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NEWS & NOTES

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ABSTRACTS

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NATIONAL TUBERCULOSIS INSTITUTE

The inauguration of the National Tuberculosis Institute by the Prime Minister of India on 16th September, 1960 will, we believe, be a landmark in the history of anti-tuberculosis movement in this country, and probably in some other countries also. What was inaugurated then was a new idea, a scheme for the control of tuberculosis on a community basis and for the training of workers for this purpose. Though it is well-known for many years that tuberculosis is a social problem, efforts to control it were mainly directed towards diagnosis and treatment of the disease, and that in hospitals and sanatoria. The Institute attempts a departure from this orthodox procedure. It will involve searching out cases in the community, treating them in their homes and studying the various social aspects connected with the spread and control of the disease. It will also mean education of the patient, his family and the public on these aspects. To this end not only the services of doctors will be mobilised but those of ancillary personnel and others engaged in Community Development programmes also.

The success of this venture will depend upon many factors, of which the most important is the human factor. While clinical work still attracts medical men, it is difficult to get doctors in sufficient numbers for a community programme for tuberculosis in which the non-clinical aspect plays a major part. Workers engaged in such a programme will be expected to work in rural areas also, identifying themselves with the rural population in facing their problems. In spite of difficulties and scepticism in certain quarters, an attempt is made to get a band of tuberculosis workers interested in such a work, who can not only teach the subjects allotted to them, but have the aptitude

and enthusiasm to inspire their associates and trainees to take to a work under difficult and exacting conditions. The Institute has already got a nucleus of such staff both Indian and foreign. All these have _taken to this work in a spirit of adventure and service.

This Institute is a National Institute, meant for tuberculosis workers all over India. It is expected that the States and other authorities will make use of this for training their personnel. While this is so, the object is to develop such a quality of work and training which will make tuberculosis workers in India feel that they miss something if they do not take some training here. Nothing succeeds like success.

This venture is a novel and pioneering one. There are still several hurdles to overcome. It would be appropriate in this connection to remind ourselves of a message given to the nation by Pandit Jawaharlal Nehru many years before Independence. He said: "Success often comes to those who dare and act; it seldom goes to the timid". The establishing of this Institute is a bold step, and we hope to succeed.

P. V. Benjamin

Nutritional Studies on Mycobacterium Tuberculosis—Effect of amino acids on the ‘in vitro’ growth of Mycobacterium tuberculosis

By

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Though tubercle bacilli can grow in a very simple synthetic medium containing salts, inorganic nitrogen and a simple source of carbon, the actual substrates utilized in the tissues of the infected animals are far from clear. The organism is intracellular in the early stages of its growth and depend upon the host cell and probably the surrounding medium—the plasma or the lymph for its nutrition. Protein intake has been recognized as a factor in modifying the course of tuberculosis, though its actual mechanism of action is not well denned (Rich, 1951).

Since the amino acids are the main sources of synthesis of both the tissue cells and the bacteria, the availability of these amino acids would determine the growth and multiplication of the bacteria. It is also known that certain amino acids reduce the virulence of pathogenic bacteria both ‘in vitro’ and ‘in vivo’ (Goodlow *et al.* 1950 ; Page *et al.* 1951) and can function as anti-tubercular agents (Kanazava, 1960).

Considering the important role of amino acids at the cellular level, studies have been undertaken to obtain information on (a) the amino acid utilization of *M. tuberculosis* ‘in vitro’, (b) amino acid changes in the serum of animals during experimental tuberculosis, and (c) the influence of amino acids on the course of the infection.

Earlier studies in this field of amino acid metabolism have yielded confusing and contradictory results as can be seen from the following table :

TABLE I
Effect of amino acids on the growth of *M. tuberculosis*

Utilizable amino acids	Non-utilizable amino acids	Author
Leucine, taurine, asparagine Alanine, alanine with asparagine, glycine		Kuhne (1894) Prosakeur and Beck (1894)
Asparagine, peptone Arginine, glycine, a-alanine, leucine, glutamic acid, aspartic acid (aspartic acid and glycine were the best)	Leucine, tyrosine	Calmette <i>et al.</i> (1909)
Asparagine+glycine, arginine+histidine+glycine, arginine+glycine dl-alanine+-lalanine	Tyrosine, phenylalanine, Histidine	Armand Delille <i>et al.</i> (1913)
dl-alanine+-lalanine, leucine +histidine (slight utilization)		Long (1922)
Glutamic acid+proline		Braun (1935)
Asparagine, tryptophan+threonine+leucins, DL-Phenylalanine, DL-Serine and tryptophan individually in the presence of leucine	Tryptophan, Phenyl-alanine, tyrosine Arginine, Phenylalanine, tyrosine, histidine	Crimm and Martos (1944)

Utilizable amino acids	Non-utilizable amino acids	Author
1-glutamic acid, 1-asparatic acid, histidine, glutamine, dl-asparatic acid None stimulate growth in the presence of asparagine acid and magnesium citrate		Marshak (1951) Youmans and Youmans (1954)
In the absence of asparagine and magnesium citrate		
Asparagine, 1-glutamic acid, dl-asparatic acid, 1-proline, 1-histidine, and dl-alanine (in order of merit)	dl <i>a</i> -amino butyric acid, 1-cystine, all amino acids except asparagine at 1.00%	” ”
In the absence of asparagine only		
None stimulate growth	dl-a-amino butyric acid, 1-cystine and 1-cysteine Hcl.	”

The cause for such varied results seem to lie in the differing compositions of the basal medium, strains of the tubercle bacilli used, the period of incubation and the mode of assessment of growth. Youmans and Youmans (1954) in their investigations have devoted more attention on the stimulating effect of amino acids as gauged by the generation-time rather than the extent of growth over a prolonged period of observation.

Some aspects of our studies on the effects of a wide range of amino acids on the *in vitro* growth of tubercle bacillus are presented in this communication.

MATERIALS AND METHODS

Test organisms: *M. tuberculosis* var *hominis* H₃₇ F_v was obtained from the National Collection of Type Cultures, England. The stock culture was maintained by regular subcultures on Patrick's solid medium (Gradwohl, 1948). For purposes of inoculation, they were transferred to Youmans medium (Youmans and Youmans, 1948) as a surface culture, and repeated subculturing was done on to fresh Youmans tubes. 14-15 days' old cultures were used for the test experiments.

Inoculation : Inoculation was done by floatation method. The inoculum was taken from the smooth spreading surface culture by means of a platinum loop (4mm) and floated on the surface of the test medium aseptically. The tubes were then sealed with paraffin.

Assessment of growth: The visual estimation of the surface culture in Prosakeur and Beck type of medium was preferred to the diffuse growth in Dubos' medium (Dubos, 1949) since the growth in the former both as regards the availability of oxygen and the growth with cord formation were considered to resemble more, the conditions of the natural environment in the tissues.

The tubes after inoculation were incubated at 37°C and the extent of growth recorded weekly over a period of 3 weeks as per notations shown under Table II.

Media : The bisal medium (Medium No. 1) was similar to the one used by Youmans excluding only asparagine. It consisted of:

Potassium dihydrogen phosphate	5.9 g
Potassium sulfate	0.5 g
Magnesium citrate	1.5g
Glycerol	20.0 ml

All the ingredients except magnesium cerate were dissolved in glass distilled water and the pH was adjusted to 7.2 using 40% sodium hydroxide. Magnesium citrate was then added and the total volume was made up to 1 litre.

Medium No. 2 : Youmans medium with asparagine at 5.0 g per litre. Either of the media were distributed into test tubes (6" x 5/8") the volume in each tube being 5.0 ml.

The amino acids were dissolved in either of the media singly and the pH was again adjusted to 7.2. From this serial dilutions were made. The tubes were plugged and autoclaved at 15 lbs. for 20 minutes. Tryptophan when used was dissolved-in either of the media and was passed through a seitz filter, the required volume collected into sterile tub;. Aseptical serial dilutions were made as before. The concentration of amino acids studied were 1/100, 1/1000, 1/10,000.

RESULTS

The results of the effect of amino acids both as single sources of nitrogen and in combination are shown under Tables II and III.

Amino Acids as Single Source of Nitrogen.

End of first week: 1-Aspartic acid supported growth as much as asparagine in all the levels tested. Only 1-lysine Hcl and dl-threonine gave as much growth as asparagine only at a level of 10^{-2} . The other amino acids were either poorly utilized or not utilized at all (Table 2).

End of second week: By this time 1 and dl-alanine besides glutamic and aspartic acids, showed as much growth as asparagine. It was clearly seen that the hetero-cyclic, aromatic and sulphur containing amino acids do not facilitate growth. 1-valine was used only to a small extent. The other amino acids exhibited varying degrees of growth.

End of third week: The trend of the previous week was seen to continue and a general increase in growth was seen. No further utilization of the heterocyclic, aromatic and sulfur amino acids was observed. β -alanine and d-aspartic acid were very slightly utilized. 1-valine was utilized better than dl-valine.

