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Editorial

## ELECTROCARDIOLOGY IN PULMONARY TUBERCULOSIS

That the heart gets involved in pulmonary tuberculosis and other lung disease has been known for over a century. Bjorkman, in his excellent monograph, has extensively referred to nineteenth century pathological reports by Virchow and others, who found changes like right ventricular hypertrophy in autopsies on those who died of pulmonary phthisis. However, evidence of cardiac involvement in the living patient of pulmonary tuberculosis was not forthcoming. Cor pulmonale was first recognized as an entity rather late, but pulmonary tuberculosis was not identified as a cause. However, the electrocardiograph prompted some investigators, notably Bjorkman, to look for evidence of cardiac involvement in pulmonary tuberculosis, presented in his monograph referred to earlier, wherein he described the various electrocardiographic patterns seen by him in his study of 1,000 cases. However, very few phthisiologists took any interest in this aspect, and reports of such investigations have been few and far between.

This Journal was probably the first in this country to publish a paper concentrating on electrocardiography as a tool to study any aspect of pulmonary tuberculosis, viz. collapse therapy. Again, the first report on cor pulmonale complicating pulmonary tuberculosis appeared in this Journal. ECG made it possible to diagnose cor pulmonale before it was far advanced, but still too late to prevent this rather unfortunate complication, besetting a patient treated successfully with modern chemotherapy.

Echocardiography as an investigation has not been exploited by pulmonologists, principally due to lack of technical expertise in a different speciality. However, it has been possible to detect pulmonary hypertension before significant damage to the right heart by this investigation.

In this issue, we publish the results of a painstaking electrocardiographic study which highlights the reversibility of cardiac damage secondary to lung disease. The bed side ECG has been meticulously analysed, a significant advance in detecting early cardiac involvement made, and hope of preventing the distressing complication of cor pulmonale aroused. Earlier work by the same group, and sponsored by the same sources, had demonstrated the relationship between the integrity of ventilatory-respiratory function and changes in the ECG.

The EGG is now a routine, bedside investigation in respiratory patients. It is in the fitness of things to submit all patients of pulmonary tuberculosis to this investigation, at diagnosis and periodically during the course of treatment. All pulmonologists need to be fully conversant with the electrocardiogram and also have access to echocardiogram.

Tuberculosis is still the most significant and frequent disease treated by the respiratory physician, and the overwhelming majority of specialised institutions dealing with respiratory disease are devoted exclusively to this disease. However desirable this may be, it has led to the tuberculosis specialist losing touch with other diseases, including those involving the respiratory system, and more particularly, the cardiovascular system. Postgraduate training in chest disease, specially the diploma course, does not pay more than a cursory attention to the cardiovascular aspects. This needs to be corrected. The training courses need to be modified. The ideal would, of course, be to recast the M.D. (Chest & Tuberculosis) syllabus, rather change it to the old system of M.D. (Medicine) with specialisation in chest disease. Super-specialisation could come later.

Some of the institutions exclusively devoted to tuberculosis and respiratory disease should probably be equipped with echocardiography and the trained personnel necessary for the same.

It may not be out of place to reiterate here that, during the haematogenous phase, any and every tissue and organ in the body is liable to seeding by the mycobacterium and consequent pathological changes. Reports on myocardial involvement have been very rare, and this issue contains one such report. Increasing and more sophisticated use of electrocardiology may help us detect more such cases in life. It may not be too rash to speculate that tuberculous myocarditis may even be responsible for some case of cardiomyopathy.

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## HEPATIC TUBERCULOSIS

Tuberculosis was declining in the West but has shown a reverse trend after the appearance of the AIDS epidemic, making tuberculosis a global health problem once again. Liver involvement in tuberculosis, though common both in pulmonary and extra-pulmonary tuberculosis, is usually clinically silent<sup>1</sup>. Occasionally, local signs and symptoms may be prominent in hepatic tuberculosis, and may constitute the initial or sole presenting feature of the disease. However, even in developing countries, liver tuberculosis accompanied by local symptoms is an uncommon entity. A study from South Africa showed that liver tuberculosis accounted for only 1.2% of all cases of tuberculosis diagnosed at a general hospital<sup>2</sup>. Lack of familiarity with this condition was apparently responsible for the diagnosis of hepatic tuberculosis being made at autopsy or surgery<sup>3</sup> in the past. Since tuberculosis remains a potentially curable disease, an awareness of its protean manifestations is very essential.

Tubercle bacilli reach the liver by way of hematogenous dissemination: the portal of entry in the case of miliary tuberculosis is through the hepatic artery whereas in the case of focal liver tuberculosis it is via the portal vein. Irrespective of the mode of entry, the liver responds by granuloma formation. Tuberculous granulomata are most frequently found in the periportal areas (zone 1 of Rappaport) but may occasionally occur in zone 3<sup>1</sup>. Both caseating and non-caseating granulomas are seen. In focal tuberculosis, various granulomas may coalesce to form a large tumor like tuberculoma. A tuberculoma which has undergone extensive caseating and liquefaction necrosis forms a tubercular abscess.

The nomenclature of hepatic tuberculosis is confusing. Multiple terms like tubercular hepatitis<sup>2</sup>, local tuberculosis<sup>3,4</sup>, secondary tuberculosis<sup>4</sup>, isolated tuberculosis<sup>5</sup>, and atypical tuberculosis<sup>6</sup>, have been used by various authors and the same term may have a different connotation when used by different authors. Thus, local tuberculosis of the liver may either mean a lesion > 2 mm diameter on gross examination<sup>4</sup> or a selective involvement of the liver without

clinically apparent disease of other organs<sup>3</sup>. There is, therefore, a dire need for a uniformly acceptable classification and nomenclature.

Broadly speaking, hepatic tuberculosis presents in three forms<sup>7</sup>. The most common form is the diffuse hepatic involvement, seen along with pulmonary or miliary tuberculosis, in 50% to 80% of patients dying of pulmonary tuberculosis. Despite the diffuse involvement of the liver pathologically, symptoms of liver disease are absent. The second form is a diffuse hepatic infiltration without recognizable pulmonary involvement (granulomatous hepatitis). The third much rarer form presents as a focal/local tuberculoma or abscess.

### Granulomatous Liver Disease

This form was referred to as granulomatous hepatitis or tubercular hepatitis in the older literature<sup>2</sup>. These terms, though technically incorrect, have the merit of distinguishing the frequent asymptomatic seeding of the liver in miliary tuberculosis from the syndrome with fever and other constitutional symptoms but without pulmonary lesions, the common denominator in both forms being the presence of diffuse hepatic granulomas.

Hepatic granulomas have varied aetiology and show considerable geographic variation. While the occurrence of sarcoidosis, primary biliary cirrhosis and fungal disease is high in the Western hemisphere<sup>1</sup>, tuberculosis is the commonest cause in India<sup>8</sup>. Therefore, the finding of liver granulomas histologically, even in the absence of caseation, necrosis/AFB, is accepted as evidence of tubercular aetiology in most parts of Asia and Africa unless proven otherwise<sup>8,9</sup>. Fever is the commonest symptom (63% - 99%) in tubercular hepatic granulomatosis followed by weight loss (50%-84%) and abdominal pain (46%-70%)<sup>2,4,8,10</sup>. Hepatomegaly is present in more than half the patients whereas splenomegaly is present in one third<sup>2,8,10</sup>. Needle biopsy is an excellent method for making the diagnosis; none of the imaging modalities (ultrasound, CT and MRI) is useful because of the small size (2mm) of the granulomas.

### Local Hepatic Tuberculosis

Local hepatic tuberculosis, defined as tubercles > 2 mm in diameter, usually occurs along with a tuberculous focus elsewhere<sup>11</sup>. Isolated hepatic tuberculoma (syn. nodular hepatic tuberculosis, macronodular hepatic tuberculosis) is<sup>1</sup> perhaps the rarest form of local hepatic tuberculosis since less than 25 cases had been reported in world literature till 1990<sup>3</sup>. Local hepatic tuberculosis has mostly been reported from South Africa and the Philippines<sup>4,9</sup>. In the former study<sup>4</sup>, local hepatic tuberculosis accounted for 14% of the 143 cases of hepatic tuberculosis in adults, (the rest had miliary involvement) Constitutional symptoms in the form of fever, anorexia and weight loss were present in 55%-90% of the patients. Abdominal pain is present in 65%-87% of patients<sup>3,4</sup>, but jaundice is uncommon, being present in 20%-35% of patients<sup>3,4,9</sup>. Most authors agree that jaundice with bilirubin values between 2.3 mg% and 5.8 mg% is due either to porta hepatis nodes causing biliary compression or to pericholangitis or the rupture of a tuberculous granuloma into the bile ducts. Hepatomegaly and splenomegaly are the commonest findings, being present in 70%-96%<sup>3,4,9</sup> and 25%-55%<sup>4,9</sup> of patients respectively. Liver is hard and nodular in about half the cases<sup>9,12</sup>. Findings from liver function tests are non-specific with the notable exception of an elevated alkaline phosphatase level in 50%-87%<sup>3,4</sup> of patients. Seventy five percent of patients with local tuberculosis of liver have abnormal chest roentgenograms<sup>2</sup> compared with only two of 21 patients with isolated hepatic tuberculosis<sup>3</sup>. Calcification in the hepatic region on plain X-ray of the abdomen may occasionally be seen in local hepatic tuberculosis<sup>9</sup>. Imaging techniques (radionuclide scan, ultrasonography, CT and MRI scans) are useful in making the diagnosis of tuberculoma or tubercular abscess. On CT scan, liver tuberculoma appears as an unenhancing, central, low density lesion due to caseation necrosis with a slightly enhancing peripheral rim corresponding to surrounding granulation tissue<sup>13</sup>. These findings though suggestive of tuberculosis have also been seen in necrotic tumours, such as metastatic carcinoma and hepatocellular carcinoma. Preliminary reports on MRI findings in large tuberculomas suggest that MRI findings are non-specific<sup>14</sup>. Ultrasonically, a tuberculoma

may be seen as a hypoechoic lesion without a distinct wall resulting from the conglomeration of numerous small tubercles or as a low density lesion with a hyperechoic rim relating to a tuberculous abscess. In both the cases, calcification may be observed<sup>15</sup>.

**AIDS and Hepatic Tuberculosis** : The outbreak of the AIDS epidemic in 1981 has been responsible for the global resurgence of tuberculosis<sup>16</sup>. Nearly 10% of patients with AIDS in the West are found infected with *Mycobacterium tuberculosis*<sup>17</sup> and more than 50% of patients with AIDS and tuberculosis have the extrapulmonary forms of tuberculosis<sup>18,19</sup>. While involvement of liver with *Mycobacterium avium intracellulare* (MAI) in AIDS patients is well recognized, and even constitutes a diagnostic criterion, the hepatic involvement with *Mycobacterium tuberculosis* is much less common, and has been recognized only recently<sup>19-23</sup>. In 1987, the presence of extrapulmonary tuberculosis along with HIV seropositivity was included as case definition of AIDS by the Centres for Disease Control (CDC)<sup>24</sup>. Fever and abdominal pain are the commonest presenting features of hepatic tuberculosis in AIDS due to the frequent occurrence of tubercular liver abscesses in such patients<sup>21,23</sup>. Aspirates from such abscess show an abundance of AFB. Unlike involvement with MAI for which no drug combination is effective therapy - the standard antituberculosis regimens is highly efficacious in *M. Tuberculosis* infection<sup>21,23</sup>.

### Diagnosis

As is true for tuberculous involvement of other organs, the final diagnosis of hepatic tuberculosis rests on histopathologic evidence of caseating granuloma or demonstration of AFB on smear or culture of biopsy specimen. This holds true both for local as well as diffuse hepatic tuberculous involvement of the liver. Using needle biopsy specimen, epithelioid granuloma formation can be demonstrated in liver tuberculosis in 80% -100% of cases; caseation necrosis in 30% - 83% and AFB on smear examination in 0% - 59% of cases<sup>2,4,8,24</sup>. Non-specific features like fatty change, Kupffer cell hyperplasia, focal parenchymal necrosis and inflammatory cell infiltration may exist *pan passu* with specific tuberculosis lesions

in a high proportion of patients<sup>8,24</sup>. The wide variation in these positive findings from different series may be related to the type of hepatic involvement i.e. the local or diffuse form, quantum of liver tissue in biopsy material and the effort of the pathologist. AFB positivity was significantly higher in autopsy material (83%) vis-a-vis needle biopsy specimens (20%), even in the same study, giving an overall confirmation rate of 33%<sup>4</sup>. Demonstration of AFB is more common in tubercular abscess versus solid tuberculomas because AFB are abundant in liquefied caseous material. For unknown reasons, the results of AFB demonstration in liver tissue in studies reported from India and the Philippines have been dismal: AFB were not found in three series from India, despite the presence of caseation necrosis and epithelioid granulomas<sup>5,8,25</sup>. In the Philippines study, AFB could be demonstrated in 2 of 30 cases of hepatic tuberculosis at autopsy<sup>9</sup>. A problem in the tissue diagnosis of local hepatic tuberculosis is the high rate of false negative results with needle biopsy technique. Guided percutaneous liver biopsy was successful in only two of 21 cases of local hepatic tuberculosis<sup>3</sup>. Even at laparotomy, the correct diagnosis may be missed<sup>3</sup>. Laparoscopy combined with direct vision liver biopsy was successful in the diagnosis of liver tuberculoma in all the cases, as reported from the Philippines<sup>9</sup> and may be the preferred mode of investigation for this form of the disease.

**Treatment and Prognosis:** Hepatic tuberculosis is treated like any other extrapulmonary tuberculosis lesion. Chemotherapy with standard anti-tuberculosis drugs remains the corner stone of treatment. This is true for both diffuse as well as the local forms of the disease. Most authors have used four drugs (INH, Rifampicin, Streptomycin and Pyrazinamide) during the initial two months, followed by INH and Rifampicin for the next seven months<sup>8,10</sup>. There are no reports on short course chemotherapy for hepatic tuberculosis. The above given recommendations have been endorsed by the CDC for the management of tuberculosis in patients with HIV infection<sup>25</sup>.

Cumulative mortality for hepatic tuberculosis ranges between 15% and 42%<sup>2,9</sup>. The factors associated with adverse prognosis are: age < 20

years, miliary tuberculosis, concurrent steroid therapy, AIDS, cachexia, associated cirrhosis and liver failure. The importance of associated disease in the outcome of hepatic tuberculosis cannot be overstressed: nearly 50% of the deaths in the Philippines study were due to respiratory failure and another third from ruptured esophageal varices due to associated cirrhosis.<sup>9</sup> Even in patients with AIDS and tuberculosis, the cause of death is invariably the former<sup>17</sup>. Drug induced hepatotoxicity is not mentioned in most reports of liver tuberculosis even with the widespread use of Rifampicin<sup>2,10</sup>. In all probability, this may be due to the small number of patients with hepatic tuberculosis rather than a true absence of hepatotoxicity in such cases. This suggests the relative safety of the use of even four drug regimens in hepatic tuberculosis with the overall risk of drug induced liver disease being the same as that associated with the treatment of pulmonary tuberculosis. Essop *et al*<sup>2</sup> have shown that when INH and Rifampicin are used together, mortality rates are significantly lower than those with the use of non-Rifampicin containing regimes (0% vs 17% - 50%). In addition to chemotherapy, anecdotal reports of successful percutaneous drainage of tuberculous liver abscesses have been made.<sup>26</sup>

In summary, symptomatic hepatic tuberculosis is uncommon. The number of cases of hepatic tuberculosis is expected to rise on account of the AIDS epidemic. Since clinical features are protean and mimic neoplastic and infective hepatic disorders, the diagnosis requires a high index of suspicion. The presence of hepatomegaly with or without right upper quadrant pain in a patient with PUO should merit consideration of hepatic tuberculosis. The demonstration of granulomas on liver biopsy remains the most sensitive diagnostic procedure. As for other forms of extra pulmonary tuberculosis, hepatic tuberculosis is a potentially curable disease. Good results have been obtained with four drug regimens without any added risk of hepatotoxicity in both immunosuppressed and immunocompetent patients.

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## INFLUENCE OF ANTITUBERCULOSIS CHEMOTHERAPY ON ELECTROCARDIOGRAPHS CHANGES IN PULMONARY TUBERCULOSIS

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*Summary.* Electrocardiographic studies were carried out in 110 patients of pulmonary tuberculosis before and after 6 months of short course antituberculosis treatment (ATT). The findings before ATT were sinus tachycardia (47), sinus bradycardia (7), sinus arrhythmia (12), P pulmonale (7), low voltage (20) P axis  $> +90^\circ$  (14), QRS axis  $> +90^\circ$  (10), SI S2 S3 syndrome (2), SMI pattern (17) and flat or inverted T wave (6). Following ATT, there was a remarkable improvement in the findings among these 110 cases : sinus tachycardia (72.4%), Sinus arrhythmia (33.3%), low voltage (60%), P axis  $> +90^\circ$  (35.7%) QRS axis  $> +90^\circ$  (50.0%), SI S2 S3 syndrome (50.0%), SMI Pattern (64.7%) and flat or inverted T wave (83.3%). The improvement supports the earlier observation that ECG changes in pulmonary tuberculosis are reversible, following ATT. The possible reasons underlying the ECG changes and their reversibility following ATT include fever, toxemia, air-flow limitation and direct myocardial involvement. Fever and toxemia can influence blood resistivity, especially in active disease which can lead to the so called Brody effect producing remarkable changes in QRS voltage.

treatment (ATT), suggesting myocardial involvement. Cor pulmonale<sup>3</sup> has also been cited as one of the mechanisms for the varied ECG changes in pulmonary tuberculosis. But pulmonary tuberculosis is not a common cause of cor pulmonale<sup>3</sup> and develops only in long standing cases due to extensive fibrotic changes.<sup>6</sup> However, Kapoor<sup>7</sup> reported that maximum number of cor pulmonale cases occurred in tuberculosis patients with the average duration of illness of less than 5 years. The present study, therefore, aims to find out (1) ECG changes in untreated cases of active pulmonary tuberculosis (ATT less than 2 weeks duration) and (2) whether the ECG changes are influenced by ATT.

### Material and Methods

The 110 cases of pulmonary tuberculosis included in the investigation satisfied the following criteria : (1) AFB positive, (2) not associated with any other respiratory or non-respiratory disease; chronic obstructive pulmonary disease (COPD), however, could not be excluded as several patients with productive cough had been moderate to heavy smokers (3) fresh cases i.e. with less than 2 weeks of ATT, this was ensured by a detailed history, clinical examination and relevant investigations, and (4) haemoglobin level of  $\geq 10$  g%. The history of symptoms ranged between 1 and 5 months. A standard 12 lead resting ECG was obtained in supine position during the postabsorptive stage i.e. at least four hour after taking meal, when the patient first reported and after six months of ATT with Rifampicin, Isoniazid, Pyrazinamide and Ethambutol by which time clearance of the lesion

### Introduction

Although several electrocardiographic (ECG) changes have been documented in pulmonary tuberculosis,<sup>1-5</sup> the likely mechanisms as to how such changes are produced remain largely unknown. Agrawal *et al*<sup>3</sup> and Jain *et al*<sup>4</sup> have reported normalisation or a marked decrease in ECG changes following anti-tuberculosis

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**Table 1.** Pre- and Post-chemotherapy ECG findings in 110 patients of pulmonary tuberculosis

Electrocardiographic finding	Number of abnormalities before ATT	Number of abnormalities returned to normal after ATT	Percentage of reversion after ATT
1. Sinus tachycardia	47	34	72.4
2. Sinus arrhythmia	12	4	33.3
3. Sinus bradycardia	1	1	
4. P waves > 2.5 mm in height in any lead	7	0	0.0
5. Low voltage	20	12	60.0
6. P wave axis > +90°	14	5	35.7
7. QRS axis > +90°	10	5	50.0
8. SI S2 S3 syndrome	2	1	50.0
9. SMI pattern (subendocardial/myocardial infarction pattern)	17	11	64.7
10. Flat or inverted T wave	6	5	83.3

clinically and radiologically, was expected.

## Results

Of the 110 patients so examined, 51 (46.4%) showed ECG abnormalities. The results are summarised in Table 1 which shows the numbers of ECG changes before and after 6 months of ATT. These ECG changes are shown in figures 1 and 2 through panels A to F. Table 1 shows disturbances in sinus rhythm, features of right sided cardiac involvement and ventricular strain of ischemic type. All these changes were reversed in a substantial number of cases, following ATT.

## Discussion

Our data show significant reversibility in respect of several ECG abnormalities, following ATT, as reported in earlier observations.<sup>3,4</sup> Malhotra & Kapoor<sup>5</sup> also demonstrated reversibility in ECG changes after collapse therapy then employed for treating tuberculosis patients. Whether the observed reversibility was a result of collapse therapy and or due to anti-tuberculosis chemotherapy, was difficult to decide.

The mechanisms underlying ECG abnormalities seen in active pulmonary tuberculosis cases and their reversibility in a

majority of the cases need to be explored. There are multiple factors that could lead to ECG changes in pulmonary tuberculosis e.g. toxemia, fever, extensive pulmonary fibrosis leading to gross positional disturbances in heart and cor pulmonale. The last reason appears unlikely in our cases in whom symptoms were of only one to five months' duration and no significant fibrosis had occurred. Besides, ECG changes associated with cor pulmonale need not be reversible following ATT.

The remarkable reversibility in ECG changes suggestive of right ventricular hypertrophy (RVH), like low voltage, verticalisation of P and QRS axis, SI S2 and S3 syndrome etc. is more difficult to explain. A majority of such cases had been smokers in whom a prolonged history of dry to productive cough could be elicited. And, as mentioned earlier, concomitant COPD in such cases of pulmonary tuberculosis is difficult to exclude. Recent evidence suggests that ECG parameter of right sided cardiac involvement may be produced by increased alveolar air-trapping due to airflow limitation.<sup>8</sup> It is possible that a variable airflow limitation might have been responsible for ECG changes suggestive of right sided cardiac involvement which got removed following ATT.

