an increasing scale in the public sector. In technically advanced countries, it is usually no problem to identify with certainty primary drug resistance, but they also have a special need to monitor the trends in immigrants and in disadvantaged sections of the community.

In the early days of chemotherapy there was a fear that the careless use of the then available drugs, streptomycin and PAS, and from 1952 onwards isoniazid, could lead to a build up of chronic excreters of drug-resistant strains who would progressively spread primary drug-resistant infections leading to very high levels of primary resistance in new cases, and rendering the available drugs increasingly less effective in therapy.

The BMRC monitored this possibility in 2 surveys, the first in 1955-56 on a weighted random sample of 80 chest clinics drawn from the 450 of the whole United Kingdom[69] and the second survey in 1963[70] sampled 125 clinics since the total of new cases per annum had declined. All new patients attending the clinics with pulmonary tuberculosis had bacteriological specimens sent to Professor Mitchison's laboratory in the Royal Postgraduate Medical School, London, for smear, culture and sensitivity testing, until each had achieved its quota. The level of isoniazid resistance in new cases of British and Irish patients (the vast majority of the cases at that time) was 0.6% and 1.3% respectively and for streptomycin it was 2.2% and 2.8% respectively, very reassuring findings. In 1978-79[71], 1983[72] and 1988 (unpublished) the BMRC conducted surveys of all newly-diagnosed patients notified by statutory requirement in England and Wales in a 6-month period (12 months' periods in children and young adults in the second and third surveys). Because the total number of patients had declined substantially since the 1960s, such comprehensive surveys were feasible. There was, moreover, increasing interest in following the trends in the white population and the now larger immigrant groups. No relevant information on ethnic origin, bacteriological status or radiographic severity of chest lesions was available from the notification system, so special surveys were necessary. In addition to a detailed review of pre-treatment characteristics of the disease, whether pulmonary or extrapulmonary, or both, we also had a special interest in knowing the regimens of chemotherapy then being prescribed and their duration and, in the 1983 survey, the results achieved as well. It will be seen (Table 9) how little drug resistance there was in the white ethnic population in each of the 3 surveys and that in the 1988 survey, where information on the patients of Indian ethnic origin was available (separately from those of the Pakistani/Bangladeshi ethnic group) the findings are very similar. It will also be seen that considering all ethnic groups combined the overall level of drug resistance in England and Wales remains low. Rifampicin resistance is not a problem, nor is resistance to ethambutol and the most frequent resistance is to streptomycin, a drug whose use is, in any case, progressively declining.

In developing countries, it is less easy to conduct representative surveys, but we have done so in 3 surveys in a weighted random sample of 11 of 30 districts of Kenya over a 20-year period, 1964[73], 1974[74] and 1984.[75] The same central reference laboratory in Nairobi using standard BMRC techniques did the cultures and sensitivity tests, supervised by the same senior laboratory technician seconded from Professor Mitchison's Unit. It was possible to do such surveys because Dr Pierce Kent (subsequently Director of the East African Tuberculosis Investigation Centre) had established in the mid-1950s a treatment register in each district and every patient brought under treatment in the district had their identification details recorded in the register. The same district register system was specifically introduced in Tanzania by Dr R Doyle so that it would be possible to conduct the first representative survey in 1969,[76] and a second one in 1978/80[77] at a time when the National

Table 9. *Results of pre-treatment sensitivity tests to Isoniazid, Streptomycin, Ethambutol and Rifampicin for previously untreated patients with respiratory disease notified in 1978/79, 1983 and 1988 in England and Wales*

Initial resistance	1978/79 survey[69]				1983 survey[70]				1988 survey*					
	White		All ethnic groups		White		All ethnic groups		White		Indian		All ethnic groups	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Isoniazid alone	3		12		2		8		4		2		10	
Streptomycin alone	7	1.2	12	2.2	6	1.4	20	3.4	7	2.0	3	3.0	14	3.0
Ethambutol alone	0		0		1		1		0		0		0	
Rifampicin alone	0		0		0		0		0		0		1	
Isoniazid and Streptomycin	3	0.4	8[$]	0.7	1	0.2	10	1.2	2	0.4	1	0.6	7[#]	0.8
Total with a resistant strain	13	1.6	32	3.0	10	1.6	39	4.6	13	2.4	6	3.6	32	3.8
Total with a sensitivity test result	801	100	1070	100	623	100	855	100	543	100	165	100	840	100

*J. Darbyshire, personal communication
[$]One resistant to Rifampicin as well
[#]One resistant to Rifampicin as well, another to Ethambutol

Programme was in a state of reorganisational upheaval and the registers were not properly kept. As with Kenya, the central laboratory used BMRC methods, and was supervised by a seconded senior technician from Professor Mitchison's Unit. This district register approach has been adopted in other countries, becoming, for example, in the last decade a standard and central feature of the International Union Against Tuberculosis and Lung Disease mutual assistance programmes.

The findings for Kenya on drug resistance are given in Table 10. They are very similar over the whole 20-year period. It is very encouraging that they show no evidence of a build-up of initial drug resistance in previously untreated cases. It must be added, however, that the great majority of Kenyan Africans are treated in the government health service and that there was very little competition from private practitioners, especially during the earlier surveys. Further, the evidence is that the rate of new registrations of pulmonary tuberculosis per 100,000 of the population of Kenya in 1964 was 65.9, in 1974 51.1, and in 1984 42.7, which probably represents a genuine decline rather than a less efficient diagnostic service, the change in rate between 1964 and 1974 being a decrease of 22% and between 1974 and 1984 a decrease of 16%. However, the estimated population in millions in the survey districts was 3.39, 4.94 and 7.24 respectively over the 20-year period, so that in absolute numbers there were more cases in 1984 than there were in 1964 and 1974. (The findings of HIV infections and the association with tuberculosis is a dramatic event, which may not, however, necessarily influence *patterns of drug resistance,* but speculation is no substitute for hard facts.) The resistance figures for Tanzania are also shown in Table 10.

Turning now to India, the problem of conducting surveys is totally different in such a large country with a population of over 800 million in 437 districts. Even so, I would remind you of 2 important ICMR surveys[78,79] coordinated from the TRC by Dr PRJ Gangadharam in the 1960s using MRC laboratory methods and ways of defining drug-resistant strains which had been introduced by Professor Mitchison in 1956. The methods have been unchanged ever since. India has the great advantage of having in Madras a national reference laboratory, which is widely recognised as an international reference laboratory too.

The first ICMR survey[78] was conducted in patients with no history of previous chemotherapy. Nine centres were chosen (Table 11), 8 because they were on convenient air routes to Madras and were eager to cooperate, the

Table 10. *Kenya/BMRC and Tanzania/BMRC tuberculosis surveys*
Initial Bacteriological Status
(in untreated patients)

	Kenya			Tanzania	
Pre-treatment sputum	1964[73]	1974[74]	1984[75]	1969[76]	1978-80[77]
Cultures					
Total tested	864	984	981	1204	932
Positive (%)	74.5	77.0	76.4	55.5	68.3*
Drug resistance					
Total tested	632	702	718	636	555
Resistant (%) to					
Isoniazid alone	8.9	7.3	7.1	4.9	7.6
Streptomycin alone	0.8	1.4	0.5	3.0	0.7
Both drugs	1.4	1.4	1.3	1.4	1.8

*This higher proportion was because in the evolving National Programme, only a doctor could authorise a smear-negative patient to be brought under treatment

sputum samples could be kept refrigerated and sent at frequent intervals to a special survey laboratory set up in the Madras centre by Dr Gangadharam. The levels of drug resistance are substantial (Table 11). However, there is evidence that this is not primary drug resistance but initial drug resistance and that the interrogation of patients about their history of previous chemotherapy was often inadequate. Thus, in the Government Tuberculosis Institute, Madras patients, the level of initial resistance was similar to the overall average for all the other centres in the study. However, patients with no history of previous chemotherapy were referred to the Tuberculosis Chemotherapy Centre which was sited in the same compound because they were eligible for admission to controlled clinical trials in the Centre. They were reinterrogated very carefully by medical staff with much experience in obtaining accurate histories who also had the time to do so. In addition, all prescriptions, all medicaments and empty containers patients still had were inspected and, when in doubt, private practitioners who had prescribed pills and injections were also visited, if need be with the patient, to see if these were antituberculosis drugs or, as they often then were, vitamins. As a consequence of excluding further patients found to have had a definite history of previous chemotherapy, a reanalysis of the rates of pre-treatment drug resistance to isoniazid and to streptomycin (shown in brackets in Table 11) when these results became available several weeks later, were strikingly lower than in the patients regarded as new and previously untreated, by the Government Institute medical staff.

In a second ICMR survey[79], also coordinated by Dr Gangadharam, involving the same 9 centres, not only patients with no history but also those with a history of previous chemotherapy,

Table 11. *ICMR drug resistance survey in patients with no history of previous chemotherapy (1964-65)*[78]

Centre	Number of cultures with results	Percentage with resistance to		
		Isoniazid	Strepto-mycin	One or both drugs
Amritsar	202	14	13	21
Bangalore	223	11	8	14
Bombay	221	20	19	29
Calcutta	191	18	20	27
Delhi	213	13	9	18
Hyderabad	245	15	10	18
Madras	217	13 (3.7)*	12 (4.3)	18
Nagpur	196	11	10	15
Patna	130	18	14	27
All centres	1,838	14.7	12.5	20.4

*The figures in brackets are the levels of resistance after excluding patients who on detailed interrogation in the TRC gave a history of previous chemotherapy, several weeks before the sensitivity test results were available.

were interrogated and its duration recorded. Specimens from all the patients were sent to Madras for examination in the special laboratory. The levels of drug resistance in patients with no history of previous chemotherapy (Table 12) are similar to those of the first survey, but increased with the duration of previous chemotherapy. These findings are similar to those of a 1962 survey in Hong Kong,[80] also conducted in outpatient clinics, the bacteriology and sensitivity tests being undertaken in the London laboratory. The somewhat higher rates in Hong Kong may well be due to a larger scale use of antituberculosis drugs, and for longer periods, not only in the Government service but from the large number of private practitioners who were treating tuberculosis before the patients registered themselves in the Government service for the first time. A similar survey is currently being repeated in Hong Kong where ambulatory short-course chemotherapy has been used on a wide scale for nearly a decade, so the findings will be of special interest.

The TRC Madras also has figures of drug-resistance in patients diagnosed in Madras city since 1956 in an area of intake within the city (enlarged somewhat over the years) and admitted to a series of controlled clinical trials (Table 13). There has, in fact, been an increase in the level of drug resistance to isoniazid, to streptomycin and to both drugs over the years, which has levelled off in recent years. The increase may, in part, represent a genuine increase in primary resistance, but it is almost certain that patients over the years have become increasingly skillful in concealing their history of previous chemotherapy and there may have been variations in the standards of interrogation, which had been conducted with almost obsessional fervour in the early years of the Centre so that, in fact, the inclusion of patients with other reasons for initial resistance has increased.

Table 12. *ICMR drug resistance survey in all patients with or without a history of previous chemotherapy (1965-1967) (comparison with Hong Kong)*

Duration of chemo-therapy (months)	ICMR survey[79]		Hong Kong survey (1962)[80]	
	Number of patients	Resistant to H or S or both (%)	Number of patients	Resistant to H or S or both (%)
None	851	22	302	19
0 -	46	26	37	27
1 -	143	46	96	66
6 -	189	74	73	94

The Madras centre has, over the years, accumulated much information on drug resistance in children, including child contacts of the patients in the chemotherapy studies and in studies of tuberculous meningitis, tuberculosis of the spine, abdominal tuberculosis and from the BCG study families, which it took over in the later years of the study. It is important that these data should be assembled and analysed since a child, especially if young and with a primary lesion, is much less likely to have had previous chemotherapy for tuberculosis than an adult eager to conceal a previous history. Reliable information on the pattern of drug resistance in paediatric practice is in my view, especially important, as it is likely to be a better reflection of the current trend of drug resistance than is provided by the older age groups, many of whom may have been originally infected 40 or more year ago, prior to the era of chemotherapy.

An important issue now is what will happen to the level of pre-treatment drug resistance, especially to rifampicin as its use in district programmes based on short-course chemotherapy progressively spreads, when there is already a substantial level of initial drug resistance to isoniazid, and an even higher level in patients who admit a history of previous chemotherapy.