Utilization of Amino Acids in the presence of Asparagine

End of first week: Except for amino acids 1-aspartic acid, histidine, lysine, dl-serine, and taurine, the rest showed some inhibitory effect in all dilutions. Only taurine stimulated growth in this medium.

End of second week: d-Aspartic acid, 1-tryptophan and dl-valine inhibited growth completely at the 10^{-2} level. The rest of the amino acids allowed growth to

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TABLE II

Effect of amino acids, as single source of nitrogen, on the growth of *Af. tuberculosis* H₃₇R_V
'in vitro'

Amino acids	First week			Second week			Third week		
	10 ⁻²	10 ⁻³	10 ⁻⁴	10 ⁻²	10 ⁻³	10 ⁻⁴	10 ⁻²	10 ⁻³	10 ⁻⁴
Acid Group									
l-aspartic acid	2	2	1	3	2	1	3	3	2
d-aspartic acid	S	S	S	S	S	S	S	S	S
l-Glutamic acid	1	1	1	3	2	1	3	2	1
Basic Group									
l-arginine	Nil	S	S	2	2	1	2	2	1
l-asparagine	2	2	2	3	3	3	3	3	3
l-Glutamine	S	S	Nil	1	1	Nil	2	1	S
l-Histidine	1	1	S	1	1	1	2	1	1
l-lysine Hcl	2	1	S	2	1	1	2	1	1
Heterocyclic									
l-hydroxy proline	Nil	Nil	Nil	S	S	Nil	S	S	S
l-Proline	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
l-tryptophan	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Neutral									
l-alanine	1	1	1	3	3	1	3	3	2
dl-alanine	S	1	1	3	3	1	3	3	3
d-alanine	S	S	S	2	2	1	3	3	3
β-alanino	S	S	S	S	S	S	S	S	S
β-amino butyric add									
β-amino butyric acid	1	S	Nil	2	1	Nil	2	1	Nil
glycine	3	S	S	2	2	1	2	2	1
l-leucine	1	1	1	1	1	1	1	1	1
dl-leucine	S	1	1	2	2	Nil	2	1	Nil
dl-isoleucine	S	S	S	2	2	1	2	2	1
dl-serine	1	1	S	2	2	1	2	2	1
dl-threonine	2	1	Nil	2	2	2	2	2	2
l-valine	Nil	Nil	S	S	S	S	2	1	S
dl-valine	S	S	S	1	1	S	1	1	S
Aromatic									
dl-phenylalanine	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
l-tyrosine	In	Nil	Nil	In	Nil	Nil	In	S	Nil
Sulphur									
l-cystine	In	Nil	Nil	In	S	S	In	S	S
l-cysteic acid	S	S	S	S	S	S	S	S	S
dl-methionine	Nil	Nil	Nil	S	S	S	S	S	S
taurine	1	Nil	Nil	1	Nil	Nil	1	Nil	Nil
l-cysteine Hcl	1	Nil	Nil	1	S	Nil	1	S	Nil

Nil=No growth; S=Growth covering less than half the surface; 1 =Growth covering almost the entire surface; 2=Growth covering the entire surface and slightly extending upto the sides; 3=More growth than 2; In = Amino acid insoluble at that concentration.

The cultures were run in triplicates and the results were found to be consistently similar.

TABLE III
Effect of some amino acids (in presence of asparagine) on the growth of *M. tuberculosis*
H₃₇Rv 'in vitro'

Amino acids	First week			Second week			Third week		
	10 ⁻²	10 ⁻³	10 ⁻⁴	10 ⁻²	10 ⁻³	10 ⁻⁴	10 ⁻²	10 ⁻³	10 ⁻⁴
Control (only with asparagine)	2	2	2	3	3	3	3	3	3
Acidic group									
<i>l</i> -aspartic acid	2	2	2	3	3	3	3	3	3
<i>d</i> -aspartic acid	Nil	2	2	Nil	3	3	Nil	3	3
<i>l</i> -glutamic acid	1	1	2	3	3	3	3	3	3
Basic group									
<i>l</i> -arginine	Nil	S	2	2	2	3	3	3	3
<i>l</i> -asparagine	2	2	2	3	3	3	3	3	3
<i>l</i> -glutamine	S	1	2	S	1	3	S	1	3
<i>l</i> -histidine	2	2	2	3	3	3	3	3	3
<i>l</i> -lysine Hcl	2	2	2	3	3	3	3	3	3
Heterocyclic									
<i>l</i> -hydroxy-proline	1	1	2	3	3	3	3	3	3
<i>l</i> -proline	Nil	S	S	2	3	3	3	3	3
<i>l</i> -tryptophan	Nil	Nil	S	Nil	2	2	Nil	3	3
Neutral									
<i>l</i> -alanine	S	S	S	2	2	2	2	2	2
<i>dl</i> -alanine	1	1	1	3	3	3	3	3	3
<i>d</i> -alanine	Nil	S	S	2	2	2	3	3	2
β-alanine	1	2	2	3	3	3	3	3	3
β- amino butyric acid									
β amino butyric acid	1	1	2	2	2	2	3	3	3
clysine	S	1	1	2	3	3	3	3	3
<i>l</i> -leucine	1	2	3	3	3	3	3	3	3
<i>dl</i> -leucine	Nil	1	1	2	3	3	3	3	3
<i>dl</i> -isoleucine	1	1	2	2	3	3	3	3	3
<i>dl</i> -serine	2	2	2	3	3	3	3	3	3
<i>dl</i> -threonine	1	S	S	2	2	2	2	3	3
<i>l</i> -valine	S	S	3	2	3	3	3	3	3
<i>dl</i> -valine	Nil	1	2	Nil	3	3	Nil	3	3
Aromatic									
<i>dl</i> -phenylalanine	Nil	Nil	Nil	Nil	Nil	Nil	S	S	S
<i>l</i> -tyrosine	In	S	2	In	1	3	In	1	3
Sulphur									
<i>l</i> -cystine	In	Nil	3	In	S	2	In	S	3
<i>l</i> -cysteine Hcl	1	1	1	1	1	1	1	1	1
<i>l</i> -cysteic acid	S	S	1	2	3	3	2	3	3
<i>dl</i> -methionine	Nil	1	2	S	2	2	S	2	3
taurine	3	3	3	3	3	3	3	3	3

Explanation: As in Table II.

various decrees in all the concentrations tested, dl-phenyl alanine extended its inhibitory effect up to 10^{-4} level. l-glutamic acid, tyrosine, cystine and cyteine Hcl inhibited growth to a large extent especially in the higher concentrations like 10^{-2} and 10^{-3} .

End of third week: Only d-aspartic acid, l-tryptophan and dl-valine completely inhibited growth at a level of 10^{-2} . Considerable inhibition in growth was seen at 10^{-2} and 10^{-2} with l-cystine and l-cysteine Hcl, the latter amino acid extending its effect upto 10^{-2} also.

DISCUSSION

As sources of nitrogen, taking the extent of growth as criterion the 10^{-2} level was found to be the best for those amino acids which could support growth. Youmans and Youmans (1954) have observed in their generation time studies that this concentration was toxic to the bacilli. A similar discrepancy in the results obtained by having different criteria for growth is evident in the case of l-histidine and proline. These amino acids were shown to have a favourable effect on generation time. But in our studies l-proline did not produce any growth and l-histidine only a moderate amount when judged at the end of three weeks, which concurs with the observations of Armand de-Lille *et al*, (1918). In the present study the basic amino acids were found to be only moderate supporters of growth. On the other hand l-aspartic acid and glutamic acids which were found to have favourable effect on the generation time also favourably affected the growth. Generation time studies concur with the early phase of growth in which the bacilli are placed in an environment slightly different from the former one. The present type of study affords a larger interval of time for the adaptation of the bacilli for the new environment.

A difference in the degree of utilisation of stereoisomers is observed with respect to l and d-aspartic acid and l and dl valine in which both the l forms are utilised better. But no distinction is observed among the leucines and the alanines. Prosakeur and Beck (18) have also observed that l, d and dl-alanines are utilised. It is to be mentioned here that the closely related β -amino butyric acid is more preferred than β -alanine.

Taurine which was found to stimulate growth in presence of asparagine is seen to be only a poor source of nitrogen when used singly.

Dl-serine does not inhibit growth but supports growth moderately. Dubos (1949) in a medium containing Tween 80 and albumin besides mineral salts, glycerol and asparagine found it to be inhibitory to the same strain. But Tween 80 is well known to modify the action of many compounds on the tubercle bacilli (Youmans and Youmans, 1948).

The emphasis in this study is to be placed upon the observation that amino acids seeming to be non-supporters of growth during the first week are gradually utilised by the 2nd and 3rd weeks of observation so well that they could be classified with asparagine as utilisable sources of nitrogen, for example, l-glutamic acid and the alanines. Thus a prolonged observation upto 3 weeks at least seems to be necessary before the effect of amino acids on growth can be definitely gauged.