Alternatively, the reversal in ECG changes following ATT might be attributable to what is

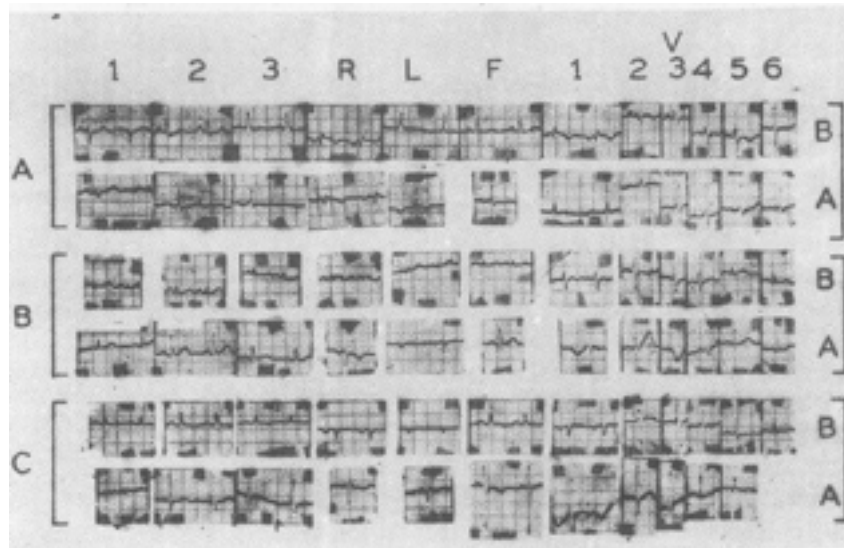


Fig. 1. 12 lead ECG before (B) and after (A) ATT. Strip A shows the attenuation of S in V5 V6 with reversals of T after ATT: the phenomenon appearing as Brody effect

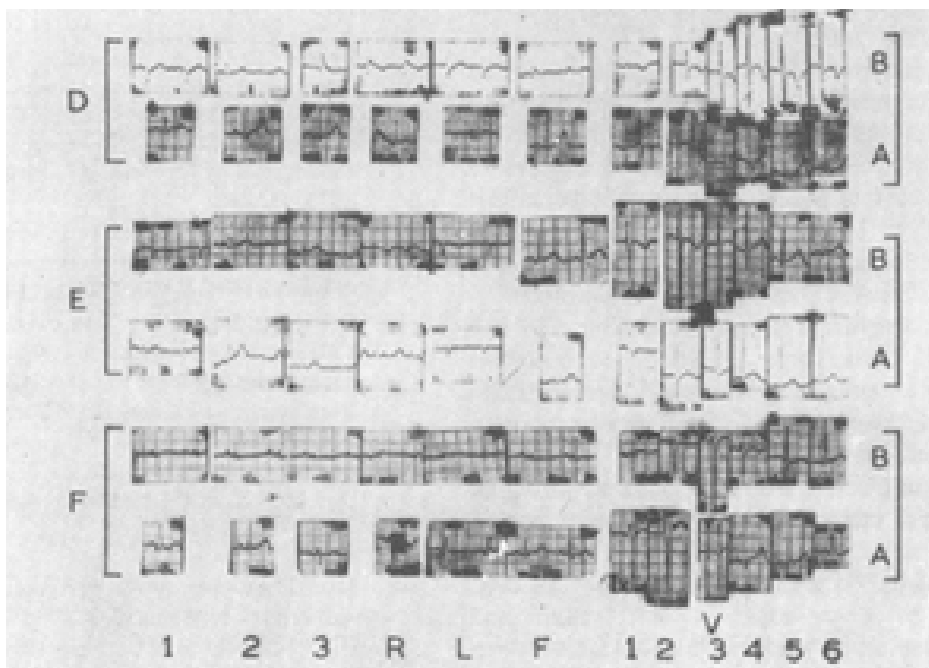


Fig. 2. 12 lead ECG before (B) and After (A) ATT. Brody effect 1 manifests in strip D also

known as the Brody effect.<sup>9-12</sup> The transmission of cardiac electric potentials to the body surface depends primarily upon the nature and composition of the conducting media, including tissues, air and body fluids which separate the heart from the recording electrodes. The electrical

non-homogeneity of these media greatly affects the transmission of cardiac potentials. According to Brody's theory, a highly conducting volume (intracavitary blood) placed in the vicinity of an electrical generator increases the manifestation of radial forces and decreases the tangential forces,

as recorded at the body surface. The Brody effect depends on both intracavitary blood mass and blood resistivity. Changes in blood resistivity which may occur during fever and toxemia<sup>10</sup> are, therefore, expected to effect the QRS amplitude or configuration. With improvement in fever and toxemia following ATT, blood resistivity will change attenuating the Brody effect. Thus, 12 out of 20 patients with low voltage improved following ATT among our patients (Table 1). In several instances, it was found that S wave amplitude in lead V6 had decreased (Fig. 1, 2) reflecting Brody effect.<sup>9,12</sup>

The present study showed no changes in the height of P wave, following ATT, in all the seven cases having P pulmonale. Non-reversible P wave may be either due to sustained alveolar air-trapping<sup>8</sup> or impending cor pulmonale. Future studies, utilizing extensive pulmonary function tests and including the blood gas and pulmonary artery pressure measurements, may help to resolved the issue.

SMI pattern and T wave changes appear to be due to myocardial involvement, which is well known in pulmonary tuberculosis.<sup>6</sup> Myocardial lesions like interstitial myocarditis and brown atrophy have been found in cases of tuberculosis at autopsy.<sup>6</sup> The QT interval increase has been reported in pulmonary tuberculosis, returning to normal after ATT<sup>4</sup> but not in the present study.

Sinus arrhythmia improved following ATT in 4 out of 12 cases. There is no evidence so far that fever or toxemia of pulmonary tuberculosis can influence the sympathetic or efferent vagal drive to produce sinus arrhythmia. However, parasystolic activity of sinus node acquiring an entrance or protection block due to inflammation of the atrial muscles, similar to interstitial myocarditis,<sup>4</sup> is a distinct possibility. In fact, recent evidence suggests that active and modulated sinus parasystole can lead to sinus arrhythmia.<sup>13,16</sup>

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## MORPHOLOGICAL CLASSIFICATION OF TUBERCULOUS LESIONS : PRELIMINARY OBSERVATIONS

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*Summary, Mycobacterium tuberculosis* produces different types of lesions in tissues. Such lesions have been analysed and correlated with AFB positivity and bacterial count. The tissue changes are classified in five distinct forms, as Type I - epithelioid granuloma without necrosis, Type II - chronic non-specific granuloma, Type III - chronic non-specific inflammation, Type IV - epithelioid granuloma with necrosis and Type V - abscess. These forms show distinct characteristics in respect of their cellular constituents, necrosis, vascularity, AFB positivity and bacillary count.

### Introduction

The morphology of tuberculous lesions is varied and has been described by several authors.<sup>1,2,3</sup> Histological diagnosis of such lesions is only suggestive but never confirmatory, unless acid fast bacilli (AFB) are demonstrated in the lesions.<sup>4</sup> Apart from Ziehl-Neelsen and File stains, AFB can also be demonstrated by various other methods. Yamaguchi and Braunstein made a comparative study of fluorescent microscopy and examination after Ziehl-Neelsen staining and observed that the latter had a better success rate.<sup>5</sup> We, in the present study, intended to classify different tuberculous lesions on the basis of their morphological features and correlated these changes with AFB positivity and bacillary count, as has been described for leprosy.<sup>6</sup>

### Material and Methods

Five hundred seventy tissues were taken for study over a period of three and a half years (July,

1989 to December 1992) at the Departments of Pathology and Microbiology, North Bengal Medical College and Hospital, Darjeeling, West Bengal. Initially, 160 tissues diagnosed as tuberculous already were taken up and then 410 tissues were added prospectively from patients with clinical diagnosis of tuberculosis. None of these patients had received anti-tuberculosis therapy prior to diagnosis. These 570 tissues had been taken from different organs and had histological appearances suggestive of tuberculous lesions. The lesions were: epithelioid granuloma without necrosis (237 cases), epithelioid granuloma with necrosis (131 cases), chronic nonspecific granuloma (130 cases), chronic nonspecific inflammation (65 cases) and abscess wall (7 cases). Of these, 213 biopsies were finally taken up for analysis (Table 1) as proved tuberculous lesions by AFB positivity (Table 2). Of them, the 153 prospective specimens were divided into two halves, using sterile instruments; one half was fixed in 10% formal-saline and the other half kept in sterile normal saline for AFB culture. The formalin fixed paraffin embedded sections were stained with Haematoxylin and Eosin, Ziehl-Neelsen and File stains.<sup>7</sup> The ZN staining was done by the conventional method using acid-alcohol as decolourising agent to exclude saprophytic organisms. Other sections from the same block were stained with ZN stain using 20% sulphuric acid as decolourising agent to exclude *Mycobacterium leprae*. The sections were studied for histopathological evidence of both typical and atypical forms of tuberculosis. Multiple sections were studied to exclude any chance of missing a granuloma or inflammatory lesion. Entire sections stained with ZN and File stains were searched for AFB under oil immersion

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**Table 1.** Distribution of histological variants according to nature of tissue specimen

Tissues	Number	Histological Types				
		I	II	III	IV	V
Lymph node	86	29	11	2	43	1
Large gut	21	4	3	7	7	-
Pleura	17	1	4	7	3	2
Endometrium and upper respiratory tract (15 each)	30	5	13	6	6	-
Skin and Cervix (9 each)	18	9	3	2	4	-
Kidneys	7	2	1	1	2	1
Ovary and Tubes	5	2	-	2	1	-
Retroperitoneum, Periarticular and soft tissues (4 each)	12	2	1	2	3	—
Gall bladder, Breast, Testis, Prostate, Empyema wall (3 each)	15	3	1	4	6	1
Liver, Pericardium, Fistula anorectal (2 each)	6	-	1	3	2	-
<b>Total</b>	<b>213</b>	<b>57</b>	<b>38</b>	<b>36</b>	<b>77</b>	<b>5</b>

objective (x 1000). For bacterial counts, five hundred consecutive oil immersion fields were taken into account and a mean index was calculated after several sections had been examined. The 153 halves kept in normal saline were processed aseptically and inoculated on Lowenstein Jensen and Middlebrook's 7119 media.<sup>8</sup> Bacterial colonies were studied with naked eye as well as by examination of the smears stained with ZN and Fite stains.

### Results

A total of 570 tissues taken from patients with relevant clinical diagnosis and morphologically suggesting tuberculosis were taken into the study. Of them, 213 were finally confirmed as

tuberculous lesions by reason of AFB positivity. Ages of these patients ranged from 2 to 80 years and male : female ratio was 1.5 : 1.0. The following histological types were observed (Table I) in them:

Type I - Epithelioid granuloma without necrosis (57 cases)

Type II - Chronic non-specific granuloma (38 cases)

Type III - Chronic non-specific inflammation (36 cases)

Type IV - Epithelioid granuloma with necrosis (77 cases)

Type V - Abscess (5 cases).

The AFB positivity in the above mentioned types was : Type I - 24 per cent (57 out of 237), Type II - 29 per cent (38 out of 130), Type III - 55 per cent (36 out of 65), Type IV - 59 per cent (77 out of 131) and Type V - 71 per cent (5 out of 7) (Table 2).

The cellular and non-cellular components of these lesions along with bacterial count are shown in Table 2. AFB positivity was maximum in Type V lesions, i.e. tuberculous abscesses (71 per cent) and minimum in Type I lesions, i.e. epithelioid granuloma without necrosis (24 per cent). Increased bacillary counts found in Types III, IV and V lesions were associated with increased degree of necrosis and neutrophilic infiltration. Culture confirmation of *M. tuberculosis* was found in 29 cases (13 per cent) and remaining samples showed either no growth or contaminants. This study did not show any case of atypical mycobacterium.

### Discussion

Tissue response to *Mycobacterium tuberculosis* is varied depending upon host immune response as well as virulence of the bacterium. It may be that antigenic variations may produce different types of immune responses in the host leading to different types of lesions like typical or atypical or some times no lesion at all. Again, only necrotic

material, either in biopsies or aspirates is useful for making diagnosis as the yield of AFB is highest.<sup>9,11</sup> Accordingly, in this study, the authors studied the different histological variants and classified the different responses to *Mycobacterium tuberculosis* into five distinct morphological types as Types I, II, III, IV and V within the 2 polar forms (Types I and V) on the analogy of a similar classification in leprosy. AFB positivity, and bacillary count, was lowest in Type I variety which is considered as one polar form and highest in Type V variety considered as the other polar form, in line of Ridley and Jopling's classification of Leprosy.<sup>6</sup> The lower AFB positivity and bacillary count in Type I may be due to presence of lymphocytes, epithelioid cells and giant cells, as these cells are thought to have some role in limiting the proliferation of the bacilli.<sup>11</sup> Liquefaction of a necrotic focus has been shown to be associated with enhanced proliferation of AFB and infiltration of neutrophils with a high degree of hypersensitivity reaction.<sup>12</sup> Of our five cases of Type V lesions which had very high AFB positivity and bacillary count showed evidence of liquefaction necrosis, marked neutrophilic infiltrations and, ultimately, abscess formation. Culture positivity found in only 13 per cent of cases might be because of dead or altered organisms in tissues. A further study is in progress to observe the results of tuberculin

**Table 2.** Showing cellular constituents, AFB positivity and bacterial count in different histological variants

Histological Types	Total tissues examined	AFB positivity	Percentage	Cellular Constituents	Bacterial counts Number per 500 o.i.f.		
					1-5	6-50	>50
Type I : Epithelioid granuloma without necrosis	237	57	24	EP (++) , L (++) , F (++) , V (+) , G (+)	46	11	-
Type II : Chronic non-specific granuloma	130	38	29	H (+) , L (+) , F (+) , V (+) , P (+)	28	10	—
Type III : Chronic non-specific inflammation	65	36	55	L (++) , F (++) , P (+) , V (+) , N «	19	13	4-
Type IV : Epithelioid granuloma with necrosis	131	77	59	EP (++) , L (++) , F (+) , N (+) , V (+) , G (+)	42	26	9
Type V : Abscess	7	5	71	N (+++) , L (+) , P (+)	-	1	4
EP	Epithelioid cell	H	:	Histiocyte	+	:	Present
L	Lymphocyte	P	:	Plasma cell	++	:	Appreciably present
G	Giant cell	F	:	Fibroblast			
N	Neutrophil	V	:	Vascularity			

response, effect of treatment and prognosis in different types of lesions.

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## FOLLOW-UP OF PATIENTS DISCHARGED AGAINST MEDICAL ADVICE IN TUBERCULOUS MENINGITIS STUDIES IN CHILDREN\*

Padma Ramachandran and R. Prabhakar

**Summary:** A total of 395 TB meningitis patients were admitted for treatment comprising regimens containing Rifampicin with and without P) razinamide. Of these, 50 patients were discharged against medical advice before completing the prescribed therapy, most being too sick and put on dangerously ill list. On follow-up, all such patients were found to have died. Discharges due to other reasons like migration, economic and domestic problems etc., Were low, i.e 6%. Drop out of patients, thus, was not a serious problem in TB meningitis studies despite the fact that 62% of the patients were from outside Madras City. This was possible due to the initial and periodic motivation of the patients.

### Introduction

Tuberculous meningitis is the most serious form of tuberculosis and carries high mortality and morbidity despite availability of potent bactericidal drugs. Even though the treatment period of most forms of tuberculosis has been reduced from the conventional 18 months to 6-9 months, this is a long period compared to treatment of non-specific acute conditions, and there is a tendency to default. The Tuberculosis Research Centre, Madras conducted four chemotherapy studies on 395 tuberculous meningitis patients in collaboration with the Institute of Child Health and Hospital for Children, Madras, from where the patients were drawn.

Patients aged between 1 and 12 years, who had not received more than 2 weeks of previous anti-tuberculosis treatment and had no evidence of renal or hepatic disease, were admitted to these studies. In the first 3 studies,<sup>1</sup> the patients were

treated with Rifampicin containing regimens with and without Pyrazinamide for a period of one year and in the last study with more intensive regimens for 9 months. The results, however, were similar in all the studies, irrespective of the regimens and duration, with a clear association between the stage of the disease on admission and the mortality, the latter being highest in patients admitted in stages II and III of the disease. All the survivors of the above four studies, except 2, were followed for a minimum period of 5 years, and a maximum of 10 years.

To ensure completeness, it was considered necessary to follow even the patients who were discharged against medical advice (DAMA) before completing the prescribed treatment. Accordingly, this was taken up as a study, which incidentally is the only one of its kind. Information was obtained from local patients by home visits and from outstation patients through correspondence. This paper covers the results of the above study.

### Study population

The total number of patients admitted to the four chemotherapy studies were 395. Of these, 50 patients were discharged prematurely before completing the prescribed chemotherapy; 32 before completing the 2 months of intensive treatment and 18 after two months of treatment. Three of these patients could not be traced and the remaining 47 were followed for a period of five years.

### Pretreatment characteristics of DAMA patients

On admission, 92% of the patients were classified as belonging to the severe stages of the disease, namely stages II and III, while only 8%

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Table 1 *Stage of disease on admission and status at long term follow-up of patients discharged against medical advice*

Stage	Total admitted		No. discharged		Follow-up status	
			Before 2mths	After 2 mths	No. died	No. alive
	I	69	4	2	2	1
II	300	41	26	15	33	8
III	26	2	2	0	2	0
Total	395	47	30*	17	36	11

\* 27 patients died

were classified as Stage I. A positive tuberculin test with 1 TU with an induration of 10 mm or more was present in 36% of the patients. A history of contact with a known case of pulmonary tuberculosis was elicited in 45% of patients and an abnormal chest radiograph suggestive of tuberculosis was present in 54%. The diagnosis of tuberculous meningitis was bacteriologically confirmed in 38% of the patients. In all, 62% of the patients were from outside Madras City.

Table 1 gives the disease stage of patients on admission and their status at long-term follow-up. It can be seen that of the 47 patients discharged against medical advice, 4 belonged to Stage I, 41 to Stage II and 2 to Stage III. Of the 4 stage I

patients, on follow-up, one had died while 3 others were alive. Of the 41 stage II patients, 33 died after discharge while only 8 were alive at long term follow-up. Both the stage III patients died after discharge. Thus, out of the 47 patients who were discharged prematurely, 36 had died at long term follow-up while only 11 survived. Majority of the deaths (27 of 36) occurred in the group of patients discharged before completing the first two months of intensive chemotherapy.

Table 2 gives the reasons for premature discharge and the status of the patients at long term follow up. Of the total 47 patients, 24 were discharged because of very good improvement or poor response to therapy, domestic/financial reasons, fear of surgery or migration to far-off places. The major chunk of patients so discharged comprised 23 who were very sick and put on dangerously ill list (DIL). The attendants of these patients were informed that the chances of survival were meagre. A premature discharge was sought in a majority of these patients because of the cost involved in transporting a dead child and for the sentimental feeling that the child be allowed to die at home. It is noteworthy that all the 23 patients put on dangerously ill list died (20 within a week of discharge and the others on the 10th, 12th and the 15th day of discharge). Of the 11 patients who were alive at follow-up, 7 had moderate and one had mild sequelae. Three

Table 2 *Reasons for discharge against medical advice and status at long term follow-up*

Reason	No.	No. died	Status at follow-up		
			Moderate sequelae	Mild sequelae	Complete recovery
Good improvement	5	1	1	0	3
No improvement	4	4	0	0	0
Domestic/financial	8	6	2	0	0
Fear of surgery	2	1	1	0	0
Migration	5	1	3	1	0
Dangerously ill	23	23 <sup>@</sup>	0	0	0
Total	47	36	7*	1*	3*

<sup>@</sup> 20 patients died within 7 days of discharge

\* 9 patients had anti-TB treatment for 3-6 months after discharge

**table 3** *Interval between discharge and death*

Stage	Total discharged	No. died	Week				Month		
			1	2	3	4	1	2	3
I	4	1	1	0	0	0	0	0	0
II	41	34	18	3	0	1	3	3	6
III	2	1	0	0	0	0	1	0	0
All	47	36	19	3	0	1	4	3	6

patients recovered completely (2 Stage I). Nine of these 11 patients (including the 3 patients with complete recovery), had received anti-tuberculosis therapy outside, for 3 to 6 months after discharge.

Table 3 gives the time interval between discharge and death. Of the 36 deaths, 23 occurred within 4 weeks of discharge while the remaining 13 died after 1 month of discharge.

### Conclusions

1. A very high proportion (94%) of patients discharged before completing the prescribed treatment could be followed for 5 years despite the fact that 62% of the patients were from outside Madras City.
2. The outstation patients responded promptly to our letters, and the local patients to the visits by the Social Workers. This cooperation indicates that the parents had genuine reasons for asking for premature discharge.
3. The mortality among these patients was very

high. In all, 36 to 47 patients died. This includes the 23 patients who were very sick and put on dangerously ill list. Excluding these 23 deaths, premature discharges due to other reasons were 6% only. Drop-out of patients, thus, was not a serious problem in the tuberculous meningitis studies.

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## CHANGING TREND OF HIV INFECTION IN PATIENTS WITH RESPIRATORY DISEASES IN BOMBAY SINCE 1988\*

K.C. Mohanty, Sudhir Nair and Tushar Sahasrabudhe

**Summary ;** Between November 1988 and October 1993, 4,054 patients admitted for various respiratory ailments to J.J. Hospital, Bombay, were screened for HIV infection and 205 were found positive by the ELISA and Western Blot Tests.

Of the 205 HIV positive cases, 182 had pulmonary tuberculosis and 23 had non-tuberculous chest disease (12 had lobar consolidation; 4 had COPD; 2 had bronchiectasis; 1 had severe ARC; 1 had pleural aspergillosis; 2 were suspected of *Pneumocystis Carinii* and 1 had malignant mesothelioma.

Seropositivity increased from 14 of 601 patients (2.3%) in 1988 to 71 of 797 cases (8.90%) in 1993.

