

INDIAN JOURNAL OF TUBERCULOSIS

*Official organ of the
Tuberculosis Association of India*

Editor:
Dr. P.K. Sen

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

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

Vol. XIX : No. 4

October 1972

Contents

Editorial: Tubercle Bacillus ... 123

**Sodium Lauryl Sulphate method of culturing
sputum for mycobacterium tuberculosis**

—*R. Narasimhan, G. P. Mathur and S. P. Pamra* ... 125

**Virulence of locally isolated strains of Tubercle
bacilli to guinea-pigs**

—*Mangala P. Bonsai, S. R. Sengupta, H. I. Jhalla
and K. D. Sharma* ... 131

**Incidence of initial drug resistance in locally
isolated strains of tubercle bacilli**

—*Mangala P. Basal, S. R. Sengupta, H. I. Jhalla
and K. D. Sharma* ... 137

Economics of Health

—*A. S. Sen and R. N. Basu* ... 144

**Toxic epidermal Necrolysis (Lyell's Syndrome)
due to P.A.S.**

—*M. S. Agnihotri and S. Rastogi* ... 159

News & Notes * Abstracts

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

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

Single copy :
Rs. 6.00

* * *

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

The Indian Journal of Tuberculosis

Vol. XIX

New Delhi, October 1972

No. 4

TUBERCLE BACILLUS

The bacillus was discovered by Robert Koch 90 years ago. It was then thought that this discovery will soon lead to complete understanding of the genesis and course of tuberculosis. Actually we do not yet know enough even about the bacillus itself. Our techniques of its isolation are still crude and not sensitive enough. For example, if the bacilli in sputum are less than 1000 per cmm, the laboratory may report the specimen as negative by direct smear. Even a negative culture does not necessarily mean that the bacilli are not present in the specimen. Since finding tubercle bacilli in the sputum is the only specific and authentic diagnostic criterion of pulmonary tuberculosis, these lacunae lead to a considerable number of false negatives.

Sputum and the other pathological specimens have to be homogenized before culture. An ideal reagent should be one which while homogenizing the specimens effectively, eliminates the contaminants without injuring the bacilli to such an extent as to hamper their growth. Such an ideal reagent has yet to be discovered. Lauryl sulphate is a new reagent being increasingly recommended but its superiority over the current favourite, sodium hydroxide, appears to be marginal.

There is another aspect of the ability of the bacilli to grow in artificial media which is unconnected with the noxious effects of chemotherapeutic substances or reagents used in processing specimens for culture. Occasionally specimens contain bacilli which are morphologically intact and are therefore detectable by microscopy, but are unable to grow *in vitro*. Are these bacilli dead or in a state of 'suspended animation' as a result of adverse ecological factors, is a problem which continues to defy solution.

Virulence of the bacillus is still something of a paradox. The Indian bacillus is known to be less virulent than the strains obtaining in U.K. Yet the disease in India is neither less prevalent nor less severe than in U.K. It seems that the severity, extent and acuteness of disease and bacillarity of the lesions have no relationship with the virulence of the bacillus. In susceptible species in which the bacillus is very virulent, lesions may often contain very few bacilli, whereas many more may be found in the lesions of species with sizable degree of resistance. This paradoxical finding demonstrates that the ability of the bacilli to multiply in tissues is not a sufficient determinant of their pathogenicity.

Our understanding of the mechanism by which bacillary resistance to drugs emerges and its exact clinical significance is still rudimentary. Sensitivity

testing techniques have yet not been standardized with the result that the same specimen processed in different laboratories may yield widely varying patterns of bacillary resistance. INH resistant bacilli are often catalase negative and of attenuated virulence; not so streptomycin resistant bacilli. Whereas the latter may thrive in the presence of streptomycin, continued administration of INH does not seem to influence the former at all.

Emergent drug resistance was believed to be mutational in origin even though it could not explain satisfactorily some important observations. To-day it is described as a heritable character transferred through non-chromosomal genes. Whether the bacilli become resistant to a drug and how quickly, therefore, does not depend upon the bacillus but the influence of the particular drug on the 'transference' mechanism. It also explains why certain drugs with little or no therapeutic action *per se* may by virtue of their suppressing 'transference' delay or prevent emergence of resistance to the companion drug.

The so called 'anonymous' or 'atypical' mycobacteria constitute another baffling phenomenon. Their exact nature and relationship, if any, to the typical bacillus is still steeped in controversy. Whereas some consider these as separate entities, others believe that they are the result of 'adaptation' on the part of the typical bacillus. If the bacillus can assume fragmented granular forms—Much's granules—as a result of 'adaptation' to adverse circumstances, the so-called atypical bacilli could also represent another form of adaptation. Another pertinent argument that is adduced in this connection is that these bacilli have come to be detected *after* the advent of anti-microbial drugs which may well be the trigger to initiate 'adaptation'. Some have attributed these to be the result of 'phage' activity. Further, it may not be without significance that we still do not know the mode of their transmission nor experimental infection with these has been possible so far.

Finally, it has been rightly said that there is no such thing as the typical tubercle bacillus. What we label as tubercle bacilli is a conglomeration of many strains differing, at times considerably, from each other in relation to their morphology, pathogenicity, viability etc. Many more diligent and meticulous studies are needed before the problems posed by the bacillus are solved and its mysteries completely unravelled.

SODIUM LAURYL SULPHATE METHOD OF CULTURING SPUTUM FOR MYCOBACTERIUM TUBERCULOSIS

R. NARASIMHAN, G.P. MATHUR and S.P. PAMRA
(From the New Delhi Tuberculosis Centre)

Various chemical agents have been employed for digestion of sputum in the culture of tubercle bacillus. An ideal agent should be one which would prevent contamination, homogenise sputum completely and effectively and yet would not affect appreciably the viability of the bacillus.

Petroff (1915) developed the first practicable method for the isolation in pure cultures of tubercle bacilli from contaminated material by using sodium hydroxide. Lowenstein (1924) investigated the use of sulphuric acid. Thirty specimens were treated with 10-20% sulphuric acid with an exposure time of 10-60 minutes and all yielded positive cultures on media.

Spendlove et al (1949) studied the relative toxicity of the common decontaminating agents e.g. sodium hydroxide, sulphuric acid, hydrochloric acid, antiformin and others. They found that all the reagents markedly reduced the viability of the tubercle bacilli; but of these reagents, sodium hydroxide was relatively less toxic than sulphuric acid.

A comparative study using sodium hydroxide and sulphuric acid in culturing sputum for tubercle bacilli undertaken at the New Delhi Tuberculosis Centre (Narasimhan et al, 1970) showed that the alkali homogenisation was distinctly superior to the acid method in the isolation of the bacilli from sputum; 56.6% specimens were found positive by alkali method as against 40.0% by the acid, out of a total of 350 specimens. Sodium hydroxide is at present the reagent of choice in most laboratories as it gives efficient homogenisation with the smallest centrifugal deposit. Nevertheless the contamination rate with sodium hydroxide is fairly high.

Tacquet and Tison (1961) used lauryl sulphate as a homogenising agent. This reagent used in combination with sodium hydroxide is reported to reduce the contamination rate considerably; the sputum is easily homogenised and the sediment is suitable for inoculation on the conventional Lowenstein Jensen medium (Engbaek et al, 1967).

In view of these promising reports, a study was undertaken in the laboratory of the New Delhi Tuberculosis Centre, to compare the

relative efficiency of sodium hydroxide and lauryl sulphate in respect of reducing the contamination rate and viability of bacilli under different situations obtaining in a routine service set up. How do sputum specimens with varying degrees of bacillarity behave with the two homogenising agents? Since treatment with antimicrobial drugs is well known to influence adversely the viability of bacilli, how do culture results compare in patients who have had treatment for varying periods?

Procedure

The study was started in August, 1970. Out of 20-30 sputum specimens received daily, the laboratory could handle only about 8 or 9 specimens per day for this special study. It was therefore decided that the first 8 specimens of sufficient quantity for both tests received in the laboratory on any day would be included in the study. Since the likely distribution of patients in respect of previous treatment was not known at the time of collection of sputum, and it was important to ensure that a sufficient number of specimens (and more specially of those likely to be positive on culture) were collected from patients with different lengths of treatment, three weeks after the start of the study distribution of patients was worked out according to the length of previous treatment. Subsequent intake was adjusted to allow a sufficient number of specimens from treated cases to be included in the trial without introducing any conscious bias in the selection of specimens. This enabled us to include specimens of varying degrees of bacillary concentration since the new untreated cases could be expected to have a higher degree of bacillarity and the treated cases on the whole would tend to show a decrease in the number of bacilli in proportion to the duration of treatment.

Specimens consisted of sputum collected by the patients overnight in sterile containers. Smears were made and strained by the Ziehl Neelsen method using 0.5% aqueous methylene blue as counter-stain. The stained smears were examined under oil immersion for a period of about 5 minutes each and the result was recorded as follows :—

Negative=No bacilli or less than 10 bacilli after 5 minutes search.

+ = 1 bacillus per field

++ = 2-10 bacilli per field

+++ = More than 10 bacilli per field

The sputum was then divided equally into two parts and these aliquots were transferred to two universal containers and randomly allocated to one or the other of the two reagents (Sod. lauryl sulphate and Sod. hydroxide).

The aliquots were then processed as follows :—

Sodium lauryl sulphate

Thirty grams of the pure salt was dissolved in 1000 ml of sterile distilled water heated to 60°C and 10 grams sodium hydroxide was added — the solution was kept in the incubator at 37°C since there was a tendency for the sodium lauryl sulphate to separate at 22°C. The solution prepared was used within a week of its preparation.

To one part of sputum, 3 parts of lauryl sulphate reagent were added and the mixture shaken well and kept at room temperature for 30 minutes with shakings at intervals of 30 minutes. The homogenized mixture was centrifuged at 3000 r.p.m. for a period of 30 minutes. The supernatant fluid was poured off and the deposit was neutralized by adding drop by drop the following neutralisation reagent :

0.9 ml of concentrated sulphuric acid was added to 100 ml distilled water and 2 ml of brom cresol purple 1 in 250 was added and the solution sterilised by autoclaving.

Usually 3-4 drops were found sufficient. Appearance of a strong purple colour marked the end point of neutralisation. The resuspended sediment was inoculated by means of a pasteur pipette on the surface of two slopes of Lowenstein Jensen medium without potato starch.

Sodium hydroxide

To one part of sputum in a universal container, an equal amount of 4% sodium hydroxide was added and the contents shaken well, and kept in the incubator at 37 °C for 20 minutes with shakings at intervals of 10

minutes. The contents were then centrifuged for a period of 20 minutes at 3000 r.p.m. The supernatant was discarded. Sterile distilled water sufficient to fill half the bottle was added and the contents shaken well and centrifuged again at 3000 r.p.m. for a period of 20 minutes. The supernatant fluid was discarded and the deposit plated on the surface of two slopes of Lowenstein Jensen medium without potato starch.

Besides the serial numbers of the cultures, numbers 1 and 2 (random numbers) were the only numbers marked on the top of the media tubes, cultures were incubated at 37°C for a period of 8 weeks with weekly readings at the end of 3, 4, 5, 6, 7 & 8 weeks. They were finally discarded if there was no growth at the end of 8 weeks. Degree of growth was categorised as follows :—

Negative=No growth

Actual No. of colonies under 20

+ =20 to 100 colonies

++ =More than 100 colonies

+++ = Confluent growth

The person who read the cultures had no idea of the homogenising agent used for that particular culture and the readings were decoded by the statistical department for evaluation purposes.

Material

In all 225 specimens were included in the study. Of these 73 (32.4%) were from patients who had had no treatment, 23 (10.2%) from those who had treatment upto 3 months, the remaining 129(47.3%) having had treatment for over 3 months.

Table 1 shows the direct smear status *in relation to* the duration of treatment that the patients had had at the time of collection of sputum. Out of 225 specimens direct smear was negative in 148 (65.8%), + in 14 (6.2%) and ++ and +++ in 63 (28.0%). In the above and subsequent tables, ++ and +++ specimens by direct smears have been combined since the numbers in both categories were small and there was no difference in the behaviour of ++ and +++ specimens.

Direct smear positives were naturally fewer among those treated than among the untreated patients.

TABLE 1

Distribution of 225 cases according to sputum status and duration of treatment

Direct smear status	Untreated	Treatment under 3 months	Treatment over 3 months	Total
Negative	31	15	102	148 (65.8%)
+	10	0	4	14 (6.2%)
++ and +++	32	8	23	63 (28.0%)
Total	73 (32.4%)	23 (10.2%)	129 (57.3%)	225 (100.0%)

Results

Results of the two methods have been compared in respect of (1) positive cultures (2) degree and speed of growth in positive cultures and (3) rate of contamination.

Table 2 shows the culture results in relation to the direct smear status of sputum in specimens treated with lauryl sulphate and sodium hydroxide respectively. Out of a total of 225 specimens processed by both methods 105 gave positive cultures by the lauryl sulphate technique (45.9%) and 101 by alkali technique (44.9%). Eight specimens (5 in

negative and 3 in positive direct smear) gave a positive culture with lauryl sulphate only and four (3 in negative and 1 in positive direct smear) with sodium hydroxide only. Due to small numbers in many cells, comparison has been made only in respect of total cases, irrespective of direct smear status and the difference is not statistically significant ($X^2=1.33$ for 1 d.f. $P>0.20$). It may also be pointed out that out of 77 specimens with positive smears, three gave a negative culture by the sodium hydroxide technique and one by lauryl sulphate technique.

In table 3 culture results by both techniques

TABLE 2

Results of cultures by Lauryl Sulphate and Sodium Hydroxide homogenisation in relation to sputum direct smear status

Techniques and classification	Direct smear			Total
	Negative	÷	++ or +++	
Lauryl Sulphate culture positive				
Sodium Hydroxide culture positive	24	13	60	97 (43.1%)
Lauryl Sulphate culture negative				
Sodium Hydroxide culture negative	5	1	2	8 (3.6%)
Lauryl Sulphate culture positive				
Sodium Hydroxide culture positive	3	0	1	4 (1.8%)
Lauryl Sulphate culture negative Sodium Hydroxide culture negative	116	0	0	116 (51.5%)
Total	148 (65.8%)	14 (6.2%)	63 (28.0%)	225 (100.0%)

have been analysed in relation to previous treatment. Apparently there is no difference in the two techniques but the numbers in some cells are too small for a statistical test of significance. Table 4 shows the degree of growth by both techniques. There is no significant difference between the two methods in respect of the degree of growth obtained in the cultures ($X^2=1.17$ for 2 d.f. $P>0.50$).

At the end of 3 weeks 10 cultures were positive by lauryl sulphate technique as against 11 cultures by the alkali technique. At 6 weeks, the number was 102 and 99 respectively. Finally, at 8 weeks 105 and 101 cultures were positive respectively. Thus, no appreciable difference in the speed of growth in the two techniques was noticed.

During the course of treatment bacilli tend to acquire resistance to anti-tubercular drugs. Whether resistant and sensitive bacilli in

sputum specimens would behave in the same manner in the two techniques could be studied in 53 cases. In 34 of these, the bacilli were sensitive and in 19 resistant to one or more of the first line drugs. There was practically no difference in the growth of resistant and sensitive bacilli with the two methods of homogenization.

