

INDIAN JOURNAL OF TUBERCULOSIS

Official organ of the
Tuberculosis Association of India

Vol. XXXII : No. 4

October 1985

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Published quarterly in the months of January, April, July & October.
Annual Subscription Rs. 50/-, £ 5.00, \$ 12.00, Single copy Rs. 15/-.
Published on behalf of the Tuberculosis Association of India.
3, Red Cross Road, New Delhi-110001.

The Indian Journal of Tuberculosis

Vol. XXXII

New Delhi, October 1985

No. 4

AVAILABILITY OF ANTI-TUBERCULOUS DRUGS

Uninterrupted availability of anti-TB drugs in adequate quantities is the *sine qua non* of tuberculosis control. It is common knowledge that sometimes one or the other of these drugs is not readily available. The pity of it is that this non-availability is neither due to inadequate funds nor due to sudden escalation of demand which producers may not be able to meet readily.

Some time ago, streptomycin was in short supply. The reason was that because of local troubles, production virtually ceased in one of the three major producing units (a public sector unit), thus creating an all round shortage of the drug in the entire country. More recently, JNH was not available for free distribution from the government treatment centres even though any quantity of the drug could be easily purchased in the market. Again, the non-availability had nothing to do with budget provision. It was entirely due to the fact that the units which were under contract to supply INH to the government defaulted. It has been seen that large concerns are usually not interested in supplying drugs to the government, probably because of the latter's cumbersome procedures and agonising delays which lead to blocking of the capital. It so happened that the price of one of the intermediate compounds in the production of INH had gone up in the international market and the concerns which were under contract to supply INH to the government at rates lower than the market rates did not find the contracted price remunerative and hence the default in supply. Ordinarily, the government revises the prices of bulk drugs only when there is a major fluctuation. However, even minor fluctuations, which may not matter much to a big producer, can upset the balance and cause hardship to the smaller producers with limited resources. And most of the suppliers to the government belong to the latter category.

Of the most frequently used important anti-TB drugs, the entire demand of INH, Streptomycin, Ethambutol and Thiacetazone is met by indigenous production. Not only are we self-sufficient in these but the licensed capacity is much higher than actual production and even when case-finding is considerably stepped up, production of drugs can also be increased *part passu* and thus there should be no shortage. The entire requirement of Rifampicin and bulk of Pyrazinamide is imported on O.G.L. Six letters of intent were issued quite some time ago for production of Rifampicin in the country, but none of these has so far been converted into a license for production simply because the cost of production of Rifampicin in the country would be much higher than the international price and therefore the intending producers have asked for the crutches of 'protection'.

It may be mentioned that the production price of almost all drugs in our country is higher than the international price. Of the various inputs, e.g., scale of production, standard of technology, availability of raw material/intermediaries, power, labour, etc., we are better off in respect of labour only,

but unfortunately pharmaceutical industry is not labour-intensive. Therefore, the cost of production in spite of cheap labour works out to more than in the western countries. Whether we should continue to import drugs at the cost of foreign exchange so that the consumer saves money or produce the drugs in the country and thereby save the drain on foreign exchange, though the consumer may have to pay more, is a moot point.

The relationship between cost of production and market price of a drug is somewhat complicated. There are about 8,000 production units in the country, of which only 300-400 are big producers. The rest of the units are small and some may even be described as 'tiny' mushroom concerns, on which no controls in respect of quantity or price and, perhaps, even quality of production, are applicable.

Under the current National Drug Policy introduced in 1978, the essential drugs were divided into three categories. In Category I, which includes Streptomycin, INH and Thiacetazone, the mark-up price is 40% above the ex-factory production cost. The mark-up price for category II is 55% and for Category III which includes Ethambutol, it is 60-100%. The industry considers the mark-up prices for Categories I and II as irrational since they cannot break even at less than 60% mark-up. Therefore, there is a demand for a mark-up price of 80-100% for all drugs.

It is also the contention of the producers of bulk drugs that they are subject to maximum and stifling controls. Whereas the current overall price index is 338 (base 100 in 1970-71), it is only 192 for drugs. The price rise for almost all other controlled commodities is much higher than in the case of essential drugs. True, essential life-saving drugs cannot and should not be bracketed with commodities like Petroleum, Cement, Steel, etc. but then, if the producers do not find it remunerative enough to produce drugs, they tend to diversify into other fields like production of agrochemicals, toiletries, etc. where the margin of profit is more attractive. Lastly, de-licensing alone cannot lead to increased production and reasonable prices and may even expose indigenous production to unfair competition and exploitation by multi-nationals. De-licensing has to be supported by rational and realistic pricing in order to improve the availability of drugs.

It is obvious that the production targets of drugs should be linked to actual and anticipated demand. Availability of the drugs is more important than their price within reasonable limits. A lower price by itself may not be of much use. If it is not remunerative enough, the production of the drug is likely to be deliberately reduced and/or the drugs may disappear from the open market. The government, therefore, must evolve a rational, simpler and growth-oriented pricing system which takes care of the interests of the producers as well as the consumers.

The Tuberculosis Association of India has recently set up a small cell to monitor the production, distribution and pricing of various anti-tuberculous drugs. It is hoped that this cell, in collaboration with the Ministry of Chemicals and Fertilizers, which controls production and pricing of drugs and the Ministry of Health and Family Welfare will be able to make an effective contribution towards making quality drugs available in adequate quantities at reasonable prices.

TREATMENT OF LONG-TERM TUBERCULOSIS TREATMENT FAILURE

B.K. KHANNA*

Summary: 15 cases of sputum positive pulmonary tuberculosis, who had failed to respond to most of the known chemotherapeutic regimens, were admitted to hospital. They were all administered an injectable (Kanamycin in 13 cases and Capreomycin in 2) along with PAS ethionamide and cycloserine in 13 cases and Rifampicin and pyrazinamide in the other 2. One case from whom *Mycobacterium Kansasii* was isolated was excluded from the study. At the end of 6 months, the injectable was stopped. The oral medication continued for subsequent 18 months in the patients' homes (unsupervised). Except for 2 cases, who deteriorated and 2 who died, remaining 10 cases were discharged, much improved, with negative sputum. One case had "stress" diabetes mellitus and another localized empyema. Out of 6 cases, followed up for 6 months to 2 years, after cessation of therapy, 1 died 2 years after discharge from the hospital. He was extremely irregular during domiciliary phase of treatment. Another case relapsed 6 months after stopping the drugs. This regimen though costly (Rs. 700 per annum) is worth attempting on patients who are given up as hopeless because of failure of previous treatment.

Introduction

Patients with a failed or failing treatment regimen remain a most difficult problem in the management of tuberculosis. This is specially true in a country like India, where almost all the drugs are freely available in the market and can be prescribed by even practitioners of other systems of medicine (Ayurvedic, Homeopathic, Unani etc.), often in ineffective doses. Furthermore, in the absence of effective control over the patients, all the factors, which can contribute to treatment failure e.g. single drug therapy, irregular drug therapy, sub-therapeutic doses of drugs and drug default, are operational. These factors are generating a group of patients who are resistant to almost all the commonly used, drugs. Most of these patients are given up as hopeless and are largely abandoned to their fate. The literature is, strangely, silent about the management of these cases. A regimen of Kanamycin, Ethionamide and Cycloserine has been recommended in one of the studies (Toman, 1979).

Below, I present my experience in the management of such cases, in strict hospital conditions.

Material and Methods

Fifteen cases of far advanced pulmonary tuberculosis, who had been suffering for the last 2 to 5 years and who had sputum positive for T.B. at the time of induction in the trial, were selected for the study. Twelve of these patients had history of irregular and unsatisfactory therapy with antituberculosis drugs in various combinations in the past. Three patients had regular chemotherapy with at least 3 anti-tuber-

culosis drugs, in adequate doses, for the last 2 years and yet had failed to respond to these regimens.

All these cases were hospitalised. In the hospital besides a very careful history of alcoholism and smoking and of previous therapy, routine Chest X-ray, sputum culture, investigations to rule out complicating disorders such as diabetes mellitus, chronic bronchitis, malignancy and endocrine disorders, renal functions and serum electrolytes were conducted. Bacteriological examination of the sputum for the presence of secondary pathogens and atypical mycobacteria was also done. A case with *Mycobacterium Kansasii* in the sputum was excluded from the study.

The regimen prescribed included, as a rule, 4 drugs consisting of one injectable (Kanamycin in 12 cases; Capreomycin in 2) and 3 oral anti-tuberculosis drugs, to which the patients' organisms were thought to be sensitive on the basis of history of previous drug regimens taken by the patient. After 6 months, the injections were stopped and oral regimens were then continued in the patient's home without daily supervision for the next 18 months. The patients were checked monthly in the hospital. The average duration of hospitalisation was 6.9 months.

In 12 cases, the 3 oral drugs chosen comprised ethionamide (0.5 g/day in a single dose at bedtime), Cycloserine (0.5 g/day in a single dose after breakfast) and PAS (8 g/day in 2 equally divided doses taken twice a day after meals). In 2 cases it was Rifampicin (450 mg./day before breakfast in persons below 50kg. bodyweight and 600 mgs per day in those above 50 kg.) and Pyrazinamide (1.5 g/day

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after breakfast). The injectable was administered in the dose of 0.75 gm. i.m. once a day for 5 days in a week.

Six cases have been followed up for periods ranging from 6 months to 2 years after the completion of their therapy.

Of the 9 male patients, history of smoking was present in 7 cases. The average amount of cigarette/bidi smoked was approximately 10 pack/year. None of the female patients was a smoker. Three of the male patients were ex-alcoholics.

Abnormality of glucose tolerance curve was seen in 6 cases. However, overt diabetes mellitus was detected in only one case at the time of admission to our study. It responded to 100 rag./day of chlorpropamide administered along with dietary control. By the time the patient was discharged from the hospital, chlorpropamide was completely withdrawn and the diabetes remitted.

Sputum culture was positive in all the cases. In one case, atypical mycobacteria (*Mycobacterium Kansasii*) was detected. The case has been excluded from our analysis of results.

Spirometric studies, done on all the cases, revealed evidence of airway obstruction ranging from severe (force expiration volume for 1 second less than 50 %) to moderate (FEV for 1 second 50% to 65%) in all of them. Besides, one patient had localised empyema (for the last 8 years) as a cause of fever, despite improvement in the pulmonary lesion. Urinary tract infection was present in 6 cases. A similar number of cases also had tender hepatomegaly which regressed with metronidazole therapy (400 mg. 3 times a day for 10 to 30 days).

Except for the case with loculated empyema, where the pus was evacuated, no other surgical procedure was undertaken on these cases.

Results

The summary of the cases is presented below in tabulated form (Table 1).

Two cases died in the hospital; 10 cases were discharged from the hospital, in a lit condition. The sputum of all these 10 cases had converted (3 consecutive over-night specimens, examined by smear examination, had become negative for acid fast bacilli) at the time of discharge. The average time required for sputum conversion was 4.7 months. As a rule, the radiographic change was not very striking; though shrinkage of collapsed lobes or segments, thinning of walls of cavities, moderate reduction in the

size of cavities and evidence of fibrosis in pulmonary lesions was commonly seen. Most of the patients were rendered symptom free, though some patients did have residual complaints of exertional dyspnoea and occasional wheezing, especially following exposure to cold, dust and fumes. Two cases continued to excrete T.B. in their sputum and deteriorated.

Side effects of drugs: Three patients developed subjective and objective evidence of damage to vestibular and auditory systems. Despite these, we continued the drug administration, because, v/e were not in a position to withdraw the injectable and replace it with any other drug. The danger was explained to the patient. In one case, Kanamycin injections had to be stopped after 70 injections due to distressing giddiness. Ethionamide and PAS caused hyperacidity and flatulence in most of the cases. Symptomatic therapy was administered leading to abatement of symptoms. In one case, persistent vomiting led to withdrawal of PAS. No case of neurotoxicity due to cycloserine was recorded in our cases.

Follow-up: A follow-up of 6 cases for 6 months to 2 years after completion of therapy revealed 4 of them in stable clinical and bacteriological condition. One case died 2 years after discharge from the hospital. He was irregular in taking drugs at his home. Another case relapsed within 6 months of stopping the drugs and has been again put on the same set of drugs.

Discussion

Failure to respond to antituberculosis drugs can be due to a number of factors. Inadequate chemotherapy happens to be the most common cause. The fault may lie with the prescribing physician or with the patient himself (drug default). In this series, physicians were found to be lacking in many instances. Administration of inadequate drug combination (only 2 drugs administered at a time, in a country like India, where primary drug resistance is seen in 21 % cases (I.C.M.R., 1968), adding one more new drug to the chemotherapeutic regimen when the original regimen had failed or administration of drugs in inadequate doses were encountered frequently. Though only 3 patients had the problem of alcoholism, drug default, in home treatment, was found to be extremely common. This could be attributed to alcoholism, to the cost of therapy (especially when under the care of general practitioners) and failure to motivate the patient to take drugs regularly (especially in TB Clinics). Irregular supply of drugs from the TB Clinics and indifferent attitude of the clinic staff towards the patients also contributed to the same end.