It is clear that with the introduction of new regimens of short-course chemotherapy and in district programme conditions there is now a need to undertake as representative surveys as is possible of pre-treatment drug resistance in India. The emphasis will increasingly be on isoniazid and rifampicin, the 2 key drugs in short-course chemotherapy (tests for pyrazinamide resistance are technically more difficult and unlikely to be so relevant). I see the need for a number of laboratories, each with a bacteriologist with an interest and knowledge of tuberculosis bacteriology, and equipped to use the same laboratory techniques for smear, culture and sensitivity tests and defining drug resistance by using the approach adopted in the Madras centre, and closely associated with Madras for reference

Table 13. *Prevalence of initially drug-resistant strains in newly-diagnosed previously untreated patients (Tuberculosis Research Centre, Madras) (Prabhakar, personal communication)*

Study	Period of intake	Number of patients	H resistant (%)	S resistant (%)	SH resistant (%)
I	1956-1957	173	3	3	0
III	1957-1958	325	6	3	2
K	1961	99	6	1	0
Va	1961-1962	159	4	4	1
Vb	1962-1963	235	6	9	3
VII	1963-1966	538	6	6	2
VIII	1967-1968	389	8	7	4
IX	1968-1969	239	9	4	1
X	1970-1972	465	9	9	4
XI	1972-1974	651	10	12	5
XII	1974-1977	652	12	11	6
XIII	1977-1980	507	10	8	5
XIV	1980-1985	1004	11	12	6
XV	1985-1986	71	13	11	7
XVI	1986-1988	317	11	9	6

purposes. Such laboratories need to be in or near cities with ready access to airlines and might be in a university department, a general hospital or a tuberculosis hospital. What is particularly important is that the laboratory should be closely associated with a doctor active in the field of tuberculosis, with epidemiological and clinical interests and who is ready to be a local coordinator of relevant studies, for example, participating in controlled clinical trials or in surveys of alternative strategies for tuberculosis control under district programme conditions and the involvement of a statistician would also be of great value. Tuberculosis in India needs an expanded research and evaluation capacity, capable of covering different regions of the country. Such a network would obviously take time to establish but as it evolves, increasingly representative information on drug resistance and other issues in addition would become available and the surveillance of tuberculosis would progressively improve. In any case, an efficient smear and culture service would be invaluable, both in identifying the most infectious cases and in supervising and monitoring the efficiency of peripheral diagnosis by smear examination, and the results of therapy. Such a network could play a major training role in District Programmes and in educating medical students, and recently qualified doctors.

Initial Drug Resistance and Response to Chemotherapy

Over the years the BMRC has accumulated from its collaborative studies, all using the same BMRC methods of cultures and sensitivity testing, an impressive amount of important, informative and encouraging information on the response to treatment with short-course chemotherapy in the presence of initial drug resistance. I have summarised the major findings on several occasions in review articles[10] and a detailed analysis and report was published in 1986 by Mitchison and Nunn.[81] The TRC also has a large body of corresponding data on patients with initial drug resistance using the same BMRC laboratory methods and treated by short-course chemotherapy, some already published but to which we have never referred. A report of the TRC's accumulated data along the same lines would be invaluable too. Such data are virtually unobtainable from the controlled trials of new cases reported from the technically advanced countries, because they have changed the regimen when a drug-resistant strain was found to have been present at the start of treatment and still do so. This is impracticable in the developing

countries and certainly not a high priority problem. The NTI has recently reported on 100 patients with isoniazid-resistant strains pre-treatment, treated by 3 alternative regimens. The data on the emergence of rifampicin resistance is of special interest, even though the drug sensitivity test techniques were unfortunately not reported.[82]

Extra-Pulmonary Disease

Extra-pulmonary disease is a decreasing problem in technically advanced countries. For example, the one lesion at all frequent in the UK is glandular tuberculosis but even then a high proportion of the patients are of immigrant ethnic origin. It is in the developing countries, where there are still, unfortunately, substantial numbers of patients with a variety of extra-pulmonary lesions, many often florid when they present, that studies can be undertaken to define the best methods of therapy. Again, there is no question but that controlled clinical trials are the most fruitful approach because there is a comparison of alternative regimens or policies.

My own BMRC group coordinated a series of studies of alternative treatments of tuberculosis of the spine on behalf of a BMRC Working Party. This programme was established in 1964 because of an important controversy between Professor A Hodgson in Hong Kong, who advocated radical surgery with a bone graft in addition to chemotherapy, and Mr PG Konstam, also a surgeon, working in Nigeria who advocated ambulatory chemotherapy as the best approach. The Working Party organised studies in Korea, Hong Kong, Rhodesia, South Africa and Madras, studying a variety of different orthopaedic approaches, including bed rest, plaster jackets, surgical debridement, radical surgery and a bone graft, as well as ambulatory chemotherapy alone from the outset, and both standard duration, and in recent years, short-course regimens. The Madras study[83] was a collaborative investigation between the ICMR and the BMRC Working Party and it was the TRC which played a pivotal role in the local coordination. This was important because six different institutions were involved in the admission of patients. The collection, checking and recording of data and its transfer to London so that the two groups had parallel information would not have been possible without the TRC which also took the high quality standardised radiographic series of the lesion and ensured a high coverage in a long-term follow-up. In summary, the outcome of the large series of studies is that ambulatory short-course chemotherapy is remarkably effective.

My own group, Professor Mitchison, and Dr DG Gibson, Brompton Hospital cardiologist, and others have also collaborated with a Transkei team (Dr JIG Strang and his colleagues) in undertaking unique controlled investigations of the therapy of constrictive pericarditis and tuberculous pericarditis with effusion, both conditions being surprisingly frequent, 383 cases being diagnosed during a 4-year period in approximately a 3 million population.[84,85] A long-term follow-up of both studies is in progress and will surely illuminate not only our knowledge of the therapy of these conditions but of the long-term course of the lesions also. This will be especially informative about the evolution of constrictive pericarditis.

In my view one of the major contributions of the TRC is its investigation of extra-pulmonary disease which is a considerable national problem (Table 1) and it is important to find for each type of lesion the optimal treatment most convenient for the patients and least demanding of resources (including hospitalisation) and staff time. In addition to the study of spinal disease it has undertaken a series of studies of the treatment of tuberculous meningitis[86] including a current controlled trial. It is investigating the therapy of brain tuberculomas, and of abdominal tuberculosis, also in randomized controlled trials. In has also undertaken an important investigation of the treatment of paediatric lymphadenitis.[87] This latter study is of particular interest because of the striking severity of the lesions that have been treated and a controlled trial of two 6-month regimens is currently in progress. These studies illuminate our knowledge of the role of short-course chemotherapy in these important extra-pulmonary lesions and the technically advanced countries will also be obvious beneficiaries on the infrequent occasions when such lesions are encountered.

Another important consequence of these investigations is that they have all been conducted in collaboration with the experts in the fields in question in Madras, such as orthopaedic surgeons, gastroenterologists, both medical and surgical, and 2 neurological teams, so that there is

cross fertilization between the specialities including university and teaching hospital groups, so that teachers and hence medical education too have benefited. The implications, therefore, are not just restricted to developing countries or to practitioners with a special interest in tuberculosis. I have no doubt that the groups in other specialities in Madras who have collaborated with the TRC will use the methodology of the controlled clinical trial more widely and with greater skill and better follow-up in consequence of their association with these investigations. Had groups in other centres in India been submitting patients to a multicentre study following the same protocol, the speed of intake to the studies would have been faster, the outcome more rapidly available, and there would have been a wider spread of the specialised methodologies to other parts of the country.

It must be added that the management of extrapulmonary tuberculosis in individual patients should always involve tuberculosis experts because it is they who are up to date in the choice of regimens, are fully aware of the problems of patient compliance, and have the experienced staff who understand the important need for careful supervision of chemotherapy, and have the organisation to take early and positive absconder action, if the need arises.

The Utilisation of Tuberculosis Beds

Currently the tuberculosis beds in India number approximately 47,000, of which 8,643 are maintained by voluntary organisations. Some agencies, e.g. the railways and the Employees State Insurance scheme, reserve TB beds in the States but they also have their own TB hospitals. The indications for hospital admission are : 1) emergencies, such as haemoptysis and spontaneous pneumothorax, (2) critically ill patients, (3) patients in need of surgery, and (4) socio-economic considerations. There is also no doubt that unsuitable patients are not infrequently admitted through influential channels. The official recommendation is that domiciliary treatment is the treatment of choice. A high proportion of patients in India prefer ambulatory chemotherapy and even the recommended categories refuse admission for socio-economic reasons, and early self-discharge is common, with loss to follow-up (Nagpaul, personal communication). A 1988 editorial in the Indian Journal of Tuberculosis[88] is critical of the advocacy of hospitalisation and the construction of cheap cottage hospital beds.

I have summarised elsewhere the advantages of treating even very ill patients in ambulatory domiciliary conditions within the family from the very outset and have listed some of the misapprehensions and fallacies of the advocacy of hospitalisation for the first 2 months, as the ideal norm,[89] based on the fallacious views and beliefs such as that this ensures the patient receives and needs every dose of a daily regimen. These issues are also considered in a recent WHO publication.[90]

India now urgently needs a review of the utilisation of the tuberculosis beds including bed occupancy rates, the areas from which the patients are admitted, not only urban, suburban and rural, but the distance from each patient's abode. The actual reasons for each hospital admission, the classification of the lesions both bacteriologically and radiographically, the duration of hospital stay, the regimens prescribed, and the frequency and timing of self discharge and losses to follow-up. How many beds should be devoted to retreatment of failure patients, which directs both staff time and financial resources away from case-finding and the therapy of new cases? The staffing structure, with particular reference to the nursing and medical staff numbers and their training is needed. The cost of a bed when occupied and when unoccupied needs calculating for each institution, because these vary widely.

With adequate background information, rational policies can be recommended about the use of tuberculosis beds and whether expansion, contraction or relocation is indicated, or whether the funds might not be put to better use. For example, how many diagnostic cultures could be performed for the cost of a single patient day in hospital on short-course chemotherapy? Might the provision of more health visitors for the ambulatory programme yield better dividends? Tuberculosis hospitals in India, as in many developing countries, range from the very good to the almost unbelievably poor (as I have recently seen in a major State institution) with minimal patient records which did not even contain the regimen, the date of its start, the bacteriological status (which had often not been assessed, even by smear examination), and medical staff with no

knowledge of tuberculosis or interest in the disease and whose main concern was to be transferred back to an urban area. Finally, each State must take an overview of the use of beds in relation to competing health priorities.

Improving Research and Training Facilities in India

Laboratory, clinical and epidemiological research, and the design and conduct of controlled clinical trials in tuberculosis require special training. Studies must be well planned and conducted if they are to provide reliable data, and the analysis and presentation of results must be dependable. Methodologies have already been well established. Thus, excellent controlled clinical trials, the findings of which have been accepted worldwide, have been conducted in the TRC, Madras, since 1956. There is, therefore, available an exceptional resource to train clinicians and their teams (social workers, public health nurses, health visitors), bacteriologists, laboratory scientists and all their technical support staff, in laboratory aspects, and, of special importance, statisticians and their assistants. An understanding of the underlying issues involved in the conduct of research, especially controlled trials and epidemiological surveys in tuberculosis, is particularly necessary because of its chronicity. A close liaison between clinical, epidemiological, laboratory and statistical staff is, therefore, a key feature of an effective research group.

Studies involving controlled clinical trials (whether of pulmonary or extrapulmonary disease) are particularly important and much more informative than a study of patients treated with a single regimen or a single policy of management. There are, for example, at least six groups in India currently studying the diagnosis and treatment of brain tuberculomata stimulated by the special interest in brain scans. The only centre currently investigating alternative regimens in a randomised controlled trial is the Madras group. This is a pity because the aim is to find the most effective and quickest cure with the least toxicity and which makes the minimum demands on patient compliance and so the least disturbance to the lives of the patient and the family. The comparative aspect is the great forte of well conducted randomised controlled trials.

An important feature of well conducted controlled clinical trials is to achieve an adequate intake of patients and a long-term follow up because of the need for an accurate assessment of relapse rates and late sequelae. In the home and sanatorium study[1] all (100%) of the 193 patients admitted were followed up to 5 years or until death, even those excluded from the main analysis.[91] The close family contacts were followed up too by tuberculin testing and chest X-ray for 5 years to compare the infection and disease rates in the 2 groups. A chest X-ray was obtained in over 99% of the surviving contacts at 5 years, including some who had emigrated to Pakistan.[92] Very high coverage has always been a feature of the Madras studies and a 5-year follow-up of patients the norm. This has been the result of a carefully planned organisation (pages 187 and 188) and the attitude of the staff to the patients and their determination that every patient would be followed up, whatever time and effort this entailed. In multicentre trials such exceptional coverage is less easily achieved. Nevertheless, if the coordination, both local and central, is skilled and close contact with the centres is maintained a high level of long-term coverage and very complete data collection on each patient can still be achieved.

The NTI has also had a long research record, inevitably more orientated to epidemiological, operational and sociological investigations, but there has also been an important controlled trial component because of its value in comparing alternative approaches and interventions.

A high proportion of all controlled clinical trials in tuberculosis, both in technically advanced and developing countries, are uninformative because they are too small or because the drop out rate is high and the period of observation too short. The aim for India should be to evade these major deficiencies because they are avoidable as the TRC and the NTI have shown. The TB Association of India's 6 controlled trials were hampered by inadequate budgets for the research and the consequences that stemmed from this basic fact (Pamra, personal communication).