Contamination rates with both techniques have been compared in table 5. In all 41 out of a total of 450 tubes inoculated were found contaminated in the sodium hydroxide series as against 23 tubes which showed contamination in the lauryl sulphate series giving a contamination rate of 9.1 and 5.1 respectively. Thirty four cultures were lost due to contamination by the sodium hydroxide technique only and 16 by the lauryl sulphate technique only. The difference is statistically significant ($X^2=6.48$ for 1 d.f. $P<.01 <.02$).

TABLE 3

Comparison of Lauryl Sulphate and Sodium Hydroxide techniques in relation to duration of treatment and sputum smear status

Period of treatment	Untreated	Under 3 months	Over 3 months	Total
Lauryl Sulphate culture positive Sodium Hydroxide culture positive	49	9	39	97
Lauryl Sulphate culture positive Sodium Hydroxide culture negative	3	2	3	8
Lauryl Sulphate culture negative Sodium Hydroxide culture positive	3	0	1	4
Lauryl Sulphate culture negative Sodium Hydroxide culture negative	18	12	86	116
Total	73	23	129	225

TABLE 4

Degree of growth by the two techniques

	Culture negative	Less than 20 colonies	+	++, + + +	Total
Lauryl Sulphate	120	3	52	50	225
Sodium Hydroxide	124	2	58	41	225

TABLE 5

Contamination in Lauryl Sulphate and Sodium Hydroxide techniques

	Number
Contamination in both techniques	7
Contamination only in Lauryl Sulphate technique	16
Contamination only in Sodium Hydroxide technique	34
Contamination in neither technique	168
Total	225

It is worth mentioning that no culture was lost by contamination of both the inoculated tubes by either technique.

Of the 23 specimens for which one tube with lauryl sulphate was contaminated, the other tube was positive in 10. Similarly with sodium hydroxide, the second tube was positive in 13 out of 41. In other words, contamination could have influenced the final result in 13 and 28 specimens (a difference of 15 in 225 specimens) by lauryl sulphate and sodium hydroxide techniques. Since the direct smear was negative in all these, how many would have still been negative by culture if one of the two tubes was not contaminated is difficult to say.

Discussion

A wide range of chemicals have been available for homogenisation of sputum before culture, but none has achieved the ideal of effectively eliminating contaminants without damaging or killing the tubercle bacilli. Of the various reagents, sodium hydroxide is the most commonly used as it is relatively the least toxic to the tubercle bacilli, though the contamination rate remains fairly high. The search for an ideal agent is therefore still on. Lauryl sulphate is the latest one to be tried and recommended.

In sputum direct smear positives in this study the recovery of the tubercle bacilli by culture by the lauryl sulphate method has been 98.5% as against 96.1% by the sodium hydroxide method. When direct smears were negative, positive cultures were obtained in 20% and 18% by the lauryl sulphate and sodium hydroxide methods respectively. This tends to prove that there is no significant difference between the two methods in respect of positive cultures. Engbaek et al (1967) in a

somewhat similar study based on 704 specimens also came to the same conclusions.

With modern antimicrobial drugs, bacillarity of the lesions is reduced very quickly and the sputum is usually scantily positive by direct microscopy, if at all. Further, antimicrobial drugs lower the capacity of bacilli to grow in culture tubes. It was observed that even in treated cases whether negative or positive by direct smear, the recovery of the bacilli by culture was almost the same with both methods of homogenisation, although due to small numbers a statistical test of significance could not be carried out. Nor has any appreciable difference been noted in the two techniques in respect of luxuriance and speed of growth of the bacilli.

The only other index which can determine the superiority of one technique over the other is contamination rate. The frequency of contamination in this study was significantly lower in the lauryl sulphate technique as compared to the sodium hydroxide technique (5.1% and 9.1%) respectively. In the study by Engbaek et al (1967) contamination rate was as low as 1% with lauryl sulphate as against 7.5% with sodium hydroxide. But they had inoculated 4 tubes for each specimen. Their figures for 1 tube contamination are 12.8% for sodium hydroxide and 3.1% for lauryl sulphate, figures which are not much different from those obtained in this study. Sodium lauryl sulphate thus can reduce, if not completely eliminate, the problem of contamination in routine culture of sputum for tubercle bacilli.

Many other factors, for example, equipment required, simplicity of technique, time and labour involved and cost have to be taken into consideration before replacement of sodium hydroxide technique by lauryl sulphate techni-

que is recommended for routine work in a service institution laboratory handling a large number of specimens daily.

The homogenisation, centrifugation and culture techniques are equally easy in both techniques and no special equipment is required in either technique. Further, the time and labour involved is exactly the same in both techniques. The cost of material used however is appreciably more in the sodium lauryl sulphate technique which offsets to a very large extent the superiority of this reagent in respect of reduction in contamination rate.

In conclusion, the lauryl sulphate technique of homogenisation of sputum for culture has practically no advantage over the sodium hydroxide with regard to number, degree and speed of positive cultures. The contamination rate is significantly lower in the former. Higher cost of the former, however, does not seem to justify the substitution of sodium hydroxide technique by lauryl sulphate technique in a service laboratory handling a large number of routine examinations.

REFERENCES

- Engbaek, H. Chr., Vergmann, B. & Bentzon, M. Weis. The sodium lauryl sulphate method in culturing sputum for mycobacteria *Se. Jour. Resp. Dis.*; 1967, 48, 268.
- Lowenstein quoted in the Bacteriology of Tuberculosis by Darzines. *Egons*; University of Minnesota Press Minneapolis, 1958.
- Narasimhan, R. Mathur, G.P., & Pamra, S.P. A comparison of the alkali and acid homogenisation technique in the culture of M. Tuberculosis. Proceedings of the 25th National Conference on Tuberculosis & Chest Diseases, Patiala; 1970.
- Petroff, S.A.; A new rapid method for the isolation and cultivation of TB directly from the sputum and faeces; *Jour. Expt. Med.*; 1915, 21, 38.
- Spendlove, G.A., Cummings, M.M. & Patnode R.A.; Toxicity of sputum digestants to tubercle bacilli in sputum and water. *Am. Rev. Tub. & Pul. Dis.*; 1949, 60, 628.
- Tacquet, A. Tison F. Nolelle technique d'isounemant des myco bacteries per le lauryl sulfate de sodium; *An. Inst. Pasteur*; 1960, 100, 676.

VIRULENCE OF LOCALLY ISOLATED STRAINS OF TUBERCLE BACILLI TO GUINEA PIGS

MANGALA P. BANSAL, S. R. SENGUPTA, H. I. JHALA and K. D. SHARMA
(From Medical College, Aurangabad.)

Ever since Robert Koch discovered the tubercle bacilli, the most significant criterion of virulence of these bacilli has been their ability to cause tuberculous disease in guinea pigs, though other methods have been described from time to time.

The inoculation of 10.100 viable bacilli in guinea-pigs can be relied on to produce progressive disease (Schavabceher and Wilson, 1937). Reports that strains from Indian patients were often unable to produce progressive disease in this animal was of considerable interest (Mitchison, 1963). Dhurandhar (1941) was the first Indian worker to observe the variations in the type of lesion produced by different strains. Later on Dhayagude & Shah (1948) classified the strain depending upon the extent of lesion in different organs. But they did not make use of control strains of American or European origin for comparison. Strains of tubercle bacilli recently isolated from European patients have been found to have fairly uniformly high degree of virulence in susceptible animals (Griffith, 1919; Lange, 1930; Jenson & Frimodt-Moller, 1936; Steward, 1951).

The implications of these observations for the epidemiology of tuberculosis in man is not yet understood.

It has been found that the virulence of tubercle bacilli to guinea-pigs is different in different parts of the world (Mitchison, 1963; Sula & Langerava, 1964). It is therefore possible, that the tubercle bacilli isolated from different parts of India may have different degrees of virulence. If environmental factors or genetic constitutions of the host would determine this difference in virulence, then it should be expected that difference in virulence of tubercle bacilli should exist in different parts of our country.

It has been observed by several workers (Gangadharam et al, cited by Burke, 1963; Mitchison, 1963) that the INH resistant strains of Indian origin and from outside India are less virulent to guinea pigs, as compared to INH sensitive strains.

The present study was carried out to determine the virulence of locally isolated strains of

tubercle bacilli by comparing their virulence in guinea-pigs with a standard virulent strain-H₃₇Rv. It was also decided to determine the difference in virulence in guinea-pigs between locally isolated Isoniazid sensitive and resistant strains of tubercle bacilli.

Materials and Methods

The strains of tubercle bacilli used in this virulence study were isolated in Lowenstein Jensen medium from sputa of treated and untreated cases of tuberculosis. In all 16 strains were tested. The virulence test was carried out according to the method described by Mitchison et al (1960, 1961).

The primary culture of sputum after 3 weeks incubation were inoculated in a quantity of 1 nag. (moist weight, approximately) into guinea-pigs intramuscularly. A loopful of the inoculum was standardized by weighing several times to 2 mgs of moist weight. This was put into 0.8 ml. of water and a suspension was made in a mechanical shaker. Half of this suspension was injected into the animals. Thirteen strains out of the total 16 strains isolated, were tested in two sets of animals. One of the animals was killed at 6 weeks, and the other at 12 weeks. The guinea-pigs inoculated with rest of the 3 strains were killed at 6 weeks.

Animals that died either of tuberculosis or from natural causes were scored in the same way, if such deaths occurred 30 or more days after injection.

Non-tuberculous deaths were defined as those occurring in animals with a total score of less than 40.

If any guinea-pig died before 6 weeks, then it was counted as 6 weeks guinea-pig. In case both guinea-pigs died, the one which died first was taken as 6 weeks and the other 12 weeks.

At the post mortem examination of animals the total extent of tuberculous disease was assessed as a score ranging from 0 to 100. The maximum score for the spleen was 40, for liver 30, lung 20 and for site of inoculation and draining lymph node 10. This method

of scoring was described by Mitchison et al (1960).

Table No. 1 indicates the method of scoring adopted at post-mortem examination.

The total score for each animal was divided by its survival time in days to give an index. This index is a measure of the rate at which the lesions develop in the organs and by inference it also measures the approximate rate at which tubercle bacilli multiply in the body. For statistical reasons the square root of 6 weeks & 12 weeks indices whenever possible, were calculated and termed 6 week and 12 week root indices respectively. The mean root indices for all the animals infected with the culture was termed root index of virulence. This index was used for assessment of virulence as it has been found that this gives statistically correct assessment of inoculated animals (Bhatia et al, 1961; Bhatia et al, 1963). The tuberculous nature of the lesion

was confirmed by making smears and demonstration of A.F.B.

For the sake of comparison the standard virulent strain H₃₇ Rv was also inoculated in 2 sets of guinea-pigs in the same way as that of the test cultures and the same method was adopted for assessing virulence.

It was also attempted to compare the virulence of INH sensitive and resistant strains in guinea-pigs. Thirteen INH sensitive strains and 3 INH resistant strains were used for this purpose. Virulence was assessed in the manner described above.

A culture of spleen was made in some animals on Lowenstein-Jensen Medium. All the gross lesions were examined histopathologically for the evidence of tuberculosis.

Results

Table II indicates the virulence of locally

TABLE I
Scoring system adopted in the present investigation

Percentage of score for extent of tuberculosis in various organs (According to Mitchison et al, 1961)			
Spleen	Liver	Lung	Site of inoculation and draining lymph nodes
40	30	20	10

TABLE II
Virulence of the locally isolated INH sensitive strains

Number of strains	Postmortem score at 6 weeks	Virulence index at 6 weeks	Postmortem score at 12 weeks	Virulence index at 12 weeks
1.	40	0.95	—	—
2.	50	1.19	—	—
3.	30	0.71	—	—
4.	40	0.95	40	0.47
5.	50	1.19	50	0.59
6.	40	0.95	40	0.47
7.	40	0.95	30	0.35
8.	30	0.71	30	0.35
9.	40	0.95	40	0.47
10.	40	0.95	40	0.47
11.	40	0.95	30	0.35
12.	50	1.19	50	0.59
13.	30	0.71	30	0.35

isolated INH sensitive strains. The total scoring of the organs in these animals at postmortem ranged from 30 to 50 at 6 weeks and also at 12 weeks. However in individual cases less score was observed at 12 weeks, than at 6 weeks. The virulence index, on average, at 6 weeks, ranged from 0.71 to 1.19 and at 12 weeks it ranged 0.35 to 0.59.

Table III indicates the virulence of standard virulent strain H₃₇Rv. The score of various

the root indices for INH sensitive strain was 0.85.

Table VI indicates the root indices of virulence of standard virulent strain H₃₇Rv. The 6 weeks root index for this strain ranged between 1.33 to 1.54 and 12 weeks root index ranged from 0.97 to 1.06. The root index of virulence varied from 1.15 to 1.80. The mean root index of virulence was 1.39.

Table VII indicates the root indices of

TABLE III

Virulence of standard virulent strain, H₃₇Rv

Number of strains	Postmortem score at 6 weeks	Virulence index at 6 weeks	Postmortem score at 12 weeks	Virulence index at 12 weeks
H ₃₇ Rv (Batch I)	100	2.38	100	1.14
H ₃₇ Rv (Batch II)	80	1.77	80	0.95
H ₃₇ Rv (Batch III)	90	2.00	90	1.07

TABLE IV

Virulence of INH resistant strains

Number of strains	Postmortem score at 6 weeks	Virulence index at 6 weeks	Postmortem score at 12 weeks	Virulence index at 12 weeks
1.	40	0.95	40	0.47
2.	50	1.19	50	0.59
3.	40	0.95	40	0.47

organs at postmortem varied from 80 to 100. The virulence indices at 6 weeks varied from 1.77 to 2.38 and at 12 weeks they varied from 0.95 to 1.11.

Table IV indicates the virulence of locally isolated INH resistant strains. The total score at postmortem varied from 40 to 50 at 6 weeks and at 12 weeks also. The virulence index at 6 weeks varied from 0.95 to 1.19 and at 12 weeks it varied from 0.47 to 0.59.

Table V indicates the root indices of virulence of locally isolated INH sensitive strains. The 6 weeks root index varied from 0.59 to 0.76. The root index of virulence varied from 0.76 to 0.87. The mean of all

virulence of locally isolated INH resistant strains. The 6 weeks root index varied from 0.97 to 1.09 and the 12 weeks root index varied from 0.68 to 0.76. The root index of virulence ranged from 0.82 to 0.92. The mean of root indices of virulence was 0.85.

Discussion

It has been observed by several workers that the Indian strains of tubercle bacilli are less virulent compared to the British strains and the strains isolated in other parts of the world (Frimodt-Moller, 1955, 1956; Bhatia et al, 1961; Mitchison et al, 1964; Singh, 1964). However it has not yet been determined whether the virulence of the organism is

TABLE V

Indicates the root indices of virulence of locally isolated INH sensitive strains

Number of strains	6 weeks root index	12 weeks root index	Root index of virulence
1.	0.97	—	—
2.	1.09	—	—
3.	0.84	—	—
4.	0.97	0.68	0.87
5.	1.09	0.76	0.97
6.	0.97	0.68	0.87
7.	0.97	0.59	0.78
8.	0.84	0.59	0.76
9.	0.97	0.68	0.87
10.	0.97	0.68	0.87
11.	0.97	0.59	0.82
12.	1.09	0.76	0.97
13.			