The order in which the amino acids can be graded according to their capacity to promote growth as observed at the end of 3 weeks is :

- (1) l-asparagine

- (2) l-aspartic acid, l-glutamic acid and the alanines
- (3) l-arginine, glutamine, histidine, lysine Hcl, glycine, l and dl-leucines, dl-isoleucine, dl-serine, dl-threonine and l-valine
- (4) dl-valine, l-cysteine Hcl and taurine
- (5) l-hydroxyproline, proline, tryptophan, dl-phenylalanine l-tyrosine, cystine, cysteic acid, dl-methionine and β -alanine.

In general an inhibition of growth during the first week is produced by a large number of amino acids. l-cystein? Hcl and dl-phenyl alanine are found to be the only two amino acids which exert more or less a completely inhibitory action at all the concentrations tested in the presence of asparagine even at the end of three weeks. Asparagine used in the basal medium at a level of 0.5% is seen to be utilised in the presence of such non-growth promoting amino acids grouped under (5) see above. Youmans and Youmans (1954) have also observed that the presence of asparagine decreased the inhibitory effect of some amino acids. Thus the normal utilisation of asparagine is seen not to be affected except in the presence of the amino acids mentioned already. These amino acids could thus be classified as true antagonists of asparagine. In *Bacillus subtilis* Kanga and Iyer (1959) have also observed the interfering action of some amino acids on the utilisation of asparagine. Among the amino acids studied taurine is the only compound which stimulated growth during the first week in the presence of asparagine.

Since tuberculostatic substances contained in the low molecular fraction of body fluid; may exist as amino acids and such fractions isolated are confirmed to be tuberculostatic 'in vitro' (Oshima *et al*, 1958). It is possible that these substances also have an inhibitory effect 'in vivo' on the multiplication of the tubercle bacilli. A detailed study of the effect of individual amino acids on the growth of tubercle bacilli in tissue cultures may throw light on the nature of the native resistance of the species to tubercle bacilli.

The significance of the role of amino acids not only as promoters or inhibitors of growth but also during therapy becomes more evident by the recent studies, showing that certain amino acids act antagonistically to INH (Pope 1956) when the drug is present is minimum concentration and that there is a definite alteration in the amino acid metabolism of INH susceptible and resistant strains (Willet 1959)

SUMMARY

The effect of amino acids on the 'in vitro' growth of *M. tuberculosis* (H₃₇Rv) in a synthetic medium has been studied. As single sources of nitrogen the l in 100 level of the amino acid was found to be the best for producing maximum growth. The influence of the amino acid in supporting growth could be classified as follows with decreasing order of merit.

- (1) l-asparagine.
- (2) l-aspartic acid, glutamic acid and l, d & dl alanines
- (3) l-arginine, glutamine, histidine, lysineHcl, glycine, the leucines, dl-isoleucine, serine, threonine and l-valine
- (4) dl-valine, l-cysteine Hcl, taurine and β - alanine
- (5) l hydroxyproline, proline, tryptophan, dl-phenylalarine, l-tyrosine, cystine. cysteic acid and dl-methionine.

The influence of these amino acids on the growth promoting action of asparagine was also found to vary. Majority of the amino acids regarded the growth only during the first week. Taurine had a stimulatory effect on the growth during this period. Only l-cysteine Hcl and dl-phenylalanine exerted an inhibitory action during the entire period of three weeks of observation in concentrations as low as 1 in 10,000. The significance of having a prolonged period of observation like 3 weeks in the above study has been discussed.

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Drug Prophylaxis in the Control of Tuberculosis in India

By

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Review of current literature shows a flood of material on the subject of Chemoprophylaxis in Tuberculosis. This term has been defined in different ways by various workers. The word prophylaxis means "prevention of disease and its manifestations" according to a dictionary of the English language. This definition has not been accepted as satisfactory in Tuberculosis. There are two distinct situations in which prophylaxis can be applicable:

1. Antimicrobial drug can be used to prevent development of infection by the tubercle bacillus in a person who had never been infected before; this is also called cheraoprevention.
2. Disease prophylaxis or secondary prophylaxis is the term defined to the use of antimicrobial drugs to prevent development of disease and its complications in a person who has already established infection as revealed by a positive Tuberculin test.

Infection Prophylaxis or Primary Prophylaxis

If a healthy person never infected before with the tubercle bacillus is given adequate dose of Isoniazid daily and subjected to infection by the tubercle bacillus, evidence of establishment of infection (tuberculin allergy) does not develop as long as the drug is administered (Debre)¹. It is presumed that organisms remain suppressed or latent in the tissues. After cessation of treatment by Isoniazid even after being given for a prolonged period and even though no further fresh infection takes place these suppressed bacilli which remained latent in the tissues for months, then set up active infection (Debre, Walsh McDermott)¹². Other different situations can also result. If the dose of organisms is large, active infection can be acquired even in the presence of Isoniazid which is the antimicrobial drug used for the purpose. Tuberculin allergy also develops¹. But complications of primary infection may be prevented. In the third situation in animal experiments at least Isoniazid may completely prevent development of infection and even though no drug is given further tuberculin allergy may never develop and on autopsy there may be no evidence of any detectable lesion, though under identical conditions control animals untreated with Isoniazid show evidence of infection and develop progressive disease².

If the bacilli are suppressed but not killed off as happens in infection prophylaxis in human beings by the administration of Isoniazid before or simultaneously with infection, they do not constitute a sufficient immunizing stimulus and immunity does not develop (Zorini)¹. This infection prophylaxis or primary prophylaxis has serious disadvantage. If a new born baby is given Isoniazid and kept with an infectious mother or any other member of the household, the child does not develop active infection as elicited by a negative tuberculin test as long as the drug is administered. Then even if the contact is broken and no fresh infection takes place, tuberculin allergy develops after the stoppage of drug, even though such drug

administration may have been prolonged for months after the contact was broken. The child then develops a classical primary complex and runs all the risks accompanying such a disease as if no drug had been administered, as no immunity could develop during that period. Though infection prophylaxis has been advocated in the new born living with an open case of tuberculosis it would be more desirable to vaccinate the child with Isoniazid resistant strain of BCG vaccine^{7,3} and after the allergy is developed then put him on Isoniazid if the contact with an open case cannot be broken. In such a situation it is said that Isoniazid should be given for 3 years by which age risk of development of complications is reduced².

On the whole, prevention of infection is not the main aim of drug prophylaxis and it is advisable only in rare and special cases e.g., in the new born when contact cannot be prevented or among negative reacting TB hospital attendants and in accidental injury and infection at an autopsy on tuberculous tissue in negative reactors. Nothing further will be discussed about primary chemoprophylaxis in this paper².

Disease Prophylaxis or Secondary Prophylaxis—Choice of the Drug in Prevention of Disease

Our concern is more in the prevention of development of disease, not only in the individual but also in the whole community as in India. Any drug that is used must be cheap, readily available, easy to take by mouth and should not deteriorate on storage in tropical conditions. It must be effective against disease without being toxic. The period of administration of the drug for effective result should not be unduly long so that it is kept within the limits of acceptability to the people concerned. Of the three anti-tuberculosis drugs, in general use, viz, Streptomycin, PAS and Isoniazid, the last named one is the only drug that meets the requirements and can be used on such a scale though a combined PAS Isoniazid prophylaxis for three to six months has been reported from Japan¹ and France¹ with considerable success in tuberculin positive young adults. We are left with only one drug Isoniazid, which meets at any rate the requirements of a prophylactic drug.

Basis of Isoniazid Prophylaxis

Isoniazid is a bactericidal and bacteriostatic drug. Only this drug has the properties of penetrating caseous lesions and, therefore, enhances its value in prophylaxis. It is a common observation that relapse rates are the lowest in all the regimens of therapy containing Isoniazid. Isoniazid alone as a single drug therapy is an effective agent in the treatment of non-cavitary pulmonary tuberculosis of limited extent. It has been repeatedly proved³ that tubercle bacilli detected later among patients who previously had Isoniazid prophylaxis do not reveal drug resistance to this drug. Treatment of primary tuberculosis by Isoniazid alone is of convincing value in reducing the serious complications and dissemination of disease. Absence of adult type of disease three years after treatment in adolescents who have received chemoprophylaxis is in sharp contrast to the 18% caseo-cavitary disease among those who have not been treated in the control¹. Similar studies in U.S.A., Greenland, Italy, France (Debre) and Japan encourage us to advocate chemoprophylaxis, though sufficient time has not elapsed after its use. We have in Isoniazid a potent agent for prevention of development of disease in the infected group as described above. If Isoniazid is given after the infection is established as shown by a positive tuberculin test, immunity is not interfered with^{1,2}. In other words, all infected persons could be treated with this drug. But this would be a stupendous task. We have, therefore, to select groups from among the infected who are most likely to become victims of disease. Tuberculin allergy as elicited by the Mantoux test using old tuberculin or PPD as now used in Mass BCG Campaign is fairly reliable as a proof

of infection, specially in the younger age groups. But over fifty years of age, allergy tends to wane and infections among them are old, which do not respond so well.

