

INDIAN JOURNAL OF TUBERCULOSIS

Official organ of the
Tuberculosis Association of India

Editor: Dr.
P.K. Sen

Co-Editors:
Dr. M.D. Deshmukh
Dr. N.L. Bordia

Associate Editors
Dr. H.B. Dingley
Dr. S.P. Pamra

Published quarterly in
the months of January,
April, July and October.

Annual Subscription :
Rs. 20/- £ 2, \$ 5.

Single copy:
Rs. 6.00

Vol. XIX : No. 2

April 1972

Contents

Editorial: Fungus Diseases of the Chest	... 45
Two controlled studies of the efficacy of isoniazid alone in preventing relapse in patients with bacteriologically quiescent pulmonary tuberculosis at the end of one of chemotherapy —O. Nazareth, S. Devadatta, Wallace Fox, N.K. Menon, S. Radhakrishna, D. Rajappa, C. V. Ramakrishnan, P. R. Somasundaram, H. Stott, S. Subbammal & S. Velu	... 47
Allergic broncho-pulmonary aspergillosis —S. P. Pamra, Z. U. Khan, R. S. Sandhu and M. Ilyas	... 61
Anti-Tuberculosis Shibir (TB Camps) where work becomes a pleasure —M. D. Deshmukh	... 68
Intramedullary Tuberculomas of spinal cord —O. Raja Reddy, B. Dayananda Rao and M. V. Raghava Reddy	... 73
Pulmonary amoebiasis presenting as a case of pulmonary tuberculosis —Jitendra Nath, M. S. Agnihotri, Zafar Jamil and Rajendra Kumar	... 75
A variety display of tuberculous lymph nodes —O. A. Sarma	... 78

News & Notes * Abstracts

Published on behalf of the Tuberculosis Association of India, by
the Secretary-General, 3, Red Cross Road, New Delhi-1

The Indian Journal of Tuberculosis

Vol. XIX

New Delhi, April 1972

No. 2

FUNGUS DISEASES OF THE CHEST

The W.H.O. Expert Committee on Tuberculosis has defined a case of pulmonary tuberculosis as a person suffering from bacteriologically confirmed disease. The main virtue of the bacteriological limitation does not appear to be exclusion of those few patients who, though sputum negative, are undoubtedly suffering from active disease but that it should make the chest physicians conscious of and eliminate all other likely causes of disease simulating tuberculosis. Fungus disease is one such possibility.

Although the occurrence of superficial Mycoses is well known in India, it is usually believed that the deep Mycoses including those of the chest are rather uncommon. There is ample evidence to show that fungal elements and spores are a frequent constituent of our environments. It is quite likely therefore that fungus diseases do exist but are not being recognized as such.

The diagnosis of fungal diseases bristles with difficulties. There is impressive evidence in support of the thesis that fungi capable of causing human disease exist as actively growing saprophytes in nature. Over 20 species have been isolated so far mostly from soil, vegetation and organic debris. When transferred to a parasitic habitat in man, change of environments bring about a change in the mode of growth and production. In this diphasic existence, if the fungus can adapt itself to the less favourable circumstances, it becomes pathogenic. If it cannot, it remains a saprophyte.

Ecological studies have failed to pinpoint factors which influence this transition and also the actual means through which change from a saprophyte to a pathogenic state is brought about. Profligacy with which anti-bacterial agents and hormones are being used may be one such factor, since many fungus diseases seem to follow in the wake of conquest of bacterial disease.

Since fungi are often present in the air which man inhales, their mere presence in the sputum does not mean that they have become pathogenic. This leads to difficulty in diagnosis. Secondly, whereas some chest physicians, when in doubt, may not take steps to prove or exclude the possibility of fungus disease, it is also a fact that even if they wish to, it is not always possible for many to do so, since facilities for diagnosis of fungal disease are sparse and inadequate in our country so far.

The third difficulty in the diagnosis of fungus disease is the bewildering variety of their manifestations in man. Taking respiratory diseases caused by

Aspergillus as an example, five clinical entities have been recognised, depending upon the nature and source of the pathogen, the circumstances of exposure and, above all, the immunological reactivity of the host. Of all these, the last which is the most important, is also the least understood. Apart from the knowledge that atopy is linked with the presence of IgE, not much more is known. Many cases of so-called 'Asthma', are undoubtedly caused by the fungus *Aspergillus* in atopic subjects with Type I Hypersensitivity. They are not often recognised as such since Asthma patients are not routinely investigated for the presence of fungus disease. Elsewhere in this issue four cases of another condition, namely 'Allergic broncho-pulmonary aspergillosis', have been described. This condition, heretofore unreported from India, is not infrequent in other countries. Though finding four cases in one centre within a period of seven months is no indicator of its frequency, (three of these had been under observation for a number of years) it does prove that cases of this disease can be found if looked for amongst patients with repeated asthmatic episodes and transient radiological shadows in the lungs.

Finally, the mode of transmission of fungi which cause deep Mycoses being relatively unknown and no immunization being possible so far, these diseases are most difficult to prevent. Fortunately however, a number of potent and effective fungicides are now available and treatment of many of these diseases is not difficult. It is imperative that all chest physicians must keep in mind the possibility of pathogenic fungi being the cause of obscure cases of respiratory disease and also the authorities that be, should see that facilities for diagnosis of fungus disease are made available at least in all medical colleges, if not in all chest clinics.

TWO CONTROLLED STUDIES OF THE EFFICACY OF ISONIAZID ALONE IN PREVENTING RELAPSE IN PATIENTS WITH BACTERIOLOGICALLY QUIESCENT PULMONARY TUBERCULOSIS AT THE END OF ONE YEAR OF CHEMOTHERAPY*

O. NAZARETH, S. DEVADATTA, WALLACE FOX, N. K. MENON, S. RADHAKRISHNA, D. RAIAPPA, C. V. RAMAKRISHNAN, P. R. SOMASUNDARAM, H. STOTT, S. SUBBAMMAL & S. VELU^o

(From Tuberculosis Chemotherapy Centre, Madras)

An earlier report from the Tuberculosis Chemotherapy Centre, Madras, had shown that in patients with bacteriologically quiescent pulmonary tuberculosis at the end of one year of chemotherapy, isoniazid alone in a single daily dose of 150-200 mg for the second year did not have a marked effect in the prevention of relapse over a 4-year period of follow-up in patients who had residual cavitation at one year (the "open-negative" syndrome), but was highly effective in patients who had no residual cavitation at one year. As a result of these findings, two controlled studies, reported here, were undertaken.

The first study was in patients with bacteriologically quiescent disease and residual cavitation at one year, and investigated the value of isoniazid in a higher daily dose of 400 mg throughout the second year; this dose is known to be optimal therapeutically, when isoniazid is prescribed alone for one year in the *initial* treatment of the disease. The second study was in patients with bacteriologically quiescent disease and no residual cavitation at one year, and investigated the value of a shorter duration of chemotherapy in the second year, namely 6 months, with a daily dose of 300 mg of isoniazid. Neither of the two isoniazid regimens was highly satisfactory, although both appeared to have had some effect in preventing relapse during a 4-year period of follow-up.

From the findings of the earlier study and the present study, it is therefore concluded that in patients with the "open-negative" syndrome at the end of one year of chemotherapy, maintenance chemotherapy with isoniazid alone is not highly satisfactory, although it is of some value; however, in patients with bacteriologically quiescent disease and no residual cavitation at one year, it is highly effective, when given for 12 months in a single daily dose of 150-200 mg.

Introduction

An earlier controlled study from this

•Deceased.

Centre showed that in patients with bacteriologically quiescent pulmonary tuberculosis and residual cavitation at the end of one year of chemotherapy, isoniazid alone in a single daily dose of 150-200 mg (approximately 4.5 mg./kg body-weight) throughout the second year did not have a marked effect in preventing bacteriological relapse over a 4-year period of follow-up (Evans et al., 1969). When the preliminary findings of this study became available, it was decided to investigate whether a higher dosage of isoniazid, namely 400 mg as a single daily dose, would be more effective. This higher dosage had been shown to be optimal therapeutically, when the drug was given alone, in a single daily dose, for one year to newly-diagnosed, previously untreated tuberculous patients with a positive sputum (Tuberculosis Chemotherapy Centre, Madras, 1963). However, it resulted in peripheral neuropathy in approximately one-fifth of the patients (Tuberculosis Chemotherapy Centre, Madras, 1960). It was therefore decided that 6 mg of pyridoxine, which was known to be highly effective in preventing the neuropathy (Tuberculosis Chemotherapy Centre, Madras, 1963), should be incorporated in each dose of isoniazid. A study, based on random allocation to treatment, was undertaken of this isoniazid regimen (400 mg for one year) in comparison with a placebo. The results over a 4-year period are reported in this paper.

The earlier study (Evans et al., 1969) also showed that in patients with bacteriologically quiescent disease and *no* residual cavitation at one year, isoniazid alone in a single daily dose of 150-200 mg for the whole of the second year was highly effective in preventing bacteriological relapse over a 4-year period. When the preliminary findings became available, it was decided to investigate whether maintenance chemotherapy with isoniazid alone for a shorter duration, namely 6 months, would also be highly effective, if the daily dose was increased to 300 mg (without any pyridoxine supplement); the 400 mg dose was not selected as it would have required a pyridoxine supplement (for the prevention of peripheral neuropathy), resulting in an increased cost. A study, based on random

allocation, was undertaken to compare this isoniazid regimen (300 mg for 6 months) with a placebo. The results over a 4-year period of this study are also reported in this paper.

Plan and Conduct of the Two Studies

All the patients reported here had had newly-diagnosed, previously untreated pulmonary tuberculosis with a positive sputum and isoniazid-sensitive organisms on admission to initial treatment, and the great majority had had cavitated disease. In the first year, they had received isoniazid, either alone or in combination with streptomycin, PAS or thiacetazone (for details, see Table 8). At one year, they all had bacteriologically quiescent disease, that is, all cultures examined at 10, 11 and 12 months (usually a total of 7-9) were negative.

Assessment of cavitation at one year

At one year, the postero-anterior radiograph and tomograms were reviewed by any two of the Centre's physicians (and in case of disagreement, by a third), and each patient was classified either as having residual cavitation or as having no residual cavitation.

Treatment in the second year (the first year of follow-up)

At the end of the first year, the patients were allocated *at random* to treatment in the second year with isoniazid alone or a placebo. The treatment regimens were as follows :

For patients with residual cavitation (study I)

- (a) Isoniazid 400 mg plus pyridoxine 6 mg, in a single tablet daily, for 12 months, *or*
- (b) a placebo (calcium gluconate 500 mg or lactose 500 mg), as a single tablet daily, for 12 months.

For patients with no residual cavitation (study II)

- (a) Isoniazid 300 mg in a single tablet daily for the first 6 months, and the placebo (see above) as a single tablet daily for the next 6 months, *or*
- (b) the placebo (see above) as a single tablet daily for 12 months.

Ind J. Tub, Vol. XIX, No. 2

Treatment in the third and subsequent years

No anti-tuberculosis chemotherapy was prescribed routinely to patients in either study in the third, fourth and fifth years.

Collapse therapy and resection

No patient in either study had collapse therapy or resection.

General management during the 4-year period follow-up

All patients were managed on an out-patient basis. During the second year, patients receiving isoniazid attended the Centre once a fortnight and those receiving the placebo attended once a month, to collect their medicaments. During the third and subsequent years, all patients attended the Centre once in 3 months for routine assessments. Throughout the period of follow-up, their homes were visited once a month by a health visitor.

The routine assessments included (a) a clinical assessment at monthly intervals in the second year and at 3-monthly intervals subsequently, (b) a postero-anterior chest radiograph at 3-monthly intervals in the second year and at 6-monthly intervals subsequently and (c) the bacteriological examination of sputum specimens as described below. In addition, for patients receiving isoniazid, the regularity of drug-intake was assessed by collecting a urine specimen at every clinic attendance (that is, once a fortnight) and examining it by the combined naphthoquinone-mercuric chloride test of Gangadharam et al. (1958).

Bacteriological investigations

The standard procedure was to obtain 14 sputum specimens from each patient in the second year, 9 in the third year, 9 in the fourth year and 11 in the fifth year (Table 1). Extra specimens were collected if a positive culture was obtained.

The sputum specimens were examined by direct smear and by culture. If a positive culture was obtained at any month, an isoniazid sensitivity test was set up, and also a test of sensitivity to any companion drug which the patient had received during the first year. The techniques employed for smear and culture examinations and isoniazid sensitivity tests, and the definition of isoniazid resistance, have been reported earlier (Tuberculosis

TABLE I

Intensity of bacteriological examination during the 4-year period of follow-up

Year	Month	Type and number of sputum specimens*		Total number of specimens for the year
		Collection	Supervised spot	
Second	13 to 23 24	1 and	or 1 2 1	14
Third	27, 30 & 33 36	1 and	and 1 2 1	9
Fourth	39, 42 & 45 48	1 and	and 1 2 1	9
Fifth	51, 54, 57 & 59£ 60	1 and	and 1 2 1	11

*A collection specimen was one collected overnight in the home, and a supervised spot specimen was one produced under supervision in the clinic after the throat had been tickled with a swab to induce cough.

Chemotherapy Centre, Madras, 1964). Identification tests (colonial morphology, catalase activity and niacin production) were undertaken on all cultures selected for sensitivity tests, using procedures described by Thomas et al. (1961).

Definition of bacteriological relapse

A bacteriological relapse is defined as 2 or more positive cultures in any 6-month period—for instance, in 7 consecutive monthly examinations in the second year or in 3 consecutive 3-monthly examinations in subsequent years.

Assessment of radiographs

An independent assessor (Dr. J. Frimodt-Moller), who was unaware of the treatment and other details of any individual patient,, made the following assessments using postero-anterior chest radiographs.

1. Total extent of radiographic lesion at the start of the initial treatment, and at one year.
2. Extent of cavitation at the start of the initial treatment.
3. For patients with residual cavitation at

one year⁰ : radiographic changes between 12 and 24 months* and between 24 and 60 months.

4. For patients with no residual cavitation at one year⁰ : radiographic changes between 12 and 18 months* and between 18 and 60 months.

To ensure uniformity standards, each of the assessments was undertaken for all the patients at a *single* session. The procedures and classifications employed have been described in detail elsewhere (Tuberculosis Chemotherapy Centre, Madras, 1960).

Results

Study of Patients with Residual Cavitation At 1 Year

Number of patients in the study

A total of 123 patients had bacteriologically quiescent disease with residual cavitation at one year. Of these, 59 were allocated to the placebo for the second year and 64 to the

⁰Assessment made by the Centre's physicians (see page 48).

[£]That is, the period for which isoniazid was prescribed for half the patients.

TABLE 2

Bacteriological relapse during the 4-year period of follow-up in patients with residual cavitation at one year

Treatment in the second year	Total patients (a)	Patients who had a bacteriological relapse	Of these, patients who required re-treatment					
			No.	% of (a)	Year of relapse			
					Second	Third	Fourth	Fifth
Placebo	58	9	8	14	5	0	2	1
Isoniazid	63	9	4	6	2	0	2	0

isoniazid (400 mg) regimen. However, one patient (placebo), while in a general hospital for cirrhosis of the liver, was given streptomycin plus isoniazid by the hospital authorities for 7 weeks in the second year. Another patient (isoniazid) was withdrawn from the study on account of psychosis induced by isoniazid (See page 52). Excluding these 2 patients, there remain 58 placebo and 63 isoniazid patients in the analysis.

Pre-study factors

All the patients had positive cultures on admission to initial treatment; moreover, the first collection specimen of sputum was smear-positive in 91% of the 58 placebo and 95% of the 63 isoniazid patients, including 62% and 59%, respectively, in whom it was moderately or heavily positive. Moderate or extensive cavitation was present in 74% of the placebo and 59% of the isoniazid patients ($P=0.1$), and moderate, extensive or gross lesions (for definitions, see Tuberculosis Chemotherapy Centre, Madras, 1960) in 90% of the patients in each series.