TABLE VI

Indicates the root indices of virulence of the standard virulent strain H₃₇-Rv

Number of strains	6 weeks root index	12 weeks root index	Root index of virulence
H ₃₇ Rv (Batch I)	1.54	1.06	1.80
H ₃₇ Rv (Batch II)	1.33	0.97	1.15
H ₃₇ Rv (Batch III)	1.41	1.03	1.22

uniformly low all over the country or there is a variation in the degree of virulence in the different parts of the country. Determination of this fact is of paramount importance as it may throw some light in the cause of this difference of virulence.

Virulence may be measured in experimental animals by (a) mortality from tuberculosis (b) the amount of tuberculosis at postmortem examination (c) the number of viable bacilli in the organs following injection with the strain.

However, all these procedures suffer from some disadvantages. The scoring method of Mitchison (1961) wherein a simple score of visible post mortem disease is recorded is not only easy to perform but gives quantitative evaluation of virulence (Bhatia et al, 1961 and Mitchison, 1961). When the degree of virulence is expressed as an index, it has several advantages. It indicates the rate of development of lesions, it allows comparison of results of different tests and the results obtained with 6 weeks and 12 weeks guinea-pigs can be

combined to give a single measure of virulence thus gaining information on the progress of the disease (Bhatia et al, 1961; Bhatia et al, 1963).

The reason for killing one of the pair of animals at 6 weeks and the other at 12 weeks was to establish whether the disease caused by strains of low virulence was regressive in the same manner as disease due to some Isoniazid resistant strains and to demonstrate that strains of same over all degree of virulence did not differ in their disease producing capacity in the early and late stages of infection.

In our study two groups of guinea-pigs were inoculated with the strains of tubercle bacilli. Thirteen Isoniazid sensitive strains were inoculated in one group and three Isoniazid resistant strains in another group. At post mortem examination the lesions were compared, with the standard virulent strain. It was observed that the overall virulence of both groups in our study was lower than the standard strain. This is in conformation with the findings of most of the workers. (Frimodt-Moller, 1955, 1956; Bhatia et al. 1963; Mitchison et al. 1961; Ramkrishnan et al. 1961; Bhatia et al. 1963; Mitchison, 1964; Singh, 1964).

When the lesions of the guinea pigs at 6 and 12 weeks were compared, it was observed that the tuberculous lesions, as judged from post mortem scoring, either remained same or even regressed after 6 weeks. This finding has been observed also by other workers (Barnett et al, 1953; Karlson, 1954; Mitchison et al, 1960). It was observed by Wallace et al (1961) that the counts of viable bacilli in the spleen of intravenously injected guinea-pigs diminished during the immune phase. This may be because of the fact that the bacilli of low virulence multiply readily during the early non-immune phase in guinea-pigs but killed in the organs when immunity develops.

It has been suggested by some workers that the difference in virulence of tubercle bacilli may be related to variation in resistance of the guinea-pigs of different areas (Goyal, 1948; Goyal et al. 1959). The guinea-pigs used in our study were of obscure parentage, but the question of their natural resistance was partly obviated by the fact that the virulence of H₃₇Rv strain was markedly higher than the locally isolated strains.

Regarding the origin of the low virulence strains in India there is controversy. The high virulence of the strains obtained in Hong Kong

and East Africa (Mitchison, 1963; Mitchison, 1964) suggests that factors specifically related to tropical countries such as high environmental temperature, exposure to large amount of ultra violet light are unlikely to provide explanations for this low virulence. It has been suggested by Mitchison (1960) that the virulence of bacillus is determined by optimal balance between virulence of the bacilli and the resistance of the host that allows the greatest chance of survival and multiplication of the bacillus. This assumes that Indians are more susceptible to tuberculosis than are other races for genetic or social reasons even though the actual relationship between the guinea-pig virulence and virulence to man is yet to be determined.

It has been reported by several workers (Gangadharam et al. 1963, quoted by Burke, 1963; Mitchison, 1963) the INH resistant strains of tubercle bacilli are less virulent to guinea-pigs. But we did not find any significant difference in virulence between the INH resistant and sensitive strains. The number of strains tested in our series was small and therefore much significance cannot be attached to this unusual finding.

It seems clear from our study as well as several other studies (Frimodt-Moller, 1955, 1956; Bhatia et al: 1961; Mitchison et al, 1961; Bhatia et al, 1963; Mitchison, 1964; Singh, 1964) that the virulence of the Indian strains of tubercle bacilli to guinea-pigs is low. The relationship of the virulence of the bacilli to guinea-pigs and humans is not just of academic interest but might be of considerable consequence to practical tuberculosis control in man. The relationship between the virulence of tubercle bacilli for guinea-pigs and man can be determined by estimating not only the prevalence of the infection but also the incidence of tuberculosis among people so infected.

Further, it is also necessary to clearly establish the differences in virulence of the strains of tubercle bacilli in different parts of this country because the diversity of environmental conditions and heterogenous composition of population would render any explanation of the origin of the comparatively attenuated strain of tubercle bacilli on the basis of environmental conditions or genetic factor in host unsatisfactory. Any significant explanation regarding the cause of this attenuation of virulence can emerge only after more adequate information regarding the virulence of strains—rather the degree of attenuation of the strains—in different parts of the country is obtained and the findings correlated with social,

environmental and genetic factors of the host and the biology of the microbe.

The low guinea-pig virulence of the Indian strains of tubercle bacilli has a great practical implication also in the laboratory diagnosis of tuberculosis. Negative results in animal inoculation tests may not rule out tuberculosis completely. In such cases more searching examinations for localised lesions in the injected animals and cultivation of spleen may sometimes reverse the findings.

Summary and conclusions

In this study an attempt has been made to determine the virulence of locally isolated strains of tubercle bacilli to guinea-pigs in a quantitative manner by comparing their virulence with that of the standard virulent strain H₃₇Rv.

Two sets of guinea-pigs were inoculated with standard suspension of the organisms and the animals were sacrificed at 6 and 12 weeks. At post mortem the extent of lesions was assessed by a system of scoring ranging from 10 to 100 depending on the involvement of different organs. The degree of virulence was expressed as virulence index and root index of virulence to eliminate statistical errors.

The locally isolated strains were found to be significantly less virulent than the standard virulent strain and the root indices of virulence ranged from 0.76 to 0.87 as compared to the root index of virulence for the standard strain which was 1.39.

The virulence of Isoniazid resistant strains was compared with the virulence of the Isoniazid sensitive strains. No significant difference was observed in their virulence.

The literature regarding the virulence of tubercle bacilli to guinea-pigs in different parts of the world has been reviewed and observations of the present study have been compared with the findings of other workers.

The significance of guinea-pig virulence in relation to human disease and the probable causes of low virulence of Indian strains have been discussed.

The need for further study to arrive at any conclusion regarding the cause of variation in virulence in different parts of the world has been emphasised.

Ind. J. Tub., Vol. XIX, No. 4

REFERENCES

1. Barnett, M.; Busbhy, S.R.M. and Mitchison, D.A. (1953) : *Brit. J. Ext. Path.* 34, 568.
2. Bhatia, A.L.; Csillang, A.; Mitchison, D.A.; Selkon, J.B.; Somsundaram, P.R. and Subbaiah, T.V. (1961): *Bull. Wld. Hlth. Org.*, 29, 313.
3. Bhatia, A.L.; Haeoh, C.V.; Hitze, K.L.; Ramchandram, K. and Selkon, J.B. (1963): *Bull. Wld. Hlth. Org.*, 29, 483.
4. Burke, H.E. (1963) : Proceedings of the XVIIth International Tuber. Conf., Rome. *Excerpt a Medico*, 69, 307.
5. Chandrashekhar, S. and Gupta, N.P. (1966) : *Ind. J. Med. Res.*, 54, 535.
6. Dhayagude, R.G. and Shah, B.R. (1948) : *Ind. J. Med. Res.*, 39, 79.
7. Dhurandhar, C.B. (1941) : *Ind. J. Med. Res.*, 29,
8. Fridodt-Moller, J. (1955) : *J. C.M.R. Tech. Rep.* New Delhi, 271.
9. Fridodt-Moller, J. (1956) : *I.C.M.R. Tech. Rep.* New Delhi, 153.
10. Goyal, R.K. (1948) : *Ind. Med. Gaz.*, 83, 35.
11. Goyal, R.K.; Gupta, D.P. and Gupta, O.P. (1959) : *Ind. J. Tuberc.*, 6, 27.
12. Griffith, A.S. (1919) : *J. Path. and Bact.*, 23, 129.
13. Jensen, K.A. and Fridodt-Moller, J. (1936) : Quoted by Mitchison, 1963.
14. Karlson, A.G. (1954) : *Amer. Rev. Tuberc.*, 70,
15. Lange, B. (1930) : Quoted by Mitchison, (1963).
16. Mitchison, D.A. (1964) : Quoted by Girard et al, 1970.
17. Mitchison, D. (1963) : Proc. of the XVII the Int. Tub. Conf. *Excerpta Medico*, 69, 302.
18. Mitchison, D.A., Bhatia, A.L.; Radhakrishna, S.; Selkon, J.B.; Subbaiah, T.V. and Wallace, J.G. (1961) : *Bull. Wld. Hlth. Org.*, 25, 285.
19. Mitchison, D.A.; Wallace, T.G.; Bhatia, A.L.; Selkon, J.B.; Subbaiah, T.V. and Landcoster, M.L. (1960) : *Tuberc.*, 41, 1.
20. Ramkrishnan, C.V.; Bhatia, A.L.; Fox, W.; Mitchison, D.A.; Radhakrishna, S.; Selkon, J.B.; Subbaiah, T.V.; Vein, S. and Wallace, J.G. (1961): *Bull. Wld. Hlth. Org.*, 25, 323.
21. Schwahaer M. and Wilson, G.S. (1937) : *Tuberc. (Edinb)*. 18, 442.
22. Shrinivas (1965) : *Ind. J. Tuberc.*, 12.
23. Singh, B. (1957) : Quoted by Mitchison, 1963.
24. Singh, B. (1964) : *Am. Rev. Resp. Dis.*, 89, 1.
25. Steward, G.T. (1951) : *Lancet*, 11, 562.
26. Sula, L. and Langerova, M. (1964) : Quoted by Gerard et al 1970.
27. Wallace, J.G.; Mitchison, D.A.; Rees, R.J.W.; Bhatia, A.L. and Gangadharam, P.R.J. (1961): *Tuberc.*, 42, 212.

INCIDENCE OF INITIAL DRUG RESISTANCE IN LOCALLY ISOLATED STRAINS OF TUBERCLE BACILLI

MANGALA P. BANSAL, S.R. SENGUPTA, H.I. JHALA AND K.D. SHARMA
(From Medical College, Aurangabad).

Since the introduction of effective chemotherapeutic agents for the treatment of tuberculosis, concern has been felt about emergence of strains of *Mycobacterium tuberculosis* resistant to three major anti-tuberculosis drugs viz Streptomycin, Isoniazid and P.A.S. Drug resistance in a case of tuberculosis can be either acquired or initial. However these two are interconnected as an acquired drug resistant patient may disseminate his resistant strain of bacterium to his contacts who would be infected with an initially resistant strain. Initial drug resistance is resistance of tubercle bacilli, in sputum from previously untreated patients. Incidence of initial drug resistance has great clinical and epidemiological significance and would influence the control programme of tuberculosis to a great extent.

Initial resistance to antituberculosis drugs has been observed in many parts of the world and its reported incidence varies widely. It was, therefore, decided to determine the incidence of initial drug resistance in this area.

Material and Methods

Tubercle bacilli isolated from untreated cases of pulmonary tuberculosis were tested for their sensitivity to three antituberculosis drugs viz Streptomycin, I.N.H. and P.A.S. A total of 80 samples of sputum were processed from untreated cases of tuberculosis. Out of these 60 strains of tubercle bacilli were isolated. The sputa were received from the Tuberculosis centre at Aurangabad, as well as from Tuberculosis centres elsewhere in Marathwada region. The study extended over a period of one and a half years, from December, 1969 to May 1971.

The sputa were collected from patients coming to the tuberculosis centres for the first time, without any previous history of anti-tuberculosis treatment. As far as possible the sputa were collected from patients of younger age group so as to avoid the change of previous chemotherapy. Cases with minimal lesion in X-ray were also screened for A.F.B. in their sputum.

After direct smear examination the sputa were concentrated by Petroffs method

(Cruickshank 1968) and primary cultures were obtained on Lowenstein Jensen medium. Screened procedures were set up to isolate and identify atypical mycobacteria. Two strains of atypical mycobacteria were isolated but they have been excluded from the study.

Tests for drug sensitivity were set up within two weeks of the slopes becoming positive. Older cultures were subcultured, if necessary, to ensure that the inoculum was composed of young viable organisms.

The sensitivity test was performed according to the resistance ratio method described by W.H.O. Expert Committee (1963). The drug concentrations which were used were same as those used by the I.C.M.R. Study Group (1969) so that the results could be compared with the report of this group. Table I indicates the drug concentrations used for different antibiotics. The results were represented on the basis of resistance ratio methods as well as by noting the minimum inhibitory concentration (M.I.C.), especially for Isoniazid and P.A.S.

A measured amount of inoculum for doing the sensitivity test was obtained by using a 3 mm. standard diameter loop as advocated by the W.H.O. Expert Committee (1963). The inoculum was standardised before starting the work. For this purpose a representative swab from the growth was taken with the standard loop and weighed a number of times, so as to ensure that there is actually 2 mg. of inoculum on the loop.

After the inoculum was standardised, the actual procedure of sensitivity test was carried out. The procedure that was followed for inoculation and recording of sensitivity were the same as described in the report of the W.H.O. Expert Committee (1963).

A standard sensitive strain H₃₇RV, obtained from the Tuberculosis Chemotherapy Centre, Madras, was tested with each batch of tests.

For Isoniazid, the strains were said to be sensitive when no growth was there on 0.2 microgram/ml. of media. The strains were labelled as resistant when growth was present on 4 microgram/ml. of media. The

strains were said to be doubtful when there was a growth on 0.2 microgram/ml. of medium but not on 1 microgram/ml. of medium. In this case the test was repeated from the control slope and if the same reading was obtained, or a more resistant one, the strain was finally classified as resistant. If there was no growth on 0.2 microgram/ml. of medium, in the repeat test the strain was classified as sensitive. The resistance to I.N.H. was recorded according to the criterion used by the I.C.M.R. Study Group, 1969 (ICMR Rep. 1969). The resistance to I.N.H. was taken to be present when M.I.C. of 5 microgram or more was present or 1 microgram followed by 1 microgram or more in the retest.

A strain was considered to be sensitive to Streptomycin when the resistance ratio was two or less, and resistant to Streptomycin when the resistance ratio was eight or more. A strain was considered to have doubtful resistance when the resistance ratio was four. A strain was considered to be sensitive to P.A.S. when the resistance ratio was two or less and resistant to P.A.S. when the resistance ratio was eight or more. A strain was considered to have doubtful resistance when the resistance ratio was four. Doubtful tests were

repeated from the control slope and interpreted as described earlier.

Results

Out of the total 60 strains tested, four strains were resistant to both Streptomycin and Isoniazid ; that is 6.6% of the strains were resistant to I.N.H. and Streptomycin. Three strains, that is, 5 percent, were resistant to P.A.S. None of the strains were resistant to P.A.S. alone. The percentage of P.A.S. resistance was lower than the percentage of I.N.H. and Streptomycin resistance.

