The
Indian Journal of Tuberculosis

Vol. XVII New Delhi, October 1970 No. 4

'CURE' OF TUBERCULOSIS

Cure is a commonly used and easily understood word. When applied to tuberculosis, not only 'cure' is elusive but difficult to define exactly and scientifically. Criteria of 'cure' have been changing with time. Before tubercle bacillus was isolated and established as the causative micro-organism, concept of 'cure' was purely clinical. Relief from symptoms was considered synonymous with the indicative of 'cure'. We know too well today that this was fallacious. Relief of symptoms, at best, signified a state of equilibrium between the parasite and the host. Any adverse environmental or constitutional factor, pertaining to the host, could upset the uneasy balance in favour of the parasite and thus cause relapse. So frequent were the relapses, that tuberculosis came to be defined as a 'relapsing disease'.

Exercise tolerance was then introduced as a more reliable criterion of 'cure'. It certainly made a few more patients ineligible to be considered as cured; but, again, tolerance of a certain grade of exercise, without toxaemia, as advocated then, is not inconsistent with activity of lung lesions, which is a negation of 'cure'.

When the rubicon between the traditional, yet non-specific sanatorium regimen and specific treatment was crossed with the advent of anti-microbial drugs, the assessment of 'cure[1] became still more stringent and rational. Today sputum conversion is the more important criterion for assessment of the result of treatment. A study reported elsewhere in this issue, as some others before, has however shown that even repeated failure to demonstrate the presence of tubercle bacilli in the sputum of a treated patient does not necessarily rule out the presence of viable bacilli in the lung lesions. Since in an infectious disease, 'cure' should ideally mean complete sterilisation of the lesions, negative sputum too, does not necessarily constitute a 'cure'.

To achieve sterilisation of lesions and to be able to demonstrate this achievement is beset with difficulties. Available methods of detection may not succeed if the bacillary content of the lesion (and, therefore, of sputum) is low. Secondly, the bacilli present in the lesions may not be capable of multiplication. Phenomenon of bacillary 'Persistence' is well known. Although some consider the so called 'persistor' bacilli as of no significance, yet others do not accept them as being innocent under all circumstances, and consider them as the 'seeds'of future relapses. Any sense of complacency, therefore, about their pathogenicity may not be justified. The farthest we can go at present is that the longer the period of sputum negativity by culture, the greater the possibility of lesions having been sterilised.

There is still another difficulty. Even if it were possible to eliminate all bacilli from the lesions, there is no known method at present which could indicate with any certainty that the bacilli have been completely eliminated and the lesions have been sterilised. In other words, 'cure' is still elusive and almost impossible to demonstrate with scientific precision. It still remains more or less clinical, rather than bacteriological, since even the potent anti-microbial drugs available at present are incapable of completely eliminating 'persistor' bacilli from the lesions.

Against this background, it is not surprising that there, still, is no agreement on what should be the optimum duration of treatment. It is customary to define a stage in the treatment, to a certain extent arbitrarily, and designate it as the 'target point' of treatment. 'Target Point' is taken as achieved when the sputum has been negative and the lesions have been radiologically stable for at least 6 months and all cavities have been closed. The consensus appears to be to treat patients for 12 months more after the 'target point' has been reached as it has been shown to cut down relapse to the utmost though not eliminate it altogether. It may be emphasised again that 'target point' of treatment does not constitute 'cure'.

Cure in the true scientific sense will only becoms attainable, when a therapeutic agent capable of killing even 'persistor' bacilli or preventing somehow the emergence of 'persistors' becomes available. Whether and when it is possible, time alone will tell. Till then, expediency lies in playing safe and over-treating rather than under-treating with a view to reduce, as far as possible, the possibility of relapse which seems to be, at present, the most practical yardstick of efficiency of treatment.

S

BACILLARY CONTENT OF LESIONS FROM RESECTED TUBERCULOUS LUNGS

S.P. PAMRA, H.B. DINGLEY & R. NARASIMHAN
(From New Delhi TB Centre & Lala Ram Sarup TB Hospital, Delhi)

Tuberculosis is a disease in which bacteriological cure is notoriously difficult to achieve. It is equally difficult to lay down definite and objective criteria of clinical cure (in the absence of bacteriological cure) and to establish if and when such a cure has been achieved. Canetti (1955) and Medlar (1955) had demonstrated the presence of tubercle bacilli in ihc lungs of persons with 'clinical'cure in the pre-chemotherapy era. With the advent of antimicrobial drugs, there was a spurt in the number of resections for pulmonary tuberculosis. As a result, lesions of different tyes and in varying stages of evolution and healing became available for studies. A number of reports appeared in the world literature in the fifties of the present century on bacillary contents of difl'erent types of lesions and the viability of the bacilli. D'Esopo (1951) and Medlar (1955) were among the first to show the presence of bacilli even in lesions which had reached the Target Point* of treatment. Whereas there was almost complete agreement on inability of even the present day therapeutic measures to eradicate the infection, there was, and still is, a controversy regarding the viability of bacilli found in necrotic and other lesions including cavities. While some think these bacilli are 'dead', others attribute their failure to grow on culture to be due to a sort of 'suspended animation' or a state of 'dormancy'. Some attempts to grow these bacilli in special media and/or longer than usual incubation have been successful.

Epidemiology of tuberculosis in India is different from that in the western countries; so may be its evolution, pathological pattern, behaviour and response to the antimicrobial drugs. Whether the situation regarding bacillary content of the lesions in Indian patients is the same as found by the western workers referred to above, remains to be established. Barua et al (1960) reported bacteriological studies on bacillary content and viability of bacilli in 52 resected lung specimens. No co-relation, however, was attempted with the pre operative sputum status or resistance of bacilli in case of positive sputum. The present study was therefore planned and undertaken with the following objectives:—

(a) To study the bacillary content of the resected lung.

(b) To compare the bacillary content of the various types of lesions.

(c) To determine viability of the bacilli present in the various lesions.

(d) To correlate bacillary content of the pre-operative specimens of sputum with the bacillary content of the lesions.

(e) To correlate the pattern of bacterial resistance of bacilli recovered from the sputum and the lung lesions.

Material

From 13-8-1966 to 31-5-1968, 76 resected lung specimens were received for this study; 74 consecutive specimens from TB Hospital Mehrauli and the remaining 2 from G.B. Pant Hospital. Out of these, 20 have been excluded from the study; 10 because the lungs were found to be non-tuberculous and the remaining 10 because at no time before the operation was sputum found to be positive and no tubercle bacilli was seen in any of the lesions in the resected lung by direct smear and/or by culture. Of the non-tuberculous cases, 7wereofbronchiectasis, one new growth, one generalized arterial disease and one lung was resected because of recurrent haemoptysis and although no tubercle bacilli could be isolated, the diagnosis could not be established because the lung could not be sent for histopathological examination. Out of the 7 cases of bronchiectasis, two were confirmed by pre-operative bronchography and the remaining 5 by histopathological examination of the resected specimen. Similarly, the diagnosis of new growth and generalized arterial disease was also based on histopathological examination of the resected lung. The study thus is based on 56 resected lungs or portions of lungs.

The main indication for resection in these cases was radiological evidence of the presence of a cavity or cavities and/or positive sputum. There were two cases where the pre-operative sputum was negative and there was no evidence

* Target Point has Iwen defined as a stage when no cavity is seen in the plain skiagram, lesions are stationary radiological y and sputum/laryngeal swab cultures have been negative for at least six months.

of cavity in the chest skiagram. One of these was a case of empyema with collapsed lung but the pre-treatment sputum was positive in this case. The other was a pneumonectomy in a child 10 years old whose sputum was positive initially, and the indication for resection was atelectatic and shrunken lung.

Out of the 10 cases excluded from the analysis because of failure to recover tubercle bacilli from the resected specimen or the sputum, all 10 had cavities in the resected specimen, 5 with thick wall and 5 with thin wall and 3 had necrotic nodules also. Four of these were re-treatment cases. Although there was no doubt about the tuberculous nature of the lungs in these cases, they have been excluded from'the analysis because of the failure to demonstrate tubercle bacilli.

Of the 56 cases included in the study, 30 were males and 26 females. Twenty two were in the age group 10 to 20 years and 29 in the age group 21 to 40 years, the remaining 5 being more than 40 years old. In 29 cases pneumonectomy had been performed and in 27, a lobe or a lobe and a segment of another lobe had been resected.

Methods

Lung or part thereof was wrapped in dry sterile gauze after the resection and transported in a sterile glass jar from TB Hospital Mehrauli/G.B. Pant Hospital to the New Delhi TB Centre laboratory as quickly as possible. No water or saline was added to the specimen in the sterile jar during transit. The lung was processed for bacteriological studies as soon after its receipt in the laboratory as possible. The total time between resection and bacteriological study was usually about 3 hours, somelimes even less but never more than 4 hours. The pre-operative skiagrams of the patients were also received alongwith the specimen. After macroscopic examination of the specimen, palpation for nodules etc. and study of skiagrams, individual lesions were selected and taken out. With a view to avoid cross contamination, different sets of sterilized instruments were used for each lesion. After the nodule had been opened up, the contents were taken out with a wet swab for direct smear and culture. If the nodule did not show any evidence of necrosis, the entire nodule was shelled out and used for direct smear and culture. Cavities were opened by a snick with the scissors and the contents, if any, swabbed out. A portion of the wall of the cavity was then taken for examination. If the wall of the cavity was necrotic at some places and clean at others, only the necrotic portion was taken out. Other lesions such as pleura, hilar glands, bronchial wall etc. were also dissected out in some cases.

In all, 312 individual lesions, including contents of the cavities*, were studied. The number of lesions from each case ranged from 2 to 12. After the material for bacteriological examination had been taken, the remaining specimen was sent for histopathological examination if the diagnosis was equivocal especially in cases where the spulum had never been found to be positive.

In the case of nodules or cavitary contents, 3 swabs were usually made. One of three swabs was used to make smears and the remaining two were used for culture. The smears were stained by the Ziehl Neelsen technique (Appendix I) and examined for the presence of AFB. The smears were marked as negative if not even 10 bacilli could be seen in the smear after 5 minutes' search. The smears were marked positive if 10 or more bacilli were seen.

The two swabs for culture were first subjected to the action of 5% oxalic acid in sterile test tubes, for a period of 20 minutes and then 5% sodium citrate solution for an equal length of time (20 minutes), after which the swabs were used for inoculating four lubes of L.J. medium without potato starch (I.U.A.T. medium)' The inoculated tubes were incubated at 37°C for a period of 6 weeks in the first instance with weekly readings; if the culture was negative at the end of 6 weeks, the culture was retained for a further period of 6 weeks before being discarded as finally negative.

In the case of hard nodules, cavity wall gland, pleura and bronchial wall, the specimen was cut finally into very small pieces with sterile scissors and forceps (separate sets for each piece of tissue) and transferred to a sterile mortar in which it was thoroughly macerated with 2-3 ml of sterile distilled water to give a suspension. This material was transferred to a sterile universal container and incubated with 4% NAOH for a period of 20 minutes at 37°C. After the incubation, it was well shaken, and twice the amount of distilled water was added and again it was shaken well. The entire contents were now centrifuged at 3000 RPM for 20 minutes. In the first 31 specimens, the supernatant fluid was discarded and the deposit was plated on the surface of four tubes

* For sake of convenence, cavily contents have been counted as separate 'lesions'.

of Lowenstein Jensen medium without potato starch (I.U.A.T. medium). The tubes were incubated as for swab cultures. It was subsequently suggested that the culture of supernatant fluid may yield more positive results and less contamination than culture of the deposit. For the last 25 specimens, therefore, two sets of tubes of L.J. media were inoculated after contrifuging; one set (i.e. two tubes) with the supernatant fluid using sterile pipettes, and the other two with the deposit after decanting the supernatant fluid. The incubation procedure was identical.

The grading of cultures was as follows: —

Actual number of colonies, if below 20

+ = 20 to 100 colonies.

+ + = more than 100 colonies or confluent growth.

Sensitivity tests to SM, NH, PAS and thiacetazone (Appendix II) were carried out on all positive cultures. The technique of sensitivity testing was identical for cultures obtained from sputum and lesions. An attempt was made to get a pre-operative specimen of sputum or a sputum culture from the hospitals so that the sensitivity testing of the sputum and lesion cultures could be carried out simultaneously in the same laboratory with the same technique. This, however, did not materilize and the sputum sensitivity tests were, in many cases, carried out in the hospital where resection was performed.

Most of the positive cultures* were further subjected to the following tests:—

1. Catalase (qualitative) Test (Appendix III)

2. Niacin (qualitative) Test (Appendix IV)

Results

Tabie 1 shows pre-operative bacillary status of the sputum in relation to bacillary status of the resected lung specimens. Out of the 56 cases included in the analysis. 19 were sputum negative (by direct smear and culture) at the time of operation, and tubercle bacilli could be recovered from the lesions in 7 of these 39 cases. This corroborates the almost universally accepted finding that negative sputum does not necessarily exclude the possibility of the presence of bacilli in the lung lesions. In all, 39 lung specimens were positive for AFB and in the case of remaining 17, where all the studied lesions were negative, the pre-operative sputum was positive in 5. This is an unusual finding since unless some lesions communicating with the bronchial tree contained bacilli, sputum could not have been positive. In 32 cases both sputum and at least one lesion were positive and in 12, sputum and all lesions were negative.

Table 2 shows the bacillary content of the lesions in relation to the period that the sputum had been negative before resection in the 19 cases. None of these had been sputum negative for more than 12 months before operation. There were 5 cases who had been sputum negative for 6 to 12 months before the operation and tubercle bacilli could be demonstrated in the lesions in only one of them. In the case of 12 who had been sputum negative only for 3 to 5 months before operation, tubercle bacilli could be demonstrated in some lesion or other in 4 of these. All lesions were positive in the two cases who had been sputum negative for less than 3 months. There is thus some suggestion that the longer the period during which sputum had been negative before resection, the lesser the chance of the bacilli being present in the resected specimen. The table also shows that the nodules were more often recative than cavities, if present.

Table 3 shows the bacillary content of lesions in relation to the duration of pre-operative chemotherapy. There appears to be negative association between duration of chemotherapy and the bacillary content of the lesions. This was only to be expected since continued positivily of sputum inspite of prolonged chemotherapy was one of the major indications for resection.

No attempt has been made to analyse the results in relation to the various drug combinations used. All the patients had had practically all the 4 standard drugs in various combinations, never less than 2 at a lime. Reserve or second line drugs were used in one case only for six weeks before the resection.

Table 4 shows the regularity* with which the patients took the drugs in relation to the bacillary content of the lesions. Of the 32 patients who were known to have taken drugs with a regularity of more than 80%, the lesions in 20 were positive, whereas 9 out of

* These tests could not be carried out for positive cultures from the first 14 specimens.

* Regularity has been defined as drugs actually consumed as a percentage of the amount that should have consumed in any period.

TABLE 1

Bacillary status of lesions and pre-operative sputum status of the 56 patients included in the study

	At least one lesion positive	All lesions negative	Total
Sputum positive	32	5	37
Sputum negative	7	12	19
Total	39	17	56

TABLE 2

Bacillary status of lesions in the sputum negative patients

Period sputum negative	Total	Cavity positive	Nodule positive	At least one lesion positive	No lesion positive
< 3 months	2	1	2	2	0
3—5 months	12	4	1	4	8
6—12months	5	1	0	1	4
Total	19	6	3	7	12

TABLE 3

Bacillary status of lesions in relation to duration of pre-operative chemotherapy in the 56 patients

Duration of chemotherapy	At least one lesion positive	All lesions negative	Total
< 6 months	1	—	1
6 — 12 months	7	9	16
13—24 months	34	6	20
> 24 months	17	2	19
Total	39	17	56

10 with regularity of less than 80% were positive. This difference though apparently substantial could_have been influenced by other factors also, apart from regularity. In 14 cases it was not possible to ascertain the regularity with which the drugs were taken, since almost

TABLE 4

Bacillary status of lesions related to regularity of pre-operative chemotherapy in 56 patients

Regularity	At least one lesion positive	All lesions negative	Total
<80%	9	1	10
>80%	20	12	32
Not known	10	4	14
Total	39	17	56

the entire treatment before resection was taken elsewhere and the patient could not give any definite idea about the quantity of drugs consumed a ad the period of treatment before admission in the hospital for surgical treatment.