In the first year, sputum conversion* had commenced by 3 months in 60% of the placebo and 67% of the isoniazid patients. At one year (that is, at the start of the present study), 40% of the placebo and 38% of the isoniazid patients had moderate, extensive or gross residual radiographic lesions.

In summary, the two series of patients were similar in all the pre-study factors.

Intensity of culture examination

The mean number of cultures per patient

*That is, all cultures negative for at least 3 consecutive months.

was 14.3 in the placebo series and 14.2 in the isoniazid series in the second year, 8.7 and 9.1, respectively, in the third year, 8.6 and 8.4, respectively, in the fourth year and 10.5 in each series in the fifth year. Thus, the two series were examined with a high and similar intensity during the 4-year period of follow-up.

Bacteriological relapse

A bacteriological relapse occurred during the 4-year period of follow-up in 9 of the 58 patients in the placebo series and in 9 of the 63 patients in the isoniazid series (Table 2). Of these, 1 placebo and 5 isoniazid patients had a sputum conversion subsequently *without* recourse to re-treatment, and remained persistently culture-negative till the end of the study. Thus, relapse requiring treatment occurred in 8 (14%) patients in the placebo series and 4 (6%) patients in the isoniazid series, a suggestive but non-significant difference ($P=0.1$)*.

Considering the reasons for re-treatment, 6 patients (4 placebo, 2 isoniazid) had a clear-cut radiographic deterioration (confirmed by an independent assessor, Dr. K.S. Sanjivi) associated with the bacteriological relapse; one of the 2 isoniazid patients had tuberculous meningitis also. In the other 6 patients, re-treatment was solely on account of bacteriological reasons. Thus, 4 patients (3 placebo, 1 isoniazid) had at least 1 positive smear and at least 5 positive cultures during the 3 months immediately preceding the start of re-treatment. A fifth (placebo) had repeatedly produced positive cultures, interspersed with

*As the progress of the isoniazid patients cannot be inferior to that of the placebo patients, P-values corresponding to 1-tail tests of significance are reported whenever progress is considered.

negative cultures, over the preceding year. The sixth (isoniazid) had produced a positive culture (20-100 colonies) at two successive monthly examinations.

Of the 8 placebo patients who needed re-treatment, 5 had the relapse in the second year, 2 in the fourth year and 1 in the fifth year (Table 2); 7 had isoniazid-sensitive cultures at the time of the relapse. Of the 4 isoniazid patients who needed re-treatment, 2 had the relapse while they were receiving isoniazid (that is, in the second year)—1 with an isoniazid-resistant culture and the other with an isoniazid-sensitive culture; the other 2 had the relapse in the fourth year, both with isoniazid-sensitive cultures.

Radiographic progress

Between 12 and 24 months, 5 patients died without any evidence of bacteriologically active tuberculosis; four patients had a bacteriological relapse for which re-treatment was started, including 3 (2 placebo, 1 isoniazid) who had an associated clear-cut *radiographic deterioration*. For the remaining 112 patients (52 placebo, 60 isoniazid), the radiographic changes between 12 and 24 months are set out in Table 3. It will be seen that 58% of the placebo and 52% of the isoniazid patients

showed improvement, which was slight in all but 2.

Between 24 and 60 months, when *none* of the patients received any routine chemotherapy, 6 patients died without any evidence of bacteriologically active tuberculosis; eight patients had a bacteriological relapse for which re-treatment was started, including 3 (2 placebo, 1 isoniazid) who had an associated clear-cut *radiographic deterioration*. Of the remaining 43 placebo and 55 isoniazid patients (Table 3), 44% and 69%, respectively, showed radiographic improvement, the difference being significant ($P=0.01$). However, it will be noted that the improvement was slight in all but 3 and, therefore, the difference observed is probably of little importance. Supporting evidence for this conclusion was obtained from the finding that the placebo and isoniazid patients had very similar distributions for the extent of the residual radiographic lesion at 60 months, as at 24 months. (These assessments were specially undertaken for all the patients, in a random order, by an independent assessor, Dr. K.V. Krishnaswamy).

Deaths

Of 49 placebo and 54 isoniazid patients who did *not* have a bacteriological relapse, 7

TABLE 3

Changes in radiographic appearances in patients with residual cavitation at one year

		12—24 months				24—60 months				
		Placebo		Isoniazid		Placebo		Isoniazid		
		No.	%	No.	%	No.	%	No.	%	
Improvement	Moderate	0	30	2	29	0	19	3	35	69
	Slight									
No change		19	37	27	45	23	53	14	25	
Deterioration	Slight	0	6	1	3	1	2	0	5	
	Moderate					0				
Total patients		52	101	60	100	43	99	55	99	
Re-treatment started for radiographic deterioration		2		1		2		1		

placebo and 4 isoniazid patients died during the 4-year period of follow-up. Of these, 4 died of respiratory causes—2 in the 14th and 56th month, respectively, in *status asthmaticus*, 1 in the 22nd month from a non-tuberculous broncho-pneumonia, and 1 in the 28th month, 10 days after a spontaneous pneumothorax. Death was due to gastro-intestinal causes in 2 and cardiovascular causes in 3. One patient died of an undiagnosed febrile condition and 1 from complications of advanced leprosy.

Of the 11 patients who died, 10 had been consistently culture-negative for periods ranging from 7 to 53 months (mean 28 months) before death. The remaining patient died of acute dysentery; he had produced one positive culture (1 colony) 5 months before death, but this was followed by 6 negative cultures. It may therefore be concluded that none of the 11 deaths was due to active tuberculosis. No autopsies were performed.

Isoniazid toxicity

None of the patients developed peripheral neuropathy. However, one patient (slow inactivator of isoniazid) became disorientated and violent 6 weeks after the start of the isoniazid regimen (400 mg, plus pyridoxine 6 mg, as a single daily dose). Isoniazid was established to be the cause of the psychosis by means of a therapeutic test and was therefore discontinued. (This patient had had no untoward symptoms in the year of *initial* treatment when he had received isoniazid 150-175 mg daily in two divided doses together with PAS.)

Study of patients with no residual cavitation at one year

Number of patients in the study

A total of 246 patients had bacteriologically quiescent disease with no residual cavitation at one year. Of these, 119 were allocated to the placebo for the whole of the second year and 127 to isoniazid 300 mg for 6 months followed by the placebo for 6 months. One patient was re-treated for what was thought to be a bacteriological relapse at the time; subsequently, however, it was found that he had been excreting only unclassified mycobacteria. Excluding this patient, there remain 118 placebo and 127 isoniazid patients in the analysis.

Pre-study factors

All the patients had positive cultures on

admission to initial treatment: moreover, 89% of the placebo and 84% of the isoniazid patient had a positive smear on the first collection specimen of sputum, including 58% and 50%, respectively, in whom it was moderately or heavily positive. Cavitation was present in 84% of the placebo and 83% of the isoniazid patients, and limited, moderate or extensive disease in 91% and 86%, respectively; no patient had gross disease. Thus, the two series were similar on admission to initial treatment.

In the first year, sputum conversion had commenced by 3 months in 69% of the placebo and 81% of the isoniazid patients ($P=0.04$). At one year, limited or moderate residual radiographic lesions were present in 32% and 21%, respectively ($P=0.07$); no patient had an extensive lesion. (For the implications of these differences on the findings, see foot note on page 54).

Intensity of culture examination

The mean number of cultures per patient was 14.2 in each series in the second year, 8.7 in the placebo and 8.8 in the isoniazid series in the third year, 8.6 in each series in the fourth year, and 10.2 in each series in the fifth year. Thus, the two series were examined with a high and similar intensity during the 4-year period of follow-up.

Bacteriological relapse

A bacteriological relapse occurred during the 4-year period of follow-up in 23 of the 118 patients in the placebo series and in 12 of the 127 patients in the isoniazid series (Table 4). Of these, 9 placebo and 6 isoniazid patients had a sputum conversion subsequently *without* recourse to re-treatment, and all except one remained persistently culture-negative until the end of the study (however, one patient (placebo) died in *status asthmaticus* and another (isoniazid) was discharged, both in the 48th month). The one exception (isoniazid) was persistently culture-negative for 10 months subsequent to the relapse, but produced one positive culture (2 colonies) in the 60th month, together with 2 negative cultures. Thus, a bacteriological relapse requiring treatment occurred in 14 (12%) of the placebo and 6 (5%) of the isoniazid patients (one other patient (isoniazid) developed extra pulmonary tuberculosis).

Re-treatment was started because of clear-cut radiographic deterioration (confirmed by the independent assessor, Dr. K.S. Sanjivi) associated with the bacteriological relapse in a

TABLE 4

Bacteriological relapse during the 4-year period of follow-up in patients with no residual cavitation at one year

Treatment in the second year	Total patients (a)	Patients who had a bacteriological relapse	Of these, patients who required re-treatment					
			No.	% of (a)	Year of relapse			
					Second	Third	Fourth	Fifth
Placebo	118	23	14	12	7	5	1	1
Isoniazid	127*	12	6	5	1	2	2	1

* One patient, whose sputum was culture-negative throughout, developed tuberculosis of the spine in the 48th month and was re-treated. Including this patient, the proportion with a relapse requiring treatment was 6%.

TABLE 5

Change in radiographic appearances in patients with no residual cavitation at one year

		12 — 18 months				18 — 60 months			
		Placebo		Isoniazid		Placebo		Isoniazid	
		No.	%	No.	%	No.	%	No.	%
Improvement	Moderate	137	33	041	33	447	50	348	44
	Slight								
No change		76	66	83	66	50	50	59	51
Deterioration	Slight	1		1		0		1	
	Moderate	1	2	0	1	0	0	2	4
	Considerable	0		0		0		2	
Total patients		116	101	125	100	101	100	115	99
Re-treatment started for radiographic deterioration		2		0		4		2	

Patients (6 placebo, 2 isoniazid), and solely for bacteriological reasons in 12 patients (8 placebo, 4 isoniazid). Of the latter 12 patients, 11 had at least one positive smear and at least 4 positive culture cultures during the 3 months im-

mediately preceding the start of re-treatment. The twelfth (placebo) had produced 8 positive culture during the 3-month period, including 4 with a growth of 20 or more colonies.

Of the 14 placebo patients with needed re-treatment, 7 had the relapse in the second year, 5 in the third year, 1 in the fourth year and 1 in the fifth year (Table 4); eleven patients had cultures sensitive to isoniazid at the time of the relapse. Of the 6 isoniazid patients who had a relapse of their pulmonary disease requiring treatment, 1 had the relapse in the last 6 months of the second year (while receiving placebo), 2 in the third year, 2 in the fourth year and 1 in the fifth year. All 6 patients had isoniazid-sensitive cultures at the time of the relapse.

One other patient (isoniazid) developed tuberculosis of the spine in the 48th month and had to be re-treated (her sputum remained culture-negative throughout). In all, therefore, 14 (12%) of 118 placebo patients and 7 (6%) of 127 isoniazid patients had a relapse requiring treatment ($P=0.06$)*.

Radiographic progress

Between 12 and 18 months, 2 patients died without any evidence of bacteriologically active tuberculosis; two patients (both placebo) had re-treatment started, both because of a clear-cut *radiographic deterioration* associated with a bacteriological relapse. For the remaining 241 patients (116 placebo, 125 isoniazid), the radiographic changes between 12 and 18 months are set out in Table 5. It will be seen that 33% in each series showed improvement, which was slight in all but 1 patient.

Between 18 and 60 months, when *none* of the patients received any routine chemotherapy, 6 patients died without any evidence of bacteriologically active tuberculosis: nineteen patients had a relapse for which re-treatment was started, including 6 (4 placebo, 2 isoniazid) who had an associated clear-cut *radiographic deterioration*. Of the remaining 101 placebo and 115 isoniazid patients (Table 5), 50% and 44%, respectively, showed radiographic improvement, which was slight in all but 7 (4 placebo, 3 isoniazid).

In summary, the radiographic progress of the placebo patients and the isoniazid patients was similar during the 4-year period of follow-up.

* The corresponding percentages after statistical standardisation for the differences between the two series in the speed of sputum conversion in the first year and the total extent of the lesion at one year (page 52) were 11% and 6%, respectively, a suggestive but non-significant difference ($P=0.1$).

Deaths

Of 95 placebo and 114 isoniazid patients who did *not* have a relapse, 2 placebo and 5 isoniazid patients died during the 4-year period of follow-up. Of these, 3 died of gastrointestinal causes, 1 died of malignancy, 1 committed suicide and 2 died of unknown causes. None of the deaths was attributed to active tuberculosis, as all the patients had been consistently culture-negative for periods ranging from 12 to 45 months (mean 29 months) prior to death. An autopsy was not performed on any of the patients.

Isoniazid toxicity

None of the patients had mental disturbance. However, one patient (slow inactivator of isoniazid) developed peripheral neuropathy in the 5th month after the start of the isoniazid regimen (300 mg as a single daily dose). Pyridoxine was prescribed and the isoniazid continued until the end of the 6th month, as scheduled. (One patient in the placebo series had symptoms suggestive of peripheral neuropathy, which were relieved by oral administration of vitamin B-complex).

Bacterial population at the time of Relapse

In the two controlled studies reported above, 20 patients had a bacteriological relapse followed by a sputum conversion (to culture negativity) *without* recourse to re-treatment, and 32 patients had a bacteriological relapse for which re-treatment was started. It is of interest to compare the bacterial populations at the time of relapse in these two groups of patients. Of the 20 patients who were not re-treated, 80% produced only negative smears at the month of relapse and in the following 3-month period as compared with 25% of 32 patients who were re-treated, a highly significant difference ($P<0.001$). Considering next the findings of culture examination during this period, the highest growth observed was 100 colonies or less for 70% of the former and 34% of the latter ($P=0.03$). Finally, the proportions of patients who produced at least 3 positive smears during this period were 0% and 47%, respectively ($P<0.001$), and those who produced at least 3 positive cultures, 10% and 75%, respectively ($P<0.001$). Thus, the patients who had a sputum conversion without recourse to re-treatment had considerably smaller bacterial populations at the time of the relapse than those who were re-treated.

Regularity of self-administration of Isoniazid

As stated earlier, a clinic urine

TABLE 6

Findings of clinic urine tests in patients while they were receiving isoniazid in the second year

Percentage of urine test results which were negative	Patients with residual cavitation at one year		Patients with no residual cavitation at one year		All patients	
	Total	Re-treated	Total	Re-treated	Total	Re-treated
		No.		%		No.
Less than 20	23	1 (4)	39	1 3	62	2 3
20—49 50 or	18	0 (0)	45	2 4	63	2 3
more	22	3 (14)	43	4 9	65	1 11
Total	63	4 6	127	7 6	190	11 6
Means percentage of test results which were negative	36		38		37	

*Parentheses indicate that the percentage is based on fewer than 25 observations.

specimen was examined once a fortnight for patients receiving isoniazid in the second year. Table 6 sets out the distributions of patients according to the percentage of negative test results, together with the mean values. It will be seen that approximately one-third of the patients had negative results on at least half the occasions, and that the mean proportion was of the order of 40%. Table 6 also examines the influence of irregularity in drug-intake on the incidence of relapse requiring treatment. Although the numbers are small, there is suggestive evidence of an association, both in patients with residual cavitation at one year and in those with no residual cavitation. Considering both groups together (it will be noted that the proportions re-treated and the proportions with negative urine test results are very similar in the two groups), the proportions re-treated were 3%, 3% and 11%, respectively, in patients with less than 20%, 20-49%, and 50% or more negative urine test results, a significant trend ($P=0.03$); these three categories of patients had similar pre-study condition (data not tabulated here). It may therefore be concluded that irregularity in drug-intake influenced the incidence of relapse requiring treatment.

Prognostic significance of various pre-study factors

The influence of various pre-study factors on the occurrence of relapse requiring treat-

ment was studied, separately for the placebo and the isoniazid series.* Within each series, however, patients with residual cavitation at one year and those with no residual cavitation have been considered together, as the incidence of relapse requiring treatment was practically the same in the two groups. Thus, in the placebo series, it was 14% of 58 in the cavitated group and 12% of 118 in the non-cavitated group; in the isoniazid series, the corresponding proportions were 6% of 63 and 6% of 127, respectively.