In the same compound as the TRC is another ICMR unit, The Institute for Research in Medical Statistics (Madras Chapter). Its director, Dr. S. Radhakrishna, was the Head of the Statistics Department of the Madras Centre from 1956 to 1975 and so has had exceptional experience of tuberculosis research and is a gifted

teacher. His unit's programme is now wide ranging, covering many medical fields and includes operational, surveillance and sociological research.

There are, therefore, in South India 3 major institutions with an unusual experience and capacity to train not just district programme teams and various categories of leaders of the profession including administrators, but to train important categories of research workers, clinical, epidemiological, laboratory (especially bacteriological) and statistical as well. It is clear that careful consideration should be given to how best to use these resources, involving both the 2 Madras units and NTI. My own view is they should at least train research workers in all the necessary specialities, for this could lead to major improvements both in the scale and the national standard of tuberculosis research (pages 204 and 205) including the investigation of the vital operational problems which seem so intractable as currently viewed.

Conclusion

Although the National 20-point Plan has had some modest impact on the tuberculosis programme, a golden opportunity to launch a national crusade against the disease, under the stimulus of your late Prime Minister, Indira Gandhi's support, has to a large degree been so far missed. The switch to short-course chemotherapy was, to some extent, inevitable. There were pressures of the demands of private practitioners to have access to the modern potent rifampicin for short-course chemotherapy and of the patients who could afford to pay for it too, in addition to Government staff, both Central and State, eager to have it available, and the pharmaceutical industry naturally pressing to open the Indian market. Even so, the speed with which it has been introduced without major strengthening of the individual units of the infrastructure, and in many States any improvement of the broad framework or removal of as many of the obvious deficiencies as possible in organisation, training and supervision, could prove disastrous. It might lead to so much drug resistance to isoniazid, to rifampicin and to both drugs in patients newly presenting for treatment as eventually to render short-course chemotherapy, based on the currently available drugs, no longer effective at a community level, unless the infrastructure, and with it, patient compliance, is greatly improved, a subject I have emphasised in this paper and repeatedly elsewhere.

In my view, the time has unquestionably come for India to set up a long-term adequately funded National Tuberculosis Standing Committee (a term I prefer to a Task Force) with wide terms of reference and authority appropriate to its important national role. It may well need its own small whole time secretariat. The membership must be the real experts in the field drawn from an appropriately wide range of disciplines (selected on the basis of ability and not seniority). They must review and rethink the national policies and in particular their priorities, the organisation and especially whether regionalisation has a role or a mobile team or teams able to undertake intensive and large-scale training at a State level, the many issues that ensue with drug supplies, the regimens, the monitoring, the involvement of the community, the framework for establishing a substantially larger scale of high quality operational research and training. The major centres in the South, the NTI and TRC, as currently staffed and constituted, are clearly not enough in a country as large as India. The ICMR obviously has a key role, and the Technical Committee of the Tuberculosis Association of India could be a further valuable resource. Also, the relationship of the Central Government and the States in the implementation must be carefully interfaced. The funds for research will also need to be substantially larger to achieve better policies of case-finding, diagnosis, regimens and their successful implementation under programme conditions. However, the prize is great and the cost would be relatively small, especially if related to the cost of continuing rectifiable failures of the National Programme which already absorbed large sums of money even as estimated in 1986[93] by a previous Adviser in Tuberculosis to the Government of India.

Abbreviations used in this Report

NTI = National Tuberculosis Institute, Bangalore
TRC = Tuberculosis Research Centre, Madras
BMRC = British Medical Research Council
ICMR = Indian Council of Medical Research
WHO = World Health Organization

NTP = National Tuberculosis Programme
DPT = District Programme Team
DTO = District Tuberculosis Officer
DTC = District Tuberculosis Centre
PHI = Peripheral Health Institution

References

1. Tuberculosis Chemotherapy Centre, Madras. A concurrent comparison of home and sanatorium treatment of pulmonary tuberculosis in South India. Bull Wld Hlth Org 1959; 21 : 51.
2. Rani Balasubramanian, Sivasubramanian, S, Vijayan, VK *et al.* Five-year results of a 3-month and two 5-month regimens for the treatment of sputum-positive pulmonary tuberculosis in South India. Tubercle, 71, December 1990.
3. Nagpaul, DR. India's National Tuberculosis programme--an overview. Ind J Tub 1989; 36 : 205.
4. Aluoch, J. Swai, OB, Edwards EA *et al.* Study of case finding for pulmonary tuberculosis in outpatients complaining of a chronic cough at a District hospital in Kenya. Am Rev Respir Dis 1984; 129 : 915.
5. Aluoch, J., Swai, OB., Edwards, EA *et al.* Studies of case-finding for pulmonary tuberculosis in outpatients at 4 District hospitals in Kenya. Tubercle 1985; 66 : 237.
6. Baily, GVJ., Savic, D., Gothi, GD., Naidu, VB., Nair, SS. Potential yield of pulmonary tuberculosis cases by direct microscopy of sputum in a District of South India. Bull Wld Hlth Org 1967; 37 : 875.
7. Nagpaul, DR, Savic, DM, Rao, KP, Baily, GVJ. Case-finding by microscopy. Bull Int Un Tuberc 1968; 41 : 148.
8. Jagota, P., Gupta, EVV., Rao, BSN, Parimala, N, Baily, GVJ. The acceptability and efficacy of two regimens of short-course chemotherapy under conditions of an urban tuberculosis programme. Ind J Tub 1983; 36 : 18.
9. Editorial. Expanded programme of health education and community involvement. Ind J Tub 1990; 37 : 55.
10. Fox, W. Short-course chemotherapy for pulmonary tuberculosis and some problems of its programme application with particular reference to India. Lung India 1984; 2 : 161. Also published in Bull Int Un Tuberc 1985; 60 : 40.
11. Radhakrishna, S., Satagopan, MC., Krishnaswami, KV., Tripathy, SP., Vaidyanathan, B., Fox, W. A study of the accuracy, and factors influencing accuracy, of home addresses of patients obtained by registry clerks and address cards in four large towns in South India. Tubercle 1980; 61 : 197.
12. Krishnaswami, KV., Somasundaram, PR., Tripathy, SP., Vaidyanathan, B., Radhakrishna, S., Fox, W. A randomized study of two policies for managing default in out-patients collecting supplies of drugs for pulmonary tuberculosis in a large city in south India. Tubercle 1981; 61 : 103.
13. Seetha, MA., Srikantaramu, N., Aneja, KS., Singh, H. Influence of motivation of patients and their family members on the drug collection by patients. Ind J Tub 1981; 28 : 182.
14. Allan, WGL., Girling, DJ., Fayers, PM., Fox, W. The symptoms of newly diagnosed pulmonary tuberculosis and patients attitudes to the disease and to its treatment in Hong Kong. Tubercle 1979; 60 : 211.
15. Hong Kong Chest Service/British Medical Research Council Survey of patients presenting to the government chest service in Hong Kong and the effects of active tuberculosis case-finding by publicity campaigns. Tubercle 1984; 65 : 173.
16. WHO Collaborating Centre for Tuberculosis chemotherapy, Prague. A comparative study of daily and twice-weekly continuation regimens of tuberculosis chemotherapy including a comparison of two durations of sanatorium treatment. Bull Wld Hlth Org 1971; 45 : 573.
17. British Medical Research Council. Co-operative controlled trial of a standard regimen of streptomycin, PAS and isoniazid and three alternative regimens of chemotherapy in Britain. Tubercle 1973; 54 : 99.
18. Editorial. General Practitioners and Tuberculosis. Ind J Tub 1981; 28 : 43.
19. Editorial. Tuberculosis service at the periphery. Ind J Tub 1981; 28 : 161.
20. Dutt, AK., Jones, L., Stead, WW. Short-course chemotherapy for tuberculosis with largely twice-weekly isoniazid-rifampicin. Chest 1979; 75 : 441.
21. Gangadharam, PRJ., Devadatta, S., Fox, W., Narayan, C., Nair, N., Selkon, JB. Rate of inactivation of isoniazid in South Indian patients with pulmonary tuberculosis. 3. Serum concentrations of isoniazid produced by three regimens of isoniazid alone and one of isoniazid plus PAS. Bull Wld Hlth Org 1961; 25 : 793.

22. Mitchison, DA., Dickinson, JM. Laboratory aspects of intermittent drug therapy. Postgrad Med J 1971; 47 : 737.

23. East African/British Medical Research Council. Controlled clinical trial of four short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. 2nd report. Lancet 1973; 1 : 1331.

24. East African/British Medical Research Councils. Controlled clinical trial of four short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. Third report. Lancet 1974; 2 : 237.

25. Wiseman, LA. Calendar (blister) packs for multidrug therapy in Leprosy : an inexpensive locally produced version. (Letter) Lepr Rev 1987; 58 : 85.

26. Ellard, G. Drug compliance in the treatment of leprosy. Lepr Rev 1981; 52 : 201.

27. Valeza, FS., McDougall, AC. Blister calendar packs for treatment of tuberculosis. Lancet 1990; 1 : 473.

28. Phillips S., Horton, GE. Pyrazinamide-isoniazid. Comparison with isoniazid-para-aminosalicylic acid in active pulmonary tuberculosis with the choice of regimens determined by chance. Am Rev Tuberc 1956; 73 : 704.

29. A United States Public Health Service Tuberculosis Therapy Trail. Sequential use of paired combinations of isoniazid, streptomycin, para-aminosalicylic acid, and pyrazinamide. Am Rev Respir Dis 1959; 80 : 627.

30. Matthews, JH. Pyrazinamide and isoniazid used in the treatment of pulmonary tuberculosis. Am Rev Respir Dis 1960; 81 : 348.

31. Hong Kong Tuberculosis Treatment Services/ Brompton Hospital/British Medical Research Council. A controlled clinical trial of daily and intermittent regimens of rifampicin plus ethambutol in the retreatment of patients with pulmonary tuberculosis in Hong Kong. Tubercle 1974; 55 : 1.

32. Hong Kong Tuberculosis Treatment Services/ Brompton Hospital/British Medical Research Council. A controlled clinical trial of daily and intermittent rifampicin plus ethambutol in the retreatment of patients with pulmonary tuberculosis : results up to 30 months. Tubercle 1975; 56 : 179.

33. Fox, W. Self-administration of medicaments. A review of published work and a study of the problems. In : Proceedings of the XVIth International Tuberculosis Conference held September 10th to 14th, 1961, at Toronto. Excerpta Medica, International Congress Series, No. 44, 1, 307, Amsterdam 1962.

34. Haynes, RB., Taylor, DW., Sackett. DL (Eds). Compliance in Health Care. The Johns Hopkins University Press, Baltimore, Maryland, 1979.

35. Fox, W. The current status of short-course chemotherapy. Bull Int Un Tuberc 1978; 53 : 268.

36. Medical Research Council. Treatment of pulmonary tuberculosis with streptomycin and para-aminosalicylic acid. Br Med J 1950; 2 : 1073.

37. Medical Research Council. The prevention of streptomycin resistance by combined chemotherapy. Br Med J 1952; 1 : 1157.

38. Fox, W. The chemotherapy and epidemiology of tuberculosis. Some findings of general applicability from the Tuberculosis Chemotherapy Centre, Madras. Lancet 1962; 2 : 413.

39. Tuberculosis Chemotherapy Centre, Madras. A concurrent comparison of isoniazid plus PAS with three regimens of isoniazid alone in the domiciliary treatment of pulmonary tuberculosis in South India. Bull Wld Hlth Org 1960; 23 : 535.

40. Dye, WE., Kass, I., Gill, R. Laboratory evaluation of the specific serum antimycobacterial activity test. Antimicrobial Agents and Chemotherapy 1961; 22 : 20.

41. National Jewish Hospital at Denver. Contributions to the study of tuberculosis and diseases of the chest, Vol. 21 1957-1960. Denver 1962.

42. World Health Organization. Tuberculosis control. Report of a joint IUAT/WHO Study Group. WHO Technical Report Series 671, Geneva, 1982.

43. Banks, J., Jenkins, PA. Combined versus single antituberculosis drugs on the *in vitro* sensitivity patterns of non-tuberculous mycobacteria. Thorax 1987; 42 : 838.

44. Banks, J. Treatment of pulmonary disease caused by opportunist mycobacteria. Thorax 1989; 44 : 449.

45. Mitchison, DA. The action of antituberculosis drugs in short-course chemotherapy. Tubercle 1985; 66 : 219.

46. Singapore Tuberculosis Service/British Medical

Research Council. Controlled trial of intermittent regimens of rifampicin plus isoniazid for pulmonary tuberculosis in Singapore. Am Rev Respir Dis 1977; 116 : 807.