Initials	Age in Years	Sex	Duration of Illness	Addiction		Complicating Disorders	Previous therapy		Hospital therapy		Response
				Smoking	Alcohol		Others	Drug	Response	Drug Combinations	
1. T.D.	35	M	8 Yrs.	10 Pack/Yr.	Yes	—	S R H P Eth.	No. Imp.	K Cyclo Et PAS	—	Sputum Converted
2. N.P.	22	F	4 Yrs.	—	—	—	S H Eth R Pz	No. Imp.	K C E PAS	—	Sputum Converted
3. G.P.M.	56	M	7 Yrs.	—	—	—	S H R Eth Pz	No. Imp.	" "	Pus Evacuation	"
4. S.N.K.	32	M	8 Yrs.	6 Pack/Yr.	Yes	—	STH Pz Eth R	Initial Imp. then deterio- ration	Capreo C Et PAS	—	Expired
5. N.S.	17	F	2 Yrs.	—	—	—	P H S Eth R	No. Imp.	K C Eth Et PAS	—	Sputum Converted
6. L.R.	32	M	3 Yrs.	10 Pack/Yr.	—	—	STH Pz Eth R	No. Imp.	K C Et PAS	—	Sputum Converted
7. H.S.R.	36	M	6 Yrs.	12/Pack Yr.	Yes	—	S T H R Eth Pz	No Imp.	" "	—	Deteriorated
8. S.	40	M	5 Yrs.	13 Pack/Yr.	—	—	S H Eth Pz R	No Imp.	" "	—	Sputum Converted
9. V.N.P.	42	M	15 Yrs.	—	—	Tobacco Chewing	S P H Eth	No Imp.	K Pz R	—	Sputum Converted
10. A.L.S.	26	F	13 Yrs.	—	—	—	S P H Eth	No. Imp.	" "	—	Sputum Converted
11. J.P.S.	42	M	3 Yrs.	6 Pack/Yr.	—	—	S P H Eth Pz R	No Imp.	K C E PAS	—	Sputum Converted
12. S.J.	35	F	8 Yrs.	—	—	—	S T P H Eth R Pz	No Imp.	" "	—	Sputum Converted
13. P.G.	40	F	10 Yrs.	—	—	—	S P H Eth R Pz	No Imp.	" "	—	Sputum Converted
14. S.K.	36	F	15 Yrs.	10 Pack/Yr.	—	—	S P H Eth R Pz	No Imp.	Capreo Et Pz PAS	—	Expired

UTI=Urinary Tract Infection
 Capreo=Capreomycin; T=Thiacetazone; S=Streptomycin; H=Isoniazid
 P=Para-amino Salicylic Acid; Eth=Ethambutol; Et=Ethionamide; C=Cycloserine;
 Pz=Pyrazinamide; R=Rifampicin; K=Kanamycin.

Since most of the drugs can be purchased even without a prescription over the counter of chemists in this part of the country, most of the patients, on the basis of carefully taken history, were considered to have become non-responsive to drugs like rifampicin, pyrazinamide, ethambutol and streptomycin. Thiacetazone is easily available from the TB Clinic in India, so much so, that many of these cases had plenty of TNH and thiacetazone combination tablets at one stage or another of their past therapy and had failed to derive any benefit. This left only the drugs which the general practitioners in India usually shun i.e. PAS, ethionamide, cycloserine and Kanamycin and capreomycin either because of their side effects or because of their prohibitive cost (Kanamycin) or because they are just not available in India (capreomycin).

Cross-resistance between thiacetazone and ethionamide and between streptomycin and other amino-glycosides has been demonstrated (Citron, 1968 and Hok et al 1964). Between thiacetazone and ethionamide, it appears to be a two way resistance (Citron, 1968). In my study, I did obtain therapeutic advantage, by using these drugs (e.g. kanamycin and ethionamide) even though, the patients had plenty of streptomycin and thiacetazone in the past.

When acquired drug resistance to more than 2 drugs is suspected in a patient, four or more antituberculosis drugs would be more desirable than 3 or lesser number of drugs; more so, when drugs, with only weak bacteriostatic effect on the T.B., have to be administered (Youmans, 1979); that too, in rather sub-therapeutic dosage (ethionamide and cycloserine : 0.5 G/day) for reasons of G.I. intolerance or C.N.S. toxicity respectively. The situation, in such cases, is not dissimilar to mycobacterium intracellulerae pulmonary disease (Kumar et al 1978 and Crofton et al 1975).

The infection with atypical mycobacteria was suspected in 3 cases. All these patients had received adequate therapy in adequate doses and drug combinations for sufficient period of time without any clinical response. Culture of sputum for T.B. revealed Myco. Kansasii in only one case. In one more case, typical human type of T.B. sensitive to all the known anti-tuberculosis drugs, was isolated, though the patient failed to respond to all the known chemotherapeutic regimens (case no. 14). This goes in to emphasise, once again, the fallacies and unreliability of sensitivity studies on the T.B. (Toman, 1978) conducted, at least, in this city. However, the immunological deficiency, if any, was not investigated in these cases; nor were immunostimulants administered to monitor their response. The remaining cases revealed human type of T.B. showing varying spec-

trum of sensitivity to various antituberculosis drugs; though, it is true, the chemotherapeutic regimen was tailored according to history of previous chemotherapy taken and response to the therapy rather than to the sensitivity pattern, of the T.B., as obtained in the bacteriology laboratory.

Chronic nonspecific large airway obstruction could, partly, be due to chronic pulmonary disease and partly to smoking. In an earlier study from this centre, we found evidence of airway obstruction in 58 % of cases of pulmonary tuberculosis (Kawoos et al 1979). Its development is significant, in that, with the passage of time, it contributes to the symptoms of the patient, and may progress relentlessly; unrelated to the progression or regression of the basic tuberculous lesion (Martin et al 1962). Hence, symptomatic therapy to control the symptoms including that of wheezing should be administered to all such cases, as and when needed.

Likewise, search for other cause of pyrexia or for causes of other symptoms (e.g. associated pulmonary, cardiac, upper abdominal pathology including amoebic hepatitis, chronic pyelonephritis and chronic cervicitis in females) may yield valuable information, which might in the long run, prove to be very useful in controlling the symptoms. The detection of diabetes mellitus in one case (probably related to active tuberculosis lesion) and a pocket of pus in the chest in another, was helpful in the ultimate management of these cases. Indeed, search for all the causes of pyrexia of unknown origin should be conducted in all these cases, who seem to respond satisfactorily to the anti-tuberculosis chemotherapy (sputum conversion and radiographic improvement) and yet have persistence of symptoms.

Surgical management of these cases is recommended as and when indicated: though, in this series, because of extensive pulmonary lesion, none was considered suitable for the same. Recurrent and persistent haemoptysis, when present, might form an emergency indication for thoracic surgery in these cases.

Chemotherapeutic treatment, at least for 2 years, to all these cases is recommended. Indeed, once the sputum becomes negative for T.B., the end point, (i.e. when chemotherapy should be stopped) becomes blurred. Owing to very chronic tuberculous pathology, the radiographic regression of the lesions may not be very striking, despite adequate chemotherapy. Even after full 2 years of therapy, many fibronodular foci and cavities (though thin walled) may be left over. However, 2 years of continuous chemotherapy seems to be adequate in the management of resistant cases of tuberculosis (Zierski, 1968).

The cost of therapy, which works to around \$ 700.00 per annum, excluding the cost of hospitalisation, is the biggest inhibitory factor in even selective application of this form of therapy.

Follow-up of 6 cases, for periods ranging from 6 months to 2 years revealed that the clinical relief obtained by this regimen is stable and lasting, provided the patient took regular chemotherapy after discharge from the hospital.

Acknowledgement

I am grateful to the residents of the Department of Tuberculosis & Respiratory Diseases, especially to Dr. G.V. Sharma, who helped me in compiling the data for these cases.

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RESULTS OF SHORT COURSE CHEMOTHERAPY IN PULMONARY TUBERCULOSIS PATIENTS EXCLUDED FROM THE MAIN ANALYSIS OF A CONTROLLED CLINICAL TRIAL

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Summary : Fate of 102 patients excluded for various reasons (51 with a history of previous treatment for tuberculosis, 20 with negative cultures, and 31 defaulters) from a controlled clinical trial to study the efficacy of 3 and 4.5 months regimens is reported. Among previously treated patients, though sputum conversion by culture was achieved in 88%, relapse rates during the two years follow-up were extremely high—90% for the 3 months regimens, and 63 % for the 4.5 months regimens. At the time of relapse, most of the patients receiving 3 months regimens had drug resistant strains while most of the patients receiving 4.5 month regimens had drug susceptible strains. In smear positive, culture negative patients both the 3 and 4.5 months regimens were highly effective and there were no relapses during 2 years' follow-up. In previously untreated but defaulter patients, results were favourable provided they continued treatment in spite of temporary default and completed the stipulated number of doses. Relapse rates were 29 % for 3 months regimens and 8 % for 4.5 months regimens during the 2 years' follow up.

Introduction

Short course chemotherapy is promising in the management of pulmonary tuberculosis provided the patients are previously untreated, they have no concomitant disease, and they take the treatment regularly.

In real situation, a good proportion of the existing cases of pulmonary tuberculosis have already had anti-tubercular treatment before they report to a specialised centre. Another problem in the management of pulmonary tuberculosis is the case-holding. With the passage of time, the patients start neglecting the treatment. Although short course chemotherapy helps in increasing drug compliance, yet default is formidable (Mehrotra et al 1981). Therefore, results of short course chemotherapy in defaulter patients may be of great help in framing treatment strategy for defaulter patients. The third problem, though rare, is the concomitant disease. The fate of such patients, treated with short course chemotherapy, is unknown so far; however a study in Argentina had shown good results of short course chemotherapy in diabetic patients (Gonzales et al 1979).

Material & Methods

TB Demonstration Training Centre and Chest Institute, Agra, has undertaken a controlled clinical trial on short course chemotherapy in the management of pulmonary tuberculosis patients. A total of 360 pulmonary tuberculosis patients who fulfilled the following criteria were admitted to the study: (1) The pulmonary tuberculosis was bacteriologically

confirmed (microscopy positive for acid-fast bacilli at the time of admission to the study was later confirmed by positive culture of the same specimen); (2) the patient was 12 or more years of age; (3) the patient was a resident of Agra City; (4) the patient had no other concomitant disease that might complicate management of the disease and was not pregnant; (5) the patient would be available for 2 years' follow-up after cessation of chemotherapy; (6) the patient had received no previous treatment for pulmonary tuberculosis or had no more than 15 days of anti-tubercular therapy-

Later, it was found that 78 cases did not conform to the criteria of case selection; 31 patients collected less than 90% of the allocated doses and were hence designated as defaulters; and in 11 patients, allocated chemotherapy had to be interrupted, because of toxicity to the anti-tuberculosis drugs. These 120 patients were excluded from the main analysis of the study. Fate of 102 patients out of these who were treated with allocated short course regimens is reported. Of these 102 patients, 51 had a history of previous antitubercular treatment, in 20 the pre-treatment culture was negative and in 31 previously untreated patients drug compliance was less than 90%.

Chemotherapeutic Regimens

Chemotherapeutic regimens were as follows:

- (i) 3 RSZH (3 months) : Rifampin (10 mg/kg), Streptomycin (0.75 g.), Pyrazinamide (25-35 mg/kg), and Isoniazid

- (5 to 8 mg/kg) in a single dose, daily, 6 days per week for 3 months (75 doses).
- (ii) 3 RSZH/RH (4.5 months) : as in 3 RSZH for initial 3 months, then Rifampin (10 mg/kg) and Isoniazid (5 to 8 mg/kg) in a single dose, daily, 6 days per week for 1.5 months.
- (iii) 3 RSZH/S_aH₂Z₂ (4.5 months): as in 3 RSZH for initial 3 months, then Streptomycin (0.75 g), Isoniazid (12 to 15 mg/kg) and Pyrazinamide (50 to 60 mg/kg) on 2 fixed days per week.
- (iv) 3 RSZHE (3 months) : As in 3 RSZH plus Ethionamide (7 to 10 mg/kg) in two divided doses, daily, 6 days per week for 3 months (75 doses).
- (v) 3 RSZHE/RH (4.5 months): as in 3 RSZHE for initial 3 months, then Rifampin (10 mg/kg) and Isoniazid (5 to 8 mg/kg) in a single dose, daily, 6 days per week for 1.5 months.

Patients were allocated to the various regimens randomly. Of 51 previously treated patients, 2 received the 3 RSZHE regimen; 14 received the 3RSZH regimen; 24 received the 3RSZH/R_sH_aZ₂ regimens; 9 received the 3 RSZH/RH regimen; and 2 received the 3 RSZHE/RH regimen. Of 20 patients with negative cultures, 2 received the 3 RSZHE regimen; 5 received the 3 RSZH regimen; 5 received the 3 RSZH/S₂H₂Z₂ regimen; 4 received the 3 RSZH/RH regimen; and 4 received the 3RSZHE/RH regimen. Of 31 previously untreated defaulter patients, 5 received the 3RSZHE regimen; 8 received the 3RSZH regimen; 7 received the 2 RSZH/S_jH₂Z₂ regimen; 7 received the 3 RSZH/RH regimen; and 4 received the 3 RSZHE/RH regimen.

All patients were ambulatory from the very first day. Protocol conditions necessitated outpatient attendance for two hours in the morning on week days (Monday to Saturday) for supervised drug administration and periodical investigations during the treatment period. Thereafter, patients had to visit the clinic once a month. To keep them on regular follow-up after completion of prescribed chemotherapy, they were given placebo tablets containing calcium lactate. For defaulter patients, the treatment was extended to complete the required number of doses.

Results

Because the number of patients under different regimens was small for various cate-

gories of patients, the results have been analysed broadly only in respect of treatment for 3 months and 4.5 months without taking into consideration the individual drug regimens, since there was no significant difference in respect of the regimens.

A. Previously treated patients

Out of 51 patients, 43 (16 receiving 3 months chemotherapy and 27 receiving 4.5 months' chemotherapy) were regular; 3 (all receiving 4.5 months' chemotherapy) were placed on other regimens after a few days of the initiation of chemotherapy.

At cessation of chemotherapy, among regular patients, 69% of the patients receiving the 3 months' chemotherapy and 100% of the patients receiving the 4.5 months' chemotherapy had negative cultures.

During 3 years' follow-up after cessation of chemotherapy, 10 (91 %) out of 11 patients with favourable response to 3 months' treatment and 17 (63%) out of 27 patients with favourable response to 4.5 months' treatment relapsed. Majority of the relapses occurred during the first year of follow-up; 70% in 3 months' regimens and 82.3% in 4.5 months' regimens.

Among patients receiving 3 months' treatment, drug sensitivity report at the time of relapse was available for 8 out of the 10 patients. Of these 8 patients, 5 had drug resistant strains. Among patients receiving 4.5 months' treatment, drug sensitivity report at the time of relapse was available for 14 out of 17 patients and of these 3 had drug resistant strains.

It may also be mentioned that out of 27 relapse patients, 8 died; 8 could not be treated further; and of the remaining 11 patients who could be re-treated, 10 got stabilized though 1 relapsed again.