Prophylaxis with Isoniazid is a direct attack on the tubercle bacillus in the body and is likely to reduce the dissemination of the bacilli and prevent breakdown of foci and thus reduce the case load more quickly than any other method. It is also likely to be the cheapest effective method. Its further advantage is that it can be developed with the existing services and not much of specially trained additional staff is likely to be required. It will also cover without additional effort or cost a large number of existing unknown patients who would be treated by Isoniazid. It is believed that Isoniazid prophylaxis can show a distinct impact on a community. Secondary effects of fairly quick reduction in total case load should also be apparent in a short while among the remaining population. Thus incidence of fresh infection and the disease will be markedly reduced.

For practical reasons priorities have to be given to high risk groups as shown hereunder who are more suitable for prophylaxis:

1. Young tuberculin positive contacts of open cases of tuberculosis (below 25-35 years of age) which are estimated at 60-70 lacs persons in the country. These are likely to be comparatively recent converters.
2. Infected children below 4 years of age. They have risk of developing severe forms of tuberculosis and its complications (estimated at 16 lacs in number).
3. All persons reacting with 20 mm induration or more (BMRC, BCG Trial^{6,8}). They have much greater risk of developing tuberculosis than those reactors who have smaller reaction. 253 lacs is their approximate number.
4. Ex-patients who never had drug therapy in the past and are traceable from clinic and sanatorium records (2 lacs). They tend to breakdown with advancing age and stress of life.
5. Diabetics, alcoholics, silicotics who react to tuberculin.
6. In situations of stress, e.g., puerperium; to cover surgery and intercurrent disease in the reactors ex-patients.
7. Positive reactors who are required to be put on prolonged corticosteroid therapy. Two lacs is the estimated number under items 5, 6 and 7 (above).

Obviously, there is lot of overlapping in these groupings. However, in spite of this overlapping the total number of persons under high risk works out to about 330-340 lacs. If 200 mgm of Isoniazid is administered daily to a person on an average for six months (and the cost of drug is kept at the present market rates) the total expenditure per patient comes to Rs. 6/-; that makes a total of about Rs. 20.5 crores. If 20 per cent of persons are handled every year by BCG Teams (which are being expanded) one round can be completed in five years by them and the cost for each year is likely to be about Rs. 4 crores. The medical practitioners, stable dispensaries and primary health centres, etc., will continue the programme uninterrupted throughout the years as discussed in the organisation of the prophylaxis programme.

Drug prophylaxis is not indicated among those who got infected many years ago and now react with small reactions, as such small reactions could also be due to non-specific infections.

Expected Results

It is difficult to predict the long-term effect of such chemoprophylaxis on the problem of tuberculosis. It can be expected that those persons who have recent infections and take the drug in adequate dose for a period of six months will be 93% protected for 3 years (Debre), others who take for more than three months but less than six months may get 75% protection (Chiba)^{1,2}.

During the period of drug administration reactivation of any existing focus will be prevented. It is agreed by various workers that in ordinary situations like usual chemoprophylaxis of the infected persons immunity is not interfered with.

It is difficult to judge how long the protection will last. It will depend upon the power of the individual to develop resistance to the organisms in the body. But longer the lesion remains stable less is the liability of the risk of a breakdown. Repetition of chemoprophylaxis should not be ruled out now after lapse of say 5 years. Much time has not passed to judge the long-term effect of such drug prophylaxis.

Dose and Duration of Drug Prophylaxis

In the present state of our knowledge, it may safely be stated that in general 4-7 mgm per kg body weight of Isoniazid should be given for a period of 6 months for prophylactic purposes.

Organisation of Drug Prophylaxis

There has to be an organisation before such a prophylaxis campaign is launched upon to carry it out on a country-wide basis. The people have to be educated to accept it. Without sustained public co-operation a preventive method can never succeed. All agencies available in the country who could co-operate must undertake this activity as part of their routine work. It will be realised that this is not an easy task. Our resources are limited. There are about 100,000 qualified medical practitioners of Western scientific medicine. There are about 12,000 dispensaries, mostly in rural parts, these include Primary Health Centres. In addition there are hospitals in urban areas. There are about 200,000 practitioners of other systems of medicine, many of them registered, some of them are employed by various agencies in the rural parts. There are about 200 mobile BCG Teams. All these agencies should take part in organising mass scale drug prophylaxis. The practitioners could give Isoniazid to their clientele, who fall in the high risk groups. Tuberculin testing should form a part of the routine examination in every dispensary so that cases of high risk groups eligible for drug prophylaxis could be detected with ease. The mobile BCG Teams should act as a routine direct strong reactors to the nearest dispensary or to any such place from where Isoniazid is available. This is a possible line of the organisation of mass chemoprophylaxis. There could be other approaches as well. It is by trial and error that organisation can be developed to meet the local conditions.

If quinine could be sold from Post Offices there is no reason why Isoniazid could not be made available on the same basis to rural areas.

Difficulties in carrying out a Planned Programme of Drug Prophylaxis

Let us not imagine that mass chemoprophylaxis is an easy task. Lack of health education, indifference of the community, lack of enthusiasm of the workers and difficulties of organisation are stupendous. However, with education and understanding of the people and the services it need not be an unsurmountable problem.

Isoniazid has admittedly many advantages as a prophylactic drug, but in view of the above-mentioned difficulties, and to get further information, it is necessary to undertake more investigations such as :—

1. A pilot study for applicability and acceptability of the drug on a community basis. How much protection would it give in terms of money spent? How fast will the tuberculosis problem be controlled if this weapon is added to our armour ? This pilot study is one of the foremost needs at present in the control of tuberculosis; for it carries with it potentialities so revolutionary as any in the field of tuberculosis up till now.
2. Estimation of the dose required and the period of administration for optimal prophylactic effect.
3. Mass production methods should be developed so that the drug is made available at every centre where it can be administered or purchased or supplied free.
4. Development of a depot dose of Isoniazid preparation. Recent development in sulphanilamide and penicillin therapy gives the hope that research may make available a catalytic drug which will prevent rapid excretion of Isoniazid from the body, thus avoiding the need for frequent administration.
5. To explore the possibility of mixing Isoniazid in the salt or articles of food like milk in reacting inmates of boarding houses, if this would succeed and tide over the difficulty of administration of drug.

SUMMARY

Isoniazid prophylaxis is proposed as a weapon for the control of Tuberculosis in India. Difficulties in organisation of the programme are stressed. Need for further studies to fill the lacuna in our knowledge of this subject is brought out. If the proposed plan can be made acceptable to the people, reduction of tuberculosis problem can be achieved in a short time at a cost which is within the reach of the country.

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Catalase and Peroxidase in Acid-fast Bacilli and their relation to Drug Sensitivity

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Acid-fast bacilli are known to produce the enzymes catalase and peroxidase (Hahn, 1897; Uecker, 1955). The catalase activity has been correlated with the Isoniazid sensitivity of tubercle bacilli, (Middlebrook, 1954), and most of the drug resistant strains are either catalase negative or exhibit a low catalase activity (Cohn *et al.*, 1954; Wolinsky *et al.*, 1954). The catalase activity varies with the experimental conditions and is particularly influenced by the pH at which the tests are performed (Schweiger *et al.*, 1958; Kubica and Pool, 1960).

Thirunarayanan and Vischer (1957) demonstrated a closer relationship between the peroxidase enzyme of Mycobacteria and their sensitivity to Isoniazid. Peroxidase positive Mycobacteria are susceptible to Isoniazid and even those strains of tubercle bacilli which are resistant to low concentrations of Isoniazid are deficient in peroxidase. However, the recent studies of Hedgecock and Fauscher (1957) and Dunbar *et al.* (1959) have shown that this is not always true. The catalase and peroxidase activities are not related to either Streptomycin or PAS sensitivity (Middlebrook *et al.*, 1954; VanLiew, 1957; Thirunarayanan and Vischer, 1957).

Isolation of a number of tubercle bacilli and unclassified Mycobacteria from pathological material in this laboratory offered the possibility of studying their enzymic activity and drug sensitivity *in vitro* particularly with a view to obtain evidence on the latter type of strains isolated in this country.

MATERIAL AND METHODS

Twenty-nine strains of acid-fast bacilli were studied. These included the following standard Strains: H₃₇Rv, Mycobacterium fortuitum, M. phlei, Nocardia asteroides, a Scotochromogen, and three atypical strains P2, P4 and P8. The last three from Dr. E. H. Runyon's laboratories (Veterans Administration Hospital, Salt Lake city, Utah) were obtained through the courtesy of Dr. Balbir Singh (Irwin Hospital, New Delhi).

The other strains were isolated in this laboratory from pathological samples viz., 7 'Wild' Strains of tubercle bacilli-human type (Niacin positive).

10 chromogenic strains, out of which one (No. 12) appears to be photochromogenic and the rest scotochromogenic, and 4 non-chromogenic rapid growers.

All cultures were maintained on modified Lowenstein-Jensen medium with 0.75% Glycerol (Jensen and Kiaer, 1959).