Table 5 describes in detail the 312 individual lesions taken out from the 56 specimens and the bacillary content of the individual lesions. Of the 98 nodules taken out for examination, 59 were necrotic and the remaining 39 were hard and fibrotic in character with no evidence of central necrosis or softening. In all, 76 cavities were studied out of which 24 cavities were dry and therefore the contents of only the remaining 52 cavities were examined. A portion of the bronchial wall was taken for examination in 34 cases; out of these the bronchial mucosa appeared to be clean and healthy only in 8 instances. A portion of the pleura was taken for examination in 12 cases and in all these the pleura was very thick and adherent to the sub-pleural lesion. Thirty eight hilar glands were examined and out of these, only 7 glands showed evidence of central necrosis or softening. In two cases, the resected lung neither showed a cavity nor any definite nodule. In one of these the lobe was considerably shrunken and fibrosed following a thoracoplasty carried out nearly 4 years ago and in the other case the entire lung was atelectatic and fibrosed following primary disease (bacteriologically confirmed) in a child 10 years old. In both these cases, a portion of the lung tissue was processed for bacteriological examination.

A noteworthy feature of this table is the very small number of lesions (7 only) which were positive by direct smear but were culture negative. This is contrary to the almost universally reported finding of the Western workers and will be discussed later. Three of these were necrotic nodules, one hard nodule and three cavity contents. These 7 lesions were from 6 cases and in 3 of these, some other lesions were culture positive. In three cases where cavity contents were positive by direct smear but negative by culture, bacilli could be grown from the cavity wall in one case but in the other two, the cavity wall and all other lesions were negative by direct smear and culture. In two cases, one necrotic nodule each was direct smear positive but culture negative and in both of these other nodules were negative by direct smear and culture but the cavities in both were culture positive. In the sixth case, one necrotic and one hard nodule were direct smear positive but culture negative and no other lesion in this case was positive by direct smear and/or culture. Pre-operative sputum was positive in four cases and the sputum in the other two had been negative for only 1 month and 5 months. In three of the cases, bacilli in sputum had always been sensitive to the four standard drugs.

Since their number is so small as compared to total positives, these 7 direct smear positive but culture negative lesions have not been considered separately and, for the sake of subsequent tables, a positive lesion has been taken to mean 'positive by any means i.e direct smear and/or culture'. In all, 73 lesions were positive by direct smear but 7 of these were negative by culture; 159 were positive by culture and 153 were negative by culture. Thus, a total of 166 specimens were positive by direct smear and/or culture and 146 were positive both by direct smear and culture.

Out of the 59 necrotic nodules, bacilli could be demonstrated in 33 or nearly 56%. In the

TABLE 5

Bacillary** slants **of different lesions from the 56 resected lung specimens

	DS pos. Cult pos.	DS neg. Cult pos.	DS neg. Cult. neg.	DS Pos Cult. Neg.	DS Pos Cult. Neg.	% positive
Nodule	N 59	12	18	26	3	56
	H 39	2	13	23	1	41
Cavity Content	C 6	0	1	5*	—	17
	N 46	28	6	9	3	80
Cavity Wall	C 16	—	2	14**	—	14
	N 60	17	30	13	—	78
Br. Wall	C 8	—	1	7	—	12
	N 26	5	11	10	—	62
Pleura	12	—	4	8	—	33
Gland	H 31	1	69	24	—	22
	N 7	1	1	5	—	28
Lung Tissue	2	—	—	2	—	0
Total	322	66	93	146	7	

C=Clean H=Hard N=Necrotic

*Includes 2 Rud wall cavities (see text)

**Includcs 3 Red wall cavities (see text)

non-necrotic nodules, only 16 out of 39 or 41% were positive for AFB. Of the 76 cavities, the wall was wholly or parity necrotic in 60; clean, smooth and glistening white in 13 and red-looking like fresh granulation tissue in 3. The last three have been grouped with the clean-wall cavities, giving 60 cavities with necrotic wall and 16 with clean wall. The cavit contents were p0sitive for AFB in nearly 80% of the cavities With necrotic walls where as of the cavities with clean wall, the contents were

TABLE 6

Comparative bacillary status of cavities and nodules in 38 cases

Nodules	Cavities		
	Positive	Negative	Total
Positive	20	2	22
Negative	11	5	16
Total	31	7	38

TABLE 7

Bacillary status of nodules and cavities related to pre-operative sputum status

	Nodule			Cavity		
	Positive	Negative	Total	Positive	Negative	Total
Sputum Positive	45	30	75	40	10	50
Sputum Negative	4	19	23	9	17	26
Total	49	49	98	49	27	76

positive only in 16%. Similarly, the cavity wall was positive in 78% of the necrotic cavities and 12% of the clean cavities.

Where bronchial wall was healthy, only one out of the 8 lesions was positive but where the bronchial mucosa did not appear to be healthy, 60% of the lesions were AFB positive. Where bronchial wall was positive, the cavity which it drained was also positive, though the draining bronchus of positive cavities was not always positive. One third of the pleural specimens were positive. As for the hilar glands, the percentage of positives was practically the same in necrotic and hard non-necrotic glands. Where unselected portion of the lung tissues was examined, both were negative for AFB.

Whereas 25.4% of all necrotic nodules were positive by direct smear, in the case of hard nodules, tubercle bacilli could be demonstrated by direct smear in only 7.7%. The difference is statistically significant ($P<0.02$). Similarly, contents were positive by direct smear in 59.6% as against 23.7% of cavity walls. This difference too is highly significant ($P<0.001$), Thus the bacilli are likely to be more numerous in the contents of a cavity than in its wall and in the contents of a necrotic nodule than in a fibrotic one.

Table 6 shows the bacillary status of the cavities and nodules in 38 cases where the resected specimen had one or more cavities and one or more nodules were also studied. In 22 cases with positive nodules, the cavities were negative in two cases only but in 31 cases with positive cavities, nodules were negative in as many as 11 cases. This again points to the probability of finding bacilli more in cavities than in the nodules.

The bacillary status of the more important lesions i.e. nodules, cavity contents and cavity walls have been analysed in respect of pre-operative sputum status in table 7. Considerably more lesions were found positive in sputum positive than in sputum negative cases. Further, more cavitary lesions are on the whole positive than nodules in both sputum

TABLE 8

Variability of lesion cultures related to pre-operative sputum state in the 56 patients

	Pre-operative sputum positive	Pre-operative sputum negative	Total
All lesions positive	12	5	17
All lesions negative	5	12	17
Some lesions positive	20	2	22
	37	19	56

positive as well as sputum negative cases. But tubercle bacilli could not be demonstrated in as many as 30 of the 75 nodules and 10 of the 50 cavities in sputum positive cases.

Table 8 shows that out of 56 specimens, only in 34 was the bacillary content of all lesions similar; all lesions were positive in 17 and all lesions negative in another 17. In the remaining 22 or 40% of the total, some lesions were positive and some negative. Further, correlation was much better in sputum negative cases than in sputum positive cases, where, in only 46% of the cases the bacillary content, whether positive or negative, was identical in all lesions.

In 10 of the 56 cases included in the study, no cavity could be demonstrated in the resected specimen (Table 9). In 23 specimens there was one cavity only, in seventeen 2 cavities each and in six there were multiple cavities. The total number of cavities studied in the forty-six cavitary cases was 76.

Table 10 shows the size* of 76 cavities and the nature of their wall. Twenty eight cavities were small, 26 medium sized and 22 large. Nearly 80% of the cavities had thick wall, and there was no appreciable difference in the proportion of thick and thin walled cavities in relation to their size. The difference in the bacillary status of necrotic cavities (which were also tbick-walled) and clean (thin-walled) cavities has already been referred to in table 5.

The frequency of positive results in relation to cavity size is shown in table 11, The chances of finding bacilli do not, on the whole, vary significantly with the size of the cavity as far as the bacillary content of the wall of the cavity is concerned (X^2=2.44 for 2 d.f., 0.20< P<0.30). However, as far as the cavity contents are concerned, the percentage of positives was somewhat less in the large cavities, although numbers being too small, test of significance is not possible. This is contrary to the findings of Stewart et al (1956) in whose series, large cavities were negative less often than small cavities.

*The cavities were graded as follows :—
Small : Less than 2 cm. in diameter.
Medium : 2-4 cm. in diameter.
Large : More than 4 cm. in diameter.

TABLE 9

Pattern of cavitation in the 56 resected lung specimens

No cavity	10
One cavity	23
Two cavities	17
Multiple cavities	6

Table 12 shows the correlation between the presence of the bacilli in the cavity contents and the cavity wall in respect of 52 cavities where the cavity content and the wall were both examined. As mentioned earlier, the remaining 24 cavities were dry and no contents could be examined. Out of the 52 cavities, both the contents and the wall were positive in 35 and in 8, both the wall and the contents were negative. There was a discrepancy between the result of cavity wall and contents in 9 only, showing very good correlation between the cavity content and the wall. In the 24 cavities where only the wall was examined

TABLE 10

Distribution of cavities according to size and thickness of the wall

Size of Cavity*	Total	Thick	Thin
Iarge	22	17	5
Medium	26	23	3
Small	28	20	8
Total	76	60	16

*For gradation of sire of cavities, see the'text.

TABLE 11

Bacillary status of cavitary contents and cavity walls according to size of the cavities

Size of Cavity	Contents			Wall		
Large	Positive. 8	Negative 6	Total 14	Positive 15	Negative 7	Total 22
Medium	20	2	22	19	7	26
Small	12	4	16	15	13	28
Total	40	12	52	49	27	76

TABLE 12

Bacillary status of cavity wall related to bacillary status of cavity conten ts

	Cavity contents		
Cavity wall	Positive	Negative	Total
Posilive	35	4	39
Negative	5	8	13
Total	40	12	52

(because the cavities were empty) 10 were positive and 14 negative.

A few words regarding correlation of cavities as seen on the skiagram and their presence the specimen would not be out of place. men

Out of the 56 total cases, there was correlation between radiological evidence of cavity and actual cavity in the specimen in only 32 i.e. 57 percent of the cases. In 18 i.e. 32 percent of the cases, cavity was present in the speci-in but no cavity was seen radiologically, in

TABLE 13

Resistance pattern of bacilli from lesions related to resistance pattern of bacilli from sputum (pre-operative)

Sputum status	Bacilli sensitive in all lesions	Bacilli resistant in some or all lesions	All lesions negative	Total
Bacilli sensitive	2	6	12	20
Bacilli resistant	0	21	4	25
Sensitivity not known	I	6	4	11
Total	3	33	20	56

a plain skiagram of the chest (absence of cavity was not confirmed by tomography). In the remaining 6 i.e. 11 percent of the cases, the radiological appearance was suggestive of a cavity but no cavity was seen in the specimen. Of these 6 cavities not confirmed in the lesion, roengenographic shadow simulating a cavity was medium sized in 3 and small in the other 3. In two cases the cavities were multiple (all small) and in the remaining 4, there was only one cavity each. In the 18 cases, where no cavity was seen in the skiagram, there were 24 cavities seen in the lung specimens. Sixteen of these were small and 8 medium or large. In 22 out of the 24, the cavity wall was thick and necrotic and in two the wall was thin and clean. It would thus be seen that failure to see a cavity in the plain skiagram does not necessarily exclude the actual presence of a cavity in the lung.

As already stated, sensitivity tests were carried out on all positive cultures. In 23 of these 29, the resistance pattern of the bacilli in the sputum tallied, by and large, with the pattern in the lesions, showing very good correlation. In only 6 cases, was the resistance pattern different.

Cultures of all lesions were negative in 20 cases*. Out of the remaining 36, the bacilli in all lesions were sensitive to all the 4 standard drugs in 3 cases. In two of these, bacilli in the sputum were sensitive and in the third the sensitivity of the sputum bacilli was not known. The duration of pre-operative chemotherapy in these three cases was less than 6 months, 6 to 12 months and over 12 months,

This leaves 33 cases, where one or more lesions harboured bacilli resistant to one or more standard drugs. In 4 cases the bacilli were resistant to one drug, in 10 cases to two drugs, in 13 cases to three drugs and in 6 cases to all the four standard drugs. Out of the 159 lesions, where culture was positive, bacilli were resistant to INH in 84, to streptomycin in 78, to PAS in 37 and to thiacetazone in 52.

A significant finding was that out of the 36 cases where the sensitivity of the lesions was known, the sensitivity pattern was similar in all lesions in only 10. In the remaining 26, the resistance pattern of the various lesions was different.

The correlation between sensitivity of bacilli in the sputum and the lesion is shown in Table 13. In the case of sputum, a case was marked as harbouring bacilli resistant to a particular drug if resistance had been demonstrated in any sputum culture, initial or immediate, pre-operative or at any other time during the course of treatment. In the 11 cases, however, sputum sensitivity tests were not available. Excluding cases in which all lesion cultures were negative there were only 29 cases where sensitivity of bacilli in the sputum was known and at least one lesion was positive.

Table 13 also shows that in the 20 cases in which the bacilli were found to be sensitive in the sputum all along, the lesions were culture negative in 12 and the bacilli were sensitive in all lesions in 2 cases and resistant in the remaining 6. But of the 25 cases where the bacilli in the sputum had shown evidence of resistance to one or more drugs, sometime or other during treatment, the lesions in only 4 cases were culture negative and in the remaining 21, some or all of the lesions showed resistant bacilli.

*In three of these, the lesion was direct smear positive.

There was no case where the sputum showed resistant bacilli but all the lesions showed sensitive bacilJi.

The frequency of finding resistant bacilli in the nodules and the cavities was almost equal though Canetti, (1954) found cavities harbouring resistant bacilli more often than nodules.

Catalase activity was tested for 84 lesion cultures which were resistant to INH and 78 cultures resistant to streptomycin. The results are shown in Table 14. Seventy-nine INH

TABLE 14

Catalase activity of drug resistant lesion cultures

	INH Resistant	SM Resistant
Catalase positive	5	20
Catalase negative	79	58

resistant cultures showed absence of catalase activity. Of the 78 streptomycin resistant culture, 58 were catalase negative. It is however, interesting to note that all these 58 cultures were resistant to INH also. All cultures where the bacilli were resistant to streptomycin but sensitive to INH were catalase positive, thus confirming that whereas INH resistant cultures are mostly catalase negative, the same does not hold for cultures resistant to streptomycin.

Table 15 shows niacin activity of the 131 cultures, where this test could be carried out. All cultures were niacin positive. In 10, the activity was rather weak and in two the niacin activity was

As already mentioned earlier, two sets (of 2 tubes each) of cultures were put up from 170 lesions, one for the supernatant fluid and the other for the deposit after homogenizing and centrifuging the material. The correlation between the culture results of the supernatant fluid and the deposit is shown in Table 16. Both, cultures were positive in only 45 lesions. There were, however, 32 lesions where the deposit culture was positive but the supernatant fluid culture was negative. There was not a single lesion where the supernatant fluid culture was positive but the deposit culture negative.

As regards contamination of cultures, it was found that 33 tubes out of 340 (9.7%; were contaminated in the case of supernatant fluid culture and 27 (7.9%) in the case of deposit cultures. The contamination rate being not higher in deposit cultures than the supernatant fluid cultures but the yield of positive culture being significantly higher (X^2=32.0for 1 d.f., P<0.001) in the former, the deposit is by far the better material for culture than the supernatant fluid.

Out of 1248 cultures set up in all (four each for 312 lesions), 92 tubes (7.4%) were contaminated. In 68 lesions, only one of the four tubes was contaminated and in 12, two tubes were contaminated. In no lesion, were more than 2 of the 4 tubes contaminated.

Further, 4 tubes were inoculated for each lesion, in order to get as many positives as possible. In all, 159 lesions were culture

TABLE

Niacin activity of resistant and sensitive lesion cultures

Niacin	Niacin Activity		
	Culture Resistant	Culture Sensitive	Total
Positive	98*	23	121
Trace	8	2	10
Total	106	25	131

*In 2 cultures niacin activity was ++.

TABLE 16

Recoverabitity of bacilli from the deposit and supernatant fluid

	Deposit		
Supernatant Fluid	Positive	Negative	Total
Positive	45	0	45
Negtive	32	93	125
Total	77	93	170

TABLE 17

Cumulative number of positive lesion cultures at successive weekly periods

Weeks	4	5	6	7	8	9	10	12	Total
Number of Positive Cultures	2	2	52	95	111	119	121	134	134

positive. Of these all the four tubes were positive in 53, three tubes positive in 54, two tubes positive in 44 and in 8 only one tube was positive. Thus if only 3 tubes had been inoculated as by Stewart et al, (1956), at least 8 out of 159 positive cultures would have been missed and if only two tubes had been inoculated for each lesion, as is usually done by many workers, 52 out of the 159 lesions found positive would have been missed. This would tend to justify the large number of tubes inoculated.