Of the 5 defaulter patients, 1 got stabilized; 1 died; 2 were lost to treatment; and the remaining 1 patient had unfavourable response to re-treatment.

B. Culture Negative Patients

Of 20 patients, 18 (5 receiving 3 months' treatment and 13 receiving 4.5 months' treatment) were regular and 2 (receiving 3 months' treatment) were defaulters. All of them were smear negative at the end of treatment. Subsequently out of the 18 regular patients, 1 died of a non-tubercular cause and 2 could not be assessed after cessation of chemotherapy. Of the 2 defaulter patients, one relapsed again.

C. Previously Untreated Defaulter Patients

Out of 31 patients, 13 belonged to the 3 months' treatment and 18 to the 4.5 months' treatment group. Among patients with 3 months' treatment, 4 had premature termination of treatment; and the remaining 9 who completed the chemotherapy schedule had favourable response. Among patients with 4.5 months' treatment, 5 had premature termination of chemotherapy and the remaining 13 patients had favourable response to treatment.

Seven patients receiving 3 months' treatment (adjusted for default) and 12 patients receiving 4.5 months' treatment (adjusted for default) could be followed up for two years after cessation of chemotherapy. Among 7 patients receiving 3 months' chemotherapy, 2 relapsed and among 12 patients receiving 4.5 months' chemotherapy 1 relapsed. All the relapses occurred during the first year follow-up and the bacilli were sensitive to all drugs.

Discussion

The analysis has clearly indicated that 3 and 4.5 month short course regimens containing 4 or 5 most potent drugs, though resulting in bacteriological quiescence in 88% of the previously grossly treated cases, were not able to prevent relapse in majority of the patients; The relapse rate was 90 % for 3 months' regimens, and 63% for 4.5 months' regimens. Further, decrease in the relapse rate with increase in the duration of treatment was clearly seen. This evidence is enough to warn against the use of 3 to 4.5 months' short course chemotherapy in previously treated patients, even when they have drug susceptible strains on admission.

Analysis of smear positive but culture negative, previously untreated patients showed that all the regimens, whether 3 months or 4.5 months in duration, are highly effective; all 20 patients treated with 3 months' or 4.5 months' regimens had favourable response to treatment and none of the patients who took regular treatment experienced relapse during the 2 years follow-up after cessation of the prescribed chemotherapy. It was observed that even the patients whose chemotherapy was interrupted were benefited.

In defaulter patients, the duration of chemotherapy was extended so as to complete

the total number of stipulated doses. Nevertheless the relapse rate during the 2 years' follow-up was found to be 29 % for 3 months' regimens and 8% for 4.5 months' regimens. Therefore, for defaulter patients, chemotherapy probably needs to be extended further. The duration of additional chemotherapy needs further investigation.

Conclusions

Short course (3 months' or 4.5 months') chemotherapy showed that :

- (i) their efficacy was poor in the case of previously treated pulmonary tuberculosis patients ;
- (ii) their efficacy was very high in the case of culture negative smear positive pulmonary tuberculosis patients.
- (iii) minor defaults do not adversely effect the outcome of short course chemotherapy and defaulter patients can be safely treated by prolonging the treatment beyond the prescribed duration, the period of prolonged treatment varying according to the pattern of default.

Acknowledgement

The writers thank all the staff of their Institute for help in carrying out this study, especially Sri N.H. Mirza, Sri J.H. Rizvi, Sri K. Kumar and Sri S.D. Awasthy, Laboratory Technicians, for carrying out laboratory work; Sri S.K. Chaudhury, Treatment Organiser, for management of patients and record keeping; Sri L.K. Sharma, Statistical Assistant, for record keeping and maintenance; Sri S.C. Singh for management of initial investigations and initial and retrieval home visits. Thanks are also due to Sri K.C.S. Nair for typographical help.

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INTERMITTENT CHEMOTHERAPY IN RETREATMENT CASES OF PULMONARY TUBERCULOSIS

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Summary : One hundred and twenty sputum positive, retreatment cases of pulmonary tuberculosis out of 150 completed the full course of 39 weeks' therapy with streptomycin, isoniazid, rifampicin and pyrazinamide. After 8 weeks of daily therapy all 4 drugs were given under supervision once a week for 7 months. Sputum conversion by culture was obtained in about 90%. The patients were followed for 12 months. Bacteriological relapse was seen in 4% of patients.

Introduction

The most important reason for the failure of chemotherapy is the patient's non-cooperation (Pamra, 1979). When the symptoms disappear in a few weeks time with good chemotherapy, the patient gets a false sense of complacency that the disease is cured and treatment is no longer necessary. He either gives up treatment prematurely or starts becoming irregular. The reasons of irregularity may partly be economic. According to Pamra (1979) even free supply of drugs does not *per se* ensure regularity.

The purpose of the study was to see how many of the patients who had abandoned treatment earlier could be cured with the particular regimen?

Material and Methods

One hundred and fifty patients with pulmonary tuberculosis aged 12 years or more were taken for the present study. Only those patients who had history of antituberculosis drug intake for not less than 3 months were included. All of them had stopped treatment prematurely and attended again when symptoms reappeared. Interval between previous treatment and reappearance of symptoms ranged from 14 weeks to 26 weeks. One hundred and five (87.4%) patients had 3 to 4 months' previous antituberculosis chemotherapy (Table 1). Only those patients who could complete the full prescribed course of therapy were included in the main analysis.

Eighty four (70%) patients were between 25 and 44 years of age. Sixty-nine (57.5%) patients were males and 51(42.5%) females (Table 2). The radiological extent of disease according to the Tuberculosis Association of India classification (1969) was: minimal in 25% patients, moderately advanced in 55% and far advanced in 20%.

Chest roentgenogram (postero-anterior view) was taken and sputum was examined for acid fast bacilli by direct smear and culture. Prescribed regimen was started only after positive culture report. All patients included in the study were positive by culture.

TABLE I

Previous antituberculosis therapy

Regimen	Number of patients	Duration in months	
		Less than 4 No.	4 to 6 No.
SEH	45	40	5
STH	35	25	10
REH	20	20	—
RHS	20	20	—

S=Streptomycin, E=Ethambutol, H=isoniazid, T=Thiacetazone, R=Rifampicin.

The patients were prescribed the following regimen:

Streptomycin (1 g i.m.), isoniazid (300 mg), rifampicin (450-600 mg), pyrazinamide (40mg/kg body weight) daily for 8 weeks (56 doses). This was followed by streptomycin (1g), isoniazid (15 mg/kg body weight), rifampicin (15 mg/kg) and pyrazinamide (70 mg/kg) once a week for 7 months (31 doses). Once a week administration of drugs was under strict supervision. Mid-week isoniazid was given to rapid inactivators who numbered 66 (44%). The total period of therapy was 39 weeks. Patients were

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TABLE 2

Age and sex distribution of patients

Age in years	Number	Males		Females		
		Percentage	No.	%	No.	%
12—24	21	17.5	12	10.0	9	7.5
25—34	44	36.7	24	20.0	20	16.7
35—44	40	33.3	25	20.8	15	12.5
45—54	15	12.5	8	6.7	7	5.8
Total	120	100.0	69	57.5	51	42.5

TABLE 3

Results of sputum examination during therapy

	Duration of treatment				
	4 Weeks	8 Weeks	12 Weeks	24 Weeks	39 Weeks
No. of cases available at each assessment	132	124	122	120	120
No. found culture negative	40	88	100	113	113
No. found smear negative	60	102	108	117	120

treated in an ambulatory manner from the onset and the majority continued with their normal occupations. The patients, after completion of chemotherapy, were followed every month for 12 months.

Results

Only 80% patients could complete the full prescribed course of therapy as 15 (10%) patients became defaulters, 10 developed severe drug toxicity and 5(3.3%) died during that period. These patients were excluded from the analysis shown in Table 1 and Table 2.

During the daily phase, severe drug toxicity was reported in 10 patients; 5 patients developed giddiness (streptomycin toxicity). Drug regimen was changed in these patients. Fifteen patients out of 122 had 'flu-like' syndrome. It occurred between 14 to 22 weeks of drug administration.

Joint pains were reported by 4 patients. Drug regimen was not changed in patients complaining of joint pains or 'flu-like' syndrome.

Sputum conversion (direct smear and culture) during therapy is shown in Table 3. Culture was negative in 88 (76%) patients at 8 weeks and in 113 (94%) at the end of therapy.

All patients were followed for 12 months. Bacteriological relapse was seen in 4% of patients. All the relapses were in the third month after completion of therapy.

Discussion

Drugs were given once a week in the continuation phase. *In vitro* experiments have shown that after a culture of *M. tuberculosis* has been exposed to certain drugs for sometimes, it takes several days (the "lag period"), before

multiplication starts again (Dickinson and Mitchison, 1966). This is the basis of intermittent therapy. A mid-week dose of isoniazid was given to rapid inactivators of isoniazid as there is substantially lower success rate if given only once weekly (Agrawal *et al* 1983).

Nevertheless the evidence is that rifampicin can largely, though not completely, eliminate the isoniazid deficiency in rapid acetylators of the drug even when the initial intensive phase with three drugs is as short as two weeks (Fox, 1979).

In the present study sensitivity of tubercle bacilli to antitubercular drugs was not tested. Owing to the complexity of the technique, it is difficult to perform sensitivity tests accurately even when skilled personnel is available and laboratory facilities are of a high standard. In countries where skilled manpower and adequate facilities for such tests are scarce, accuracy is even more difficult to attain.

Pyrazinamide was given throughout the course of therapy in this study. In newly diagnosed, untreated cases of tuberculosis pyrazinamide is mainly effective during initial 2 to 3 months of therapy but in retreatment cases the drug is to be given for entire period of therapy (Stead and Dutt, 1982).

Fifteen (12%) patients had 'flu-like' syndrome. The symptoms were relieved by mere symptomatic treatment with or without lowering the rifampicin dosage. In 5 patients the dosage of rifampicin had to be lowered by 150 mg for the remaining period of therapy. 'Flu-like' syndrome may be attributed to an immunological reaction. Antibodies may develop against rifampicin, which during the uninterrupted treatment are continually absorbed, whereas in the intermittent regimens the antibody production continues and when a new dose of antigen is administered, an intense reaction may take place (Daddi *et al* 1983).

Thrombocytopenia may occur when rifampicin is given intermittently. The absorption of anti-rifampicin antibodies may occur on platelets, which after fixing complement, result in platelet damage (Addington, 1979). The patients were instructed to check for 'red-spots' prior to taking each dosage (Agrawal & Pal, 1983). None of our patients developed those 'red-spots'.

According to Mitchison (1979) culture negativity at two months is an early index of the relative sterilizing activity of regimens. In the present study it was found to be 76 % at 8 weeks. Addition of pyrazinamide to SHR in

previously untreated cases increased the culture negativity at 2 months from 70% to 82% (Second East African/BMRC Study, 1974), and from 75% to 87% in Third East African/BMRC Study (1978). These studies show the potent sterilizing role of pyrazinamide. The bacteriological relapse rate after stopping chemotherapy is the best index of sterilizing activity (Mitchison, 1979), and in our study only 4 % of the patients relapsed. The regimen used in the present study may, therefore, be considered to be therapeutically effective and acceptable to the patients who had abandoned treatment earlier.

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IMMUNOLOGICAL STATUS OF TREATED AND UNTREATED, B.C.G. VACCINATED AND NONVACCINATED TUBERCULOUS CHILDREN

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Summary: The cell mediated immune responses in 60 treated and untreated BCG vaccinated and non-vaccinated tuberculous children was studied. Leucocyte migration inhibition test (LMIT) in the presence of P.P.D. and blast transformation in the presence of phytohemagglutinin (P.H.A.) was done in all cases. Amongst untreated cases the LMIT was positive in a significantly higher number of children as compared to non-vaccinated children. Blast transformation was also significantly higher in BCG vaccinated untreated tuberculous children.

The controversy over the usefulness of BCG vaccination in protection against tuberculosis continues despite its use for over 60 years. In eight different community trials from 1953 onwards, the efficacy of BCG vaccination has been found to be between 0-80%.

BCG vaccine is one of the most potent stimulants of cell mediated immunity available today (WHO Scientific Group, 1980). Mackaness (1970) stated that the immunological basis for increased resistance to tuberculosis was provided by tuberculin hypersensitivity. Youmans (1975) however postulated that delayed hypersensitivity and immunity were different processes. While there are a number of studies on the cell mediated immune responses of BCG vaccinated tubercular subjects, few have compared these responses with those in tubercular no vaccinated subjects. An attempt to compare the immune status of BCG vaccinated and no vaccinated tuberculous subjects has been made in this study.

Material and Methods

The present study has been conducted on 60 tuberculous children attending the OPD and or admitted to the indoor services of the Department of Paediatrics, Kalawati Saran Children's Hospital and associated Lady Hardinge Medical College, New Delhi.

The diagnosis of tuberculosis was presumptive in 48 cases based on history, tuberculin reaction, X-Ray chest and biochemical examination of C.S.F. and pleural fluid (Achar and Viswanathan, 1981).

In 12 cases the diagnosis was confirmed by histo-pathological examination. Tubercle bacilli were not isolated in any case.

It was decided to include 30 cases who had a scar of previous BCG Vaccination; the other

30 were without a scar. Half the cases in each of the above two groups were previously untreated and the other half had some treatment of varying durations before reporting to us. Consecutive cases were allocated to the various groups and sub-groups.

All children were put on anti-tubercular treatment as soon as diagnosis was established. The treatment regimen was the same in all cases.

Investigations

Following tests were performed on each case.