Drug Sensitivity

Modified L-J medium was used for all indirect sensitivity tests. The drugs were incorporated in the medium in the required strength just before inspissation. The following concentrations were employed: Streptomycin 10 meg/ml, PAS-10mcg/ml, Isoniazid 0.1, 0.5, 1.0, 5.0, and 10.0 meg/ml. Final results were recorded after 4 weeks incubation at 37°C.

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Inoculum

One loopful of an opalescent suspension (Mac Farland's Nephelometer Tube I approx. 300,000,000 organisms/ml) was streaked on the slope. Most of the control tubes showed confluent growth after 4 weeks.

Qualitative Catalase—Peroxidase Test

This was done as advocated by Bogen (1957). 2.0 ml of a freshly prepared mixture of equal volumes of 0.2 % catechol and 1 % hydrogen peroxide solutions in distilled water, was poured on the L-J slope showing growth. Evolution of bubbles within 3 to 5 minutes was taken as an indication of the presence of catalase. If the colonies turned brown or black within 45 to 60 minutes they were termed as peroxidase positive.

Quantitative Catalase Estimation

The method of Schweiger *et al.*, (1958) was followed with a few modifications. Bacilli from L-J medium without drugs, (3-4 weeks' growth for all strains except for saprophytes and rapid growers where a 7-10 days' growth was taken) were washed twice in physiological saline and weighed : 100 mgms (wet wt.) of each strain was suspended in 1 ml of saline. Of this 0.5 ml aliquots were put in each of two tubes containing 2 ml of Sorensen's citrate buffer (pH 1) and 2 ml of phosphate buffer (pH 7). 1 ml of H_2O_2 , 3 % by volume was added to both the tubes. Controls were put up without mycobacteria. The mixtures were kept at 0-4°C for 15 minutes. The reaction was brought to a stop by the addition of 2 ml of 20% sulphuric acid. The remaining H_2O_2 was estimated by titration with N/10 KMnO_4 solution.

The amount of H_2O_2 broken down by catalase was found out by subtracting the test reading from the control reading for that day. This gave the Catalase activity in ml of N/10 KMnO_4 .

RESULTS

Table I shows the results for the 8 strains of human tubercle bacilli (Niacin positive). Out of these only one, (A109), was partially resistant to Isoniazid 5 meg/ml. However, most of the colonies of this strain were peroxidase and catalase positive. Quantitatively the catalase activity of this strain was weak. The catalase activity of all these strains was only slightly diminished at pH 1 as compared to their catalase activity at pH 7. One strain, (A323), exhibited a greatly diminished activity at pH 1. Streptomycin resistance was noted in one strain, (A109) and none of the strains was resistant to PAS.

The behaviour of the chromogenic strains varied (Table II). Most of them were resistant to all the three drugs. Two photochromogens, (P4 and 12), and one scotochromogen, (23), were sensitive to Isoniazid (10 meg/ml). These were peroxidase negative and showed vigorous catalase activity. The rest of the chromogenic strains were fully or partially resistant to 10 meg/ml of Isoniazid. The standard strains and four of the "wild" chromogens showed considerably diminished catalase activity at pH 1. However, 6 of the chromogenic strains retained a fairly high degree of catalase activity at pH 1. None of the strains was sensitive to PAS. Two of the strains (P8 and Scotochromogen), were sensitive to Streptomycin.

Among the saprophytes and *N. asteroides* (Table III) only *M. phlei* appeared to be susceptible to Streptomycin. Resistance to Isoniazid and PAS was observed in all three. Their catalase activity was high at pH 7 and at pH 1 they had lost their catalase activity almost completely.

TABLE I
Drug sensitivity, Catalase and Peroxidase activity of 10 strains of
M. tuberculosis (Niacin +)

No. Strain	Control	SM 10/mcg/ PAS 10mg/ ml.	INH 0.1mg/ ml.	INH 0.5 mg/ml.	INH 1.0 mg/ml.	INH 5.0 mg/ml.	INH 10.0 mg/ml.	Peroxi- dase	Cata- lase	Cata- lase pH 1	Catalase pH 7
1. H37 Rv	14/++++	--	--	--	--	--	--	+	+	2.1*	3.1
2. A13	14/++++	--	--	--	--	--	--	+	+	1.5	4.1
3. A42	13/++++	--	--	--	--	--	--	+	+	0.7	3.1
4. A175	13/++++	--	--	--	--	--	--	+	+	3.1	5.2
5. A307	15/++++	--	--	--	--	--	--	+	+	0.7	3.1
6. A315	9/++++	--	--	--	--	--	--	+	+	1.1	2.9
7. A323	12/++++	--	--	--	--	--	--	+	+	1.0	6.6
8. A109	15/++++	14/++++	20/++++	21/++++	20/++++	18/++	--	+	+	0.2	0.5

@ = Numbers indicate day on which growth first appeared.

* = Catalase activity expressed as ml of N/10 KMnO₄ equivalent to quantity of H₂O₂ broken down. SM = Streptomycin.

PAS = Para-amino salicylic acid. INH = Isoniazid. + = Less than 10 colonies. ++ = 10 to 100 colonies. +++ = Innumerable colonies.

++++ = Confluent growth. -- = No growth. + = Positive for Catalase and Peroxidase.

TABLE II

Drug sensitivity, Catalase and Peroxidase activity of 14 strains of chromogenic mycobacteria.

No. Strain	Control	SM 10mcg/ ml.	PAS 10mcg/ ml.	INH 0.1 mcg/ml.	INH0.5 mcg/ml.	INH 1.0 mcg/ml.	INH 5.0 mcg/ml.	INH 10.0 mcg/ml.	Peroxi- dase	Cata- lase pH 1	Cata- lase pH 7
1. P2	@10/++++	10/++++	13/++++	9/++++	10/++++	10/++++	12/++++	15/++++	-	+	3.8*
2. P4	4/++++	10/++++	6/++++	7/++++	12/++	17/++	26/+	-	-	+	0.1
3. P8	2/++++	-	2/++++	2/++++	2/++++	2/++++	2/++++	3/++++	-	+	0
4. Seo- tochrome.	3/++++	-	5/++++	6/++++	8/++++	10/++++	15/+	14/+	-	+	0
5. 2	6/++++	10/++	9/++	8/++++	7/++	12/++	14/++	21/++	-	+	7.4
6. 6	7/++++	12/++	9/++	15/++++	12/++++	13/++++	15/++	13/++	-	+	5.5
7. 7	8/++++	26/+	10/++	4/++++	5/++++	12/++	25/+	26/+	-	+	6.6
8. 10	8/++++	24/+	13/++++	8/++++	7/++++	8/++++	12/++++	15/++++	-	+	3.9
9. 11	4/++++	10/++	9/++	8/++++	8/++++	9/++++	10/++++	9/++++	-	+	6.2
10. 12	4/++++	4/++++	4/++++	10/++++	15/++++	27/+	-	-	-	+	1.5
11. 14	5/++++	8/++++	4/++++	7/++++	12/++++	17/++++	14/++	14/++	-	+	3.7
12. 20	8/++++	26/+	12/++	9/++++	4/++++	4/++++	26/+	28/+	-	+	2.6
13. 22	9/++++	28/+	12/++	12/++	15/++	20/++	26/+	26/+	-	+	5.9
14. 23	8/++++	15/++	11/++	4/++++	4/++++	10/++++	20/++	-	-	+	6.8

@ = Numbers indicate day on which growth first appeared.

= Catalase activity expressed as ml of N/10 KMnO₄ equivalent to quantity of H₂O₂ broken down. SM = Streptomycin.

PAS = Para-aminosalicylic acid. INH = Isoniazid. + = Less than 10 colonies. ++ = 10 to 100 colonies. +++ = Innumerable colonies.

++++ = Confluent growth. - = No growth. + & - = positive and negative for Catalase & Peroxidase.

TABLE III

Drug sensitivity, Catalase and Peroxidase activity of Saprophytes, Nocardia asteroides, and rapid growing Acid-fast bacilli

No. Strain	Control	SM 10mcg/ ml.	PAS 10mcg/ ml.	INH 0.1 mcg/ml.	INH 0.5mcg/ ml.	INH 1.0 mcg/ml.	INH 5.0 mcg/ml.	INH 10.0 mcg/ml.	Peroxi- dase.	Cata- lase pH 1	Cata- lase pH 7	
1. M. @	2/++++	-	2/++++	2/++++	2/++++	2/++++	2/++++	4/++++	-	+	2.6*	15.6
2. M.	2/++++	2/++++	2/++++	2/++++	2/++++	2/++++	2/++++	9/++++	-	+	0	4.4
3. N.	4/++++	10/++++	8/++++	6/++++	7/++++	7/++++	9/++++	4/++++	-	+	0.2	13.2
4. A169	7/++++	-	11/++++	20/++++	18/++++	17/++++	12/++++	4/++++	-	+	0.6	3.5
5. 9	4/++++	7/++++	5/++++	4/++++	4/++++	4/++++	4/++++	4/++++	-	+	0.7	2.6
6. A89	5/++++	7/++++	6/++++	5/++++	5/++++	5/++++	4/++++	3/++++	-	+	0.8	4.1
7. B39	4/++++	8/++++	7/++++	5/++++	5/++++	5/++++	4/++++	3/++++	-	+	0.7	12.4

@—Numbers indicate day on which growth first appeared.