Table II indicates the pattern of resistance of the strains to Streptomycin.

Table III indicates resistance of the strains to P.A.S.

Table IV denotes the resistance pattern of the 4 strains to Isoniazid.

Table V indicates the over all drug resistance pattern of all the strains to the three antituberculosis drugs viz. I.N.H., Streptomycin and P.A.S. No strain was found to be resistant to only one drug. Resistance to more than one drug was found to be present in 6.6 percent of the strains.

TABLE I

Drug concentrations used in the sensitivity tests

Drug concentration in microgram per ml. of medium

Drug	Test strain	H ₃₇ Rv
Isoniazid	0.2, 1, 5, 50	0.25, 0.05, 0.1, 0.2, 1
Streptomycin	4.8, 16, 32, 64	1, 2, 4, 8
PAS	0.5, 1, 2, 4, 8, 16	0.125, 0.25, 0.5, 1, 2

TABLE II

Showing resistance of the strains to Streptomycin

No. of strains tested	Number sensitive	Number resistant	MIC Microgram/ml.	Resistance ratio	Percentage resistance
60	56	4	2(16), 1 (8), 1 (32)	3(8), 1 (8)	6.6

Figures in brackets indicate minimum inhibitory concentration.

TABLE III

Showing resistance of the strains to PAS

No. of strains tested	Number sensitive	Number resistant	MIC Microgram/ml.	Resistance ratio	Percentage resistance
60	57	3	2(4), 1(8)	3(78)	5

Figures in brackets indicate minimum inhibitory concentration.

TABLE IV

Showing the resistance of the strains to INH

No. of strains tested	Number sensitive	Number resistant	MIC microgram/ml.	Resistance ratio	Percentage resistance
60	56	4	2(5), 2(50)	-	66

Figures in brackets indicate minimum inhibitory concentration.

TABLE V

Indicates overall resistance to all the three drugs

Total number of strains	Number resistant to PAS	Number resistant to streptomycin	Number resistant to INH	Percent resistant to one drug	Percent resistant to more than one drug
60	3(5)	4 (6.6)	4 (6.6)		6.6

Figures in brackets indicate minimum inhibitory concentration.

Discussion

Bacterial resistance to antituberculosis drugs is a complex subject and there is little agreement on the nature of the phenomenon, the technique for detection, the interpretation

tance is undesirable and on both theoretical and practical grounds the assumption appears reasonable.

Initial drug resistance could have two explanations : the patient could have been infected by a person whose bacilli had become resistant during treatment or the bacterial population in the patient could have contained naturally resistant organisms (Citron, 1968).

The incidence of initial drug resistance

reported from different parts of the world cannot be strictly compared because of the different methods used in the study of initial drug resistance. These methods present two major problems. First, the correct definition of resistance is essential to obtain results. Secondly, certain questions of technique, particularly concerned with the size of inoculum, influence the results to a great extent (Mitchison, 1961). However, when the techniques are comparable and the method of selection of cases is known a more or less valid comparison can be made regarding the incidence of initial drug resistance reported in different parts of the world.

The incidence of initial drug resistance obtained in our study is in close agreement with the results of most of the workers reported from different parts of the world (Chaves,

TABLE VI

Drug resistance of tubercle bacilli isolated from patients with no history of previous chemotherapy

Study and name of the investigators	Country	Date and year	Number of strains tested	Percentage resistance to		
				Isoniazid	Streptomycin	PAS
1	2	3	4	5	6	7
Fox and others (1957)	Great Britain	1955—1956	974	0.7	2.3	2.2
Miller and others (1966)	Great Britain	1963	896	1.7	3.5	1.1
U.S. Public Health service 1964	U.S.A.	1961—1962	2,400	1.6	2.8	0.8
Hobby and others (1964)	U.S.A.	1962—1963	1,204	3.9	3.1	2.9
Hobby et al (1970)	U.S.A.	1963-1969	3,183	4.2	1.6	7.2
Canetti (1965)	France	1963—1964	2,144	4.6	7.6	2.2
Pepys and others (1960)	East Africa	1953—1955	56	Nil	—	—
	Uganda	—Do—	26	—	—	0.9
	Uganda Kenya and Tanganyika	1956-1957	140	7.9	—	2.9
			69 40	7.5	—	10.7
			151	12.6	—	12.9
			162	16.0	—	—
Bell and Brown (1960)	Uganda	1958-1959	172	9.9	—	4.1
	West Africa Ashanti	1958	342	9.1	8.5	5.5
Hongkong MRC (1964)	Hongkong	1962	302	14.0	11.1	3.5
B.T.A. (1964)	Hongkong	1962	150	10.0	7.5	Nil
Chaves et al	U.S.A.	1953—1955	1,016	6.8	6.5	—
Thibier et al	Paris	1958—1959	123	9.0	9.0	0.7

Compiled from Meissener, 1961 and Citron, 1968.

1955 U.S. Public Health Service Rep. 1964, Zaki et al, 1969, Hobby et al 1970).

Table VI indicates a comprehensive list of the prevalence of initial drug resistance in different parts of the world reported by various investigators. The variation in incidence in different reports can be accounted for by the geographical differences in the incidence of initial drug resistance and the carefulness with which the cases have been selected for the study.

Initial drug resistance of tubercle bacilli has been reported by several investigators from different parts of India. Table VII indicates the incidence of initial drug resistance.

observed by different Indian workers in different parts of the country. In most of the reports the incidence is very high. It is difficult to say whether these figures reflect the actual incidence of initial drug resistance in different parts of the country. The higher percentage of resistance could be either because of improper selection of cases or different criteria used for assessment of resistance. Our results correspond more to the results obtained by the ICMR Study Group (1968, 1969).

Table VIII indicates a comparison of results reported by the I.C.M.R. Group (1969) and observed in our series. It is evident from the table that the incidence, of P.A-S. and

TABLE VII

Comparison of the incidence of initial drug resistance observed by other Indian workers and in the present study

Investigator	Year and area investigated	Number of patients or strains examined	Chemotherapy	Resistance to		
				INH	PAS	Streptomycin
Balbir Singh	Delhi 1956	—	—	24	8	16
Mitchison	Madras 1959	143 cases	—	3.6	2.6	—
Ganguly	1960	409 strains	—	10.45	6.75	8.9
Frimodt Moller	Mission 1960 hospital sanatoria Madras	283 cases	—	16	—	10
Menon	Hyderabad 1963	100	—	15	—	4
Gupta	U.P. 1963	356	Receiving treatment	82	45	70
Mahapatra	Delhi 1964	193	Receiving treatment	83.45	—	—
M.R.C. Report	Madras 1964	165 strains	No treatment	7	2	5
Mahajan et al	Chandigarh 1968	180	No treatment	27	28	42
ICMR Study Group	1968	1,861	No treatment	9.1	—	7
Present Study	Marathwada	60	No treatment	6.6	5	6.6

TABLE VIII

Comparison of results of ICMR study and present study

Centre	Percent of cultures resistant to INH	Percent of cultures resistant to Streptomycin
Amritsar	16	12
Bangalore	14	10
Bombay	17	21
Delhi	19	15
Hyderabad	21	15
Madras	15	14
Nagpur	11	9
Patna	5	16
Present study	6.6	6.6

I.N.H resistance of strains from many center studied by the I.C.M.R. group is high. The reason for this difference is not clear. But in obtained at different centres.

quit close to that attained by us and three is a wide variation in incidence of resistance obtained at difference centers.

Apart from the question of technique and

the selection of cases there are many other factors which may influence the reported incidence of initial drug resistance ; such as the relationship between the resistance of infection source and initial resistance (Thibier et al 1960, Meisner, 1961), the incidence of atypical mycobacterial infections and the carefulness with which they are excluded from the study (Selkon and Mitchison, 1959, Raj Narain et al, 1968). According to Hobby (1963) one can hope to obtain a correct information concerning the prevalence of resistant organisms among previously untreated patients only by studies conducted in children who once infected develop active primary tuberculosis.

In considering the possible risks for the patient who has a strain with initial drug resistance, the evidence demonstrated by Mitchison (1961) clearly shows that the initial resistance to I.N.H. results in an unsatisfactory response to treatment. However, it is much less certain that initial resistance to P.A.S. has any considerable influence on the response to treatment with P.A.S. and I.N.H. In part this may be explained by the greater importance in treatment of I.N.H. than the other drugs.

One can consider the problem of drug resistance both from the point of view of the response of the individual and from the point of view of the danger of spread of drug resistant organisms in the community. The problem is a very real one for the developing countries. Not only is the prevalence of initial resistance, particularly to Isoniazid, higher than in Western countries there are, in addition, many patients who have had short courses of treatment with I.N.H. and who either do not know that they have received such treatment or do not tell the physician on their first examination.

The problem of initial resistance is a problem of the last act in the fight against tuberculosis. How long there will still be a problem of tuberculosis depends in great measure on the number of chronic carriers of such resistant bacilli endangering their environment.

Summary

This paper presents the incidence of initial resistance of tubercle bacilli to the first line of antituberculosis drugs, namely Streptomycin, P.A.S. and Isoniazid, as obtained in this region.

Ind. J. Tub., Vol. XIX, No. 4

Tubercle bacilli isolated from untreated cases of pulmonary tuberculosis were tested for their sensitivity to three antituberculosis drugs viz. Streptomycin, I.N.H. and P.A.S. by using the resistance ratio method for Streptomycin and P.A.S. and by determining the minimum inhibitory concentration for Isoniazid. The standard H₃₇RV strain was used as a control.

A total of 60 isoniazid strains were tested. Resistance to Streptomycin was observed in 6.6 percent of strains, to P.A.S. in 5 percent of strains and to Isoniazid in 6.6 percent strains. Resistance to more than one drug was found in 6.6 percent of strains.

The literature regarding the incidence of initial drug resistance in different parts of the world has been reviewed and the results obtained in the present study have been compared with the available data regarding the incidence of initial drug resistance in India and other parts of the world.

The difficulties involved in such comparisons have been emphasised.

The significance of initial drug resistance in relation to the epidemiology and treatment of tuberculosis has been discussed.

ACKNOWLEDGEMENTS

The authors are grateful to M.R. Dhamdhare, Dean, Medical College Aurangabad for permission to publish the material. The authors also wish to express their gratefulness to Dr. K.P. Ganguly, Deputy Director of Health, Aurangabad Division for help in obtaining the material. The authors are thankful to the Director, Tuberculosis Chemotherapy Centre, for supplying the H₃₇RV strain.

REFERENCES

1. Bell, W.J. and Brown P.P. (1960), *Tuberc. Land.* **41**, 247.
2. British Tuberculosis Association Hongkong, *Tuberc. Land.* 45, 299.
3. Canetti, G., Froman, S., Grosset J., Hauduroup, Miloslava Langerova Mather, H.J. Meissner Mitchison, D.A., and Sula, H. (1963), *Bull. Wld. Hlth. Org.* 29, 565.
4. Canetti, G. (1965), *Am. Rev. Resp. Dis.* **92**, 687.
5. Chavas, A.D., Ropins, A.B., Abeles, H., Peizer, L.R. Douglas, G. and Widelock, D. (1955). *Am. Rev. Tuberc.* 72, 143.

6. Cruickshank, R. (1968). *Medical Microbiology* XIth. ed. E. & S. Livingstone Ltd. London.
7. Citron, K.M. (1968). *Rec. Adv. Resp. Tub.* XI ed. 90.
8. Fox, W., Wiener, A., Mitchison, D., Selkon J.B. and Sutherland, T. (1957). *Tuberc. Lond.* 38, 71.
9. Hobby, G.L. (1963). *Am. Rev. Resp. Dis.* 87,29.
10. Hobby, G.L., Johnson, P.M., Lennert, T.F., Crawfordgagliardi, Greetham, L., Iwasaki, T., Lapin A., Maier, J.O., Melley P., and Trembly C. (1964). *Am. Rev. Resp. Dis.* 89, 337.
11. Hongkong, British Medical Research Council (1964). *Tuberc. Lond.* 45, 77.
12. Hobby G.L., Johnson, P.M., and Boytar-papirnyik (1970). *Amer. Rev. Resp. Dis.* 102, 347.
13. Indian Council of Medical Research (1969). *Ind. J. Med. Resp.* 57, 832.
14. Meissner, G., (1961). *Excerpta Medica*, No. 44, Proceedings of the XXI. International Tuberculosis Conference, Vol. I Sept., 10-14.
15. Miller, A.B., Tall, R., Fox W., Leflord, M.J.. and Mitchison, D. A. (1967). *Tuberc.* 47, 92.
16. Mitchison, D.A. (1961). *Excerpta Medical*, 1, 81.
17. Pepys, J.A., Mitchison, D.A., Kingsley, B.J. (1960). *Tuberc.* 41, 32.
18. Raj Narain, Chandrashekhar, P., Satyanarayanch, R.A. and Pyarelal (1968). *Bull. Wld. Hlth. Org.* 39,681.
19. Selkon, J.B. and Mitchison, D.A. (1959). *Tuberc. Lond.*49, 141.
20. Theiber, R., Canetti, G., Lepeuple, A., Grosset, J. and Vivien, J.N. (1960). Quoted by Meissner, (1961).
21. United states Public Health Cooperative investigation (1964). *Am. Rev. Resp. Dis.* 89, 327.
22. W.H.O. Expert Committee on Antibiotics *Wld. Hlth. Org. Resp. Ser.* 210. Quoted by Canetti et al. (1968).

ECONOMICS OF HEALTH—THE COST OF TUBERCULOSIS

A. S. SEN and R. N. BASU

(From Health Division, Planning Commission and D.G.H.S., New Delhi.)

In an overall and integrated concept of social and economic development of a country, health cannot be considered exclusively as an end in itself. One must take into account also its role as one of the social sectors in overall development and try to establish measurable relationships between health and the macroscopic variables, such as consumption, productivity and labour on which it depends or with which it is involved most directly. In other words, it is necessary to determine the investment in health required for development or the rate of development. At the present time, it is only possible to establish this theoretically based on an expression of the limits within which an investment in health can produce determined effects as the scarce resource is to be distributed among schemes of great magnitude, such as the prevention, control of communicable diseases, training of medical and paramedical personnel, medical care and medical research.

To plan for health, that is, to meet the basic needs of the community and, at the same time, to satisfy the requirements of the overall pace for development is a complex process. It will be possible to achieve it fully when the economic benefits obtained with a specific health measure can be expressed in quantitative terms and when it is possible to measure precisely the degree of benefit to health from activities which are carried on outside this direct operational sphere. Though progress has been made in the analysis and estimation of costs and benefits in public programmes, but cost-benefit analysis in public health area has lagged.

The economics of health is a newer term than medical economics ; it encompasses the medical care industry, extends into such fields as the analysis of the economic costs of diseases and the benefits of control programmes, returns from investment in education and training, the conditions conducive to medical research, and so forth.

The economic aspects of health services as defined by Klarman are those aspects of the health problem that deal with the determination of the quantity and prices of the scarce resources devoted to this and related purposes and

with the combinations in which these resources are employed. The quantitative relations between resources and the human capital is difficult to ascertain, for there is no easily determinable health value of a healthy being as there is for a house or a machine. For determining the quantities and measuring them properly for exact analysis, require many conceptual and accurate health data for the application of economic theory.