History of heterosexual promiscuity in self or sexual partners was obtained in 197 of 205 cases (96.09%), while 6 had used contaminated blood or blood products and 2 probably got infected because of contaminated instruments. Commercial sex workers accounted for 42 of 80 female patients (70.0%) with HIV infection,

One hundred thirty-seven of 182 HIV positive tuberculosis patients responded favourably to therapy; 45 tuberculous and 4 non-tuberculous HIV infected patients died.

1985. WHO estimates that over a million people are infected by HIV in India. Added to this is the fact that there are around 300 million tuberculin positive individuals in India - a situation similar to that in a number of developing countries, particularly in sub-Saharan Africa. HIV infection results in an impairment of cell-mediated immunity and entails a substantial risk of developing tuberculosis in individuals who are infected with the tubercle bacillus, with high attendant risk of further transmitting *M. tuberculosis* infection to others.

The diagnosis of opportunistic lung infections in developing countries is often difficult, even given the best facilities. It may be that tuberculosis is being over-diagnosed in HIV patients with lung infections.<sup>5</sup>

### Material and Methods

The admission policy of the Respiratory Diseases Ward of the J.J. Hospital, Bombay is that patients are admitted from the OPD because they have either an emergency condition or need active respiratory management or need investigations and further evaluation. There is no deliberate admission connected with HIV infection related with tuberculosis.

All the patients admitted to the Respiratory Diseases Ward of the J.J. Hospital, Bombay, were screened for HIV infection by ELISA (Wellcozyme) test from November 1988 onwards. Patients examined from November 1988 to October 1991 were included in an earlier report.<sup>6</sup>

The study protocol included complete bio-data, presenting symptoms, history of recognised risk factors and immunosuppressive conditions (e.g. alcoholism, diabetes mellitus) and detailed clinical examination.

### Introduction

*Pneumocystis Carinii Pneumonia* (PCP) was the first respiratory infection recognized in AIDS when the first case of AIDS was reported by the Centres for Disease Control (CDC) in USA.<sup>1,2,3</sup> Since then, a number of other respiratory conditions like pulmonary tuberculosis, bacterial pneumonias, parasitic infestations, and lymphocytic interstitial pneumonitis have been described in the HIV infected.<sup>4</sup>

The first case of HIV was reported in India in

\* Paper presented at the 48th National Conference on TB & Chest Diseases held at Bhopal from 9 to 12 December, 1993.

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Table 1 Distribution of patients examined according to year of intake and HIV seropositivity

Year	Total patients	No. HIV positive
1988-89	601	14 (2.32%)
1989-90	925	21 (2.27%)
1990-91	845	29 (3.43%)
1991-92	886	70 (8.90%)
1992-93	797	71 (8.90%)

Apart from ELISA test for HIV confirmed by Western Blot Test, all patients underwent tuberculin test, blood counts, chest X-ray and sputum examination by Gram and Ziehl-Neelsen staining.

Complications developing during stay in hospital and response to therapy at the time of discharge, or death, were also recorded.

## Results

All the patients examined were Indian nationals except for one of African origin. The period of study extended from 1.11.1988 to 31.10.1993. The total number of patients hospitalised during the period were 4,054; 3,090 cases were tuberculous and 964 had other respiratory disorders. Of the 4,054 cases, 205 were seropositive for HIV.

Table 2 Age and sex distribution of HIV positive patients

Age group	Male	Female	Total
11-20	18	14	32
21-30	60	29	89
31-40	37	21	58
41-50	10	6	16
51-60	7	0	7
60	3	0	3
Total	135	70	205

Table 1 gives the distribution of 4,054 patients admitted for respiratory disorders according to year and HIV seropositivity.

As shown in Table 1, the proportions of HIV positive cases were approximately the same in the first two years of surveillance but increased from the third year onwards.

In all, 23 out of 964 (2.38%) non-tuberculous chest cases were HIV positive compared with 182 out of 3,090 (5.89%) cases of tuberculosis.

Table 2 shows that the HIV seropositivity was maximum in the age-group 21-30 years followed by those 31-40 years for both sexes. HIV seropositivity was less common in the extremes of age.

Forty two out of 60 (70.0%) female HIV infected patients were commercial sex workers.

Table 3 shows that heterosexual contact with multiple partners of single promiscuous partner formed the most frequent mode of transmission (95.12%) of HIV infection. This was found to be the case both in males and females.

Six out of the 12 cases of lobar consolidation (Table 4) showed *S. pneumonia* and 3 showed *H. influenza* on sputum culture. A6 organisms were isolated in the rest. All cases of consolidation responded to a broad spectrum antibiotic.

Among 182 seropositive tuberculous patients, generalised lymphadenopathy was seen in 31 cases. One case each had TB spine, TB meningitis and TB liver abscess.

Of the 2,908 seronegative tuberculosis cases, 93.12% were tuberculin positive. (1 TU PPD), while 52.19% of 182 seropositive tuberculosis patients had tuberculin induration of at least 10 mm. Table 5 also shows that the HIV seropositive tuberculosis patients had significantly less sputum positives and exudative lesions, miliary lesions and pleural effusions were more common in these patients.

Table 3 Distribution of HIV infected cases according to recognised risk-factor

Mode of Transmission	No. of cases	% of total cases
Heterosexuals	195	95.12%
Homosexuals	2	0.98%
Blood & blood products	6	2.92%
Contaminated instruments	2	0.98%

**Table 4** Showing various diagnoses in non-tuberculosis HIV infected cases

Lobar consolidation	12
COPD	4
Bronchiectasis	2
Suspected of PCP	2
Severe AIDS-related complex	1
Pleural aspergillosis	1
Malignant mesothelioma	1
<b>Total</b>	<b>23</b>

**Table 5** Distribution of tuberculosis patients according to seropositivity and tuberculin, bacteriological and radiological status

	Seropositive	Seronegative
Number	182	2,908
Tuberculin positive	52.19%	93.12%
AFD Positive	47.80%	70.12%
<i>X-ray</i>		
Cavitary	56.04%	57.0%
Exudative	21.98%	10.40%
Fibrotic	10.99%	20.60%
Miliary	1.64%	1.0%
Pleural effusion	5.49%	3.79%
Mediastinal		
lymphadenopathy	2.75%	2.0%
Hydropneumothorax	2.19%	5.21%

Response to treatment was good in 137 out of 182 (75.27%) HIV positive tuberculosis patients whereas it was good in 19 out of 23 (82.6%) of non-tuberculous cases. Response was better in tuberculosis patients who were tuberculin positive.

There were 49 deaths among the 205 seropositive cases. The case fatality rate in seropositive tuberculosis patients was 27.7% as compared to 9.6% in seronegative tuberculosis patients.

## Discussion

HIV infection rate among our hospital

admitted patients increased to 8.90% in 1992-93 from 2.32% in 1988. A similar trend has been reported in other studies among the high risk populations in India like promiscuous females<sup>7</sup> and patients attending STD clinics.<sup>8</sup>

Sexual promiscuity amongst HIV infected patients or their sexual partners was found to be the single most important risk factor i.e. among 95.12%; 70% of sero-positive female patients were commercial sex workers. Similar findings were reported from countries in sub-Saharan Africa.<sup>9,10,11</sup> Bhave *et al* have reported HIV infection in over 23% in promiscuous females in Bombay.<sup>7</sup>

Age distribution of seropositive patients shows that most cases were in the age group of 21-30 years (43.4%). In Zaire, peak seroprevalence for HIV was between 16-29 years and under 1 year of age.<sup>9</sup> In Lusaka, HIV seropositivity was highest in people at high risk in the age group 2-40 years."

It is estimated that 4% of global tuberculosis is HIV related and 10% of those having dual infection (HIV & TB) develop active forms of TB.<sup>12</sup>

Among HIV seropositive TB patients 52.2% were tuberculin positive as compared to 93.1% of seronegative TB patients. A similar observation was made in Zaire where 33% seropositives were tuberculin negative as compared to 7% in seronegative.<sup>13</sup>

Sputum positivity for AFB was present only in 47.8% of seropositives as compared to 70.1% of seronegatives. A Zambian study has shown that 63% of HIV positive tuberculosis patients had positive smear compared to 82% of the seronegative TB patients.<sup>14</sup>

Cavitation in a chest X-ray was seen in 56.0% of seropositive cases of TB and 57.0% of seronegative tuberculosis cases. This observation has been substantiated by the Zairian & Zambian studies.<sup>13,14</sup> However, American studies show that 10.5% of HIV positive tuberculosis patients had even a normal chest-X-ray.<sup>15</sup> Lobar pneumonia was the commonest presentation in the non-TB HIV positive patient. The case fatality rate among seropositives was 24.7% as compared to 9.6% in seronegatives. In a study in Zaire, 38% of HIV positive TB patients died within 12 months of diagnosis of TB.<sup>16</sup>

Response to treatment was good in 75.3% of

HIV positive TB patients and 82.6% of non-tuberculous cases. The CDC report about transmission of multiple drug-resistant TB to health workers and HIV infected patients indicates the potential for rapid transmission of resistant TB in the HIV setting.<sup>17</sup>

It appears that HIV prevalence in patients with respiratory diseases had increased in the past few years. Since good number of female patients were commercial sex workers, they should be actively involved in any strategy for prevention of both HIV and Tuberculosis.

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**PREVALENCE, INCIDENCE AND RESOLUTION OF ABSCESSSES AND  
SINUSES IN PATIENTS WITH TUBERCULOSIS OF SPINE : 5-YEAR  
RESULTS OF PATIENTS TREATED WITH SHORT-COURSE  
CHEMOTHERAPY WITH OR WITHOUT SURGERY IN MADRAS**

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**Summary.** A controlled clinical study comparing 6 or 9 months of ambulatory chemotherapy alone with radical surgery plus 6 months of chemotherapy was undertaken in patients with spinal tuberculosis in Madras.

The prevalence of sinuses and/or clinically evident abscesses was 49 (19%) of 253 patients, with significantly higher proportions in patients with lumbar or lumbo-sacral lesions. The incidence of lesions appearing after the start of chemotherapy was 32 (16%) of 204 patients. By five years, all had resolved. The resolution of the lesions was significantly faster and the incidence significantly lower in the radical surgery group than in the two ambulatory series.

Mediastinal abscesses were observed on radiographs in 66 (66%) of 100 patients with thoracic or thoraco-lumbar lesions. By five years, the lesions had disappeared in all except two patients and the disappearance WAS significantly faster in the radical surgery group than in the two ambulatory series.

There was no recurrence of these lesions during a period of five years.

undertaken in patients with spinal tuberculosis to compare 6 or 9 months of ambulatory out-patient chemotherapy (Isoniazid and Rifampicin daily) with radical surgery plus 6 months of the same chemotherapy.<sup>10</sup> This report presents the prevalence, incidence and resolution of sinuses and/or clinically evident abscesses and mediastinal abscesses during a period of 5 years in these patients.

#### Material and Methods

*Eligibility criteria:* Patients with clinically and radiographically active spinal tuberculosis, involving any vertebral body from the first thoracic to first sacral inclusive, were eligible for admission to the study provided they did not have paralysis (of lower limbs) severe enough to prevent them from walking across a room (about 6 metres), and had not received previous anti-tuberculosis chemotherapy for 12 months or more. Patients were admitted from 6 participating hospitals in Madras.

*Pre-treatment investigations :* The investigations included : (a) complete clinical (including neurological) examination, (b) antero-posterior (AP) and lateral radiographs of the whole spine, (c) examination by culture of 2 specimens of pus from any abscess or sinus, if present, and (d) sensitivity tests to Isoniazid and Rifampicin of positive cultures. Details of other investigations have been given in an earlier report.<sup>10</sup>

#### Introduction

Abscesses and sinuses (besides spinal cord involvement) are common complications of spinal tuberculosis. Abscesses can be either clinically evident or only radiographically visible, and the former may co-exist with sinuses.<sup>1-9</sup> In Madras, a controlled clinical study was

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Allocation of treatment : Patients were allocated at random to one of the following 3 series.

1. Rad 6 : Radical anterior resection with bone grafting plus Isoniazid and Rifampicin in one dose daily for 6 months.
2. Amb 6 : Ambulatory treatment with Isoniazid and Rifampicin in one dose daily for 6 months.
3. Amb 9 : Ambulatory treatment with Isoniazid and Rifampicin in one dose daily for 9 months.

The dosages were based on patients' body-weights, and were 5-7 mg/kg body weight for Isoniazid and 10-15 mg/kg for Rifampicin. In the Rad 6 series, surgery was undertaken within one month of the start of chemotherapy.

*Administration of anti-tuberculosis drugs:* For all in-patients and for outpatients aged less than 5 years, every dose of drugs was administered under the direct supervision of a staff member. Out-patients aged 5 years or more attended the clinic twice-weekly and at each attendance, the dose for that day was administered under direct supervision, and the medicament (2 or 3 doses) supplied for self-administration (or administration by the parent) for the days until the next visit.

*Assessment of progress:* Progress was assessed monthly until the end of chemotherapy, then every 3 months until 30 months, then at 6-monthly intervals until 5 years. The assessments included : (1) clinical (including neurological) examination, (2) AP and lateral radiographs of the vertebrae involved, and (3) bacteriological

examination by smear and culture of pus from any sinus or abscess.

*Bacteriological examination* .-Bacteriological examinations (smear, culture, sensitivity and identification tests) were undertaken by standard techniques<sup>11</sup> using additional media for culture of pus specimens.<sup>12-14</sup> The following definitions of drug resistance were used:

*Isoniazid:* growth of 20 colonies or more on 0.2 mg/1 or a higher concentration.

*Rifampicin :* growth of 20 colonies or more on 64 mg/1 or a higher concentration.

## Results

*Study population :* In all, 304 (10 Rad 6, 101 Amb 6, 103 Amb 9) patients were admitted to the study. For various reasons, 51 patients were excluded from analysis. The details of exclusions for 44 patients during the first 3 years were given in a previous report;<sup>10</sup> during the 3-5 year period of follow-up, 7 other patients (1 Rad 6, 2 Amb 6, 4 Amb 9) were excluded-2 were lost to follow-up and 5 died of non-tuberculous causes. After these exclusions, there remained 253 patients (84 Rad 6, 81 Amb 6, 88 Amb 9) in the analysis.

*Condition on admission :* The patients who had sinuses and/or clinically evident abscesses on admission and the patients who did not have sinuses and/or abscesses on admission were broadly similar with respect to sex, radiographic activity, vertebral body loss and number of vertebrae involved. but of the 63 patients aged 9 years or less, 5 (8%) had abscess and/or sinus, as compared with 44 (23%) with abscess/sinus

**Table 1.** Prevalence and resolution of sinuses and/or clinically evident abscesses

Treatment series	Total patients	No. of patients with sinuses and/or clinically evident abscesses		Resolution (by months)							
		initially									
		No.	%	1	2	3	6	9	12	60	
Rad 6	84	16	19	7	14	14	15	16	16	16	
Amb 6	81	20	25	3	7	13	17	20	20	20	
Amb 9	88	13	15	1	4	7	11	12	12	13	
Total	253	49	19	11	25	34	43	48	48	49	

among the 190 patients aged more than 9 years ( $p = 0.01$ ).

*Prevalence of sinuses and/or clinically evident abscesses (present on admission)* : The proportions of patients with sinuses and/or clinically evident abscesses on admission (Figures 1 & 2) were similar in the three series, being 16 (19%) of the 84 Rad 6, 20 (25%) of the 81 Amb 6 and 13 (15%) of the 88 Amb 9 patients (Table 1). In all, 49 (19%) of 253 patients had this lesion on admission, 38 (11 Rad 6, 17 Amb 6, 10 Amb 9) had clinically evident abscess only, 6 (1 Rad 6, 2 Amb 6, 3 Amb 9) had sinus only and 5 (4 Rad 6, 1 Amb 6) had both.

*Resolution of sinuses and/or clinically evident*

*abscesses* : The resolution of sinuses and/or clinically evident abscesses is shown in Table 1. An abscess or sinus has been considered as resolved only if this assessment was made at two or more consecutive scheduled examinations. The speed of resolution was similar for abscesses and sinuses and, therefore, the results have been amalgamated.

The sinuses and/or clinically evident abscesses had resolved by the first month in 7 of the 16 Rad 6 patients, by 2 months in a total of 14 and by 6 months in 15. In contrast, in the Amb 6 and Amb 9 series combined, resolution occurred in 4 of the 33 patients by 1 month, 11 by 2 months, 29 by the end of chemotherapy and in a



Fig. 1. External abscess in the right inguinal region



Fig. 2. A sinogram showing the sinus-tract from the sinus to the abscess

**Table 2.** Incidence and resolution of sinuses and/or clinically evident abscesses

Treatment series	Total patients at risk	No. of patients with sinuses and/or clinically evident abscesses appearing during treatment		Onset (months)		Resolution (months)	
				1-6/9*	7/10-60**	1-6/9*	7/10-60**
		No.	%				
Rad6	68	5	7	5	0	4	1
Amb6	61	12	20	9	3	7	5
Amb9	75	15	20	15	0	12	3
Total	204	32	16	29	3	23	9

\* Treatment phase

\*\* Follow-up phase

total of 32 patients by 9 months. In the remaining patient (Amb 9), the abscess had resolved by 3 months; 2 sinuses were evident at 9 months but both had resolved by 21 months. The resolution was faster in the Rad series than in the 2 ambulatory series, the difference being statistically significant ( $p = 0.04$  at 1 month,  $p < 0.001$  at 2 months).

None had additional chemotherapy or surgery. Further, there was no recurrence of the lesions during the 5-year period.

In 9 of the 16 Rad 6 series patients, the sinuses and/or clinically evident abscesses resolved without aspiration or incision compared with 8 of the 33 patients in the two ambulatory series. In the other 7 patients in the Rad series, 1 or more aspirations of abscesses were performed. In the ambulatory series, 20 patients (11 Amb 6, 9 Amb 9) had 1 or more aspirations of abscesses and in the remaining 5 (3 Amb 6, 2 Amb 9) the abscesses were incised.

*Incidence of sinuses and/or clinically evident abscesses observed after the start of chemotherapy:* The incidence and resolution of sinuses and/or clinically evident abscesses observed for the first time after start of treatment is presented in Table 2. Of 204 patients (68 Rad 6, 61 Amb 6, 75 Amb 9) who did not have a sinus and/or clinically evident abscess on admission, 32 (5 Rad 6, 12

Amb 6, 15 Amb 9; 16%) developed the lesions, 29 (5 Rad 6, 9 Amb 6, 15 Amb 9) during the treatment phase and 3 (all Amb 6) in the follow-up phase. The incidence was 7% of 68 in the Rad 6, and 20% of 136 in the two ambulatory series, the difference being significant ( $p=0.03$ ). Of these 32 patients, 25 (3 Rad 6, 11 Amb 6, 11 Amb 9) developed clinically evident abscesses alone, 3 (2 Rad 6, 1 Amb 6) had sinuses alone and 4 (all Amb 9) developed both. The lesions had resolved in 23 (4 Rad 6, 7 Amb 6, 12 Amb 9) by the end of treatment and in the remaining 9 (1 Rad 6, 5 Amb 6, 3 Amb 9) by 60 months.

In the vast majority, namely 28 (4 Rad 6, 9 Amb 6, 15 Amb 9) patients, the lesions had resolved without additional surgery or chemotherapy and the remaining 4 needed additional chemotherapy and/or surgery (For details, please see pp.156-157).

Of the 32 with incidence, aspiration was done in 24 (2 Rad 6, 8 Amb 6, 14 Amb 9), incision in 1 (Rad 6) and both in 1 (Amb 9). No recurrence of the lesions was observed during the 5-year period.

*Prevalence, incidence and resolution of sinuses and/or clinically evident abscesses :* The overall prevalence, incidence and resolution of sinuses and/or clinically evident abscesses from admission till 60 months is presented in Table 3.

Table 3. Prevalence, incidence and resolution of sinuses and/or clinically evident abscesses

Treatment series	Total patients	No. of patients with sinuses and/or clinically evident abscesses during 5 years		Resolution on allocated treatment		Resolution after additional		
		No. (a)	%	No.	% of (a)	Surgery only	Chemo-therapy only	Surgery & chemo-therapy
Rad6	84	21	25	20	95	1	0	0
Amb6	81	32	40	29	91	0	2	1
Amb9	88	28	32	28	100	0	0	0
Total	253	81	32	77	95	1	2	1

Of the 253 patients, 81 (32%) patients (21 Rad 6, 32 Amb 6, 28 Amb 9) had sinuses and/or clinically evident abscesses and the lesions resolved on the allocated treatment in 20 of the 21 Rad 6 patients, in 29 of the 32 Amb 6 and in all 28 of the Amb 9 patients, that is, in a total of 77 (95%) of the 81 patients. In the remaining 4 patients, one (Rad 6) developed persistent post-operative sinus at the site of surgery and the graft was removed in the 33rd month; the sinus was observed last at the 42nd month. One patient (Amb 6) developed an abscess during treatment which persisted till the end of treatment; additional chemotherapy was given and the abscess resolved by 9 months. The other 2 patients (both Amb 6) developed abscesses during follow-up; both had additional chemotherapy - one for clinically active disease at the end of treatment in whom the abscess resolved by 18 months, and the other for persisting paraparesis for whom excision of a diseased rib also was done in the 10th month and the abscess subsided by 12 months.

*Sinuses and/or clinically evident abscesses on admission in relation to the level of the spinal lesions* : The distribution of the prevalence of sinuses and/or clinically-evident abscesses in relation to the initial level of vertebral involvement is shown in Table 4. Of the 93 patients who had a spinal lesion in the thoracic region, 11 (12%) had an abscess or sinus; the corresponding figures were 7 (21%) in the

thoraco-lumbar region and 31 (25%) in the lumbar region (26 lumbar, 5 lumbo-sacral). Thus, the prevalence of abscess and/or sinus was significantly more in patients with lumbar or lumbo-sacral lesions ( $p=0.05$ ).