47. Hong Kong Chest Service/British Medical Research Council. Study of a fully supervised programme of chemotherapy for pulmonary tuberculosis given once-weekly in the continuation phase in the rural areas of Hong Kong. Tubercle 1984; 65 : 5.

48. Mitchison, DA., Ellard, GA., Grosset, J. New antibacterial drugs for the treatment of mycobacterial disease in man. Br Med Bull 1988; 44 : 757.

49. Ellard, GA., Ellard, DR., Allen, BW *et al.* The bioavailability of isoniazid, rifampin, and pyrazinamide in two commercially available combined formulations designed for use in the short-course treatment of tuberculosis. Am Rev Respir Dis 1986; 133 : 1076.

50. Hong Kong Chest Service/British Medical Research Council. Acceptability, compliance, and adverse reactions when isoniazid, rifampin, and pyrazinamide are given as a combined formulation or separately during three-times weekly antituberculosis chemo-therapy. Am Rev Respir Dis 1989; 140 : 1618.

51. Geiter, LJ., O'Brien, RJ., Combs, DL., Snider, DE. United States Public Health Service tuberculosis therapy trial 21 : preliminary results of an evaluation of a combination tablet of isoniazid, rifampin and pyrazinamide. Tubercle Suppl 1987; 68 : 41.

52. Combs, DL., O'Brien, RJ., Geiter, LJ. USPHS tuberculosis short-course chemotherapy trial 21 : effectiveness, toxicity, and acceptability. An Int Med 1990; 112 : 397.

53. Algeria Working Group/British Medical Research Council Cooperative Study. Short-course chemotherapy for pulmonary tuberculosis under routine programme conditions : a comparison of regimens of 28 and 36 weeks duration in Algeria. Tubercle Vol. 72, March 1991.

54. Cavenaghi R. Rifampicin raw material characteristics and their effect on bioavailability. Bull Int Un Tuberc Lung Dis 1989; 64 : 36.

55. Aspesi, F. Dissolution testing. Bull Int Un Tuberc Lung Dis 1989; 64 : 37.

56. Acocella, G. Human bioavailability studies. Bull Int Un Tuberc Lung Dis 1989; 64 : 38.

57. Long, MW., Snider, DR., Farer, LS., US Public Health Service cooperative trial of three rifampin-isoniazid regimens in treatment of pulmonary tuberculosis. Am Rev Respir Dis 1979; 119 : 879.

58. Pamra, S. Discussion. Bull Int Un Tuberc Lung Dis 1989; 64 : 40.

59. Editorial. Multi-drug formulations. Ind J Tub 1988; 35 : 161.

60. Satellite symposium on quality control of antituberculosis drugs. Bull Int Un Tuberc Lung Dis 1989; 64 : 36.

61. Reichman, Discussion. Bull Int Un Tuberc Lung Dis 1989; 64 : 42.

62. WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce : Guidelines for use. WHO Drug Information 1989; 3 : 109.

63. Brechbuhler, S., Fluehler, H., Riess, W., Theobald, W; The renal elimination of rifampicin as a function of the oral dose. A convenient way to assess relative bioavailability. Arzneim. Forsch./Drug Res. 1978; 28 : 480.

64. Sunahara, S., Nakagawa, H. Metabolic study and controlled clinical trials of rifampicin. Chest 1972; 61 : 526.

65. Editorial. Availability of anti-tuberculous drugs. Ind J Tub 1985; 32 : 169.

66. Dubey, GR., Shah, RC., Kamat, ST *et al.* A study of efficacy and toxicity of short-course chemotherapy with ethambutol, rifampicin, pyrazinamide and isoniazid in pulmonary tuberculosis. Lung India 1985; 3 : 115.

67. Tiwari, US., Mishra, BP. Ocular toxicity of ethambutol. A clinical study. Lung India 1987; 5 : 111.

68. Editorial. The new drug policy. Ind J Tuberc 1987; 34 : 179.

69. Fox, W., Wiener, A., Mitchison, DA., Selkon, JB., Sutherland, I. The prevalence of drug-resistant tubercle bacilli in untreated patients with pulmonary tuberculosis : A national survey, 1955-56. Tubercle 1957; 38 : 71.

70. Miller, AB., Tall, R., Fox, W., Lefford, MJ., Mitchison, DA. Primary drug resistance in pulmonary tuberculosis in Great Britain : Second national survey, 1963. Tubercle 1966; 47 : 92.

71. Medical Research Council Tuberculosis and Chest Diseases Unit. National survey of tuberculosis notifications in England and Wales 1978-79. Br Med J 1980; 281 : 895

72. Medical Research Council Tuberculosis and Chest Diseases Unit. National survey of notifications of tuberculosis in England and Wales 1983. Br Med J 1985; 291 : 658.

73. East African/British Medical Research Council Co-operative Investigation. Tuberculosis in Kenya : a national sampling survey of drug resistance and other factors. Tubercle 1968; 49 : 136.

74. East African and British Medical Research Council Co-operative Investigation. Tuberculosis in Kenya : a second national sampling survey of drug resistance and other factors, and a comparison with the prevalence data from the first national sampling survey. Tubercle 1968; 59 : 155.

75. A Kenyan/British Medical Research Council Co-operative Investigation. Tuberculosis in Kenya 1984 : a third national survey and a comparison with earlier surveys in 1964 and 1974. Tubercle 1989; 70 : 5.

76. An East African and British Medical Research Council Co-operative Investigation. Tuberculosis in Tanzania : A national sampling survey of drug resistance and other factors. Tubercle 1975; 56 : 269.

77. Tanzanian/British Medical Research Council Co-operative Investigation. Tuberculosis in Tanzania : A national survey of newly notified cases. Tubercle 1985; 66 : 161.

78. Indian Council of Medical Research. Prevalence of drug resistance in patients with pulmonary tuberculosis presenting for the first time with symptoms at chest clinics in India. Part I. Findings in urban clinics among patients giving no history of previous chemotherapy. Ind J Med Res 1968; 56 : 1617.

79. Indian Council of Medical Research. Prevalence of drug resistance in patients with pulmonary tuberculosis presenting for the first time with symptoms at chest clinics in India. Part II. Findings in urban clinics among all patients, with or without history of previous chemotherapy Ind J Med Res 1969; 57 : 823.

80. Hong Kong Government Tuberculosis Service/ British Medical Research Council Co-operative Investigation. Drug-resistance in patients with pulmonary tuberculosis presenting at chest clinics in Hong Kong. Tubercle 1964; 45 : 77.

81. Mitchison, DA., Nunn, AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. Am Rev Respir Dis 1986; 133 : 423.

82. Jagota, P., Srinivas, TR., Parimala, N., Chaudhuri, K. The fate of resistant cases treated with three different drug regimens of short course chemotherapy under programme conditions. Ind J Tub 1990; 37 : 83.

83. Indian Council of Medical Research/British Medical Research Council Working Party Study in Madras, South India. A controlled trial of short-course regimens of chemotherapy in patients receiving ambulatory treatment or undergoing radical surgery for tuberculosis of the spine. Ind J Tub 1989; 36 : (Suppl) 1.

84. Strang, JIG., Kakaza, HHS., Gibson, DG., Girling, DJ., Nunn, AJ., Fox, W. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. Lancet 1987; 2 : 1418.

85. Strang, JIG., Gibson, DG., Mitchison, DA *et al.* Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous pericardial effusion in Transkei. Lancet 1988; 2 : 759.

86. Ramachandran, P., Duraipandian, M., Nagarajan, M., Prabhakar, R., Ramakrishnan, CV., Tripathy, SP. Three chemotherapy studies of tuberculous meningitis in children. Tubercle 1986; 67 : 17.

87. Jawahar, M.S., Sivasubramanian, S., Vijayan, U.K. *et al.* Short course chemotherapy for tuberculous lymphadenitis in children. Br Med J 1990; 301 : 359.

88. Editorial. Hospitalization for pulmonary tuberculosis. Ind J Tub 1988; 35 : 1.

89. Fox, W. Tuberculosis case-finding and treatment programmes in the developing countries. Br Med Bull 1988; 44 : 717.

90. World Health Organization. Tuberculosis control as an integral part of primary health care. WHO, Geneva, 1988.

91. Dawson, JJY., Devadatta, S., Fox, W *et al.* A 5-year study of patients with pulmonary tuberculosis in a concurrent comparison of home and sanatorium treatment for one year with isoniazid plus PAS. Bull Wld Hlth Org 1966; 34 : 533.

92. Kamat, SR., Dawson, JJY., Devadatta, S *et al.* A controlled study of the influence of segregation of tuberculous patients for one year on the attack rate of tuberculosis in a 5-year period in close family contacts in South India. Bull Wld Hlth Org 1966; 34 : 517.

93. Gupta, SP. Financial implications of tuberculosis control. Ind J Tub 1986; 33 : 101.

- strong biomed / chemother / apper. + research — one particular 'source' influenced one's perspective
- technology + hence implicitly industry oriented
- very presumptive - the 'expert' telling us what to do
- A large no. of these ideas are now incorporated into the RNTP ! indicating power + influence of some thinkers
- Harnesses + uses data extremely well

PTB for Asia

1. lack of drugs, drug prod + supply, diff in obtaining info / secrecy about the
2. drug use
3. danger of resistance (SCC) community / [illegible] for ISR 2 mths
4. controversy over advocacy of hospitalisation / domiciliary (Styblo & IUATLD) to enable all dosage and taken + ambulatory / dose & even for village pts — Fox, India, WHO

Ind. J. Tub., 1988, 35, 110

DIRECT IMPACT OF TREATMENT PROGRAMME ON TOTALITY OF TUBERCULOUS PATIENTS IN THE COMMUNITY*

S. RADHAKRISHNA**

The direct impact of any tuberculosis treatment programme depends upon the extent to which cases are detected in the community by radiographic, bacteriological and other investigations ('case-finding' efficiency), the degree of success attained in getting patients to complete their prescribed course of treatment ('case-holding' efficiency), and the therapeutic efficiency of combinations of anti-tuberculosis drugs employed ('chemotherapy' efficiency). Some patients have a successful outcome even without completing their prescribed course of treatment; the proportion who do so, relative to the proportion who have a favourable response at the end of the prescribed course, may be defined as the "relative efficacy" of chemotherapy in patients not completing the prescribed duration of treatment.

Available information (Table 1) indicates that in the National Tuberculosis Programme, the efficiencies are about 30% for case-finding (Nagpaul, 1967), about 35% for case-holding (National TB Programme, 1979), about 80% for chemotherapy (Radhakrishna, 1983), and about 50% for efficacy (Baily et al, 1974). From these estimates, it can be deduced that the proportion of tuberculous patients in the community who are successfully treated is 16% (Fig. 1).

More generally, if X, Y and Z denote the efficiencies of case-finding, case-holding and chemotherapy and K denotes the relative efficacy, the overall success rate (S) is given by $S=XZ\{Y+(1-Y)K\}$, where X, Y, Z, K and S are all proportions.

If the case-finding efficiency is increased from 30% to 40%, but all the other efficiencies remain unaltered, the overall success rate turns out to be 21.6%, i.e. there is an increase of 5.4%. The increase is the same for a 10% increase from 40% to 50%, 50% to 60%,... or 90% to 100% (Table 2), i.e., it is independent of the base level of the case-finding efficiency. The same independence can be demonstrated for any specified increase in case-holding efficiency (case-finding and chemotherapy efficiencies being fixed) and for any specified increase in chemotherapy efficiency (case-finding and case-holding efficiencies being fixed). It may therefore be concluded that the increase in the overall success rate for a specified increase in the efficiency of only one of the components is the same, whatever the basic level of component.

The increase in the overall success rates(S) following a 10% increase in case-finding efficiency is set out in Table 3, for various levels of case-holding efficiency and chemotherapy efficiency but keeping the relative efficacy of chemotherapy in patients not completing the prescribed course at 50%. It is clear that the increase in overall success rate tends to increase with case-holding and chemotherapy efficiency levels. Indeed, when they take values of 95% and 95%, the increase in success rate becomes as high as 9.3% (cf 5.4% above).

Table 1

Factors affecting overall success rate

Factor	Efficiency
Case-finding	30%
Case-holding	35%
Chemotherapy	80%
Patients who do not complete prescribed course of treatment	
Relative efficacy	50%
Actual efficacy	40%

Table 2

Increase in overall rate for 10% increase in case-finding efficiency, case-holding and chemotherapy efficiencies being fixed at 35% and 80%

Case-finding efficiency	Overall success	Increase
30%	86.2%	
		5.4%
40%	21.6%	
		5.4%
50%	27.0%	
		5.4%
60%	32.4%	
		5.4%
70%	37.8%	
		5.4%
80%	43.2%	
		5.4%
90%	48.6%	
		5.4%
100%	54.0%	

The corresponding increases in the overall success rate (S) following a 10% increase in only the case-holding efficiency are set out in Table 4. At current efficiency levels of case-finding (30%) and chemotherapy (80%), the increase is only 1.2% (cf 5.4% in Table 3). The general pattern of the findings is very similar to that in Table 3. However, a close comparison of the two tables (Tables 3 and 4) shows that the increases in overall success rate are consistently and appreciably greater for a specified increase

*Special lecture delivered at 42nd National Conference on Tuberculosis and Chest Diseases, held at Lucknow in December 1987.