Many have tried to evaluate man or in other words, to put a price upon his economic worth. One of the earliest attempts was that of Sir William Petty (1623-1687) who originated many ideas later used by the political economist Adam Smith in his "Wealth of Nations" and other works. Dublin, Lotka and Spiegelman have attempted to translate the figures of life expectancy into terms of financial value to the community. One of the conclusions arrived at by them is that the period of infancy and early childhood represent a drain upon family and community resources. This investment is made towards a productive return in later life. Death at the early productive age is therefore a loss to the community, not only in the investment made but also of the future earnings of the individual. But, loss due to sickness, on the other hand, is limited to the duration of illness when the individual remains unproductive or under-productive from ill-health. Poverty prolongs the process of chronic ill-health. Sinton (1936) observed that a community afflicted with malaria has as a whole, a reduced earnings and productive power. The income of the individual is reduced and his spending is proportionately diminished, so a vicious circle arises whereby malaria begets poverty and poverty malaria. There is a cumulative process in the operation continuously pressing levels downwards. Poverty and disease form a vicious circle. Men and women become sick, and sicker because they are poorer.

Economic value of human being has a direct bearing on poverty and disease. Human beings who eke out a miserable existence in a social setting where their work is unproductive, their food scarce, their housing inadequate, their life span short and their health bad or in constant danger, are not in a position to make

gainful contribution to the society. On the other hand, an improved health standard will raise the productivity which *per se* always tend to improve all other component factors in the place of living. With the reduction in the incidence of malaria among the plantation workers in Assam, absenteeism has become considerably reduced. In 1959 the rate was 20.49%, and it has come down to 7.45% in 1963. This naturally increased the production capacity of the employees, the tea plantation was employing 3.21 persons per hectare of land in 1950 and in 1961 for the same area 2.16 persons are being engaged.

Eradication and control programmes of some of the communicable diseases which have been taking heavy toll of life have made marked progress under the Five Year Plans. Of these, the malaria eradication programme has reduced considerably the incidence of the disease, its morbidity and mortality. The Public Health commissioner of India reported 3,662,557 deaths due to fevers in 1933, of which one-third to one-fourth was due to malaria. The number of deaths due to this disease is at present negligible.

Tuberculosis control programme has made some headway through the plan periods. In view of the progress made in eradication and control of these two diseases, certain measurable benefits have been gained, and a study to quantify the cost and benefits of the national programme has been made.

Sinton (1936) made an assessment of the financial loss due to malaria to the individual and the family alone at not less than Rs. 11,000 lakhs annually and pointed out that the effects of the disease are reflected upon all aspects of labour problem and the successful development of industries of the country. Bhombore (1952) and C. S. Narahari Rao et al (1956) estimated the cost of social benefit accruing from DDT sprayings in the villages near Mysore. Anderson (1962), dealing with some aspects of the economics of Tuberculosis in India, estimated the direct cost of tuberculosis at 18.8 crores annually.

Methodology

Weisbord, after considering what from society's point of view are economic costs of a disease and which of these costs is practicable to quantify, arrived at three important categories of losses, from poor health, premature death, sickness and treatment.

The calculations of the Health and Medical care expenditure (direct cost) poses fewer

conceptual problems than output loss, for costs of treatment of a patient in hospitals, dispensaries or clinics, prevention or control measures, training of personnel, research and other non-personal service. Indeed, research which may require large sums, opens out avenues for fresh approach either in the prevention or treatment of a disease. Research expenditure should, therefore, legitimately be included under direct costs.

Conceptual problems arise in the calculation of output loss, indirect cost due to a disease transfer payments, taxes, consumption, the work of housewives, assumptions regarding employment and discount rates.

Direct Cost

There are about 35,000 beds in Government and private hospitals and sanatoria for treatment of patients suffering from tuberculosis. Expenditure for maintaining these hospital beds varies from State to State and from one hospital to another according to the services provided by it. The cost for hospitals with surgical facilities will be higher than the ones without it and a hospital which has a larger turnover of patients will have higher cost than one with a lower turnover. Accurate information of the annual cost of these beds is not readily available and it is unlikely that all these institutions will follow a uniform pattern for calculating the cost, hence an average expenditure has been employed in the calculation of the total annual cost for maintaining the TB beds in the country with full recognition that further refinement of the data can be and should be made. This can be done if considerable amount of time and staff is given. It is however considered that this average expenditure will take care of the variations in the cost of construction and equipment. The annual expenditure for maintaining a bed varies from Rs. 2,000 to 3800 and an average rate, Rs. 2,500 per bed per year has been taken for calculating the total cost which amounts to Rs. 875 lakhs. It includes the cost of physician and nursing services, investigations, other charges and cost of drugs.

The interest on the capital locked up in the buildings, instruments and appliances, etc. has been calculated on the basis of the estimated capital cost per bed. On the basis of the Hospital Equipment Standardisation Committee's (1963) estimate, the cost for building and equipment for the TB hospitals and sanatoria has been estimated at Rs. 3,850 lakhs and interest on the capital invested at 15% will be Rs. 577.5 lakhs. The total esti-

mated cost for the hospitals and sanatoria, therefore, amounts to Rs. 1,452.5 lakhs per annum.

Since the introduction of potent anti-tuberculosis drugs, domiciliary treatment is being given extensively and institutional treatment is restricted chiefly for the bacillary positive and other cases which require hospitalisation. There are 502 tuberculosis clinics, of which 155 have X-ray, laboratory, other facilities for investigation and form domiciliary follow up of cases and are running the district TB programme. The annual recurring expenditure for each of these upgraded clinics is estimated at Rs. 1.5 lakhs. This expenditure includes the pay and allowances of the staff, the cost of case detection, X-ray, laboratory examinations and other investigations, cost of drugs, treatment and follow-up of patients. The annual estimated recurring expenditure for the remaining 347 clinics is Rs. 20,000 each. The total annual recurring cost for these clinics amounts to Rs. 301.9 lakhs. The estimated capital cost of a upgraded Tuberculosis clinic is Rs. 2.1 lakhs and that of the other is about Rs. 50,000. The total estimated capital cost of the clinics is Rs. 571 lakhs and the interest on capital locked up for these clinics at the rate of 15% is Rs. 85.65 lakhs. The total cost for these clinics is estimated at Rs. 387.55 lakhs per year.

Drugs

There are certain specific drugs used for the treatment of tuberculosis and an estimate of their consumption has been made on the basis of their production in the country and the quantities imported. The consumption for the year 1966 and their cost is as follows :—

	<i>Quantity (in tonnes)</i>	<i>Cost (in lakhs)</i>
Isoniazid PAS	82.98	82.1
Streptomycin	474.60	161.2
Thiacetazone	114.25	663.0
	7.00	0.1

Besides the above mentioned drugs, a tuberculosis patient requires other medicines for symptomatic relief and supportive measures. As no data is available of the proportionate

cost of other medicines, no attempt has been made to calculate it.

It has been observed from various survey reports that not all patients come for treatment in the TB clinics, for they prefer to receive treatment from private medical practitioners, no data regarding their number is available for making an estimate. But Banerjee, from a survey in the rural districts of Bangalore, has reported that 5% of the sputum positive cases in that area sought treatment from private practitioners. It has been estimated that there are about 1.5 million infectious cases of tuberculosis in the country and it is not likely that all the patients treated by the private medical practitioners take the full course of treatment which is long and costly, drugs alone cost Rs. 87—100 for a case. These patients may cease to undergo the treatment after the alleviation of symptoms or die due to inadequate treatment. It is assumed that on an average a patient may spend Rs. 100 for his treatment on cost of medicine and doctors fees. On this basis, the cost of treatment by private medical practitioners of these cases is estimated at Rs. 75 lakhs.

Advances made in the prevention or cure of disease are fruits of research work. Their cost can broadly be divided into two groups, namely, drugs and clinical research. It is not proposed to include the cost of research on drugs in the direct cost structure of tuberculosis, as all these drugs were discovered and marketed first by foreign firms.

The Indian Council of Medical Research provides funds for most of the research projects and in 1965-66 it spent Rs. 16.09 lakhs for research on this disease.

Training of TB workers, field trial and other types of workers as well as research work are being done in the under-mentioned institutions. The expenditure incurred by them annually has been shown against them.

<i>Institution</i>	<i>Annual expenditure Rs. (in lakhs)</i>
National Institute of Tuberculosis	7
Tuberculosis Chemotherapy Centre	7
BCG Vaccine Laboratory	5

Besides these institutions, there are 13 State TB Centres where training of field workers and treatment of TB patients are

being given. The estimated annual cost of each of these Centres is Rs. 2.2 lakhs. The total annual expenditure of these Centres is Rs. 28.6 lakhs. There are 216 BCG vaccination teams. The annual recurring expenditure for each team is Rs. 30,000 and the cost of vehicles and equipment provided to each team is Rs. 40,000. The annual expenditure incurred for this campaign is Rs. 77.7 lakhs.

The total direct cost for the year 1966 is estimated at Rs. 2,965.94 lakhs.

Direct cost of tuberculosis

Item	Rs.
	(in lakhs)
Hospitals	1,452.50
Clinics	387.55
Drugs	912.00
Private medical practice	7500
Research	16.09
Training	47.60
BCG Vaccination	77.70
	2,968.44

Indirect cost

Loss due to morbidity

To measure output loss due to a disease certain baseline data, such as age and sex-wise mortality, morbidity rates, age and sex-wise income, degree of employment etc. are necessary, inadequacies of these add to the

difficulties of calculation of indirect cost. The data used in this study have been obtained from surveys and reports of various organisations such as Indian Council of Medical Research, National Council of Applied Economic Research and the Census Survey 1961. Though the data obtained from these reports are not of the same year, it is considered that the variations, if any, are not likely to be significant.

The National Sample Survey (1955-58) of tuberculosis has estimated the prevalence of active and probably active cases of tuberculosis in towns, cities and villages of different zones of the country separately. For calculating the average prevalence rate for urban areas for the whole country the rates for the cities and towns have been combined together and for the rural area the rates found for the various rural areas have been combined for calculating the average for the whole country. These rates according to the various age groups and sex is given in Table I

The Census (1961) Report has classified the population broadly into workers and non-workers according to their sex, age-group and residence. The probable number of these workers who may be affected by the disease has been estimated, in Table II, on the basis of the prevalence rate given in Table I. It may be mentioned that age groupings of the Tuberculosis Survey Report and that of the Census are similar except for the first, third and fourth groups. These differences, being small, have not been taken into account.

It is estimated that there are 37,30,148 active and probably active cases among the workers. The period of lost production due to the disease will be more for those cases which are admitted to hospital or sanatoria for treatment than those who are treated without

TABLE I

Prevalence rate of tuberculosis cases, age, sex and residencewise per 1000 population

Age group	Rural		Urban	
	Male	Female	Male	Female
5—14	9.28	8.62	10.01	10.91
15—34	13.83	11.12	16.54	15.40
35—54	28.29	17.54	34.10	23.14
55 and above	49.46	34.05	56.49	31.46

TABLE II

Estimated number of Tuberculosis cases among workers

Age group	Rural		Urban	
	Male	Female	Male	Female
0-14 years	75,395	47,813	5,664	2,536
15-34 years	7,04,845	3,14,458	1,95,806	30,449
35-59 years	11,11,084	3,35,113	3,03,745	35,764
60 and above	4,13,555	86,961	62,425	6,635
Total	23,04,879	7,84,345	5,65,640	75,384

confinement or cases discovered only at the time of death. The cases detected in the early stage of the disease will reduce the average period of lost production and it is estimated that on an average the period of production loss will be about one year. The one year of illness per case is applied to the age and sex specific incidence of tuberculosis in table II for calculating productivity losses.

The NCAER in their Report on Rural Household Survey (1962) Appendix I and another on urban household Survey (1962) have indicated the age-wise earnings of the chief earner in the household, the chief earner being male, earnings of female and child workers have not been given in it. But these are required for calculating their economic values. The National Sample Survey Report (No. 152) for rural areas, the average daily wage of a casual adult male, female and child worker engaged in agricultural occupation has been given as follows :—

<i>Rural</i>	
Male	96 paise
Female	59 paise
Child	53 paise

The age-wise average annual earnings of female and child worker have been estimated bearing the same ratio as the daily wages of the male to that of the female and child worker. And their average annual incomes have been computed, and are shown in Table III.

TABLE III

Age group	Average annual income	
	Male	Female
0-14	305	305
15-34	559	339
35-55	689	413
56 and above	722	443

At the above rates of income, the total income loss of the rural workers due to tuberculosis is given in Table IV.

The total morbidity loss among rural workers is estimated at Rs. 174.11 crores.

It is estimated that 6,41,024 urban workers suffer from the disease of which about 5,65,640 are male and about 75,384 are female, Table I. The annual average income of an urban worker for the various age groups is given in table V and the production loss for one year due to the disease is given at Table VI.

The total annual loss due to tuberculosis of the workers in urban India has been estimated at Rs. 114.47 crores.

There is a large section of the population who, though they may not have a definite earned income, are contributing to the total economy of the country by their labour in the form of household duties. If the housewife is not able to do these duties, the same work would be done by some other person such as a

TABLE IV
Annual loss due to Tuberculosis among rural workers

Age group	Male	Total loss	Female	Total loss
0-14	75,395	2,29,95,475	47,813	1,45,82,965
15-34	7,04,845	38,97,79,285	3,14,458	10,66,01,262
35-59	11,11,084	76,55,36,876	3,35,113	11,36,03,307
60 and above	4,13,558	29,85,88,876	86,961	2,94,79,780
Total	23,04,882	1,47,69,00,532	7,84,345	26,42,67,314

TABLE V

Age group	Average annual income	
	Male	Female
0-14	853	853
15-34	1,546	928
35-55	2,063	1,238
56 and above	2,030	1,218

domestic servant who would be paid for his labour. It would thus appear that household work has an economic value. But it is difficult to measure this value, since they occur outside the market mechanism. From practical stand point it may be easier to compute it on the basis of average earnings of a domestic worker. This imputed value is clearly on the low side, for it makes no allowance for the housewife's longer hours of work and takes no account of the size of the household cared for.

The Census Report (1961) has indicated the number of non-workers engaged in household work and on the basis of the prevalence rate of the disease the number of domestic workers suffering from the disease has been estimated and shown in Table VII.

Since there is no adequate data on the wage of domestic workers the monetary loss for them has not been estimated.

Quantification of losses from premature mortality

To measure the mortality effect of the disease is to determine the present value of the production which the deceased would have contributed, for this, mortality data at various age groups, sex and residence is necessary. Though certain mortality data are available for the different parts of the country, they lack in age-wise distribution and information on the relation between mortality and morbidity. Even isolated surveys conducted in small areas do not give adequate information on these headings. A review of these insufficient data has been made and a procedure has been

TABLE VI
Annual loss due to Tuberculosis among urban workers

Age group	Male cases	Annual loss	Female cases	Annual loss
0-14	5,164	48,31,392	2,536	21,64,208
15-34	1,95,806	30,27,16,076	30,449	2,82,44,492
35-59	3,03,745	62,66,25,935	36,764	4,55,06,479
60 and above	62,425	12,67,22,750	6,635	80,81,430
Total		1,06,08,96,153		8,39,96,609

TABLE VII

Age group	Rural		Urban	
	Male	Female	Male	Female
0—14	1,513	51,321	227	9,187
15-34	1,028	2,81,353	393	1,38,643
35-59	1,181	2,71,922	495	1,10,252
60 and above	1,475	1,12,057	424	24,566

adopted to estimate production loss due to premature mortality.