Table 17 shows the speed of growth in various cultures. Out of a total of 134* cultures found positive after 12 weeks' incubation there were only two cultures which gave a positive result in the 4th week. upto six weeks only 52 i.e. nearly 39 percent had become positive. One hundred and eleven i.e. 82 percent cultures gave a positive result upto 8 weeks and only in 18 percent the cultures became positive between the 8th and 12th week. The speed of growth was analysed in respect of culture of various types of lesions also. Jt was found that in the case of nodules, 29 of the 39 positive cultures were obtained upto 8 weeks. In the case of cavity content, 26 out of 32 and for the cavity wall 29 out of 34 gave growth within 8 weeks. Thus the speed of growth does not seem to vary with the type of the lesions.

Table 18 shows the degree of positivity of the lesion cultures in relation to the bacillary content of the sputum. In sputum direct smear positive cases where the bacillary content is likely to be very high, 41 cultures out of 90 were + + . In direct smear negative but sputum culture positive cases, ++ cultures were 4 out of 20 and in sputum direct smear and culture negative cases, 7 were + + out of 22. However, taking +and ++cultures together, there is hardly any difference between direct smear positive, direct smear negative culture positive and culture negative and culture sputum cases, in respect of the degree of the lesion cultures.

Out of the 56 cases, hilar glands were seen in 33 cases. Sixteen of these were amongst the 22 below 20 years of age and 17 amongst the 34 above 20 years of age. In half of the cases with glands in each of the groups (below and above 20 years) the glands were appreciably enlarged (about the size of an almond). As already shown in Table 5, 9 glands from 7 specimens were positive and only 2 of those 9 glands were necrotic, the remaining 7 being hard and fibrotic. Five other glands with evidence of necrosis were however negative. Enlargement of hilar glands is considered to be an evidence of primary infection. It

*In the remaining 25 positive cultures, the speed of growth was not recorded.

TABLE 18

Degree of positivity of lesion cultures related to pre-operative sputum status

	Lesion culture			
Sputum	+	++	20 colonies	Total
DS pos-	40	41	9	90
DS neg. Cult. pos.	15	4	1	20
DS neg. Cult, neg.	14	7	1	22
	69	52	11	132

appears however unlikely that in 17 cases over 20 years of age who had hflar glands, the progressive pulmonary disease was the direct continuation of the primary disease, which the presence of hilar gland* would ordinarily tend to show. It is more likely that the presence of glands in 33 out of 56 cases may not have^ any significance in relation to evolution of disease but merely shows that following primary infection, appreciable enlargement of glands persists in many cases.

Discussion

Study of resected specimens provides excellent means for testing the validity of criteria commonly employed for determining the achievement or otherwise of 'clinical' cure. Sputum conversion and cavity closure as judged from radiological examination of the chest are the two main objective criteria employed for this purpose,

Almost all workers whose work has been referred to in this report and numerous others have reported that negative sputum does not necessarily exclude the presence of viable bacilli in the lyng lesions. In the present study, there were 19 cases who were sputum negative by culture at the time of resection. In 7 of these at least one lesion showed the presence of bacilli. Of all the lesions examined from these 19 cases, nearly l/3rd were AFB positive. Pecora (1959) reported recoverability of bacilli from sputum being only 10 percent less than from the lesions. Bell (1956) on the other hand found that 60 per cent of the lesions in sputum negative cases were negative. These differences may very well be due to the duration for which the cases had been sputum negative. It is plausible that if the lesions had reached the Target Point, the recoverability of bacilli from the lesions would be less than if the lesions were still active, though the sputum may have been converted. Negative sputum, even by culture, does not eliminate altogether the presence of viable bacilli in the lung lesions.

Auerbuch and Small (1957) have pointed out not only to the deficiency of sputum examination as an indicator of healing of lesions but also highlighted the pitfall of the radiological assessment. Falk et al (1954) showed that out of 89 cavities seen in the lesions, 11 were not seen radiologically. Jn the present study 24 cavities present in the specimens were not seen in the pre-operative skiagrams. Fifteen of these cavities were positive, a proportion which is almost similar to the proportion of positive cavities in the entire material. The reverse situation i.e. cavity suspected in the skiagram but not confirmed in the lesion was also seen in 6 of the 56 cases.

An interesting feature of the study was that in 5 cases, not a single lesion was found positive even though the sputum was positive at the time of the operation. A total of 160 lesions were examined in sputum positive patients and 45 out .of these were negative, though some other lesions in many of these patients were positive. This seemingly odd finding could be explained by the bacilli being present in some portion of the lesion and not in the other ; and the portion of the lesion selected for examination was probably not harbouring any bacilli. Canetti (1954) has also referred to the irregular distribution of bacilli ui a lesion. This also explains why in the same lung, some lesions are found positive

and some negative. In the 22 specimens out of 56, some lesions were positive and some negative whereas there were only 17 specimens where all the lesions were positive. Steels (1953) and Barua et al (1960) also made a similar observation.

The bacillary status of the lesions in relations to the duration of chemotherapy has also provided some interesting information. Table 3 shows that out of 19 patients who had chemotherapy for more than 24 months, the lesions were negative only in 2 cases, whereas among those who had treatment for, say, 6 to 12 months, 9 out of 16 were negative. This appears to be paradoxical. However, the type of cases and the indications for surgery have to be taken into consideration. Resection was carried out when sputum was not converted and/or cavities were not closed inspite of prolonged chemotherapy and this would tend to explain the apparent paradox. Johnson et al (1956) reported a similar situation where all specimens in patients with 18 months'treatment gave a positive culture whereas among those with 12 months' treatment only 41 per cent specimens gave a positive culture. The reports in literature on the relation of duration of chemotherapy to the bacillary status of the lesions are extremely conflicting. Barua et al (I960) and Auerbach et al (1955), among others, leported no relationship of bacillary status of the lesion with the length of pre-operative antimicrobial treatment. Pecora (1959) and Hurford and Valentine (1957), on the other hand, are of the opinion that longer chemotherapy reduces the chances of finding viable bacilli in the lesions. The conflict however is to a very large extent due to the different status of patients at the time of resection, most of whom had reached the target point of treatment by that time. Tt appears that the type and extent of disease and positive sputum at the time of operation even in non-cavitary cases, are more significant for the frequency of positive lesions rather than the duration of chemotherapy per se (Falk et al, 1954).

In the present study no cases had been sputum negative for more than 12 months before the operation. Where the sputum had been negative for over 6 months, only one out of the 5 cases had positive lesions, whereas if the sputum had been negative for less than 3 months, all the 2 cases had positive lesions. Stewart et al (1955) reported one positive out of 11 where the pre-operative sputum had been negative for more than 12 months and one out of 4 positive if the sputum was negative for less than 12 months. It appears logical, therefore, to conclude that the chance of finding positive lesions is significantly *reduced* if the sputum had been negative for six (or preferably 12) months before resection.

The bacillary content of the various types of lesions has also been found to vary considerably. Whereas 56 per cent of the necrotic nodules were positive, of the hard nodules only 41 per cent were positive. Many amongst the latter were direct smear negative and only culture positive thus indicating that the bacillary content of the hard nodules is rather low. Canetti (1955) also found necrotic nodules more often positive than hard nodules. The bacillary content of the nodules reported in literature varies considerably. Whereas Heaton et al (1959) found only 5 per cent nodules culture positive, Bell et al (1956) and Hurford and Valentine (1957) found nearly 40 per cent positive. Further, cavities were more often positive than even necrotic nodules (Canetti 1954). When the cavity wall was necrotic, 80 per cent of these were found positive. This difference in the positive rate of necrotic cavities and necrotic nodules has been commented upon and ascribed to lack of air in a necrotic nodule as opposed to a cavity [Canetti (1955) and Klingensmith, (1963)].

Counting cavities with a granulomatous wall amongst the so called 'clean' cavities, there were 16 such cavities in the entire series. Of these 16, the cavity wall was found positive by culture in two and by direct smear in none. In one of these cases where the clean cavity was found to be positive, the bacilli isolated from the lesion were resistant and the sputum had been negative only for 5 months before the operation. In the other case, the bacilli in the lesion were resistant but the pre-operative sputum was positive with bacilli sensitive to all the drugs even though the patient had antimicrobal treatment for 18 months. Although the percentage of positives in this type of cavity is low, it however shows that even a clean looking cavity does harbour bacilli sometimes. Stewart et al (1956) found 2 clean cavities positive out of 11 whereas Decker et al (1955) found 40 per cent open negative positive by culture. The discrepancy between Stewart's study and this study on the one hand and Decker's study on the other is quite likely to be due to the difference in the material. All open negative cavities need not necessarily be thoroughly clean cavities.

The resistance pattern of the bacilli isolated from the sputum and various lesions was correlated. In 23 out of 29 cases where the

resistance pattern of bacilli both from the sputum and the lesion was available, the pattern tallied, by and large. This has also been reported by Heaton et al (1959). An interesting finding was that where the resistance pattern did not tally, it was always a case of bacilli from the sputum being sensitive but the bacilli from the lesion being resistant and never vice versa. Further, even in the same specimen, the resistance pattern of the bacilli isolated from the various lesions also varied. Only in 10 out of 36 cases, the resistance pattern was similar in all lesions. Johnson et al (1956) also came to a similar conclusion.

Table 13 showed that if the bacilli in the sputum were sensitive at the time of operation, there was a greater chance of the lesion being negative. Out of 20 cases where the sputum bacilli were sensitive, all lesions were negative in 12 specimens and some lesion or all resistant in 6. Out of the 25 cases where the sputum bacilli were resistant, all lesions were negative in 4 specimens only and some or all lesions were resistant in the remaining 21 and as pointed out earlier if the sputum was resistant, there was not a single lesion where the bacilli were sensitive. This is in conformity with the finding of Stewart et al (1956) and Bell (1956).

The speed of growth in lesion cultures was also studied. It was found that nearly 82 per cent of the cultures gave a positive result within 8 weeks and about 18 per cent of the positive cultures, needed incubation from 8 to 12 weeks. In the material of Stewart et al (1956), 87 per cent of the cultures were positive in 8 weeks and only 13 per cent required incubation for 8 to 12 weeks. Barua et al (1960) however obtained 30 per cent positive cultures in 3 weeks;. 70 per cent in 4 to 8 weeks and no culture negative at 8 weeks became positive with incubation for any length after 8 weeks. Barua's findings, however, are contrary to the findings of almost all other workers. Tarshis (1952), Hobby (1954), Jones and Gentry (1955) and many others have reported slow growth of the bacilli in cultures from resected lung lesions. Jones, and Gentry (1955) attributed slow growth to the exposure of the bacilli to INH in vivo during treatment but whether this is a significant factor or not is impossible to say, though all patients in our series had had INH. It was also noticed that the speed of growth was no different in lesions which were positive or negative by smear. Heaton et al (1955) have reported that if the lesion was positive by direct smear, prolonged incubation did not increase the number of positive cultures in any way.

One of the most important observations of the study has been that only 7 lesions out of a total of 312 were positive by direct smear and negative by culture after 12 weeks' incubation. Out of a total of 73 lesions positive by direct smear, the culture was positive in 90 percent. This finding is contrary to almost all other reports. (D'Esopo 1952, Canetti 1955, Medlar 1955, Hobby 1955, Heaton et al 1959, Kass et al 1960, Barua et al 1960, Kazlowski, et al 1964 etc. etc.). In some reports the percentage of positive culture among direct smear positives is as low as 5 percent and in others about 50 percent. This difference persists irrespective of pre-operative sputum status of the patients and cavitary and non-cavitary cases. It is difficult to explain this difference. The majority of the cases included in the study were active and more or less 'failures' of chemotherapy., which would be labelled as 'ineffective' in the usual sense of the word since, only the four standard drugs were used for treatment, even if the bacilli were resistant to all or some of them. Though the material on which the western reports are based could have been different, it is unlikely that the material of Barua et al could have been much different from ours, though the latter report does not give much information on type of cases and pre-operative sputum status.

This phenomenon of direct smear positive culture negative lesions has been attributed to various factors e.g. defective culture technique; injurious effect of acid or alkali used as a homogenizer before culture; pH and lactic acid concentration in the lesion and streptomycin injection given to the patients shortly before the operation etc. None of these, however, explains the discrepancy. Some (Steenken 1963) think that most of these bacilli are, in fact, 'dead' bacilli since bacilli are known to be capable of persisting without disintegration, in an intact morphologic (stainable) state for a long time (Canetti, 1955). Others (Hobby, MeDermott) believe that these bacilli are in a state of 'suspended animation' or a state of 'dormancy' or 'decelerated re-production' (Klingensmith, 1963), and can be made to grow by special technique, using special media and prolonged incubation. It could therefore be postulated that either some 'host' or chemotherapy factor [reverse of physico-chemical factor which, in the reported cases, according to Canetti (1955) inhibited the metabolic process of the bacilli] working *in vivo,* is responsible for the viability of bacilli being much less affected in our material than in the case of other reports.

Finally, a study like this should provide

some guidelines for policies regarding treatment of pulmonary tuberculosis in our context. These guide-lines would appear to be :—

1. The modern antimicrobial drugs are incapable of sterilizing all lesions and to that extent, therefore, fall short of an ideal treatment. Whether an ideal drug, capable of eradicating bacilli from all lesions, will ever be available is besides the point. Even when the lesions have reached the 'Target Point' of treatment, some viable bacilli are likely to persist in residual lesions and these constitute the 'seeds' of future relapse (Hobby 1955, Medlar 1955, Ryan et al 1952).

2. Radiology is a very undependable criterion of presence or otherwise of residual cavities in the lung and/or their healing since residual cavities even in sputum negative patients do sometimes contain viable bacilli. Nor are the so called 'clean' cavities always free from bacilli. Sputum conversion alone, too, cannot be a very dependable index of bacteriological cure.

3. Since the duration of chemotherapy depends on several variables such as the type of the lesions, the extent of disease, the sputum status, 'host' factor etc., fixing the duration of optimal chemotherapy at 18 or 24 months is unrealistic. The period for which the sputum has remained negative appears to be a more realistic criterion. If the sputum has been negative for at least 6, preferably 12 months, the bacillary content of the residual lesions is *reduced* to the very minimum.

4. If the sputum at any time during the course of treatment showed the presence of resistant bacilli, the chances of the lesions be coming sterilized are very poor. This would tend to indicate that resection, if possible, would be desirable for patients who during the course of treatment had shown resistant bacilli, even though the sputum may later on have been converted.

5. The large number of positive lesions found in this study, whether due to inadequate pre-operative chemotherapy or otherwise, would tend to justify the approach to surgery that has been adopted in this material. A tentative indication for surgery would appear to be persistent positive sputum and/or radiological evidence of a persistent cavity, even after sputum conversion, especially if the bacilli in the sputum are or had been found to be resistant. If the skiagram does not show any definite cavity and the sputum remains converted for at least 12 months, resection may not be essential as the chance of viable bacilli (and therefore relapse) being present in the residual lesions in such cases would be minimal.

Appendix I

Ziehl Neelsen Staining

Smears were made on new grease-free glass slides from swabs or pieces of macerated tissue. The smears were then fixed by gentle heat by passing the slide rapidly over a bunsen burner flame. The smears were covered with Carbol-Fuchsin solution and heat was applied to the under surface of the slide taking care not to allow the stain to boil over, but to allow steam to rise from the surface of the stain. The stain was allowed to act for 7 minutes. The stain was washed away by water. 25 percent sulphuric acid was poured on the slide and allowed to act for 2 minutes to effect decolourisation. The acid was poured off and slide washed in water. Then methylated spirit was poured over the slide and kept for 1 minute. The slide was washed in tap water. Counter-stain 0.5 percent aqueous methylene blue was poured over the slide and allowed to stand for 30 seconds. The counter-stain was then washed away by tap water and the slide was dried by gentle heat. The smear was examined under an oil-immersion lens for a period of at least 5 minutes.

Appendix II

Sensitivity Tests

The indirect method of sensitivity testing was carried out as follows :—

Sensitivity tests were put up for each positive culture (one of the two tubes which were positive) for streptomycin INH PAS and thiacetazone.

The sensitivity tests were done within 3-4 days of the culture becoming positive.

Approximately 2 mgr (½rd of a loop) of growth from the primary culture on Lowenstein Jensen medium was transferred to a sterile Bijou bottle containing 0.5 ml of sterile distilled water and *5* glass beads of 3 mm diameter. The bottle was shaken manually for 5 minutes to give a suspension.

With a 3 mm external diameter loop of 27 SW.G Nichrome wire, a loopful of the suspension was inoculated on the surface of each slope of the medium used in the sensitivity test.

A control drug free slope was also set up for each culture tested.

The standard H 37 Rv strain was tested with each set of tests.