1. *Mantoux test:* 1 TU P.P.D. RT23 with Tween 80 (ITU=0.1 ml of solution=0.00002 mg P.P.D.) was injected intradermally and reaction read after 48-72 hours. Induration of less than 10 mm diameter was considered as negative and 10 mm or more was taken as positive reaction.
2. *Lymphoblastoid transformation: in response to Phytohaemagglutinin* (Verma, Gupta & Ghai, 1974). The lymphoblasts were identified on the basis of their morphology.
3. *Leucocyte Migration Inhibition Test:* (Bloom, 1971). Human peripheral blood lymphocytes, when incubated with specific antigen *in vitro* produce a soluble factor which inhibits the migration of leucocytes. This was measured by allowing the leucocytes to migrate from capillaries over a glass surface with and without P.P.D. Percentage inhibition =
$$\frac{\text{Migration area with antigen} - \text{Migration area without antigen}}{\text{Migration area without antigen}} \times 100$$

Inhibition of less than 20% was considered negative.

Results

Pattern of tuberculosis in each group is shown in Table I. Among vaccinated children, no case of advanced tuberculosis was detected.

TABLE I

Pattern of Tuberculosis

Disease	Vaccinated		Non- vaccinated	
	No.	%	No.	%
Lymphadenitis	5*	16.7	4*	13.3
Pulmonary	25	83.3	20	66.7
Meningeal			1	3.3
Skeletal	—	—	3*	10.0
Miliary			2	6.7
Total	30	100.0	30	100.0

*Histologically proved.

Larger number of children were tuberculin negative in the non-vaccinated group (Table II). Most of the children with advanced forms of tuberculosis were tuberculin negative.

Table II

Tuberculin reaction in Vaccinated and Non-vaccinated cases

Size of induration	Vaccinated		Non-vaccinated	
	No.	%	No.	%
<10	6	20	11	36.7
10—14	3	10	1	3.3
15—19	9	30	10	33.3
20 or more	12	40	8	26.7
Total	30	100	30	100

A significantly better leucocyte migration inhibition was seen in B.C.G. vaccinated as compared to non-vaccinated children before

treatment (P<0.05). Among previously treated children no significant difference was found in the two groups (Table III.) Two nonvaccinated children died. Both were Mantoux and LMIT negative and failed to respond to anti-tubercular therapy instituted immediately after diagnosis.

Leucocyte

TABLE III Migration

Inhibition

Group	<20%	>20%
<i>A. BCG vaccinated</i>		
Untreated	0	15
Treated	0	15
<i>B. Non-vaccinated</i>		
Untreated	7	8
Treated	4	11
<i>C. Previously Untreated</i>		
BCG vaccinated	0	15
Non- vaccinated	7	8
<i>D Previously Treated</i>		
BCG vaccinated	0	15
Non-vaccinated	4	11

*P<0.05

*Significant

Among the previously untreated children, BCG vaccinated group showed significantly better (P<0.01) blastogenesis as compared to the non-vaccinated children (Table IV).

Discussion

In the present study no case of advanced haematogenous disseminated tuberculosis was detected in the vaccinated group whereas 20% of the non-vaccinated cases had advanced tuberculosis. This was consistent with the observation of Bhandari & Mandowara (1982), Parthasarathy *et al* (1982) found pulmonary and lymphnode tuberculosis, the commonest type of lesion in vaccinated children. Udani (1982) found that of 119 BCG vaccinated children none had tubercular meningitis and only one had miliary tuberculosis as compared to 27% of non-vaccinated children.

TABLE IV

Blast Transformation (Percentage of lymphoblasts)

Vaccinated		Non-vaccinated	
Previously Untreated	Previously Treated	Previously Untreated	Previously Treated
45	30	26	14
43	43	12	15
54	53	3	35
47	54	2	25
40	60	25	35
37	42	9	30
45	48	10	22
60	50	25	54
31	10	27	36
54	25	30	37
45	32	19	20
38	34	10	5
57	38	40	45
52	49	36	48
59	40	2	45
Mean 47.13*	40.53	18.4%	31.2+
S.D. 8.66	12.95	12.95	14.12

*P<0.01

+P<0.05

Mantoux test was negative in a greater number of non-vaccinated children possibly reflecting a lower immune status in these children. Most of the cases with advanced tuberculosis were Mantoux negative. Lothe *et al* (1973), Choudhry (1977) and Benakappa *et al* (1983) also found that nearly 50-60% of patients with miliary TB or tubercular meningitis were Mantoux negative. Agnihotri *et al* (1974) observed that patients who were Mantoux negative, showed decreased response to other antigens and concluded that these patients were immune-deficient.

In the present study, all previously untreated vaccinated children showed significant inhibition of LMIT as compared to only 7 out of 15 in the non-vaccinated group, which was statistically significant. Among the previously treated children, there was no statistically significant difference between the vaccinated and the non-vaccinated. Blast transformation was significantly higher (P<0.01) in previously untreated vaccinated children as compared to non-vaccinated children. However, blast transformation was significantly higher in previously treated non-vaccinated children, suggesting an improvement in the immune status with treatment.

Bhatnagar *et al* (1977) reported that of 10 patients of miliary TB only two were Mantoux and LMIT positive. Repeat LMIT done in two patients showed return to normal values. Thus it is possible that in moribund states associated with advanced tuberculosis, there is depression of cell-mediated immune responses which may improve on treatment.

The various immunological indices indicate that the BCG vaccinated children with tuberculosis had a better immune response than non-vaccinated children. This may explain the lower incidence of advanced, hematogenously disseminated forms of tuberculosis in vaccinated children.

Shapiro *et al* (1974) found that although delayed hypersensitivity reaction wanes in the vaccinated guinea pig, cell-mediated immunity does not, thus implying that cellular immune response depends on the ability of the host to make an amnestic response, which may explain Mantoux negativity in BCG vaccinated children. Bhatnagar *et al* (1977) observed that patients of miliary tuberculosis had a general depression of cell-mediated immune responses while only a subtle abnormality was seen in patients of pulmonary tuberculosis. The cell-mediated immunity was good in patients who had successfully controlled the infection and broke down completely in those with generalised disease.

Lenzini *et al* (1977) suggested that an immune spectrum exists similar to that found in leprosy. At one end is the non-reactive form of tuberculosis e.g. miliary, patients of which had poor cell-mediated immunity and a poor response to treatment. At the other extreme was the reactive form in patients who showed good cellular immune responses and had a good prognosis. In between, lies the intermediate forms which may shift to either, extreme depending on the improvement/deterioration in immune responses.

Thus BCG vaccinated children are shown

to have a better cell mediated immune response than the non-vaccinated. Vaccination, therefore, appears to protect the subject from haematogenously disseminated disease. The immune status of the non-vaccinated children appears to improve after treatment to a minor degree although further studies are required to support this.

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THE ACUTE PHASE REACTING AND IMMUNOMODULATING SUBSTANCES SERUM COMPLEMENT THREE AND ALPHA ONE ANTITRYPSIN IN PULMONARY TUBERCULOSIS

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Summary : Fifty cases of pulmonary tuberculosis and 42 controls were studied. They were classified according to the immunological spectrum. Sera of cases were measured for complement component three (C₃) and alpha one antitrypsin (A1AT) by radial immunodiffusion. The values were significantly higher in patients as compared to controls. There was no significant difference in the immunological varieties of cases in respect of these two acute phase reactants,

Introduction

Tuberculosis continues to be a serious problem of developing countries though it has been eradicated from developed ones. It is therefore attracting little attention and there are very few attempts at utilizing recent methods and advances in knowledge for understanding the pathogenesis of the disease. Information regarding cell mediated immune mechanisms has grown exponentially during the last decade. It is now clear that both cell mediated and humoral antibody responses are closely interrelated. Moreover, there are a number of modulating mechanisms to amplify or suppress both inflammatory and immunological reactions.

The description of Koch's phenomenon at the turn of the century indicated the importance of the immunological apparatus in the pathogenesis of tuberculosis. Currently, the caseous necrosis of tuberculosis is aptly described as a type IVB or bystander cell mediated tissue destruction. Recently, Lenzini, Rottoli and Rottoli (1977) described an immunological classification of tuberculosis which is very much like that for leprosy. This is a novel approach and seems worth probing from the point of view of understanding the detailed pathogenetic mechanism of tissue destruction in tuberculosis.

Grange, Kardjito and Setiabudi (1984) drew attention to a group of serum globulins called "acute phase reactants" because they showed a marked increase in disease states. These included alpha one antitrypsin (A1AT), alpha 2-macroglobulin, transferrin, alpha 1-acid glycoprotein, C-reactive protein, cruloplasmin, haptoglobins and complement component three (C₃). Of these C₃ is the pivotal substance in the complement cascade. This pathway can be activated by bacterial endotoxins (alternate pathway) or by immune complexes and brings about inflammatory responses and lysis of cells. It generally

amplifies immune mediated reactions. A1AT is a protease inhibitor which can inactivate both endogenous (from leucocytes) and exogenous (from bacteria) proteases to reduce proteolytic destruction in inflammatory reactions. Recently A1AT has been shown to even modulate immune responses (Arora, Miller and Aronson, 1978). A careful study of literature has shown no reports of studies of serum A1AT in tuberculosis. There are two reports of studies of complement system (Ganguly *et al* 1977; Brostoff *et al* 1981). But these did not measure the serum C₃ in tuberculosis. We describe here a summary of two reports describing serum A1AT (Yemul, Jad and Kelkar, 1983a) and serum C₃ (Yemul, Jad and Kelkar, 1984) in tuberculosis.

Material and methods

Cases: A total of 50 cases of pulmonary tuberculosis admitted at the Sir J.I. Group of Hospitals, Bombay were studied. In each case an X-ray of the chest, results of tuberculin testing and a smear examination of the sputum for acid fast bacilli were available. The cases were grouped into Lenzini's immunological varieties on the basis of the size and variety of pulmonary lesion, the size of induration of the TT (tuberculin test) and the presence of acid fast bacilli in the sputum. A sample of blood was collected, the serum separated, a trace of sodiumazide added and stored in a deep freeze.

Controls: Sera were collected from 42 normal healthy adults for estimating C₃ levels. Sera were collected from a different set of 50 normal adults for estimating A1AT levels.

Serum C₃ quantitation: This was done by single radial immunodiffusion technique (Mancini *et al*, 1965; Pole, 1984). Monospecific and C₃ was from Immunodiagnostic Laboratories, New Delhi and control serum from Hyland Laboratories, USA.

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TABLE I

Results of quantitation of serum C'3 and A1 AT in cases of pulmonary tuberculosis and controls

Group	Nos.	Mean±SD mg/dl.	Range mg/dl.
Controls serum C'3	42	114±37	70- 270
Patients serum C'3	50	161.7±32	108—251
Controls serum A1AT	50	247 ±55	106—440
Patients A1AT	48	441 ±202	144_740

In both the groups the difference was statistically significant ($P<0.05$).

Serum A1 AT quantitation: This was also done by single radial immunodiffusion technique (Mancini *et al*, 1965; Pole, 1984). Monospecific anti-A1AT and the calibration standards were from Kallestad Laboratories, USA.

Results

The cases included three of reactive (RR), 24 of reactive intermediate (RI) and 23 of unreactive intermediate (UI). There were no cases of the unreactive (U U) variety. There were 30 males and 20 females and the mean age was 38 ± 11 years (range 20-60 years). Table I summarises the results in cases and controls. In the A1AT group two cases, one of RI and one of UI could not be included as the sera were insufficient.

Results of statistical analysis using the Students 't' test showed that in cases of pulmonary tuberculosis both C'3 ($P<0.05$) and A1AT ($P<0.05$) were significantly raised when compared with values in controls. Analysis of immunological groups with each other showed no significant differences. Also, analysis of groups on the basis of number of acid fast bacilli and the serum C'3 and A1AT levels showed no significant differences.

Discussion

The "acute phase reactants" C'3 and A1AT are significantly raised in all groups of pulmonary tuberculosis. The complement system acts as an amplifier of all immune responses, particularly humoral ones. Formation of Antigen-antibody complexes triggers the complement system and splits the C'3 into C'3a and C'3b which cause vascular changes and activation of

further complement components leading to lysis of cells and bacteria. The utilization of components stimulates its synthesis. An initial depletion is followed by higher levels of some of the components. Thus high level of complement components signifies ongoing inflammatory or antigen-antibody complexing in the body. Townes (1967) suggested that chronic diseases would be associated with increase in serum complement components. Such increases have been reported in leprosy and erythema nodosum leprosum (ENL) (Saitz, Dierkse and Shepard, 1968).

A careful survey of the literature has shown only two studies of complement in tuberculosis. Ganguly *et al* (1977) estimated the haemolytic activity, C'2 and C'3 by an immune adherence method. The C'2 and C'3 did not show any changes though haemolytic activity was significantly raised. Brostoff *et al* (1981) determined immune complexes in sera of patients with pulmonary tuberculosis by a Clq radio-immunoassay. Unreactive cases showed a greater frequency and quantity of immune complexes. In the present study C'3 levels were significantly raised but the haemolytic activity was not determined. Such studies may be useful in understanding more details of the changes in the whole complement cascade in tuberculosis.

The quantitation of C'3 in the present study was done by single radial immunodiffusion. We have recently shown that this does not distinguish between active and inactive fractions of C'3. The active and inactive fractions of C'3 could be recognized by their electrophoretic mobilities (β_1C active slow; β_1A inactive, fast moving using two dimensional crossed immunoelectrophoresis (Yemul, Jad and Kelkar,

1983b). Such a study has been carried out in tuberculosis.

Alpha one antitrypsin or protease inhibitor (Pi) is another acute phase reactant globulin. The activity of diverse proteolytic enzymes like trypsin, chymotrypsin, collagenases, thrombin, fibrinolysin, granulocytic proteases and caseinases is controlled by AIAT. The synthesis of AIAT is under the control of a pair of fully dominant penetrating alleles. So far nine alleles and 17 phenotypes have been recognized (45 have been predicted.) The association of certain phenotypes with diseases is well known. The ZZ phenotype (deficiency) is prone to develop pulmonary emphysema (Williams and Fajardo, 1974). Considering the important immunoregulatory and inflammation regulatory functions of AIAT, the studies will be more important in understanding disease mechanisms. Raised values were reported in leprosy and its complications (Yemul *et al* 1980; Chauhan *et al* 1982). There is no such literature on tuberculosis. Grange *et al* (1984) studied 107 Javanese patients with pulmonary tuberculosis. Eight acute phase reactants were measured and these included AIAT. Quantitation was done by laser nephelometry. The healthy controls (144 in numbers) had mean AIAT levels of 256 mg/dl \pm 182, while the cases had 410 \pm 182 mg/dl. The difference was highly significant ($P < 0.001$).