Data on the number of cases of Tuberculosis therefrom among all Railway Employees in India, annual reports of the Railway Board, the years 1962-63 and 1963-64 are presented below :—

Year	Attack	Death
1962-63	13,754	348
1963-64	13,956	402

For these deaths the case fatality rate works out to about 2.5 in each of these years. This would be an underestimation for application as an average for the urban areas of the country, for Railway employees are a category of employees who are in receipt of special medical care.

In the "Vital Statistics 1962", medically certified cases of death for Bombay, Poona, Rajasthan and Nagpur has been given. Only the data for Bombay and Poona are claimed to cover the entire population of these areas. The average rate of death for Bombay per lakh of population from all forms of Tuberculosis in 1962 was reported at 82 for males and 72 for females. This is the only available source of complete data of Tuberculosis deaths covering a sizeable urban population. Since the pattern of incidence and the prevalence rates for most of the urban areas do not vary significantly, the mortality rates for Bombay has been assumed to be representative of the urban areas of the entire country. A survey in an area in Punjab has reported a mortality rate of 90 referred to by Bordia. After making necessary adjustments age and sex-wise, tuberculosis death rate per lakh of population, of Bombay State, has been applied to the urban population Census Report (1961).

TABLE VIII Estimated number of tuberculosis deaths in urban India

Age-group	Males		Females	
	Death rate per lakh population	No. of tuberculosis deaths	Death rate per lakh population	No. per tuberculosis deaths
0-41	110	6051	114	6054
15—14	15	1566	23	2184
15—24	27	2199	44	2951
25—34	60	4366	72	4170
35-44	93	4881	98	3659
45-49	209	3717	121	1543
50—54	261	4238	134	1679

All India mortality data for rural areas is also inadequate. Frimodt-Moller (1950 to 1956), conducted an extensive morbidity and mortality study covering about 300 villages around Madanapalle in South India and estimated the death rate from tuberculosis at 200 per lakh population at the commencement of intensive anti-tuberculosis work. The rate however was found to have been reduced at the terminal period of this Survey which cannot be applied to all the areas in the country. The other possible data available for rural area is in the Report from Health Training Centre (1961) of Ram Nagram, Mysore State and Health Unit Bavla, Ahmedabad, the number of cases and deaths occurring there in 1951 is given below:—

Centre	No. of tuberculosis	No. of deaths
Ramanagaram	45	12
Bavla	89	48

The case fatality rate in these centres work out to 27 and 54 respectively which seem to be fairly high. It is considered that the reporting of cases of death is likely to be more specific in an area where field study is being conducted, than the reporting of sickness due to Tuberculosis.

The lack of adequate mortality data for rural areas pose a problem for estimating the age-wise deaths. The mortality rates at the Ramanagram and Bavla Centres according to the case fatality rates mentioned above is estimated at more than 400 per lakh population. Benjamin and associates (1939) reported a mortality rate of 462 per lakh population in a suburb of Madras. Both these estimates are considered high in the present context. Frimodt-Moller estimated the rate at 200 per lakh at the commencement of his study in Madanapalle. This works out an average case fatality rate of 13.5%.

In this connection the morbidity, mortality and case fatality rates of some other countries have been examined. It is seen that the age-wise 1954 pattern of morbidity in U.S.A. when reduced to comparable age-group broadly falls into the same pattern of morbidity as obtaining in India (Appendix II). Taking into consideration the morbidity pattern as reported by the National Sample Survey (1955-58) conducted by the Indian Council of Medical Research, the case fatality rate mentioned above, the age-wise tuberculosis death rate and number of deaths in rural areas for 1961 Census population has been estimated as given below :—

TABLE IX

Estimated tuberculosis death rate and number of deaths age-wise and sex-wise in rural India

Age group	Male deaths		Female deaths	
	Rate per 100,000	Number	Rate per 100,000	Number
0-4	81	22599	194	53508
5-14	19	9532	47	21530
15-24	20	5754	81	23969
25-34	118	32401	184	49977
35-44	201	41075	285	53854
45-49	764	61062	374	26476
50-54	1001	75462	430	29019
55-59	1238	54311	485	18703
60-69	1593	109630	567	37960
Total	230	411826	182	314996

Thus the total number of deaths from Tuberculosis per year comes to 7.26 lakhs in the rural area and 0.59 lakhs in urban area making a total of 7.85 lakhs in the country.

For the purpose of working out the expected working life of the mortality cases data of their probability of survival and of gainful employment at each age and sex is necessary. The Indian life table (1951-61) represents the age-wise and sex-wise chances of survival or death. This probability pattern of survival would also be applicable to these cases of premature deaths due to tuberculosis. It has also been assumed, the present pattern of proportions of gainfully employed persons to the total population at each age, to represent the probability, that any of the deaths from tuberculosis prevented would, have been gainfully employed. Super-imposing the second pattern on the first, an age-wise chance, a person would have for being gainfully employed if premature death had not taken place has been estimated. On the basis of this pattern the expected number of years of gainful employment during the entire span of working life has been calculated. The estimate of proportion of working population in rural and urban areas to the total population, made by National Sample Surveys of Urban and Rural Labour Force (1963) have been adopted to build up the 'Working Life Table', taking into consideration the variations, in numbers of the males to the female workers and the proportions at each of the age groups. These variations have been worked out by means of simple interpolation between successive age group

proportions. Applying these proportions to the Life Table (1951-61), the expectancy of working life at each age has been calculated.

If l_x denotes the hypothetical population in the life table at the beginning of age x , L_x as the number of living between x and $x+1$ and W_x as the proportion of population working between ages x and $x+1$ then the expectancy of working life at the the beginning of any age is given by:

$$\frac{L_x W_x}{l_x}$$

The expectancy of working life at each age has been calculated (Table X).

The expected number of remaining years of working life in respect of the number of cases of mortality in each age group is estimated by multiplying the number of cases by the expectancy of working life at the midpoint of the age-interval. The expected number of man-years thus worked out is then rearranged by each successive future years which are then discounted and aggregated to give the present value of the total number of man years of working life of the cases of mortality from tuberculosis.

The simple aggregate of the expected number of man-years over all age-intervals gives an estimate of the expected remaining man-years of working life of all the victims of Tuberculosis. However, this simple aggrega-

TABLE X

Expectancy of working life in number of years selected ages

Age	Rural		Urban	
	Male	Female	Male	Female
0	25.97	11.67	24.96	6.41
5	33.46	15.04	32.17	8.27
10	34.35	15.49	33.16	8.56
20	30.48	13.48	31.83	7.92
30	23.04	10.34	25.02	6.49
40	15.98	7.12	17.86	5.04
50	9.66	3.77	11.60	3.44
60	3.50	0.97	6.22	1.85

tion assumes that the number of man-years worked in different future periods are worth the same. This, however, is not a correct assumption since the future consumption is always valued less vis-a-vis present consumption whether from individual or social point of view. There are a variety of considerations in choosing an appropriate rate of discount for evaluation of public investment projects including programmes for health such as, social vs individual time preference, the social concern for future generations, relationship with planned rate of growth etc. At one extreme is the market rate of interest which has a strong relationship with productivity of private capital investment, which may reflect only private but not social (i.e. collective) time preferences. The total effect of these considerations will be to choose social rates considerably below the private rates. In this study

two alternative rates; one high (10%) and one low (4%) have been adopted; the former i.e. 10% would roughly correspond to the market rates of interest. The lower figure of 4% discount rate has been assumed as a plausible social rate taking into consideration the planned rate of growth of course, qualified by the actual rate achieved so far. The total number of discounted man-years worked out according to the two rates of discount are shown in the table XI.

On the basis of the methods and assumption indicated above the estimates of monetary loss to society from premature mortality due to Tuberculosis are summarised at Table XII. The increase in population since 1961 has also been taken into account and pro-rata adjustments have been made in the calculation of monetary loss.

TABLE XI

Expected working list (in years) of the victims of tuberculosis

	Rural		Urban	
	Male	Female	Male	Female
Total expected no. of man years (Undiscounted)	4270641	2573135	632838	151200
Total discounted number of man years (4%)	3124482	2117442	422984	135145
Total discounted number of man-years (10%)	2247196	1664762	276609	116566

TABLE XII

	Working life years 1961	Average earnings	Monetary loss in crores	% rise of 1966 in population over	Monetary loss in 1966
<i>Monetary loss taking 4% discount</i>					
Rural : Male	31,24,482	636	198.72	12.83	224.22
Female	21,17,442	375	79.40	12.54	89.36
Urban : Male	4,22,984	1879	79.48	12.83	89.68
Female	1,35,145	1128	15.24	12.54	17.15
					420.41
<i>Monetary loss taking 10% discount</i>					
Rural : Male	22,47,196	636	142.92	12.83	161.26
Female	16,64,762	375	62.43	12.54	70.26
Urban : Male	2,76,609	1879	51.97	12.83	58.64
Female	1,16,566	1128	13.15	12.54	14.80
					304.96

The present value of the total annual loss due to preventable mortality for the year 1966 is estimated at Rs. 420.41 crores at—4% time rate of discount, and Rs. 304.96 crores at 10% discount rates.

Discussion

Direct cost of tuberculosis has been estimated at Rs. 29.69 crores the items comprising it and their percentage to the total direct cost are given below :—

Direct cost of tuberculosis

Item	Amount (in lakhs)	Proportion %
Hospitals	1452.50	49.2
Clinics	387.55	13.0
Drugs	912.00	30.7
Private medical practice	75.00	2.5
Research	16.09	0.5
Training	47.60	1.5
B.C.G. vaccination	77.70	2.6
	2968.44	100.00

It has been variously estimated that there are about 6 million active and probably active tuberculosis cases in the country of which about 1.5 million are bacillary positive. These patients may require to be isolated for treatment and if all of them are treated in hospitals and sanatoria, there would be one bed for forty patients. These patients and the acutely ill ones would require special medical care, facilities for which are available in hospitals only, where the bulk of the cost, 49% of the total direct cost is incurred. On the other hand, the annual cost for 502 tuberculosis clinics is only 13% and in view of the varied nature for their functions these clinics cater to a larger number of patients than the hospitals. The number of patients treated at these clinics, hospitals and by private medical practitioners are not readily available, an estimate of their number has however been made from the amount of INH consumed in the country.

In 1966, 82.98 tonnes of Isoniazid, representing the total production of the country and the quantity supplied by the International agencies (UNICEF), was consumed. A

patient requires about 300 milligram of the drug per day for a period of one year for a full course of treatment. Accordingly, it is estimated approximately 8,29,300 patients could have been treated with this quantity of Isoniazid in one year. In order to arrive at a probable number, it is assumed that all the patients may not have been treated with other anti-tuberculosis drugs. Allowing these probabilities, it is likely that about 10 lakh patients are receiving treatment annually by anti-tuberculosis drugs. It appears the quantity of the drugs available is not sufficient even for the treatment of all the bacillary positive cases. These patients and the active cases have probably been receiving insufficient or symptomatic treatment. These under and inadequately treated patients constitute a danger to the society.

The 5% of the total sputum positive cases in the rural areas who sought treatment from private practitioners is very much an underestimate. As data in this respect are not available, it has not been possible to estimate accurately the cost of this item which, it is estimated, would be very much higher, for a large number of active and probably active cases must also have been treated by private medical practitioners and may not have attended the TB clinics or the hospitals.

In computing the cost for hospitals and clinics their average construction cost has been taken into account. The cost of those institutions constructed prior to 1963 was lower than the ones built later when the cost has increased, to offset the variation, an average rate as estimated for the year 1963 has been taken for calculating this expenditure. It may be mentioned that if these buildings were valued at their depreciation value on the existing stock of capital valued at historical cost would be of lower value. It is considered that if depreciated value of the buildings is taken for estimating their present value, the depreciated value of the hospital equipment instruments and appliances should also have to be taken into account. But there is not only a lack of information on the depreciated value of these articles in hospitals and sanatoria but there is no information to the extent to which depreciation expenses are reported in the annual expenditures of these institutions.

The total annual production loss due to tuberculosis morbidity among the workers has been estimated at Rs. 288.87 crores, of which 114 crores is for urban and 210 crores for rural workers.

The active working age of labour force of urban India is between the ages of 15-54 years and that of the rural workers is between the ages of 14-56 years and above. The incidence of the disease among both the urban and rural workers is lowest in the lower age groups i.e. between 5-14 and it increases at higher age groups reaching the peak in the age group of 55 and above. It will be seen from Table I that the prevalence rate is slightly higher among the males of the rural and urban areas than the female workers.

The average income of a rural worker is highest in the age group of 56 and above, whereas among the urban workers it is in the age group of 35 to 55. For these workers the income decreases after 55 years. Production loss due to morbidity of tuberculosis will therefore be highest in the higher age group and thus would adversely affect the production.

The extent of production loss will also depend on the incidence of disease among the various income groups. Since no data of the tuberculosis incidence among different income groups is available, uniform distribution of the disease has been assumed for estimating the income loss.

The number of workers engaged in production and which has been quantified, has been enumerated in the Census Report, 1961. In this Report and in the various surveys, referred to earlier, any person who is directly or indirectly employed in any type of work or with a job in an establishment for at least one day during the reference week has been treated as working. And it is assumed that all these workers are gainfully employed. Recent work on increased productivity and expanded labour force in agrarian society has estimated that disguised unemployment probably does not exceed 5% of labour force. What is more, recent comprehensive surveys of Indian agriculture, show no labour surplus.

Production loss due to morbidity of tuberculosis in respect of the workers as defined above and who are gainfully employed has been estimated and the workers who do not come within the purview of this definition and may be unemployed have been regarded as not contributing to the economy. Besides, tuberculosis does not follow a seasonal pattern like malaria, influenza or small-pox which may produce large scale shortage of labour affecting the productivity. Morbidity due to tuberculosis extends over longer period than the epidemic diseases and substitute is generally employed for a worker affected by the disease.

There may, therefore, not be an apparent loss of production. But the person who is suffering from the disease is not able to make any contribution to the economy as his labour cannot be utilised towards production, while his consumption will continue. As such, he is a loss to the economy of the society. In a developing economy, there is an increase in employment opportunities and employment can be found for the worker when he is cured of the disease.

Premature deaths due to tuberculosis at various age groups for urban and rural workers has been given in Table IX. It has been assumed that had these deaths been prevented, the survivors would have had the same chances of employment as those who are now employed and would have contributed to the economy of the country. The economic benefit of prevention of premature deaths depends on whether a survivor is in fact offered productive work and the benefit can be estimated at the present value of their future earnings, i.e., the income they would have earned. To determine this income some economists calculate it according to the gross income whereas other deduct consumption from the income as a matter of course, in their work, the calculation benefit can result in negative figures which may be subjected to erroneous interpretations. In this paper consumption has not been deducted from the gross earnings.