**Director, Institute for Research in Medical Statistics, Spur Tank Road, Madras-600 031.

FIG. I

OVERALL SUCCESS RATE

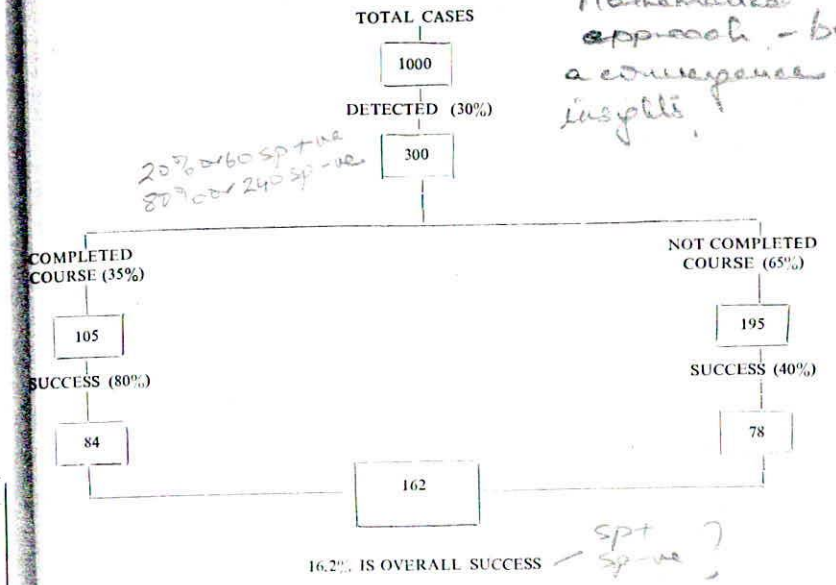

Table 3

Increase in overall success rate following 10% increase in case-finding efficiency, at various levels of case-holding and chemotherapy efficiency

Efficacy of chemotherapy*	Case-holding efficiency (%) 35	55	75	95	Range
80%	5.4	6.2	7.0	7.8	5.4—7.8
85%	5.7	6.6	7.4	8.3	5.7—8.3
90%	6.1	7.0	7.9	8.8	6.1—8.8
95%	6.4	7.4	8.3	9.3	6.4—9.3

*In those completing the course

Table 4

Increase in overall success rate following 10% increase in case-holding efficiency, at various levels of case-finding and chemotherapy efficiency

Efficacy of chemotherapy*	Case-finding efficiency (%) 30	50	70	90	Range
80%	1.2	2.0	2.8	3.6	1.2—3.6
85%	1.3	2.1	3.0	3.8	1.3—3.8
90%	1.3	2.2	3.1	4.0	1.3—4.0
95%	1.4	2.4	3.3	4.3	1.4—4.3

*In those completing the course

(10%) in case-finding efficiency compared to the same increase (10%) in case-holding-efficiency.

Next, the increases in the overall success rate(S) following a10% increase in the efficacy of chemotherapy are set out in Table 5. At current levels of case-finding (30%) and case-holding (35%), the improvement in success rate is only 2.0%. However, if both these efficiencies begin to increase, the benefit from better chemotherapy *per se* will also increase; for instance, if both case-finding and case-holding efficiencies increase by 40%, to 70% and 75%, respectively, the increase in overall success rate for a 10% increase in chemotherapy efficacy is 6.1%, as compared to the earlier 2.0%.

A modest target in the national tuberculosis programme could be to successfully treat at least 50% of the totality of tuberculous patients in the community. Table 6 sets out various "mixes" of case-finding, case-holding and chemotherapy efficiencies that are the needed for the attainment of this objective. When deriving these, it has been assumed that the efficiency of case-holding will always be higher than that of case-finding, or at least the same but never lower. Such a stipulation is necessary if we are avoid a situation where large numbers of patients are diagnosed and brought under treatment because of better case-finding efficiency, but very few complete the course because of low case-holding efficiency; such a situation could lead to a dangerous increase in the level of drug resistance in the community, with all its consequent epidemiological implications.

With standard regimens that are currently in vogue in the treatment programme and have an efficacy of approximately 80%, we need a case-finding efficiency of 65% provided we can ensure case-holding efficiency of 95%. If case-holding efficiency cannot be raised to such a high level but can be made 80%, the level of case-finding efficiency required is 70%. If better chemotherapeutic regimens are introduced and the efficiency of chemotherapy is raised from 80% to 90%, a case-finding efficiency of 60% and a case-holding efficiency of 85% are required; alternatively, these could be 65% and 70% respectively. Even if very highly effective (95%) short-course chemotherapeutic regimens containing Rifampicin and Pyrazinamide are introduced in the programme, unless case-holding efficiency is 75%, and case-finding efficiency is 60% (or 90% and 55%, respectively), the modest target of successfully treating 50% of the tuberculous patients in the community cannot be attained.

The major implication of this mathematical study is that there should be a drastic reorientation of priorities in applied research in tuberculosis. While controlled clinical trials to evaluate new drugs and combinations and to evolve better regimens under experimental conditions

Table 5

Increase in overall success rate following 10% increase in chemotherapy efficiency, at various levels of case-finding and case-holding efficiency

Case-finding efficiency (%)	Case-holding efficiency (%)			
	35	55	75	95
30	2.0	2.3	2.6	2.9
50	3.4	3.9	4.4	4.9
70	4.7	5.4	6.1	6.8
90	6.1	7.0	7.9	8.8

Table 6

*Combinations leading to overall success rate of 50%**

Efficacy of chemotherapy**	Case-finding efficiency	Case-holding efficiency
80%	65%	95%
	70%	80%
85%	60%	95%
	65%	80%
	70%	70%
90%	60%	85%
	65%	70%
95%	55%	90%
	60%	75%

*With the stipulation that the efficiency of case-holding is at least as high as that of case-finding.

**In patients completing the prescribed course of treatment. In the others, the efficacy is taken to be half this efficiency.

will continue to have a place, the focus has to shift in a big way to operational research aspects under programme conditions. Unfortunately, very little attention has been devoted to these aspects in the last three decades. A brief review of the limited research undertaken in these areas by institutions such as the National Tuberculosis Institute, Tuberculosis Research Centre and the New Delhi TB Centre was made earlier (Radhakrishna, 1983).

Short-course chemotherapy has been demonstrated to be very highly effective in clinical trials; practically all patients have a favourable response, i.e bacteriologically quiescent disease at the end of the course of treatment, and relapses occur in no more than 5% of the patients. In consequence, short-course regimens have already been introduced into the District Tuberculosis Programme in 18 districts in the country, and plans are afoot to bring more districts into this activity. This development presents both a tremendous opportunity and a stiff challenge. It is vital that this special input (short course chemotherapy) should be utilised as an occasion for initiating quality research on operational aspects. In particular, innovative strategies must, to begin with, be explored empirically under DTP conditions, and those that appear promising must then be evaluated scientifically, with adequate replication and controls. These investigations need to be directed towards vital aspects such as improved case-holding and case-finding efficiencies, smooth drug delivery systems and reliable documentation.

REFERENCES

Baily, G.V.J., Rupert Samuel, G.E. and Nagpaul, D.R. A concurrent comparison of an unsupervised self-administered daily regimen and a fully supervised twice-weekly regimen of chemotherapy in a routine out-patient treatment programme. *Indian J. Tuber.*, 1974, *21*, 152.

Nagpaul, D. R. District Tuberculosis Control Programme in concept and outline. *Indian J. Tuber.*, 1967, *14*, 186.

National Tuberculosis Programme—Report for IVth quarter (sputum positive cases), 1979.

Radhakrishna, S. National Tuberculosis Programme—Relative merits of enhancing the operational efficiency of different components of the treatment programme. *Indian J. Tuber.*, 1983, *30*, 3.

ted from leprosy patients three hours after the administration of clofazimine (and dapsone), 7 specimens (26%) gave a positive reaction by the chloroform method. No specimen was reported positive by the benzene method by any of the three readers, a significant difference (P=0.01).

Reader variation: Of 700 tests (by each method) from patients receiving rifampicin, one reader disagreed with the other two on five occasions by each of the two methods. In the remaining 695 tests, identical results were reported by all three readers.

In the case of the 27 urine specimens containing clofazimine, on 11 occasions one reader disagreed with the other two by the chloroform method, while there was no disagreement on any specimen by the benzene method.

Discussion

Tests for the detection of rifampicin in urine have been described using simple extraction of the urine with either chloroform or benzene. Both tests gave 98-100% positive reactions between 3 and 11 hours after the administration of approximately 15 mg/kg body-weight of rifampicin in this study.

The tests described by Eidus and Harnanansingh (1969) yielded 100% positive reactions from two to eight hours after 300 mg dose using urine and chloroform in the ratio of 5 : 1. The microbiological method of Mitchison et al (1970) yielded positive results upto 12 hours after the conventional dose of 600 mg. This test, though simple, can be performed only in laboratories equipped to carry out microbiological work, and further, it requires at least 24 hours before the results are available.

The present method using chloroform is a simplification of the Eidus and Harnanansingh (1969) procedure and can be performed even under field conditions. The tests are simple, specific and sensitive, and no positive reactions were obtained among the O-hour specimens or among specimens from patients receiving other anti-tuberculous drugs with either test. Clofazimine, which also yields a reddish coloration of the urine similar to rifampicin, gave positive reactions only with the chloroform method. Further, chloroform has a tendency to form an emulsion with the aqueous layer, necessitating centrifugation on some occasions (Eidus and Harnanansingh, 1969). Also, chloroform being heavy, forms the lower layer, and hence, there is a reflection of the upper aqueous layer, especially in dark-coloured urines, which might interfere with the reading. Finally, chloroform is twice as expensive as benzene. Thus, the benzene method appears to be superior to the chloroform extraction procedure. The benzene extraction procedure in this study yielded 98-100% positive results for rifampicin in urine between 3 and 11 hours after oral administration of the drug. In clinical practice, this means that if the drug is self-administered in the morning, on rising, or a supervised dose is given on attendance at a clinic, then positive results could be expected at any time between 3 hours after the administration of drug to midday or late in the evening.

Acknowledgement

The authors thank the clinical and nursing staff of this Centre for collection of specimens, and Shri K.J. Ilampurnan and Shri P. Peter for technical assistance and reading the tests. The valuable suggestions of Prof. Wallace Fox in the preparation of this manuscript are gratefully acknowledged.

REFERENCES

Eidus, L. and Harnanansingh, A.M.T.: Simple procedures for checking rifampicin in urine. Amer. Rev. Resp. Dis., 1969, **100**, 738.

Hobby, G.L.: Practical methods of detecting major anti-tuberculosis drugs in the urine. Adv. Tub. Res., 1964, **13**, 98.

Mitchison, D.A., Allen, B.W. and Miller, A.O.: Detection of rifampicin in urine by simple microbiological assay. Tubercle, 1970, **51**, 300.

Rao, K.V.N., Eidus, L., Jacob, C.V. and Tripathy, S.P.: A simple test for the detection of pyrazinamide and cycloserine in urine. Tubercle, 1965, **46**, 199.

Rao, K.V.N., Eidus, L., Jacob, C.V., Radhakrishna, S. and Tripathy, S.P.: Sodium nitroprusside test for the detection of isoniazid and acetylisoniazid in urine. Tubercle, 1967, **48**, 45.

Venkataraman, P., Eidus, L., Tripathy, S.P. and Valu, S.: Fluorescence test for the detection of ethionamide metabolites in urine. Tubercle, 1967, **48**, 291.

Ind. J. Tub., 1988, 35, 117

ALTERNATIVE TUBERCULOSIS CONTROL STRATEGIES AND THEIR POTENTIAL IMPACT

V. SIVARAMAN*, V. BALU,** AND V. FLORA**

The merits and demerits of various tuberculosis control strategies have been engaging the attention of the programme planners since the very evolution of the national tuberculosis programme. Among the parameters used for finding the suitability of the strategies one can cite (i) Operational feasibility, (ii) Resources involved, (iii) Cost effectiveness. Another parameter which can be used is the long term epidemiological impact, which can be assessed through epidemetric models. Such models in the Indian context have been discussed before by Waaler et al (1974). Nair (1977), Sivaraman and Umasankar (1979).

The aim of this paper is to present the use of a model to assess the impact of possible alternative strategies with a view to help in decision-making on choice of a suitable strategy.