Placebo series

Considering factors on admission to initial treatment among patients in the placebo series (that is, those who, by random allocation, received no chemotherapy after the first year), there was clear-cut evidence that the total extent of the radiographic disease influenced the likelihood of relapse requiring treatment (Table 7); thus, re-treatment became necessary for 6% of 47 patients with limited or less disease, 11% of 84 patients with moderate disease and 22% of 45 patients with extensive or gross disease, a significant trend ($P=0.01$). The extent of cavitation, however, was of no prognostic importance. Next, there was a suggestion that the smear result of the first

* As only positive associations were expected, P-values corresponding to l-tail tests of significance have been employed.

TABLE 7

Relapse requiring treatment related to pre-study factors

			Placebo series		Isoniazid series			
			Total patients	Re-treated		Total patients	Re-treated	
				No.	%		No.	%
On admission to initial treatment	Total extent of the radiographic disease	Limited or less	47	3	6	68	4	6
		Moderate Extensive	84	9	11	79	5	6
		or gross	45	10	22	43	2	5
	Extent of cavitation	Nil or slight	86	10	12	103	6	6
		Moderate or extensive	90	12	13	87	5	6
	Direct smear result of first collection specimen	Negative or 1-plus	72	6	8	89	9	10
2-plus or 3-plus		105	16	15	101	2	2	
In the first year	Month of sputum conversion	1 or 2 *	59	3	5.3	80	5	6.4
		4 or more	57	5.16	27	65	6.2	4
			60			45		
At one year	Total extent of the residual radiographic lesion	Nil or trivial	48	4	8	58	3	5
		Slight Limited or more	50	4	8	62	2	3
			78	14	18	70	6	9
All patients			176	22	12	190	11	6

collection specimen was of some importance (P=0.1).

Considering the speed of sputum conversion in the first year, 5% of 116 patients with an early sputum conversion (that is, by 3 months) were re-treated as compared with 27% of 60 patients who had a later sputum conversion (that is, at 4 months or later), a highly significant difference (P<0.0001).

Finally, the total extent of the residual radiographic lesion at one year was also of prognostic importance, the proportions requiring re-treatment being 8% of 98 in patients with slight or less disease as compared with 18% of 78 in patients with limited or more disease (P=0.04).

Ind. J. Tub., Vol. XIX, No. 2

Isoniazid series

In the two isoniazid series combined (that is, among patients who received 6 or 12 months of isoniazid in the second year), none of the pre-study factors appeared to influence the likelihood of relapse requiring treatment (Table 7).

Efficacy of isoniazid in patients having an unfavourable pre-study condition

A further point of interest that emerges from Table 7 is the clear-cut evidence of the value of isoniazid in patients who had an unfavourable pre-study condition. For instance, in patients with extensive or gross disease on admission to initial treatment, the proportion

TABLE 8

Relapse requiring re-treatment related to chemotherapeutic regimen in the first year

Regimen in the first year	Efficacy in the first year*	No. of patients in the present study	Patients requiring re-treatment during the 4-year period	
			No.	%
isoniazid 14 mg/kg body-weight, given alone in one dose daily	66%	56	3	
streptomycin 1 or 0.75 g plus isoniazid 15 mg/kg body-weight, given together once weekly	71%	25	2	7
isoniazid 200 mg plus PAS 6 g, given together in one dose daily for the first 6 months, followed by isoniazid 7 mg/kg body-weight, given alone in one dose daily for the next six months	67%	40	3	
isoniazid 4 mg/kg body-weight plus PAS 0.2 g/kg body-weight, given together in two divided doses daily	83%	98	10	
isoniazid 7 mg/kg body-weight plus thioacetazone 3 mg/kg body-weight, given together in one dose daily	82%	44	7	12
streptomycin 1 or 0.75 g plus isoniazid 14 or 15 mg/kg body-weight, given together twice weekly	93%	103	8	8

*Assessed as the percentage of patients with bacteriologically quiescent disease at one year.

requiring re-treatment was 22% of 45 in the placebo series and 3 % of 43 in the isoniazid series ($P=0.02$). The corresponding proportions were 15% of 104 and 2% of 101, respectively, in patients with a 2-plus or 3-plus smear result initially ($P<0.001$), and 27% of 60 and 4% of 45, respectively, in patients who had a sputum conversion at 4 months or later ($P<0.01$).

Influence of chemotherapeutic regimen in the first year on the occurrence of relapse requiring treatment

The patients reported in this paper had received 1 of 6 chemotherapeutic regimens in the first year. The details of these regimens and their efficacies in the first year are set out in Table 8, which also presents, for each regimen, the proportion of patients who had a relapse requiring treatment during the 4-year period of follow-up.

The 6 regimens can be clearly divided into 3 categories, namely those of low-efficacy (the first 3) of moderate-efficacy (the fourth and the fifth) and of high-efficacy (the sixth). Analyses, not tabulated here, showed that the pre-study condition of the patients was similar for the 3

categories of regimens; further, the proportions of patients who received maintenance chemotherapy with isoniazid for (a) 6 months or (b) 12 months in the second year were also similar for the 3 categories.

Of 121 patients who had received a low-efficacy regimen in the first year, 7% had a relapse requiring treatment in the 4-year period of follow-up; the corresponding proportions were 12% of 142 for patients who had received a moderate-efficacy regimen and 8% of 103 for those who had received a high-efficacy regimen. Thus, there was no evidence that the efficacy of the regimen, assessed as the percentage of patients with bacteriologically quiescent disease at 1 year, influenced the likelihood of relapse requiring treatment in the subsequent 4 years.

Discussion

In the two controlled studies reported in this paper, a total of 53 patients had a bacteriological relapse, that is, 2 or more positive cultures amongst 6 or more examined in a 6-month period. However, 20 (38%) of these patients had a sputum conversion subsequently *without* recourse to re-treatment,

and remained persistently culture-negative thereafter. Thus, a bacteriological relapse, as defined above, did not always have an unfavourable prognosis. Consequently, the value of maintenance chemotherapy with isoniazid has been assessed mainly by the reduction in the incidence of relapse *requiring treatment*. (It must be emphasized that the patients in these studies were under intensive bacteriological surveillance, approximately 43 cultures per patient being examined during the 4-year period of follow-up. In situations where the intensity of bacteriological examination is less, a finding of 2 positive cultures in a 6-month period could be of greater prognostic significance).

Considering patients with bacteriologically quiescent disease and residual cavitation at 1 year, a relapse requiring treatment occurred in 14% of 58 patients who received a placebo in the second year and in 6% of 63 patients who received isoniazid in a single daily dose of 400 mg throughout the second year; the reduction of 8% is suggestive but not significant ($P=0.1$). In an earlier study at this Centre (Evans et al., 1969), the corresponding proportions were 10% of 41 for patients who received a placebo and 7% of 55 for patients who received isoniazid in a single daily dose of 150-200 mg throughout the second year, the reduction due to isoniazid being 3%. These findings indicate that 400 mg of isoniazid in a single daily dose is not sufficiently satisfactory as maintenance chemotherapy in the second year, although it may be slightly better than 150-200 mg in a single daily dose. It may therefore be concluded that a double-drug regimen is indicated for the prevention of relapse in patients with residual cavitation at one year (it must be noted that none of the patients had received intensive chemotherapy with three or more drugs in the early stages of treatment in the first year). In this context, it is of interest that in a group of British patients with bacteriologically quiescent disease and residual cavitation at one year, 28% of 50 who were allocated to no chemotherapy in the second year had to be re-treated on account of a bacteriological relapse during a 3-year period of follow-up, as compared with 6% of 34 who were allocated to isoniazid plus PAS for the second year (Great Britain, Medical Research Council, 1962), a significant difference ($P=0.01$).

Considering next the patients with bacteriologically quiescent disease and *no* residual cavitation at one year, a relapse requiring treatment occurred in 12% of 118 patients who received a placebo in the second year and in 6% of 127 who received isoniazid in a single

daily dose of 300 mg for the first 6 months in the second year*. Thus, 6 months of maintenance chemotherapy with isoniazid 300 mg appears to have had some effect. However, it was not as effective as 12 months of isoniazid in a single daily dose of 150-200 mg; none of 103 patients who received the latter regimen in an earlier controlled study (Evans et al., 1969) had to be re-treated as compared with 12% of 107 who received a placebo in the same study ($P<0.0001$).

Considering patients who did not receive any maintenance chemotherapy in the second year, the cavitation status at one year was of little prognostic importance—a finding similar to that in an earlier study (Evans et al., 1969). However, there was clear-cut evidence that the total extent of the lesion on admission to initial treatment and at one year, and the speed of sputum conversion in the first year, influenced significantly the likelihood of relapse requiring treatment. Finally, in patients with a relatively high risk of relapse (for instance, those who had a late sputum conversion in the first year), there was convincing evidence that maintenance chemotherapy with isoniazid alone was valuable.

Considering patients who received maintenance chemotherapy with isoniazid in the second year (for 6 or 12 months), none of the pre-study factors appeared to be prognostically important. However, there was some evidence that irregularity in drug-intake, as assessed by the proportion of urine test results that were negative, influenced the likelihood of relapse requiring treatment. In the present study, the mean proportion of negative urine test results was of the order of 40%, a finding which suggests that the isoniazid regimens reported in this paper would have been more efficacious if the patients had been more regular in their drug-intake. It will be appreciated, however, that in *symptom-free* patients with bacteriologically quiescent disease at the end of one year of chemotherapy, it is extremely difficult to ensure high degrees of regularity in the long-term self administration of medicaments.

An earlier study from this Centre (Evans et al., 1969) demonstrated that the occurrence of a relapse in the second to fifth years was not related to the efficacy of the regimen in the first year, even when the latter varied con-

* The corresponding percentages after statistical standardisation for the differences between the two series in the speed of sputum conversion in the first year and the total extent of the lesion at one year (page 52) were 11% and 6%, respectively, a suggestive but non-significant difference ($P=0.1$).

siderably (Tuberculosis Chemotherapy Centre, Madras, 1960). The findings in the present investigation confirm this observation, the proportions of patients who had a relapse requiring treatment being 7% of 121, 12% of 142 and 8% of 103, respectively, for regimens with low, moderate and high efficacies in the first year. It must be noted that the above conclusion is based on regimens, none of which contained an initial intensive phase with three or more drugs.

In the first study reported in this paper, 64 patients were prescribed isoniazid 400 mg plus pyridoxine 6 mg as a single daily dose for the second year. None of the patients developed peripheral neuropathy. However, 1 patient developed a toxic psychosis due to isoniazid after 6 weeks. In an earlier study (Tuberculosis Chemotherapy Centre, Madras, 1960), mental disturbance attributed to isoniazid occurred in 1 of 70 patients who were prescribed to 400 mg of isoniazid, without pyridoxine, in a single daily dose for one year. Finally, in a study in East Africa (East African/British Medical Research Council, Fourth Thiactazone Investigation, 1966), none of 181 patients who received isoniazid 450 mg plus pyridoxine 6 mg (plus thiactazone 150 mg) in one dose daily showed any sign of mental disturbance. It may therefore be concluded that mental disturbance is a relatively rare occurrence in patients receiving a moderately high dosage of isoniazid.

In the second study reported in this paper, 127 patients were prescribed isoniazid 300 mg as a single dose daily for 6 months in the second year. None of the patients had a mental disturbance. However, 1 developed peripheral neuropathy in the 5th month. When the same dosage of isoniazid was given, together with thiactazone 150 mg, as a single daily dose for 12 months (Tuberculosis Chemotherapy Centre, Madras, 1966) or for 18 months (East African/British Medical Research Council Fourth Thiactazone Investigation, 1966), the incidence of peripheral neuropathy was of 1 of 80 and none of 179, respectively. No pyridoxine supplement was given to the patients in any of the above three studies. It may therefore be concluded that the incidence of peripheral neuropathy with 300 mg of isoniazid is low. Furthermore, even the two cases of peripheral neuropathy observed at this Centre could have been due to or precipitated by nutritional deficiency, since 1 of 176 patients who received a placebo developed symptoms suggestive of peripheral neuropathy (page 49), and tuberculous patients attending this Centre are known to have a vitamin-

deficiency (Ramakrishnan et al., 1961, 1966; Krishnamurthy et al., 1967).

In conclusion, in patients with bacteriologically quiescent disease and residual cavitation at one year, isoniazid alone in a single daily dose of 400 mg throughout the second year was not highly satisfactory, although it was of some value. In patients with bacteriologically quiescent disease and no residual cavitation at one year, isoniazid alone in a single daily dose of 300 mg for 6 months in the second year was of some value, but was considerably less satisfactory than 150-200 mg given as a single daily dose throughout the second year.

ACKNOWLEDGEMENTS

We wish to acknowledge the devoted work of the entire staff of the Centre, particularly the public health nurses, social workers and health visitors whose efforts have largely been responsible for the completeness of the data.

Summary

Two controlled studies were undertaken to determine the efficacy of isoniazid alone in preventing relapse among patients with bacteriologically quiescent pulmonary tuberculosis at the end of one year of chemotherapy.

In the first study, patients with bacteriologically quiescent disease and residual cavitation at one year were allocated, at random, to (1) isoniazid 400 mg (incorporating 6 mg pyridoxine) in a single daily dose throughout the second year (63 patients), or (2) a placebo (calcium gluconate 500 mg or lactose 500 mg) throughout the second year (58 patients). During a 4-year period of follow-up, (a) a bacteriological relapse requiring treatment occurred in 8(14%) of the placebo and 4 (6%) of the isoniazid patients, the relapse commencing in the second year in 5 and 2, respectively; and (b) of 2 patients who were receiving isoniazid at the time of the relapse, 1 had isoniazid-resistant organisms; of the remaining 10, 9 had the relapse with isoniazid-sensitive organisms.

In the second study, patients with bacteriologically quiescent disease and no residual cavitation at one year were allocated, at random, to (1) isoniazid 300 mg (without any pyridoxine supplement) in a single daily dose for the first 6 months in the second year, followed by the placebo for the next 6 months (127 patients), or (2) the placebo throughout the second year (118 patients). During a 4-year period of follow-up, (a) a bacteriological

relapse requiring treatment occurred in 14 (12%) of the placebo and 6 (5%) of the isoniazid patients, the relapse commencing in the second year in 7 and 1, respectively; one other patient (isoniazid) developed tuberculosis of the spine in the 48th month and had to be retreated; and (b) of the 20 patients who had a bacteriological relapse, none was receiving isoniazid at the time of the relapse, and all but three had isoniazid-sensitive organisms.

In patients with bacteriologically quiescent disease at one year who received no maintenance chemotherapy subsequently, there was clear-cut evidence that the total extent of the radiographic lesion on admission to initial treatment and at one year, and the speed of sputum conversion in the first year, influenced the likelihood of relapse requiring treatment. In patients who received maintenance chemotherapy with isoniazid alone in the second year (for 6 or 12 months), none of the above factors appeared to be prognostically important; however, there was some evidence that irregularity in drug-intake influenced the incidence of relapse requiring treatment.

The findings in the above 2 studies, when considered together with those in earlier studies, indicate that (a) in patients with bacteriologically quiescent disease and residual cavitation at one year, isoniazid alone in a single daily dose of 400 mg throughout the second year is not highly satisfactory in preventing relapse, although it is of some value, and (b) in patients with bacteriologically quiescent disease and no residual cavitation at one year, isoniazid alone in a single daily dose of 300 mg for 6 months in the second year is of some value but is not as highly satisfactory as 150-200 mg for the whole of the second year.