The total losses from mortality/morbidity and the direct cost of the disease is summarised below :—

<i>Form of Loss</i>	<i>Amount of loss (in crores)</i>
	420.41® 304.96*
Mortality	288.58
Morbidity	29.68
Direct cost	© at 4% discount * at 10% discount

The value of the production loss due to mortality and morbidity from tuberculosis represents a very large amount of economic loss. Against this, the amount of direct expenditure of Rs. 29.68 crores which is being made for the control programme is very small. This annual direct cost for a tuberculosis population of about 6 million works out to about Rs. 49 per person per annum. And the services provided within this amount range from institutional care, case findings, cost of

drugs, etc. This cost falls far short of the estimated cost of Rs. 87 to 100 for drugs alone for treating a case. The 502 tuberculosis clinics set up under the National Tuberculosis Control Programme, of which only 155 are upgraded for diagnostic services, running of district anti-tuberculosis programmes, etc., cannot provide sufficient facilities for a countrywide control programme. The annual expenditure incurred for these clinics is equivalent to spending Rs. 6 annually for an active and probable active case. Another item of expenditure in the direct cost, namely, the B.C.G. vaccination scheme may be referred to. This scheme was one of the earliest measures introduced in the control programme and its present cost represents 2.6% of the total direct cost. Though this may appear to be small, yet in view of the results obtained from researches on newer methods of approach to the problem of control of the disease and discovery of potent anti-tuberculosis drugs, an economic evaluation of the programme vis-à-vis domiciliary treatment may be worthwhile. The armamenture for the control of the disease are not unknown and their application can reduce the morbidity and mortality as has been amply borne out in the community-wide tuberculosis study by Frimodt-Moller. By systematic case-finding and treatment and hospitalisation of infectious cases a reduction of mortality in the community from 200 to 21 per 100,000 in less than 4 years was obtained.

The effectiveness of domiciliary treatment, services in the control of the disease has opened up new vistas and one may reasonably expect the possibility of reducing the large economic losses due to the morbidity and mortality of this disease, if adequate treatment and other facilities are made available.

Summary

In a study of the cost of tuberculosis in India, a direct cost of Rs. 29.68 crores annually has been estimated. The morbidity and mortality losses have been quantified taking into account the urban and rural population separately. The data on mortality in rural areas is very meagre and is not available according to age and sex. This and the expected working life for premature mortality have been calculated by the application of statistical methods. The morbidity loss has been estimated at Rs. 288.4 crores and the mortality losses at Rs. 420.41 crores at 4% deduction and Rs. 304.96 crores at 10% deduction.

ACKNOWLEDGEMENT

We thank Dr. B.D. Nag Choudhuri, Member, Planning Commission, for his interest in the subject of Health Economics and encouragement, and Dr. Hugh R. Leavell, M.D., Adviser to the National Institute of Health Administration and Education, for his keen interest and valuable suggestions, in writing this paper.

Grateful acknowledgements are made to Dr. M.K. Ganguli, Joint Director, Central Statistical Organisation, and Dr. V. Vikraman, Deputy Director, Central Statistical Organisation, who have helped, in the compilation of conceptual value of mortality loss, to Col. B.L. Taneja, Director General, Indian Council of Medical Research, and the officers of the National Tuberculosis Control Programme in the Director-General of Health Services, for making available the data utilised in this paper.

Appendix I

Average income per earner

Age group of chief earner	No. of household	Average No. of earners per household	Total No. of earners col. 2 and col. (3)	Total income (in Rs.) and col. (4)	Average income per earner col. (3)
Below 21 years	1,688,000	1.9	3,207,200	167,21,00,000	521
22—25 years	5,032,000	1.9	9,560,800	555,57,00,000	581
26—30 years	9,179,000	1.8	16,522,200	1085,79,00,000	657
31—35 years	9,446,000	2.6	24,559,600	1171,74,00,000	477
36—40 years	10,822,000	1.8	19,479,600	1362,36,00,000	699
41—45 years	7,944,000	2.0	15,888,000	1075,06,09,000	677
46—50 years	9,058,000	2.2	19,927,600	1348,96,00,000	677
51—55 years	4,470,000	2.3	10,281,000	732,94,00,000	713
56 years and above	8,094,000	2.1	16,997,400	1226,84,00,000	722

Appendix II

Rate of morbidity caused by TB per 1000 population and number of cases of TB

Age group	Rural Males		Rural Females		Urban Males		Urban Females	
	Morbidity per 1000	No. of cases of TB	Morbidity rate per 1000	No. of cases of TB	Morbidity per 1000	No. of cases of TB	Morbidity per 1000	No. of cases of TB
0 - 4	10.2	282009	10.1	278417	10.0	55010	10.9	57890
5—14	10.2	498097	10.1	455035	10.0	104410	10.9	103528
15-24	10.6	303043	9.2	272826	12.7	103454	16.8	112711
25-44	18.3	871885	15.2	698014	23.0	286971	18.4	175278
45—49	40.4	1082437	24.5	597310	48.0	267408	26.8	118108
Total	16.9	3037471	18.3	2301602	19.4	817253	16.0	567515

REFERENCES

1. Klarman Hebert E.; The Economics of Health; Columbia University Press, New York. 1965.
2. Dublin L.I., Lotka A.S. and Spiegelman M. (1957); The Money Value of Man, New York.
3. Sinton : J.A.; What Malaria costs India, Malaria Bureau No. 13.; Malaria Institute of India, Delhi 1956.
4. Chatterjee N.N., Report on Employment Position in Plantation, Ministry of Labour & Employment, Government of India. 1965.
5. Bhombore S.R. Worth Brooke C. and Nanjundiah K.S., A Survey of the Economic Status of Villages in a Malarious Irrigated Tract in Mysore State; Indian Journal of Malariology, 6, 4 December 1952, page 355.
6. Narahari Rao C.S. and Bombore S.R. A Survey of the Economic Status of villages in a Malarious Tract in Mysore State after Residual Insecticidal Spraying, Bulletin of the National Society of India for Malaria and other Mosquito Borne Diseases, Vol. IV., No. 3, page 71. 1956.
7. Anderson Stig., Some Aspects of the Economic of Tuberculosis in India, Proceedings of Eighteenth Tuberculosis and Chest Disease Workers' Conference held in Bangalore, January 1962.
8. Weisbrod Burton A.; Economics of Public Health; University of Pennsylvania Press, Philadelphia.
9. Swasthya Samachar, Special Issue, Central Bureau of Health Intelligence, Government of India, New Delhi.
10. Binerjee, D. More Recent findings on Awareness of Symptoms of Tuberculosis in a Rural Population, Personnel Communications, Miniographed, 1964.
11. Tuberculosis in India—A sample Survey (1955-58). Indian Council of Medical Research, New Delhi.
12. Mitra A., Census of India. 1961, Volume I Part II-B (i) General Economic Tables.
13. National Council of Applied Economic Research, All India Rural Household Survey (1962).
14. National Council of Applied Economic Research, Urban Income and Saving (1962).
15. The National Sample Survey No. 152, Income of Rural Labour Households : Indian Statistical Institute, Calcutta.
16. Report by the Railway Board for 1961-62 and 1963-64, Statemnt 40-vi- Government Railway Statistics of Disease of Staff.
17. Registrar General of India; Vital Statistics of India for 1962.
18. Frimodt Moller : A Community Wide Tuberculosis Study in South Indian Rural Population, 1954-1955. Bulletin of World Health Organisation 1960. 22, 60-170.
19. Annual Report of Director General of Health Services, 1961.

20. Vital Statistics of the United States, 1954 V. 2, US Department of Health Education and Welfare, Public Health Service, National Office of Vital Statistics, US, Washington.
- National Sample Survey : Rural Labour Force, Tables with notes : Cabinet Secretariat, Government of India (February 1963 January 1964).
- National Sample Survey, Eighteenth Round
Cabinet Secretariat, Government of India.
23. Paglin, M.; American Economic Review 1965, Vol. 55, page 815.
24. Bordia N.L., Economic Aspect of Tuberculosis Control; Unpublished.
25. Indian Life Table. 1051-61 Registrar General of India.
26. Winslow, C.E.A. The cost of sickness and price of Health, W.H.O. monograph Service 1951.
27. Benjamin PU, Jesudian K.T. Verghese M.C. and Varkey C.E. (1939) *Indian Medical Gaz.* 74. 516.

CASE REPORT

TOXIC EPIDERMAL NECROLYSIS (LYELL'S SYNDROME) DUE TO P.A.S.

M.S. AGNIHOTRI AND S. RASTOGI
(From King George's Medical College, Lucknow)

PAS can cause allergic reactions in skin. Rashes and even Stevens-Johnson syndrome (Snelling et al. 1965) involving skin due to P.A.S. toxicity have been reported in literature.

Lyell's (1956) described toxic epidermal neerolysis having three cardinal features, prodromal toxaemia, epidermal involvement and death of epidermal cells. Lyells (1965) reported toxic epidermal neerolysis due to adverse drug reactions. We are reporting here a case of toxic epidermal neerolysis (T.E.N.) due to PAS.

Case Report

Patient S.W., female aged 20 years, married, was admitted on 30-5-71 in Kasturba TB Clinic, Lucknow as a case of bilateral pulmonary tuberculosis. Total duration of illness was six months. Sputum smear for A.F.B. was positive. On admission, she was kept on streptomycin, INH and PAS in usual doses. Patient showed clinical improvement. But after three weeks of chemotherapy rashes all over the body were observed. Taking them as toxic manifestation, P.A.S. was withdrawn on 22-6-71.

Skin lesions disappeared within two days under cover of antihistaminic drugs. After 7 days PAS was again added to therapeutic regimen. After three days of addition of PAS she developed severe toxaemia with high fever ranging between 104-105°F associated with marked malaise, dysphagia swelling and acute tenderness of affected skin was present. After 3 days, bullous eruptions developed all over the body and were more marked on the extremities. On E.N.T. examination, glottis and larynx, tongue, angle of mouth showed ulcerations. Investigations revealed normochromic general blood picture with normal R.B.C. Reticulocyte count 1%, platelets 1.5 lac/cu.mm, M.C.V. 31 cu/u, M.C.H.-C-97 percent observed E.S.R.-14mm for 1st hour liver function test (L.F.T.) demonstrated negative vandenbergh, serum bilirubin 0.5 mg percent, thymol turbidity 2 units, prothrombin time 15 seconds and prothrombin concentration was 100 percent. Blood urea Was found to be 71 mg percent. At this

stage, all anti-tubercular drugs e.g. streptomycin, INH and PAS were withdrawn and prednisolone 20mg with tetracyclin 1 gm per day orally in divided doses were started. She was also given blood transfusion on 12-7-71. Within two weeks of therapy marked improvement was observed. Bullae over the extremities disappeared leaving a burnt appearance over the effected parts. INH was started on 28-7-71 as no toxicity was observed with 7 days of INH therapy, streptomycin was added on 4-8-71, which patient tolerated well and was discharged on 25-8-71, with an advice to continue streptomycin and INH.

Discussion

One female case of bilateral pulmonary tuberculosis developed toxic epiderma neerolysis due to PAS toxicity. Lyell's reported that toxic epidermal neerolysis occurs predominantly in females. The initial skin rashes observed in our case were due to PAS because the rashes disappeared by temporary withdrawal of PAS from therapeutic regimen. But subsequent addition of PAS in chemotherapy, precipitated marked toxaemia with high fever, malaise, acute tenderness of affected skin and blister formation over extremities. The association of stomatitis and ulceratipn of larynx with epidermal lesion was described by Lyell's in T.E.N. due to adverse drug reaction. In our case dysphagia stomatitis and ulcerations in larynx and glottis were marked and thus provisional diagnosis of Stevens-Johnson syndrome was kept. But within few days, the skin lesion in form of diffuse bullous eruption over the body, confirmed the diagnosis of T.E.N. in our patient. Lyell's describes that drug induce toxic epidermal neerolysis is a clear cut variant of Stevens-Johnson syndrome with predominance of epidermal involvement.

Lyell's (1967) reported that T.E.N. may be associated with marked loss of fluid. Initial high blood urea in our patient may be due to fluid loss during acute phase. The improvement by steroid therapy was associated with healing without scar formation indicating involvement of epidermis only.

Summary

A case of toxic epidermal necrolysis due to PAS toxicity was reported. Patient presented with classical triad of toxic epidermal necrolysis-prodromal toxæmia, epidermal involvement and death of epidermal cells. The initial cutaneous eruption subsided by withdrawal of PAS. Again, addition of PAS resulted in acute skin toxicity and confirmed that the toxic manifestation were due to PAS. Patient tolerated

Streptomycin and INH later on and was discharged, improved.

REFERENCES

1. Lyell, A. (1956) : *Brit. J. Derm.* **68** : 355
2. Lyell, A. (1956) : *Lancet.* **1** : 1155.
3. Lyell, A. (1956) : *Lancet.* **1** : 787.
4. Snelling, M.R.J. and Chooi Mun Kam (1956); *Tubercle Londen* **46** : 284.

NEWS AND NOTES

THE PRESIDENT'S MESSAGE

The 23rd TB Seal Sale Campaign will commence on 2nd October, 1972. The President V.V. Giri in a message on the occasion, said :

“Gandhi Jayanthi, beginning on October 2, is a historic occasion in the life of our nation when we rededicate ourselves to the service of our people. On this day the Tuberculosis Seal Campaign begins. The campaign terminates on another important day—the 26th January which is our Republic Day. The Seal Sale Campaign provides the opportunity to all of us to indentify ourselves with the cause of TB sufferer and help the campaign against this disease.

I wish the Tuberculosis Associations and the Seal Sale Campaign success and commend the Seal Sale Campaign to my countrymen and appeal to them to buy TB Seals in large numbers.”

NATIONAL CONFERENCE

The 27th National Conference on TB & Chest Diseases which was postponed due to National Emergency will be held in Patna from 19th to 22nd November, 1972. Dr. K.N. De of Calcutta is the President of the Conference. The programme includes Scientific Sessions on important subjects relating to tuberculosis control, “Population Dynamics and Tuberculosis”, “Changing trends in the prevalence and incidence”, “Surgery”, “Chemotherapy including management of resistant cases”, “Role of paramedical personnel in community programme”, “Sensitivity Testing”, “Non pulmonary tuberculosis” and “Non tuberculosis chest conditions”.

Those who have not yet registered themselves as delegates may kindly do so with the Joint Secretary, 27th National Conference on TB & Chest Diseases, TB Demonstration Centre, Bankipur, Patna-4, Bihar.

TEXT BOOK ON TUBERCULOSIS

The Tuberculosis Association of India is happy to announce that the Text-Book on Tuberculosis has been published. The cost of this book is Rs. 60/- per copy (£5.00 and \$12.50 for overseas). Copies can be had from Messrs Kothari Book Depot, Acharya Dhonde Marg, Parel, Bombay-12.,

SHIBIRS- MAHARASHTYRA

37th Anti-Tuberculosis Shibir of the Maharashtra State Anti-Tuberculosis Association was held in Ranjangaon, Ganapati, Taluka Sirur, Dist. Poona on Monday the 28th August, 1972. 20 Medical Internees from the neighbouring rural Medical Centre working for ½ weeks had carried out a thorough house to house survey before the camp. The attendance of noted symptomatics and children for BCG was almost 100%. This shibir has given us the correct methodology of preparation.

The total work carried out was as follows: Medical Examination—Male 18, Female 9, Children 5,—Total Screening 30, No. of X-Ray cases 19 (two with healed disease) and BCG Vaccination 1130.