*Mediastinal abscess shadows on admission without sinuses and/or clinically evident abscesses at any time* : The disappearance of mediastinal abscess shadows radiologically evident on admission, which were never manifest externally, was studied by an independent assessor. The allocated regimens of these patients had not been

Table 4. Prevalence of sinuses and/or clinically evident abscesses in relation to the initial level of the spinal lesion

Initial level of spinal lesion	Total patients	Patients with sinuses and/or clinically evident abscesses	
		No.	%
Thoracic	93	11	12
Thoraco-lumbar	34	1	21
Lumbar	109	26	25
Lumbo-sacral	17	5	
Total	253	49	19

**Table 5.** Prevalence of mediastinal abscesses without sinus and/or clinically evident abscess at any time, and their resolution

Treatment series	Total pts. •	Patients with mediastinal abscess	Resolution by (months)								
			1	2	3	6/9	12	18	24	60	Not resolved
Rad6	34	21	8	13	13	15	19	20	21	21	0
Amb 6	31	21	1	6	6	9	16	17	19	21	0
Amb9	35	24	0	5	5	15	19	20	21	22	2
Total	No. 100**	66	9	24	24	39	54	57	61	64	2
	% 700	66	14+	36	36	59	82	86	92	97	3

\* Excluding patients with lumbar or lumbo-sacral lesions

\*\* Excluding 27 patients with sinuses and/or clinically evident abscesses at any time

+ This and subsequent percentages are based on the total patients with mediastinal abscess initially.

modified by surgery or additional chemotherapy based on the radiographic findings. A total of 66 (66%) (21 Rad 6, 21 Amb 6, 24 Amb 9) patients had a radiographically visible mediastinal abscess on admission (Table 5). Considering the 21 Rad 6 patients, the mediastinal abscess disappeared by 1 month in 8, by 2 months in 13, by 6 months in 15, by 18 months in 20 and by 24 months in all. In the 45 (21 Amb 6, 24 Amb 9) ambulatory patients, the lesions were not seen by 1 month in 1, by 2 months in 11, by 6/9 months in 24, by 18 months in 37, by 24 months in 40 and by 60 months in 43 patients. Of the remaining 2 patients (both Amb 9), one had a persistent abscess shadow which had calcified; the other had a persistent abscess shadow, even though he had decompression surgery for worsening of paraparesis in the 2nd month. The mediastinal abscesses had disappeared more rapidly in the Rad 6 series than in the combined Amb series, the difference being statistically significant ( $p < 0.001$  at 1 month;  $p < 0.01$  at 2 and 3 months). In all, the mediastinal abscess disappeared during the treatment phase in 39 (15 Rad 6, 9 Amb 6, 15 Amb 9) patients, during the follow-up period without any intervention in 25 (6 Rad 6, 12 Amb 6, 7 Amb 9) patients and did not resolve in 2 Amb 9 patients even by 60 months.

No information is available on the incidence of mediastinal abscess.

#### *Bacteriology of pus from abscesses and sinuses*

(both aspirated and at surgery) : Of the 49 (16 Rad 6, 20 Amb 6, 13 Amb 9) patients with sinuses and/or clinically evident abscesses on admission, aspiration or incision was done in 32 (7 Rad 6, 14 Amb 6, 11 Amb 9) patients; the specimens were examined bacteriologically and the culture was positive for *M. Tuberculosis* in 18 (56%) patients. Pus was collected during surgery from 13 Rad 6 patients, of which 4 were positive by culture including one from a patient for whom the aspirated pus also yielded *M. tuberculosis* on culture. These 13 patients included the 7 (Rad 6) who had aspiration also. In the remaining 3 Rad 6 patients, pus was neither aspirated nor collected during surgery. Thus, bacteriological examination of the pus was undertaken in 38 (13 Rad 6, 14 Amb 6, 11 Amb 9) Of the 49 patients and culture was positive in 21 (55% - 7 Rad 6, 8 Amb 6, 6 Amb 9) patients; all were sensitive to Rifampicin and Isoniazid.

*Prevalence, incidence and resolution of sinuses and/or clinically evident abscesses in patients who were excluded from the analysis* : Among 51 patients excluded from the analysis, 19 were either found to have no evidence of active tuberculosis or were withdrawn from the study as unsuitable for surgery; 1 patient who had an abscess on admission died 12 (days after starting treatment. Of the remaining 31 (6 Rad 6, 13 Amb 6, 12 Amb 9) patients 8 (2 Rad 6, 3 Amb 6, 3 Amb 9) had a sinus and/or clinically evident abscess on admission; 6 had an abscess alone and

2 had both abscess and sinus. The sinus and/or clinically evident abscess resolved by the end of chemotherapy in six (2 in each series) and by 21 months in the other 2 (1 Amb 6, 1 Amb 9) patients. There was no recurrence of the lesions during the 5-year period, and none developed an abscess or sinus during treatment or in the follow-up phase.

### Discussion

Sinuses and/or clinically evident abscesses and mediastinal abscess (besides spinal cord involvement) are common complications of spinal tuberculosis. The present report gives 5-year findings of these two complications, encountered during an investigation of short-course chemotherapy in the treatment of spinal tuberculosis.

Unlike in pulmonary tuberculosis, bacteriological confirmation of tuberculosis in extra-pulmonary forms, which are paucibacillary, is difficult. However, with the introduction of selective and multiple media, the culture positivity rates are high.<sup>12-14</sup> In the present study, pus obtained from sinus and/or clinically evident abscess present on admission, by aspiration or incision, was examined in 32, of which 18 (56%) were culture positive. This result compares favourably with the culture positivity rate of 40% obtained by examination of aspirated pus in British Medical Research Council studies.<sup>15,16</sup>

The prevalence of sinus and/or clinically evident abscess was 49 (19%) of 253 patients in this study. This is similar to the prevalence of 22% observed among 587 patients in Masan, Pusan, Bulawayo and Hong Kong.<sup>1-4,9</sup>

The incidence of sinus and/or clinically evident abscess was not influenced by the kind of chemotherapy given; it was 27 (20%) of 136 patients receiving 6 or 9 months of daily Isoniazid plus Rifampicin (present study) and 59 (22%) of 273 patients treated with 18 months of daily Isoniazid plus PAS, with or without an initial Streptomycin supplement<sup>1-3</sup> in Masan, Pusan and Bulawayo. Considering the role of surgery, in the present study the incidence was 5 (7%) of 68 in the Rad 6 series treated with 6 months of daily Isoniazid and Rifampicin plus modified Hong Kong surgery and 9% of 44 Hong Kong patients treated with a regimen similar to the present Rad

6, excepting that the duration of chemotherapy was either 6 or 9 months,<sup>9</sup> as compared with 27 (20%) of 136 in the Amb 6 and Amb 9 series combined in the present study ( $p = 0.03$ ). A similar difference has been reported in studies with 18 months of daily Isoniazid plus PAS; the incidence was only 2% of 142 patients who had chemotherapy plus surgery (i.e. debridement or radical operation) as compared with 22% of 273 patients who had chemotherapy alone.<sup>14</sup> These findings indicate that surgery substantially reduced the incidence of sinuses and/or clinically evident abscesses.

The speed of resolution of sinuses and clinically evident abscesses with short-course or standard chemotherapy, with or without additional surgery, is also of interest. Of 86 patients treated with 18 months of daily Isoniazid plus PAS, the lesions resolved in 29 (34%) by 3 months, 46 (53%) by 6 months and 71 (83%) by 12 months.<sup>1-3</sup> In the present study, of 33 patients treated with 6 or 9 months of daily Isoniazid plus Rifampicin, the corresponding figures were 20 (61%), 28 (85%) and 32 (97%), respectively. This finding suggests that the resolution was faster in those treated with short-course chemotherapy (SCC) than in those treated with standard chemotherapy. Considering the 23 patients (Madras : 16; Hong Kong : 7) treated with radical surgery plus short-course chemotherapy (6 or 9 months of daily Isoniazid plus Rifampicin), the lesions resolved in 20 (87%) by 3 months and in 21 (91%) by 6 months.<sup>9</sup> These proportions are higher than in those treated with ambulatory short-course chemotherapy, suggesting that surgery enhanced the speed of resolution further. In the patients treated with surgery (debridement or radical operation) plus 18 months of daily Isoniazid and PAS, the lesions resolved in 25 (71%) by 3 months, in 29 (83%) by 6 months and in 33 (94%) by 12 months.<sup>14</sup> These proportions are higher than in those treated with 18 months of daily Isoniazid plus PAS without surgery.<sup>1-3</sup> Thus the speed of resolution was greater when surgery was undertaken in addition to chemotherapy.

By 5 years, the lesions had resolved in all 81 (100%) patients treated with short-course chemotherapy of 6 or 9 months' duration with or without surgery (present study), as compared to 117 (92%) of 127 patients who were treated with

18 months of chemotherapy alone and in all 67 patients who were treated with surgery in addition to 18 months of chemotherapy.<sup>1-4</sup>

Considering the disappearance of radiographically visible mediastinal abscesses present on admission, at the end of chemotherapy, that is at 6 or 9 months in the present study and the second study in Hong Kong,<sup>9</sup> the abscesses had disappeared in 15 (71%) of 21 patients in the Rad series and in 24 (53%) of 45 patients in the combined Amb series in Madras and in 8 or 9 of 12 patients treated with radical surgery plus short-course chemotherapy in Hong Kong. This finding suggests that the disappearance of the abscesses was faster in patients treated with radical surgery in addition to short-course chemotherapy. In patients treated with 18 months of Isoniazid plus PAS (standard chemotherapy), the abscesses had disappeared in 69 (83%) of 83 patients at the end of treatment.<sup>1-3</sup> The corresponding figures for patients treated with additional debridement were 26 (81%) of 32<sup>3</sup> and with additional radical surgery, 19 (86%) of 22<sup>4</sup>. This similarity suggests that surgery (debridement or radical) did not enhance the rate of resolution of mediastinal abscesses in patients treated with PAS and Isoniazid daily for 18 months. By 18 months, the lesions had disappeared in 95% in short-course chemotherapy series even though they did not receive any anti-tuberculosis drugs beyond 6 or 9 months. These proportions are similar to the 81-86% observed at the end of 18 months of Isoniazid plus PAS, with or without surgery (see above). Unlike the resolution of sinuses and/or clinically evident abscesses, the radiological disappearance of mediastinal lesion was *not* influenced by the kind of chemotherapy given.

It is concluded that clinical abscess/sinus and mediastinal abscess do not pose any special problems in management and respond well to short-course chemotherapy consisting of daily Isoniazid plus Rifampicin of 6 or 9 months duration. The resolution of sinuses and clinically evident abscesses was faster with short-course chemotherapy than with standard chemotherapy. When surgery was undertaken in addition, the resolution was faster irrespective of the type of chemotherapy. The incidence of sinuses and/or clinically evident abscesses was also significantly less in patients who underwent surgery. The resolution of mediastinal abscesses was also faster

in the surgical series. These findings are different from the conclusion reported in another paper, on 5-year findings in patients with spinal tuberculosis<sup>17</sup> that, ambulatory chemotherapy with daily Isoniazid and Rifampicin for 6 or 9 months was highly effective in spinal tuberculosis and radical surgery did not enhance the efficacy of the 6-months regimen. However, by 5 years, the resolution of sinuses and/or clinically evident or mediastinal abscesses was equal in both ambulatory and surgical series.

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## PLEURAL BIOPSY AND ADENOSINE DEAMINASE IN PLEURAL FLUID FOR THE DIAGNOSIS OF TUBERCULAR PLEURAL EFFUSION\*

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**Summary** The study of pleural biopsy and ADA in pleural fluid for the diagnosis of TB was carried out at Govt. Medical College, Nagpur in 125 cases of pleural effusion from March 91 to June 92 to find out diagnostic efficacy of both methods\* and make a comparison.

Pleural biopsy was done in 105 cases and reported positive in 69 (65.7%) cases. Definite diagnosis of TB was obtained in 36 (45.56%) and "suspected TB" in 17 (21.51%) cases.

ADA levels in pleural fluid were significantly raised in clinically diagnosed as well as in biopsy confirmed cases of tubercular pleural effusion. Also serum ADA levels were significantly raised. No significant difference was found between ratio of pleural fluid and serum ADA.

Best cut off point of pleural fluid ADA level for the diagnosis of tubercular pleural effusion was found to be 60 U/lit, with 60.32% specificity, 80.55% sensitivity, 52.73% positive predictive value, 80% negative predictive value, the finding was confirmed on ROC curve.

As compared to biopsy, ADA estimation is a simple, cheap, non-invasive biochemical test for diagnosis of tubercular pleural effusion.

deaminase and various markers have been studied by various authors. ADA in pleural fluid has been found to be significantly raised in tubercular pleural effusion.<sup>4,12</sup>

With this idea we compared ADA levels in various etiologies of effusions with pleural biopsy to find out diagnostic efficacy of ADA in pleural fluid and pleural biopsy for the diagnosis of tubercular pleural effusion and comparison of both methods.

### Material and Methods

The study was carried out in Govt. Medical College, Nagpur during March 91 - June 92 in adult patients of both sexes, in the age group of 13 and above, admitted as cases of pleural effusion.

Following investigations were done: X-ray chest, Mantoux test, sputum examination, diagnostic thoracentesis, pleural fluid cytology, biochemistry and bacteriological examination by Z-N stain, AFB culture, pleural biopsy and pleural fluid and serum ADA. Pleural biopsy was done by Abram's needle. ADA estimation in pleural fluid and serum was done by the method described by Giusti, G.<sup>13</sup>

To detect a difference between observed values of pleural fluid ADA levels and serum ADA levels in different type of pleural effusions as compared to tubercular pleural effusion, Mann-Whitney's test was applied. ROC curve was plotted to confirm the best cut off point of pleural fluid ADA for the diagnosis of tubercular pleural effusion.

### Results

Out of 125 cases studied, 85 were male and 40 female. According to the clinic diagnosis, there were 83 cases of tuberculous pleural effusion of

### Introduction

The diagnosis of pulmonary tuberculosis is confirmed mainly by sputum examination for acid fast bacilli. Problem is more difficult in the diagnosis of extrapulmonary tuberculosis. For etiological confirmation, of pleural diseases, various investigations like pleural aspiration, fluid biochemistry, cytology and culture, Mantoux test, pleural biopsy<sup>1,2,3</sup> and histopathology, adenosine

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**Table 1.** 725 cases of pleural effusion according to etiology by clinical exam. & routine investigations

Etiology	No. of cases	%
A. Exudative (total)	108	86.4
1. Tuberculous	83	66.4
2. Malignant	19	15.2
3. Parapneumonic	6	4.8
B. Transudative	17	13.6
1. Non Specific	3	2.4
2. Anemia/ Hypoproteinemia	7	5.6
3. CCF	6	4.8
4. Liver cirrhosis	1	0.8

which 63 were male and 20 female. Age of patients ranged between 13 years and 70 years, with a mean of  $33.74 \pm 14.40$  years. There were 19 cases of malignant pleural effusion of which 6 were males and 13 females and mean age was  $43.42 \pm 16.69$  years.

According to etiological distribution of 125 cases by clinical examination, routine investigations and pleural fluid biochemistry, there were 108 (86.4%) cases of exudative pleural effusion, out of which 83 (76.85%) were tubercular, 19 (17.60%) malignant, 6 (5.55%) parapneumonic and 17 (13.6%) cases of transudative pleural effusion. (Table 1).

Pleural biopsy was done in 105 patients (Table 2). Out of 79 patients of tubercular pleural

**Table 2.** Results of pleural biopsy

Etiology	Biopsy done	Positive cases	%
* Definite	/9	36	45.56
* Suspected		<u>17</u>	<u>21.51</u>
		53	67.07
2. Malignancy	16	6	37.5
3. Parapneumonic	6	6	100
4. Others	4	4	100
Total	105	69	65.7

effusion, 36 (45.56%) were diagnosed as definitely tubercular and 17 (21.51%) were diagnosed as suspected tubercular by pleural biopsy. Total 53 (67.07%) cases were diagnosed as tubercular pleural effusion by biopsy. Out of 16 cases of malignant pleural effusion, 6 (37.5%) were diagnosed by pleural biopsy. Out of 105 patients biopsy was diagnostic in 69 (65.7%) cases.

Among cases of tubercular pleural effusion, there were 83 cases which showed greatly elevated ADA levels in pleural fluid ranging from 30 U/Lit to 300 U/Lit, with a mean value of  $77.20 \pm 32.63$  U/Lit at 37°C. In all cases responding to anti-TB drugs ADA levels were significantly raised compared to other cases of pleural effusions ( $P < 0.0001$ ). In malignant effusion, all cases except one showed pleural fluid ADA value from 20 U to 40 U/Lit with mean of  $26.84 \pm 6.92$

**Table 3.** Pleural fluid ADA levels in 125 cases

Etiology	Total	0-20	21-40	41-60	61-80	>80	Mean $\pm$ SD
1 Tubercular	83	0	3	25	27	28	77.20 $\pm$ 32.63
2 Malignant	19	4	14	1	0	0	26.84 $\pm$ 6.94
3 Parapneumonic	6	0	6	0	0	0	29.16 $\pm$ 2.04
4 N.S.	3	2	1	0	0	0	20.00 $\pm$ 5.00
5 Anemia/hypopr	7	6	1	0	0	0	17.42 $\pm$ 4.42
6 CCF	6	4	2	0	0	0	20.00 $\pm$ 4.47
7 Liver cirrhosis	1	1	0	0	0	0	10.00
Total	125	17	27	26	27	28	

**Table 4.** Pleural fluid ADA levels in B positive cases

Etiology	Total	0-20	21-40	41-60	61-80	>80	Mean $\pm$ SD
1. Tuberculous	36	0	0	7	14	15	81.04 $\pm$ 19.78
2. Malignant	10	2	7	1	0	0	28.50 $\pm$ 8.83
3. Parapneumonic	6	0	6	0	0	0	26.84 $\pm$ 6.92
4. Transudates	4	2	2	0	0	0	20.00 $\pm$ 5.77

**Table 5.** Serum ADA level in 125 cases

Etiology	Total	0-20	21-40	41-60	60-80	>80	Mean $\pm$ SD
1. Tuberculous	83	5	55	26	1	0	32.72 $\pm$ 11.5
2. Malignant	19	15	4	0	0	0	15.00 $\pm$ 5.50
3. Parapneumonic	6	6	0	0	0	0	13.33 $\pm$ 2.58
4. N.S.	3	3	0	0	0	0	10.83 $\pm$ 1.44
5. Anemia/hypor	7	7	0	0	0	0	11.43 $\pm$ 2.43
5. CCF	6	6	0	0	0	0	10.83 $\pm$ 2.04
7. Liver cirrhos	1	1	0	0	0	0	10.00
Total	125	43	59	26	1	0	

**Table 6.** Serum ADA levels in B positive cases.

Etiology	Total	0-20	21-40	41-60	61-80	>80	Mean $\pm$ SD
1. Tuberculous	36	0	23	13	0	0	31.5 $\pm$ 15.41
2. Malignant	10	7	3	0	0	0	15.50 $\pm$ 6.75
3. Parapneumonic	6	6	0	0	0	0	13.33 $\pm$ 2.58
4. Transudates	4	4	0	0	0	0	10.60 $\pm$ 1.25

**Table 7.** Statistical analysis of pleural fluid ADA levels

Si. No.	F.ADA levels	Sensitivity %	Specificity %	Positive Pred. value %	Negative Pred. value %
1.	>40U	100.00	34.78	44.44	100.00
2.	>50U	83.33	59.42	51.73	87.24
3.	>60U	80.55	62.32	52.73	80.00
4.	>70U	75.00	65.22	52.94	83.33
5.	>80U	41.66	81.16	53.57	72.72
6.	>90U	41.66	81.16	53.57	72.72
7.	>100U	2.77	98.55	50.00	66.02

( $P < 0.0001$ ). Only one case of malignant adenocarcinoma had pleural fluid ADA 50 U/Lit. All 6 cases of parapneumonic effusions had value of pleural fluid ADA between 25-30 U/Lit with a mean value of  $29.16 \pm 2.04$  U/Lit. All 17 cases of transudative pleural effusion showed values of pleural fluid ADA ranging from 12-25 U/Lit with a mean value of  $18.47 \pm 4.96$  U/Lit (Table 3). Similar results were obtained in biopsy confirmed cases (Table 4).

In majority of the cases of tubercular pleural effusion serum ADA was  $> 20$  U/Lit while in all others except 4 cases with malignant effusion it was  $< 20$  U/Lit (Table 5). Similar results were obtained in biopsy confirmed cases (Table 6).

The ratio of pleural fluid ADA/serum ADA in 83 cases of tubercular pleural effusion ranged between 1.1 and  $> 4$  with a mean of  $2.49 \pm 1.12$ . In cases of malignant pleural effusion it was between 1.1 and 3 with mean of  $1.89 \pm 0.42$ , in parapneumonic 1.1-3 with mean of  $2.26 \pm 0.58$ , in transudates 1.1-3 with mean of  $1.69 \pm 0.44$ . Difference of F/S ratio was not significant, hence it is not helpful for the diagnosis of tubercular pleural effusion.

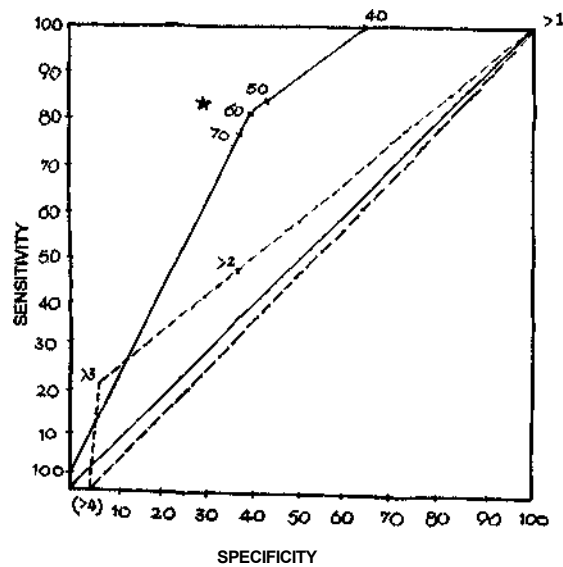
The values of pleural fluid ADA levels in tuberculosis were significantly raised when compared with malignant pleural effusion ( $P < 0.0001$ ), parapneumonic effusion ( $P < 0.0001$ ), transudative effusion ( $P < 0.0001$ ).