REFERENCES

- East African/British Medical Research Council Fourth Thiacetazone Investigation (1966) *Tubercle (Edinb.)*, 47, 315.
- Evans, C., Devadatta, S., Fox, W., Gangadharam, P.R.J., Menon, N.K., Ramakrishnan, C.V., Sivasubramaniam, S., Somasundaram, P.R., Stott, H. and Velu, S. (1969), *Bull. Wld. Hlth. Org.*, 41, 1.
- Gangadharam, P.R.J., Mitchison, D.A., Subbaiah, T.V. and Short, E.I. (1958), *Tubercle (Edinb.)*, 39, 191.
- Great Britain Medical Research Council (1962), *Tubercle (Edinb.)*, 43, 201.
- Krishnamurthy, D.V., Selkon, J.B., Ramachandran, K., Devadatta, S., Mitchison, D.A., Radhakrishna, S. and Stott, H. (1967), *Bull. Wld. Hlth. Org.*, 36, 953.
- Ramakrishnan, C.V., Rajendran, K., Jacob, P.O., Fox, W. and Radhakrishna, S. (1961) *Bull. Wld. Hlth. Org.*, 25, 339.
- Ramakrishnan, C.V., Rajendran, K., Mohan, K., Fox, W. and Radhakrishna, S. (1966), *Bull. Wld. Hlth. Org.*, 34, 553.
- Thomas, K.L., Joseph, S., Subbaiah, T.V. and Selkon, J.B. (1961), *Bull. Wld. Hlth. Org.*, 25, 747.
- Tuberculosis Chemotherapy Centre, Madras (1960), *Bull. Wld. Hlth. Org.*, 23, 535.
- Tuberculosis Chemotherapy Centre, Madras (1963), *Bull. Wld. Hlth. Org.*, 29, 457.
- Tuberculosis Chemotherapy Centre, Madras (1964), *Bull. Wld. Hlth. Org.*, 31, 247.
- Tuberculosis Chemotherapy Centre, Madras (1966), *Bull. Wld. Hlth. Org.*, 34, 483.

ALLERGIC BRONCHO-PULMONARY ASPERGILLOSIS

S.P. PARMA¹, Z.U. KHAN², R.S. SANDHU³ AND M. ILYAS⁴

Every chest clinic has on its rolls some patients who radiologically and clinically appear to be tuberculous but tubercle bacilli are not demonstrable in their sputum, even on repeated examinations including culture. Though many of these may eventually turn out to be tuberculous, some are undoubtedly non-tuberculous. Since tuberculosis is a great clinical and radiological mimic, diagnosis, unless confirmed bacteriologically, remains equivocal. It is imperative to rule out non-tuberculous aetiology before such sputum negative cases are treated as tuberculous. Diseases caused by pathogenic fungi could be one such possibility. Although a few cases of disease caused by *Nocardia*, *Candida*, *Cryptococcus* etc. are reported in literature, fungus is not usually looked for by most chest physicians as one of the aetiological possibilities in obscure respiratory disorders, partly because facilities for special mycological investigations are lacking.

Diseases caused by another ubiquitous fungus—*Aspergillus*—have frequently been reported. Though aspergilloma is the better known manifestation, allergic broncho-pulmonary aspergillosis is being increasingly recognised. To Hinson and associates (1952) goes the credit for recognising and describing this latter entity for the first time. Since then Pepys et al (1959), Campbell and Clayton (1964) and Henderson (1968), among others, have reported over 200 cases from U.K. Some reports have also appeared from North America and Europe (Agbay et al 1967, Charpin et al 1967, Spotnitz & Overholt 1967, Warren & Rose 1969, Slavin et al 1969, Golbert & Petterson 1970, Zimmerman & Miller 1970 and Chan-Yeung et al 1971). In India, Gupta and Viswanathan (1963) and Sandhu et al (1966) have reported a few cases of aspergilloma and the two cases of so called "Aspergillosis" reported by Reddy et al (1965) and Chitnis & Deshpande (1967) appear to be of the invasive type. Although from India no report on allergic aspergillosis has so far been published, extensive investigations done in the Medical Mycology Laboratory of the V.P. Chest Institute reveal that the disease may not be uncommon in this country (Mishra, 1971; R.S. Sandhu, unpublished data). Thirty-two sputum negative patients attending the New Delhi Tuberculosis Centre from April to November,

1971 were subjected to thorough mycological investigations for possible fungal infections. Of these, six patients yielded *A. Fumigatus* in their sputum cultures. Skin and serological testing were further carried out in these 6 patients with a view to establish the diagnosis. The results of these laboratory investigations along with clinical and radiological features of four* of the six cases proved to be cases of 'Allergic broncho-pulmonary aspergillosis', are summarised below.

Clinical and Radiological Features

Case 1

K.S., married female, aged 33 years attended the New Delhi Tuberculosis Centre on 29.6.1971 with complaints of cough, sputum, low grade pyrexia and haemoptysis. She gave a history of repeated asthmatic episodes during the previous two years, for which she was investigated in the Allergy Clinic of the V.P. Chest Institute and gave positive reaction to skin test with house dust antigen. Desensitization was attempted but asthmatic episodes continued. She developed severe pain in the chest with increased cough, expectoration and high grade pyrexia on 19.6.1971. Skiagram of the chest taken that day (figure 1) showed conso-

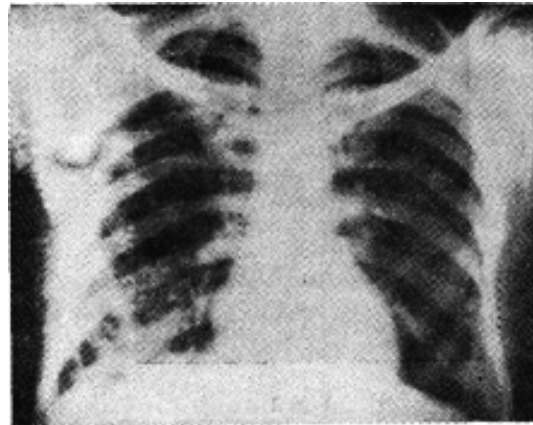


Fig. 1

Case 1. P.A. view of the chest on 19-6-1971 shows collapse of the right middle lobe and infiltration in the left mid-zone. Round hilar shadows are not well seen.

* In the other two cases, *Aspergillus* was isolated from one of the three sputum specimens each and skin testing and serology were negative though clinical and radiological features were consistent with allergic broncho-pulmonary aspergillosis.

1, Director, New Delhi TB Centre, New Delhi.
2, 3, 4 Department of Medical Mycology, V.P. Chest Institute, Delhi.

lidation/collapse of the right middle lobe with two round shadows, one in each hilar region, and some infiltration in the left mid zone. She was bringing out nearly an ounce of mucopurulent sputum in 24 hours, occasionally containing dirty looking brownish plugs, which she had been expectorating off and on for two years. Sputum was repeatedly negative for AFB. Total WBC count was 7800 per cmm with 17% eosinophils. Tuberculin reaction to 1 TU PPD was 15 mm. Examination of urine and stool and serum for calcium, A/G ratio and L.E. cells did not reveal any abnormality. On 9.7.1971, a fresh patch of pneumonitis appeared in the right upper zone and the infiltration in the left mid zone also increased. Bronchoscopy did not reveal any abnormality and the bronchial aspirate was negative for AFB. Bronchography showed a round mass impacted in the middle lobe bronchus about 3 cms distal to its origin with absence of dye beyond the mass (figure 2). Treatment with broad spectrum antibiotics and corticosteroids resulted in some initial clinical and radiological improvement but deterioration soon set in.



Fig. 2

Case 1. Right lateral view of the bronchogram shows collapse of the middle lobe and the round impacted mass in the middle lobe bronchus

Case 2

T.J., male, 26 years old, attended the New Delhi Tuberculosis Centre for the first time on 30.6.1962 with cough, sputum, low grade pyrexia and bilateral infiltration in the upper

zones of both lungs and in the right cardio-phrenic angle (figure 3). He gave a history of repeated asthmatic attacks during the previous

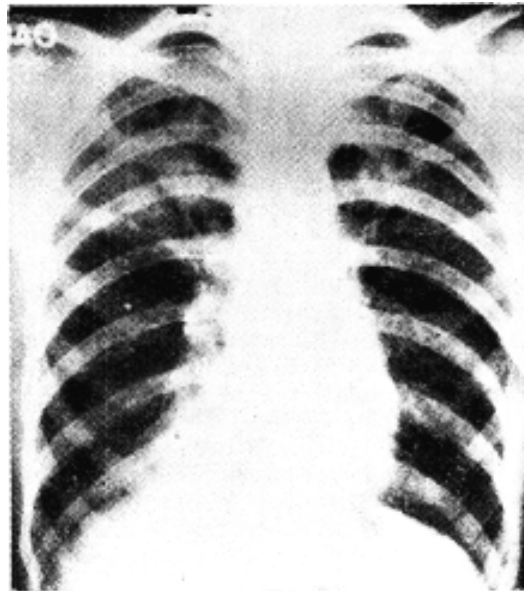


Fig. 3

Case 2. P. A. view of the chest on 30-6-1962 shows infiltration in the upper zone of both lungs and right cardio-phrenic angle

2/3 years. There was a family history of asthma also. Sputum was negative for AFB and total WBC count was 12,700 per cmm with 16% eosinophils. With Hetrazan, the symptoms were relieved quickly and the lung lesion cleared in a few days time. From 1962 to 1966 he had three further episodes with infiltration in upper portions of both lungs, each of which cleared with Hetrazan. In 1966 he went to USA for studies and remained free from all symptoms till August 1971 when he returned to India. Soon after his return, he had another attack of cough, sputum, breathlessness and high fever. The skiagram showed pneumonitis in the left mid zone which cleared partially with broad-spectrum antibiotics and corticosteroids. He gave up treatment prematurely and within a few days there was a recurrence of symptoms and the pneumonitis. Total WBC count at this stage was 13 000 per cmm with 24% eosinophils. There was no history of haemoptysis and the urine and stool examinations did not show any abnormality at any time.

Case 3

R.J.D., male, 49 years old, attended the New Delhi Tuberculosis Centre for the first time on

5.10.1966 with complaints of low grade pyrexia, cough, profuse expectoration and breathlessness. Skiagram of the chest (figure 4) showed



Fig. 4

Case 3. P.A. view of the chest on 3-10-1966 shows pneumonitis in the left hilar region with diffuse infiltration in the mid and lower zones of the right lung.

pneumonitis in the left hilar region with diffuse infiltration in the mid and lower zones of the right lung. He gave a history of repeated asthmatic episodes during the past several years. Sputum was negative for AFB. Total WBC count was 10,300 with 3% eosinophils. Urine and stool did not show any abnormality. Lesions cleared with broad-spectrum antibiotics. He kept on having repeated attacks with patches of pneumonitis, mostly in the left hilar region. When he attended with another such episode on 20.8.1971, total WBC count was 12,200 per cmm with 11% eosinophils. This was the only occasion during the last 5 years when he had moderate increase in eosinophils in peripheral blood, though the WBC count had been carried out several times. The last episode also cleared with broad-spectrum antibiotics and corticosteroids. There was no history of haemoptysis at any time.

Case 4

K.T., married female, aged 37 years attended the New Delhi Tuberculosis Centre for the first time on 10.10.1964 with complaints of cough, sputum, breathlessness and fever. Skia-

gram of the chest showed pneumonitis in the lower zone of the right lung and the mid and lower zones of the left lung. Sputum was negative for AFB and total WBC count was 10,000 per cmm with eosinophils 2%. The lesions completely cleared in a few days with broad-spectrum antibiotics. She attended again in December, 1966 with a cavitory lesion in the left upper zone and infiltration in the upper and lower zones of the right lung (figure 5) which

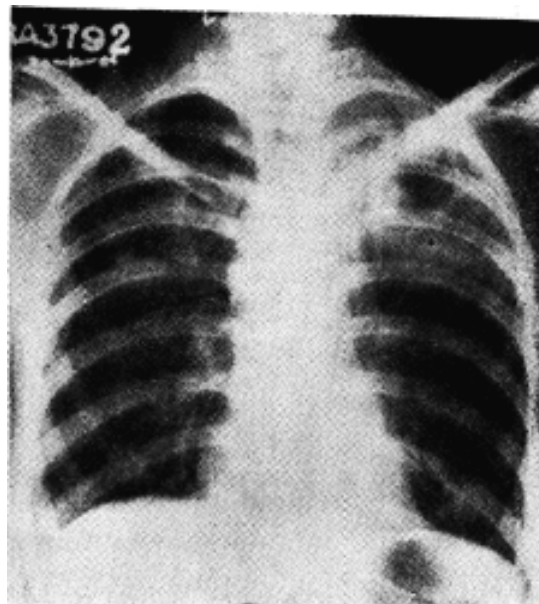


Fig. 5

Case 4. P.A. view of the chest on 24-12-1964 shows pneumonitis in the upper zone of the left lung with an area of breakdown and infiltration in the upper and lower zones of the right lung

again cleared with broad-spectrum antibiotics. She continued to have episodes of cough and breathlessness which were treated as asthma. When the symptoms persisted for a long time in September 1966, she was referred again to this Centre as possibly a case of pulmonary tuberculosis. Skiagram of the chest at that stage did not show any evidence of pneumonitis. Instead, coarse nodular and linear opacities suggestive of alveolitis were seen in both lungs. The sputum was again negative for AFB and the total and differential WBC count was within normal limits. She was partially relieved clinically by broad spectrum antibiotics and corticosteroids without any change in the radiological picture. She continued to attend the Centre periodically from 1968 to 1971. Sputum was always negative. Total WBC count was 14,200 per cmm with 20% eosinophils in September 1971. Biopsy of the

cervical lymph node did not show any granulomatous changes and bronchography showed crowding and slight distortion of bronchi but no bronchiectasis. Radiological picture continued to worsen gradually (figure 6). Breathlessness which was periodic previously had become constant by September, 1971 when she was investigated for fungus disease.

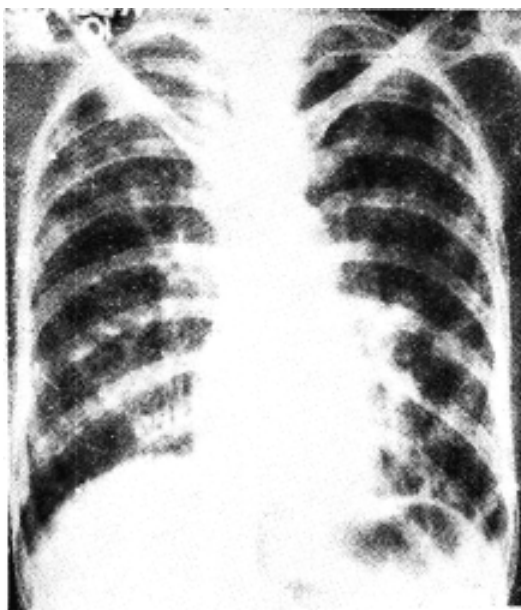


Fig. 6

Case 4. P.A. view of the chest on 10-9-1971 shows diffuse nodular and linear opacities in both lungs

Of the four cases, one (case 1) was investigated for fungus disease soon after registration. Of the other three, under observation for some years before this study, the previous diagnosis of case 2 was 'pulmonary eosinophilic infiltration' (P.E I.); of case 3 asthma with occasional superadded pneumomtis and of case 4 pulmonary fibrosis of undetermined aetiology.

Laboratory investigations

For mycological investigations, repeated specimens of fresh morning sputum were examined from each patient. The sputum was first liquefied by incubation with equal volume of 1% pancreatin at 37°C for one hour and centrifuged. A loopful of the deposit was mounted in a drop of 20% KOH and examined under the microscope for fungal hyphae and it was also streaked liberally on slants of modified Sabouraud's agar containing 0.05 mg/ml chloramphenicol (Emmons et al, 1970).

Ind. J. Tub., Vol. XIX, No. 2

Fungal hyphae compatible with *Aspergillus* were seen in direct mounts and *A. Fumigatus* was isolated in culture from each patient on repeated occasions.

Intracutaneous skin tests were performed by injecting about 0.02 ml of dialyzed culture filtrate of *A. fumigatus* grown in synthetic medium, and using normal saline as the control. Readings for induration (with or without pseudopodia formation) and erythema were recorded after 20 minutes indicating the immediate wheal reaction, i.e. Type I hypersensitivity. The late Arthus reaction (Type III hypersensitivity) was recorded as a large oedematous swelling at 6-8 hours after the immediate type of reaction had subsided. The immediate type of reaction was classified from 1+ to 4+ according to Shivpuri and Aggarwal (1969) and Arthus type was expressed as average diameter in mms of the swelling. This dual reaction was observed in all the 4 patients although Arthus reaction in case 1 was weak.