*Catalase activity expressed as ml of N/10 KMnO₄ equivalent to quantity of H₂O₂ broken down. SM=Streptomycin.

PAS=Para-amino salicylic acid. INH=Isoniazid. + = Less than 10 colonies. ++ = 10 to 100 colonies. +++ = Innumerable colonies.

++++ = Confluent growth. -- = No growth.

+ and -- = Positive and Negative for Catalase and Peroxidase.

Of the four rapid growing non-chromogenic strains three were not inhibited by the drugs in the concentrations used (Table III). One strain (A169) behaved in an interesting manner, and was sensitive to Streptomycin and appeared to be stimulated by Isoniazid. AH were catalase positive and peroxidase negative. The catalase activity was weak at pH 7 and considerably diminished at pH 1.

DISCUSSION

In this work an attempt has been made to correlate catalase and peroxidase activity of certain acid-fast bacilli isolated in our laboratory with the drug sensitivity. The study also aimed at grouping these bacilli on the basis of catalase activity at pH 1 and pH 7.

The only strain of typical human tubercle bacillus which was resistant to Isoniazid (5 meg/ml) and Streptomycin was not deficient in catalase and peroxidase. Though this is not the usual finding (Middlebrook, 1954; Wolinsky *et al.*, 1954), similar strains have been reported by Middlebrook *et al.*, 1954; Hedgecock and Fauscher, 1957; Dunbar *et al.*, 1959.

Thirunarayanan and Vischer (1957) have reported that Mycobacteria other than *M. tuberculosis* do not exhibit peroxidase activity. Our findings are similar. Even the two Isoniazid sensitive chromogenic strains were peroxidase negative. All strains of unclassified mycobacteria were resistant to PAS, and all but two strains to Streptomycin. No clear cut over-all pattern of drug sensitivity has emerged out of various studies on unclassified mycobacteria. (Wolinsky *et al.*, 1957; Tarshis *et al.*, 1955; Middlebrook *et al.*, 1959; Steenken *et al.*, 1958).

Saprophytes, *N. asteroides* and rapid growers were fully resistant to PAS and Isoniazid. *M. phlei* and A-169 were sensitive to Streptomycin. Others were resistant. All these strains were strongly catalase positive and peroxidase negative. Strain A-169 appears to be stimulated by Isoniazid. This strain is being investigated further.

The value of estimation of catalase at pH 1 and pH 7 appears to be doubtful in the case of certain chromogenic mycobacteria. Six of the fourteen chromogenic strains retained 30% or more of the catalase activity of pH 7 at pH 1 though the typical human strains, saprophytes and most of the atypicals behaved as reported by other workers in the field (Schweiger *et al.*, 1958; Kubica and Pool, 1950). This is not surprising in view of the fact that these chromogens belong to the group of unclassified mycobacteria and we do not expect a uniform behaviour from them. The six chromogenic strains that retained their catalase activity at pH 1 may belong to a different group though culturally and morphologically they appeared to be similar to the other chromogens.

Kubica and Pool (1960) have tried to classify Mycobacteria on the basis of a qualitative catalase test. In this work also except for non photochromogens catalase activity was variable at pH 1. We, therefore, feel that this test cannot at present be used in the routine laboratory for identification of Mycobacteria.

SUMMARY

Twenty-nine strains of Acid-fast bacilli including saprophytes and atypical strains were tested for drug sensitivity *in vitro* against Isoniazid, PAS and Streptomycin. The results were correlated with their catalase and peroxidase

activity. The quantitative determination of catalase was done at pH 1 and pH 7 to see if these Mycobacteria could be classified on this basis.

Catalase activity was well correlated with Isoniazid sensitivity in the human strains of this series except in one strain. Peroxidase activity was correlated with Isoniazid sensitivity in all strains except one human and three atypical strains. It seems that catalase activity at pH 1 and pH 7 cannot be relied upon to identify unclassified mycobacteria.

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Management of Tuberculous Empyema*

By

R. N. TANDON AND B. K. KHANNA

(Kasturba T.B. Clinic & Hospital, Lucknow)

The management of tuberculous empyema has long been controversial. A conservative approach to this problem has been challenged several times by surgeons. Chandler (1942) believed that the treatment of choice was the medical treatment. Rosenblat (1947) after a study of 51 cases treated conservatively advocated the medical treatment. However, these views have not gone unopposed (Coryllos, 1937; Brock, 1943 and Cuthbert, 1950). It appears important to realise that the protagonist of conservative treatment had been working at a time when thoracic surgery was still in its infancy and at a time when about one-third of the cases subject to pneumonectomy were fatal. The situation has changed now. The results of treatment of the empyema by the surgeons gives a new picture (Kastl and Knopp, 1952 and Pecora and Brock 1958). Recently, however, Nair *et al*, in 1956 have reported encouraging results in the management of tuberculous empyema by ethyl alcohol lavage of the pleural cavity, Hence it again aroused interest in healing empyema cases on conservative lines.

MATERIAL & METHODS

40 cases of tuberculous empyema admitted to our hospital from 1954 to 1953 treated mainly on conservative lines in addition to int a pleural Kaolin therapy have been analysed in detail. The cases, whose stay in the hospital was less than one month or those who had left the hospital against medical advice have been excluded from the series.

(A) Technique of Intra-pleural Kaolin Administration

The technique adopted h is been a modification of Maxwell's (1954) recommendations. The patient on admission was first given a course of antibiotics. Diagnostic aspiration (5 10 cc) of the pleural fluid was done and the material had been routinely examined. In the mean time the patient was put on the head-low position with the foot of the bed elevated 6-9".

When the patient's condition improved and the toxemia diminished, he was rescreened to assess the extent of effusion and the collapse of the lung. Thereafter the pleural cavity was aspirated so as to render it dry.

Autocalved Kaolin solution (20%) was used for intra-pleural medication. At fi st a test dose of 0.5 cc to 1 cc was injected in the pleural cavity. If no untoward reactions namely, a rise of temperature, sweating or allergic rashes were noted, the patient was considered to be a fit case for the intra-pleural Kaolin therapy.

The precaution taken was to see that the pleural cavity was more or less completely evacuated before the intra-plural medication was started. The first therapeutic dose of Kaolin was 3 to 5 ccs. This was allowed in most instances by

*Based on a paper presented in the 15th Tuberculosis Workers' Conference (1959).

rigor and rise of temperature which ranged from 100° to 103° F. within another 12 hours. No special therapy excepting the diaphoretics were used. The patient was screened on the third day and the pus and the air removed from the pleural cavity by Potain's aspirator. The patient was rescreened after a week and again all the pus and air evacuated.

The next intra-pleural injection was given after a fortnight and the dose of Kaolin increased by 1 cc. This procedure was repeated every fortnight, while increasing the dose every time by 1 cc. till it was stabilised at 10 cc every time.

(B) Chemotherapy

All the cases had received double drug treatment. The usual dosage was Streptomycin 1 gram IMI O.D. with INH 200 mgms twice a day or with PAS 10 grams a day for 5 days a week. As a rule Streptomycin was withdrawn after 60 days of it had been administered. The patient was then put on PAS and INH in usual dosage.

(C) The final results obtained were analysed on the basis of (1) posture, (2) duration of empyema, (3) etiological factors, (4) extent of collapse of the lung, (5) condition of the collapsed lung, (6) condition of the other lung, (7) bacteriology of the sputum.

RESULTS

The final results and its analysis are being presented below in the Tables No. 1-2.