Since AIAT is an important protease inhibitor its levels will be more reflective of disease process than any other acute phase reactants. We noted that other parameters like erythrocyte sedimentation rate (ESR) and radiological pictures correlated better with AIAT levels than with C'3 levels. Though an in-depth study on a larger sample size is essential to come to some definitive conclusions.

In conclusion, it appears that both serum C'3 and AIAT are significantly raised in pulmonary tuberculosis. The disease process with its cell mediated destruction of tissues in the form of a bystander cell injury consumes complement components. Since injury is chronic, there is a stimulation of production of C'3, the pivot of the complement cascade. *Pari passu* there is an outpouring of AIAT, a known protease inhibitor with a broad spectrum of action on exogenous and endogenous proteases to restrict tissue damage and destruction.

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EAC—ROSETTE FORMING CELLS IN PULMONARY TUBERCULOSIS

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Summary: Quantitation of EAC-rosette forming cells (EAC-RFC) in the peripheral blood of patients with pulmonary tuberculosis showed that active cases had significant increase in the level. An inverse relation between EAC—RFC level and T-lymphocyte subpopulations was observed.

Introduction

Cell mediated immunity (CMI) is responsible for protection against tuberculosis and tuberculin hypersensitivity is an essential part of CMI (Mackness, 1968). Even though most of the patients produce humoral response against various antigens of tubercle bacilli, it is not protective. Bhatnagar *et al* (1977) have demonstrated an inverse relation between humoral and cellular responses in tuberculosis. An immunological spectrum resembling leprosy has been demonstrated in tuberculosis patients (Bhatnagar *et al* 1977, Daniel *et al* 1981).

In our previous study (Prabhu and Venkata Reddy 1983), we had found reduced levels of T-lymphocyte subpopulations in active and relapse cases of pulmonary tuberculosis. In the present paper we describe EAC-rosette forming cell (EAC-RFC) levels in pulmonary tuberculosis patients, and their relation to T-lymphocyte subpopulations.

Material and Methods

The subjects of the study consisted of bacteriologically proved patients of pulmonary tuberculosis, admitted to S.D.S. Sanatorium, Bangalore.

The patients were classified into 3 groups, viz; active cases, relapse cases and treated cases. Except for the treated cases—who were on treatment for more than 2 months—others were not treated at the time of study. Normal healthy persons served as controls.

Enumeration of EAC-RFC was carried out according to Mendes *et al* (1973) technique with slight modifications. In brief, about 8 ml of blood was collected in a vial containing preservative free heparin (20 units per ml). Lymphocytes were separated using Ficoll-type FP solution (Sigma Chemical Company, St. Louis, USA). Fresh sheep red blood cells (SRBC) were sensitised with anti-SRBC serum

(at subagglutination titre) and mouse serum (source of complement). These sensitised indicator cells were diluted to give 0.05 percent in Hanks saline. Equal volumes of indicator cells and lymphocytes (1×10^8 cells per ml) were incubated at 37°C for 1 hour. Rosettes were counted in haemocytometer and the percentage and absolute numbers were calculated.

Results and Discussion

Enumeration of circulating B-lymphocytes using EAC-rosette technique has been employed to study several aspects of immunity in various clinical conditions (Wybran 1974). The mean percent and absolute number of EAC-RFC of the present study was significantly increased in active cases compared to that of controls (Table). There was a gradual increase of EAC-RFC from treated cases to relapse cases and active cases.

Williams *et al* (1973) and Zwolinski *et al* (1976) have found no deviation in B-lymphocyte levels in active pulmonary tuberculosis, while Shima *et al* (1976) have observed a decrease in B-lymphocyte levels. However, Bhatnagar *et al* (1977) have found a significant increase in the B-lymphocyte levels in miliary tuberculosis compared to controls. The discrepancy could be due to the selection of patients and different experimental conditions.

B-lymphocytes are responsible for production of humoral antibodies. Since B-lymphocytes are also shown to secrete certain lymphokines (Weisbart *et al* 1978 and Mackler *et al* 1974) and involve in delayed hypersensitivity reaction (Caruso *et al* 1977), their role in CMI though doubtful cannot be excluded. In the present study in treated cases increase in the levels of active E-rosette forming cells₀ (A-RFC) and total E-rosette forming cells₀ (T-RFC) was associated with the decrease in EAC-RFC level. Conversely, in active and relapse cases decrease in A-RFC and T-RFC levels was associated with increase in EAC-RFC

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* T-lymphocyte subpopulations.

TABLE

Mean percent and absolute number of EAC-rosette forming cells in different groups of patients and controls

Clinical type	EAC-rosette forming cells				
		Mean percent ±SD	Range	Mean absolute number±SD	Range
Active cases	15	32.4±11.0*	13.4—59.9	867.2±315.0	369.8—1429.6
Relapse cases	11	28.0±14.0	13.2—55.0	786.8±451.7	312.7—1632.0
Treated cases	8	26.2±8.8	13.5—38.3	634.2±331.0	257.9—1112.6
Control cases	20	24.6±8.7	11.1—40.2	646.0±347.0	186.9—1458.1

*P<0.05 when compared with controls (Student's 't' test).

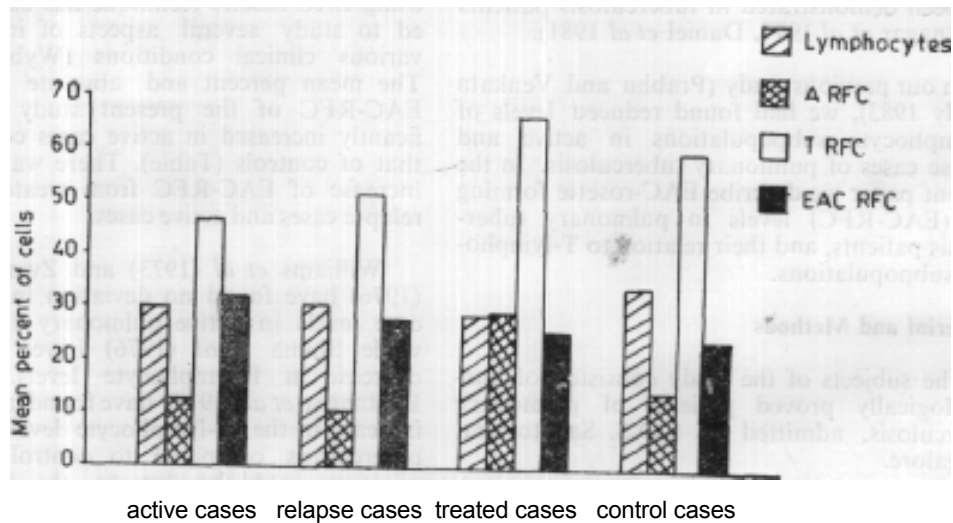


Fig: Relative distribution of lymphocytes and lymphocyte subpopulations in patients and controls.

level (Fig.). Bhatnagar *et al* (1977) while studying spectrum of immunological abnormalities in tuberculosis, found an inverse relation between humoral and cellular responses, and increased B-cells level was associated with decreased T-cells in miliary tuberculosis. B-lymphocytes have been found to suppress PPD induced lymphocyte transformation (Bona *et al* 1976) and delayed hypersensitivity (Neta and Salvin 1974).

Acknowledgements

This work was supported by the grants from I.C.M.R., New Delhi.

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SERUM MUCOPROTEIN AND MUCOPOLYSACCHARIDE LEVELS IN PULMONARY TUBERCULOSIS

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Summary : Serum mucoprotein and mucopolysaccharide levels were measured in patients with pulmonary tuberculosis and nontuberculous respiratory diseases. In these patients glucose tolerance was also studied. In tuberculosis both serum mucoprotein and mucopolysaccharide levels were found to be significantly increased. These subjects also showed abnormal glucose tolerance. It is suggested that the increased serum levels of the two constituents may be due to their increased synthesis in these patients. This may have same diagnostic value.

Introduction

Mucopolysaccharides (polysaccharides which contains hexosamine and uronic or sulfuric acids, also called glycosaminoglycans) and their protein conjugates (mucoproteins or proteoglycans) are important constituents of the cell membrane, connective tissue, basement membrane and mucous secretions. Elevated levels of either mucoproteins or mucopolysaccharides have been reported in various acute and chronic diseases both localised and systemic, e.g. malignant neoplasms, collagen diseases, tuberculosis and other infections where destruction, inflammation or proliferation of the tissue is a marked feature (Seibert *et al* 1947; Kelly *et al* 1950; Greenspan *et al* 1951; Chakravorti, 1965; Singh and Jain, 1982).

In the present study it was proposed to estimate the levels of both serum mucoproteins and mucopolysaccharides in patients with pulmonary tuberculosis, to see if the estimations of these ground substances could be helpful in the laboratory diagnosis of such cases. Further, an attempt was made to correlate the changes in the levels of these two serum constituents with the glucose tolerance of the patients since the association of tuberculosis and diabetes is well known (Warwick, 1957; Zack *et al* 1973; Seth *et al* 1982).

Material and Methods

Fifteen fresh cases of active pulmonary tuberculosis (9 males and 6 females) in the age group of 20-50 years, were selected for the study. The activity of the disease was proved by positive sputum for acid fast bacilli (AFB) and by the presence of the pulmonary lesion radiologically. These individuals had cough, expectoration, mild to moderate evening rise of fever, generalised weakness and malaise.

These subjects also showed 15-20% weight loss when compared with the normal weight for their age and height. They were not receiving any drugs prior to study. For comparison 15 non-tuberculous patients (8 males and 7 females) who had chronic respiratory illness other than tuberculosis, e.g. bronchitis or bronchial asthma were also studied. The possibility of tuberculosis was ruled out in these patients after clinical, radiological and repeated sputum examination for AFB at least on 3 occasions. Fifteen apparently healthy subjects (9 males and 6 females), not having any illness or infection for at least two weeks prior to study, served as controls. All the control subjects and the nontuberculous patients were comparable to tuberculous cases in respect of age and socio-economic status.

Serum mucoprotein and mucopolysaccharide levels were measured as described by Cannon *et al* (1974). For the estimation of mucoproteins, proteins other than mucoproteins were precipitated by perchloric acid. Mucoproteins were precipitated from the filtrate by phosphotungstic acid and then dissolved in alkali. The oligosaccharides were cleared from the polypeptide chains by acid hydrolysis and the hexoses converted to furfurals by prolonged heating. The colour resulting from condensation with orcinol was read at 520 nm and compared with the galactose-mannose mixture used as standard. For the estimation of Mucopolysaccharides the hexose moiety of protein-carbohydrate conjugates was precipitated by 95 % ethanol at 25°C and was determined by the orcinol reaction. Blood glucose was determined using o-toluidine reagent (Dubowski, 1962). For the estimation of blood glucose, fasting sample was taken and each subject was thereafter orally administered 100 g of D-glucose in 2-3 dl of water. Blood samples were again taken after 1 and 2 hours of the glucose administration.

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Results

Serum mucoprotein and mucopolysaccharide concentrations

The mean serum mucoprotein concentration for the control group was 9.1 ± 0.40 mg/dl. (Table 1). The value for the tuberculous group was 19.4 ± 1.21 while for the non-tuberculous group it was 12.3 ± 1.06 mg/dl. The mean value for the tuberculous group was significantly higher when compared with the control group ($P < 0.001$) or with the nontuberculous group ($P < 0.05$)

TABLE 1

Serum mucoprotein and mucopolysaccharide levels in normal subjects, patients with tuberculosis and non-tuberculous cases (values are Mean \pm SEM for 15 subjects in each group)

Group (mg/dl)	Mucoproteins (mg/dl)	Mucopolysaccharides (mg/dl)
1. Control	9.1 ± 0.40	91.9 ± 8.67
2. Patients with tuberculosis	19.4 ± 1.21	178.6 ± 12.08
3. Nontuberculous cases	12.3 ± 1.06	121.3 ± 9.76

The mean mucopolysaccharide concentration for the control group was 91.9 ± 8.67 mg/dl. The value for the tuberculous group was 178.6 ± 12.08 while for the nontuberculous group was 121.3 ± 9.76 mg/dl. The mean value for the tuberculous group was significantly higher when compared with the control group

($P < 0.001$) or with the nontuberculous group ($P < 0.05$).

Blood Glucose

The mean fasting blood glucose levels for the control, tuberculous and nontuberculous groups were 61.6 ± 1.78 , 64.8 ± 2.19 and 58.5 ± 2.02 mg/dl, respectively while after one hour of glucose load the corresponding values for the 3 groups were 97.1 ± 4.07 , 99.5 ± 6.47 and 85.5 ± 2.28 mg/dl (Table 2). When compared with each other, the fasting and the one hour values for the three groups were not significantly different ($P > 0.05$).

After 2 hours of glucose load the mean blood glucose concentrations for the control, tuberculous and nontuberculous groups were 70.7 ± 3.00 , 95.1 ± 8.70 , and 69.7 ± 3.02 mg/dl, respectively. The value for the tuberculous group was significantly higher when compared with the other two groups ($P < 0.05$).

Lastly it may be pointed out, that since the variances in groups to be compared were widely different in some cases, non-parametric tests of significance (specifically Wilcoxon's Rank Sum Test) were carried out instead of the conventional tests.

Discussion

The results of the present study demonstrated increased levels of serum mucoproteins and mucopolysaccharides in active patients of pulmonary tuberculosis as compared to the control subjects and to the nontuberculous cases. The increased levels of serum mucoproteins have been reported by various workers both in clinical and experimental tuberculosis (Seibert *et al* 1947; Weimer and Hohns, 1953; Singh and Jain, 1982). Catchpole (1950) and Chakravorti (1965) suggested that the

TABLE 2

Blood glucose levels in normal subjects, patients with tuberculosis and nontuberculous cases (values are for 15 subjects in each group)

	Blood glucose (mg/dl)		
	Fasting	After 1 hour	After 2 hours
1. Control	61.6 ± 1.78	97.1 ± 4.07	70.7 ± 3.00
2. Patients with tuberculosis	64.8 ± 2.19	99.5 ± 6.47	95.1 ± 8.70
3. Non-tuberculous cases	58.5 ± 2.02	85.5 ± 2.28	69.7 ± 3.02

increased serum levels of proteins-bound hexosamine may be due to the direct release of the solubilised preformed glycoproteins from the inflamed tissue.