The slopes of media were incubated at 27°C for 4 weeks. Growth was positive when 20 colonies or more were present. The following were the concentrations of the drugs used in the tests :

Drugs	*Strain*	*Concentration in micrograms per ml of medium*
Streptomycin	Test atrain H 37 Rv	8, 16, 32 1, 2, 4
I.N.H	Test strain H 37 RV	0.2; 1.0; 5.0 0.2; 1.0
P.A.S.	Test strain H 37 RV	2, 4, 8 1, 2, 4
Thiacetazone	Test Strain H 37 RV	1, 10, 50 1, 10, 50

Definition of Resistance

I.N.H. Sensitive : No growth (less than 20 colonies) on 0.2 mcgr/ml isoniazid

Resistant : Growth in 1 mcgr/-ml isoniazid

Doubtful : Growth on 0.2 but not on 1 mcgr/ml

Doubtful tests were repeated and if the same readings were obtained or a more resistant readings, then the organisms were classified as Resistant. On a repeat test when there was no growth on 0.2, the strains were classified as sensitive.

Streptomycin Sensitive : When R.R. was 2 or less

Resistant :When R.R. was 8 or more

Doubtful : When R.R was 4

A doubtful test was repeated from the control slope. On repeat when a R.R. of 4 or more was obtained, the organisms were 'Resistant' and when R.R. was 2 or less the organisms were 'sensitive'.

Thiacelazone A strain which grew on 10 mcgr/ml was classified as Resistant.

P.A.S A strain which grew on 4 mcgr/ml was classified as Resistant.

Appendix III

Qualitative Catalase Test

A qualitative test was performed on all positive cultures slopes.

Reagents (A) 10% v/v Hydrogen peroxide in distilled water

(B) v/v Tween 80 in distilled water.

Method

Equal volumes of reagents A and B were mixed before commencing the tests (any reagent left over from the previous day was discarded). One c.c of this mixture was poured over the surface of the slope of the culture on L.J. medium tube. The L.J. medium tuber was stoppered and laid on the bench in an almost flat position except that the stoppered end was raised one inch above the surface. The reagent was allowed to act for 60 seconds, the reaction being observed all the time during this 60 seconds period.

Results of reaction were recorded as follows : —

O = No bubbles arising from the surface of the colonies in 1 minute.

Positive (+) =Bubbles arising from the surface of the colonies; ranging from easily countable bubbles to marked frothing.

Niacin (Qualitative) Test

Appendix IV

A qualitative test for the presence of niacin activity was performed on all positive cultures.

Reagents

(A) 10% W/V cyanogen bromide in distilled water.

(B) 3% W/V Benzidine in alcohol.

(A control was put up using a H 37 R.V. Strain)

Method

0.5 m of distilled water was added to each Lowenstein slope culture and the stopper well screwed. The culture was now autoclaved with the bottles kept in a sloping position inside the auto-clave, so as to allow the distilled water to cover the surface of the colonies; for 30 minutes at 15 Ibs. pressure to extract the niacin during the first 15 minutes and to ensure sterilisation of the tubercle bacilli in the culture which was complete in 30 minutes. The tubes were removed from the autoclave and set on the bench to allow them to cool to room temperature.

0.25 ml of the aqueous extract (from the autoclaved media tube) was pipetted on to a depression in a porcelain tile.

0.25 ml of reagent B 3% W/V Benzidine in alcohol was added to the extract first followed by 0.25 ml of reagent A 10% W/V cyanogen bromide in distilled water. Reading of the test was done at the end of 10 minutes.

White colour	Negative
Pink to Red	Positive

With each set of tests, a control was set up using an aqueous autoclaved extract of H 37 Rv culture which when treated with reagents A and B gave a pink colour.

ACKNOWLEDGEMENT

This study was carried out with a special grant from the Indian Council of Medical Research, to whom the authors are highly grateful.

Gratitude is also due to Dr. D.N. Gupta, Professor of Pathology, Maulana Azad Medical College Delhi, who carried out histopathological examination of some of the resected specimens.

The authors are grateful to Shri G. P. Mathur, Statistician of the New Delhi TB Centre for statistical evaluation. Several members of the staff of New Delhi Tuberculosis Centre and TB Hospital Mehrauli have helped in the conduct of the study and the preparation of this report. Their help is gratefully acknowledged.

REFERENCES

1 .Auerbach, O. et al; *J. Th. Surg.;* 1955, 29, 109.
2. Auerbach, O. & Small, M.J.; *Am. Rev. Tub.;* 1957,75, 242.
3. Barua, D. et al; *Ind. J. Med- Res.;* 1960, 48, 263.
4. Bell, J.W.; *Am. Rev. Tub.;* 1956, 74, 169.
5. Canetti, G.; *Bull. an. Int. Tub.;* 1954, 24, 144.
6. Canetti, G.; The Tubercle bacillus in the pulmonary lesions of man; 1955.
7. D'Esopo, N.D. et al; Transactions of 10th V.A. Conference on Chemotherapy of Tuberculosis; 1951, 78.
8. D'Esopo, N.D. et al; Transactions of 12th V.A. Conference on Chemotherapy of Tuberculosis; 1953,229.
9. Decker, A.M. et al; *J. Th. Surg-,* 1955,29, 151.
10. Falk, A. et al.; *Am. Rev. Tub.;* 1954, 70, 689.
11. Heaton, A.D. et al.; *J.Clin. Invest,,* 1959, 38, 1376.
12. Hobby, G.L. et al.; *Am. Rev. Tub.,* 1954, 70,191.
13. Hobby, G.L. et al.; Transactions of 14th V.A. Conference on Chemotherapy of Tuberculosis: 1955.
14. Hurford, J.V. & Valentine, W.H.; *Tubercle;* 1957,38,194.
15. Johnson, B.H. & Syer, F.J.: *Dis. Chest.;* 1956, 30, 69,
16. Jones, A.W. & Gentry, W.H.; *Am. Rev. Tub,:* 1955,71,319.
17. Kass, I. et al.; *New Eng. J. Mad.;* 1960, 262, 315.
18. Kazlowski, J.P. et al.; *Tubercle;* 1964, 45, 101.
19. Klingensmith, W.E.; *J. Th. & Card. Vas. Surg.;* 1963, 45, 146.
20. McDermott, W.; Panel Discussion; *Am. Rev. Tub.;* 1953,68,477.
21. Medlar, E.M ; *Am. J. Med.;* 1950, 9, 611.
22. Medlar, E.M.; The behaviour of Pul. Tub. Lesions; *Am. Rev. Tub.;* 1955; Supplement 71.
23. Pecora, D.V.; *Am. Rev. Tub.;* 1959, 79, 41.
24. Ryan, B.J. et al.; *J. Th. Surg.;* 1952, 23, 327.
25. Steele, J.D.; Transactions of 12th V.A. Con ference on Chemotherapy of Tuberculosis; 1953, 209.
26. Steenken Jr. W.; Panel Discussion; *Am. Rev. Tub.:* 1953,68,477.
27. Stewart, S. M. et al.; *Tubercle;* 1956, 37, 388.
28. Tarshis, M.S.; Transactions of 11th V.A. Conference on Chemotherapy of Tuberculosis; 1952, 237

A REPORT ON A SURVEY OF TUBERCULIN SENSITIVITY IN ARMY RECRUITS IN DELHI CANTT.

K.K. GHULIANI AND R.N. VARMA
(From Army Hospital, Delhi Cantonment)

Introduction

The value and limitations of tuberculin testing as an epidemiological tool in determining the prevalence of tuberculous infection are well known. A number of workers from different parts of the country have reported varying tuberculous infection rates (Ukil 1930, Benjamin 1938, Lal *et al.* 1944, Sikand *et al* 1952, and Frimodt-Moller, 1961). Fifty percent of the total population of the country was estimated to be infected during the mass BCG vaccination programme launched in 1951; using 5 mm or more induration as the criterion for positive response to tuberculin test.

In the National Tuberculosis Control Programme tuberculin testing upto the age group 20 years has been done away with as a prelude to BCG vaccination. However, this practice has not been adopted in the Armed Forces where except for new born children tuberculin testing is still a requirement prior to BCG vaccination.

All recruits at the time of enrolment in the Army, school going children of service families, and high risk groups; comprising of medical officers, nursing officers and other nursing staff tending tuberculosis patients are protected with BCG; 10 mm or more being taken as the positive reaction.

This paper reports the findings of a study carried out amongst Army recruits at Delhi Cantonment during the years 1967-69, to determine their status as regards reaction to tuberculin.

Method and Material

Recruits in the .age group 17-25 years joining the Rajputana Rifles Regimental Centre at Delhi Cantonment were the subjects for the study. The recruits hail from parts of Rajasthan, Haryana and Western Uttar Pradesh. A total of 3207 recruits were studied. Each individual was given one Tu RT 23 containing 0,05 per thousand Tweea 80 on the middle of the flexor surface of the left forearm using the standard WHO BCG kit* The reactions were read and recorded after 72 hours. Some of the recruits had been vaccinated earlier during the mass BCG campaign, but it was not possible to elicit the exact time when these vaccinations were given. The only criterion used for judging whether or not a recruit had been vaccinated during the mass campaign was the presence of the vaccination scar.

An induration of 10 mm or more (the standard used in mass BCG vaccination campaign in India at present) was taken as the positive reaction. Individuals showing a reaction of 15 mm and above induration were subjected to a full size chest x-ray and sputum examination. The negative reactors were given BCG vaccination and were retested after 8-10 weeks.

Results

The results of tuberculin testing done on a total of 3207 recruits consisting of both the previously vaccinated and not vaccinated with BCG are shown in the table.

It is seen from the table that in the previously vaccinated group 46.2 percent were found to be negative reactors ; whereas in the previously not vaccinated 58.9 percent gave a negative reaction.

The frequency distribution of the sizes of indurations in both the groups is shown in figures 1 and 2. Fig. 1 shows that in those previously vaccinated 25.3 percent exhibited a low grade sensitivity with induration between 3 and 8 mm, whereas 465 (53.8 percent) could be classified as positive with induration of 10 mm and above. It is noted from Fig. 2 that 31.2 percent of those previously not vaccinated had induration between 3 mrn and 8 mm and 41.1 percent were positive reactors.

A total of 1734 negative reactors was given BCG vaccination. 1 194 of these were retested after an interval of 8-10 weeks ; retesting stowed 107 (89.4. percant)— conversion to tuberculin positivity

Of the 960 positive reactors in the previously not vaccinated group 225 had shown a tuberculin reaction of 15 mm or more. 105

* Tuberculin testing and BCG vaccination were carried out by a Health Inspector trained as BCG Technician at the New Delhi Tuberculosis Centre.

TABLE

Results of tuberculin testing in 3207 recruits

S. No.	Age group	BCG previously given			BCG previously not given		
			Positive			Positive	
		No. tested	No.	Percent	No. tested	No.	Percent
1.	16-20	714	369	51.7	1695	696	41.1
2.	21—25	156	96	61.5	692	264	41.1
3.	Total	870	465	53.8	2337	960	41.1

DISTRIBUTION OF THE SIZE OF INDURATION

Fig. 1

PREVIOUSLY VACCINATED

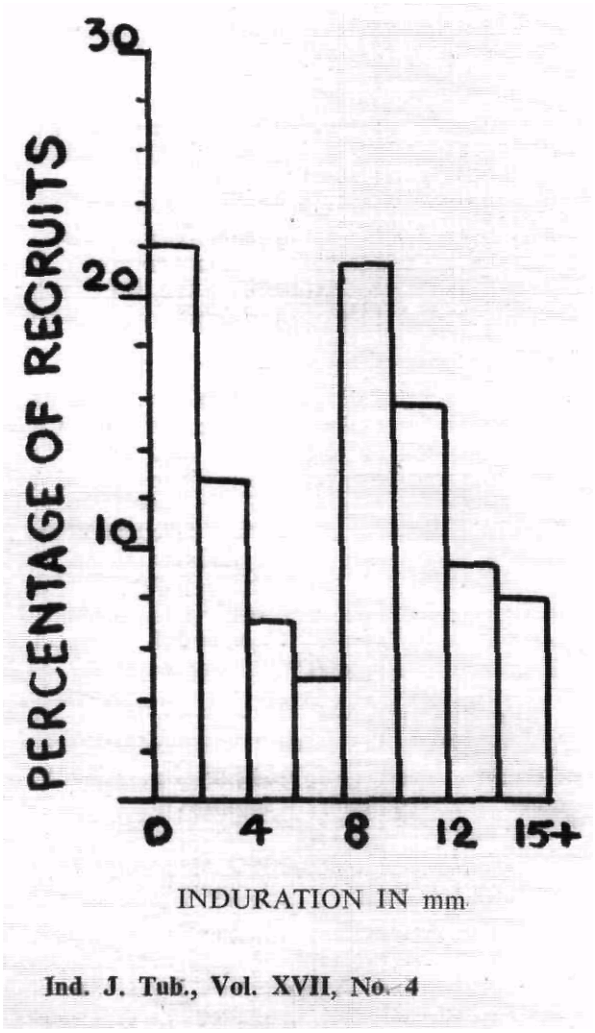
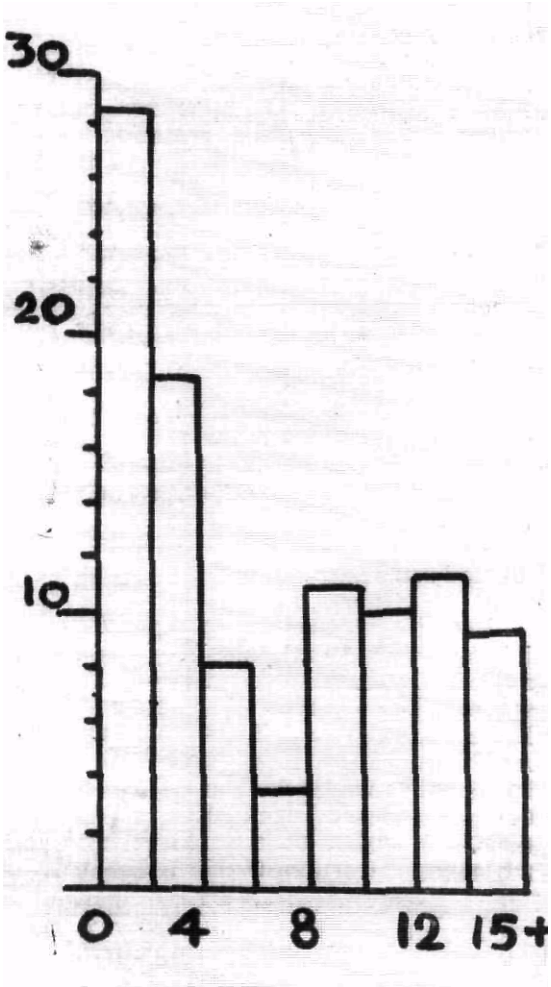


Fig. 2

PREVIOUSLY NOT VACCINATED



(46.8 percent) of them were further investigated with a full size chest x-ray and sputum examination. None of them showed any evidence of active disease. However, none of the positive reactors were subsequently followed up to determine whether the risk of developing tuberculosis for those with an induration of 15 mm or more was any greater than for those with an induration of less than 15 mm initially.

Discussion

Prevalence of tuberculin positivity in various pans of the country has been reported to be more than 65 percent above 15 years of age by Ukil (1930), Benjamin {1938), Sikand and Raj Narain (1957) and Raj Narain (1962). These rates may not, however, be comparable because of the varying dose and tuberculins used and the criterion of positivity. However, contrary to the above findings this study has shown that in the previously not vaccinated group only 41 percent in the age group 16-25 years were positive to tuberculin.

In the group previously vaccinated 46.2 percent were found to he negative reactors. On further analysis of the table it is noted that in the age group 16-20 years 48.3 percent were negative whereas in the age group 21-25 years 38.5 percent were negative ; this difference is not statistically significant. However, it is apparent that there is a definite waning off of tuberculin allergy with the passage of lime, which is known to occur ; this is evident from the table which shows that 46.2 percent of the previously vaccinated group exhibited a negative reaction to tuberculin. Therefore, for protection against the disease to continue, re-vaccination is considered necessary, preferably at an age when the individual is exposed to the population at large with a change in environment.

A conversion rate of 89.4 percent in 1194 recruits re-tested was obtained. This is fairly high and compares favourably with the conversion rates obtained under the mass BCG campaign.

The value of the size of tuberculin reaction vis-a-vis selection of persons for x-ray examination in tuberculosis case finding is also reported : adolescents presenting a strong tuberculin reaction run an increased risk of developing tuberculosis (Almeda and Almeda, 1964 ; and Medical Research Council of Great Britain, 1959). Griffith (1961) reported that the intensity of the tuberculin reaction may be of diagnostic significance. He found cases of tuberculosis only in children with strong reactions to the test. On the other hand, a study of the Tuberculosis Chemotherapy Centre Madras in which the close family contacts of index cases treated at home were followed up for a period of 5 years showed that the attack rate of tuberculosis during the five years was unrelated to the size of the reaction to the initial tuberculin test with 5 TU (Kamat *et al.* 1966).