Similarly, the serum ADA values were raised significantly in TB pleural effusion as compared to other types of pleural effusion. ( $P < 0.0001$ ).

The sensitivity, specificity, positive and negative predictive value of pleural fluid ADA level at various cut off points ranging from  $> 40$  U/Lit to  $> 100$  U/Lit were calculated. At  $> 60$  U/Lit, the sensitivity and specificity of the test was 80.55% and 62.32%, with a positive predictive value 52.73% and negative predictive value 80%. This was the best cut off point and confirmed by plotting ROC curve. (Figure 1).

## Discussion

Pleural biopsy was done by Abram's needle in 79 out of 83 cases of TB pleural effusion and 36 (45.66%) showed definite evidence of caseating tubercular granuloma. In 17 (21.5%) cases mostly epithelioid cells, group of lymphocytes, fibroblasts without definite evidence, caseous granuloma was



Dark curve - Sensitivity vs. specificity of pleural fluid ADA  
Dotted curve - Sensitivity vs. specificity of F/S ADA ratio  
\* indicates best cut off point

Fig. 1. ROC Curve

reported as suspected TB and responded to anti TB drugs.

Diagnostic accuracy of pleural biopsy reported by various authors by various methods is as follows:

Douglass<sup>1</sup> (1956) diagnosed TB in 5 out of 19 patients (26.3%) by open pleural biopsy, Breckler (1958) reported diagnostic accuracy of 59.39%, 42.22% Donohoe<sup>1</sup>, 68%.

Paul Mestitz (1959)<sup>3</sup> reported a diagnostic accuracy of pleural biopsy and aspiration by Abram's needle of 80% in tubercular pleural effusion, but biopsy procedure was repeated, which may be the reason for higher diagnostic efficacy compared to our study.

The mean pleural fluid ADA in case of TB pleural effusion in present study is  $77.20 \pm 30.63$  U/Lit, which is significantly higher as compared to other types of pleural effusions. All cases of TB pleural effusion had pleural fluid ADA value above 40 U/Lit. The pleural fluid ADA values reported by various authors are Piras *et al*<sup>4</sup> (1978)  $83.04 \pm 25.51$  U/Lit, Blake and Berman\* (1982)  $46 \pm 13$  U/Lit, O'cana<sup>6</sup> *et al* (1983)  $92.43 \pm 29.43$  U/Lit, Patterson<sup>7</sup> *et al* (1984)  $32.0 \pm 3.3$  U/Lit,

Niwa K.<sup>8</sup> *et al* (1985)  $49.4 \pm 19.0$  U/Lit.

The pleural fluid ADA values reported by Indian authors are Sinha *et al*<sup>9</sup> (1985)  $76.8 \pm 23.8$  U/Lit, Baldev Raj<sup>10</sup> (1985)  $99.56 \pm 9.78$  U/Lit, Chopra R.K.  $114.2 \pm 7.22$  U/Lit and Gilhotra R.<sup>11</sup> (1989)  $82.9 \pm 30.32$  U/Lit, Saoji<sup>14</sup> (1987)  $73.6 \pm 28.1$  U/Lit respectively.

The value of serum ADA in cases with TB pleural effusion was  $32.72 \pm 17.5$  U/Lit,  $15 \pm 5.5$  U/L in malignant cases,  $13.33 \pm 2.58$  U/L in parapneumonic and  $11.02 \pm 7.92$  U/L in transudates. The serum ADA levels were significantly raised in tubercular pleural effusion ( $P < 0.0001$ ). The serum ADA values are not very reliable for the diagnosis of TB pleural effusion as these can be high in cases of typhoid fever, rheumatoid arthritis, lymphoma etc. as reported by Muller Bissenhertz and Keller, Patterson T. *et al*<sup>7</sup>

The sensitivity, specificity, positive and negative predictive value of pleural fluid ADA at various cut off points starting from 40 U/Lit to 100 U/Lit shows that the best cut off point is 60 U/Lit, where sensitivity is 80.55%, specificity is 62.32%, positive predictive value 52.73%, negative predictive value 80%, which is also confirmed by plotting ROC curves.

O'cana<sup>6</sup> reported a specificity of 0.97%, sensitivity of 1 at cut off point of 45 U/Lit and Chopra 86% and 90%.

Thus, simple, cheaper, and quicker biochemical test of ADA estimation in pleural fluid can diagnose and differentiate tubercular pleural effusion from other etiologies of pleural effusions compared to pleural biopsy.

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## ACCURACY AND SAFETY OF UNGUIDED TRANSTHORACIC FINE NEEDLE ASPIRATION BIOPSY IN THE DIAGNOSIS OF INTRATHORACIC LESIONS\*

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**Summary ; The accuracy and safety of unguided percutaneous fine needle aspiration biopsy in the diagnosis of intrathoracic lesions was studied in 58 patients. The diagnostic yield with fine needle aspiration cytology was obtained in 49 out of 59 patients (84.48%). Out of the 49 patients, 38 (77.55%) had malignant and 11 (22.45%) had non-malignant lesions. Squamous cell carcinoma was the commonest malignant lesion and tuberculosis as well as pneumonia were the common non-malignant lesions. Minor complications of the procedure were observed in 17.24% and managed conservatively. Thus, unguided transthoracic fine needle aspiration biopsy was found to be accurate, safe, quick and economical if used as an effective outpatient procedure in properly selected patients in developing countries.**

the 1960's when Nordenstrom<sup>3</sup> revitalised the aspiration technique using a thin needle (18 or 20 gauge) with low incidence of complications and increased diagnostic yield with the added use of biplane fluoroscopy, image intensification,<sup>4,7</sup> ultrasonography,<sup>8,9</sup> computerised tomography<sup>10</sup> (CT) and refined cytologic technique.

However, radiation hazard with fluoroscopy and CT, localization problem with ultrasound and the prohibitive cost of CT undermine their utility. Unguided FNAC based on clinical and chest X-ray finding present a potentially promising method for the diagnosis of intrathoracic lesions.<sup>11-13</sup> The aim of the present study is to determine the accuracy and safety of unguided percutaneous transthoracic FNAC in the diagnosis of intrathoracic lesions.

### Material and Methods

The study was carried out on 58 hospitalized patients found to have demonstrable radiographic intrathoracic lesion where conventional investigation of sputum, blood, fiberoptic bronchoscopy etc. were inconclusive. Patients with poor general condition, pulmonary hypertension, suspected vascular lesion, a bleeding disorder, severe emphysema and bullous changes within the region of lung to be biopsied were excluded. There were 48 men and 10 women with ages ranging from 18 to 83 years. Forty three patients were of more than 40 years of age.

An informed consent was obtained and bleeding as well as clotting time were estimated

### Introduction

Various diagnostic techniques have been employed to obtain tissue for the diagnosis of intrathoracic lesions. Central lesions are diagnosed with the help of fiberoptic bronchoscope.<sup>1</sup> For peripheral lesions, thick needle biopsy was first undertaken by Leyden (1883) when he aspirated organisms causing pneumonia, and Menetrier (1886) was the first to diagnose a lung cancer by needle biopsy. Since then, several series have been reported but the procedure did not gain popularity because of the fear of serious complications.<sup>2</sup> Interest in transthoracic needle aspiration was rekindled in

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**Table 1.** Diagnostic accuracy of FNAC

Nature of lesion	No. of cases	Positive results	%
Malignant	44	38	86.36
Non-malignant	14	11	78.57
Total	58	49	84.48

for each patient prior to undertaking aspiration. The only premedication given was 0.6 mg of Atropine intramuscularly thirty minutes before the procedure. In apprehensive patients, 10 mg Diazepam was given orally thirty minutes before the procedure. All the FNACs were performed in the Department of Tuberculosis and Chest Diseases in K.G. Medical College, Lucknow. The point and depth for putting in the needle were decided according to clinical examination and postero-anterior and lateral chest roentgenograms. After preparation of the site, 5-10 ml of 2% xylocaine was infiltrated into the skin, subcutaneous tissue, muscle plane, upto the parietal pleura. Needle aspiration was done in sitting position during shallow respiration with 23 gauge (0.65 mm) eight cm long lumbar puncture needle. The needle was inserted perpendicularly into the lesion close to the upper border of the rib to avoid damage to neurovascular bundle. Following the insertion of the needle's point into the lesion, a disposable 20 ml syringe was attached to it. After retraction of the piston, the needle was moved to and fro and in various directions within the lesion. Then the piston was released and needle was withdrawn.<sup>14</sup> The aspirated material was put on glass slides, smears were made and wet smears fixed immediately in 95% alcohol for 30-40 minutes. The aspirated material was also inoculated on to culture tubes. In the event of inadequacy of the aspirate, the aspiration procedure was repeated upto a maximum of three times from different parts of lesion until apparently adequate material had been obtained. After the procedure, each patient was re-examined and X-rayed to rule out pneumothorax and kept under observation for about 24 hours. The aspirate was examined for AFB and other organisms by staining, culture and sensitivity, and cytological examination.

**Table 2.** Tumour typing by FNAC

Cell type	No. of cases	%
Squamous cell carcinoma	15	39.47
Small cell carcinoma	11	28.95
Adenocarcinoma	4	10.53
Metastatic deposit	3	7.89
Lymphoma	1	2.63
Malignant cells	4	10.53
Total	38	100.00

### Results

Of the 58 patients, unguided fine needle aspiration cytology provided specific diagnosis in 49 i.e. a diagnostic yield of 84.48%. There was no false positive result. Of the 49 patients diagnosed by FNAC, 38 (77.5%) had malignant lung lesion and 11 (22.45%) had non-malignant lesion (Table 1). Of the 38 malignant lung lesions diagnosed by FNAC, squamous cell carcinoma was the commonest (39.47%) followed by small cell carcinoma (28.95%) and adenocarcinoma (10.53%) and in 7.89%, metastatic carcinoma was diagnosed. In 10.53% patients, positive for malignant cells, tumor typing was not possible (Table 2). Of the 11 non-malignant lung lesions, tuberculosis and pneumonia were diagnosed in 4 patients each, followed by lung abscess in three patients (Table 3).

Table 4 gives the proportion (17.24%) and nature of complications. Three patients each developed small pneumothorax and haemoptysis which were managed conservatively. One highly uncooperative patient developed hemothorax, 2

**Table 3.** Non-malignant lesions by FNAC

Diagnosis	No. of cases	%
Tuberculosis	4	36.36
Pneumonia	4	36.36
Lung Abscess	3	27.28
Total	11	100.00

developed subcutaneous emphysema around the site of the needle and 1 had syncope during the procedure, but regained consciousness immediately and the procedure was completed at the same sitting. There was no death.

**Discussion**

This study of unguided percutaneous transthoracic fine needle aspiration biopsy (FNAB) has demonstrated that the technique is useful in diagnosing a variety of intrathoracic lesions, including malignant and non-malignant lung diseases. Traditionally, FNAB is performed under biplane fluoroscopic guidance. In recent years ultrasound and CT guidance have been utilized for FNAB. The present study was designed to evaluate the usefulness of unguided FNAB which, apparently a step backward, merits consideration because of high cost and significant radiation hazard of CT and biplane fluoroscopy, and problem of localization with ultrasound due to the presence of bony cage and the aerated lung. In the present study, diagnostic yield of unguided FNAC was 84.48%, comparable with most published reports of FNAB done with guidance, where the yield ranged from 80 to 97%<sup>4-10</sup> The diagnostic yield of unguided FNAC in previous studies was between 58 and 72%,<sup>11-13</sup> lower than our results. The high success rate achieved in our study may be due to the selection of cases as most cases had lesions of more than 2 cm diameter, while other studies included smaller lesions. Repeated needle aspiration from different parts of lesion could also have contributed to better results.

In our study, no conclusion was reached in 9 cases out of 48 (15.52%), with no false positive result. Of the 9 patients, 6 were later diagnosed as primary lung cancer and 3 as non-malignant (tuberculosis - two, lung abscess - one). The principal reason for failure to diagnose was inadequacy of the aspirate due to small size (diameter < 2 cm) and depth of the lesion. Thus, while a positive result by fine needle aspiration cytology is of immense value, a negative result does not exclude the presence of disease.

Complications were observed in 17.24% of patients, similar to reports of other series including studies of unguided needle aspirations.<sup>11-13</sup> In fact Sharma et al<sup>12</sup> observed no complications. Pneumothorax occurred in 5.18% of patients and did not require intercostal drainage. Hemoptysis occurred in 5.18% patients, none of whom required treatment. One patient had haemothorax (1.72%) which was aspirated and cleared off completely within a week.

Thus, unguided transthoracic fine needle aspiration cytology is a safe, accurate, quick and economical procedure for the diagnosis of intrathoracic lesions not less than two cm in diameter beyond the reach of usual diagnostic procedures and can be used as an effective outpatient procedure in developing countries in properly selected patients.

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**Table 4. Complications of FNAC**

Complication	No. of cases	%
Pneumothorax	3	5.18
Haemoptysis	3	5.18
Haemothorax	1	1.72
Subcutaneous emphysema	2	3.44
Syncope	1	1.72
None	48	82.76
Total case with complications	10	17.24

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**MILIARY TUBERCULOSIS PRESENTING AS MYOCARDITIS**M.P. Agarwal<sup>1</sup> and R. Avasthi<sup>1</sup>

(Received on 28.6.93; Accepted on 24.10.93)

*Summary:* A case of miliary tuberculosis presenting with features of myocarditis is being reported on account of its **rarity**

**Introduction**

Tuberculosis is a fairly common cause of pericardial disease in our country but myocardial involvement, though known, is often not diagnosed during life. Definitive diagnosis can be established only by tissue studies or on autopsy. We report here a patient with miliary tuberculosis who presented with features of fever, congestive heart failure, electro- and echocardiographic abnormalities and made an excellent recovery on antituberculosis chemotherapy.

**Case Report**

A twenty four years old lady was admitted with fever of forty days' duration. The fever was irregular, associated with chills, generalised body ache, malaise and anorexia. She also complained of grade II dyspnoea and palpitations off and on. There was no history of cough, hemoptysis, sore throat, joint pains, skin rash, abdominal pain or rheumatic heart disease.

Examination revealed average build and nutrition, pallor, pulse 140/minute with occasional premature beat, B.P. 100/70 mm and JVP 4 cm above the sternal angle. There was no significant lymphadenopathy, clubbing or pedal oedema. Cardiovascular examination showed tachycardia, occasional extrasystole and a left ventricular S<sub>3</sub>. There was no murmur or pericardial rub but bilateral basal crepitations were present. Liver was enlarged 3 cm below right costal margin and spleen tip was palpable. Pelvic examination, nervous system examination

and fundoscopy were normal.

Investigations showed Hb 12.1 g/dl, TLC 10,000/mm<sup>3</sup>, DLC P<sub>66</sub>L<sub>33</sub>M<sub>1</sub>, ESR 72 mm in 1st hour (Westergren) and peripheral smear was negative for malarial parasites. Blood and urine cultures were sterile. Liver and kidney function tests and prothrombin time were all within normal limits. Rheumatoid factor, LE cell, antinuclear antibodies, ASO, C-reactive protein and Widal test were all negative as were blood viral antibody studies. Chest X-ray was normal while ECG showed sinus tachycardia with occasional supraventricular ectopic and non-specific ST-T wave changes. Abdominal ultrasonography showed moderate hepatosplenomegaly but no space-occupying lesion or lymphadenopathy. Liver biopsy and bone marrow examination did not reveal granulomata or AFB. Echocardiography revealed diffuse hypokinesia of left ventricle (LV), especially the posterior wall, with poor systolic thickening and resting LV dysfunction. LV dimensions were in systole 4.8 cm (normal 1.9-3.2/m<sup>2</sup>) and in diastole 5.7 cm (normal 30-40% increase), LV ejection fraction was 40.3% (normal 64-84%) and LV fractional shortening 15.8% (normal 28-40%).

During hospitalization the patient's temperature showed a remittent pattern upto 104°F, and she developed a dry cough. A chest radiograph on the 12th day showed miliary mottling with right paratracheal lymphadenopathy. The patient was started on standard antituberculosis therapy (EHRZ, changed later to EHS/EH) and became afebrile after three weeks of treatment when she was discharged. Her congestive heart failure subsided and ECG and echocardiogram became normal. The patient stopped antituberculosis treatment after five months. Three months later she presented with right cervical lymphadenopathy.

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A lymph node aspiration cytology revealed necrotic material with acid-fast bacilli. Lymphadenopathy subsequently also subsided completely with antituberculosis therapy.

### Discussion

Tuberculous myocarditis is rare and occurs as a complication of tuberculosis elsewhere. The myocardium is affected by direct extension or, less often, by retrograde lymphatic drainage from tuberculous mediastinal nodes. Infection via the hematogenous route may develop in miliary disease. Direct spread from tuberculous pericarditis can also occur.<sup>1</sup>

Horn and Saphir<sup>2</sup> have described three histological types of myocardial tuberculosis : (1) nodular tubercles (tuberculomas)? of the myocardium, varying from pea to egg size, with central caseation, (2) miliary tubercles of the myocardium complicating generalised miliary disease and (3) the uncommon diffuse infiltrative type usually associated with tuberculous pericarditis in which the myocardium is diffusely infiltrated by granulation tissue containing giant cells, endothelial cells and lymphocytes.

Myocardial tuberculosis is rarely diagnosed during life and most of the literature is based on autopsy reports. A clinical picture of disseminated miliary tuberculosis is usually evident and cardiovascular symptoms, when present, are mainly in the form of rhythm disturbances such as supraventricular

arrhythmia, ventricular tachycardia or atrioventricular block.<sup>3-5</sup> Sudden death has been reported and has been attributed to a fatal ventricular arrhythmia or a conduction defect.<sup>1</sup>

It has been suggested that myocardial involvement should be suspected in a patient with tuberculosis if CHF supervenes<sup>6</sup> or valve dysfunction develops.<sup>7</sup>

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## ENTERO-VESICAL FISTULA WITH TUBERCULOUS CYSTITIS - A CASE REPORT

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**Summary:** A case of entero-vesical fistula is described in which a loop of ileum was communicating with urinary bladder. The patient was known to have pulmonary tuberculosis. However, she presented with acute renal failure. Emergency ultrasonography revealed bilateral hydronephrosis. IVU with delayed films outlined the full length of colon. Cystoscopy confirmed the presence of a fistula. At surgery, an ilcovesical fistula was found. She had an uneventful recovery after surgical correction. Histopathology confirmed the diagnosis of tuberculosis of urinary bladder.

### Case Report

A 50 years old female was referred from a district hospital with acute renal failure. She gave a history of therapy for pulmonary tuberculosis for the preceding 6 months, recurrent urinary problems and pain in lower abdomen recently. Physical examination revealed suprapubic tenderness. Her haemogram showed Hb 7.5/dL, WBC  $8.0 \times 10^9/L$  and ESR 68 mm. Liver functions were within normal limits; urea level was 70 mg/dL, creatinine 4.1 mg/dL, serum Na<sup>+</sup> 138 mEq/L and serum K<sup>+</sup> 4.9 mEq/L. There was severe urosepsis with E. coli. Emergency ultrasonography (3.5 MHz) revealed bilateral hydronephrosis with usual changes, more on the right side. She recovered from acute renal failure on conservative management. Subsequently, IVU demonstrated right sided hydronephrosis, and hydroureter upto the vesico-ureteric junction on the right side. The left kidney was non-excreting. Urinary bladder was very small with a faint opacity behind it. The 24 hours film showed the whole length of the colon (Fig. 1). A diagnosis of direct communication between urinary tract and gut was made. A day after IVU, she had a bout of haematuria and cystoscopy revealed a small capacity, angry looking bladder full of blood clots. While removing the clots with Elick's evacuator, there was a sudden release in tension suggesting a rupture of the bladder. An emergency laparotomy revealed ruptured dome of the bladder. The loops of ileum adherent to the peritoneal surface of urinary bladder were separated from the bladder and the portion of small gut which had a communication with the bladder was resected followed by an end to end

### Introduction

Entero-vesical fistulae are rare and account for 0.01% to 0.05% of all surgical admission.<sup>1</sup> To date, only 876 cases of such fistulae have been reported, of which only 1.9% were due to urological diseases.<sup>2</sup> Localised disease in urinary bladder such as cystitis, tuberculosis, or carcinoma may cause this condition.<sup>3,4,5</sup> Primary disease in urinary bladder with perivesical abscess formation or embedded stones, formerly responsible for approximately 10% of this disease,<sup>6</sup> has now become a clinical curiosity.

The usual presenting features are pneumaturia, faecaluria, and passage of bowel content through urethra. Most of the patients have a history of recurrent, intractable urinary tract infections.<sup>7</sup> Haematuria may also be a presenting feature in some cases.<sup>8</sup> Our case presented with acute renal failure due to entero-vesical fistula caused by urinary tract pathology.

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Fig. 1. IVU showing small urinary DMUUCI wnu faint opacity behind it and dilated lower right ureter



Fig. 2. 24 hours IVU film demonstrating whole length of colon

anastomosis. The bladder was then closed in two layers on an urethral catheter. The recovery was uneventful.

Formaline fixed paraffin embedded sections from the bladder showed features of chronic non-specific inflammation as granulation tissue formation, mononuclear cell infiltration and irregular fibrosis. There was no specific granuloma. However, Ziehl-Neelsen staining revealed acid fast bacilli. Meticulous examination of the resected bowel revealed no specific intestinal pathology.