The increased levels of glycoproteins as a result of their increased production have also been reported in diabetes mellitus and insulin deficiency (Spiro, 1969). The microangiopathy of diabetes has been shown primarily to be the result of alterations in the basement membrane (Farquhar *et al* 1959). Sipro (1963) reported that insulin deficiency which is responsible for altered glucose metabolism and in turn for the rerouting of glucose, leads to the increased production of serum glycoproteins. The increased serum mucoproteins and mucopolysaccharides levels observed in tuberculous patients of the present study may therefore be due to their increased production, as a result of insulin deficiency, since these patients also had poor glucose tolerance. The high incidence of glucose intolerance in tuberculosis has been reported by Seth *et al* (1982), as well.

The increased levels of these ground substances in patients with pulmonary tuberculosis may thus be useful in confirming the metabolic derangements of the condition. However, a detailed study is desired before any definite conclusions can be drawn.

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DEPRESSION IN TUBERCULOSIS PATIENTS: CORRELATION WITH DURATION OF DISEASE AND RESPONSE TO ANTI-TUBERCULOUS CHEMOTHERAPY

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Summary : One hundred and fifty patients of pulmonary tuberculosis were studied using Beck Depressive Inventory. Depression was observed in 49%. It was observed more often among elderly persons and in females, Labour class patients, illiterates, separated or widowed and those with low per capita income. No difference was observed with marital status and religion. The severity of depression was directly related to the duration of illness, severity of disease and response to chemotherapy. Depression was present in 48 % of freshly diagnosed patients. It decreased to 30 % in those who responded favourably to chemotherapy, but those with persistently positive sputum had a significantly higher percentage (64 %).

Introduction

Both psychiatric illness and tuberculosis are social stigmas, at least in our country. Even now, tuberculosis is thought to be a serious incurable disease, specially by illiterate and rural population. It is a psychological trauma for some persons to be diagnosed as patients of tuberculosis. So it is quite probable that this trauma may precipitate or predispose them to a psychiatric disorder.

This study has been designed to determine the occurrence of depression in patients of tuberculosis and to find out the relationship, if any, between depression and the socio-demographic characteristics of tuberculosis patients. An attempt has also been made to elucidate the relationship between depression and duration of illness and response to chemotherapy.

Material and Methods

The study included 150 patients of pulmonary tuberculosis admitted in Hospital for Chest Diseases and Tuberculosis, Jaipur. The patients belonged to the following three categories.

Group I : 50 freshly diagnosed sputum positive cases.

Group II : 50 patients who had received treatment for more than 3 months with sputum conversion.

Group III : 50 patients who had received treatment for more than 6 months but were still sputum positive.

Socio-demographic variables were studied in detail and depression scores were rated on Beck Depressive Inventory (1967). Patients having scores of 0-9 were labelled as normal. Those with scores of 10-15, 16-23 and 24 or above were labelled as having mild, moderate and severe depression respectively as per criteria suggested by Sharma (1983).

Results

Depression was observed in 49 per cent of the patients more among elderly persons, labour class patients, illiterates, separated and those with low per capita income. But no difference was observed with marital status and religion (Table 1). The depression was directly related to the duration of illness, severity of disease (Table 2) and response to chemotherapy (Table 3); 65 per cent of the patients with illness of more than one year were depressed as compared to only 29 per cent who were ill for less than 3 months (Table 2). Depression was present in 48 per cent of freshly diagnosed cases (Group I). The percentage decreased to 38 in those who responded favourably to chemotherapy (Group II) but in failures of treatment i.e. those with persistently positive sputum (Group III) depression was present in 64%. Moreover, depression was mild to moderate in most of the Group I and II patients while majority of patients in Group III had severe depression (Table 3).

Discussion

The study shows depression in 49 per cent of hospitalized tuberculosis patients, which is definitely higher than that reported in other non-tuberculous pulmonary disease like chronic

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TABLE 1

Socio-Demographic Characteristics

	Sex		Age Group					Marital Status			
	M	F	Below 20	20-29	30-39	40-49	50 & above	Married	Single		
No. of patients	99	51	18	31	46	43	12	120	30		
No. depressed	46	27	7	13	22	23	8	58	15		
Percentage	48	53	39	42	48	53	67	48	50		
	Religion		Education				Per Capita Income (Rs.)				
	Hindu	Muslim	Illi. above	Prim.	Middle	Sec.	Upto 30	30-69	70-149	150-299	300& above
No. of patients	90	60	61	43	29	17	5	55	65	21	4
No. depressed	45	28	35	21	13	4	3	31	34	50	50
Percentage	50	47	57	49	45	24	60	56	52	24	0
	Occupation						Family type				
	Housewife	Farming	Service	Business	Labour	Student	Joint	Nuclear			
No. of patients	27	34	15	13	56	5	99	51			
No. depressed	11	16	7	6	32	1	43	30			
Percentage	41	47	47	46	57	20	43	59			

TABLE 2

Correlation of Depression with Duration of illness and extent of X-Ray lesions

	Duration of Illness (months)				Extent of X-ray Lesions		
	.Less than 3	3-6	6-12	More than 12	Minimal advanced	Moderately advanced	Far advanced
No. of patients	24	27	36	63	20	56	65
No. depressed			16	41	12	18	33
Percentage	29	33	44	65	60	32	51

TABLE 3

Extent and severity of depression in different groups

Group of cases	Total No.	Number depressed	Severity of Depression		
			Mild	Moderate	Severe
I	50	24 (48)	10(42)	7(29)	7(29)
II	50	17 (34)	8(47)	6(35)	3(18)
III	50	32 (64)	7(22)	10(31)	15(47)
Total :	150	73 (49)	25(17)	23(15)	25(17)

Note : Figures in parentheses indicate percentage.

bronchitis, emphysema and lung cancer (Purohit *et al.* 1978; Tandon, 1980). This may be due to the fact that illiteracy and low socio-economic status which are some of the important factors responsible for depression (Sethi and Gupta, 1970; Davies, 1973; Bagadia *et al.* 1973) also make a person more susceptible to tuberculosis. But this alone cannot explain the entire difference as the attitude of society, relatives and family members and of the patient himself as well as other psychological variables are also important factors in the causation of depression (Moudgil and Prashad, 1972; Dubey 1975).

A greater occurrence of depression was also observed in patients with prolonged illness. This may be due to longer period of suffering and consequent strain on psychological coping mechanism. Hospitalization itself, loss of earning, sense of worthlessness and hopelessness may lead to self devaluation, conscious and unconscious fear of disease and death. A positive correlation between duration of illness and occurrence of depression has also been observed by Purohit *et al.* ~1978, Tandon 1981. *et al.* 1980 and Mathai *et al.* Still another factor responsible for higher incidence of depression in our study was severity of illness. Thus, there is a complex interplay of duration, nature and severity of illness on one hand and psychological factor on other. This is corroborated by Dubey 1975, Mathur 1977 and Purohit *et al.* 1978.

An important observation in our study is that with institution of chemotherapy and amelioration of symptoms, the depression decreases while in those with persistently positive sputum (Group III) it further increases. Since some of the anti-tubercular drugs like

isoniazid, ethionamide and cycloserine are known to cause depression (Storey and McLean 1957, Duncan and Kerr 1962, Devadutta 1966, Landsdown *et al.* 1967, B.T.A. 1968, Olsen and Torning 1968, Curci 1970, Mitchess and Lester 1970, Narang 1972) and most of group III patients were on these drugs for long periods which might have contributed to some extent to depression observed in this group of patients. But it seems unlikely that these drugs alone could explain the difference between the two categories of patients. Though the exact role of these drugs (especially isoniazid) is difficult to assess but it may be pointed out that it caused psychosis in only eight out of 4960 patients in one of the studies (Gupta *et al.* 1981). It seems more likely that with regular intake of drugs the patients' condition improves, the fear of prolonged suffering and death disappears and the confidence thus gained leads to easing of psychological stress and strain. Return to work consequent on relief of symptoms reduces financial strain which again makes the patient less vulnerable to depression. However, persistence of symptoms in Group III patients further aggravates the depression.

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THROMBOCYTOPENIC PURPURA INDUCED BY DAILY ADMINISTRATION OF RIFAMPICIN

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P. DURLABH***** and S. KOOLWAL*****

Summary : A case of rifampicin induced Thrombocytopenic purpura is reported. The reaction developed in the patient while on the drug therapy in daily doses.

Introduction

Thrombocytopenic purpura is an uncommon adverse reaction during rifampicin therapy. It mainly occurs during intermittent administration of the drug (Blajchman, Lowry and Pettit *et al* 1970; Poole, Stradling and Worlledge, 1971 and Hong Kong Tuberculosis Treatment Services/Brompton Hospital /British Medical Research Council, 1975) and is attributed to the production of drug dependent complement fixing antibodies (Blajchman *et al* 1970). Thrombocytopenia with overt bleeding is an extremely uncommon side reaction in a patient on daily rifampicin therapy. Such a reaction is reported.

Case Report

A 22 years old Hindu lady was admitted in the Hospital for Chest Diseases and Tuberculosis, Jaipur on 8th September, 1983 with complaints of fever, cough and pain in the chest for 3 months. She was a non-smoking, non-alcoholic, vegetarian house-wife. On examination, she was fairly built but poorly nourished. Respiratory system examination revealed bronchial breathing and crepitations in the right upper chest. Cardiovascular and abdominal examination revealed nothing abnormal. On investigations, blood haemoglobin was 10.5 gm. %; Total leucocyte count 12,000/ cmm with predominance of polymorphs. Sputum smear was positive for acid fast bacilli. Skia-gram chest (postero-anterior view) revealed homogenous opacity in the right upper zone.

The patient was put on Inj. streptomycin 0.75 gm intramuscularly with isoniazid 300 mg, pyrazinamide 1.5 gm and rifampicin 450 mg orally, daily. On this therapy the patient was improving but on the 10th day she developed anorexia and vomiting. Serum alanine transaminase as measured on that day was 64 k. units. All the drugs were stopped and the patient was managed symptomatically.

Resumption of all the drugs was possible within 7 days of withdrawal but on 11th October, 1983 she developed epistaxis, haemetemesis, malaena and haemoptysis. Blood haemoglobin at this time was 9 gm%; total red blood cell count 2.85 million/cmm, total leucocyte count 7,800/cmm, polymorphs 70 % and lymphocytes 30%. Bleeding and clotting time were 2.30 and 4 minutes respectively. Platelet count was 75,000/cmm (Indirect method).⁰ Serum alanine transaminase at this time was within normal limits. Considering that the bleeding disorder was drug-induced, all the drugs were stopped again and the patient was given symptomatic treatment only. After 3 days of this, the bleeding disorder subsided and platelet count returned to normal (1.75 lacs/cmm by indirect method). Isoniazid, streptomycin and pyrazinamide were resumed uneventfully and platelet count did not decline even after 7 days of resumption of these drugs (1.80 lacs/cmm). Presence of anti-rifampicin antibodies in her serum could not be shown due to lack of facilities but rifampicin was never resumed after this episode. Bone marrow biopsy with a view to confirm peripheral sensitization and destruction of platelets was not done as the patient was bleeding.

Discussion

Thrombocytopenic purpura in the present case was induced by rifampicin, as the reaction developed in the patient while on therapy with the drug and subsided on its withdrawal. Further, streptomycin, isoniazid and pyrazinamide could be resumed uneventfully at a later date.

Such a reaction is extremely uncommon in a patient on daily rifampicin therapy. To the best of our knowledge, only two such cases have been reported in the English literature (Ferguson, 1971 and Hong Kong Tuberculosis Treatment Services/ Brompton Hospital/ British Medical Research Council, 1975). The case reported by Ferguson (1971) was not a confirmed one. Although his patient, developed

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⁰Facilities for count by direct method were not available.

thrombocytopenic purpura while on rifampicin, ethambutol and pyrazinamide therapy, the patient was not subjected to a challenge even with the two latter drugs. A patient in Hong Kong also developed purpura while on daily phase of ethambutol and rifampicin therapy. The purpura was observed in the 1st month of therapy during a cutaneous reaction and was transient. Compared to these cases, our patient had a severe bleeding disorder. Although such an occurrence is extremely unusual, it should be kept in mind as continuation of rifampicin in such a case may prove fatal. Readministration of the drug is contra indicated in such a patient (Sepulveda/fl/1971).

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ANNOUNCEMENT

The R.C. Memorial Trust (Regd.), Rohtak, has donated to the Tuberculosis Association of India a sum of Rs. 10,000/- to institute, in memory of the late Shri R.C. Garg, who was the first employee of the Lady Linlithgow Sanatorium, Kasauli, Shimla Hills, a cash award of Rs. 1,000/- every year for the best article published in the Indian Journal of Tuberculosis. The cheques will be presented to the winner of the award at the time of the Annual General Meeting of the Association every year.

NEWS & NOTES

36TH TB SEAL CAMPAIGN

The 36th TB Seal Campaign organised by the Tuberculosis Association of India and its affiliates in the States, was inaugurated on 2nd October, 1985—Gandhi Jayanti Day—by Giani Zail Singh, President of India and Patron, Tuberculosis Association of India, at a special function held at Rashtrapati Bhawan, New Delhi. The function was attended by the President and members of the Tuberculosis Association of India and representatives of the Delhi TB Association.

In a message issued on the eve of the inauguration of the campaign, the President said "This campaign is designed to assist Tuberculosis Associations in fighting this major disease and bringing relief to those affected. This campaign is inaugurated on the Gandhi Jayanti Day so as to remind ourselves of the paramount duty on our shoulders in eradicating this dreadful disease. I am happy to associate myself with this campaign and renew my appeal to the people to buy TB Seals liberally and help the TB Associations to carry out their mission with increased zeal. I wish the coming TB Seal Sale Campaign success".