In the present study, a total of 105 recruits showing an induration of 15 mm and above from the group not previously vaccinated were further investigated with a full size chest x-ray and sputum examination ; none of them showed any evidence, whatsoever, of active disease. This study, though limited, does not lend any weight to the value of the size of tuberculin reaction as an indication of further investigation in finding active disease.

Summary

A study of tuberculin sensitivity carried out amongst Army recruits at Delhi Cantt is reported. In the group previously vaccinated 53.8 percent and in those not previously vaccinated 41.1 percent were found positive. This finding is discussed. A conversion rate of 89.4 percent in those given BCG vaccination was obtained on re-test after 8-10 weeks. The study does not justify the value of the size of tuberculin reaction in adults in selecting casss for further detailed investigations.

ACKNOWLEDGEMENTS

The authors feel grateful to Dr. N. K. Menon, Adviser-in-Tuberculosis, Directorate General of Health Services, Government of India, New Delhi for a critical review of the paper and for offering valuable suggestions.

REFERENCES

1. Almeda, F. Das Neves ; and Almeda J.M. Das Neves. (1964) *Bull Wld, Hlth. Org.* 30, 519.
2. Benjamin, P.V. (1938) *Indian Medical Gazette ;* 73,540.
3. Frimodt-Moller, .1. (1961). Proceedings of the Seventeenth Tuberculosis and Chest Diseases Workers Conference. Cultack, Presidential Address.
4. Great Britain Medical Research Council, Tuberculosis Vaccine Clinical Trials Committee, (1959) *Brit. Meet. J.*. 2, 370.
5. Griffith, A.H. (1961) *Chest Heart Bull., **24*** 104.
6. Kamat, S.R. ; Dawson, J.J.Y. ; Devdatta, S.: Fox, Wallace.; Janardanam, B.; Radhakrishrnan, C.V. Somasundaran. P.R.; Stott, H. and Velu, S. (1966) *Bull. Wld. Hlth. Org.*, **34,** 517.
7. Lal, R.B. ; Majumdar, S-M. and Ahmed, J. (1944) A Report on tuberculosis survey in an urban arid rural area in Bengal, Government ol' Bengal Publication Department.
8. Narain, Raj. (1962) *Ind. Jour. Tuberc.,9,* 147.
9. Sikand. *et. al.* (1952) Proceedings of the Ninth Tuberculosis Workers Conference Lucknow. P. 116.
10. Sikand, B.K. and Narain, Raj (1957) *Ind.Jour. Tuber.,* 5, No.1.
11. Ukil, A.C. (1930) Indian Council of Medica Research, 17 January.

A DOUBLE-BLIND STUDY TO DETERMINE THE MAXIMUM TOLERATED DOSE OF ETHIONAMIDE, WHEN ADMINISTERED TWICE-WEEKLY TO PATIENTS WITH PULMONARY TUBERCULOSIS

S. DEVADATTA, N.K. MENON, O. NAZARETH, S. RADHAKRISHNA, C.V. RAMAKRISHAN, P.R. SOMASUNDARAM, S.P. USHA AND S. VELD*
(From the Tuberculosis Chemotherapy Centre, Madras)

Introduction

ATI earlier report from this Centre (Tuberculosis Chemotherapy Centre, Madras, 1964) showed that a fully supervised twice-weekly regimen of streptomycin plus high-dosage isoniazid was highly effective in the treatment of patients with newly-diagnosed bacteriologically confirmed pulmonary tuberculosis. However, this regimen involves intramuscular injections of streptomycin and may not always be easy to organize, especially in rural areas and in developing countries with limited resources. For this reason, it was decided to investigate the possibility of replacing streptomycin in the twice-weekly regimen by two oral drugs, namely ethionamide and PAS. Ethionamide was chosen since, apart from isoniazid and streptomycin, it was the most potent drug available at the time, and PAS was included with a view to enhance the efficacy of the regimen. Finally, it was decided that the patients should be given an intensive phase of daily treatment with streptomycin, PAS and isoniazid for two weeks.

Experiments in the guinea-pig had shown that the size of the individual dose of a drug needed to be increased as the interval between successive doses was increased (Dickinson & Mitchison, 1966). As PAS is bulky and the dosage of isoniazid in the twice-weekly regimen was already high, namely 15 mg./kg. body-weight, it was decided to explore the possibility of increasing the dosage of ethionamide to a level higher than that usually employed (0.5—1.0 g.) in daily regimens. An investigation was therefore undertaken to determine the maximum tolerated dose of ethionamide. when administered twice-weekly together with isoniazid plus PAS. Since the assessment of ethionamide intolerance is largely subjective, the study was conducted 'double-blind' with respect to the dosage of ethionamide.

Plan and conduct of the study

The patients came from the poorest sections of the population of Madras City, were aged 12 years or more and had newly-diagnosed bacteriologically confirmed pulmonary tuberculosis.

* Deceased.

Treatment

In the first two weeks, the patients received daily chemotherapy with streptomycin I g., sodium PAS 6 g. (in four cachets) and isoniazid 400 mg. as a single tablet incorporating pyridoxine 6 mg. Subsequently,they received a *twice-weekly* regimen of sodium PAS 6 g., isoniazid 15 mg./kg. body-weight* (incorporating pyridoxine 6 mg.) and ethionamide in the dosage described below, all the drugs being administered at the same time in a single dose under the direct supervision of a nurse at the Centre.

Plan of administration of ethionamide

The prescription of ethionamide was made, in accordance with the plan below, by one of two physicians ('prescribing' physicians), neither of whom interviewed the patients after the commencement of treatment.

Ethionamide was administered to the patients in cachets, each cachet containing either one or two uncrushed tablets of ethionamide 0.25 g.; these cachets were identical in appearance to the cachets containing PAS.

Short-term study

To begin with, ethionamide was administered in a dose of 0.5 g. on four occasions, together with isoniazid and PAS, at intervals of three and four days alternately.

(A) If clear-cut intolerance (that is, intolerance warranting a modification of treatment) did not occur, the dose was increased by 0.25g.; for the next four occasions. This procedure after every *fourth* dose until a dose of 1.5 g. had been tolerated on four consecutive occasions, unless clear-cut intolerance was reported.

(B) If clear-cut intolerance to *any* dose was observed, ethionamide was withdrawn, and

* that is, 400 mg., 600 mg. and 750 mg. for patients weighing less than 30.0 kg., 30.0-44.9 kg. and 45.0 kg. or more, respectively.

instead, *an* equal number of dummy cachets** was prescribed for two weeks, or longer if the toxic manifestations persisted. At the end of this period, ethionamide was reintroduced in the *same* dose and tentatively prescribed for four occasions.

(1) If clear-cut intolerance did not re-emerge, the dose of ethionamide was increased by 0.25 g. for the next four occasions, the subsequent management being as stated in (A) and (*B*).

(2) If dear-cut intolerance did re-emerge, it was considered that the maximum tolerated dose (defined below) had been established. Ethionamide was withdrawn for two weeks (or longer if the toxic manifestations persisted), and an equal number of dummy cachets prescribed. At the end of this period, a longer-term study was commenced.

Definition of maximum tolerated dose of ethionamide

The maximum tolerated dose of ethionamide for a patient was defined as the highest dose of ethionamide (not exceeding 1.5 g.) tolerated twice-weekly for two weeks.

Longer-term study

Once the maximum tolerated dose of ethionamide was determined, the aim was to prescribe this dose for a period of eight weeks, in order to obtain information on longer-term tolerance. If clear-cut intolerance emerged at any time during the eight weeks, ethionamide was withdrawn and the patient prescribed dummy cachets for two weeks, or longer if the toxic manifestations persisted. At the end of this period, ethionamide was introduced in a dose which, was lower by 0.25 g, and prescribed for a period of eight weeks. This procedure was repeated, if necessary.

Assessment of intolerance to ethionamide

The assessment of intolerance lo ethionamide was undertaken by three physicians ('assessing' physicians), who were *unaware* of the plan of administration of ethionamide. In consequence, although they knew that the patients were attending the Centre twice a week to receive an ethionamide-containing regimen, they had no knowledge of the dose of ethionamide received by any patient at *any* point in time during the study.

At the start of treatment, the patients were allotted in equal numbers to the three assessing physicians. On all subsequent occasions, that is, (a) at monthly examinations, (b) after spontaneous complaints, and (c) after default from attendance, each patient was seen by his assessing physician. The patients were never questioned to *elicit* symptoms of intolerance to ethionamide. However, whenever a *spontaneous* complaint was made, the assessing physician interrogated the patient carefully and assessed the severity of the symptoms. If the symptoms were mild, he reassured the patient and persuaded him to continue the chemotherapy. If however, the symptoms were severe or persistent (clear-cut intolerance), he recommended a modification of treatment. The actual modification was made, in accordance with the design of the study, by one of the *two prescribing* physicians. Autiemetic drugs, antihismines and tranquilizers, which might have ameliorated the symptoms, were not prescribed.

Results

In all, 30 patients were admitted to the study. Of these, three stopped attending the Centre, because of domestic problems, before their maximum tolerated dose could be determined. Two were receiving 1.0 g, of ethionamide and the third 0,75 g. at the time. There remain 27 patients (18 males, nine females) in the analysis. Of these, 15 were aged less than 35 years, six were aged 35-44 years and six were aged 45 years or more. The weight was less than 30.0 kg. in two, 30.0—44.9 kg. in 19, and 45.0 kg. or more in the remaining six.

Maximum tolerated dose of ethionamide

Table 1 presents the distribution of patients according to the maximum dose tolerated on four consecutive occasions. Of the 27 patients, 10 (37 per cent) tolerated the highest planned dose of 1.5 g., while three (11 per cent) tolerated 1.25 g. On the other hand, four (15 per cent) tolerated only 0.5 g. and five (19 per cent) tolerated 0.75 g. but not more. When expressed as mg./kg. body-weight, the maximum tolerated dose was 40 mg./kg. or more for four (15 per cent) patients and 30-39 mg./kg. for seven (26 per cent) ; however, it was 19 nig./kg. or less for seven (26 per cent) patients.

** The dummy cachets, each containing a tablet of calcium gluconate 0,5 g., were identical in appearance to those containing ethionamide. They were employed in order to conceal, both from the patient and the 'assessing' physicians that ethionamide was being withdrawn during this period. However, to reassure the patient that some action had been taken following the complaints of side-effects, one undisguised placebo tablet (calcium gluconate 0.5 g.) was also administered with each dose.

TABLE I

Maximum tolerated dose of ethionamide

Maximum tolerated dose* (g.)	Patients No.	%	Maximum tolerated dose* (mg./kg.)	Patients No.	%
0.50	4	*15*	10-19	7	*26*
0.75	5	*19*	20—29	9	*33*
1.00	*5*	*19*	30-39	*7*	*26*
1.25	3	*11*	40-49	4	*15*
1.50	10	*37*			
Total	27	*101*	Total	27	*100*

Complaints of ethionamide intolerance

Of the 27 patients, 24 had complained of *one or more* symptoms of ethionamide intolerance before their maximum tolerated dose was established ; 18 patients complained of vomiting, 11 of giddiness, six of nausea, seven of anorexia and seven of abdominal pain. Of the 24 patients, 16 made the *first* complaint on the 0.5 g. dose, six on the 0.75 g. dose, one on the 1.0 g. dose and one on the 1.25 g. dose.

Number of weeks for which the maximum tolerated dose was received

Once the maximum tolerated dose was determined, the aim was, as already stated, to prescribe it for a further period of eight weeks. In the event, this was not attempted for four patients (with maximum tolerated doses of 0.5, 0.5, 0.75 and 1.0 g.), mainly because of non-cooperation induced by the occurence of ethionamide intolerance in the course of determining the maximum tolerated dose. Another patient, whose maximum tolerated dose was 1.0 g., developed peripheral neuropathy attributed to isoniazid and was withdrawn from the study. Of the remaining 22 patients, only two, both with a maximum tolerated dose of 1.5 g., completed the 8-week period on this dose. Indeed, of the 20 patients who did not complete the 8-week period, 17 developed clear-cut intolerance within two weeks, and remaining three in the third, the fifth and the seventh week.

Tolerance, over an 8-week period, of doses lower than the maximum tolerated dose

It will be recalled that if clear-cut intolerance to ethionamide developed during the 8-week period, as it did in 20 patients, the dose was reduced in steps of 0.25 g. to determine whether the patient could tolerate a lower dose for eight weeks. In the event, only two patients, having maximum tolerated doses of 1.5 g. and 1.25 g., completed eight weeks on a reduced dose, namely 1.25 g. and 0.75 g, respectively. The remaining 18 did not complete eight weeks on any one dose; the last dose received was 0.5 g. for 10 patients, 0.75 g. for three, 1.0 g. for three and 1.25 g. for two patients (Table II), It is of interest that of the 10 patients whose last dose was 0.5 g., five had tolerated earlier, for two weeks, the highest planned dose, namely 1.5 g.

When expressed as mg./kg. body-weight, the last dose received was less than 20 mg./kg. in 14 (78 per cent) of the 18 patients. In none of the patients was it 30 mg./kg. or more, although 6 (33 per cent) of them had earlier tolerated 30-45 mg./kg. for two weeks.

Omission of PAS

Since PAS, like ethionamide, is capable of producing gastro-intestinal side-effects, it was thought that its omission might result in higher values for the maximum tolerated dose of ethionamide. Consequently, a further group of 30 patients (18 males, 12 females) was investigated, the plan of the study being the same except that no PAS was prescribed.

Of the 30 patients, one could not tolerate even 0.5 g. of ethionamide ; the maximum tolerared dose was 0.5 g. for seven patients, 0.75 g, for two, 1.0 g. for four, 1.25 g. for

TAULE II

Last dose of ethionamide received by patients who did not complete eight weeks on any one dose

Last dose of ethionamide received (g.)	Total patients	Maximum tolerated dose* (g.)				
		0.50	0.75	1.00	1.25	1 50
0.50	10	2	1	2	0	5
0.75	3			0	0	0
1.00	3	—	3	1	1	1
1. 25	2	—	—	—	1	1
Total	18	2	4	3	2	7

seven and 1.5 g, for nine patients. Thus, one-third of the patients (10 of 30) could not tote-rate even l.0g. (it will be recalled that the corresponding proportion in patients who received PAS in addition to ethionamide and isoniazid was indentical, namely nine of 27). When these findings became known, the study of longer-term tolerance was terminated.

Maximum tolerated dose of ethionamide related to sex, age and weight

Since females have been reported to have a higher incidence of ethionamide side-effects than males (Verbist and others, 1967 ; Fox and others, 1969), the data were examined for the presence of an association between sex and the maximum tolerated dose in the 57 patients reported in this paper. On average, the maximum tolerated dose was 1.03 g. for 36 males compared with 1.14 g. for 21 females, a non-significant difference (P=0.3).

There was also no evidence that the maximum tolerated dose was influenced by either the age or the weight of the patient.

Discussion

The 'double-blind' investigation reported here was undertaken to determine the maximum dose of ethionamide that could be administered twice weekly to patients with newly-diagnosed bacteriologically confirmed pulmonary tuberculosis. The results are disappointing in that one-third of the patients could not tolerate even 1.0 g. of ethionamide twice-weekly for two weeks, when the drug was administered with isoniazid plus PAS or, indeed, with isoniazid alone. Moreover, of 22 patients who were prescribed their maximum tolerated dose (that is, the maximum dose tolerated on four consecutive occasions) for a period of eight weeks, 20 developed clear-cut intolerance during this period, 17 of them within two weeks. Indeed, nearly all had had symptoms of intolerance before they attained their maximum tolerated dose. These findings are discouraging for the *long-term* use of even a moderately high dosage of ethionamide on a twice-weekly basis in Madras patients.

Fox and others (1969) studied, also in a 'double-blind' investigation, acute intolerance to *individual* doses of ethionamide and prothionamide in East African patients who were under treatment with a daily regimen of isoniazid plus streptomycin. They concluded that in these patients, it would not be possible, as a routine, to increase the dosage of either ethionamide or prothionamide in intermittent regimens above the conventional dosages used in daily regimens.

It has been reported by Prignot, Everaents and Tyberghein (1962) and Gyselen and others (1963) that vitamin B-complex preparations substantially reduce the frequency and severity of the side-effects of ethionamide. Later studies, however, have shown that this is not the case (Verbist and others, 1967 ; Fox and others, 1969).