### Discussion

Clinical diagnosis of entero-vesical fistula is made by the cardinal symptoms which were absent in our case. Investigations are aimed at confirming the clinical diagnosis and finding the underlying cause. The escape of the contrast medium, from the bowel to the bladder or vice-versa (as in our case), confirms the diagnosis. As bowel diseases are the usual aetiological causes barium examination of the gut from above or below helps in revealing the underlying disease. IVU is only done when upper urinary tract disease is suspected.<sup>9</sup> Ultrasonography confirmed the IVU findings in our case. Acute renal failure due to bilateral upper urinary tract pathology, with no clinical features of entero-vesical fistula was the unusual presentation of

our case. Cystoscopic findings of generalised inflammation and gross involvement in the region of the fistula were also present.

Chakrabony *et al*<sup>10</sup> could find acid fast bacilli in spite of the absence of classical histological evidence of tuberculosis. The history of tuberculosis in our case and the observation of above authors led us to search for acid fast bacilli in bladder and gut. The demonstration of acid-fast bacilli in the bladder tissue helped us to make a definite aetiological diagnosis. The patient made excellent recovery on anti-tuberculosis drugs.

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## REVERSIBLE CLUBBING IN A CASE OF KOCH'S SPINE

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(Received on 2.11.1993; Accepted on 11.1.1994)

*Summary* ; A case of Koch's spine associated with clubbing which reversed during the course of anti-tuberculosis treatment is discussed.

### Introduction

Since Hippocrates<sup>1</sup> first described clubbing in the 5th century B.C., digital clubbing has long been recognised as a physical sign associated with many diseases. Despite the various known cardiac, pulmonary, hepatic, gastrointestinal and other miscellaneous causes, little is known as to how the clubbing develops.

We report here a case of Koch's spine with clubbing which reversed during the course of antituberculosis treatment.

### Case Report

C.S., a 20 year old male student, was referred to us from Singrauli Colliery with the complaint of progressively increasing backache, loss of appetite and loss of weight for the preceding 4 years, and clubbing of all the digits for 1 year. He was a non-smoker and non alcoholic, Four years earlier, the patient had developed a swelling in the back, which ulcerated and discharged thin yellowish pus with flakes. The ulcer was dressed daily with hydrogen peroxide and chlorine water by a general practitioner, and it healed in 6 months. However, no anti-tuberculosis treatment was prescribed then. Despite the healing of the ulcer, the patient continued to have persistent backache, loss of appetite and loss of weight.

Clinical examination revealed evidence of advanced clubbing of all the digits i.e. increased



Fig. 1 Digital clubbing before starting anti-tuberculosis treatment

curvature of nails in both longitudinal and transverse axis (Fig. 1). There was an irregular hyperpigmented scar measuring 3 cm x 2 cm in the right infrascapular region in the paraspinal area. Spinal tenderness was present at T<sub>9</sub>-T<sub>10</sub> area. There was no obvious swelling and kyphoscoliosis. The examination of the respiratory system was within normal limits and there was no neurological deficit. The weight of the patient was 39 kg.

Investigations revealed; Hb : 9 gm%, TLC : 9600/cumm, DLC : P<sub>50</sub>L<sub>47</sub>M<sub>3</sub> and ESR : 27 mm in the first hour. Routine blood chemistry, i.e. B. urea, B. sugar, etc. was normal. X-ray chest — PA and lateral views showed no evidence of active pulmonary lesion. X-ray dorsolumbar spine, AP view (Fig. 2) and lateral view revealed a paravertebral large soft tissue shadow with peripheral calcification. There was erosion of left lateral margin of T<sub>9</sub>-T<sub>10</sub> vertebrae along with rib

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Fig. 2 X-ray dorsolumbar spine AP view showing a paravertebral large soft tissue shadow with peripheral calcification and erosion of left lateral margin of the border to T<sub>9</sub>-T<sub>10</sub> vertebrae with rib involvement: Twelfth ribs on both the sides absent

involvement. Osteoarthritic changes were seen between T<sub>9</sub>-T<sub>10</sub> on the right side. The intervertebral disc spaces were normal. The X-ray findings were, thus, suggestive of peripheral type of tuberculous involvement of spine and ribs at T<sub>9</sub>-T<sub>10</sub> with a paravertebral abscess. There was no evidence of hypertrophic osteoarthropathy, in X-ray forearm of the patient.

A needle aspiration was performed in the right infrascapular area in the paraspinal region at the level of T<sub>10</sub> vertebra, wherefrom a thick cheesy aspirate was obtained which on microscopy examination proved to be caseous material and showed the presence of acid fast bacilli, thereby establishing the diagnosis of Koch's spine.

The patient was prescribed Rifampicin 450 mg OD, INH 300 mg OD and Ethambutol 800 mg OD. After regular anti-tuberculosis treatment for 6 months, the patient was referred back to us for checkup. He had improved appetite and there was no backache. He had gained weight by 7 kg (weighing 46 kg) and there was no spinal tenderness. The patient himself reported that the



Fig. 3 No evidence of clubbing after anti-tuberculosis treatment for 6 months

“boggyness” of his fingers had disappeared and on clinical examination there was no evidence of clubbing (Fig. 3).

The repeat X-ray of dorsolumbar spine, after 6 months, showed regeneration of ribs at T<sub>9-10</sub>, but the paravertebral soft tissue shadow remained unchanged and no other change in status was observed. The patient was advised to continue the same anti-tuberculosis treatment for a few more months under regular follow-up.

### Discussion

The statement by West<sup>2</sup> in 1897 that “Clubbing is one of the phenomena which we are all so familiar with that we appear to know more about it than we really do”, still holds true, after nearly a century. Many workers have put forward various theories to explain the development of clubbing such as hypoxic, hormonal, shunt, neurogenic, trophic, circulatory, mechanical, etc., but the exact mechanism remains obscure, till date. Therefore, we are unable to offer any explanation for the development of clubbing in this case of Koch's spine and its reversal during the course of anti-tuberculosis treatment. Reversibility of clubbing has been reported earlier in a case of tuberculous empyema following its management with pneumonectomy and subsequent thoracoplasty on the affected side.<sup>3</sup> Similarly, reversal of pulmonary hypertrophic osteoarthropathy following

pneumonectomy<sup>4</sup> and vagotomy<sup>2,5</sup> in cases of bronchogenic carcinoma has also been reported. To the best of our knowledge, this is the first report of a case of Koch's spine associated with clubbing which reversed during the course of antituberculosis treatment.

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**SUMMARIES OF PAPERS PRESENTED AT THE 48TH NATIONAL  
CONFERENCE ON TUBERCULOSIS AND CHEST DISEASES,  
BHOPAL : 9TH TO 12TH DECEMBER, 1993**

**TREATMENT OF SINGLE AND MULTIDRUG RESISTANT PULMONARY TUBERCULOSIS:  
EXPERIENCE IN ARMED FORCES**

**R.S. Pahwa, B.N. Panda, J. Jena, K.E. Rajan and S.P. Rai**

The paper reports on the results of treatment of initially drug resistant patients among 594 bacteriologically proved cases of pulmonary tuberculosis in the Armed Forces. The number includes 571 freshly diagnosed cases and 23 who had relapsed after earlier short course treatment. Of the 594 cases, 45 were resistant to a single drug (S-27, H-6, R-6, Z-4, ETN-2), 20 to two drugs (SH-7, SR-7, RH-2, SZ-2, RZ-1, ER-1) and 10 to more than two drugs. All cases of single

drug resistance could be managed successfully with routine short course chemotherapy (SCC) given for an extended period. Patients with double and multi-drug resistance required the use of reserve drugs in addition, with nearly 20% success. All the 7 cases of drug resistance among the 23 relapse cases responded well to the SCC administered. The only 4 deaths recorded were among the multi-drug resistant cases who were irregular in their treatment.

**SHORT COURSE CHEMOTHERAPY IN TUBERCULAR LYMPHADENITIS**

**V.K. Arora, Amit Johri and K. Gowrinath**

The purpose of the study was to assess the value of short course chemotherapy in patients of tuberculous lymphadenitis in paediatric and adult groups put on domiciliary treatment.

Two hundred subjects (176 adults and 24 children aged below 12 years) diagnosed by histopathological/FNAC examination were put on 2EHRZ/4HR regimen on domiciliary basis. Sixty-two percent compliance was noted and out of those patients who completed six months of chemotherapy, 91% showed favourable response. Eleven patients who continued to show increase

in the size of the lymph gland after six months of chemotherapy were subjected to excision biopsy and the lymph gland was sent for histopathological examination and culture for tubercle bacillus and for fungus. Of these, 3 who showed reactive hyper-plasia responded to longer therapy while 1 each had filariasis and lymphoma.

Eighty percent cases had regression of lymphnodes. In 4 there was a relapse between 6 months and 2 years and FNAC showed active disease. Toxicity was met with in 4 cases.

**EFFCACY OF SHORT COURSE CHEMOTHERAPY USING RIFAMPICIN, ISONIAZID AND  
PYRAZINAMIDE FOR TWO MONTHS FOLLOWED BY ISONIAZID AND  
THIACETAZONE FOR SIX MONTHS**

**R.P. Singh, S.K. Katiyar, Sudhir Chaudhri and Santosh Singh**

A total of 70 sputum smear positive cases of pulmonary tuberculosis were taken up for study. Chest X-ray was done in all cases at the time of inclusion in the study. Sputum smear examination for AFB was done at 0,3, 8,9 and 12

months. Drugs, 15 days at a time, were supplied free from the hospital for self administration. A patient who did not collect his/her drugs for one month continuously, was labelled as a lost case. Out of the 70, 3 cases died during first month

after starting chemotherapy; in 5 cases chemotherapy was stopped within first month due to development of jaundice. There remained only 62 cases for analysis. Out of these remaining 62 cases, only 49 (79%) completed the intensive

phase of treatment and just 13 (21%) the full chemotherapy. At 2 months, all the 49 cases had become sputum negative, at 8 months 12 out of 13 cases were negative and one case had a relapse in the ninth month.

### SHORT COURSE CHEMOTHERAPY FOR TUBERCULOUS LYMPHADENITIS

**K.B. Gupta, Kamal Arora, Baldev Raj and T.S. Jaiswal**

Fifty cases of histopathologically proved untreated cases of peripheral tuberculous lymphadenitis were treated with either of two short course chemotherapy regimens, one of 3 months' duration (3 SHRZ) and the other of 5

Months' duration (3 SHRZ/2S<sub>2</sub>H<sub>2</sub>Z<sub>2</sub>). Though both the regimens were found to be effective, the 5 month regimen was superior (cure rate 92%) as compared to the 3 month regimen (cure rate 74%).

### PULMONARY HYDATID AS SEEN IN RURAL AND TRIBAL POPULATION OF GUJARAT

**A.L. Anand**

One hundred and fifty cases of pulmonary hydatid (74 found during tuberculosis surveys and 76 reporting symptomatically at out-patient service) are described. No case of liver hydatid was reported. The one case involving the chest wall was a recurrence following a previous lung operation. Most of the cases were from the rural

population. The distribution between sexes was almost equal and most cases found were between 30 and 40 years of age. In only 8 cases were the cysts multiple. In those with suppuration (8 cases), the picture was similar to that of lung abscess. In two cases, the cyst was mistaken for malignant disease and diagnosis could be established only after thoracotomy.

### MYCOLOGICAL PROFILE IN CHRONIC RESPIRATORY DISEASE

**G. Gopi Krishna, G. Radhika Chetana, K. Kotilingam and B. Raja Rao**

Sputa of 50 patients of pulmonary tuberculosis, 30 cases of chronic airway obstruction disease and 20 with suppurative lung disease were examined for fungi by direct microscopy and culture on Sabouraud's dextrose agar medium at 25°C. If growth was obtained, 2 more specimens were also cultured. Appropriate tests were performed on the cultures to identify the particular fungus grown.

Fungi were grown in 36 (72%) cases of tuberculosis, 12 (33.3%) cases of obstructive disease and in 9 (45%) suppurative cases. *Candida albicans* was the most frequent growth (41%) in tuberculosis cases with *Aspergillus* (28%), *Helminthosporium* (42%) and *Fusarium* (25%) in obstructive airway disease, and *Candida* (67%) in suppurative cases. *Aspergillus* was more frequently seen in cavitary (9/29) than in non-cavitary (2/21) tuberculosis.

**ACCURACY AND SAFETY OF UNGUTOED TRANSTHORACIC FINE NEEDLE ASPIRATION BIOPSY IN THE DIAGNOSIS OF INTRATHORACIC LESIONS**

**R. Prasad, R.A.S. Kushwaha, P.K. Mukherjee, J. Nath, P.K. Agarwal and G.N. Agarwal**

*(Paper is being published in full)*

**RURAL SAMPLE SURVEY - PREVALENCE OF TUBERCULOSIS IN MEDAK DISTRICT, ANDHRAPRADESH**

**B. Iswariah**

A survey was carried out in the rural areas of Medak District (A.P.) to detect cases of pulmonary tuberculosis. In a population of 48,217 aged 5 years or more, 1,460 were found to have chest symptoms; of these 936 could be examined bacteriologically by a single direct smear. Of

these 102 were found to be sputum positive. In addition, there were 61 known tuberculosis cases in the area who did not attend during the survey. The survey generated a lot of enthusiasm in the community and was instrumental in increasing TB awareness in the population.

**PREVALENCE OF TUBERCULOSIS IN BCG VACCINATED AND UNVACCINATED AND AMONG TUBERCULIN REACTORS AND NON-REACTORS IN RURAL POPULATION AS DETECTED BY A MOBILE CHEST CLINIC**

**S.K. Katiyar, R.P. Singh, S. Chaudhri, K.P. Singh, Chandra Shekhar and A.K. Srivastava**

The study was carried out to find out prevalence of pulmonary tuberculosis and its relation with tuberculin reactivity and BCG vaccination. It was conducted in village Purana Bithoor of Kanpur which had a population of 1250. It was found that 19.96% were tuberculin reactors (reaction 15 mm & above), prevalence of infection was lowest (7.17%) in 0-10 year age group and it gradually rose to maximum of 38.33% in 51-60 year age group. The prevalence of active and probably active disease was 2.30% and about 1/4 cases were sputum positive.

Prevalence of active and probably active disease was maximum (9.22%) in reaction size 15 mm and above. It was found that maximum proportion with active disease (18.37%) was among persons having > 30 mm reaction. Similarly proportion of bacillary cases also increased with increasing reaction.

Prevalence rates of pulmonary tuberculosis as well as of tubercular hilar adenopathy and tubercular cervical adenopathy were higher in non BCG vaccinated group as compared to vaccinated group.

**SEASONAL VARIATIONS IN RESPIRATORY DISEASES AND CLINICAL CONDITIONS**

**K.C. Mohanty, Sudhir Nair, Rekha Asawa and Ajay Deshpande**

This retrospective study of hospital admissions during the period June 1990 to May 1991 showed a seasonal trend in various respiratory conditions. It was seen that respiratory tract infections showed a peak in the winter months

with small peaks in summer. A similar trend was seen in cases of exacerbation of bronchial asthma and chronic obstructive pulmonary diseases. Tropical eosinophilia cases and cases of severe haemoptysis were seen more often during the summer months.

### CLINICO-RADIOLOGICAL PRESENTATION OF HIV POSITIVE CASES WITH SPECIAL REFERENCE TO TUBERCULOSIS

V.K. Arora and K. Gowrinath

Eight hundred and sixty-five patients were subjected to ELISA test for HIV, after taking informed consent. Because of resource constraints, from January 1990 to December 1992, the ELISA test was done in (i) patients with extra-pulmonary tuberculosis proved by FNAC and/or histopathological examination and (ii) sputum smear positive cases with extensive disease and (iii) patients with atypical lesions with or without HIV risk factors. From January 1993, all newly diagnosed cases of tuberculosis (proved/suspected) and all admitted cases in the chest ward of the department were so examined.

Forty-four consecutive patients with HIV positivity confirmed by Western Blot test (HIV Reference Centre, C.M.C., Vellore) comprised the study group. Thirty-one patients (30 males and 1 female) had history of heterosexual promiscuity and in 12 (3 males and 9 females) no HIV risk factor could be identified. One patient

had donated his kidney and received multiple blood transfusions.

Thirty-two patients had tuberculosis, 5 had non-tuberculous/respiratory conditions, 2 interstitial pneumonitis, one interstitial fibrosis associated with neurofibromatosis and one had acute upper respiratory tract infection, 4 were asymptomatic and 3 were undiagnosed. The patients with pulmonary and extra-pulmonary tuberculosis, except one in whom clinical drug resistance was suspected, showed improvement on short course chemotherapy (2EHRZ/4HR). However, four patients with disseminated tuberculosis, two with interstitial pneumonitis and one with tuberculous lymphadenitis, who fulfilled CDC's new AIDS criteria for defining AIDS, died within a month of diagnosis. One patient with suspected interstitial pneumonitis (radiologically with linear basal shadows) responded to cotrimoxazole.

### CHANGING TREND OF HIC INFECTION IN PATIENTS WITH RESPIRATORY DISEASES IN BOMBAY SINCE 1988

K.C. Mohanty, Sudhir Nair and Tushar Sahasrabudhe

*(Paper is being published in full)*

### THE VALUE OF MANTOUX TEST IN THE MANAGEMENT OF PATIENTS WITH TUBERCULOSIS AND HIV INFECTION

K.C. Mohanty, R.B. Pasi and T.R. Sahasrabudhe

A total of 4,054 patients have been screened for HIV infection since 1st November, 1988, with 205 being detected as HIV positive. One hundred and eighty-two out of these 205 patients were diagnosed as having active tuberculosis.

All the patients with HIV and TB were given a Mantoux test. Those who were positive with 1 TU RT 23 with Tween 80 were tested every month in

the course of their treatment. Twenty-three, out of 66 who were tested serially, became negative. All these patients died within 8 months, whereas 43, who remained positive did well on the treatment. The study, thus, suggests possible usefulness of tuberculin testing as a prognostic indicator in the management of pulmonary TB + HIV patients especially when CD4\* count is not available.

### **PATHOGENESIS OF TUBERCULOSIS : INTEGRATION OF AYURVEDA AND MODERN MEDICINE**

**M.S. Agnihotri and V.K. Agarwal**

The aetiological factors of tuberculosis are different according to modern medicine and Ayurveda. *M. Tuberculosis* is the causative organism according to modern medicine and socio-economic factors predispose towards the disease development. According to Ayurveda, tuberculosis is a multi-factorial disease affecting all the tissues of the body. The present study was undertaken to investigate the abnormalities produced in different body tissues.

Twenty five patients of pulmonary tuberculosis

and 10 healthy controls were examined. Impaired glucose tolerance and hypoproteinemia were observed in 8% of TB patients, 92% were anaemic, 56% had leucocytosis, 20% had eosinophilia. Muscle atrophy in arms and legs was marked compared to the controls and 70% had suffered considerable loss in weight. In the bone marrow normoplastic hyperplasia was seen in 32% and lymphocytosis in 12% and sperm count as well as motility were significantly less in TB patients compared to controls.

### **AN EVALUATION OF THE CLINICAL AND SOCIO-ECONOMIC DIMENSIONS IN HOSPITALISED PATIENTS OF PULMONARY TUBERCULOSIS IN A RAILWAY SECTOR**

**S.K. Gupta, Dheeraj Saxena and Rajesh Tekchandani**

Three hundred patients of pulmonary tuberculosis (225 males and 75 females) who remained hospitalised in a Railway Chest Clinic were included in the study. An attempt was made to study clinical profile, awareness, social attitudes towards disease, reasons for default,

medical and socio-economic reasons for seeking hospitalisation. Each patient was subjected to a detailed questionnaire. Analysis of the answers was correlated with socio-economic factors. General knowledge about tuberculosis was found to be poor among patients who were illiterate or had a low socio-economic status.

### **A PSYCHOLOGICAL STUDY OF PERSONALITY DIMENSIONS : DEATH ANXIETY AND VARIOUS COPING MECHANISMS AMONG TUBERCULOSIS PATIENTS**

**G.K. Agarwal**

A complex, structural study was undertaken on 20 patients of tuberculosis (mean age 27.0 years) and 20 patients of non-tubercular diseases (mean age 32.65 years) serving as controls, to determine

if personality dimensions etc. were different in tubercular individuals. Deterioration in various dimensions was noticed among tuberculosis patients, but was not statistically significant.

### **PHARMACOLOGICAL BASIS OF MODE OF DRUG ADMINISTRATION TO TUBERCULOSIS PATIENTS**

**R. Chatterjee, S. Dutta Choudhury and P. K. Sen**

*(Paper will be published in full in a subsequent issue)*

### COMPARATIVE STUDY OF CASE HOLDING AMONG DOMICILIARY VERSUS INITIALLY HOSPITALISED PATIENTS TAKING SHORT COURSE CHEMOTHERAPY

V.K. Maini, B.M. Kallan, A.S. Bhatia, B. Malhotra and A.P. Singh

Three hundred sputum positive cases of pulmonary tuberculosis divided into three groups of 100 patients each were included in the study. Patients in group I were initially hospitalized and provided free drugs. Group II patients were initially hospitalized and took own drugs while group III were domiciliary patients taking own

drugs. All patients were prescribed short course chemotherapy. Case holding in groups I, II and III was observed to be 89% 88% and 59% respectively. It is concluded that initial hospitalization for motivation and a regular free drug supply have a definite role in improving case holding.

### INFLUENCE OF INITIAL AND SUBSEQUENT MOTIVATION ON CASE HOLDING IN RURAL PUNJAB

Vitull K. Gupta and Vineeta Gupta

The influence of initial and subsequent motivation on case holding was studied among new tuberculosis patients attending the tuberculosis clinic at P.H.C. Goniana in Punjab. Group I (58 patients) was given only initial motivation and group II (54 patients) initial as well as subsequent motivation. Both SCC and Standard Regimen

cases were included in the two groups. Overall treatment completion was found to be better in Group II (85.1%) than in Group I (68.9%). In the SCC patients the rates were 71.8% (Group I) and 85.1% (Group II) and in the Standard Regimen patients the corresponding rates were 65.3% and 77.7% respectively.