Serological tests were performed according to the standard agar gel double diffusion technique in 50 mm Petri plates each containing 3.5 ml of 1% Difco noble agar in McIlvain buffer of 7.3 pH. Six peripheral wells and one central well of 6 mm each were cut with template. Into the peripheral wells were added concentrated (10%) culture filtrates of *A. fumigatus* and some other fungal species while the test serum was added into the central well (Longbottom & Pepys, 1964). The plates were incubated at 28°C for about a week and observations were made for precipitin bands which were later stained with amido black. If no bands were appearing, the serum was concentrated about three times and the double diffusion test was repeated with it. One to two distinct bands were observed in all the four cases of allergic aspergillosis.

The laboratory examinations are summarized in the accompanying table.

Discussion

Aspergillus fumigatus besides being a common saprophyte, is a known opportunistic invader and a potent offending allergen. When it becomes pathogenic, the clinical manifestations are protean and are governed by the immunological reactivity of the host and the nature and circumstances of exposure to the pathogen.

Originally all types of disease caused by this fungus were grouped under one heading

Laboratory findings in the four cases of allergic broncho-pulmonary aspergillosis

Case No.	Eosinophils in		Intracutaneous test with Aspergillin		Serology Agar gel double diffusion test	Aspergillus fumigatus in sputum No. of positive specimens/ Total examined	
	Peripheral blood	Sputum per cmm	20 minutes immediate type I	6-8 hours late Arthus type	No. of precipitin bands	Direct microscopic Culture examination	
1. K.S.	1326	+	3 H-	20 mm weak	2 (concentrated serum)	2/3	4/5
2. T.J.	3120	+	4+	56 mm	2	3/7	4/7
3. R.D.	1342	+	4+	53 mm	1	2/3	3/5
4. K.T.	2840		3+	62mm	1 (concentrated serum)	2/3	3/6

Of 'Aspergillosis'. In fact, aspergillosis comprises a group of which diseases which need to be considered as separate clinical and pathological entities. Out of the various systems of classification, the one proposed by Pepys (1969) seems to be the most satisfying. According to him, if the subject is atopic the fungus gives rise to the following two manifestations :—

1. Asthma mediated through non-precipitating reaginic antibodies i.e. Type I allergy (as defined by Gell and Coombs, 1968).

2. Allergic broncho-pulmonary aspergillosis in asthmatic subjects manifesting both type I and type III (mediated through precipitating antibodies) hypersensitivity.

In non-atopic subjects, there are 3 important manifestations :—

(a) Aspergilloma where the fungus grows as a saprophyte in pre-existing dilated bronchi, or pulmonary cavities without invading the tissues (Buechner, 1971). Strong precipitins are invariably present.

(b) Extrinsic allergic alveolitis resulting from massive inhalation of fungal spores and antigen antibody reaction taking place in the alveoli.

(c) Invasive aspergillosis in patients with reticulo-endothelial disturbances e.g. Leukaemia, Hodgkins' disease, Reticulosis etc., massive x-ray radiation, or where cytotoxic or immunosuppressive drugs are being administered. This type is rapidly fatal and may involve haemato-

genous dissemination to other organs in the body, though lungs are the most common site.

The diagnostic criteria of 'Allergic broncho-pulmonary aspergillosis' are now fairly well established and according to Henderson, (1968) these are isolation of *Aspergillus* repeatedly and in large numbers from sputum, transient pulmonary patches radiologically, asthmatic episodes with air-way obstruction and F.E.V. less than 70% of V.C. in 1 second, presence of type I and III hypersensitivity (dual skin reaction) and precipitins in the serum; increased eosinophils in the peripheral blood and their presence in sputum.

Species of *Aspergillus* are notorious laboratory contaminants, although the prevalence of different species like *A. fumigatus* can vary from one locality to another and also seasonally. The spores of *Aspergillus* are inhaled and expectorated by the population at large and hence mere isolation of *A. fumigatus* from sputum cannot be regarded as diagnostic. However, its repeated isolation from the same patient should not be disregarded particularly if other evidence is also in favour of aspergillosis (Mishra 1971). *A. fumigatus* has been found to be the commonest species in air-borne fungal flora in London and has significantly higher incidence in the sputum cultures of asthmatic patients than in other chest diseases (Pepys et al, 1959). But no such correlation has been observed in Delhi (Sandhu, 1965).

It has also been shown that absence of fungus in the sputum does not rule out the diagnosis altogether because it can be absent

even during acute episodes. Campbell and Clayton (1964) advocate 6 repeat examinations of sputum specimens of suspected subjects before labelling it negative for fungus. In the present series all the four cases of allergic aspergillosis yielded *A. fumigatus* in their sputum cultures on more than one occasion.

Increase of eosinophils in peripheral blood is also both inconsistent and variable. Hinson et al (1952) reported eosinophils upto 4,000 per cmm. Subsequent workers, however, report only moderate eosinophilia. Out of 87 cases studied by Campbell and Clayton (1964), 78 had eosinophils more than 500 per cmm and 46 more than 1,00 per cmm. Warren and Rose (1969) also did not find peripheral eosinophilia in all their cases. All our cases showed increase of eosinophils in the peripheral blood, the range being 1,300 to 3,000 per cmm.

Presence of eosinophils in sputum is also not consistent. In Campbell and Clayton series eosinophils were present in the sputum of 52 out of 87 patients. Three of the four patients included in this report showed eosinophils in the sputum.

Clinically, all the four patients had a history of asthmatic episodes. Pulmonary function tests were not carried out. Haemoptysis is not a constant feature of this entity, whereas almost all cases of aspergilloma complain of haemoptysis. Fever is often present and is believed to be due to secondary bacterial infection.

Radiologically, the most important and consistent characteristic is transient patches of pneumonitis, often labelled as P.E.I. Syndrome. Apart from fungus, parasitic infestation and drug reaction are the only other common conditions which can give rise to such shadows (Editorial note, *Lancet*, 1969). In allergic aspergillosis, these shadows are seen most often in the upper zones and have a tendency to recur at the same site. (Henderson, 1968). Pepys et al (1959) attributed pneumonitis to Arthus phenomenon in the pulmonary parenchyma. Earlier, Citron and Pepys (1958) had shown that in experimental conditions infiltration occurred several hours after bronchial provocation test. The role of anaphylactoid phenomenon associated with type I hypersensitivity in the production of pulmonary infiltration has also been postulated (Campbell and Clayton, 1964) but not favoured. However, it is admitted that type I hypersensitivity is an important initiator or preparative for the subsequent occurrence of Arthus reaction.

Of the four cases reported above, cases 1, 2

and 3 showed typical shadows. Case 1 in addition had consolidation/collapse of the right middle lobe. This is not an uncommon finding. Spotnitz and Overholt (1967) also reported collapse of the upper lobe in one of their cases. Ellis (1965) reported total collapse of lung in two cases. In Henderson series, 8 cases out of 32 had segmental or lobar atelectasis. Whenever present, collapse, segmental or lobar is due to impaction of bronchi with a mass consisting of fungus, mucous, fibrin and exudate resulting from Arthus phenomenon (Spotnitz and Overholt, 1967).

Case 4 is a little peculiar. Originally, she had pneumonitis with evidence of breakdown, which is rather unusual though one of the cases reported by Zimmerman and Miller (1970) also showed similar-looking lesion. A noteworthy feature of this case is that the latest skiagram (figure 5) resembles allergic alveolitis, a condition seen usually in non-atopic individuals. How then could the same patient manifest both types of reaction? Perhaps an alternation in the host-defence mechanism is responsible for this anomalous situation. It is interesting to note that one patient in the Henderson series developed invasive aspergillosis and died of it. Invasive aspergillosis too, like allergic alveolitis, is seen in non-atopic individuals only.

For practical purposes, therefore, the diagnosis should be based on repeated isolation of fungi in abundant numbers from sputum, asthmatic episodes, transient lung shadows with dual skin reaction and presence of precipitins. Judged by these criteria, all the four cases may be considered as definite cases of allergic broncho-pulmonary aspergillosis.

REFERENCES

- Agbay, D.F. et al; *J. Allergy*; 1967, 40, 319.
- Buechner, H.A.; 'Management of Fungus Diseases of the Lungs'; Charles C. Thomas, 1971.
- Campbell, M.J. & Clayton, Y.M.; *Amer. Rev. Resp. Dis.*; 1964, 89, 186.
- Chan-Yeung, M. et al; *Chest*; 1971, 59, 33.
- Charpin, J. et al; *J. Franc. Med. Chir. Thor*; 1967, 21, 517.
- Chitinis, V.R. & Deshpande, C.K.; *J. Post Grad. Med.*; 1967, 13, 31.
- Citron, K. & Pepys J.; in 'Fungus Diseases & their treatment' edited by Riddell, R.W. & Stewart, G.T.; Butterworth London; 1958.
- Editorial Annotation; *Lancet*; 1969, 11, 1237.

- Emmons, C.W. et al; *Medical Mycology*; Lea & Febiger, Philadelphia; 1970.
- Ellis, R.M.; *Thorax*; 1965, 20, 118.
- Gell, P.G.H. & Coombs, R.R.A.; *Clinical aspects of Immunology*; Blackwell; 1968.
- Colbert, T.M. & Patterson, R.; *Ann. Int. Med.*; 1970, 72, 395.
- Gupta, I.M. & Viswanathan, R.; *Ind. Med. Ass.*; 1963, 40, 514.
- Henderson, A.H.; *Thorax*; 1968, 23, 501.
- Hinson, K.F.W., Moon, A.J. & Plummer, N.S.; *Thorax*; 1952, 7, 317.
- Longbottom, J.L. & Pepys, J.; *Path. Bact.*; 1964, 88, 141.
- Mishra, S.K.; Ph.D. Thesis, University of Delhi; 1971.
- Pepys, J. et al; *Amer. Rev. Resp. Dis.*; 1959, 80, 167.
- Pepys, J.; *Hypersensitivity Diseases of the lungs due to fungi and organic dusts—monographs in allergy No. 4*; S. Karger; 1969.
- Reddy, D.J. et al; *J. Ind. Med. Ass.*; 1965, 45, 384.
- Sandhu, O.K.; Ph.D. Thesis; University of Delhi; 1965.
- Sandhu, O.K. et al; *Ind. J. Dis. Chest*; 1966, 7, 198.
- Shivpuri, D.N. & Aggarwal, M.K.; *J. Allergy*; 1969, 44, 204.
- Slavin, R.G. et al; *Amer. J. Med.*; 1969, 47, 306.
- Spotnitz, M. & Overholt, E.L.; *Dis. of Chest*; 1967, 52, 92.
- Warren, W.P. & Rose, B.; *Dis. of Chest*; 1969, 55, 415.
- Zimmerman, R.A. & Miller, W.T.; *Amer. J. of Roentgen*; 1970, 109, 505.

ANTI-TUBERCULOSIS SHIBIRS (TB CAMPS) WHERE WORK BECOMES A PLEASURE

M. D. DESHMUKH

(From *J. J. Group of Hospitals & Grant Medical College, Bombay*)

Introduction

Institutional treatment which was the only succour to the tuberculosis patients yielded place about two decades ago to specific drug treatment at home. The core of tuberculosis control programme adopted in India is the establishment of Tuberculosis Control units in districts usually at the Headquarter level fed by health centres at the periphery. Still, the gap between the urban and rural areas as regards the facilities for diagnosis and treatment appear wide enough to defeat the basic purpose of comprehensive anti-tuberculosis drive in the country unless we take the time by the forelock and apply corrective measures.

We are all aware that facilities for diagnosis and treatment are woefully lacking in rural areas. The idea of holding camps for medical relief to rural areas is not a new one. Eye camps were probably the first rural camps where thousands of people were examined and cataract operations were performed on hundreds. Lately, organised surgical camps are also being held and very recently camps for vasectomy and tubectomy to accelerate the family planning drive.

Camps have a terrific psychological impact. People who have put up with their illness or disability for years are awakened from lethargy born of despair. The news that specialists are coming to their neglected villages spreads like forest fire. People throng to a camp, often travelling long distance by any available transport or even on foot. It may also be mentioned that this effort was in addition to our routine work, involving one Sunday if the camp site was near (2 to 3 hours travelling time), or Saturday and Sunday if the travelling time involved was more than 3 hours.

Nature of help provided

1. *Diagnostic facilities*

- (a) Examination of symptomatic cases by specialists.
- (b) X-ray or screening of suspected cases.
- (c) Sputum examination of patients showing shadows suspected to be of Koch's origin.

2. *Treatment facilities*

- (a) Supply of Anti-tuberculosis drugs for domiciliary treatment.
- (b) Follow up treatment through the local centres.

3. *Preventive treatment*

- (a) Systematic BCG vaccination of children from the Primary schools in area.
- (b) BCG vaccination of pre-school age children.
- (c) Other preventive inoculations such as Oral Polio vaccine and injection of Triple vaccine.
- (d) Nutrition clinic for mothers of under nourished children.

4. *Educative propaganda*

- (a) For public.
- (b) For local doctors and Social Workers.

Meetings for the educative propaganda were usually held at the end of the camp or on previous evening, so as not to interfere with the working of the camp.

Composing of visiting team

1. Chest physicians
2. Pediatricians
3. Lady doctors
4. Medical Assistants—Post graduate and under-graduate medical students
5. X-Ray technicians
6. Laboratory technicians
7. BCG technicians
8. Dieticians
9. Treatment organisers
10. Social workers
11. Driver
12. Attendant.

The number in various groups naturally depends on the estimated amount of work. A team of 2 physicians with 2 assistants, 1 female doctor with an assistant and 2 to 3 Pediatricians with assistants was sufficient for most of the camps. 2 BCG technicians are usually taken. Their rate per hour per technician comes to about 150. Highest number of vaccinations done in one full day's work was Rs. 2,500.

Equipment

1. Van with trailer containing screening machine. (Local screening machine can also be used).
2. Field laboratory with microscope, slides, stains etc.
3. Oral Anti-TB drugs, treatment cards and index cards.
4. Propaganda material—posters, pamphlets, exhibits, films etc.
5. BCG and other vaccines.

We take our mobile screening machine whenever possible but sometimes we have to depend upon local screening machine.

At some places we have transported patients as far as 25 miles for screening. When the number of patients was large we have used two screening machines.

Local assistance

We try to get as much local co-operation as possible. Often we have attended one or two meetings of the local committee and visited the camp site to work out the details.

Apart from the local and district medical authorities, administrative authorities at State level are also notified in advance.

The success of the camp depends largely on the local organisation which in turn depends on local leadership. Once convinced about the usefulness of the project and sincere desire to help on the part of the visiting team, the local response is very satisfactory. In some places it may be the President of the local Municipal Council, at others the Sarpanch or some other leaders who take the lead. In one of our outstandingly successful camps (Khed of Ratnagiri District) the Medical Officer in-charge of the local dispensary did all the organising work almost by himself. Organised social clubs like the Lions, Rotary club and women's organisations have also successfully

organised some of our camps. Perhaps the best of all so far was the Panvel (Kolaba District) camp, organised by the Rotary Club of Panvel. This camp was a part of our last State Conference on Tuberculosis and Chest Diseases. The local response was so overwhelming that instead of 2,500 children we could manage to vaccinate with BCG in course of the day, some 5,000 to 6,000 children who had collected. We sent a full BCG team of 7 technicians a fortnight after the camp to vaccinate the remaining 5,000 children. Even on this latter day the organisation was perfect. 6 Centres had been kept with list of children to attend at each and 5 villages for the afternoon work. It is only when local organisation is good that the work proceeds smoothly. It may be mentioned that at the time of camp an adequate number of volunteers is essential (30 to 40 volunteers are required). School teachers look after school children. At each site of activity at least 4 volunteers are necessary. Boy scouts or High School pupils make good volunteers but some older people are required for general supervision. Every one should have a specific task assigned to him. Primary or secondary schools make good camp sites where class rooms can be used for purposes of examination of patients and school yards for queues of waiting patients and children for BCG vaccination.

Output of work

18 TB Camps were held from January 1969 to April 1971. Leaving 8 months of the two rainy seasons during this period, average comes to one TB camp per month.