I. The Model

An epidemetric model is a mathematical representation of the epidemiological situation in a community. The construction of the model rests upon grouping of population in different epidemiological classes determining their sizes and transfer rates and on a series of established facts and assumptions. A simulation model of tuberculosis epidemiology evolved by Azuma (1976) has been shown to be suitable to Indian conditions with slight modifications (Sivaraman and Umasankar *loc cit*), Predictions have been made upto the year 1986. The predictions were very close not only to survey results from National Tuberculosis Institute and New Delhi Tuberculosis Centre but also to predictions from a more sophisticated model.

Need for taking a fresh look at the projections and conclusions drawn from the previous model has arisen, not only because the previous predictions were made only upto the year 1986 but also because of the following subsequent developments.

(1) Demonstration of a very low efficacy for B.C.G.
(2) Possibility of using short course chemotherapy.
(3) Data from N.T.P. reports which indicate a rising trend of case finding coverage.

The modifications now made in the model include the following.

(1) Birth and Death rates were calculated by applying b=0.9817 and d=0.9674 to BO=0.0439 & DO=0.0223 (This is to facilitate operation by computer and agrees very closely with the initial parameter used).

(2) It is assumed that BCG does not offer any protection, other assumptions made in the previous paper (Sivaraman and Umasankar *loc cit*) remain valid but different operational and technical input data are used depending upon the programme envisaged.

These changeg and the longer time horizon envisaged entail time consuming and cumbersome calculations. Hence a computer programme has been written in Basic and run, and outputs analysed.

II. Simulations Done

(1) A hypothetical non-interference situation when no control programme is operated.

(2) The past programme from 1961 to 1986 has been simulated by feeding the model with the data on operational parameters obtained from N.T.P. reports.

(3) As for the future, 4 alternative strategies are envisaged :

(a) The case finding coverage maintains the same trend noticed in the previous years but short course chemotherapy is introduced with effect from 1988.

(b) Same as (a) above but short course chemotherapy introduced with effect from 1990.

(c) Same as (a) above but short course chemotherapy is introduced with effect from 1996.

(d) Efforts are made to realise the full potential of the district tuberculosis programme.

*Medical Superintendent **Assistant Surgeon
T.B. Sanatorium, Gorimedu, Pondicherry-605 006

III. Computation of Input Parameters for Different Simulations

(1) Non-interference situation serves as a base line and is obtained by assigning the value O to case finding coverage and treatment regularity.

(2) *Past Programme* : Annual reports on the performance of DTPs are being published; (N.T.I. 1985-1986) the reports indicate that the number of sputum positive cases diagnosed per DTP has risen from 536 in 1981 to 735 in 1985. If it were assumed that the number of sputum positive cases prevalent in an average DTP is around 6,000, the case finding coverage thus has varied from 9% to 12%. From this a "guesstimate" of case finding coverage in 1961 has been arrived at and is assumed to be 6%. From these annual reports it is also known that the percentage of patients completing chemotherapy has been more or less stationary at 27% from 1981 to 1985. The cure rate among patients completing 80% or more of prescribed treatment is set at 65%. The cure rate in those incompletely treated and not treated is assumed to be 10%.

(3) **Future Programmes**

(A) The case finding coverage and the percentage of patients completing 80% and more of treatment are the same as before. Introduction of short course chemotherapy is simulated by assigning a higher treatment completion rate of 45% and a higher cure rate among fully treated 75% as well as among inadequately treated (21%). Death rate among incompletely treated will be assigned the value of 13% (Death rate among lost cases).

These figures are derived from the findings of the TRC study on application of short course chemotherapy under programme conditions in North Arcot.

(B & C) In these simulations only the year of implementation of short course chemotherapy 1990 in B, and 1996 in C, is different from the previous one.

(D) Operational studies carried out in National Tuberculosis Institute have shown that if D.T.P. is implemented as per manuals, 85% cure rate among fully treated, 48% treatment completion rate and 33% case finding coverage can be achieved. In this simulation, it is assumed that the case finding coverage increases steadily over the years from 12.7% in 1986 to 33% in 1995.

The trend in case finding coverage (observed in the past and predicted for the future) is shown in Figure 1. The varying parameters in different simulations are summarised in Table I.

Results

The reduction in the various indices brought about by alternative strategies is shown in Table II.

The postponement of introduction of short course chemotherapy by 8 years (1996 in strategy C, 1988 in strategy A) has led to a marginal drop of reduction potential, the difference being 0.7% for problem reduction. 0.6%, 0.5% and 1.2% for prevalence, mortality and risk of infection respectively.

The likely epidemiological situation in 1995 is shown in Table III. Here also it is seen that differences between strategies A, B, and C are only marginal while a full potential programme is likely to lead to considerable improvements.

The trend in prevalence of disease and the risk of infection with alternative strategies is shown in figs. 2 and 3. As the trends with A, B and C are very close only B is shown. It is seen that there is a rise in prevalence rate with programmes A & B after 1999.*

The conclusion to be drawn is that no effort should be spared to increase the case finding coverage otherwise the tuberculosis problem is likely to worsen. Radhakrishna (1983) has observed that the overall success of the programme rests much more heavily on improving the efficiency of case finding and case holding than on evolving more and more effective drug regimens under study conditions.

Another interesting feature is that the *absolute* number of cases goes on increasing with all strategies although the prevalence *rate* decreases.* In this connection the following observations by Waaler (1982) are relevant. "The population of India increased by 2.2% per year between 1971 and 1977 and that aged 55 and more, increased by 11% per year with 8% of the population above 55 years of age and with, say a 3 times higher incidence above this age, this demographic change alone will increase the tuberculosis problem by 3.4%. Even an annual reduction in the overall rate of 2.2% per year (equal to the increase in the population) cannot prevent an increase in the absolute number of cases"

*Detailed tables may be obtained directly from the author, if so desired.

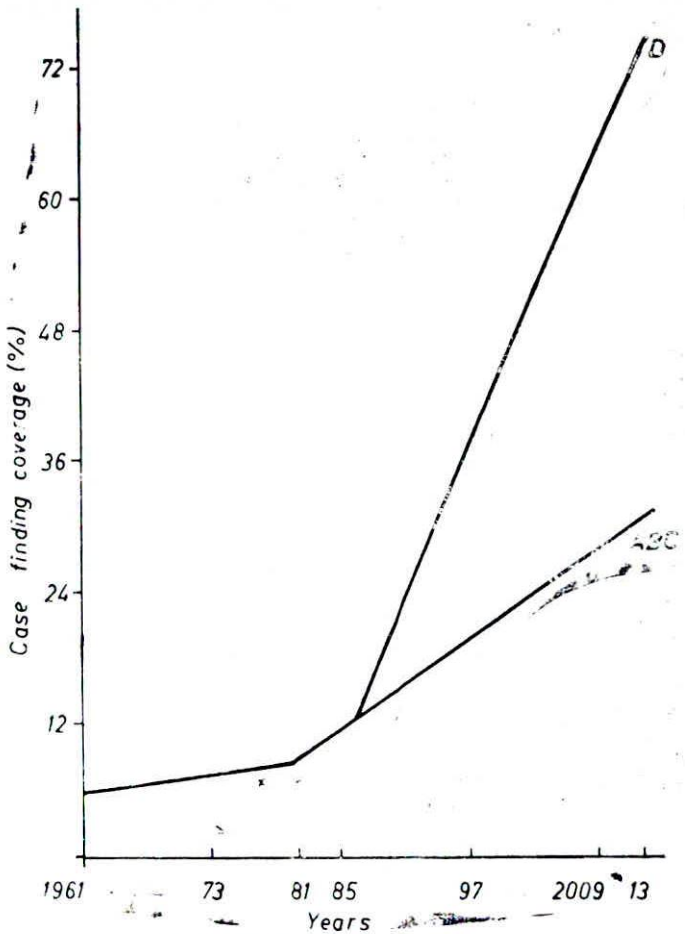

Fig. 1. Trend in case finding coverage

Table I
Parameters ssed in different simulations

		Non Interference	Past Prog-1961-'86	SCC A, B, C.	Future Prog-D
PERCENTAGE REG.		0	27%	45%	27%
AMONG REG :	Cure rate	—	65%	75%	85%
	Death rate	—	4%	4%	4%
AMONG IRREG :	Cure rate	—	10%	21%	10%
	Death rate	—	17%	13%	17%

REG : Patients completing Treatment IRREG : Patients with incomplete treatment

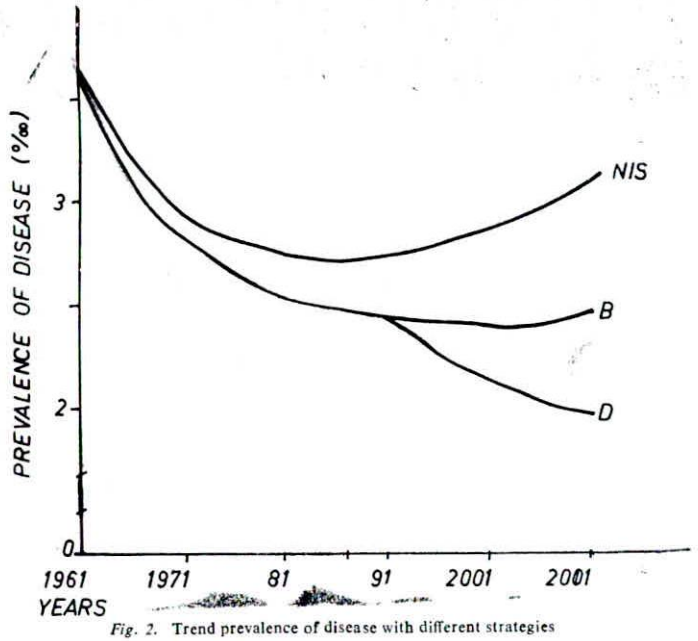

Fig. 2. Trend prevalence of disease with different strategies

Table II

Potential impact of alternative strategies

Strategies	TB Cases	TB Problem*	TB Mortality			Prevalence (Per thousand)			Risk of Infection (5		
	Number	Reduction %	Initial (1987)	Final (2012)	Reduction	Initial	Final	Reduction %	Initial	Final	Reduction**
No. TB Programme	253553	0	0.4612	0.5829	+12.8**	2.85	3.26	+12.6**	114	1.30	+12.3**
A. Introduction of SSC in 1988	226126	10.82	0.4234	0.3993	5.7	2.51	2.46	2	0.87	0.79	9.2
B. Introduction of SCC in 1990	226551	10.65	0.4234	0.4001	5.5	2.51	2.46	2	0.87	0.80	8
C. Introduction of SSC in 1996	227900	10.12	0.4234	0.4018	5 1	2 51	2.47	1.5	0.87	0.87	8
D. Full potential of D.T.P.	211702	16.51	0.4234	0.2905	31.4	2.51	1.89	35	0.87	0.33	62

*Defined as number of years of active infectious tuberculosis.
**In this situation there is no reduction, only a rise.

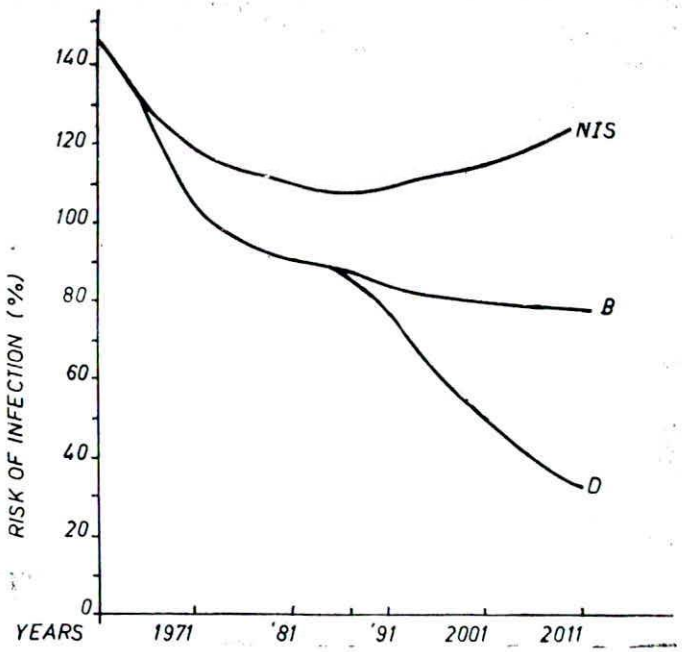

Fig. 3. Trend of risk of infection with two different strategies

Table III

Possible epidemiological situation in 1995

	Prevalence of Disease (Per 1,000)	Risk of Infection (Per 100)
NON INTERFERENCE	2.77	1.10
Introduction of SCC in A. 1988	2.40	0.82
B. 1990	2.41	0.82
C. 1996	2.49	0.84
Full Potential of Programme	2.28	0.64

The implications for the programme planner are clear, namely, the workload for the tuberculosis programme personnel is likely to increase both at the periphery and at DTC. To cope with it, more staff is likely to be required. Of course with the concept of integrated health care the burden has to be shared by multipurpose workers and a global view of the

workload from different health programmes has to be taken and staffing pattern might need a dynamic change.