### COMPLIANCE WITH THE SCC AND ANALYSIS OF DRUG DEFAULTERS

Anil Jain and A. Kavishawar

The paper is based on an analysis of 364 patients (276 male and 88 female) who were lost to treatment in Ujjain during the pilot study of short course chemotherapy carried out by the Tuberculosis Research Centre, Madras. Of these patients, 261 were on regimen I (6 months' SCC supervised) and 103 on regimen II (8 months' SCC unsupervised); 225 were lost during the first 2 months, 68 during the next two months and the remaining 71 during subsequent months. An attempt was made to contact all these patients and ascertain the reasons for their default. Sixty-six patient could not be contacted due to wrong/incomplete address, "address changed" and other similar reasons. Results are based on interviews with the remaining 298 patients. Causes of default were classified as:

(i) Patient related (178) including 37 who

- migrated, 53 who had social problems, 38 who had financial problems 32 for other reasons and 18 who had died since,
- (ii) Disease related (49) including 37 who gave up treatment after symptomatic improvement and 5 who were found to have been hospitalised;
  - (iii) Drug related (45) i.e. patients who left treatment due to emergence of drug toxicity;
  - (iv) Hospital related (10) i.e. patients who were not satisfied with the treatment or the behaviour of hospital staff; and
  - (v) Others (16) who could not give any cogent reason for dropout.

It was also found that 175 of the patients had restarted treatment after symptomatic deterioration, 142 in DTP and 33 with private doctors/clinics/hospitals etc.

**HORMONE PROFILE OF FEMALE CASES OF PULMONARY TUBERCULOSIS,****Mrs. S.N. Tripathy and S.N. Tripathy***(Paper will be published in full in a subsequent issue)***ABNORMALITIES OF LUNG FUNCTION IN QUIESCENT CASES OF PULMONARY TUBERCULOSIS AND ITS RELATION TO RADIOLOGICAL ABNORMALITIES****B.R. Maldhure, M.V. Dhakata, S.S. Kubde and V.B. Ghotkar**

One hundred and sixty quiescent cases of pulmonary tuberculosis were bacteriologically and radiologically assessed along with pulmonary function test. Lung function values remained significantly low even after complete radiological clearing of lesion. Lung function values showed inverse relation with extent of disease. Far advanced and moderately advanced lesions had significantly lower values compared to minimal

and cleared cases ( $P < 0.05$ ). Lung function tests showed significantly lower values when residual lesions were bilateral or left sided ( $P < 0.05$ ). Pattern of lung function is "restrictive" in the presence of complete radiological clearance or pleural fibrosis whereas it is "combined" when pleuro-parenchymal fibrosis or fibrocavitary residual lesion is present. Lung function tests correlated well with residual lesions and gave an idea of the extent of disability/limitation.

**FOLLOW-UP OF PATIENTS DISCHARGED AGAINST MEDICAL ADVICE IN TUBERCULOUS MENINGITIS STUDIES IN CHILDREN****Padma Ramachandran and R. Prabhakar***(Paper is being published in full)***TROPICAL PULMONARY EOSINOPHILIA IN RURAL INDIA : RADIOLOGICAL MANIFESTATIONS - AN ANALYSIS BASED ON 400 CASIJES****A.L. Anand**

Tropical pulmonary eosinophilia (TPE) as a separate clinical entity is well established. It has a set pattern of clinical signs and symptoms, changes in chest X-ray picture and massive eosinophilia. The paper attempts to enumerate important radiographic findings obtained in patients suffering from TPE observed during a period of 20 years. All these cases gave history of cough and asthmatic episodes, absolute eosinophil count in peripheral blood above 2000-cu mm- and specific response to Diethyl Carbamazine including reversal of X-ray changes. A detailed radiographic examination of 400 cases of tropical pulmonary eosinophilia conducted before

treatment revealed following patterns of abnormalities. Normal lung picture (8%), increased broncho-vascular marking (BVM) (36%), increased BVM with hilar adenitis (31%), BVM with pulmonary mottling (14%), increased BVM, pulmonary mottling and basal pneumonitis (5%), diffuse extensive pulmonary mottling (5%), emphysema (5%), Pleural thickening, pleural effusion, pneumothorax, emphysematous bullae, cavity, cough, fracture of ribs and congestive heart failure were also seen, but cannot definitely be claimed to be due to eosinophilia, as other aetiological factors may be responsible, but not recognised. Relapse occurred in 14% of cases.

The lesions seen in X-ray are quite often attributed to pulmonary tuberculosis, and not only institution of appropriate, therapy is delayed, but

therapy directed at non-existent tuberculosis may further vitiate the diagnosis.

#### **AN EXPERIMENT ON OBJECTIVE ASSESSMENT OF BRONCHIAL ASTHMA AND IMPLICATIONS IN HOSPITAL ADMISSIONS**

**S.K. Gupta**

Bronchial asthma accounted for 2.84% of all medical admissions and 5.72% of patients seen in the Medical Casualty during year 1990-91 at the Western Railway Hospital, Bhavnagar.

One hundred unselected hospitalised patients of bronchial asthma who could be followed up in respiratory clinic were studied. Patients were assessed clinically and the severity was scored according to Fischl's Index. Of these, 66%

belonged to the early onset group i.e. had onset of disease before attaining 30 years of age. Seasonal asthmatics formed the largest group (56%) followed by perennials (27%) and the irregulars (17%). Dust and humidity were the commonest precipitating factors for others. Hospital admission could be avoided in 30% on the basis of the objective assessment. Therefore, a careful objective assessment is considered mandatory in cutting down hospitalisation.

#### **PROGNOSTIC SIGNIFICANCE OF HEPATIC INVOLVEMENT IN CASES OF PULMONARY TUBERCULOSIS**

**B.N. Panda, A.K. Basu, R.K. Jetley, R.S. Pahwa, K.E. Rajan and S.K. Nema**

Eight hundred twelve adult pulmonary tuberculosis patients in the age group 1-45 years (Mean 29.4 years) were analysed for clinical evidence of hepatic dysfunction. Out of these, 72 had signs and symptoms of hepatic involvement. They were evaluated for any biochemical derangement and percutaneous liver biopsy was

done with informed consent. Out of the 70 successful biopsies, 25 (35.7%) had histological evidence of hepatic derangement and 11 patients had obvious biochemical derangement. Almost a third of the patients with pretreatment histopathological evidence of hepatic derangement had unsatisfactory therapeutic response.

#### **ARTIFICIAL PNEUMOPERITONEUM IN DRUG RESISTANT CASES OF PULMONARY TUBERCULOSIS**

**B. Raj, Kamal Arora, K.B. Gupta and Ashok Kumar Janmeja**

After four decades of chemotherapy, we are now facing the problem of increasing multi drug resistance (M.D.R.). Reserve drugs have their own problems, of cost, availability and toxicity, so that it becomes difficult, or even impossible, for the average patient to take adequate treatment with them. This study was undertaken to find an alternative means of helping such patients.

Sixty such patients from among those taking treatment at the Department of Tuberculosis and Chest Diseases, Medical College, Rohtak, were taken up for the study. All of them had persistence of symptoms and sputum positivity after 2 years or more of anti-TB treatment and radiological picture was stationary or deteriorating. Sensitivity tests were available in some of them. thirty of

these patients were started on pneumoperitoneum (P.P.) along with appropriate drugs, while the remaining 30 received only the drugs and served as controls. P.P. was instituted by a primary fill of 200 ml followed next day with 800 ml and thereafter with 1000 ml every week. The extent of disease was comparable, and those with complications were excluded.

After 6 months, smear negativity was achieved

in 13 (43.3%) of the P.P. patients against 2 (6.6%) of controls and radiological improvement in 8 (26.6%) P.P. cases against 4 (13.3%) controls. Symptoms also abated in 90% of P.P. cases but in only 45% controls. There were no complications attributable to P.P.

The study suggests that P.P. may be a useful adjunct to chemotherapy by alternative drugs, in resistant cases.

### SEQUELAE OF PULMONARY TUBERCULOSIS AFTER SIX MONTHS' CHEMOTHERAPY

**Balbir Malhotra and B.M. Kalia**

Out of 100 previously untreated patients of pulmonary tuberculosis, 85 satisfactorily completed a 6-months' course of short term chemotherapy while the remaining 15 had to be continued on treatment. However, of the 85

patients, 32 continued to attend the clinic for their medical problems during a 6-months' post-treatment follow-up. Of these, 10 had COPD, 16 upper respiratory infection, 5 repeated episodes of haemoptysis and 1 had tuberculosis of the abdomen.

### PLEURAL BIOPSY AND ADENOSINE DEAMINASE IN PLEURAL FLUID FOR THE DIAGNOSIS OF TUBERCULAR PLEURAL EFFUSION

**B.R. Maldhure, S.P. Bedarkar, H.R. Kulkarni and S.P. Papinwar**

*(Paper is being published in full)*

### PILOT STUDY - FEASIBILITY OF INVOLVING TRIBAL LITERATE YOUTHS FOR CASE-FINDING IN A TRIBAL AREA IN TAMIL NADU

**Rani Balasubramanian, K. Sadacharam, R. Selvaraj and R. Prabbakar**

*(Paper will be published in full in a subsequent issue)*

### RESULTS OF TREATMENT OF MICROSCOPY NEGATIVE SYMPTOMATIC PATIENTS WITH RADIOLOGICAL EVIDENCE OF ACTIVE PULMONARY TUBERCULOSIS IN RURAL PUNJAB

**Vitull K. Gupta and Vineeta Gupta**

Forty two patients having persistent symptoms attending the TB clinic at P.H.C. Goniana, who had three negative sputum smear examinations for AFB and chest X-ray showing evidence of active pulmonary tuberculosis during 1990-1993 were

studied. Effect of therapy was evaluated by symptomatic relief, weight gain, fall in ESR and radiological status. Symptomatic relief, weight gain and fall in ESR was recorded in all 42 (100%) patients. Assessment of radiological

abnormalities at the start and at the end of therapy was done by joint parallel reading. Extent of radiological abnormalities at the start of therapy was minimal in 11.9%, moderately advanced in 71.4% and far advanced in 16.7% patients. Radiological status reviewed at the end of therapy showed normal X-ray in 35.7%, small residual

fibrosis and calcification in 50%, insignificant change in 4.7%, no change in 7.1% and increase in lesion, especially fibrosis, in 2.3% patients. We suggest that microscopy negative symptomatic patients with radiological evidence of active pulmonary tuberculosis may need chemotherapy.

**STATUS OF SHORT COURSE CHEMOTHERAPY UNDER NATIONAL TUBERCULOSIS  
PROGRAMME**

**L. Suryanarayana, K. Vembu, C. Satyanarayana and R. Rajalakshmi**

*(Paper will be published in full)*

**FATE OF SMEAR POSITIVE PATIENTS OF PULMONARY TUBERCULOSIS AT AN URBAN  
DISTRICT TUBERCULOSIS CENTRE FIVE YEARS AFTER TREATMENT**

**P. Jagota, E.V. Venkatarama Gupta and R. Channabasavaiah**

*(Paper will be published in full in a subsequent issue)*

**A SHORT STUDY OF BLEEDING AND COAGULATION FACTORS IN 50 MALE PATIENTS  
PRESENTING WITH PERSISTENT HEMOPTYSIS**

**Kaushal Kumar**

A study was conducted in 50 patients (27 sputum positive and 23 sputum negative) admitted at TB Hospital, Bhopal with hemoptysis continuing over 15 days inspite of treatment. Bleeding time, clotting time, clot retraction study, prothrombin time and peripheral smear were done at 37°C using siliconised glassware, while patients and controls (100 patients who did not have hemoptysis) were fasting.

Bleeding time (BT) of controls ranged between 3 minutes 6 seconds and 7 minutes 58 seconds while in 40 patients (80%) it ranged from 3 to 8 minutes; in 6 patients (12%) from 8 to 14 minutes and in 4 patients (8%) it was over 14 minutes.

Coagulation time, CT (Lee & White) ranged from 5 minutes 20 seconds to 13 minutes 12 seconds in controls and from 5 minutes to 13 minutes in 41 patients (82%), 13 minutes to 18 minutes in 7 patients (14%) and over 18 minutes in 2 patients (4%).

Clot retraction, CR, after 1 hour was between 50% and 62% in controls, between 50% and 60% in 46 patients (94%), between 40% and 50% for 1 patient (2%) and between 30% and 40% for 2 patients (4%).

Peripheral smear (PS) revealed normal morphology and quantity of platelets in controls and 46 patients (92%) while 3 patients (6%) showed reduced number of platelets with the presence of giant forms, later diagnosed as immune thrombocytopenic purpura, ITP. One patient (2%) showed increased platelets (diagnosed later as chronic myeloid leukemia, CML).

Prothrombin time, PT, estimated by one stage Quick method (using reagents of Tulip Diagnostics Pvt. Ltd.) ranged between 12 seconds and 16 seconds for controls, 12 and 16 seconds for 31 patients (62%), 16 and 23 seconds for 12 patients (24%) and over 23 seconds for 7 patients (14%).

The abnormal values obtained for BT, CT and PT and for CR in 6% and abnormal peripheral smear 8% point to an etiology existing apart from and in addition to tuberculosis. Abnormal CR and abnormality in peripheral smears is due to abnormalities in platelets, ITP and CML; prolonged PT could be due to deficiency of factor I, II, V, VII, X, hypofibrinogenemia or vitamin K

deficiency due to malabsorption or malnutrition. It appears to be prolonged due to an inability to form proper hemostatic plug, while prolonged CT is a rough measure for activity of intrinsic pathway. A possibility of the above and/or vitamin deficiency should, therefore, be kept in mind in all cases of persistent hemoptysis and a further detailed study on these lines is warranted.

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<b>ASIA-PACIFIC TUBERCULOSIS WORKSHOP</b>
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While considering the WHO global tuberculosis strategy and policy package, and examining the worsening epidemiological situation with respect to tuberculosis, the Asia-Pacific Tuberculosis Workshop held at Tokyo in December, 1993 strongly recommended the following:

#### *Resource mobilization*

The principal objective is to mobilize resources both internally and externally for national tuberculosis programmes.

(a) *Internal resources:* The group recommends that every national authority provides higher allocations within the health sector for their national tuberculosis control programmes. To aid this process, programmes should determine what proportion of the national health budget they currently receive and set a target for a more reasonable allocation, if justified. Dialogue with local NGOs should be initiated to secure support to the NTP. Given the relative importance of tuberculosis, in relation to other diseases, it is recommended that the WHO country budget for tuberculosis be increased.

(b) *External resources :* In addition to reallocation of existing internal resources, it is necessary to raise funds from external sources for initial upgrading of revised programme activities.

Possibilities of bilateral governmental assistance, international assistance (e.g., World Bank, Asian Development Bank) and cooperation with non-governmental organizations should be investigated.

Within the Asia-Pacific region, a number of countries including Australia, Brunei, China, Hong Kong, Japan, Korea, Malaysia, New Zealand, Singapore and Thailand, have the resources to provide support to neighboring countries for revitalizing national programmes. These countries should also consider initiating or increasing direct support to the WHO Tuberculosis Programme to make possible global, interregional, regional and country-level activities for tools development, programme support,

research and advocacy.

#### *Technical Cooperation*

In order to develop plans for the design and implementation of the policy package, technical cooperation between national tuberculosis programmes and the World Health Organization is crucial. Possible areas for technical cooperation include : programme review, development of a plan of action, manual preparation or revision, and programme monitoring. The type and extent of cooperation will vary depending on the needs of the country, and may be provided by WHO headquarters and/or the regional offices. The financial resources of the World Health Organization's Tuberculosis Programme for technical cooperation must be increased. In addition, the regional offices must be strengthened (both staffing and financing) in order to make this cooperation possible.

#### *Programme Manual*

A tuberculosis programme manual must be developed or revised based on this policy package.

#### *Demonstration Areas*

A key to successful development of national tuberculosis programmes is the initial implementation of the policy package in demonstration areas. Only when a high cure rate is achieved in these areas, should gradual expansion of control activities take place. The ultimate aim is national coverage. Demonstration areas can serve as training grounds for staff throughout the country, in the expansion phase. The manual may also be revised based on experiences in the demonstration areas, and then distributed throughout the country.

#### *Training*

Implementation of the policy package will require training a large number of professionals. The WHO modules on "managing tuberculosis at the district level," have been found to be a useful instrument for training and should be adapted, if required, for use in some countries. Staff in

demonstration areas must be given the first priority for training. Training for laboratory and other peripheral staff must also be strengthened.

### *Advocacy*

The low priority given to tuberculosis in a majority of the countries has resulted in inadequate funding and, consequently, lack of drugs. Advocacy efforts must be advised to improve the visibility of the problem and of the national tuberculosis programme in each country. Understanding of the burden of disease, the resulting impact on economic and social development, and the cost-effectiveness of the TB control strategy must be increased. The likely outcomes of these efforts include greater political commitment; financial and human resources; endorsement of technical policies by the medical community; and the trust of patients and of the community in the programme.

### AMERICAN AIDS EPIDEMIC

American epidemiologists have begun an exercise with aim to review the true extent of the American AIDS epidemic as evidence has accumulated to show that the earlier estimates were, in reality, overestimates.

The Centres for Disease Control (CDC), Atlanta had estimated, in 1989, that between 0.8 to 1.2 million Americans were HIV seropositive. The estimate was based on available statistical techniques because American laws preclude HIV testing without permission, ensure confidentiality of information and respect civil resistance to proper surveys. It now appears that the total HIV positives may be around 0.6 million. Besides, there is need to know the trend of the epidemic and identify the geographical "hot spots" in the country.

Recent evidence suggests that there is more than one HTV epidemic in the U.S.A. and each is behaving in a different way. The main epidemic was, and still is, among the white homosexuals among whom the incidence of new infections is levelling off, or even showing steady decline. Now, about 2.5% of white and 5% of black homosexual males in their teens or early 20s are getting newly infected every year, compared with

10% to 20% a year respectively in the early 1980s. However, the epidemic among black females in the south is still rising. The observed rise in frank cases of AIDS is too complex to understand because it takes, on an average, 10 years for HTV seropositives to become AIDS cases. The recent rise in the cases of AIDS, therefore, reflects HIV transmissions of the early to mid 1980s. However, there are sufficient data to suggest that the newly infected, as a class, are characteristically different from those infected a decade back, and that the driving force of the epidemic appears to have changed. A study among the child bearing females has shown a steady increase in HIV infection among them, in general, and black females in the south, in particular. And, there is probably no rise in infection among the users of intravenous drugs.

Since many estimates of the HIV/AIDS epidemics worldwide were modelled on the American epidemic, notwithstanding different sexual mores, drug abuse practices and use of biological products, etc, it stands to reason to presume that many such widely accepted estimates are also overestimates.

### TUBERCULOSIS EPIDEMICS

Paradoxically, the comparatively recent scientific process-Polymerase Chain Reaction or simply PCR-developed to unravel the frequently met with problems of diagnosing "TB or not TB" has put to rest some old popularly held notions.

It was generally believed that Christopher Columbus who landed in the New World just 500 years ago brought tuberculosis to the native Indians through his crew, triggering an epidemic which has lasted all these centuries to decline only during the last few decades. Unlike the more convincing evidence from the pre-Vedic Harappan civilisation flourishing in the Indian subcontinent over 5000 years ago of the existence of tuberculosis in epidemic form the evidence from pre-Columbian mummies in favour of the existence of tuberculosis in the Americas before 1492 was always regarded as equivocal.

Now, PCR applied to a 900 year old Peruvian mummy has conclusively proved that a 45 years old woman from the Chiribaya community settled

at the southern sea coast had died of tuberculosis. The DNA particle of ancient vintage, obtained from her lymph gland, and replicated/amplified a million times was found to have sequences that matched perfectly those of the present day mycobacterium. Scientists, surprised by the closeness of the match, searched for any evidence

of “contamination” Of the specimen but found none.

Going by the Indian analogy, again, *it* stands to reason that most ancient civilisations have had more than one tuberculosis epidemic, controlled by the well recognised forces that govern epidemics.

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## FORUM

Sir,

At present, tuberculosis is the leading cause of death from a single infectious agent in the world. There are an estimated 2.9 million deaths occurring every year and India is perhaps the main contributor. And there is every prospect that tuberculosis mortality will further increase. In recognition of the increasing problem of tuberculosis in India, the Ministry of Health & Family Welfare, in consultation with World Health Organisation (WHO) is analysing the National Tuberculosis Programme (NTP) and revising the strategy of NTP to combat the menace of Tuberculosis.

Rightly did Dr. D.R. Nagpaul say recently that "tuberculosis was a social disease with medical aspects in the pre-chemotherapy era, but it is now an infectious disease with some social aspects." However, there is no evidence of any decrease in the tuberculosis morbidity indices in India, even after the availability of anti-tuberculosis drugs. In the United States, where TB was the leading cause of death at the turn of the 20th century, it decreased progressively during the first half of the century. With the availability of specific anti-tuberculosis drugs around the middle of the century, both morbidity and mortality indices fell rapidly in the U.S.A. So much so that a strategic plan was drawn up in 1989 to eliminate TB with aim to achieve an incidence rate of 1 case/million by the year 2010. However, the recent trend in TB and multi-drug resistant tuberculosis (MDR-TB), has put the clock back by almost one century. We, in India, never had a ride on this roller coaster and are probably still near the peak of the secular epidemiological curve. We may not have had the benefit of socio-economic progress but the specific drugs were definitely available to us. Yet, drugs have not made any impact on the scenario in our country, resulting in the need for revision of NTP strategy. But the most unfortunate part of the revision process is that neither we learn from others' experiences nor from our own. That is why the old public health saying that "our programmes are eradicated before the disease" is still true. The short course chemotherapy trials conducted by TRC Madras have clearly shown the problems in

the implementation of SCC and bring out very clearly the multifactorial non-medical aspects, resulting in the development of acquired resistance to Isoniazid and Rifampicin. The two crucial drugs for treating TB in the SCC regimens are Isoniazid and Rifampicin, and resistance to these drugs is the core of the problem of multiple drug resistance leading to high morbidity and mortality rates world wide. The problem of multiple drug resistant tuberculosis (MDR-TB) has raised public awareness and concern. Drug resistance carries obvious clinical consequences but there are social and economic ramifications too. Dr. Nagpaul has also highlighted the problem of MDR-TB in his editorial (January, 94), but it lacks the sharpness of its consequences, particularly in the context of our country. We are humans and should not behave like a pigeon which closes its eyes on seeing the cat.