Table 1, shows the total work carried out at the 18TB Camps.

TABLE I
Total work done in 18 camps

	Total	Average per camp
1. No. of persons examined	7,351	408
2. No. of persons screened	2,732	151
3. No. of X'ray positive	562	31
4. No. of sputum examined	562	31
5. No. of sputum positive	152	8
6. No. of BCG vaccinations	23,308	1,294
7. Oral Polio vaccinations	2,393	133
8. Triple vaccinations	2,191	122

All the persons attending the camp are first registered at the registration counter. The adults (males and females) are directed to chest physicians for examination. Persons with symptoms suggestive of tuberculosis are screened and radiologically diagnosed cases directed for sputum examination. Sputum is examined on the spot by Ziel-Neelsen method. All sputum and X-ray positive cases are given oral anti-TB drugs i.e. INH and Thiacetazone for two months and they are instructed to attend for further treatment at local centres.

All symptomatic patients with non-tuberculosis lung or heart disease are advised to go to the nearest Civil Hospital for further investigations or to the local dispensary or Primary Health Centre for medicines.

The children of pre-school age are first given direct BCG vaccination and then if necessary Oral Polio and Triple vaccine. Children going to primary schools receive only BCG vaccination. All children with symptoms are examined by the children's specialists. Children having symptoms suggestive of lung disease are screened and dealt with just like the adults. Most of the other sick children are usually having malnutrition and vitamin deficiencies and are given protein food, multi-vitamin and iron preparations and their parents are given demonstration regarding balanced food and nutritious diet.

Time spent for work is usually $\frac{1}{2}$ to $1\frac{1}{2}$ day. Total time spent away from headquarters including travelling time varied from one to three days.

The distance covered from headquarters to camp site varied from 40 to 420 kms. The average cost to the Association per camp worked out at Rs. 300. If we add an equal amount—expenses incurred by local organisers—the total cost is approximately Rs. 600. When we consider that on an average 31 radiological positive cases per camp were diagnosed it works out at Rs 20 per case. If we consider the sputum positive cases which numbered 8 per camp the cost works out at Rs. 75 per case.

An average of 408 cases were examined per camp, out of which 151 (37%) were selected for screening. Out of 151 selected for screening on an average 31 (21%) showed radiological positive disease. With better propaganda and better selections for screening the work load could be lessened and output of positive cases increased. Age and Sex distribution of all the 562 tuberculous cases is shown in Table 2.

Ind. J. Tub., Vol. XIX, No. 2

It is observed that of the 562 patients detected 419(75%) were males and only 143 or 25% females. The preponderance of males over females is seen in all age groups but especially in the age group of 45 years and above (88% as against 12%).

The extent and severity of disease in the 562 patients is shown in Table 3 & 4.

Of the total 562 cases detected 317 were known cases of tuberculosis and 245 cases were detected because of our camps.

Of the total 562 cases, 144 had far advanced disease and of these only 72 (50%) were positive by direct microscopy indicating that the microscopy is not an efficient method of case finding because 50% of the far advanced cases would not have been detected by this method. 258 cases had moderately advanced disease and of these 74 (29%) were positive by direct microscopy. 160 cases had minimal disease and only 6 (4%) of these cases were positive by direct microscopy.

Of the total 562 radiologically proved cases only 152 or 27% were positive by direct microscopy indicating that microscopy is very much inferior to X-ray in case finding programme.

To assess the role of culture, 79 microscopy negative specimens from 7 of the 18 camps were cultured on Lowenstein-Jensen medium after treating the sputum specimens with 4% sodium hydroxide. Of these 79 specimens 27 or 34% showed growth of tubercle bacilli. This is an indication that culture method has added advantage over microscopy in detecting the case of bacillary tuberculosis.

Table 5, shows that 5,564 BCG vaccinated children (3,229 males and 2,344 females) were in the pre-school age group and 17,744 (10,349 males and 7,395 females) were in Primary school age group.

Other diseases

While carrying out the tuberculosis case finding programme the patients with other diseases like bronchiectasis, emphysema and heart diseases have also been observed. In children undernourishment is commonly seen.

Besides the diagnostic, treatment and preventive services rendered at camps there are diverse incidental benefits, which may be summarised as follows :—

1. To start a Peripheral Centre,

TABLE 2

Age and sex distribution of radiologically positive cases

Age in years	Males		Females		Total
	No.	%	No.	%	
0 — 4	—	—	—	—	—
5 — 14	15	58	11	42	26
15 — 19	12	60	8	40	20
20 — 24	34	60	23	40	57
25 — 29	58	76	18	24	76
30 — 34	52	68	25	32	77
35 — 39	42	76	13	24	55
40 — 44	43	78	12	22	55
45 — 49	46	88	5	12	41
50 — 54	34	88	5	12	39
55 and above	36	86	6	14	42
No age mentioned	57	72	17	28	74
Total	419	75	143	25	562

TABLE 3

Distribution of tuberculous patients according to extent of the disease as seen on screening

Group	Old cases		New cases		Total
	No.	%	No.	%	
Far advanced	87	27	57	23	144
Moderately advanced	148	47	110	48	258
Minimal	82	26	78	29	160
Total	317	100	245	100	562

TABLE 4

Distribution of sputum positive cases

Group	Old cases	New cases	Total
Far advanced	42	30	72
Moderately advanced	34	40	74
Minimal	3	3	6
Total	79	73	152

2. Review of cases on treatment.
3. Possibility of BCG vaccination on permanent basis.
4. Training for young specialists—training for under-graduates and Internees.
5. Clearer picture of rural health problems especially Tuberculosis.

Diabetes mellitus can also be detected. Staff of the Diabetic Association of India had joined our camps on some occasions to carry

TABLE 5

BCG vaccinations done in various groups with Sex distribution

Group	Male	Female	Total
Pre-school age children	3,220	2,344	5,564
School going children	10,349	7,395	17,744
Total	13,569	10,739	23,308

out examination to detect cases of diabetes. At Gargoti out of 100 patients examined we found 9 cases of diabetes out of which 3 had tuberculosis i.e. tuberculosis and diabetes.

Summary and conclusion

With the total number of persons examined in 18 camps coming to 7,351 (averaging 408 per camp) ; number of persons screened 2,732 (averaging 151 per camp) ; number of radiological cases of pulmonary tuberculosis seen 562 (averaging 31 per camp) ; number of sputum positive 152 (averaging 8 per camp) ; number

of BCG vaccinations done 23,308 (averaging 1,294 per camp) ; there is no doubt that tuberculosis camps can play a substantial part in our Anti-TB measures especially in rural areas. It is recommended that other underdeveloped countries should take up this project.

ACKNOWLEDGEMENTS

I am grateful to the authorities concerned for the help in organising the camps and also the local organisers and to the specialists, technicians and others who took active part in the camps.

INTERAMEDULLARY TUBERCULOMAS OF SPINAL CORD

—A Case Report

D. RAJA REDDY, B. DAYANANDA RAO AND M. V. RAGHAVA REDDY
(From Osmania Medical College, Hyderabad.)

Intramedullary tuberculomas of the spinal cord are rare. Lin in 1960 could collect only 16, surgically verified cases from the world literature. First report of intermedullary tuberculoma of the spinal cord in the Indian literature was that of Sarin and Chandy in 1961. Since then various authors have reported their experiences and 12 more cases were added to the Indian literature (Dastur and Shah, 1968). Majority of these reports were single case records.

During the period 1957-1971 inclusive, 232 cases of spinal cord compression (excluding those due to trauma, spondylosis, prolapsed intervertebral discs and pott's spine) were treated at Neuro Surgery unit of Osmania General Hospital. 3 of these cases were tuberculomas of the spinal cord. All of these three cases occurred in women between the ages of 20-30. Two of these cases had earlier received treatment for tubercular meningitis. Details of the clinical, radiological, operative findings and the course of the disease are listed in table 1.

Discussion

Lin opined that intramedullary tuberculomas of the spinal cord are the result of blood borne infection from a primary focus elsewhere in the body. Case No. 3 reported above may be an example of this. Patient was cachectic and had irregular pyrexia, even though had no obvious radiological focus of tuberculosis. She could have had a small primary focus elsewhere and may have had blood borne infection to the spinal cord. Other two cases had previous attack of tubercular meningitis. Both recovered well from the meningeal infection and 3-7 months later developed slowly progressive spinal cord compression. Both these cases did not receive intrathecal streptomycin. We have excluded from this study cases of spinal cord complications concomitant with the tubercular meningitis. It is possible that the cord lesion may be primary in these cases and meningitis was its complication. Bawa and Wahi (1961) referred to tubercular meningitis as a complication of primary spinal meningitis.

Recently, Wadia and Dastur in their mono-

TABLE 1

No.	Age	Sex	Antecedent TB Meningitis	Clinical findings	Radiological findings	Operative findings evidence of TB	Result	Associated systemic
1	20	F	Seven months after TB meningitis developed spinal cord complication	Spastic paraplegia with indeterminate sensory level	Myelographic block at dorsal 7	Intramedullary tuberculoma with adhesive arachnoiditis	Good recovery	None
2	23	F	3 months after the onset of TB meningitis developed Spinal Cord compression	Flaccid paraplegia with sensory level upto dorsal 10	Myelographic block at dorsal 11 region	Adhesive arachnoiditis with intramedullary tuberculoma	No improvement	None
3	30	F	Absent	Flaccid paraplegia of lower motor neurone type with retention of urine. Level lumbar one	Myelographic block at lumbar one vertebra	Large intramedullary tumour in the conus medullaris	Complete recovery	Cachectic with weight of only 32 kg.

graph on spinal meningitis with radiculomyelopathy grouped together various manifestations, either primary, those following tubercular meningitis or those secondary to tubercular focus elsewhere in the body. The manifestations of tubercular disease in the spinal cord varied over a wide spectrum from arachnoiditis to intramedullary granulomas.

Prognosis

Ramamurthi (1967) commenting upon the intramedullary tuberculomas said that the prognosis is poor. Our experience, even though small, has been different. Two of our cases almost made complete recovery. Third patient had flaccid paraplegia on admission and also had extensive arachnoiditis. Surgical

enucleation of these intramedullary tuberculomata is not difficult and should be readily undertaken (Rao and Subrahmaniam, 1962).

REFERENCES

1. Dastur, A.M. and Shah, M.D., *Ind. Pediat.* (1968); 5, 469.
2. Lin, T.M.; *J. Neurosurg.* (1960); 17, 497.
3. Ramamurthi, B.A., Paper presented at Second Asian and Oceanian Congress of Neurology held at Melbourne, 1971.
4. Rao, B.D. and Subrahmaniam, M.V.; *Neurology* (1962); 10, 63.
5. Wadia, N.M. and Dastur, D.K.; *J. Neural. Sci.* (1969); 8, 239.

PULMONARY AMOEBIASIS PRESENTING AS A OF CASE PULMONARY TUBERCULOSIS

JITENDRA NATH, M. S. AGNIHOTRI, ZAFAR JAMIL AND RAJENDRA KUMAR

(From King George's Medical College, Lucknow.)

Introduction

Pleuro-pulmonary amoebiasis, nowadays, is not regarded as an uncommon condition but still the diagnosis is very often missed through lack of awareness of the condition and paucity of the characteristic clinical features. Such avoidable lapses in the diagnosis invariably result in prolonged ill health and sometimes in death. A case is presented here which was twice subjected to laparotomy, being diagnosed as a case of cholangitis and after the second laparotomy, presented as a case of right basal pulmonary tuberculosis with haemoptysis.

Case Report

C.P., a 30 years old male, smoker but non-alcoholic, was admitted in the surgical ward with the history of acute pain in the abdomen especially the right hypochondrium, referred to the right shoulder and right side of the neck, associated with intermittent pyrexia with rigor of one year duration. There was leucocytosis and increased number of polymorphs. Liver function tests were normal. Provisional diagnosis of cholangitis was made but on laparotomy only a few adhesions were found especially near porta-hepatis. Liver and gallbladder was normal and there was no abscess in the liver. Adhesions were divided. Post-operative period was uneventful, but after 3 days of removal of stitches, patient suddenly developed cough and had severe haemoptysis. There was moderate degree of pyrexia with rigor. Patient was transferred to our side.

On going through the past history, patient revealed that he had similar complaints 4 months back and was operated upon, being diagnosed as a case of cholangitis. On exploration nothing abnormal was found. There was also history of intermittently loose motions with mucus.

Physical examination revealed that the patient was mal-nourished, toxic and febrile. He had clubbing of the nails. Abdominal examination showed tender right iliac fossa and palpable ascending colon. Liver was not palpable. Chest examination revealed centrally placed trachea and mediastinum. In right

infra scapular region there were diminished movements, impaired percussion notes and coarse crepts with diminished air entry. Nothing abnormal was found in any other system.

Investigation :—E.S.R. was raised. There was polymorphonuclear leucocytosis of moderate degree. Liver function tests were normal. Urine was normal. Stool examination showed presence of cysts of *Entamoeba histolytica*. Sputum smear examination for acid fast bacilli and smear and culture for pyogenic organisms was negative. Sputum smear however showed vegetative form of *Entamoeba histolytica*.

Fluoroscopy and radiograph of the chest (P-A view) showed consolidation in the right lower zone with cavitation and a localised hump in the right dome of diaphragm (Fig. 1).



Fig. 1

X-ray chest (P.A. View) showing consolidation at the right lung base with cavitation and localised hump in the right dome of diaphragm (before starting the treatment)

Needle was put in the liver but no pus came out. Within two days of transfer,

patient started expectorating anchovy sauce like pus. Emitine hydrochloride 60 mg. intramuscularly per day for 10 days were injected. It was followed by a course of chloroquin for 3 weeks. Complete and dramatically rapid cure of the disease was found with the anti-amoebic treatment (Fig. 2).

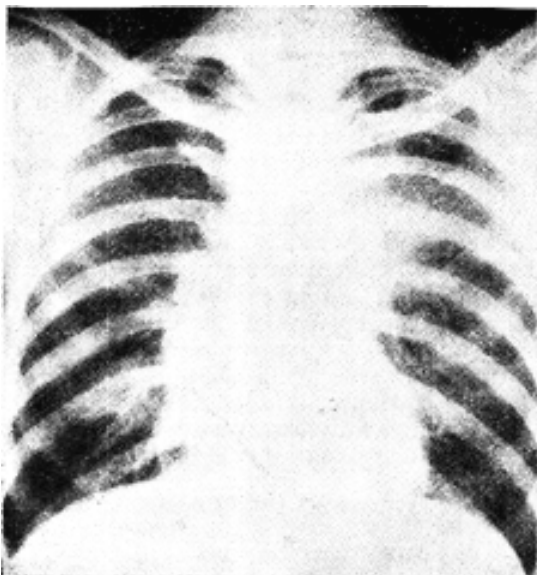


Fig. 2

X-ray chest (P.A. View) showing clearing of consolidation with anti-amoebic treatment

Discussion

Pain in the right hypochondrium at times referred to the right shoulder and right side of the neck, aggravated by coughing along with intermittent fever as an evidence of toxemia associated with chill and rigor and earthy hue complexion were sufficient symptoms for the surgeon to suspect the patient as a case of cholangitis. This state of affairs happened twice and the patient was subsequently operated upon but nothing significantly abnormal could be found out. Kasliwal and Sethi (1961) have observed similar symptoms in pleuro-pulmonary amoebiasis.

In the last post-operative period patient presented as a case of haemoptysis and he was thought to be a case of tuberculosis or lung abscess (Pyogenic). The two are very common causes of haemoptysis (Chaves, 1951 and Rao, 1960). Amoebic etiology could not be suspected because haemoptysis is a far less common symptom of pulmonary amoebiasis (Kasliwal & Sethi, 1961 ; Chaterjee, 1962 ; and Subramaniam & Madan Gopalan, 1970 have

observed haemoptysis in only 11.6%, 25% and 16% of cases respectively).