Acknowledgement

We are grateful to the Director, Health and Family Welfare, Pondicherry for permission to present this paper; Thiru Kumararaja for his kind help in writing the computer programme and running it in the Computer; to Thiru Venkataramani for placing the Computer service at our disposal.

REFERENCES

Waaler, H.T., Gothi, G.D., Bailey G.V.J. Tub 26,4 Nair S.S. (1974) Bull. Wld. Hlth. Org. 51, 473.

Nair SS (1977) Ind. J. Pub Hlth 111, 31

Sivaraman, V. and Umasankar, V. : A Simulatio Model of Tuberculosis Epidemiology Adaptabilit to Indian Condition; 1979, 26, 4.

Azuma Y. (1975) Bull. Wld. Hlth. Org. 52, 313

NTI Newsletter (1985) 21/2. 38.

NTI Newsletter (1986) 22/2, 38

Radhakrishna, S. : National Tuberculosis Programm —Relative Merits of Enhancing the Operational Efficiency of Different Components of the Treatment Programme; 1983, 30, 3.

Waaler, H.T.; Tuberculosis and Socio-Economic Development; Bull. I.U.A.T., 1982, 57, 202.

---

2. SALIENT FEATURES OF WORK IN SELECTED MEDICAL AND PUBLIC HEALTH FIELDS

2.1. COMMUNICABLE DISEASES

2.1.1. Tuberculosis

National Tuberculosis Survey

For the effective planning of any measures against tuberculosis, it is essential to have precise information about its prevalence. Attempts had previously been made, on the basis of random surveys, to estimate the prevalence of the disease in different parts of the country. It was, however, considered essential to undertake a wider survey in an organised manner for determining the precise incidence of the disease both in urban and rural areas. Accordingly, a National Tuberculosis Survey was started by the I.C.M.R. in 1955 and completed in 1958. This survey was limited to pulmonary tuberculosis. Six zones around Calcutta, Delhi, Hyderabad, Madanapalle, Patna and Trivandrum, which had mobile miniature X-ray units, were included in the survey. Within each zone the population to be surveyed was selected on a sampling basis, due consideration being given to both urban and rural populations. The technical direction in regard to field work, X-ray readings and laboratory examinations was given by the T.B. Sub-Committee of the I.C.M.R. In all, the survey covered 6 cities, 30 towns, and 151 villages, the total number of persons submitted to radiographic testing amounting to 290,758.

Preliminary findings of the survey were given in the report of the Council for the years 1950 to 1957. The final report of the survey was published recently. The salient findings may be summarised as below :—

1. Prevalence rate for 'active' and 'probably active' tuberculosis varied from 13 to 25 per 1,000 population in cities, towns and villages in the different zones.
2. The rate of bacteriologically positive cases for 1,000 population in these areas varied from 2 to 8.
3. Prevalence rates were lower for females than males, specially in age groups above 35 years.
4. In general, the prevalence rate showed a steady increase with age.
5. In cities, higher prevalence among persons living in 'kutcha' houses than among those living in 'pucca' houses indicated the possible effect of economic conditions.
6. A large majority of 'active' and 'probably active' cases had moderately advanced disease.

1960.
ICMR, Report of the Indian Council of Medical Research for the years 1958-59 & 1959-60. New Delhi: ICMR.

7. Definite cavitation was observed in 4 to 33 per cent of the 'active' and 'probably active' cases, this percentage being generally lower in cities.

The survey showed that the differences, if any, in morbidity rates between cities, towns and accessible villages were much smaller than expected. Though the incidence of tuberculosis in villages was generally lower than that in the cities and towns, the difference was not marked. The villages covered by the Survey were either those that had roads or tracks for the transport of X-ray machines or a few others that were very close to such roads. The places therefore were those that had possibility of dissemination of the disease through normal channels of communication. The exact incidence of the disease in remote villages and mountainous areas is still not known, but attempts are now being made to survey some of these 'inaccessible' villages with the help of portable X-ray units.

The Survey also showed that the incidence of tuberculosis was significantly higher in the population living in insanitary conditions than in those living in healthier surroundings.

In addition the survey served to indicate the probable number of infective cases in the country as well as the number of 'active' or 'probably active' cases. The estimated number of infective cases was in the neighbourhood of 1·5 million, and that of 'active' or 'probably active' cases amounts to about 5 million. These figures are higher than those roughly arrived at previously. The facts thus showed the need for devoting greater consideration to the problem and indicated the necessity for giving high priority to anti-tuberculosis measures on a national basis. While such measures should, in the first instance, be concentrated in urban areas, steps should also be taken to extend them to rural areas at an early date.

Assessment of efficacy of BCG vaccine

In view of the importance of the tuberculosis problem in the country, the Government of India have been paying special attention to the development of techniques for the control of the disease. As a practical measure a mass BCG vaccination campaign was initiated in 1950. By the end of 1958 more than 120 million persons had been tuberculin tested, out of whom 42 million were vaccinated with BCG.

The value of BCG vaccination in the control of tuberculosis has been well brought out in recent studies carried out in England and other parts of the world. In 1954 and 1955, a study of the results of BCG Vaccination in regard to the allergy produced by it was undertaken by a WHO team. This team reported that :—

1. A low-grade tuberculin sensitivity, presumably caused by

micro-organisms other than mycobacterium tuberculosis, was widespread in the country ; and

2. the level of BCG-induced allergy was reasonably high and uniform from group to group examined, though somewhat lower than what could be achieved under controlled conditions.

The study is being continued by an Indian team under the aegis of the I.C.M.R. The results so far obtained have confirmed the findings of the WHO team. The maximum allergy produced by the BCG vaccination as observed in other countries, fell short of the allergy produced by natural infection by 1 to 3 mm. Even after taking this fact into consideration, it would appear that allergy produced by BCG vaccination in India was about 4 mm lower than that observed elsewhere.

It is yet early to expect the results of BCG vaccination to manifest themselves in relation to the total incidence of tuberculosis in the country, but in view of the lower allergy already noted, it is worthwhile considering whether the BCG vaccine produced in India can be improved. Attempts are therefore being made to produce freeze-dried vaccine to counteract the influence of climatic and other factors which might be responsible for the production of a low grade allergy in India.

The question of BCG vaccination in the prevention of tuberculosis was considered by the Tuberculosis Sub-Committee and the Communicable Diseases Advisory Committee at their recent meetings in Poona. Both the Committees expressed the view that it would be necessary to initiate a full-fledged study to further assess the effects of BCG vaccination todate. These recommendations will be considered by the Governing Body in due course. However, it must be noted that such an extended study will deal only with the question of allergy produced after BCG vaccination. The value of BCG vaccination in the control of tuberculosis can only be assessed later.

Tuberculosis Chemotherapy Project, Madras

The Tuberculosis Chemotherapy Project in Madras was started in 1956 under the auspices of the Indian Council of Medical Research in collaboration with the WHO/BMRC and the Government of Madras. The object of the project was to find out how effectively the new anti-bacterial drugs can be used in treating tuberculous patients in their homes as compared to the treatment in hospitals. The study was also utilised to ascertain the prevalence of tuberculosis in family contacts at the time a case was detected as well as in the subsequent years.

A detailed protocol was drawn up for conducting the investigations, indicating, among other things, criteria for the selection of pateints for the study. For the purpose of comparing the effectiveness of domiciliary

treatment with that given in hospitals, 100 beds were reserved in the Tuberculosis Sanatorium, Tambaram.

So far over 600 patients and over 2,000 contacts were covered by the study. The contacts of every patient were X-rayed before the case was put on treatment and, as far as possible, all the contacts were followed up regularly. The contacts of both the groups of cases treated at home or in the hospital were included in the study. This is expected to give an indication of the risk, if any, to which contacts were exposed when patients were treated at home.

Information is being collected about the family structure and living conditions of the patients. This is an important factor, as the economic and environmental conditions in which the patients have to be treated in their homes have to be taken into consideration.

The study also included an investigation to compare the diets of sanatorium and domiciliary group of patients with a view to find out the role played by the diet, if any, in the attainment of quiescence when treatment is given with modern anti-bacterial drugs.

The study as planned would also indicate whether it would be possible to secure co-operation of patients for long periods of treatment at home.

The Centre has developed a well-equipped laboratory which is undertaking approximately 1200 cultures and 300 sensitivity tests a month. Tests to identify the causative organism and virulence studies of different strains are also being carried out.

Some of the virulence studies which were completed a few years ago, yielded very interesting results. These studies covered 83 Indian and 29 British strains of Mycobacterium tuberculosis and were carried out in two laboratories in Britain and one in Madras. A majority of them which were tested were all found to be of human type and all were sensitive to streptomycin and isoniazid. Three strains of guinea-pigs one bred in London, one in Madras and the third in both places were used in those studies. The results showed that although Madras strains were no less infective than British strains, they were definitely less virulent in the guinea-pigs. The Madras strains were found to have a wider range of virulence and only 30 per cent of them were as virulent as British strains. The least virulent of the Indian strains caused little more than local lesions. It is rather paradoxical that there is apparently more human tuberculosis in India than in Britain even though the Indian bacilli are less virulent to animals. The investigators believe that since the disease is spread mainly by patients with chronic cavitating lesions, it is perhaps possible that attenuated strains often produce such lesions and continue to exist among people who are ill

nourished and among whom risk of infection remains high. On the contrary, in a country like Britain where the risk of infection is falling and the people are well-nourished attenuated strains may be unable to establish sufficient chronic cavitating disease for the organisms to spread and survive and under the circumstances only high virulence has the greatest survival rate. These studies however, brought forth convincing evidence that there are differences in virulence of strains obtained from one country to the other.

The incidence of drug resistance in the tuberculous population is an accepted fact, but there is as yet no information available about the size of this problem and the extent to which it will jeopardise the effective use of drugs on a mass scale. The laboratory is at present carrying out a large number of sensitivity tests and is expected to play an important part in drug resistance surveys.

The duration of the follow-up period of patients and their contacts is to be a minimum of 5 years from the start of treatment of the patients. The follow-up of the first batch of patients admitted in 1956 will be completed by 1961.

The results of the study on sanatorium treatment versus home treatment have been published in the Bulletin of the World Health Organisation (1959, **21**, 51-144). A few salient features of the results obtained may be noted :—

1. In all, 193 patients were admitted to a comparison of treatment at home (96 patients) with treatment in sanatorium (97 patients) for a period of 12 months, the patients being allocated at random to one of these two series.
2. Patients in both series were given the same chemotherapy for the 12 months namely, isoniazid 200 mg. plus PAS (sodium) 10 g. daily (given together in the same cachet in two doses) for patients weighing 100 lb. (45 kg.) or more. The dosage was reduced for lighter patients, the range of dosage being from 3·7 to 6·6 mg. isoniazid/kg. body-weight and from 0·19 to 0·33 g. PAS (sodium)/kg. body-weight.
3. Although all the survivors were examined at 12 months, the main analysis in this report concerns the 82 home and 81 sanatorium patients who (*a*) had organisms sensitive to the two drugs (*b*) had little or no previous chemotherapy and (*c*) followed the allocated treatment regimen.
4. The intake of patients began on 24th September, 1956 and ended on 24th September, 1957.
5. In spite of the random allocation for treatment, the home series had more severe disease even at the time of admission than the sanatorium series in respect of the extent of cavitation, total extent of the disease, and bacterial content of the sputum, although they were similar in other respects ; the pre-treatment differences between the series were greater for females than for males.
6. Infection with primary isoniazid-resistant organisms occurred in 3·6 per cent primary resistance to PAS in 2·6 per cent and primary resistance to streptomycin in 2·2 per cent of the patients.
7. There is evidence that different criteria of interpretation should be used for PAS sensitivity tests on Indian strains of tubercle bacilli from those that apply to British strains.
8. The diet of the home and the sanatorium series was similar before the start of treatment, but there were important differences during treatment, the sanatorium diet being clearly superior in terms of animal protein.

Despite some of these differences at the start and in the course of treatment the study still showed that "the results of domiciliary chemotherapy as carried out in the study, approach sufficiently closely the results of sanatorium treatment to suggest that it is appropriate to treat the majority of patients at home."

The investigations reported so far, while of considerable interest, leave two important questions still unanswered. Does the treatment of cases at home expose the contacts to greater risk of infection because of the source of infection remaining at home than does treatment of cases in the sanatorium when the focus of infection is removed from home ? Again, while the results of one year treatment of patients both at home and in the sanatorium, are encouraging enough, what exactly happens to them after the cessation of treatment ? Does their condition deteriorate in any way, thus necessitating continuance of treatment for another year ? Unless answers to these questions are available, it will not obviously be possible to recommend domiciliary treatment as a basis of the national campaign for the control of tuberculosis. The data collected during the course of the work are under analysis from these two points of view. Preliminary analysis has, however, revealed that domiciliary treatment of tuberculous patients for an year, drawn from an undernourished section of the community and living in comparatively unfavourable environment, does not in any way expose the contacts to any additional risk of infection, even though the main case, i.e. the source of infection, remains in the family till the patient becomes bacteriologically negative. Preliminary analysis of data has also revealed that continuation of treatment in the second year does not confer any

further benefit. If these preliminary results are confirmed by a detailed analysis of data, they would certainly provide the basis for the initiation of a national tuberculosis control programme based on sound scientific lines.