Shri S. Ranganathan, President, Tuberculosis Association of India, in his message said: "The TB Seal Campaign is an important activity of the TB Association of India calculated to involve our people at large in the fight against tuberculosis, the age-old enemy of mankind. The campaign provides us with an opportunity to mobilise public support to the TB Control Programme and to raise resources for implementing the various activities of our Associations. During the past 35 years this campaign has been responsible for building up a strong public opinion in favour of voluntary effort for combating tuberculosis. In the coming months, we have many festive occasions, which should remind us of our unfortunate tuberculous people. As President of the Tuberculosis Association of India and as an old worker in the cause, I appeal to one and all of you to buy TB Seals in large numbers and strengthen the hands of your TB Associations in fighting the scourge of tuberculosis in our country.

Dr. D.B. Bisht, Chairman of the Tuberculosis Association of India and the Director General of Health Services appealed to the Directors of Health Services in the States to extend their full support and cooperation to

the State TB Associations in making the 36th Seal Campaign a great success.

REFRESHER COURSES

Andhra Pradesh: Three refresher courses for general practitioners were held in Vikarabad, Warangal and Nizamabad on 5th, 14th and 28th July, 1985 respectively. The course at Vikarabad was inaugurated by Shri G. Sudhir, IAS, Collector and District Magistrate, Ranga Reddy District and was attended by 50 doctors. The course at Warangal was inaugurated by Dr. Kalpana Devi, M.P. and was attended by 156 doctors. The course at Nizamabad was inaugurated by Dr. C.R. Rajagopalan, Retd. Superintendent, Gandhi Hospital and Cardio-Thoracic Surgeon and was attended by 76 doctors. The courses were organised by the respective District TB Associations under the joint auspices of the TB Association of India and the Tuberculosis Association of Andhra Pradesh and were sponsored by M/s Pharmaceutical Company of India, Bombay.

Haryana: The TB Hospital, Hissar organised a refresher course on 25th August, 1985, under the auspices of the Tuberculosis Association of India. The course was inaugurated by Dr. C. Prakash, Director-Principal, Medical College Rohtak and was attended by 50 doctors. M/s Lupin Laboratories Pvt. Ltd., Bombay, sponsored the course.

Rajasthan: Three courses were held in Jaipur on 7th and 24th May and 6th June, 1985. The courses were organised under the auspices of the Directorate of Medical and Health Services, Rajasthan, Jaipur. In all, 113 doctors attended the courses.

Tamil Nadu: The Anti-TB Association of Tamil Nadu, in cooperation with their respective District TB Associations, organised two refresher courses at Dindigul and Ooty on 28th July and 18th August, 1985 respectively. The course at Dindigul was inaugurated by Dr. K.R. Jacob, Dean, Madurai Medical College. The course at Ooty was inaugurated by Dr. S. Sundarajan, District Medical Officer and was attended by 81 doctors.

With these courses, the total number of refresher courses so far held in various parts of the country under the Tuberculosis Association of India and its State affiliates has reached 91.

NATIONAL CONFERENCE

Smt. Mohsina Kidwai, Union Minister for Health and Family Welfare, will inaugurate the 40th National Conference on TB & Chest Diseases Workers to be held in Shillong (Meghalaya) from the 16th to 18th November, 1985. Those who wish to attend the Conference may kindly write to the Secretary-General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-110 001.

AWARDS

Shri R.C. Garg Memorial Cash Award: The R.C. Memorial Trust (Regd.) Rohtak, has donated to the Tuberculosis Association of India a sum of Rs. 10,000/- to institute, in memory of the late Shri R.C. Garg, who was the first employee of the Lady Linlithgow Sanatorium, Kasauli, Shimla Hills, (since closed down), a cash award of Rs. 1,000/- every year for the best article published in the Indian Journal of Tuberculosis. The cheque will be presented to the winner at the time of the Annual General Meeting of the Association every year.

Ranbaxy-Robert Koch Oration: Prof. V. Ramalingaswami, Director-General, Indian Council of Medical Research, New Delhi, has been selected by the TB Association of India for the Ranbaxy-Robert Koch Oration for the year 1984. As Prof. Ramalingaswami could not attend the Cuttack Conference held in January this year, he will be delivering this Oration at the 40th National Conference on TB & Chest Diseases to be held in Shillong on the 16th November, 1985. The subject of the Oration will be "Resisters and Persisters in Microbial Diseases".

Prof. A.S. Paintal, Director, Vallabhbai Patel Chest Institute, University of Delhi, has been selected by the Association for the 1985 Ranbaxy-Robert Koch Oration. He will be delivering his Oration at the time of the 40th National Conference on TB & Chest Diseases to be held in Shillong in November 1985. The subject of the Oration will be "The significance of dry cough breathlessness and muscle weakness".

Wander-TAI Oration: Dr. S.B. Trivedi, Director, TB Research Centre, Amargadh, has been selected by the TB Association of India for the Wander-TAI Oration award for the year 1985. The title of his Oration will be "Surgery in Respiratory Diseases" and it will be delivered at the 40th National Conference on TB & Chest Diseases to be held in Shillong in November 1985.

Chanchal Singh Memorial Award:

The paper on "A study of chronopharmacokinetics of pyrazinamide in tuberculosis patients" by Dr. (Mrs.) Sandhya Kulshreshta of the Maulana Azad Medical College, New Delhi, has been selected by the TB Association of India for the Chanchal Singh Memorial Award for 1985. The cash prize of Rs. 1,000/- will be presented to her at the inaugural session of the 40th National Conference on TB & Chest Diseases.

Junior Award: The cash award of Rs. 500/- instituted by the TB Association of India for the best Essay by a senior medical student on "Management of Tuberculous Meningitis" has been won by Shri Rakesh M. Gupta, final year student of the Medical College, Baroda. The award will be presented to Shri Gupta at the inaugural session of the 40th National conference on TB & Chest Diseases.

ANTI-TB CAMP

Under the joint auspices of the TB Association of Andhra Pradesh and District TB Association, Ranga Reddy District, a Free Health Check-up and TB Camp was conducted at Ramanathapur, Hyderabad from 16th to 18th August, 1985. The Camp was inaugurated by Shri G. Sudhir, IAS Collector and District Magistrate, Ranga Reddy District. A total of 1,533 persons were checked up. Out of 268 who were x-rayed 25 were found to be suffering from pulmonary tuberculosis and out of 13,8 whose sputum was examined, 8 found sputum positive. Vaccinations for BCG, D.P.T., D.T., TT and Polio was carried out on 611; 49; 68; 92 and 47 persons respectively. The camp was sponsored by M/s Warner Hindustan Limited.

HEALTH CHECK-UP CAMPS

Two Health Check-up Camps, under the auspices of the Ranga Reddy District Association (Andhra Pradesh) were conducted on 26th and 30th July, 1985 at the Primary Health Centres in Maheshwaram and Mominpet respectively. At the Maheshwaram Camp, out of 173 x-rayed, 5 were found positive, and of the 153 sputum examined 1 was found positive. 110 BCG vaccinations were done. At the Mominpet Camp, out of 67 x-rayed, 17 were found positive and of 65 sputum examined 2 were found positive. 480 BCG vaccinations were done.

WORKSHOP ON TUBERCULOSIS

A workshop on Tuberculosis was organized by the Ramakrishna Mission Hospital, Itanagar (Arunachal Pradesh) on 19th and 20th

May, 1985 under the supervisions and guidance of Dr. S.P. Pamra, Honorary Technical Adviser, Tuberculosis Association of India. The workshop was inaugurated by the Hon'ble Chief Minister of Arunachal Pradesh, Shri Gegong Apang and the function was presided over by the Hon'ble Minister for Agriculture Shri T. Basar. The workshop was attended by 35 doctors comprising the entire staff of the Ramakrishna Mission Hospital and the Government Itanagar Hospital with a few general duty doctors from peripheral institutions around Itanagar. The workshop was sponsored

by M/s Lupin Laboratories (Private) Limited, Bombay.

INTERNATIONAL CONFERENCE ON HYPERTENSION

The National Council of Hypertension is organising the second International Conference on Hypertension from 7th to 9th December, 1985 at Birla Matushri Sabhagraha, Bombay. For further details kindly contact Dr. P.J. Mehta, Secretary-General, National Council on Hypertension, 64, Pedder Road, Hari Bhawan, Bombay-400 026.

The Indian Journal of Tuberculosis

ABSTRACTS

Vol. XXXII

October 1985

Post-Vaccination Tuberculin Sensitivity for Assessing BCG Vaccination in Areas with High Prevalence of Non-Specific Sensitivity

Raj Narain, et al; Tubercle; 1981, 62, 231.

The relationship of non-specific sensitivity and post-vaccination tuberculin sensitivity has been the subject of controversy. This relationship has an important bearing on the common practice of using post-vaccination tuberculin sensitivity for assessing BCG vaccination in areas with a high prevalence of non-specific sensitivity. In a recent BCG trial in India, a large number of persons were tested with PPD-S and PPD-B and also vaccinated with BCG vaccine or injected with placebo, by random allocation. Mutually exclusive random samples of the study population were retested with PPD-S at 2 months, 2 years and 4 years after vaccination. At each post-vaccination test the tuberculin sensitivity obtained among the placebo-injected controls provided a measure of the tuberculin sensitivity due to non-specific sensitivity that would have been present in the absence of BCG vaccination. The difference between the mean size of reactions to the post-vaccination test among the vaccinated and among the unvaccinated controls provided a measure of tuberculin sensitivity that was wholly due to BCG vaccination. Thus it was possible to separate and study the two components of post-vaccination tuberculin sensitivity. The results of the study indicate that post-vaccination tuberculin sensitivity can be used to assess BCG vaccination in areas with a high prevalence of non-specific sensitivity, provided the assessment is done in younger age groups and based on post-vaccination tuberculin sensitivity as measured 2-3 months after vaccination and not later.

Radioactive bromide partition test in the diagnosis of tuberculous meningitis

O.K. Ahuja, et al; Indian J. Med. Res.; 1983.

The utility of radioactive bromide partition ratio (BPR) test was studied in 19 patients (aged 10-41 years) with tuberculous meningitis (TBM) who had CSF findings compatible with the diagnosis of TBM and 5 symptom-free patients of TBM with normal CSF who had

been on treatment for 3 months or more. Six patients of pyogenic meningitis who were responding to antibiotic therapy and 16 patients who had no evidence of meningitis but required lumbar puncture for other reasons, served as controls. Adults were given a dose of 50(i. CiNH₄Br⁸² and children (below 18 years) a dose of 0.6 μ . Ci per kg. body weight orally, and lumbar CSF and blood samples were collected 48 hours later. Eighteen patients who had active tuberculous meningitis were found to have a BPR ratio below 1.3 All TBM patients on treatment and those with partially treated pyogenic meningitis and non-meningitis controls had a BPR ratio above 1.3. The findings suggest that this is a very useful test in the differential diagnosis of TBM and BPR values below 1.3 strongly indicate tuberculous meningitis. However, studies on a larger series are required to firmly establish the usefulness of the test.

Pulmonary Sarcoidosis and Serum Angiotensin-converting Enzyme

Michael S, et al; Mayo Clinic Proceedings; 1982, 57, 64.

Lungs have an important role in the normal physiology of the renin-angiotensin system, viz. conversion of angiotensin I, to angiotensin II by pulmonary epithelium. The conversion is mediated by an enzyme called "Serum Angiotensin-Converting Enzyme" (S.A.C.E.). SACE range was studied in 60 normal controls and 236 sarcoidosis patients. 83% of active pulmonary sarcoidosis cases had elevated SACE activity, against only 11 % of patients with inactive pulmonary sarcoidosis. 12% of the sarcoidosis patients had normal SACE activity as against 2-3% of normal subjects having elevated SACE. Although SACE does not permit an absolute diagnosis of sarcoidosis, it provides an important supportive evidence. SACE activity is also increased in patient with primary biliary cirrhosis, amyloidosis or myeloma. But these disorders can rarely be confused diagnostically with sarcoidosis. Other granulomatous diseases of the lungs such as tuberculosis, fungal infections, or berylliosis, which can be confused with sarcoidosis, generally have normal SACE activity.

Controlled clinical trial of 4 short course regimens of chemotherapy (Three 6-months and one 8-months) for pulmonary tuberculosis

East and Central African j British Medical Research Council, Fifth Collaborative Study, Tubercle, 1983,64,153-166.

Four daily short-course chemotherapy regimens (three 6-months and one 8-months) for pulmonary tuberculosis have been compared. All four had the same initial 2-month intensive phase of streptomycin, isoniazid, rifampicin and pyrazinamide (SHRZ). The continuation phase of the regimens was: 1) Isoniazid and rifampicin for 4 months, or 2) isoniazid and pyrazinamide for 4 months or 3) isoniazid alone for 4 months or 4) isoniazid alone for 6 months. All patients have been followed up for 12 months after stopping chemotherapy.

In patients with fully sensitive pretreatment strains the 6-months regimen with rifampicin throughout (4HR) was highly effective with a bacteriological relapse rate of 2% of 167 patients, significantly better ($P < 0.01$) than the rate of 9% of 158 patients in the 6-month regimen with isoniazid alone in the continuation phase (4H). The 8-month regimen (6H) was also highly effective, with a relapse rate of 3% of 119 patients but was not significantly better ($P < 0.1$) than the 6-month isoniazid regimen (4H). The regimen with pyrazinamide throughout (4HZ) had a relapse rate of 4% of 165 patients, not significantly different from any of the other regimens. An important finding in the two regimens with isoniazid alone in the continuation phase (4H and 6H) was that 1 of the 2 failures during chemotherapy and 17 of the 18 bacteriological relapses after stopping occurred with strains still sensitive to isoniazid.

In patients with strains resistant to isoniazid pretreatment, 8 of 19 patients on the 4H or 6H regimens had an unfavourable response during chemotherapy compared with none of 26 on the HR or HZ regimens ($P < 0.005$).

Of the 851 patients who started treatment, 24 developed possible adverse reactions but only 6 required modification of their chemotherapy.