The design and conduct of this study merit special mention. The study was conducted 'double-blind' with respect to ethionamide

dosage because the assessment of ethionamide intolerance is largely subjective. Further, the plan according to which the ethionamide was administered was withheld from the physicians who assessed intolerance to the drug. In consequence, although these physicians knew that the patients were attending the Centre twice a week to receive an ethionamide-containing regimen, they were completely unaware of the dose of ethionamide received by any patient at *any* point in time during the study. Indeed, they were not even aware that the aim was to increase the dose gradually to 1.5 g. for each patient, that tolerance to each dose was to be assessed on four consecutive occasions or that the ethionamide was temporarily withdrawn whenever clear-cut intolerance developed. Next, by prescribing for eight weeks the maximum dose which had been tolerated on four consecutive occasions, valuable information has been obtained on longer-term tolerance to the drug. The finding that the maximum dose could seldom be tolerated for eight weeks emphasizes the need to have adequately long periods of observation in studies undertaken to assess tolerance to ethionamide.

We are grateful to the clinic nurses who played an important role in the conduct of this 'double-blind' study.

Summary

A 'double-blind' study was undertaken to determine the maximum dose of ethionamide that could be tolerated for two weeks, when administered twice-weekly together with isoniazid plus **PAS.** Of 27 patients, 10 (37 per cent) tolerated the highest planned dose of 1.5 g..;.on the other hand, nine (33 per cent) could not tolerate even 1.0 g.

Of 22 patients who were prescribed their maximum tolerated dose for a further period of eight weeks, only two completed the 8-week period on this dose; two more completed an 8-week period on a reduced dose.

The omission of PAS, in another group of 30 patients, did not result in better tolerance of ethionamide, the number who failed to tolerate 1.0 g. for two weeks being 10 (33 per cent).

These findings are discouraging for the use of even a moderately high dosage of ethionamide on a twice-weekly basis in Madras patients.

REFERENCES

Dickinson, J.M., and Mitchison, D.A. (1966). Short-term intermittent chemotherapy of experimental tuberculosis in the guinea-pig. *Tubercle, Load., 41.* 381.

Fox, W., Robinson, D.K., Tall, R., Mitchison, D.A., Kent, P.W., and Macfadyea, D.M**.** (1969). A study of acute intolerance to ethionamide, including a comparison with prothionamide. and of the influence of a vitamin B-complex additive in prophylaxis. *Tubercle, Lond.,* 50, 125.

Gyselen, A., Prigaot, J., Cosemans, J., and Verbist, L. (1963). Experience sanatoriale des tuberculostatiques de relais. *Lille Medical,* 8, 1151,

Prignot, J., Everaerts, J., and Tyberghein, J. (1962). Manifestations d'intoierance et de toxicite an cours des traitements tuberculostatiques. *Acta Tuberc, Pneumol. Belgica,* 53, 276.

Tuberculosis Chemotherapy Centre, Madras (1964). A concurrent comparison of intermittent (twice-weekly) isoniazid plus streptomycin and daily isoniazid plus PAS in the domiciliary treatment of pulmonary tuberculosis. *Bull. Wld Hlth Org.,* 31, 247.

Verbist, L., Prignot, J., Cosemans, J., and Gyselen, A. (1967). Tolerance to ethionamide and PAS in original treatment of tuberculosis patients. *Scand, J, resp. Dis., 47,* 225.

SOME OBSERVATIONS ON THE OTOTOXIC1TY OF THIACETAZONE

D. DAYAL AND Miss H. SHANTA
(From K.G. Medical College, Lucknow)

Soon after the discovery of streptomycin by Waksman in 1944 its toxic effects on the vestibular apparatus were reported by Hinshaw and Feldman (1945). Since then a constant effort is being made to discover an anti-tubercular drug which is more potent and less toxic.

Thiaceiazone was one of the earliest drugs synthesized in 1946 by Doggak but the frequency of toxic manifestations, especially renal and hepatic, observed in initial trials restricted the use of this drug in special circumstances. Partly because of its toxicity and partly due to the introduction of PAS and INH at about the same time, the drug went into background till the observations of Medical Research Council of Great Britain (1963) showed that the combination of thiacetazorie (150 mg) and INH (200 mg) compared well in its therapeutic effect with that of INH and PAS and was not so toxic as reported earlier.

Encouraged by the good results and convenience of administration this combination is being advocated in our country for the domicilliary treatment of tuberculosis. However, a wide variety of toxic reactions including nausea, vomiting, giddiness, vertigo and bone marrow depression have been reported with the use of this combination. Deshmukh and Master (1962 & 1963) and Menon (1965) reported giddiness as one of the frequent toxic manifestations of. thiacetazone therapy but it could not be said whether vertigo was due to thiacetazone or buclizine hydrochloride. Miller (1966) reported that the drug not only caused vertigo but even potentiated streptomycin toxicity.

However, there is a lack of clinically controlled studies on the detailed examination of cochleovestibular function with long continued use of thiacetazone.

Material & Method

Patients of pulmonary tuberculosis getting treatment at Tuberculosis hospital of K.G. Medical College. Lucknow and Rajendra Nagar T.B. Clinic were taken up for this study.

Detailed clinical examination of every case was done and patients presenting with any other clinical disorder, besides tuberculosis, were not included in the series. A thorough Otolaryngological examination was then done and cochleovestibular functions assessed by tunning fork tests, audiometric examinations, examination for any spontaneous nystagmus, Romberg's test and caloric test. Any patient showing initial cochleovestibular damage was excluded.

A total of 469 patients were studied in five groups of different drug regimens as shown in table I.

Thiacetazone and INH combination was given to two groups of cases ; in 122 patients these being secondary drugs as the patients had previously received more than 30 Gm. streptomycin while in another group of 175 cases these were used as primary drugs. As thiacetazone alone was not given to patients a

TABLE I

Shows the number of cases with various drug regimen

Drug	INH alone as primary drug	TZN+INH as primary drug	TZN+INH as secondary drug	Streptomycin TZN+INH	Streptomycin +INH
No. of cases	70	175	122	82	20
Dosage	300 mg.	150+300 mg.	150+300 mg.	1 Gm.+300 mg. +150 mg.	1 Gm.+300 mg.

TZN—Thiacetazone.
Strep.—Streptomycin.

156

group of 70 cases was given INK for control study. The fourth group of 82 cases was given a three drug regimen of streptomycin + INH+Thiacetazone while 20 cases were given only streptomycin + INH daily.

After start of therapy, these patients were examined at fortnightly intervals, or earlier if indicated by any symptom of toxicity for assessing cochleo-vestibular function or any other side effect of the drug. The follow up period ranged from 6 months to 18 months.

Observations

As shown in table II, TZN+INH combination showed ototoxic symptoms in 9.7% cases when used as primary drug and in 12.3% cases, when used as secondary drug, vertigo, and tinnitus being the commonest symptoms. When, however, streptomycin was administered simultaneously with TZN+ INH, the frequency of toxic manifestation was as high as 82.9% and in this group 4 patients were found to be atoxic.

Table III again shows that with TZN + INH combination labyrinthine damage was found in very small number of cases (4% to 7.4%) while with the addition of streptomycin 46.3% patients showed labyrinthine damage. Deafness was mostly unilateral while vestibular tests showed that unilateral partial canal paresis was most frequent.

Table IV shows that while occasional toxicity was met in the first month with TZN, Streptomycin + TZN combination showed toxicity in 42.7% cases in this period.

It was further observed that TZN+INH combination can be given safely for a period of 6 months or more in as many as 87%-90% cases.

Thus not only the frequency of toxicity increased disproportionately in thiacetazone + Streptomycin combination but the symptoms also appeared much earlier.

Comments

The present investigations thus show that definite cochleovestibular damage does occur in some cases receiving thiacetazone and all the toxic symptoms of thiacetazone therapy cannot be accounted by hypersensitivity or GIT disturbances as reported by Deshmukh (1962) and Goodman and Gilman (1965).

The ototoxic symptoms with the use of TZN + INH combination as primary drugs were observed in 9.7% cases and in 12.3% cases when used in patients who had previously received streptomycin. The

TABLE H

Shows the clinical manifestations pertaining to ototoxicity with various drug combination

Symptoms	INH	TZN+INH as primary drug	TZN+INH as secondary drug	TZN-HNH +Strep.	Strep.+INH
Total cases	70	175	122	82	20
Tinnitus	3	5	8	7	—
Vertigo	5	12	10	54	5
Giddiness		1	1	18	2
Vomiting	1	1	—	5	—
Headache	—	1	5	25	3
Deafness	—	1	3	15	—
Pain in ear	—	1	—	2	—
Ataxia	—	—	—	4	—
Total cases	9(12.9%)	17(9.7%)	15(12.3%)	68(82.9%)	5(25%)

TABLE III

	INH	TZN + INH As primary drug	TZN + INH as secondary drug	TZN + INH + Strep.	Streptomycin + INH
Total No. of cases	70	175 I	122 II	82 III	20
Cochlear					
Unilateral deafness	—	1	2	17	1
Bilateral	—	—	4	3	—
Vcstibular					
Partial canal paresis					
(a) Unilateral	—	5	3	11	1
(b) Bilateral	—	1	1	9	1
Complete					
Canal paresis					
(a) Unilateral	—	—	1	3	—
(b) Bilateral	—	—	1	4	—
Partial in one and complete in other	—	1	—	—	—
Hyperactive	—	—	—	5	—
Total toxicity	—	7(4%)	9(7.7%)	38(46.3%)	3(15%)

TABLE IV

Showing percentage frequency of ototoxicity in relation to the duration of treatment

	INK	TZN+INH as primary drug	TZN-KNH as secondary drug	Strep. + INH+TZN	Strep. + INK
30-days	—	0.5%	0.8%	42.7%	5.0%
31-60	—	4.6%	4.9%	20.8%	10.0%
61.90	1.4%	3%1.6%	4. 1%	10. 9%	5.0%
Abovc-91	11.5%		2 .5%	8. 5%	5-0%
Over all toxicily	1.2.8%	9.7%	12.3%	82.9%	25%

frequency of toxic manifestations is thus nearly the same in the two groups and the previous treatment with streptomycin does not seem to give added risk of labyrinthine damage with TZN therapy. Chemotherapy centre (1965) reported 12% ototoxicitv with thiacetazone but how many of them had ototoxic symptoms is not mentioned. Pines

(1964) in a trial on British patients reported toxicity in 48% of his cases, while only 5% toxicity was found in East African patients (East Africa British MRC 2nd investigation 1963). Pines inferred that racial and genetical differences in susceptibility to thiacetazone may exist accounting for this marked difference in frequency of ototoxicity.

When however, thiacetazoue was administered together with 1 Gm. streptomycin daily, the subjective symptoms of ototoxicity were observed in 82.9% cases while the frequency of objective damage was also as high as 46.3% cases. The incidence is quite high as compared to SM+INH daily regimen (25%) and INH+TZN (9.7 & 12.3%), indicating thereby that addition of streptomycin increases the incidence of toxicity disproportionately. This observation has also been made by Miller et al (1966) who, in a double blind control comparative study of SM+INH and SM+TZN reported 7.8% and 21.4% toxicity respectively.

The high incidence of toxicity with this group may be either due to direct effect of TZN on 8th nerve, and or due to potentiation of streptomycin toxicity by one of the mechanism of drug interaction described by Macgregor (1965).

The chief ototoxic symptoms observed with the use of TZN+INH combination were vertigo, giddiness, tinnitus and deafness. Deshmukh et al (1962) thought that vertigo and giddiness were due to hypersensitivity to drug and in his subsequent studies added antihistamine to this combination with much difference in the frequency of toxic manifestation. Menon (1965) has experienced his doubt whether giddiness was due to antihistamine bucclizine hydrochloride or due to thiacetazone or both. But in our study the patients were given INH+TZN only without any antihistaminic and still they showed giddiness and vertigo, thus ruling out the doubt of antihistaminic being responsible for these symptoms. As no objective ototoxicity was observed in patients receiving INH alone, the toxicity found with INH +Thiacetazone combination can be attributed to thiacetazone alone.

The cochleovestibular investigations have shown that vestibular damage was more common with thiacetazone than cochlear damage in all the three groups. Out of a total of 54 patients showing objective damage with thiacetazone therapy, 27 showed isolated vestibular damage, 9 cochlear lesions while 18 had cochleovestibular damage.

The commonest presentation of the vestibular toxicity observed was partial canal paresis. The vestibular toxicity was observed to be quantitatively severe in 3 drug regimen cases than observed with the use of either streptomycin INH or INH+TZN- Therefore, in agreement with Pamra (1967) it can be concluded that thiacetazone is not a good combination with streptomycin.

Investigations of cochlear component revealed high tone loss ranging between 60 to 80 db.

The periodic follow up of these cases showed that TZN+INH combination can be given safely for a period of 6 months or more in as many as 87%-90% of cases, as the overall toxicity ranged from 9 to 12.3%.

In the patients who complained of symptoms pertaining to ototoxicity continuation of thiacetazone+INH resulted in objective cochleo-vestibular damage in the form of perceptive deafness or canal paresis in about half of them and the drug had to be discontinued. Compensation occurred within 6-8 weeks of cessation of the therapy.

In the remaining 50% of cases when the drug was continued for another 2-3 months, the symptoms increased in severity in 2 cases only. Stoppage of drug in cases of subjective ototoxicity resulted in disappearance of majority of symptoms 4-6 weeks. Thus if thiacetazone is stopped soon at the appearance of symptoms, this early toxicity is reversible in majority as also reported by Goodman and Gilman (1965).

"With 3 drug regimen, continuation of the therapy in patients showing subjective toxicity only resulted in exaggeration of most of the symptoms and the drug had to be discontinued which resulted in disappearance of the majority of the symptoms. But 2 of them developed delayed ototoxicity and showed canal paresis. Out of the 38 cases showing objective damage one case of partial canal paresis developed complete paresis in follow up. In agreement with Gupta and Bhatia (1966) toxicity may progress even after stoppage of drug and may be due to cumulative effect of hypersensitivity of streptomycin.

The clinical efficacy of TZN and INH was favourably comparable to other anti-tubercular drugs. In most of the cases drug was well tolerated and besides the ototic symptoms, other toxic reactions were negligible, only 5 patients complained of pain in abdomen, 2 of

skin rashes, while hepatoxicity was observed only in I case. Except hepatoxicity none of the general toxic symptoms warranted discontinuation of the drug.

Thus the findings of the present study show that the ototoxicity due to thiacetazone is less than what is generally found with streptomycin. The over all ototoxicity occurs in only about 10% of cases and the drug is more toxic to the vestibular than cochlear system. The subjective symptoms appear earlier than objective cochleo-vestibular damage and the cessation of the drug at this stage results in recovery from most of the symptoms. With periodical check up the drug can be given safely to ubout 90% oases for 16-18 months. Combined therapy of thiacetazone with streptomycin has, however, to be completely avoided.

Summary

Otoloxioity to thiacetazone was studied with detailed periodic follow up of cohleo-vestibular functions. A total of 469 patients was divided into five groups. Thiacetazone + 1NH combination was given as primary drugs in 175 patients and as secondary drugs in 122 patients. 82 patients received a 3 drug regimen of TZN+INH+Streptomycin. In a group of 70 patients INH alone was administered, while the last group included patients who were given only streptomycin + INH therapy.

The frequency of subjective symptoms in patients receiving thiacetazone+INH was 9.7% when these were used as primary drugs, and 12.3% when used as secondary drugs. The objective toxicity was present in only 4% and 7.4% respectively in the above two groups. Combined therapy of streptomycin + INH+ TZN, however, gave alarmingly high frequency of objective ototoxicity (46.1%). Thiacetazone + INH combination was found to be satisfactory in clinical outcome as well as tolerance.

BIBLIOGRAPHY

1. Deshmukh, M.D., & Master, T.B. (1962) ; *J.Ind. Med. Prof. 9 :* 4273.

2. Deshmukh, M.D., Master, T.B. & Kulkarni, K.G. (1963), *Current Med. Prac.* 7 : 491.

3. East African British M.R.C. Thiecetazone, *Diphenyl Thionurea Invest, Tubercle* London 41 : 399, 1960.

4. Goodman & Oilman (19665 ; The pharmacological basis of therapeutics HI Edn.

5. Hinshaw, H.C. & Feldman, W.H. (1950) ; *Proc. Mayo. Clin.* 20 : J45.

6. Macgregor, (1965) ; Quoted *Tubercle* London.

7. Menon, N.K. (1965) ; *Tubercle* London 46 : 19.

8. Miller, A.B., Fox, W. & Tall, R. (1966) *Tubercle* London 47 : 33.

10. Pamra, S.P. (1967) ; *Ind. J. Tub.,* 15 : 30.

METASTATIC CARCINOMA LUNG ASSOCIATED WITH SPONTANEOUS PNEUMOTHORAX

O.P. MITAL, R.K. NARANG AND S.K. JAIN
(From G.S.V.M. Medical College, Kanpur)

Pulmonary metastasis is an uncommon cause of spontaneous pneumothorax. Most of the previous reports of this association have been those of metastatic sarcoma. Deposits in the lung secondary to a carcinoma rarely cause pneumothorax; hence our interest in recording this case.