The diagnosis of hepatopulmonary amoebiasis is not difficult on clinical grounds when typical signs are present but difficulty arises when the clinical signs in the liver are absent or not sufficiently diagnostic. This is more so when the presenting symptoms and signs are predominantly in the lung. The same state of affairs was present in this case. Liver was non-palpable and non-tender, impaired percussion notes and diminished breath sound in the lower part of the right side of the chest and coarse crepts were enough for suspecting the suppuration in the lung. But because of the absence of bronchial or tubular breath sound, pyogenic pneumonitis could be ruled out (Subramaniam, 1968). Moreover sputum did not show any pyogenic organism on smear or culture examination. Similarly pulmonary tuberculosis was disproved by the absence of sufficient clinical and bacteriological evidence.

As Kasliwal & Sethi (1961) have emphasized that in all cases having signs at the right lung base amoebic etiology should be considered. So it was thought to be a case of hepatopulmonary amoebiasis. As far as non-palpable and non-tender liver is concerned, such is frequently present in cases of complicated hepatic amoebiasis as observed by Stephen & Uragoda (1970), Subramaniam & Madan Gopalan (1970) and Kasliwal & Sethi (1961). They all have observed that tender liver and inter-costal tenderness is an important feature of uncomplicated hepatic abscess. Amoebic infection by itself may be associated with clubbing as was in this case (Stephen & Uragoda, 1970). It is a general observation that leucocytosis and raised E.S.R. are frequently present in pulmonary amoebiasis.

The symptomatology and h/o dysentery with presence of *Entamoeba histolytica* in the stool are suggestive though not diagnostic but failure to find out *Ent. histolytica* in the anchovy sauce like pus does not rule out the possibility of pleuro-pulmonary amoebiasis (Sullivan & Bailey, 1951). Characteristic radiological picture of the lung makes the diagnosis very probable and quick and complete clinical and radiological cure with emetine favours the amoebic nature of the lesion as stressed by Chaudhuri & Chaudhuri (1946), Dormer & Friedlander (1941), Hameed (1945), Oschner & Debakay (1936) and Shaw (1949). In our case presence of vegetative form of *Ent. histolytica* in sputum confirms the diagnosis of pleuro-pulmonary amoebiasis and there was

quck and complete clinical and radiological recovery also (Fig. 2) with emetine.

Pathology :—The causative organism is *Entamoeba histolytica* which produces lesions in the bowel. The liver is secondarily infected via the portal blood stream. Extension of amoebic infection from the liver into the thorax may occur in the absence of frank rupture of hepatic abscess (Huard et al, 1933). In this case we also think that there was an extension of hepatic amoebiasis to the lung by a (i) contiguous spread either through the adhesions binding the lung and pleura with diaphragm or through the interlobar fissure through which the amoeba can crawl and invade the internal tissue of any part of the lung or (ii) trans-diaphragmatic extension into the lung along lymphatic channel into the right lower pulmonary area where amoeba may cause cytolytic necrosis of the lung tissue which may be secondarily infected producing the clinical picture of pneumonitis and abscess (Kasliwal & Sethi, 1961) and thus the patient presented as a case of haemoptysis. Later on anchovy coloured pus was expectorated out probably because of the intrathoracic rupture of the hepatic abscess which in this case was probably pointing upward (Sullivan & Bailey, 1951) and thus establishing bronchial fistula.

Summary

A case report 'Pulmonary amoebiasis presenting as a case of pulmonary tuberculosis' is presented with its clinical picture, course and treatment. The relevant literature is also given herewith.

ACKNOWLEDGEMENT

We are thankful to the Superintendent K.T.B. Clinic and Hospital for giving permission to publish the present case.

REFERENCES

1. Chaves, A.D. : (1951) *Am. Rev. Tuberc.* 63, 194.
2. Chatterjee, P.K. : (1962) *Ind. J. Ch. Dis.* 4, 151.
3. Chaudhuri, R.N. and Chaudhuri, M.N.R. (1946) *Ind. Med. Gaz.* 81, 66.
4. Dormer, B.A. & Friedlander, J.: (1946) *Brit Med. J.* 2, 258.
5. Hakim Abdel, M. & Hikazi, A.M. : (1958) *Dis. Chest.* 34, 607.
6. Hameed, A : (1945) *Ind. Physician.* 4, 273.
7. Huard, P., Roques, P. and Dejou, L. : (1933), Quoted from Stephen, S.J. and Urugoda C G (1970), *Brit. J. Dis. Chest.* 64, 96.
8. Kasliwal, R.M. and Sethi, J.P. : (1961) *Ind J. Ch. Dis.* 3, 157.
9. Oschner, A. & Debakey, M.: (1936), *J. Thoracic Surg.* 5, 225.
10. Rao, P.U. : (1960), *Ind. J. Ch. Dis.* 2, 219.
11. Shaw, R.P. : (1949), *Surg. Gynaec. & Obst.* 88, 753.
12. Singh, R.D. & Swami, A.K. : (1968), *Ind J. Ch. Dis.* 10, 43.
13. Stephen, S.J. & Urugoda, C.G. : (1970) *Brit J. Ch. Dis.* 64, 96.
14. Subramaniam, R. : (1968) *J. Assoc. Phy Ind* 16, 291.
15. Subramaniam, R. and Madan Gopalan, N. : (1970), Sandoz Monograph "Amoebiasis" 47.
16. Sullivan, B.S. Jr and Bailey, F.N. : (1951), *Dis. Chest.* 20, 34.
17. Yadav, S.N.S., Gopal Rao, V., Goldmann, M Laxmi, V. and Naik, B.K. : (1968), *J Assoc. Assoc. Phy. Ind.* 16, 275.

A VARIETY DISPLAY OF TUBERCULOUS LYMPH NODES

O. A. SARMA

(From Hospital for Chest Diseases & T.B., Irrammnuma, Hyderabad.)

A conventional approach to the subject is begun with reference to the King's Evil and cure by the royal touch. The study of the lymphatic gland and its behaviour in tubercular infections must start with the assumption that the various scattered lymph nodes are regarded as a single functioning organ, the so called lympho-reticular apparatus. Hadfield (1949) opines that a single lymph node takes part in the same generalised cellular response of the entire lympho-reticular system, when exposed to an irritant in the general circulation. By virtue of the phagocytic action the reticulo-endothelial cells destroy the particulate matter carried to them. Thus the lymph nodes not only act as filtering dustbins but also as incinerators, an evidence of the latter activity is the presence of puckered scars in the region reminiscent of previous disease. When deposition of calcium salts occurs at or after the stage of cessation, calcification is the radiological finding.

The following clinical variants may be encountered :

- (1) Suppurating or caseous glands
- (2) A single, large freely mobile gland with little periadenitis
- (3) Diffuse tubercular adenitis, rubbery in consistency
- (4) Moderately firm or even hard groups if productive reaction predominates
- (5) Cold abscesses with or without secondary infection
- (6) Calcined nodes

One of the earliest features of tuberculous lymphadenitis is insidious onset and early matting. Resolution may occur at this stage or it may progress to suppuration and caseation. Sinuses form, scrofuloderma may develop.

Case No. 1 :

An illiterate middle aged female sought admission for treatment of multiple large swellings in the groin, of moderate size in axillae and medium size in the cervical region. The cervical swelling added a picture of 'bull

neck' to the slender frame and build (Fig. 1). Puckered appearance with irregular scarring was noticed in the neck, axilla and groin; this feature was reminiscent of previous old healed reaction to the disease. The tuberculin testing observed on the volar surface of the left forearm bordering the bangle worn by her recorded a reaction of 25 mm erythema and induration, thus proving the allergic reaction of the tissues to tuberculo-protein. Biopsy of cervical node proved histopathological diagnosis of tuberculosis.

The point of curiosity in this case is the giant sized nodes in the groin and axilla of tuberculous etiology which are rather not common.

Case No. 2 :

An emaciated male adult consulted for a swelling in the anterior aspect of the neck, more towards the right of mid line, of 15 days duration. (Fig.2). There was progressively increasing oedema of the right upper extremity with the veins over the anterior aspect standing out prominent with bluish hue. The lymph nodes along the anterior border of sternomastoid, lower in the chain, were affected in this case and extension of the process led to accumulation of caseated contents producing pressure upon subclavian vein. Evidence of pressure upon the great venous trunks was present with obstruction to venous return. The swelling was aspirated and A.F.B. demonstrated in the contents consisting of wheat coloured cheese like material. The oedema of the right upper limb promptly cleared after aspiration of the swelling. With anti-TB treatment the general condition improved steadily.

Case No. 3 :

Male 45 came for the treatment of swelling in the left axilla (Fig. 3a). Evidence of puckered scars in the neck was present. Aspirated contents from the swelling measured 24 ozs each time; it has been aspirated twice. A.F.B. were found in moderate numbers in the aspirated contents, which on naked eye inspection was found to be ashy white in colour. Fig. 3b showed the follow up after a month with subsidence of the cold abscess. A swelling one inch in size has appeared anterior to

the right sternomastoid (fig. 3b), which was also later aspirated.

This case is curious in the sense that a cold abscess arising from superficial lymph nodes has assumed such a huge dimension: hence it is a sight for display.

Case No. 4 :

A female child aged about 6 years admitted by parents for the treatment of lymph node swellings with ulceration (Fig. 4a). On close



Fig. 4 (a)

scrutiny the preauricular lymph node on the right side was found enlarged (Fig. 4b depicting the close up view). This is an instance of chronic tuberculous lymphadenopathy involving the preauricular lymph node. There is no evident lesion in the field of drainage of this node to account for the enlargement; the eyes are full of lustre and bright, conjunctiva, lids and skin surrounding are quite healthy.

Case No. 5 :

A middle aged female was found to be suffering from generalised tuberculosis involving the pulmonary parenchyma, cervical and hilar lymph nodes. The history dated back 7



Fig. 4 (b)

to 8 years with insidious onset of cough and lymph nodal swellings. There are numerous puckered scars in the neck and chin featuring the vestiges of previous diseased nodes. Bead like calcific hard nodules arranged in a string-like fashion were palpated on both sides of the neck and underneath the chin. The evidence of this finding is well observed in the skiagram (Fig. 5) which demonstrates the calcific beaded braids on either side of the neck and discrete calcifications in the pulmonary parenchyma too. This case is an instance of burnt out phase of the disease.

A case has been reported by the author wherein tuberculous lymph nodes presented as unusual mediastinal enlargement (Sarma, 1970).

Discussion

Tuberculosis is known to involve the lymph nodes anywhere in the body: amongst the superficial, cervical being the most commonest region to be involved, axillary and inguinal



Fig. 5

though less frequent are involved in that order of frequency. Multiple and combined involvement at various superficial sites has been observed in case no. 1. The hilar and mesenteric group of nodes do not escape invasion by the disease process. The commonest cause of calcification of lymph nodes is tuberculosis in our country. Deposition of calcium salts lends them evident in the skiagram. As healing occurs the lymph node shrinks and the calcific spots come close together and often fuse to form a homogeneous mass resembling a craggy rock or coral (Indra et al, 1964). Conglomerate calcification in the axilla is noted

at times in skiagrams in the wake of tubercular affliction.

Amongst the superficial cervical chain, submental, preauricular (parotid) post auricular (mastoid) and occipital groups are affected; also, the groups of glands lying alongside the external and anterior jugular veins, do not escape. Taking into consideration the deep cervical chain, two sets lie in relation to the sternomastoid along its anterior and posterior borders respectively. The upper anterior sternomastoid sub group (tonsillar or jugulo digastric) is often involved. The lower anterior sternomastoid sub group receives afferents from other cervical nodes and mediastinal nodes. Lower posterior sterno-mastoid subgroup (supraclavicular) receives afferents from axilla and mediastinal nodes. The calcific beaded string like appearance in the neck in case No. 5 is due to involvement of the nodes along the sterno-mastoid as described above.

REFERENCES

- Bailey, H. and Love, M., 1959 A Short Practice of Surgery, 11th ed., Lewis, London.
- Cecil Wakeley and John B. Hunter., 1947 Rose & Carless Manual of Surgery, Bailliere, Tindall and Cox, London.
- Farquharson Eric. L., 1969., E. & S. Livingstone Ltd, Edinburgh and London, Text book of Operative Surgery.
- Hadfield, 1949 as quoted in Heaf F.R.G.
- Heaf F.R.G., 1957 Symposium of Tuberculosis, Cassell and Company Ltd, London.
- Indra et at., 1964 /. *Indian Med. Ass.* 43 : 520.
- Sarma, O.A. 1970., *Ind. J. Tub.*, Vol. XVII No. I, 43,44.

NEWS AND NOTES

ANNUAL MEETINGS

The Thirty-third Annual General Meeting of the Tuberculosis Association of India will be held on 29th April, 1972 in the Conference Hall of the Association. This will be followed by a meeting of the Central Committee of the Association. Dr. J.B. Shrivastav, Chairman of the Association, will preside over both these meetings.

The Technical Committee of the Association will meet on 28th April and the Conference of the Secretaries of State TB Associations and Seal Sale Committees will be held on 29th April, 1972.

SEAL SALE TROPHY

The Association's Seal Sale Trophy for the 21st Campaign will be awarded to Tamil Nadu TB Association. The Tamil Nadu Association, which took 58,00,000 Seals for this campaign and collected Rs. 3,74,325.93 had not only made the highest collections in the last five campaigns but had also made significant progress in its activities both at State and District levels. The Runner-up Cup will be awarded to the Delhi TB Association which took 8,00,000 Seals and collected Rs. 50,000. The Committee also recommended that certificates of Merit be awarded to the TB Associations of Andhra Pradesh, Kerala and Tripura in view of their good performances during the 21st Campaign.

HEALTH VISITORS' COURSE

A nine month TB Health Visitors' Course will commence from July next. The minimum qualification for admission to this course is Higher Secondary/Pre-University with Science or Hygiene and Physiology in the Matriculation.

Expenses connected with this training will have to be met either by the candidate or his/her deputing authority. They are also expected to make their own arrangements for boarding and lodging in Delhi. Application for admission to this course should reach the Tuberculosis Association of India, 3, Red Cross Road, New Delhi on the prescribed form on or before the 15th May, 1972.

23RD TB SEAL

The Tuberculosis Association of India has selected the design depicting the "Sun Rise"

submitted by M/s. Three Brothers & Fils, Bombay, for the 23rd TB Seal. The theme symbolises that Sun rays are always associated with activity, energy and health and that by eradicating TB the darkness of ill-health, ailment and disease is banished. The 23rd TB Seal Sale Campaign will commence as usual, on 2nd October, 1972.

T.A.I. GOLD MEDAL

The Gold Medal instituted by the Tuberculosis Association of India has been awarded to Dr. R. Viswanathan, Emeritus Scientist, Vallabhbhai Patel Chest Institute, Delhi University for the year 1972. The award will be made at the time of the National TB Conference, the dates for which will be announced later.

TB & CHEST DISEASES WORKERS CONFERENCE : PATIALA

The 5th Punjab State TB Workers' Conference was held in Patiala on 18th and 19th February, 1972 under the auspices of TB Association of Punjab. The highlight of the conference was a Seminar on District Control Programme in which 31 doctors from all over the State and outside participated. Special invitees to the Conference included Dr. S.P. Pamra, Director, New Delhi TB Centre and Dr. N.M. Vanderhoff, WHO representative.

The Executive Committee of the Association and the Secretaries of district branches met on 19th February and discussed plans and programmes for strengthening the district branches. The Annual General Meeting of the Association was also held on the same day.

MAHARASHTRA STATE CONFERENCE

The 10th Maharashtra State TB & Chest Diseases Conference was held at Amaravati on 22nd and 23rd January, 1972. The Conference included organisation of Symposia, panel discussion and papers on various aspects of TB and Chest conditions. Dr. V.N. Rao, Joint Director of Health Services, Government of Maharashtra, presided over the Conference.

The Maharashtra State Association also organised an anti-TB Shibir Camp during the Conference at Gurukunj, Mozari, a place 35 kilometres away from Amaravati. This is a model village where the Ashram of the late Shri Rastrasant Tukdoji Maharaj is situated and moreover surrounded by many villages.

Hence, maximum benefit of the Shibir could be catered to the poor rural masses.

A symposium on Pulmonary Tuberculosis and Panel discussion on the role of district TB Associations and primary health centres in anti-TB Campaign, besides reading of scientific papers were also held.