Undesirable side effects of Isoniazid and Rifampicin in Largely Twice-Weekly Short-course Chemotherapy for Tuberculosis

Asim K. Dutt, et al; American Review of Respiratory Diseases; 1983, 128, 419.

Eight hundred and fourteen previously untreated sputum positive patients of pulmonary-tuberculosis were treated with IN H and Rifampicin daily for one month and twice-

weekly for the subsequent 8 months between January 1976 and June, 1981. Treatment was successful in 95% of the 586 patients who completed the therapy. In 15, the sputum culture continued to be positive. Ten patients relapsed after stopping chemotherapy. Major adverse reactions occurred in 22 patients, 14 during the daily phase and 8 during the twice-weekly phase. Hepatic toxicity occurred in 13 patients during the daily phase and in 5 during twice-weekly phase and it was caused by Rifampicin in 5, IN H in 10 and was undetermined in 3. Haematologic abnormalities developed in 4 patients, one during the daily phase and 3 during the twice-weekly phase. Minor side-effects which did not necessitate termination of therapy were encountered in 62 patients, 35 during the daily and 27 during the twice-weekly phase. The symptoms were gastro-intestinal in 18, drug fever in 27 (including 11 with flu-syndrome during the twice-weekly phase), skin rashes in 14 and headache with general malaise in 3. Hypersensitivity reactions in the twice-weekly phase were infrequent. Clinical surveillance for toxicity is preferred over routine and regular bio-chemical monitoring.

Acute Isoniazid self poisoning: A report of 2 adult cases and review of literature

Sucharita A. Nanivadekar ; The Indian Practitioner; 1983, 36, 599.

Two female patients swallowed 50 and 18 tablets of 300 mgm INH respectively with a view to commit suicide. They were brought to the hospital in an unconscious state with recurrent generalised seizures. There were no signs of meningeal irritation. Deep tendon reflexes were suppressed and plantars were flexors. Pupils were semidilated but reacting to light. Blood pressure and pulse were within normal limits. Both were treated with intramuscular diphenyl hydantoin, intravenous glucose, sodium bicarbonate and pyridoxine. The seizures ceased by the next day. Consciousness improved gradually and both patients recovered fully within 4 days.

A continuing study of primary drug-resistant Tuberculosis among children observed at the King's County Hospital Medical Center between the years 1961 and 1980

Phillip Steiner, et al; American Review of Respiratory Diseases; 1983, 128, 425.

A 20-year prospective study of the incidence of primary drug-resistant tuberculosis among children treated at the King's County Medical Centre was undertaken in January 1961 and extended through December 1980. There were 355 strains of Mycobacterium Tuberculosis

isolated during this period, 56 of which were found to be primarily resistant to one or more anti-tuberculosis drugs, giving an overall resistance rate of 15.8%. The study was divided into five 4-year periods. The resistance rate to isoniazid was 9.9%, varying from a peak of 15.2% in the third period of study (1969 to 1972) to 4.5% in the last period of study. The changes in the rate were not significant. The overall resistance rate for streptomycin was 9.2%. There were significant increases in the resistance rate in the second (1965 to 1968) and third (1969-to-1972) periods of study, but not in the last 2 periods. The rates for PAS (3.4%), Rifampicin (1 %) and Ethambutol (0.7%) were low. The type and severity of disease among those infected with a resistant strain were no different from those infected with a susceptible strain. Life-threatening disease was found in 10 of the 56 patients infected with a drug-resistant strain. There was one fatality in a child with meningitis who was treated early in the study. Our experience suggests that rifampicin and ethambutol be included in the initial treatment regimen of all children with a life-threatening form of tuberculosis until the susceptibility pattern of the infecting strain is determined, after which the drug regimen can be modified if necessary.

Bulletin of the Pan American Health Organisation 1983, 17,355

Virulence of 159 *M. Tuberculosis* strains recovered from previously untreated patients in 9 American countries (Argentina, Brazil, Canada, Chile, Colombia, Costa Rica, Ecuador, Mexico and Venezuela) was tested. 152 strains were catalase-positive and sensitive to INH. 9 of these strains (5.9%) showed attenuated virulence in guinea pigs (root index values ranging from 0.40 to 0.79). 4 of these strains were from Mexico, 4 from Costa Rica and 1 from Chile. The overall percentage of low virulence strains was far less than that prevailing in Southern India.

The Smear-positive and Culture-negative Phenomenon of Mycobacteria in Sputum Specimens in Relation to the Problems of the Detection of Mycobacteria

Sukeyoshi Kudoh; Reports on Medical Research Problems of the Japan Anti-Tuberculosis Association, 1981,30,20.

It is estimated that the number of sputum smear-positive and culture-negative cases (SPCN) has recently been increasing in Japan, but its clinical significance is as yet not so clear. The phenomenon may sometimes be due to technical errors related to staining or microscopy. Many of these specimens give a growth

if the period of incubation of cultures is extended up to sixteen weeks. The SPCN cases found during the course of primary chemotherapy with intensive regimens are regarded as a normal step prior to negative conversion of bacilli both on smear and culture, in spite of the possible growth in extended incubation period. If colonies grow during the extended incubation in such a case a risk of deterioration in the future is high and the prognosis is not favourable, but they have no clinical significance, if there is no growth during the extended incubation period.

Acid-fast bacilli in sputum smears of patients with pulmonary tuberculosis

Talk Chae Kim, et al. American Review of Respiratory Diseases, 19S4, 129, 264.

Results of sputum smear vs. culture in 977 patients of pulmonary tuberculosis were analysed. Nearly 1/4th of the patients were smear negative but culture positive before start of treatment, the rate varying inversely to the extent of disease and the presence of cavities. These patients had the fastest sputum culture conversion rate provided the bacilli were sensitive to the drugs used. Patients who were smear positive and culture positive before treatment had a significantly slower conversion rate. It was slowest if the pre-treatment disease was far advanced and cavitory. Patients with drug resistant bacilli had slower conversion rate than those with sensitive bacilli in all groups. 20% of the 727 patients who were both smear and culture positive before treatment continued to have a positive smear with negative culture after treatment. This phenomenon was far more prevalent in patients with advanced and cavitory diseases and it was also significantly more in patients whose treatment regimen included rifampicin. This phenomenon however did not alter the ultimate rate of sputum conversion and does not call for a change in chemotherapy even if the smear continues to be positive but culture is negative. Only if positive smear persists for more than 14 weeks after the culture has become negative a change in regimen may be considered on the basis of positive smear.

Tuberculous Meningitis with multiple tuberculomas of the brain

Suhasini Gopal et al; The Indian Practitioner; 1983, 36, 594

A 24-year-old female patient presented with features of tuberculous meningitis of 8 days' duration prior to admission. Subsequently she developed right-sided hemiparesis, bilateral loss of vision and choroid tubercles even when

she was on anti-TB treatment. Three weeks later she developed features of raised intracranial tension which were due to multiple tuberculomas as revealed on CT scan.

Content of a-Tocopherol and Serotonin in blood serum of female patients with tuberculosis of the genitalia

V.N. Sharipov, et al

Serotonin and a-tocopherol were estimated in 70 female patients with genital tuberculosis. Serotonin was increased and a-tocopherol decreased where the genital tuberculous lesion was active. In patients with marked degree of fibrosis, a-tocopherol was fairly low while serotonin was high. For estimation of the *efficiency* of treatment, it is suggested that serotonin and a-tocopherol contents in the blood serum can be used as a monitoring procedure.

(Abstract from Russian literature).

Gastric Secretion in Patients with Respiratory Tuberculosis

N.A. Brezhenko

Fifteen percent of nearly 600 patients with active pulmonary tuberculosis had a deranged function of the stomach. The association between an exudative tuberculous lesion in the lung and hyper-acidity was significant.

(Abstract from Russian literature).

Clinicobacteriological characteristics of Tuberculosis of the peripheral Lymph Nodes

M.A. Karachunskyi, et al

One hundred and nine lymphnode biopsies were examined bacteriologically. Mycobacterium Tuberculosis was found in 31% and L-forms of Mycobacterium Tuberculosis were detected in 35% of the biopsies. In 13%, both the bacillary and L-forms were present.

(Abstract from Russian literature).

Morphological forms of Cancer in Patients with associated Lung Cancer and Tuberculosis

I.P. Zhingel, et al

Two hundred and one patients with concomitant tuberculosis and cancer of the lung were studied. Squamous cell carcinoma was present in 58%, adenocarcinoma in 22% and undifferentiated form in 20%. Squamous cell type was found more in patients with central

tumour and in association with active tuberculosis of the lung.

(Abstract from Russian literature).

Co-existent Pulmonary Tuberculosis and Bronchogenic Carcinoma with involvement of a solitary Lymph Node

A.K. Kundu, et al; *J. Ind. Med. Ass;* 1983,81,57.

A case is described where tuberculosis and malignancy co-existed. A 48-years old non-smoker, male had tuberculous infiltration in the right upper zone and a lesion in the left hilar region suggestive of malignancy. Sputum was positive for AFB. Biopsy of the single cervical lymph node showed co-existing tuberculous and a metastatic adeno-carcinomatous lesion. Bronchoscopy could not be done.

Survival of Cancer Patients in Finland in 1953-1974

T. Hakulinen. et al; *Annals of Clinical Research (Finland)}*; Vol. 13 Suppl 31, 1981.

The basis of assessment is the Relative Survival Rate (RSR) which is defined as the ratio of the observed survival rate in the patient group to the survival rate expected in a group similar to the group of patients at diagnosis with respect to all other factors (sex, age, calendar time, etc) affecting the survival, except the cancer in question. The material in respect of the cancer of lung consisted of 30,039 males and 2572 females. The proportion of localised cases was 35% in males and 27% in females. These proportions decreased with time. The mean age at diagnosis was 62.4 years in males and 64.2 years in females. The 5-year RSR was 7% in males and 10% in females, the rate was higher in younger than in older patients, reaching approximately 100% in the 14th year of follow-up. The survival improved with time in all stages. Of patients with a localised tumour diagnosed in 1967-1974, 28% of the males and 36 % of the females were given radical treatment. The 5-year RSRs for these cases were as high as 49% in males and 62% in females. Of all the lung cancer cases diagnosed in 1953-1974, the proportion of patients without treatment was 31% in males and 42% in females. Their 5-year RSR was 1.5% in males and 2.2% in females. The proportion of histologically confirmed cases in 1967-1974 was 69% in males and 70% in females. The diagnosis was confirmed cytologically in a further 20% of the cases. The 5-year RSR was higher for histologically than for cytologically confirmed cases except for non-localised cases in males. Localised adenocarcinoma cases had higher 5-years RSRs than localised cases with other

histological types. Among patients with a non-localised tumour epidermoid carcinoma was the most favourable type. The expected mean length of life at diagnosis was 14 years in males and 16 years in females. The estimated mean length was around 2 years for both sexes.

Sarcomas of the Lung

Antonio G. Nascimento, et al; Mayo Clinic Proceedings; 1982,57,355.

Of 18 patients with primary sarcoma of the lung during the period 1950-1978, 10 were women and 8 were men whose ages ranged from 22 to 77 years; 6 patients were in the sixth decade of life. Nine patients had no symptoms referable to the tumor. When present, symptoms were cough, chest pain, or dyspnea. One patient had attacks of hypoglycemia. Radiographically the tumors were generally large and well circumscribed. Grossly, three tumors were intrabronchial; one of these had invaded the lung. The remaining lesions were intrapulmonary. The sizes of the tumors ranged from 2 to 16 cm in greatest dimension. Histologically, there were nine fibrosarcomas, four leiomyosarcomas, three hemangiopericytomas, and two osteosarcomas. Most of the fibrosarcomas and leiomyosarcomas were poorly differentiated; all hemangiopericytomas were considered malignant, and both osteosarcomas were high grade. Treatment consisted of complete removal when feasible. At last follow-up, four patients were alive without disease from 3 to 18 years after surgery. The common factor in all four of these cases was the size of the tumor, 2 to 3 cm. in greatest dimension. Hence, the size of the tumor is the most important prognostic indicator in sarcomas of the lung.

Tuberculosis of the Penis

P. Sengupta, et al; Jr. Ind. Med'Ass. f 1982, 78, 47.

A 30-year-old male patient reported with a slowly progressing ulcer over glans penis. Serological tests for syphilis and smear for gonorrhoea were negative. Partial amputation of the penis was carried out. Histopathological exami-

nation proved tuberculous aetiology of the ulcer. No evidence of tuberculous lesion elsewhere in the body was detected. Response to anti-tuberculous treatment was satisfactory.

A case of Pyrexia of prolonged duration with Hepatosplenomegaly

Sucharita A. Nanivadekar, et al; The Indian Practitioner; 1983, 36, 587.

who had pyrexia with massive enlargement of liver and spleen and vague intermittent pain, in the abdomen. Apart from slight anaemia, other blood, urine and stool examinations did not show any abnormality. Barium swallow and chest x-ray also did not show any abnormality. There was nothing particular in the past history except jaundice 10 years ago. Pulse-respiration and blood pressure were within normal limits. Supratrochlear lymph nodes were palpable. Examination of the abdomen did not reveal anything extraordinary except fullness of the upper abdomen with enlargement of liver and spleen. Bone marrow aspirate, showed hypercellularity. Liver biopsy showed a normal lobular pattern with changes suggestive of chronic venous congestion. Aldehyde test was strongly positive. There was no response to treatment with Camoquin and Neostibamine. Direct and indirect Coombs' test and blood culture were also negative. Laparoscopy showed multiple white patches on the surface of the enlarged liver. Spleen was not enlarged but a big tumor was seen on the left side of the stomach. The intestinal coils were displaced. There was minimal fluid in the abdomen. Histopathological examination of the laparoscopy biopsy reported necrotic material of uncertain aetiology. Liver scan showed a few areas of reduced concentration in the right lobe. A repeat liver biopsy corroborated the result, of earlier biopsy and the changes were labelled as non-specific. Serum protein electrophoresis was within normal limits. The patient continued to go downhill and died after 16 weeks. Autopsy showed extensive tuberculous involvement of the para-aortic and coeliac lymph nodes and liver and spleen with no evidence of tuberculosis in the lungs or any other organ in the body.