Case report

C.S., a 50-year-old Hindu farmer, had no complaint until July, 1963 when he noticed a lump on the left side of the neck. He was treated by a quack in his village but without getting any relief. On October 8, 1963, while working in his fields, he felt severe pain in the left side of the chest. Later he observed that he could not carry on his work due to shortness of breath and general weakness.

He consulted one of us **(O.P.M.)** on October 25, 1963. He was breathless at rest but there was no cynosis or clubbing of the ringers. A mass of hard glands was palpable on the left side of the neck. It was fixed to the overlying skin. There were signs of pneumothorax on the left side of the chest. The cardiovascular system was clinically normal, the blood pressure was 120/80 and the pulse was regular at a rate of 98 per minute. Liver was palpable two fingers—breadth below the costal margin.

X-ray film of the chest taken on the same day (fig. 1) showed a large pneumothorax on the left side. An ill defined 2 cm. size shadow could be made out in the collapsed lung. There were five rounded opacities of 1-2 cm. size scattered in all zones of the right lung.

Sputum cytology was negative for malignant cells. Bronchoscopy did not show any endobronchial lesion. Biopsy of the glandular mass in the neck revealed highly anaplastic carcinoma. Needle biopsy of the liver snowed fatty infiltration only.

The patient was treated with air aspiration and inhalation of oxygen. In an X-ray of the chest taken one month later (fig. 2) multiple oval and circular homogenous shadows, varying considerably in size, were now evident in the partially expanded left lung. The opacities in the right lung were more numerous as compared to the previous film.

The diagnosis of the case was metastatic carcinoma of the lungs and of the cervical glands. The site of the primary growth could not be ascertained.

The patient left the hospital against medical advice. He died three months later at his home. No autopsy was done,

Discussion

There are previous reports of secondary deposits in the lungs associated with spontaneous pneumothorax (Thorton and Bigelow, 1944; Lodmell and Capps, 1949; Christamann et al, 1950, Shaw, 1951; Leigh and Thompson, 1951: Sherman and Brant, 1954 and D' Angio and lanaccone, 1961). A total of 29 cases are included in these reports. In all but one of the cases sarcoma was the cause of pulmonary metastases. The exception is a case of carcinoma reported by Sherman and Brant (1954). This was a 55 years old man who had a shadow in the apex of the right lung. Six months later he developed a pneumothorax on the

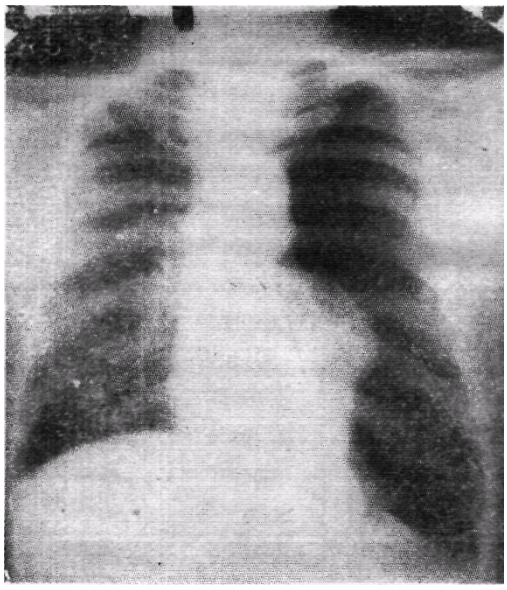


Fig. 1
X- ray chest PA View. There are metastatic shadows on the right side and a large pneumothorax on the left

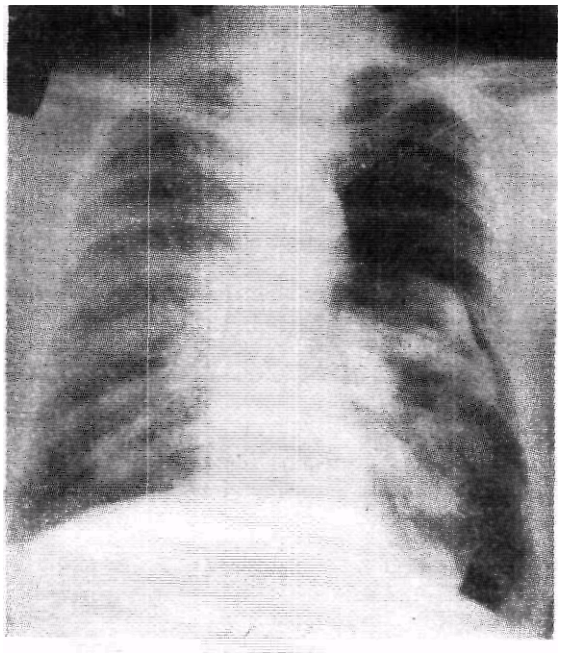


Fig. 2

X-ray chest taken one month later. The shadows on the right side are larger and more numerous, Meta-static shadows are also evident in the partially expanded left lung.

same side. Metastatic adenocarcinoma of the lung was diagnosed on thoracotomy. Site of the primary growth was not known.

The machanism of the production of spontaneous pneumothorax in cancer metastases is a matter of speculation. The most favoured view is that pneumothorax is caused by rupture of a necrotic nodule causing communication between the bronchus and the pleural cavity (Thorton and Bigelow, 1944). Although necrosis is common in secondary tumour nodules, involvement of a bronchus is uncommon. Hence the rarity of occurrence of pneumothorax in such cases. Lodmell and Capps (1949) are of the opinion that ballvalve action over-distension, is caused by a tumour situated at the lung periphery. The consequent tearing of the walls permits air to leak along the interlobular septa to the pleura. It has also been suggested by the same workers that involvement of the blood vessels with consequent poor nourishment of the tissues may be responsible in some cases. Muscular efforts, by producing an increase in intrathoracic pressures, in patients who are up and about may be a precipitating factor.

However, there is no obvious explanation as to why a sarcomatous deposit rather than a carcinomatous metastasis should cause pneumothorax more frequently.

Summary

A case of carcinomatous metastatic deposits in the lungs associated with pneumothorax is reported. This is the second recorded case of the type. There is no explanation for sarcoma rather than carcinoma being a more frequent cause of spontaneous pneumothorax.

REFERENCES

Christmann, F.E., Schopowski, F. & Deschamps, H. Jr., Spontaneous pneumothorax in pulmonary melastates of endothelima of the carcaneum. *Dia. Medico, 22,* 58, 1950.

D' Angio, GJ. & lannaccone, G., Spontaneous pneumothorax as a complication of pulmonary metastases in malignant **tumours of childhood. *Amer. J. Roentgenology,* 86, 1092, 1961.**

Leigh, T.F. & Thompson, E.A., Pulmonary metastatic sarcoma with associated pneumothorax. *Am. J. Roent.* and *Rad, Ther.,* 66, 900, 1951.

Lodmell, E.A. & Capps. S.C., Spontaneous pneumothorax associated with metastatic sarcoma, *Radiology,* 52, 88,1949.

Shaw, A.B., Spontaneous pneumothorax from secondary sarcoma of lung. *Brit. M.J.,* I. 278,1951.

Sherman, R.S. & Brant, E.E., An X-ray study of spontaneous pneumothorax due to cancer metastases to the lungs. *Dis. Chest,* 26, 328,1954.

Thorton, T.F. & Bigelow, R.R., Pneumothorax due to metastatic sarcoma- *Arch. Path.* 37, **334,** 1244.

MAJOR-GENERAL C.K. LAKSHMANAN

We regret to announce that our Vice-Chairman Major-General C.K. Lakshmanan passed away on 3rd October, 1970 in New Delhi.

Cheruvari Kottieth Lakshmanan was born on 5th April, 1898 in Cannanore, Kerala. He had his early education in the Christian College, Madras. He passed his L.M & S from Madras Medical College. He continued his medical education in St. Bartholomew's Medical College & Hospital, London, and took his MRCS, DTM & H and DPH in the U.K.

General Lakshmanan was commissioned in the Indian Medical Service in 1925 and was in military service uptp 1935. He held various responsible civil positions in the Government of India. He was the Director of Public Health, Bengal, and Director and Professor of Public Health Administration in the All India Institute of Hygiene and Public Health, Calcutta. He was Director General of Health Services, Government of India, for six years from 1952. He was Honorary Surgeon to the President of India from 1957-58. After retirement from Government he joined the Indian Red Cross Society as its Secretary-General in July 1958 and continued in that capacity until April, 1969. He was made Honorary Major General in June, 1960.

General Lakshmanan had several distinctions to his credit. He was awarded the Coronation Medal, War Medal, India Service Medal, Centenary Medal of the Swedish Red Cross, Centenary Medal of the USSR Red Cross and Silver Jubilee Commemorative Medal of Pere Damien Leprosy Foundation. He was awarded Padma Bhushan in 1967.

General Lakshmanan was a noted all-round sportsman. During his college days he captained the Madras University Cricket Team. He won many Trophies in Tennis and Atheletics. He represented India in the Olympic Games in Paris in 1924.

General Lakshmanan was the first Indian Honorary Fellow of the American Public Health Association in 1952. He was chief delegate to the International Health Conference in New York in 1964, Government representative to Nutrition Conference in Singapore (1946), Special Consultant to UNICEF, etc., Vice-President, Association for Moral and Social Hygiene, Honorary Secretary, Hind Kusht Nivaran Sangh, member of Family Planning Council, Society for Prevention of Blindness, Executive Committee of Indian

Ex-Service League, Geneva Convention Advisory Committee of the Ministry of Defence etc.

General Lakshmanan was Chairman of the Tuberculosis Association of India from 1952-58 in his capacity as Director General of Health Services. After retirement his services were available as member of the Executive and other Committees of the Association. He was elected as our Vice-Chairman and as Chairman of the Managing Committee of the New Delhi TB Centre in 1963. His advice and guidance was always respected. In his passing away the Association and its institutions, those working in the tuberculosis field, the various committees he was associated with have all lost a towering personality and an astute administrator. He leaves behind a very wide circle of friends and relations. We offer our most sincere condolences to Mrs. Lakshmanan and to the bereaved family.

Dr. Edward Francis Fredericks

We deeply regret to announce the death in England of Dr. E. Francis Fredericks, M.D., Medical Superintendent, Government TB Hospital, Pulayanarkottah, Trivandrum (Kerala) and Associate Professor in Tuberculosis, Medical College, Trivandrum on October 18, 1970. It is reported that the death came all of a sudden when Dr. Francis was taking part in a Seminar on "Tuberculosis and its connected problems" in Ipswich.

Dr. Francis, aged 41, was on a study tour in European countries and was presently working in the Honey Lane Hospital, Essex. He had earlier worked under Professor Sighart, TB Specialist and Secretary of the Tuberculosis Association of Australia, and also worked at the South Wales Sanatorium, Talgarth, Brecon, S.Wales. Dr. Francis's desire was to obtain the Z.S. (Chest) Diploma of the University of Vienna and then to work in the Forlanini Institute under Professor G. Daddi before returning to India early in 1971. He had contributed a great deal for the success of the 24th National Conference on TB and Chest Diseases held in Trivandrum in January, 1969. We have lost in Dr. Francis's death a very promising TB worker in our country. On behalf of the Tuberculosis Association of India and TB and Chest Diseases workers we offer our deepest condolences to Mrs. Padma Francis and the bereaved family.

OUR CHAIRMAN

Dr. P.K. Duraiswami retired as Director-General of Health Services, Government of India, on 23rd July. Dr. J.B. Shrivastav, who succeeded Dr. Duraiswami as Director-General, is now the Chairman of the Tuberculosis Association of India.

TB SEAL CAMPAIGN

The 21st TB Seal Sale Campaign commenced as usual, on October 2, 1970. The Railway Board, All India Radio, Rotary and Lions Clubs and other welfare organisations have been requested to help the Campaign. The Seal Sale Campaign was inaugurated in all the State Capitals with great interest. In Delhi, the Campaign was inaugurated by the Lt.-Governer A.N. Jha. The Campaign is in progress.

NATIONAL CONFERENCE IN TB& CHEST DISEASES

The Twenty-fifth National Conference on TB and Chest Diseases will be held in Bangalore from 2nd to 5th January, 1971. Dr. K. Somayya of Hyderabad is president of the Conference. The Mysore State TB Association will play the host.

The main subjects selected for the Conference are: "Progress and Evaluation of National Tuberculosis Control Programme", "Chemotherapy", "Role of Steroids in Tuberculosis", "Emphema", and "Social aspects of Tuberculosis". Details can be had from the Tuberculosis Association of India, 3, Red Cross Road, New Delhi-1.

CASE-FINDING SHIBIR—NEW DELHI TUBERCULOSIS CENTRE

Development department of the Delhi Administration has been holding 'Shibirs' for treatment of eye diseases in various villages of Delhi in furtherance of the community development. Tuberculosis 'case-finding' alongwith the investigations and treatment of gastro-intestinal and E.N.T. diseases was combined with eye diseases in the last 'shibir held in Alipur village from 30th September to 6th October, 1970. Advance publicity in the Alipur block and adjacent villages was directed towards asking persons with cough of 3/4 weeks duration and/or haemoptysis to come to the 'Shibir' for investigations. The New Delhi Tuberculosis Centre carried out direct smear examination of the sputum followed by x-ray examination (miniature x-ray) of all symptomatics "on the spot. Those found suffering from active tuberculosis were referred to the regional clinic for further treatment and those with non-tuberculosis diseases were referred to the nearest general hospital/dispensary.

Two hundred and ninety nine symptomatics attended the 'Shibir', of which 214 were males and 85 females. All age groups were males and 85 females. All age groups were more or less equally represented except that there were very few persons above the age of 55 years. Out of 299, 88 had some abnormality. Thirty one were suffering from active pulmonary tuberculosis needing treatment. Sputum was positive for AFB by direct smear in 8 of these. There was one case of primary disease in a child below 15 years and one case of pleurisy with effusion Chronic non-tuberculosis pulmonary like Emphysema, chronic bronchitis, Bronchiectasis etc. were the most common conditions detected, being present in 44 persons.

The new Delhi Tuberculosis Centre propases to hold several such 'Shibirs' in different parts of Delhi during the coming year.

TB CONTROL PROJECT ANDHRA PRADESH

The Tuberculosis Association of Andhra Pradesh has decided to initiate a Pilot Project for TB control wosk in Hyderabad and Secunderabad on the basis of Tumkur Project. Dr. K.S.N. Murthy, Secretary, TB Association, City Branch, Hyderabad, has been deputed to study the set up and working of the Tumkur Project.

ANTI-TB 'SHIBIR'—HYDERABAD

The TB Association of Andhra Pradesh in collaboration with the Rotary Club has decided to organise a general Medical check-up Camp (including TB) at Ibrahipatnam and in the rural areas.

BIHAR ASSOCIATION

The Hon'ble Health Minister, Director of Health Services, Bihar, Dr. K.K. Sinha, Director of the TB Training and Demonstration Centre, Patna have taken steps to reorganise the activities of tne Bihar State TB Association. It is understood that an *ad-hoc* Committee has met to review the rules and regulations of this Association with a view to

bring them at par with those of the other Associations affiliated to the Tuberculosis Association of India.

GOA ASSOCIATION

The 21st TB Seal Sale Campaign of Goa TB Association was inaugurated by Shri B.M. Cariappa, Secretary-General of the Tuberculosis Association of India, on 2nd October, 1970 in the National Club at Panaji.

The Secretary-General opened an Exhibition organised by Mrs. Sulekha Chowgule to collect funds for the After-Care in Vaseo-Da-Gama. The show was a great success and about Rs. 10,000/-were collected.

SEMINAR IN KERALA

The TB Association of Kerala proposes to organise a Seminar on TB Control Programme sometime in December this year for the benefit of medical officers in the State. Senior TB specialists and workers in the country are expected to take part in tin; Seminar.

PONDICHERRY

The Lt.-Governor of Pondicherry, Shri, B.D. Jatty, Health Minister, Shri Subbiah, and Shri P.V, Swaminathan, the Chief Secretary to the Government of Pondicherry, have takeh steps to reorganise the Pondicherry TB Association. As Dr. Selvaraja the former Secretary of the Association, has taken over as me Director of Health Services and Family Planning, Dr. Karunakaran has been appointed as the Honorary Secretary of the Association.