The 38th Shibir conducted by Maharashtra State Anti-TB Association was held at Nagothana, Taluka Roha, Dist. Colaba on 9th September, 1972. The local Gam Panchayat, Block Development Officer, Medical Officer-in-charge of Primary Health Centre and local doctors actively cooperated with the organisers. Of the 462 persons examined 102 were screened and 27 cases of TB were found. BCG was given to 2100 children and triple vaccine to 87 babies. Besides, mothers of malnourished children were given food demonstration and nutritional advise. Dr. M.D. Deshmukh and Dr. H.S. Gupta and Dr. (Mrs) Borwankar (of the Indian Medical Association, Bombay) formed the team.

HYDERABAD CONFERENCE

The Tuberculosis Association of Andhra Pradesh will be organising the Vth Andhra Pradesh TB and Chest Diseases' Workers' Conference in Hyderabad on 2nd and 3rd October, 1972. The Conference will be held at Niloufer Hospital, Hyderabad and the Scientific Sessions will be inaugurated by Dr. J.B. Shrivastav, Director General of Health Services, Government of India and Chairman, T.A.I., New Delhi. There will be Panel Discussions on “National TB Control Programme”, “Integration of TB with General Health Services” and “Problem of Drug resistance cases and their management”.

CASH AWARD FOR PAPER ON “RECOVERY OF DEFAULTERS”

The Bharatiya Arogya Nidhi will award two prizes of Rs. 50C/- and Rs. 300/- for the first

two outstanding papers on "RECOVERY OF DEFAULTERS DURING DOMICILIARY TREATMENT IN TUBERCULOSIS". This competition is open to Medical and Para-Medical personnel working in the field of tuberculosis. The paper should be typewritten in English (5 copies) and should not be more than 3000 words.

The paper should be submitted to the Honorary Secretary, Maharashtra State Anti-Tuberculosis Association, Organised Home Treatment Clinic, Jerbai Wadia Road, Sewree, Bombay-15 on or before 15th January, 1972.

INDIAN ACADEMY OF MEDICAL SCIENCES

The Indian Academy of Medical Sciences conducts post-graduate examination in different disciplines of Medical sciences on an all India basis with a view to admit candidates to the *Membership of the Academy*. A registered medical graduate of an Indian University, or equivalent qualification included in the First Schedule of the Indian Medical Council Act, is eligible. He/she must have undergone a recognised course of training for not less than two years for Part I and four years for Part II (including one year's housemanship or its equivalent).

Full particulars about the examinations and application forms can be obtained from the Executive Director, Indian Academy of Medical Sciences, C-II/16, Medical Institute Campus, Ansari Nagar, New Delhi-16 on payment of Rs. 3/-.

XXIIND INTERNATIONAL TB CONFERENCE

The XXIIInd International Tuberculosis Conference under the joint auspices of the International Union Against Tuberculosis, Paris and the Japan Anti-Tuberculosis Association will be held in Tokyo from the 24th to 28th September, 1973. Mr. Tadatsugu Shimazu is the President of this Conference. The programme covers scientific and social aspects of tuberculosis control programmes both in high and low prevalence countries, as well as some scientific topics such as patho-genesis and immunity in tuberculosis. Persons who wish to submit a free communication are requested to send an abstract of the same, in triplicate (300 words in English) together with a three line summary, also in triplicate, to the Secretariat of the International Union Against Tuberculosis, 20 rue Greuze, 75 Paris (16e) (France).

The Indian Journal of Tuberculosis

ABSTRACTS

Vol. XIX

October 1972

Abst. No. 4

A co-operative trial on the toxicity and efficacy of thiacetazone

S.P. Parma. Int. J. Med. Res. : 1971, 683

In view of conflicting reports about the toxic reactions following thiacetazone administration, the Indian Council of Medical Research organized a co-operative study with a common protocol from 13 Tuberculosis centres in different parts of the country. Nine of the centres included domiciliary patients, 106 hospital patients and the remaining two both domiciliary and hospital patients. Treatment regimen consisted of 300 mg of INH and 150 mg of thiacetazone daily in two divided doses. The duration of treatment was 26 weeks. Of 652 patients included in the trial, 476 were domiciliary patients, 106 hospital patients; 410 completed the treatment and 242 dropped out at various stages. One hundred and sixty-one patients complained of some toxic reaction or other. The reaction was minor in 109 requiring no interruption of treatment and in 25, the reactions disappeared following a temporary interruption in treatment. Major toxic reactions requiring from the study occurred in 27 or 4-1% patients. Amongst these 27, there were 6 cases of exfoliative dermatitis and 4 cases of jaundice. The study failed to reveal any geographical variation in the incidence of severe toxicity, though marked variation in the incidence of minor reactions were noticed in different centres. These differences were more marked in the case of subjective reactions such as gastro-intestinal disturbances, giddiness, etc. than in objective reactions like skin rash, etc.

S.P.P.

Intermittent Therapy with Rifampicin. Experimental Basis

L. Verbist. Trans. 30th VA-Armed Forces Pulmonary Diseases Research Conference USA; 1971, 55.

Experimental studies on treatment of mice with established tuberculosis, using Rifampicin

are reported. The treatment was started 8 to 11 days after infection. Evaluation was based on comparison of the mean survival time or comparison of the mean counts of viable bacilli in the lungs and spleen of mice killed at intervals in the course of a long term therapy. The experiments show that Rifampicin either alone or combined with INH is more effective in mice when administered intermittently rather in a daily equivalent dose. The experimental results have been corroborated in a few human patients treated with Rifampicin, INH and Ethambutol intermittently and daily.

S.P.P

Early and late results of initial treatment with Rifampicin in advanced pulmonary tuberculosis

A. Gyselen, J. Prignot, R. De Brabandere, L. Veribist, P. Simon-Pouthier, J. Cosemans, L.M. Lacquet. Trans. 30th VA-Armed Forces Pulmonary Disease Research Conference USA; 1971, 54.

Nineteen adult, previously untreated, sputum positive patients of pulmonary tuberculosis were randomly allocated to the following four chemotherapy regimens : group 1 : INH -f Rifampicin; group 2 : Rifampicin -f Ethambutol; group 3 : INH r Ethambutol; group 4 : INH+ Streptomycin. The regimens were given for 4 months. Six patients were excluded from the study, 4 because of streptomycin toxicity and 2 because of severe cutaneous hypersensitivity to Ethambutol.

Although 100% sputum conversion was obtained in all the groups, the conversion was quickest in group 1 followed by group 4 and then group 2. Group 3 was found to be the least effective combination. The authors recommend that standard treatment in USA may now be taken as Rifampicin+INH (combined with Ethambutol if 3rd drug is necessary) instead of previous standard treatment of INH and streptomycin with or without PAS,

S.P.P.

Effects of chemoprophylaxis on minimal Pulmonary Tuberculosis lesions of doubtful activity

S.P. Pamra & G.P. Mathur. Bull Wld. Hlth. Org.; 1971,45, 593.

In mass radiographic surveys, minimal pulmonary lesions of tuberculous appearance but doubtful activity are often found in persons without symptoms of tuberculosis. Whether to treat such persons or merely keep them under observation is a problem, as many of them manifest tuberculosis subsequently. The New Delhi Tuberculosis Centre carried out a controlled study from 1958 to 1968 to study this question in the conditions prevailing in India. A randomly selected group of 210 persons with this type of lesion was given isoniazid prophylaxis for 1 year, with the control group of 214 persons receiving placebo during the same period. Both were regularly re-examined, radiologically and bacteriologically, over a period of 6 years, and persons who developed clinical tuberculosis were immediately referred to the appropriate treatment services.

The results show that the treated patients fared much better than those in the control group; fewer of them developed tuberculosis and more of them showed radiological improvement. This superiority was maintained for at least 4 years beyond the treatment year. However, this advantage must be weighed against the comparative inacceptability of treatment by such persons and the consequent high cost of organising the treatment. It is concluded that, except when special circumstances justify it, prophylaxis of this kind cannot be recommended as a routine procedure.

S.P.P.

Primary drug resistance: A continuing study of drug resistance in tuberculosis in a veteran population within the United States September 1969—September 1970

G.L. Hobby, P.M. Johnson, Papirnyk Trans. 30th VA-Armed Forces Pulmonary Disease Research Conference USA.; 1971, 12.

During the 8th year of a continuing study of primary drug resistance in tuberculosis in a Veteran population in USA, 405 strains of mycobacterium tuberculosis isolated from patients in 1969-70 were tested for their resistance to SM, INH, PAS, Ethambutol and Rifampicin. The incidence of total primary Resistance during this year was found to be

2.22% to SM, 3.46% to INH, 1.73% to PAS, 0.99% to Ethambutol and nil to Rifampicin. The incidence of resistance to SM, INH, PAS, Ethambutol alone was 1.48%, 2.47%, 0.99% and 0.49% respectively. Two strains were resistant to SM and INH, 2 to INH and PAS, one to SM and Ethambutol and one to Ethambutol and PAS. These figures do not show any significant increase in primary drug resistance since earlier years.

S.P.P.

Diagnosis and Treatment of 20 tuberculosis patients who entered a community hospital

Sydney Jacoss & Harry B. Greenberg. Amer. Rev. Resp. Dis.; 1972, 105, 528.

The need for a tuberculosis control programme involving physician practicing in a general hospital was illustrated by a study of 20 patients with proved active pulmonary tuberculosis who were admitted in a hospital during 1966-70. Thirteen patients were acutely and 7 were chronically ill. The attending physicians did not consider pulmonary tuberculosis as a plausible diagnosis initially in 19 out of 20 patients. Five were suspected to be cases of bronchogenic carcinoma, 3 of heart failure, 7 of pneumonitis and the remaining of other rare conditions. In 2 cases diagnosis of tuberculosis was made after necropsy and 6 after resection of the lung. In the remaining, sputum was found to be positive for AFB while they were being treated for other conditions.

S.P.P.

Tuberculin anergy in patterns with active tuberculosis

Lee B. Reichman and Jeanne Smith. Trans. 30th VA-Armed Forces Pulmonary Disease Research Conference. USA.; 1971, 48.

Since many proved cases of tuberculosis are some times found to be tuberculin negative, the occurrence of *in vitro* lymphocytes transformation in patients with tuberculosis but negative tuberculin test has been studied.

Tuberculin test and lymphocytes transformation tests were carried out on 51 patients, 33 of whom had clinically active disease. Six healthy volunteers without any evidence of tuberculosis were also included in the study. In 21 of the 33 active cases both tuberculin test and lymphocytes transformation test were positive; 3 had positive skin test but negative lymphocyte transformation test; 2 had negative

skin, test and negative lymphocyte transformation; 7 had negative skin test and positive lymphocyte transformation. All these 7 had extensive disease. The authors conclude that tuberculin anergy due to extensive or terminal disease may be limited to the skin whereas the lymphocytes retain their sensitivity or at least reflect it earlier. The lymphocyte transformation test is recommended as a useful diagnostic procedure when active disease is suspected in a tuberculin negative individual.

S.P.P.

Regional Chronic Bronchitis

Dennis E. Niewoehner, Jerome Kleinerman & James D. Knoke. Amer. Rev. Resp. Dis.; 1972, 105, 586,

A review of approximately 100 cases of chronic bronchitis revealed four patients who had localized or regional bronchial mucous gland enlargement. The percentage of mucous glands at different sites in the bronchial tree of normal lungs and in other patients with chronic bronchitis was also determined and little variability was found. All four lungs with regional glandular enlargement were from elderly men with a long history of cigarette smoking, sputum production, and functional disability. Pulmonary function tests indicated severe obstructive airway disease. Each lung was involved by more than 40% emphysema. The clinical, physiological and pathological similarity of these cases in association with regional bronchial gland enlargement suggests that these findings constitute a distinct entity. The physiological derangements that might relate to such regional chronic bronchitis particularly accentuation of local ventilation-perfusion abnormalities are discussed.

S.P.P.

Pulmonary alterations in systemic lupus

Martin Gross, John R. Esterly & Richard H. Earle. Amer. Rev. Resp. Dis.; 1972, 105, 572.

Interstitial pneumonitis, focal alveolar hemorrhage, broncho-pneumonia, and chronic pleural thickening were found in most histologic specimens from 44 patients with systemic lupus erythematosus. Interstitial thickening was also frequent, but diffuse fibrosis, such as is present in scleroderma, was not seen. An acute vasculitis was present in one fifth of the patients and sclerosis of arteries, in less than one-third. No pathognomonic lesions were demonstrated, and changes were probably com-

plicated by sepsis and uremia. Radiographic findings were not related to the histologic lesions except for the presence of severe pleural disease. Evidence of bronchiolar dilatation loss of alveolar septa, or foci of panacinar emphysema was found in histologic samples from all of the patients. Although the overall distribution and severity of these alterations of peripheral lung structure is unknown, they might contribute to the decreased diffusing capacity of the lung observed in some patients with systemic lupus erythematosus.

S.P.P.

Controlled clinical trial of short-course (6 months) regimens of chemotherapy for treatment of pulmonary tuberculosis.

East African I British Medical Research Council, Lancet, Satu 20 May, 1972.

A comparison between four 6 months daily regimens, all containing streptomycin plus isoniazid and 3 of them a third drug—rifampicin, pyrazinamide, or thioacetazone and a standard 18 months regimen in the treatment of newly diagnosed extensive smear positive pulmonary tuberculosis showed that the bacteriological relapse rates between 6 and 12 months were 18% of 94 patients on the two drug combinations 4% of 99 patients on the rifampicin, 6% of 88 on the pyrazinamide, 21 % of 84 patients on the thioacetazone, and 2% of 83 patients on the standard regimen.

Most of the relapses occurred by 9 months and all these had drug sensitive organisms.

Both the rifampicin and pyrazinamide containing 6 months regimens are highly effective and prospectus of developing effective and practicable short course regimens are excellent.

H.B.D.

The Birmingham tuberculosis drug resistant register 1956-70.

H.E. Thomas. Tub., (1972), 53, 1.

The number of native born patients discovered with initial drug resistance has fallen from 9 to about 5 per year during this period, whereas the number of immigrants patients has risen from 0 to 15 per year.

In the years 1965-67 the incidence of drug resistance in sputum positive patients is assessed at 5.6%, of which the incidence among native born is 3.6% and among the immigrant population 7.9%.

The number of patients with the first diagnosis of acquired drug resistance has fallen from an average of 19.4% per year for the years 1959-1963 to an average of 8.4 per year for the year 1966-70.

In the period under review the known pool of patients with persistent drug resistant cultures has fallen from 69 to 14.

H.B.D.

The concept of classic interstitial pneumonitis—fibrosis (CIP—F) as a clinicopathologic syndrome.

Rich A. Dermee, Edgar G. Harrison and How A. Anderson. Chest Vol. 61, No. 3, March 72.

Eighty one patients with a roentgenographic pattern of diffuse reticulo-nodular pulmonary disease and a pathologic diagnosis of chronic interstitial pneumonitis and fibrosis showed restrictive pattern on pulmonary function testing with impairment of co diffusing capacity.

The common features were dry rales, digital clubbing and evidence of altered immune activity.

The concept of classical interstitial pneumonitis fibrosis (CIP—F) as a clinicopathologic syndrome has been proposed with the following categories :

(1) Definite—complete syndrome with rales, clubbing and evidence of altered immunity activity,

(2) Probable rales, clubbing and evidence of altered immune activity, and (3) possible histopathologic finding with or without evidence of altered immune activity but no rales or clubbing. Some patients progress from possible CIP—F to definite CIP—F; the latter category implies chronicity and commensurately worse prognosis.

H.B.D.