(*d*) In the Chemotherapy Centre at Madras, patients were selected on random basis for observation and treatment which had to be continued for several years. An elaborate machinery had to be devised in order to ensure that the patients did take treatment and that too in the manner indicated. The results mentioned above, were, therefore, arrived at after a thorough check-up and a thorough follow-up of all the cases under investigation. Obviously, such an approach would not be feasible in a mass campaign. A special set up was, therefore, created in Madanapalle in order to ascertain the applicability of domiciliary treatment on a mass campaign basis. It will be recalled that work at Madanapalle was conducted for a number of years under the Ministry of Health as a joint project of the Government of India and the WHO. Towards the end of 1958, the work of this centre was reoriented, keeping in view the standpoint described above, and the technical execution of the programme was entrusted to the I. C. M. R. During the year 1959 domiciliary treatment was started on 189 patients—some receiving PAS+ INH and others receiving INH alone. It was soon apparent that it was difficult to ensure that the patients continued under treatment according to schedule. Four cases ceased treatment during the first month and this trend increased as months went by. 92 per cent were continuing treatment at the end of three months, 87 per cent at the end of six months and 57 per cent only at the end of 10 months. It is too early, however, to draw any significant conclusions from this. Nevertheless, the trend is worth noting. At the end of six months, the sputum conversion rate from positive to negative, was in the neighbourhood of 78 per cent. This finding is encouraging. At any rate, this investigation when completed will provide information on factors which will have to be taken into account in instituting a mass campaign against the disease.

2.1.2. Leprosy

The Government of India have embarked on a national campaign for the control of leprosy by the establishment of treatment and study units in different regions of India. The attempt is to make leprosy cases free from infection with suitable treatment in order to prevent spread of the disease. Recent experience, however, appears to show that such a measure alone is not likely to control the incidence of leprosy. The reason for such a presumption is obvious. Before a patient comes up for treatment, he, in all probability, has already infected others, both children and adults. The problem in leprosy, therefore, is not only the

treatment of obvious cases of infection but also prevention of spread of infection to those in close contact with active leprosy cases. Timely prevention of infection in children is doubly important because they tend to develop lesions much earlier than others. Many attempts have been made to prevent infection among children, primarily by their segregation at the earliest possible moment from infected parents. Such an approach, it will be realised, is not easy to adopt, because of the various socio-economic factors involved in the segregation of children from their parents. Any lead, therefore, which may provide the know-how for the prevention of infection in children, will be most valuable in the organisation of a national campaign against this disease.

There are yet other problems in leprosy. Sulphones have no doubt been found very suitable for the treatment of the disease. Nevertheless, there are not enough grounds to say that with adequate sulphone therapy, the disease can be completely got rid of. It is, therefore, necessary to try out other remedies as and when they become available. There are yet other handicaps. It has not yet been possible to cultivate the causative organism of leprosy in artificial media as can be done in respect of many other bacterial infections. No suitable laboratory animal, susceptible to leprosy, is available for the study of the evolution of the disease under controlled conditions. The Council, recognising these limitations, has had a programme of research during the last few years to obtain, if possible, some information on these various problems. However, it is only during the last two years or so that some insight has been gained in them. Results obtained from the work carried out hitherto are summarised below and future lines of work are also indicated.

(*a*) *Evolution of the disease in relation to lepromin reaction*

In the Acworth Leprosy Home, an elaborate investigation on the evolution of the disease together with its reactions to lepromin amongst those in contact with leprosy patients has been in progress for a number of years. A detailed report on these observations has been published in a recent issue of the Indian Journal of Medical Research. Four thousand contacts have been under observation for a period of ten years. Of these contacts, 60 have developed characteristic neural lesions of leprosy, while 73 have developed what are called primary lesions, e.g. hypopigmented patches more or less erythematous and without sensory changes. It has been established that *ab initio* every individual is lepromin negative and that leprous infection is the most potent factor responsible for lepromin-positivity. It has also been found that tuberculous infection can induce lepromin-positivity, but it plays a limited role in bringing about such a change in the reaction. Follow-up study in a limited number of contacts of

neural patients has shown a significant reduction in lepromin-positivity in those showing bacteriological regression. It has, therefore, been suggested that continued maintenance of lepromin-positivity requires a continual immunological inducement in the form of lepra bacilli. It has been concluded that, in the evolution of leprosy, three phases can be recognised (*i*) an initial transient phase which does not react to lepromin (*ii*) the sensitized phase which shows bacilli in the skin and reacts to lepromin and (*iii*) the de-sensitized phase which is really the lepromatous phase when lepromin reaction is negative. It would, therefore, appear that lepromin reaction indicates the sensitivity of the patient to infection and not the resistance of the individual towards infection. However, some workers do not ascribe specificity to this reaction, as, in their experience, similar reactions can be elicited with use of other non-specific substances. This study will provide a background to the efforts that will be made for the control of leprosy through the administration of BCG vaccine to which reference will be made later.

(*b*) *Effect of prophylactic treatment with sulphone in the development of disease amongst contacts of leprosy cases*

An attempt has been made to study the response of contacts to prophylactic treatment with DDS. The long incubation period in leprosy necessitates a correspondingly long period of observation before the value of prophylaxis in this disease can be correctly assessed. However, this difficulty can be overcome by observing the progressive and regressive changes that occur in contacts under prophylaxis who are in one or the other of the three stages, *viz*, (*a*) uninfected, (*b*) infected, i.e. harbouring bacilli but without lesions, and (c) the stage of primary lesions which precede the appearance of manifest lesions of leprosy. The dosage schedule has been varied according to the period of contact : those in contact for five years or under have been given only 5 mg. of DDS twice a week, those in contact for 15 years or over received 25 mg. twice a week, and varying dosages have been given to cases of contact periods in between. The results of this study have given encouraging results. In the normal course, the period required for the infection to manifest itself in contacts varies from three months to four years in children and a little over two years in adults. In the present series, children found to be negative to infection at the time of commencing prophylactic treatment tended to remain free from infection as compared to those not so treated. The response to prophylactic treatment was also similar in those contacts, who had the bacilli in the skin even at the time the treatment was commenced. Majority of those treated did not develop any lesions and many of them became bacteriologically negative. In the case of the untreated group, the majority remained infected and

quite an appreciable number developed progressive lesions. The significance of these findings is obvious.

(*c*) *Experimental transmission of human leprosy to laboratory animals*

(i) At the School of Tropical Medicine, Calcutta, organisms obtained from leprosy nodules of untreated human cases have been used to infect laboratory animals like hamsters, white mice and a special breed of black mice. The latter have yielded encouraging results. Over a period of many months, these animals developed generalised infection and acid-fast organisms were noted in many of their tissues and organs. The possibility of contamination by tubercle bacilli or some saprophytic acid-fast organism was excluded. It was also ensured that Stenfanski's bacillus which usually produces fatal infection in rats did not enter the picture. This is the first time that successful infection of a laboratory animal is produced with human lepra bacilli, but these findings obviously require to be confirmed by further investigation in other laboratories.

(ii) Following an early lead obtained in the laboratory that the leprosy organism has a special affinity to nerve tissue, attempts were made to cultivate this organism in tissue culture with spinal ganglia tissues at the Indian Cancer Research Centre, Bombay. This work is not entirely financed by the Council, but is reported here as the results are of special interest. The material for inoculation was obtained from leprosy nodules of untreated human cases. It was observed that multiplication of organisms took place very readily in such tissue cultures. Material from the tissue culture was further inoculated in the fluid part of the tissue culture medium, *i.e.* the portion without live cells. Growth was obtained even in this medium. Further, the passage of the material from the latter into the usual laboratory media also showed growth of acid-fast organisms simulating the leprosy bacillus. In the absence of specific immunological criteria it is obviously difficult to conclude that the organism so cultivated is the leprosy bacillus, but presumptive evidence appears to be rather strong. It has been ascertained that this organism, labelled at present as ICRC bacillus, is not identical with any of the known acid-fast organisms. Immunological tests conducted with it have shown some degree of specificity. It is interesting to record that extracts from these organisms give a reaction more or less similar to that obtained with standard lepromin. Inoculation of the organism into special strains of mice available at the Cancer Research Centre has also resulted in lesions simulating early lesions of leprosy. The disease apparently does not progress further in these animals. These results are extremely interesting and further work on this important aspect is proceeding. However, the workers themselves are aware that there is a need for caution in

interpreting these results in view of the repeated claims of successful cultivation of the leprosy bacillus by several workers in the past.

(iii) In order to elucidate the pathways by which lepra bacilli metabolise nutrients, certain enzyme studies are being carried out at the Indian Cancer Research Centre, Bombay, with organisms isolated from lepromatous nodules by differential centrifugation. These studies have shown, for the first time, the presence of several respiratory enzymes in these organisms. Enzymes oxidising both lactate and pyruvate are also demonstrable, of which those oxidising pyruvate appear to be less stable. An interesting aspect of this study is the metabolism of amino-acids particularly glutamic acid and tyrosine by the lepra bacilli. These two amino-acids are chosen, because the former is intimately associated with nerve metabolism and the latter with pigment formation (in skin) both of which are usually affected in human leprosy. The results do indicate the presence of enzymes in the mycobacterium lepra which are capable of metabolising the above amino-acids. Pursuit on these lines may help to throw light on the biochemical mechanisms responsible for hypopigmentation and nerve degeneration closely associated with human leprosy.

THERAPEUTIC STUDIES

A number of newer drugs for treatment of leprosy have been tested for their therapeutic value. Some of them are S.U. 1906, diphenyl thiourea (DPT), acidomycin, pomegranate extract, etc. It has been found that both S.U. 1906 and DPT produce clinical improvement similar to that with DDS, but neither of them is as effective as DDS in producing bacteriological improvement. Acidomycin has been found to be of only limited therapeutic value in lepromatous cases. Other drugs tested have had no special therapeutic effect. It would appear, therefore, that for the present there is no drug which will replace DDS in the treatment of leprosy.

TREATMENT OF DEFORMITIES

The pioneering work at the Christian Medical College, Vellore, on the treatment of deformities by suitable operative procedures, has been reported previously. Efforts to develop further operative procedures have been continued and special techniques have been developed for the surgical reconstruction of the foot, the thumb and the nose. As a result of the adoption of these techniques, it can be said that a majority of leprosy deformities, which are not preventable, can be suitably corrected. It has been possible to develop a programme of physiotherapy on the basis of the results thus obtained, which may be useful in limiting secondary deformities and in the correction of existing ones. A number

of suitable splints have been designed and are being manufactured for the purpose.

The basic question, however, is how do these deformities develop? If the mechanism underlying the process of development is known, it will pave the way for evolving further ameliorative techniques. Some basic principles of tendon transfer, tendon free-grafting and joint function have been studied in anaesthetic hands and feet and compared with those of healthy subjects. The relative vulnerability of different nerves and different muscles has also been studied. Variation in the temperature over the surface of the body has been considered to be an important factor in the production of deformities. Indeed, the work conducted at the Centre has paved the way for achieving good results not only in the treatment of leprosy deformities but also in the treatment of deformities caused by other paralytic conditions.

BCG VACCINATION IN THE PREVENTION OF LEPROSY

In recent years, many reports have appeared indicating the utility of BCG vaccination in the control of leprosy, particularly childhood leprosy. The subject is no doubt controversial. Opinion is yet divided as to whether one single BCG vaccination is enough or whether a number of injections with BCG vaccine would be necessary to obtain the desired degree of lepromin-positivity which is one of the criteria to be observed in the assessment of the utility of BCG vaccination. A recent small scale observation in this connection, on the incidence of leprosy amongst BCG-vaccinated children in an area in India may be mentioned. In the study, the closeness and duration of contact with infected cases of leprosy was kept in mind. The study revealed that only five cases of leprosy developed in 678 BCG vaccinated children during the period of observation of five years, while 283 cases occurred in 1651 children of the same group who did not receive BCG vaccination. Further work in this regard is necessary.

The Leprosy Advisory Committee of the Council has taken note of these results and has recommended the institution of a comprehensive programme of investigation of the role of BCG vaccine and chemoprophylaxis in the prevention of leprosy. It is essential, however, to plan such a programme on sound scientific lines with considerable care, so that the results may yield information of value for the initiation of adequate control measures against the disease.

2.1.3. Smallpox

As an unusual rise in the incidence of smallpox and cholera was reported from many States in India during the early months of 1958, an Expert Committee on Smallpox and Cholera was constituted under