DR. K.N. RAO

Dr. K.N. Rao, former Director-General of Health Services and Chairman of the Tuberculosis Association of India, has recently taken over as Secretary-General of the Population Council of India with headquarters in Delhi. The Population Council of India is a registered body established in April last. Its objectives are to supplement the activities of the Government in the field of Family Planning and population control and in executing the policies and programmes of the Government.

TEXT BOOK ON TUBERCULOSIS

The Text-book on Tuberculosis which the Association has compiled under the General Editorship of Dr. K.N. Rao will be available for;ale in December this year. The publication will cost about Rs. 50/-. The Text-book idcludes chepters on epidemiology of Tuberculosis, methods of diagnosis, differential diagnosis and tuberculosis of different organs like bones, joints and genito-urinary tract etc. The book also covers details on radiology, BCG and TB control in rural and urban areas. Messers Kothari Book Depot, Acharya Dhonde Marg, Parel, Bombey-12, are the Publishers.

TAIPEI CONFERENCE

The 7th Eastern Regional TB Conference wilt be held in Taipei (Taiwan) from 16th to 21st November, 1970. The National TB Association of the Republic of China, Taipei, is playing host to the Conference.

PROFORMA ON 'NEW DRUG' MANUFACTURE

Under the provisions of the Drugs and Cosmetics Rules, no 'New Drug' can be marketed unless it is approved under the provisions of the Rules. Manufacturers desiring import or manufacture a 'new drug' are required to furnish detailed particulars on the chemical composition, analytical specifications, pharmacological and bio-chemical studies, toxicity and teratogenic studies and reports of clinical studies carried out on the drug.

Suggestions had been received from time to time that the particulars required to be furnished for approval of a 'new drug' should be standardized and made known to the Industry. In accordance with the suggestions received, the Directorate General of Health Services prepared a proforma in which the information could be furnished. This proforma has been finalised in consultation with the Drug Technical Advisory Board. Details and copies of the proforma can be had from the Drug Controller (India), Directorate General of Health Services, Government of India, Nirman Bhavan, New Delhi.

The Indian Journal of Tuberculosis

ABSTRACTS

Vol. XVII October 1970 Abst. No. 4

Epidemiological basis of tuberculosis eradication

Ole Horwitz, Erik Wilbek & Pennifer A. Erickson. Bulletin W.H.O. ; 1969, 41. 95.

The introduction of chemotherapy has dramatically changed the epidemiology of tuberculosis in Denmark, by reducing the risk of infection very considerably. A large and representative segment of the Danish population, a total of over 626,000 persons aged 15 to 44 years, was examined in 1950-52 and has now been followed for 12 years with a view to determine the risk of disease in the altered epidemiological situation.

The time trend in disease rates among vaccinated persons and natural reactors suggests that post-primary tuberculosis is of great significance in the present tuberculosis situation. Three quarters of all cases stem from the natural reactors. It would have been of great practical significance to identify high-risk groups which yielded more cases. This was not found possible since the majority of cases developed among reactors whose distinctive feature was that they were infected at the time of examination. The data also shows that the post-primary phase has a long duration, perhaps lasting most of the persons' fife. The reason why only a few breakdown whereas the vast majority live peacefully with their infection is unknown and merits further research.

S.P.P.

La Transmission du bacille tuberculeux

K. Styblo, J. Meijer & Ian Sutherland, Bulletin W.H.O. 1965, 41, 137.

A detailed study has been made of the extensive data on the prevalence of tuberculous infection in the Netherlands at different ages during the past 40 years. Only a small portion of children have been BCG vaccinated and non-specific low-grade allergy has been found to be very infrequent in Netherlands. The study shows that since about" 1940 the risk of tuberculous infection in the Netherlands closely followed an exponential downward trend, the risk decreasing annually by 30.8 per cent. The estimated annual risk of tuberculous infection was 2.08 per cent in 1940 and 0.058 per cent in 1966. The annual risk was about 9 per cent greater for boys than for girls in each calendar year. There was no definite association between the annual risk of infection and age up to the age of 20 years ; but the figures were consistent with the possibility that there might be a small increase in the risk of tuberculous infection with increasing age. The risk of infection had shown a downward trend even in the period 1930 to 1939 but the annual decrease was 5.5 per cent in that period. The estimated annual risk of tuberculous infection was 9.68 per cent in 1933 and 2.41 per cent in 1939. The more gradual decrease in the annual risk of infection before 1940 is probably related to the high and unchanging risk of bovine tuberculous infection in that country during that period.

The incidence of fresh primary infection under the age of 15 years decreased steeply from cohort to cohort during the 50 years. The incidence at age 9 decreased from 2940 per 100,000 for the cohort of 1910 to 39 for the cohort of 1960. At ages 15-40, the incidence remained at a high level until about 1935 and has since decreased steeply. At ages above 40 the incidence for fresh primary infection was relatively low for the early cohorts (because few individuals survived uninfected to these ages) and has remained low for the later cohorts (because, although a larger proportion now remains susceptible, these individuals will encounter very much lower risks of infection in future).

S.P.P.

Epidemiological significance of the local reaction to direct BCG vaccination

7. *Chavganc, K. Hanak & H.C. Ten Dam. Bulletin W.H.O. : 1969, 41, 45.*

The study has shown that direct BCG vaccination as applied in Mongolia does not cause any untoward reactions in persons who are tuberculin reactors at the time of

vaccination and, therefore, can be considered a rational public health procedure.

The results of the study have also been analysed with a view to investigate the possibility of using the local BCG reaction for determining the status of tuberculin sensitivity before vaccination. The authors conclude that it is impossible to deduce with any accuracy from either the local induration or the tissue destruction at the site of vaccination whether the person had tuberculin sensitivity before vaccination or not. Further, the results obtained with two different vaccines were inconsistent. The local BCG reaction, therefore, has no epidemiological significance in this respect.

S.P.P.

The trend of tuberculosis in Japan during the period 1953-64

Eiichi Wakamatsu, Harumiti Oka, Hideo Kumabe & Akira Kobayashi. Bulletin W.H.O. : 1969, 41, 115.

Japanese Ministry of Health & Welfare conducted a nationwide tuberculosis prevalence survey in 1953, 1958 and 1963, using the stratified random sampling technique. The prevalence of tuberculosis of all forms fell from 3.4 per cent in 1953 and 3.3 per cent in 1958 to 2.1 per cent in 1963. The decrease in active tuberculosis was more marked in the most advanced forms of bacteriologically positive cases falling from 0,75 per cent in 1953 to 0.55 per cent in 1958 and to 0.19 per cent in 1963. Cavitary disease also fell from 0.6 per cent in 1953 to 0.4 percent in 1938 and 0.3 per cent in 1963. The prevalence ratio showed a marked fall in the under 50 years age group but remained more or less similar in over 50 years age group.

The incidence of pulmonary tuberculosis fell from 0.37 per cent in 1954 to 0,23 per cent in 1959 and 0.17 percent in 1964. The age-specific incidence was high in 0 to 4 years and 30-44 years age groups in 1953 survey. In subsequent surveys the incidence fell in the younger age groups and increased in the older.

Thus the epidemiological situation in Japan has been improving in recent years except in certain groups such as older individuals, unemployed persons and artisans and employees in small enterprises in which the coverage of tuberculosis control programme was inadequate.

S.P.P.

The immediate effects of BCG re-vaccination

Jorgen Nyboe. Bulletin W.H.O. ; 7969, 41, 63.

Although re-vaccination with BCG has been practised for many years, the effects of this procedure have not been studied in detail. Data have been presented to confirm that tuberculin test is not a reliable tool for distinguishing between persons needing re-vaccination and not needing ra-vaccination. Because of the variability of the tuberculin test results, a consistent distinction between the two groups cannot be made. But, even worse, the phenomenon to be measured is influenced by the tool of measurement itself; the result of tuberculin test in a BCG vaccinated person depends on whether or not the person has been tested previously. It is strange, therefore, to find that the decision about re-vaccination is based entirely on an outcome of tuberculin test in usual vaccination programmes. It would be much more rational to take into consideration controlled studies on protection given by BCG for this purpose. Most studies tend to indicate that re-vaccination may be necessary 10 to 15 years after the original vaccination. The introduction of such a criterion would help to reduce the cost of many programmes which include repeated tuberculin testing, apart from being more rational.

S.P.P.

Changes in SGOT activity during treatment with Ethionamide

E. Simon, E. Veres &Gy. Banki. Scand. J. Resp. Dis. : 1969, 50, 314.

SGOT estimations were carried out in 99 patients with recent or previously treated chronic pulmonary tuberculosis patients who were on ethionamide in combination with other drugs e.g. INH, streptomycin, cycloserine etc. SGOT values were pathological in 37 cases. Enhancement of SGOT levels was accompanied by gastro-intestinal or other side effects in 2/3rd of the cases. Of 20 patients where ethionamide had lo be withdrawn because of severe intolerance, pathological SGOT levels were observed in 13 cases only at the time of interruption of treatment. In one case icterus was present. It is suggested that ethionamide during its metabolism in the organism affects enzyme reactions in the liver and, not rarely, causes liver damage. Tolerance of ethionamide was better and the frequency of pathological SGOT values was lower with than without prophylactic nicotinamide but the difference was not significant.

Modification by Para-Aminosalicylic Acid and Snlphamethazine of the Isoniazid Inactivation in Man

Hilkka Tiitinen. Scand, J. Resp. Dis.; 1969, 50, 281.

Modification by para-aminosalicylic acid or sulphamethazine of the INH inactivation in rapid and slow inactivators was studied in 26 patients. The ability to inactivate sulphamethazine co-related well with their ability to inactivate INH. When given together with INH, sulphamethazine had no constant effect on INH concentration in serum, and the absolute or percent amount of free INH excreted in the urine by rapid or slow inactivators. When PAS was given with INH, it lengthened the activity of INH both in rapid and slow, inactivators. It also increased the absolute and percent amount of free INH in the urine of rapid but not slow inactivators. About 50 percent of serum INH was bound to serum protein and this binding was absent in the presence of PAS.

S.P.P.

Diphenylhydantoin Intoxication—A Complication of Isoniazid Therapy

Hetm Ktttt, Robert Brennan, Harsha Dehejia & Kari Verebely. Amer. Rev. Resp. Dis; 1970, 101,377.

Diphenylhydantoin intoxication was seen in approximately 10 per cent of epileptic patients who took the drug in the commonly prescribed dose (300 mg daily) together with isoniazid and aminosalicylic acid or cycloserine. All patients thus afflicted were slow insoniazid inactivators in whom the concentration of isoniazid in the blood remained 7 (µg per ml or more three hours after a test dose of 10 mg per kg body weight.

Studies in animals and in *vitro* revealed that isoniazid was a very strong inhibitor of diphenylhydantoin metabolism and caused accummulation of the unmetabolized drug. The type of inhibition was non-competitive. Diphenylhydantoin intoxication in the very slow isoniazid inactivators could be avoided by giving them smaller doses of diphenylhydantoin (100 mg to 200 mg daily).

S.P.P.

Serum levels, Urinary Excretion, and Side-effects of Cycloserine in the presence of Isoniazid and P-Aminosalicylic Acid

M.J. Mattila, E. Nieminen & H. Tiitinen. Scand. J. Resp Dis.; 1969, 50, 291.

Serum levels and urinary excretion of cycloserine (CS) were measured in 11 patients with and without simultaneous administration of INH or PAS. Cycloserine was given in 3 oral doses of 250 mg at 6 hours intervals followed by 500 mg the next morning. The INH did not consistently modify the serum CS levels. In some cases PAS and INH prolonged CS concentration in serum. Excretion of CS in urine was not modified by INH or PAS. Nine patients out of II complained of dizziness or drowziness after CS + INH but only one after CS alone. The results suggest some indirect mode of action rather than increased CS serum concentration only being responsible for toxic reactions.

S.P.P.

Demonstration of acid-fast rods in sarcoidosis

J. Vanek and J. Schwarz. Amer. Rev. Resp. Dis.; 1970, 101, 395.

In 30 consecutive cases of sarcoidosis, including 18 of American origin, acid-fast bacilli were found microscopically in every instance. Patients with progressive healing and patients with caseous necrosis were exclu-ded. The acid-fast bacilli were seen either as isolated bacilli or in groups. The staining properties and morphologic features of the observed bacilli were representative of mycobacteria. In 17 cases, the diagnosis of sarcoidosis was based on involvment of at least two organ systems, usually lymph nodes and lungs, on lack of reaction to PPD, and on laboratory and histologic findings universally accepted as diagnostic of the disease. In 13 cases, the diagnosis was based mainly on histologic . features, even though bilateral adenopathy existed in several of these patients and skin tests for tuberculosis gave no reaction.

S.P.P.

Byssinosis in Cotton Textile Mills

Peter E. Schrag and A. Dale Gullett. Amer. Rev. Resp. Dis.; 1970, 101, 491.

The study documents the occurrence of byssinosis in a large American textile complex of 509 workers. Byssinosis was present in 63 persons. The prevalence was highest in carders but spinners, weavers and winders also had the disease. There is a very good co-relation between duration of exposure and prevalence. Persons with byssinosis were found to represent a significant proportion of workers complaining of shortness of breath. Byssinosis is confined to textile workers who are exposed to pharmacologically active cotton

dust. Bacteria and fungi in cotton dust have not been conclusively implicated. The presence of symptoms and disease corelates more closely with the protein plant debris in dust particles than with the cellulose or the mineral ash residue in cotton dust. No co-relation with allergy has been found and persons with byssinosis are not hyper-sensitive to inhaled histamine. An antibody whose importance is yet not clear has been identified in the serum of cardroom workers. The prevention of disability from byssinosis is feasible with better dust suppression in the industry and closer medical supervision of exposed workers.

S.P.P.

Pulmonary Aspergillosis in Sanatoriums in the South Central United States

James D. Parker, George A. Sarosi, Irene L. Doto & Fred E. Tosh. Amer. Rev. Resp. Dis.; 1970, 101, 551.

A prospective one-year study was undertaken lo detect pulmonary aspergillosis in sanatoriums in the South-Central part of the United States, using the aspergillin complement fixation test. Fifty four patients or 1.7 per cent of all newly admitted patients had 1:8 or greater titre of aspergillin antigen. Additional information including sputum culture for fungi, chest skiagrams and further serological studies was obtained in 50 of these patients. Sixty percent had one or more culture positive for A. Pumigatus or had aspergillomas or both, although only 2 percent of matched controlled patients with no serological evidence of infection with aspergillus had positive cultures. Twenty of the 50 aspergillin reactors were regarded as having aspergillosis clinically. Twleve of the 20 patients had aspergillomas. The clinical course of suspects varied from spontaneous cure in one patient to respiratory death in 4. Therapy included Amphotericin B in 7 patients and pulmonary resection in 2. The effectiveness of Amphotericin B therapy is however still uncertain.

S.P.P.

Suitablity of Rifampicin for Intermittent Administration in the Treatment of Tuberculosis.

Jean M. Dickinson and D.A. Mitchison. Tuber, Lond, (1970), 51,82.

Log phase cultures of mycobacterium tuberculosis were exposed to 0.2 ug/m.l. rifampicin for various periods showed it was more bactericidal in the first 24 hours than 1 ug/m.l. streptomycin and there was a log before growth restarted after exposure for two hours. The log period to rifampicin was shorter than after exposure to other bactericidal drug. Guinea pigs with established tuberculosis were treated for six weeks with rifampicin at various dose levels. At each mean daily dosage/level, groups were given doses at intervals of one, two, four or eight days,

The response to treatment was assessed from the amount of macroscopic disease in the organs and the viable counts on the spleen.

The efficacy of treatment increased as the interval between doses was spaced out. The benefit from high doses of rifampicin given inter-mittently may partly arise from the disproportionatly high peak serum concentration and prolonged exension of large doses.

The findings suggest that rifampicin may be particularly suitable for intermittent administration in man provided that the increase in the size of the individual dose given does not produce serious toxicity.

H.B.D.

Rifampicin in the Treatment of Experimental Tuberculosis in Mice: Sterilization of Tubercle Bacilli in the Tissues.

John Batten. Tuber, Lond, (1970), 51, 95.

Groups of mice were injected intravenously with mycobucterium tuberculosis and treated with rifampicin alone or with rifampicin and isoniazid.

After completion of daily treatment for four months with rifampicin at 40 mgm/kg, in combination with isoniazid 25 mgm/kg. no tubercle bacilli could be cultivated from the lungs and spleen upto three months later, even when high doses of cortisone were given during the second or third months.

When rifampicin was given alone daily in the same dose, tubercle bacilli revived in only one animal out of 10, two months after completion of treatment. On the other hand when rifampicin (120 mg/kg.) was given twice weekly there was significantly greater revival of tubercle bacilli.

H.B.D.