TABLE 1

Results obtained	Number
! Complete lung expansion i Partial lung expansion j <i>Not improved</i> (No lung expansion) l Dead	20 5 9 6
Total ...	40

TABLE 2

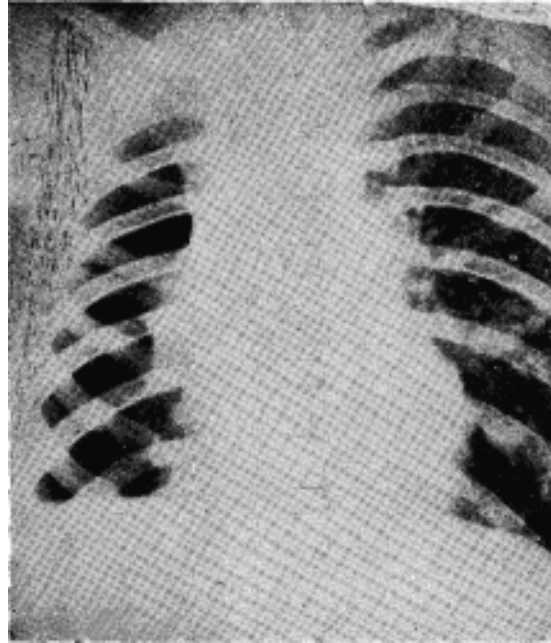
Results obtained	Number
Less than 6 months 6 months to 1 year 1 year to 2 years Above 2 years	22 6 8 4
Total ...	40

Representative Case Report

SB aged 18 years, student, was admitted to our hospital on September 10, 1958 with complaints of cough, fever and pain in right chest for last 4 months. The past history revealed a history of severe pain in right chest 3 months back, after which right pleural cavity was aspirated 6 times and every time pus was brought out. Simultaneously he was being treated for tuberculosis with usual chemotherapy. X-ray chest revealed a right-sided hydropneumothorax with lungs in para hilar

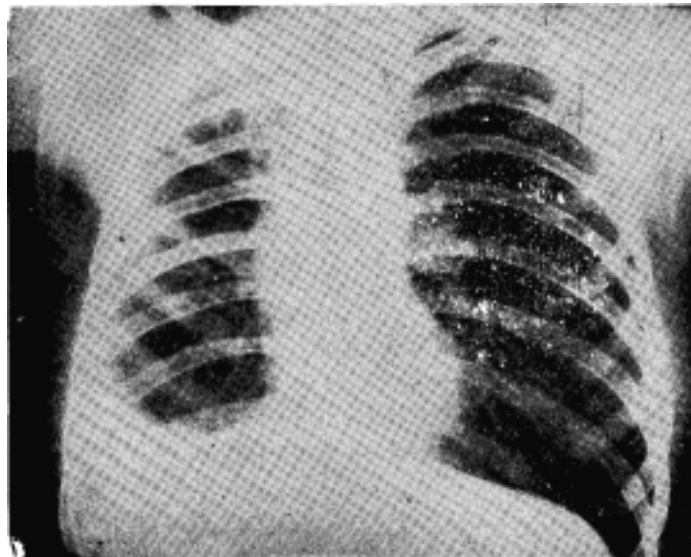
position. The patient was put in head-low position and was given anti-tuberculous chemotherapy. When he became afebrile was put on intra-pleural Kaolin therapy. His lung completely expanded by the end of February, 1959.

FIG. I



X-ray chest taken before the start of therapy.

FIG. II



X-ray chest showing full expansion of Right lung.

DISCUSSION

The introduction of chemotherapy in the management of tuberculous empyema has radically changed the outlook. Systemic chemotherapy not only promotes the healing of the lung lesion but also renders the patient non-toxic. Such cases can thus be put on conservative treatment for a much longer time today than it would have been possible in the pre-chemotherapeutic era.

The important point to realise regarding the administration of the chemotherapy is that it should be given in adequate dosage. Besides the factors of individual variation in the metabolism of drugs, absorption of the drugs may also vary when administered orally (Slades and Folly, 1958). This was well exemplified by one case of ours, where following the failure of the oral therapy, the same dosage of INH given intramuscularly produced a remarkable improvement.

In the past we have tried various agents for producing pleurodesis in our cases. These agents which include glucose solution and patient's own blood failed to satisfy us. However, the results obtained with intra-pleural Kaolin therapy have been most gratifying in our hands.

Another observation which aroused our interest was the head-low position. It was observed that when the patients were put in this position, a rapid defervescence and a more complete expansion of the lungs was obtained. Mason (1952) mentions that temporary phrenic paralysis could reduce the rate of effusion formation and even when the fluid is turbid, may lead to its absorption. It has been observed that when the patients are in head-low position the abdominal viscera are resting against the diaphragm, resulting in its slight elevation. This may in part explain the beneficial results obtained. Besides pooling of the pus to the apices of the lungs may act as a splint to the diseased area and leave the comparatively healthier lower part of the lung to expand. Thus maximum conservation of the functional efficiency is obtained. Further, the absorption of pus in this position, it was found, was speedier.

Duration of empyema and the etiological factors in the causation of empyema were found to exert important influence on the results obtained. Naturally a case who has got grossly thickened pleura, due to long-standing empyema, is likely to fail to respond to conservative treatment. Similar appears to be the situation with empyema following A.P. Empyemas usually do not appear during A.P. treatment unless it (A.P.) is continued in spite of atelectasis and/or effusion. Such cases, obviously have endobronchial disease. Consequently, pleural infection with tubercle bacillus follows. Possibly the lesion in the lung, even initially in some cases, might have been such as to forbid the A.P. Such are the cases, we believe, who should go for straight surgery.

Extent of collapse had its bearing on the results obtained. The cases who had atelectasis or para-hilar collapse were found most resistant to our conservative treatment. Similar were the influences of the extent of disease in the underlying lung, in the other lung and the bacteriology of the sputum. A diseased lung showing the area of atelectasis or of gross fibrosis obviously can't expand. Such lung have to be removed. The extent of disease in the other lung probably is an indicator of the disease in the collapsed lung and hence it had an important bearing on the results obtained. The improvement in pulmonary condition followed the conversion of sputum in many cases. It is noteworthy that none of the cases, who were initially sputum-negative, became sputum-positive after the lung expansion,

In conclusion, an over-all study of our series reveals that the ideal cases for conservative treatment with intra-pleural Kaolin therapy are as follows : —

- (a) The duration of empyema on admission should be less than 1 year.
- (b) The etiological factor be a spontaneous pneumothorax.
- (c) The extent of collapse should not be beyond intermediate zone.
- (d) The underlying lung or the opposite lung should not be grossly diseased.
- (e) Effective chemotherapy must be able to convert the sputum.

However, we must stress that every case must be given a preliminary trial with conservative methods for at least 3 months before a decision in favour of a surgeon or a physician is taken.

SUMMARY

The hospital records of 40 cases of tuberculous empyema admitted to our hospital from 1954 to 1959 have been scrutinized. With the rational use of the chemotherapy, observation of strict head-low position, and intra-pleural Kaolin medication 62.5% cases registered an improvement. Complete expansion of the lungs was noted in 50% cases. Only 15% cases had expired. We believe that still the management of tuberculous empyema is essentially medical and surgery should be done in only selected cases.

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“K”-Endocavitary Aspiration

By

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Endocavitary aspiration used for the first time in 1938 in the treatment of tuberculous cavities is still being used with a slow but ever growing rhythm.

OBJECTIVES

1. To reduce the positive pressure within a tension cavity and maintain it on negative side thus enabling the collapsed lung tissue, which it is now believed constitutes the opaque rim of many cavities, to reinflate once more.
2. To syphon off constantly the secretions which collect in the cavity and so assist endobronchial granulations, if present to heal.
3. The walls of the cavity to become clean preparatory to fusion into a scar.
4. The patient to surmount the tuberculous toxemia.
5. If closure cannot be achieved unaided, the method reduces the size of the cavity and brings it within the sphere of surgical collapse.

Cavities with thick fibrotic walls are not selected. As the closure of cavities in suction drainage depends mainly on the expansion of surrounding alveoli, it is unreasonable to expect that this can happen when these alveoli have already been replaced by fibrous tissue.

CASE REPORTS

Case No. 1: *Fig. 1-1.* X-ray shows a large cavity of 4” diameter with fluid level excavating Right Upper and Mid Zone. Right apex is hazy. Right costophrenic angle is clear and disseminated infiltration left lung. Patient had approximately thirty months of anti-microbial treatment for tuberculosis, he was acutely ill on admission, coughing incessantly and toxemic. Sputum positive for A.F.B.



FIG. 1-1

Fig. 1-2. One month after Endocavitary aspiration; a cavity much smaller in size, general condition improved, Sputum remained positive; patient waiting to undergo Right Upper Lobectomy.



FIG. 1-2

COMMENT

Endocavitary aspiration had reduced toxemia and prepared the patient for pulmonary resection.

Case No. 2. *Fig. 2-1.* Far advanced Bilateral disease. Extensive exudative infiltration with breakdown on Right side. Huge cavity excavating the whole of Left Upper and Mid Zone with fluid level. Scattered infiltration left Lower Zone with obscuration of costophrenic angle. Sputum positive for A.F.B. Patient acutely ill.



FIG. 2-1

Fig. 2-2. One month after Endocavitary aspiration and chemotherapy cavity size much smaller. Infiltration in Right side considerably cleared. Patient's general condition improved.



FIG. 2-2

COMMENT

This treatment will be continued till his infiltration on Right side clears and a subsequent thoracoplasty on Left side becomes possible.

In every sanatorium, there are large number of desperate cases of Pulmonary Tuberculosis which are considered usually completely hopeless from the standpoint of active therapy. Among these are patients whose disease has worsened under the most ideal treatment situations in spite of adequate chemotherapy. We have all seen patients who have developed retention cavities, whose sputum has remained constantly positive, whose bacilli have developed resistance to the drugs, and in whom there have occurred rather massive spreads of the disease to the remainder of the lungs on both sides while under chemotherapy. Obviously resection is out of the question in such cases and Endocavitary aspiration provides some method of salvage.