The myth that drug resistant tubercle bacilli are less virulent and do not infect new hosts has now been blown apart through animal studies. It could not be proved earlier due to the usual time lag of many years between TB infection and disease, but in the recent past an increasing number of tuberculosis cases, and some community outbreaks of MDR-TB, have occurred in immunocompetent individuals. There has been a large number of tuberculosis transmissions among HIV positive patients in hospitals and correctional centres in the United States. Moreover, health care workers have been infected in some outbreaks as documented by tuberculin skin test conversion. In each instance, the epidemiological evidence of nosocomial transmission has been compelling and has been corroborated by laboratory evidence in the form of DNA finger-printing, using restriction fragment length polymorphism. Nearly all the patients in these outbreaks had organisms resistant to both Isoniazid and Rifampicin. The case fatalities ranged from 40 to 60% in immunocompetent individuals and > 80% in immunocompromised individuals.

Multi drug resistant TB is our own creation. It stands to reason that we should also prevent it. And, if we can not prevent it, then control of such an outbreak (MDR-TB) may be beyond our control. The scientists in the field of genetic

engineering are making great efforts and have made us wiser in the last few years in understanding the biological properties of tubercle bacilli, which we could not learn even one century after its discovery. The various genes of the bacillus have been cloned and the discovery and identification of the genes responsible for imparting drug resistance to Isoniazid and Rifampicin, the two most important anti-tuberculosis drugs, may put us back on the road that leads, if not to complete eradication, at least to control if the disease. One of the great drawbacks of fighting MDR-TB was the slow process of establishing the drug susceptibility of tubercle bacilli to the various anti-tuberculosis drugs. Thanks to molecular biologists, a rapid method of assessment of drug susceptibilities has been found which now takes only two days as against four weeks. This new test 'luciferase reporter mycobacteriophage' (LRM) will not only help to find drug susceptibilities quicker but may also help in rapid screening of the drugs for anti-tuberculosis activity, resulting in the availability of newer drugs faster.

Are we sure that the revised strategy of NTP is flexible enough to accommodate scientific advances and utilises the fruits of continuing research? We may not get another 30 years to revise either the NTP or its strategies, if we do not plan today for some of the problems which are already surfacing. No wonder, the epidemic of MDR-TB may in effect push us back to the pre-chemotherapy era. Now is the time to say 'No more'.

**N.K. Jain**  
Bacteriologist,  
New Delhi Tuberculosis Centre,  
New Delhi.

Sir,

In the article "Mycobacteriuria in pulmonary tuberculosis patients in Madras, South India" by Selvakumar *et al* in the January 1994 issue of your esteemed Journal (*Ind. J. Tub.*; 1994, 41, 43), variations in the estimates of mycobacteriuria reported by different investigators have been attributed to a lack of systematic approach. In my opinion, a comparison of such results will be more meaningful if the methods adopted by the

respective investigators and the objectives of their studies are also considered. To be specific, while quoting the results from our study (*Ind. J. Tub.*; 1989, 36, 107), the following variations in the Material & Methods should have been considered:

1. Their intake of 137 bacteriologically confirmed patients (irrespective of the previous treatment taken) compares with our 236, untreated, pulmonary tuberculosis patients who were smear positive.
2. Multiple culture media were used by them, with certain changes adopted during the course of study, compared with same culture medium (Lowenstein-Jensen) used for culture throughout our study.
3. Malachite green-treated membrane filters used for filtration in their study compared with untreated millipore membrane filters used in our study.
4. Sodium dodecyl sulphate in a final concentration of 2 mg/ml of urine (known to have cidal effect on tubercle bacilli) used by them compared with 0.5 mg/ml concentration used in our study. Extensive preliminary experiments were conducted prior to starting our study keeping in view our laboratory conditions.

The time lapse between collection of urine specimen and its processing for culture, besides the already pointed out bacteriological status of cases (one spot sputum positive specimen) can also play a role in the recovery rate, especially when urine specimens contain very few tubercle bacilli. Besides, in our study, the bacteriological status of all the specimens was confirmed by an independent reader and the processing of sputum and urine for culture was carried out by different persons to avoid bias.

Dr. Selvakumar has remained in touch with me from time to time, yet I would like to suggest that a more extensive study with broader objectives involving comparison of tubercle bacilli isolated from two different sources, namely urine & sputum or/and CSF & sputum in the same individual, incorporating the latest technique like Restriction Fragment Length Polymorphism (RFLP), as a marker, may lead to a better understanding of the pathogenesis, besides providing scope for innovating prophylactic

measures for the effective control of tuberculosis.

**Vijay K. Challu**  
National Tuberculosis Institute,  
Bangalore.

Sir,

I read the leading article "Early Detection of Resistant *M. tuberculosis* from Sputum specimens" by Ashok Rattan *et al* (January 94) with great interest and, if I might say so, with great surprise. There are many statements which I feel need correction.

To begin with, the authors have used the terms primary drug resistance and initial drug resistance as if they were synonymous. This is not so, and for clinical studies the term initial drug resistance is used as a normal practice.

The authors quote an unidentified report from TRC, Madras for the conclusion that "71% of patients with primary INH resistance had an unfavourable response with bacteriologically active disease at the end of treatment, as compared with only 14% of patients with sensitive organisms on admission. The results are so alarming that they should have at least taken the trouble of giving full reference. They have also quoted in corroboration of the above statement, reports from Mitchison & Nunn<sup>1</sup> and Goble *et al.*<sup>2</sup> This is factually incorrect. Mitchison and Nunn,<sup>1</sup> in their report, have stated that "17% of the 23 patients resistant to INH and/or Streptomycin failed during chemotherapy when given a 6-month regimen of INH and Rifampicin (as against) 12% of 246 patients given Rifampicin only in an initial 2-months intensive phase of their regimen". This can hardly be regarded as supportive of the quoted findings of the Madras study. Similarly, the "Study groups" of Goble *et al*<sup>2</sup> are altogether different.

The suggestion that "when single drug resistance is found (usually to INH), treatment must be continued for 12 months with the three other drugs" is astonishing and goes contrary to contemporary opinion. I doubt if any clinician would consider omitting INH from a drug regimen even in cases of INH resistance. The authors state that "it has now been recommended that drug susceptibility tests should be put on all culture positive cases". I am not aware of any responsible technical authority who would make such a recommendation in India where even basic facilities such as direct microscopy are difficult to provide and culture facilities are all but non-existent, except in metropolitan areas. To talk of BACTEC etc. is like recommending cake where bread is not available.

The methods mentioned can also be used for early detection of drug resistance to *M. tuberculosis* from specimens other than sputum alone. Thus, the title of the article creates confusion in the minds of the reader, regarding the limitations of these methods.

*Leading articles*, whatever else they do, should not mislead.

#### References

1. Mitchison D.A., Nunn A.J. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *Am. Rev. Respir. Dis*; 1986, 133,423.
2. Goble M., Iseman M.D., Madten L.A. *et al* Treatment of 171 patients with pulmonary tuberculosis resistant to INH and RIF. *N. Engl. Med*; 1993, 328,527.

*Name withheld on request*

*The letter was referred to the authors for their comments. No reply has so far been received.*

*Editor*

## NEWS & NOTES

### PRESIDENT, TUBERCULOSIS ASSOCIATION OF INDIA

Dr. P.K. Sen, Chairman of the Bengal TB Association, Emeritus Editor of the Indian Journal of Tuberculosis and eminent senior TB worker, has been nominated as President of the Tuberculosis Association of India, *vice* Dr. M.S. Chadha. Dr. Chadha has been made President-Emeritus of the Tuberculosis Association of India.

### ANNUAL MEETINGS

The Annual General Meeting of the Tuberculosis Association of India was held on 29th April, 1994. Since Dr. A.K. Mukherjee, Chairman of the Association could not be present, the Secretary General presented the Chairman's report on the activities of the Association for the period 1991-93. Shri S. Ratnam, the Honorary Treasurer, presented the audited accounts of the Association for the period 1991-93 and Dr. Bhai Mohan Singh gave away the awards for outstanding activities by the State Associations during 1991-92 and 1992-93 and also for the highest collections made by them during the 41st and 42nd TB Seal Campaigns.

The General Body elected Drs. I. Ranga Rao, M.M. Singh, R.P. Bhagi, M.S. Agnihotri, Baldev Raj and B.M. Soni as members of the Central Committee of the Association for the year 1994. Dr. C. Srinivasa Rao, Hony. General Secretary, TB Association of Andhra Pradesh, proposed the Vote of Thanks.

Earlier, a meeting of the Standing Technical Committee of the Tuberculosis Association of India was held on 28.4.1994 with Dr. D.P. Verma in the Chair.

The Conference of the Secretaries of State TB Associations was held on 29.4.1994. It reviewed the activities of the State TB Associations with special emphasis on TB Seal Campaign.

### CONTINUING MEDICAL EDUCATION PROGRAMME

A C.M.E. Programme - an update on Chest Diseases - was organised at Yellandu Club,

Bellampally, on 13.3.1994 by M/s Singareni Collieries Company Limited. Mr. Kamat, Managing Director of Singareni Collieries, inaugurated the programme, Dr. (Mrs.) M. Ramalakshmi, Chief Medical Officer, the Singareni Collieries, welcomed the guests and Dr. C. Srinivasa Rao, Honorary General Secretary of the TB Association of Andhra Pradesh, highlighted some of the activities of the Association. About 100 physicians attended.

### COMMUNITY LEADERS TRAINING PROGRAMME

The regional TB Committee, Shahdara, organised a Community Leaders Training Programme on Saturday, the 19th March, 1994, at Little Flowers Public School, Shivaji Park, Delhi. The Programme was inaugurated by Shri D.S. Negi, IAS, Development Commissioner & Chairman, Delhi Pollution Committee. During the programme, video films on TB & AIDS were shown. Nearly 100 persons attended the Programme.

### NEWSLETTER FROM KIYOSE

Those who have participated in the various training courses, especially the popular Regular TB Control Course and the Advanced Course, at the Research Institute of Tuberculosis (RIT) at Kiyose of the Japan Anti-Tuberculosis Association (JATA) can look forward to something interesting and educative.

RIT has started publishing a Newsletter and its 7th number came out in March, 1994. Dr. M. Aoki, Director RIT is its publisher and Dr. N. Ishikawa is the editor. It contains reports on important seminars and workshops, activities - routine and special, announcements regarding various training courses, reports on NTPs of different countries, letters received from ex-participants, their present addresses and the response from RIT faculty, reviews of books, etc. The recommendations arising out of their recently held Asia-Pacific Tuberculosis Workshop are being published in the current issue of our journal under *Contemporary Issues*.

Those who wish to get copies of the said

Newsletter or contribute to it should get in touch with the Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, 3-1-24, Matsuyama, Kiyose-shi, Tokyo, Japan.

**SPECIAL INTEREST GROUP ON MEDICAL INFORMATICS (SIGMI)**

In realization of the importance of medical informatics in the overall development of health sector in our country, the Computer Society of India has taken the initiative in forming a Special Interest Group on Medical Informatics (SIGMI). Those interested in any aspect of medical informatics (health information system, hospital

information system, databases on medical measurements and health indicators, literature bases, bio-statistical computation, graphics, medical lessons, expert system, networking for consultation, computerized equipments, etc.) and willing to contribute to the activities of the Group are invited to join the Group. For this, please write a brief on your past and current medical informatics activities and future plans, and mail to Dr. A. Indrayan (Convener SIGMI), Professor of Biostatistics and Officer Incharge, Computer Centre, University College Of Medical Sciences, Dilshad Garden, Delhi-110 095, Phone (011) 229-6637, (011) 228-2971, 72, 73; Telex : 031-62032 UCMS IN.

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## **RECOMMENDATIONS OF THE 17th EASTERN REGIONAL CONFERENCE ON TUBERCULOSIS AND RESPIRATORY DISEASE**

The recommendations of the previous conference were reviewed. It was felt that a new format of recommendations should be adopted which would specify to whom the recommendations were directed and which could be evaluated at the next regional conference. These recommendations are meant to form the basis of the programme of the Eastern region of the IUATLD over the next two years term of the Region.

### **General Recommendation**

Member associations of the Eastern Region are asked to review the recommendations of the 16th Eastern Regional Conference and to evaluate the activities which resulted from these recommendations.

### **Tuberculosis**

1. Member associations of the Region are requested to:
  - (a) review and comment upon the protocol for surveillance of drug resistance in their national tuberculosis programmes currently under development by IUATLD and WHO
  - (b) review and comment upon the protocol for surveillance of HIV infection in tuberculosis patients currently under development by IUATLD and WHO
  - (c) contribute to an evaluation of the magnitude of the problem of tuberculosis in the Region by:
    - (i) assembling available information in the Region from national prevalence surveys, tuberculin surveys, and routine information on tuberculosis notifications
    - (ii) analysing the reliability, applicability and methodology of these data
  - (d) provide a full report on the history and subsequent development of the Mutual Assistance Programme in the Region from its commencement in the 1960s
2. Member association of the Region should encourage governments to :

- (a) identify tuberculosis as a priority in
  - (i) national plans and budgets
  - (ii) international collaborative activities
- (b) ensure that national tuberculosis programmes comply with the new global tuberculosis control strategy developed by IUATLD and adopted by the WHO in view of the HIV epidemic, to achieve at least 85% treatment cure rate of sputum smear-positive patients detected, through the introduction of short-course chemotherapy, as the prime objective of all tuberculosis control programmes.
- (c) implement in an orderly fashion this strategy, by taking into consideration the existing health services system. Once the 85% cure rate is achieved, the programme should start to expand case finding activities to detect and treat more cases
- (d) continue BCG vaccination of the newborn, unless the infants have AIDS-related symptoms

### **Other Respiratory Diseases**

1. Acute Respiratory Infections (ART)

Member associations of the Region are encouraged to:

  - (a) implement the WHO standard case management for ARI aimed at reduction of pneumonia mortality in young children
  - (b) ensure that ARI is included in the programme of scientific meetings in the Region and at World Congresses
  - (c) encourage publication of scientific investigations in *Tubercle and Lung Disease Journal*
  - (d) participate in the development of a database concerning research activities developed by IUATLD and WHO
- 2 Control of Tobacco Use
  - (a) Member organization of the Region are requested to participate in and monitor anti-smoking policies in their countries

- (b) The Conference strongly recommends that all governments in the Region adopt a plan for the limitation of exposure to tobacco smoke, in particular, health education, tobacco control legislation, for example ban on all advertising and other promotion, health warnings, creation of smoke-free areas, etc., and pricing policy.
- (c) The Conference strongly urges and supports all national governments and NGOs in the Region to develop and implement a comprehensive national control policy. The conference condemns the tobacco industry in encouraging and expanding tobacco use in the Region.

### 3. Asthma

Member associations are encouraged to:

- (a) participate in international studies of the epidemiology of asthma in adults and children
- (b) participate actively in the international network of Asthma Associations (a patient-oriented network) developed in collaboration between the IUATLD and the Canadian Lung Association

### 4. Research Development

Member associations of the Region are encouraged to develop research by :

- (a) participating in the international network of pulmonary epidemiology courses developed by the IUATLD
- (b) establishing links between recognized research groups and institutions from which the trainees in (a) are selected to formulate these collaborative links in the framework of the International Respiratory Disease Research Units developed by the IUATLD
- (c) collaborating with other scientific organizations : member associations are requested to identify all other organizations dealing with lung health in the Region and identify means of collaboration with these bodies.

### 5. Nursing Groups

In view of the need to expand the membership of the IUATLD consideration should be given to extend this to the newly formed nursing group, and to encourage more active participation in the tuberculosis control programme, particularly in the help to enhance compliance in treatment. The same principle holds true for paramedical personnel.

- 6. In conclusion, because of all the preceding views it is recommended that the Executive Committee of the Region be asked to review and to make necessary revision of the Constitution of the Region.

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## GUIDELINES FOR CONTRIBUTORS

### General

1. All correspondence relating to the Indian Journal of Tuberculosis (IJT) may please be addressed to:

The Editor, Indian Journal of Tuberculosis,  
Tuberculosis Association of India,  
3, Red Cross Road, New Delhi-110 001.

2. The four issues of IJT, appearing every year in January, April, July and October, contain original articles on all aspects of tuberculosis and non-tuberculous respiratory diseases, case reports, reviews and leading articles (see item 6) as well as abstracts of articles/matter published in other scientific journals and books dealing with same subjects. Besides, each issue has an Editorial, sections on Contemporary Issues and Continuing Medical Education, News and Notes as well as Forum wherein readers can express opinions on the published articles or ask questions on the subjects covered by the Journal.

3. Two copies of the article (including diagrams and photographs) typed on one side of the paper with double spacing and wide margins should be submitted.

4. It is understood and accepted that the submitted matter would be editorially revised to make it suitable for publication. The decision of the Editor regarding acceptance or revision can not be contested. However, every effort is made to communicate the reason or deficiencies to the author(s) in order to associate him with the steps to improve the article.

5. All the received articles are serially registered and usually published in the order of registration. However, the date of registration will be after the completion of the basic formalities, if the authors have overlooked these guidelines. The articles registered are reviewed by the IJT Editorial Board to judge suitability for publication and to give suggestions for improvement.

6. Original articles deal with planned studies that have been duly completed and convey definite conclusions from the data presented in the text. However, preliminary communication from research still in progress could be submitted, exceptionally, if the topic is important and the interim results could be of interest. Case reports present problems of unusual clinical interest

which have been systematically and fully investigated and where a firm diagnosis has been established with reasonable certainty or the result of therapeutic management is of great significance. Review Articles are those specially requested from persons who have acknowledged competence in given subjects. These are useful for updating knowledge. Leading articles are contributed by those who have expertise in selected aspects of a subject.

Forum provides a platform to readers for expressing opinions and a channel of communication with the Journal and its other readers. It could be used for making suggestions, scientific critique on published articles or for reaching independent conclusion, asking questions on the subjects covered by the Journal and for providing supplementary information either confirming or contradicting the conclusions reached in the articles.

7. Twenty five reprints of each published article are supplied free of cost to the author whose address is indicated for correspondence. More reprints are, exceptionally, supplied if the order is placed at the time of acceptance of the article. The cost of the order will be intimated and must be paid for in advance of the publication of the article.

### Format and Procedure

8. All submitted articles shall have a definite format. Each article should comprise sections *ad seriatim*, on Summary, Introduction, Material and Methods, Results, Discussion, Acknowledgements (if necessary) and References. Additional sections could be interposed. In Case Reports, the sections on Material and Methods and Results are replaced by the section "Clinical Record" and all other sections are appropriately shortened.

Care should be exercised in making the language grammatically correct and free flowing, ensuring that all pertinent information has been included, irrelevant details omitted and repetitions, especially from section to section, avoided. **Tables and figures must be self explanatory and their number kept to the minimum. It is not usually necessary to present the same information both in a table as well as**

**a diagram : the more effective of the two presentations has, therefore, to be chosen.**

Tables must be numbered, have a descriptive legend on the top, minimum essential data in the body and necessary explanatory notes at the bottom. Tables (and diagrams) should be made on separate sheets of paper, with their place in the text indicated clearly, and attached at the end of the article. **Drawings are best made with black India Ink and of a size larger than required in the text.** Legends for the photographs should be typed separately with appropriate indication regarding the photograph to which a legend pertains. **Photographs (black and white prints) should be clear, glossy and unmounted. The attached sheets should carry the title of the paper and name of the author in pencil on the backside.** Photographs with poor contrast may not be accepted. Photographs, inscribed in pencil at the back, should be put in an envelope and properly labelled on the outside and attached to the article last.

It is understood that the planning of the study submitted for publication as well as the analysis of the data, presentation in the text and the reaching of conclusions have been done in consultation with a statistician.

9. After the title of the article, the name of the principal author should be followed by names of other authors.

10. The position held by each author in any institution is indicated only in the footnote against Arabic numerals indicated on the top of each name. This information is followed by any special annotation such as title of oration, or, say, paper presented at a scientific conference, etc. Lastly, the name and address of the author to whom correspondence regarding the article has to be sent should be indicated.

11. In respect of preliminary communications, the nature of the paper must be clearly indicated so that editorial processing could be specially expedited.

12. References cited in the text and at the end should conform to the procedure recommended by

the International Steering Committee of Medical Editors. Therefore, special care must be taken to ensure that:

- Only the most important published papers related directly to the study in hand are cited in the text.
- Text reference should be numbered in Arabic numerals as a suffix in the order of their mention, avoiding the names (s) of authors (s) and year of publication.
- While citing an abstract (when it is the sole source of information) or personal communication or unpublished work in the text, authors must provide the necessary particulars of the source, but this is not a preferred mode of citation. Permission from the source (s) of information of citing their work must be obtained beforehand.

- **All the numbered references in the text should be typed out in detail, in the same consecutive order, on a separate page and attached at the end. Abbreviation of the titles of the cited journals should be according to the Index Medicus. Example;**

**Kakar, A., Aranya, R.C. and Nair, S.K.: Isolated gastric tuberculosis; Ind. J. Tuber.; 1979,26, 205k**  
**Crofton, J. and Douglas, A.: Respiratory Diseases, 1st Edition, Edinburgh, Blackwell Scientific Publications Ltd. 1969.**

13. The abbreviations or acronyms used in the text must be defined at the first mention. Their number should be kept to a minimum.

14. Contributions to Forum should be in the form of letters to the Editor. Such letters must be brief and to the point : only the most important agreements/disagreements/suggestions on published papers may be chosen for commenting. It is usual to send a copy of such letters to the author concerned for obtaining a response, if any, after editorial reformulation. The response, similarly, has to be selective, brief and relevant.