REFRESHER COURSE : TAMIL NADU

The Tamil Nadu Anti-TB Association, Madras conducted a Refresher Course on "Tuberculosis and Chest Diseases" at Cuddalore on 11th and 12th March, 1972. The course which was organised by South Arcot District TB Association was attended by a large number of medical practitioners.

CHEST DISEASE CASH PRIZE AWARD

The Indian Association for Chest Diseases has instituted a cash prize of Rs. 200/- to be given to the author of the best article published during the previous year either in Indian or foreign journals on any subject on the speciality of Chest Diseases. The prize is confined to doctors under the age of 40 years. Articles are to be sent to the Secretary, Indian Association for Chest Diseases, D-1/138 Chanakya Puri, New Delhi, to reach not later than 31st July, 1972.

DR. B.C. ROY NATIONAL AWARDS

Dr. B.C. Roy National Award Fund has given awards to (1) Dr. B.G. Prasad, Head of the Department of Social and Preventive Medicine, K.G. Medical College, Lucknow in the category of "Good and Capable Teacher",

(2) Dr. K.K. Datey, Prof. & Director of Cardiology, St. George Hospital, Fort, Bombay in the category of "Development of Speciality of Cardiology" and (3) Dr. M.N. Sarkar in the category of "To recognise the best services in the field of socio-medical relief". The awards are of the value of Rs. 2000/- and will include a Gold Medal of the value of Rs. 1,000/-.

Major General Inder Singh, Senior Consultant in Medicine, Directorate of Armed Forces Medical Services, Ministry of Defence, New Delhi, delivered the Dr. B.C. Roy Oration for 1971 and was awarded a Gold Medal.

OBITUARY

Dr. Caroll E. Palmer, an international authority on the epidemiology of Tuberculosis, died suddenly in his home in Rochester, Minnesota, U.S.A. Taking his doctorate from the University of Minnesota, U.S.A. Dr. Palmer joined the Johns Hopkins as a biostatistician. In 1936 he joined the USPHS as Director of Research, Child Hygiene. From 1942 until his retirement in 1967 he directed the TB Research Programme of the United States Public Health Services. From 1949 to 1955 he served in addition to his duties for the public health services as Chief of the TB Research Officer of WHO in Copenhagen. In 1967 he became Professor of Bio-Statistics and Epidemiology at the School of Public Health of the University of California in Berkeley. His work on dental caries in child health programme developed the DMF Index. His work on histoplasmosis is a standing monument to his clinical and epidemiological research.

The Indian Journal of Tuberculosis

ABSTRACTS

Vol. XIX

April 1972

Abst. No. 2

Isoniazid and liver disease

Report of the Adhoc Committee of the department of Health, Education and Welfare, USA 1971. Amer. Rev. Resp. Dis. 1971, 104, 454.

An Adhoc Committee consisting of specialists in chest diseases, liver diseases and epidemiology was constituted to review the incidence of liver damage following chemoprophylaxis with INH. Important general conclusions of the Committee on which there was consensus were as follows :—

1. Liver disease can occur in patients receiving INH, the risk varying from 0 to 10 cases per 1000 patients on INH per year. The risk seems to vary from place to place and time to time, depending on factors not yet known.

2. It is not certain whether the INH-associated liver damage is reversible. This liver damage can result in death.

3. Although there was some evidence that some of the variations could have been due to differences in surveillance techniques yet the differences were too large to be merely apparent.

4. The liver damage following INH can be described as "non-predictable, drug-induced hepatitis resembling viral hepatitis. Differentiation from viral hepatitis is extremely difficult."

5. Age seems to be a predominant factor in the causation of liver damage. The damage does not appear to occur in children.

6. The damage cannot generally be reproduced in animals, does not appear to be dose-dependent nor any predisposing factor has been identified.

7. The damage is probably an expression of delayed hypersensitivity although many questions regarding patho-physiological mechanism remain unanswered.

8. Present knowledge does not call for any revision or modification of the programme of chemoprophylaxis with INH.

9. Base-line or routinely carried out serial tests for liver function e.g. SGOT, SGPT etc. are not recommended unless there are symptoms or signs suggestive of liver damage.

10. No individual should be given more than one month's supply of drug at a time. Careful vigilance must be kept up for any evidence of liver damage.

S.P.P.

Hepatic injury and multiple drug treatment

E. Sotaniemi, O. Hokkanen and W.J. Kaipainen. Annals of Clinical Research, Helsinki; 1971, 3, 220.

Of the 15,000 patients admitted in the Helsinki hospitals between 1955 and 1970, 55 were found to have drug-induced toxic liver damage. Sixteen of these 55 (29%) were taking only one drug and the other 39 (71%) were taking more than one drug. The liver function tests of all the patients receiving several drugs showed a tendency to more severe liver damage than the patients receiving a single drug. The most offending drugs were Sulphonamides, nitrofurantoin, oral contraceptives, hydralazine, and phenothiazine derivatives. Anti-tubercular drugs found to cause liver damage were Ethambutol, INH and Rifampicin. The authors hypothesize that in patients treated with multiple drugs, there may occur competition for drug metabolism in the liver, leading to partially or completely liberated substances which may induce toxic reactions in the liver.

S.P.P.

Clinical effects of Rifampicin for pulmonary tuberculosis patients

Co-operative Study Unit of Rifampicin, Japan. Kekkaku; 1971, 46, 393.

The co-operative study was based on newly

diagnosed, previously untreated pulmonary tuberculosis patients With positive sputum. Sixty two patients were treated with Rifampicin, Ethambutol and INH and the 60 control patients were treated with Streptomycin, PAS and INH. The two groups were almost similar except for a slight advantage in respect of younger age and less extensive disease in the control group. The dose of Rifampicin was 450 mg once daily, Ethambutol 750 mg once daily, INH 400 mg once daily, PAS 10 gm daily in 3 divided doses and Streptomycin 1 gm daily. Sputum conversion was obtained in 98.1% in six months in the trial group, as against 96.1% in the control group. Radiological improvement in the two groups was 98.1% and 94.3% respectively. The frequency of major side effects was almost similar in two groups but the minor side effects were slightly more frequent in the control group. It is concluded that streptomycin + PAS + INH combination in the original treatment of pulmonary tuberculosis is as good as the more costly Rifampicin + Ethambutol + INH combination.

S.P.P.

Effect of tuberculous infection on mortality risk

Ole Horwitz and Erik Wilbek. Amer. Rev. Resp. Dis.; 1971, 104, 643.

Mortality from all causes was studied during 12 years follow-up period among 626,260 persons, 15 to 44 years in age who participated in the Danish Mass Campaign during 1950-52. The mortality was identical for natural reactors, those who had been BCG vaccinated prior to the campaign and for non-reactors who were vaccinated during the campaign. It was 20% higher amongst those non-reactors who refused BCG vaccination. The excess mortality however showed no predilection for any specific cause. The mortality did not vary with the size of tuberculin reaction.

The death rate among persons with suspicious radiological lesions was much greater than among normal persons. The rate amongst those with fibrotic and calcined lesions was only slightly higher than amongst the normals. The mortality rate in 266,703 persons who did not participate in the campaign was 1/3rd greater than amongst the participants on the whole but five times greater from tuberculosis.

S.P.P.

Epidemiology of Active Tuberculosis in hospital employees in Ontario, 1966-69

Mary Jane Ashley and William D. Wigle. Amer. Rev. Resp. Dis.; 1971, 104, 851.

The epidemiological features of active pulmonary tuberculosis in hospital employees in Ontario were investigated for the period 1966-69. One hundred and sixty four fresh cases developed during the period giving an average annual morbidity rate of 33 per 100,000. Two-thirds of the cases were in the nursing staff, though the morbidity in student nurses was low. Nearly 60% of the cases were foreign-born of whom 62% had lived in Canada for less than 5 years. Out of the total of 164 cases, 140 were new cases and 24 were relapses. Of the new cases, 23 were amongst those who had been recently converted, 66 among known natural reactors, 21 amongst those who had become reactors following BCG, 20 amongst those with previous abnormal chest films and the remaining 10 from amongst those whose previous status was unknown.

Employees of tuberculosis institutions had the highest morbidity rate. This was not due to increased risk of super-infection but because of all employees of tuberculosis hospitals being tuberculin reactors at the time of recruitment. Naturally, the rate of breakdown was highest amongst them. The sources of infection in the series were both patients as well as employees.

S.P.P.

Reactivation of Inactive Tuberculosis in Northern Canada

Moir Chan-Yeung, J.D. Galbfaith, N. Schulson, Ann Brown and S. Grzybowski. Amer. Rev. Resp. Dis.; 1971, 104, 861.

The study is based on all cases of reactivation of disease occurring in the Eskimo population between 1965 and 1969. The average rate was 1.3 per year which is much higher than in the white Canadian patients, the latter being 0.1 to 0.2 per annum at present. The risk amongst the Eskimos was fairly small during the first 4 years but increased steadily thereafter reaching a peak after 10 years as against white patients in whom reactivations occurred much more frequently during the first 5 years of follow-up. The other interesting features were the high reactivation rate amongst Eskimos treated earlier for primary tuberculosis and also that the bacilli

were found to be fully sensitive to all three standard drugs in 80% of the relapses.

Good chemotherapy for the original disease had little influence in preventing reactivation. Patients with more advanced original disease had higher rate of reactivation. The authors believe that increased frequency of reactivation was unlikely to be due to exogenous super-infection but due to endogenous exacerbation owing to poor native resistance with adverse environmental factors.

S.P.P.

Tuberculosis in Canine and Feline Population

William R. Snider. Amer Rev. Resp. Dis. ; 1971, 104, 877.

The authors have given a comprehensive review of the contemporary literature on this topic. Dogs and cats are both susceptible to human and bovine types of bacillus and also atypical strains. However, active disease in dogs is most often the result of human type of bacillus whereas in cats the disease caused by the bovine bacillus is more frequent. Pathologically the disease in both animals begins as a primary complex, following thereafter the same pattern as tuberculosis in men and cattle. Treatment with standard drugs is usually successful as in human beings. BCG vaccination also affords considerable protection. The dogs and cats can both be the source and victim of disease in relation to human beings and cattle. Tuberculous pet dogs and cats have been identified as the source of tuberculin conversion in human contacts.

S.P.P.

Ten-years-interval-changes in mass radiographic survey results among Cairo University applicant students

El-Sayed Salem et al. The Egyptian J. Chest Dis. & Tuberc. ; 1971, 14, 193.

The results of mass radiography of 6,566 University entrants in the year 1957, 1958 and 1959 and of 13,442 entrants in 1967, 1968 and 1969 were studied to determine changes, if any, in the prevalence of tuberculosis in this group over a period of 10 years. The prevalence during the period came down from 1.35% to 0.85% on the whole.

Whereas females constituted 15.7% of the entire group in the earlier series, they constituted 38.9% in the latter series. The decline in the prevalence in female students was insignificant (0.7% to 0.6%) but in the males,

it dropped from 1.4% to 1.04%, which is significant. The pattern, form and extent of disease did not show any significant change over the period of study. Breakdown of disease into sputum positive and sputum negative categories has not been given by the authors.

S.P.P.

Epidemiological analysis of tuberculosis in Okinawa

Torn Mori, Kekkaku ; 1971, 46, 357.

The results of tuberculin test which formed a part of the tuberculosis prevalence survey in Okinawa in 1968 have been analysed and the following conclusions have been drawn :—

1. The annual risk of infection has been decreasing exponentially from 7% in 1940 to 0.3% in 1970.

8. The decrease of infection risk is steeper in rural area than in urban area.

3. The risk of infection is somewhat higher in males than in females, though the declining trend is equal in both sexes.

4. The effect of age factor becomes less influential on the tuberculin positive rate in higher age-groups due to decrease of population at risk among them and decrease of the risk in later calendar years, namely older age-groups of each cohort.

S.P.P.

Disparity of potency between stabilized and non-stabilized dilute tuberculin solutions

S. Landi, H.R. Held and M.C. Tseng. Amer. Rev. Resp. Dis. ; 1971, 104, 385.

Non-stabilized solutions of tuberculin (solutions containing no anti-absorption agent) lose their potency considerably during storage due to absorption of tuberculo-protein to the walls of the containers. This loss often renders the tuberculin test unreliable and non-reproducible. The concentration of PPD solution of the strength of 5 TU per dose decreased to 60% of its original concentration after 24 hours storage in a glass vial. The loss was even greater in plastic containers and disposable syringes. After 24 hours storage in a plastic container there was very little tuberculin left in the solution. If however tween 80 in 0.0005% strength was added, no loss was incurred under identical storage conditions.

Non-stabilized solutions of tuberculin, therefore, should not be used in practice.

S.P.P.

Studies on the transient lung shadow detected in radiographic examination

Tamio Sato, Shozaburo Ohara, Shoji Nakamura, Isao Ebisawa. Amer. Rev. Resp. Dis. ; 1971, 104, 938.

During 6 monthly routine radiographic examination of 12,000 civilian persons during a period of 12 years, 255 cases of transient lung shadows were detected, constituting nearly 12% of all abnormal shadows discovered during this period. The ratio of transient lung shadows to active tuberculosis was 2:1. Twenty percent of all patients with such shadows were asymptomatic. In 18 cases the transient lung shadows were found repeatedly and 70% of these had some other underlying chest disease. In an out-patient clinic where patients attend voluntarily because of symptoms the ratio of transient lung shadows to acute respiratory illness was found to be 1 : 5. *Mycoplasma pneumoniae* was the most frequently found causative agent.

S.P.P.

A double-blind study of disodium cromoglycate for prophylaxis of bronchial asthma

J.N. Toogood, N.M. Lefcoe, D.K. Rose and D.R. McCourtie, Amer. Rev. Resp. Dis.; 1971, 104, 323.

A double-blind trial indicated that disodium cromoglycate (proprietary names cromalyn sodium ; intal) given in the form of inhalation is a useful drug in the treatment of asthma. Significant differences favouring the drug were found in 10 of the 11 indices on the basis of which the results were assessed. Although the improvement in the subjective indices was greater, the improvement registered in respect of three pulmonary function tests was also significant. The drug was further shown to have a persistent effect. No evidence of drug toxicity was found.

S.P.P.

Melioidosis : The remarkable imitator

Rober H. Poe- Charles L. Vassallo and Bill M. Domm Amer. Rev. Resp. Dis. ; 1971, 104, 427.

American military personnel returning from

South East Asia have made imperative an awareness of diseases endemic in that region. Among these is Melioidosis, an infectious disease of man and animals caused by a Gram negative bacillus, *Pseudomonas pseudomallei*. The disease is frequently characterized by cough and sputum, fever and marked clubbing of fingers. Radiologically, it manifests as pulmonary infiltration, cystic cavities, pleural effusion, empyema etc. It can easily mimic pulmonary tuberculosis or other granulomatous diseases. The portal of entry has been attributed variously to inhalation, to the skin at sites of burn or to a local lymphangitis from a superficial ulcer. Although local suppurative infections of bones, joints, liver kidney, spleen and skin are described, the lung is a very frequent site. The danger of chronic form is the ability of the organism to lie dormant for prolonged periods and then suddenly to flare into a severe fulminating infection.

The diagnosis is based in isolation of the organism from the sputum culture, haemoglutination and complement fixation tests. Tetracycline, chloramphenicol and kanamycin appear to be chemotherapeutic drugs of choice.

S.P.P.

The diagnosis of primary lung cancer with special reference to sputum cytology

N.C. Oswald, K.F.W. Hinson, G. Canti and A.B. Miller Thorax (1971), 26, 623.

Of the 2545 patients with primary lung cancer pathological proof of the diagnosis was obtained by sputum cytology in 48%, by bronchoscopy in 32%, by biopsy from miscellaneous sites in 12%, at thoracotomy or necropsy only in 19% and on clinical and radiological evidence in 8%.

One or more satisfactory specimens of sputum from 2035 gave a positivity rate of 59%, when three specimens of sputum were tested, the positivity rate was 69% and when four or more were 85%. The maximum false positivity rate was 0.7%. Co-relationship between the type of malignant cell found in the sputum and in resected or necropsy specimens occurred in 84%.

H.BD.