CONCLUSIONS

I believe that there is a very definite place for Endocavitary aspiration in the surgery of Pulmonary Tuberculosis. Cavity drainage should be considered in those cases in whom resection or collapse seem to be contra indicated and when there is desperate need of help in turning the tide of events towards a favourable outcome.

Follow up of B.C.G. Vaccination Programme

By

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(Ardeshir Dalai Memorial Hospital, Jamshedpur)

An attempt was made to follow up 2,113 children whose ages ranged from 3 to 12 and who were part of a Jamshedpur Schools B.C.G. programme in 1950. Of these 1,028 had shifted or could not be traced and although in some cases there was some information available from friends or relatives they have been left out of account. The remaining total of 1,086 cases were as follows:

Mantoux Positive		Given B.C.G.	
Male	Female	Male	Female
553	153	235	145

Among the cases that were given B.C.G. only 1 male developed pleurisy with effusion.

Of the Mantoux Positive cases 5 males subsequently suffered from tuberculosis of the lungs and one developed pleurisy with effusion.

Significance of relationship of T.B. attacks & B.C.G. Vaccine

Let us assume that there is no relationship between B.C.G. vaccination or sex and T.B. attacks (Null-hypothesis). We take it that the samples of 553 of males not given B.C.G. 235 males given B.C.G., 153 females not given B.C.G. and 145 females given B.C.G. are random samples belonging to the same homogeneous population. In that case, we have to check statistically whether it is possible purely by chance factors that the actual attacks be 4 in the first case and nil in other cases. The method is worked out as follows:

	No. of persons	Actual attacks	Theo. No. expected	
Male— Not given B.C.G.	553	4	2.04	1.89 .86
Given ,,	235	—	.86	.56 .54
Female — Not given ,,	153	—	.56	
Given ,,	145	—	.54	3.85
TOTAL	1,086	4 (.3683%)	4.00	

The probability that $X^2=3.85$ is .28, that is to say, we can expect the observed high incidence of attacks on a sample of 553, in about 1 out of 4 cases purely due to chance. While this is not a very significant result, still it would appear that a larger number of observations may give a significant result.

I wish to express my gratitude to Mr. N. Srinivasan for the statistical analysis and my welfare worker Miss Sukhmandan for going round and collecting data on the cases and finally to Lt. Gen. Master, Director, Town Medical & Health, for permission to publish this note and for defraying the expenses involved.

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

Tuberculosis in Steel Industry

An attempt has been made to try and assess the risks, if any, to workers employed in a Steel Plant.

A modern Steel Plant has many different stages and processes through which the raw materials pass before it emerges as the finished steel product. For the sake of convenience I have grouped the various departments of the industry under nine heads. These together with⁷, their possible environmental hazards:

TABLE I

<i>Department</i>	<i>Special hazards</i>
(1) Outside the factory proper Accounts etc.	None
(2) Brick	Silica, Chrome and Magnesite Dust.
(3) Foundry	Silica Dust. Heat, Sand & Shot blasting & Fettling.
(4) Blast Furnaces	Iron, Limestone Coke Dust.
(5) Coke Ovens	Coal Dust SO ₂ Coke Oven gas.
(6) Sheet Mills	Heat 130° F.
(7) Merchant Mills	-do-
(8) Steel Melting Shops	Heat, Lime, Dolomite, Magnesite Dust.
(9) Miscellaneous Depts.	Factory smoke, etc.

During the past 5 years 525 cases of definitely proved sputum + ve cases have been detected at the chest clinic, Tata Main Hospital. In addition there were an approximately equal number of cases who were probably tubercular on clinical and radiological grounds but these were all sputum-ve and have been left out of the context of this paper. The cases detected were distributed as follows:

TABLE II

<i>Department</i>	<i>Total employees</i>	<i>No. of T.B.</i>	<i>% age of T.B.</i>
Outside the Factory	8,000	101	1.26
Miscell. inside Factory	12,500	179	1.43
Brick	2,230	59	2.64
Foundry	830	14	1.68
Blast Furnaces	930	14	1.50
Coke Ovens	1,000	15	1.50
Sheet Mills	2,500	40	1.60
Merchant Mills	4,900	58	1.18
Steel Melting Shops	2,900	45	1.55

An attempt was also made to find out how long each individual had been engaged in his particular environment but due to certain major changes in the Works this could not be evaluated. The incidence by age groups is given in Table III.

TABLE III

<i>Age</i>	<i>No.</i>	<i>Age</i>	<i>No.</i>
20-25	52	41-45	70
26-30	77	45-50	87
31-35	76	51-55	30
36-40	103	56-60	25

It can readily be seen that the main emphasis on tubercular disease has shifted from the younger age groups of a decade ago to an older age group in their forties.

I am indebted to Dr. Sukhatme, our Chief Statistician, for the analysis on the data. The significant rate has been calculated according to the formula

$$\frac{P_1 Q_1 + P_2 Q_2}{N_1 + n_2}$$

where P, is the average incidence, Qi the specific incidence to be investigated.

T.B. ATTACKS

	<i>No. of men</i>	<i>Attacks</i>	<i>%</i>
Outside Depts (Total)	8,000	101	1.26
Inside Depts (Total)	27,790	424	1.53

It is observed from the above table that of the 8,000 employees outside the Works, 101 were attacked with T.B., i.e. 1.26%, whereas 424 from 27,790 employees inside the Works, i.e. 1.53% were attacked with T.B. To determine whether this difference of 0.27% shows that the employees inside the Works are more prone to T.B. attack or whether this difference occurred due to chance only, statistical tests (both by calculating chi-square and standard error of the difference between the percentages) showed that the difference was significant at 7% level; i.e., that a difference of 0.27% or more may occur due to chance only 7 times in 100. Therefore, from the available data it cannot be concluded that employees outside the Works are equally prone to T.B. attack as those inside the Works. Observation over a further period may show a significant difference between the two percentage.

Again, among the groups within the Works, Group II comprising of the Refractories Dept., has the maximum proportion attacked with T.B. Statistical tests show this group is definitely more prone to T.B. attack than the other employees inside the Works.

It appears, therefore, that there is some statistical significance between the disease seen inside the factory and outside the factory walls and also that within the factory itself there is a significant increase in the disease in the Brick Dept.

According to the Registrar General's list in the U.K. the following trades found in a Steel Plant are more often attacked by tuberculosis than others, namely, Masons, Kiln workers, Foundry workers, Metal Machinists, Metal Grinders and Sand Blasters.

A steel worker, generally speaking, may be subjected to extremely high environmental temperatures going upto 130°-140°F and is exposed to sudden variations of temperature.

Industrial fumes including SO₂, SO₃, H₂SO₄, Ammonia, Acroline may all cause severe respiratory irritation. Various dusts the most important of which Silica may predispose to tuberculosis. Of these it would appear that although all of them act as respiratory irritants, none of them predispose to T.B. as such, with the exception of Silica where it is to probably the favourable nidus and not Silica dust *per se* which predispose to tuberculosis. I believe I am correct to say that modern views emphasise that it is close contact which is mainly responsible for the spread of T.B. Broadly speaking the occupational hazards consist of three main groups namely, (1) those responsible for looking after the tubercular; (2) certain trades in public life such as shop keepers, waiters, etc., who are more liable to meet the tubercular than others; and (3) those exposed to Silica dust.

We shall realize that in discussing the problem of tuberculosis the factors of age, sex and race play a large part in determining the results. I shall content myself with saying that there is no significant deviation from the expected pattern in our series of cases. Another factor which I have always considered paramount is the economic one. This aspect has been proved too often for me to dwell on the subject. Here again in our series although the per capita income is higher than the average for India, generally the majority still fall within the lowest income group. What remains to be considered is whether or not the Brick Dept. conduces to T.B. In 1949 I did a small survey of the Steel Plant on similar lines but at that time I found no significant difference between any of the departments mentioned.

The Brick Dept. is a rather loose term wherein many different types of processes are carried out. That there is some exposure to Silica is undoubted and that may be the contributory factor, except that in no case could I say that I definitely found T.B. superimposed on Silicosis. This will need further investigation which I hope to take up later on.

I am publishing this Note because, the number of Steel Plants in our country has increased and to see if this experience is common to all of them and if so what measures can be undertaken to prevent it.

I am indebted to Dr. J. R. Sen, our Plant Medical Officer, in the preparation of this paper and to Lt. Col. A. F. Lassado, Supdt. Tata Main Hospital, for permission to publish this note.

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News & Notes from States

Tuberculosis Association of Andhra Pradesh

The Tuberculosis Association of Andhra Pradesh held a preparatory conference for the organisation of Fight-TB-Fund on 26th June, 1960. The conference was convened to check the downward trend in T.B. Seal Sale Campaign by enlisting the support of businessmen, politicians and social workers in the State.

The conference was presided over by Dr. D. Sanjivayya, President of the Association. Among high officials present were Shri V. K. B. Pillay, Union Health Secretary and Lt.-Col. V. Srinivasan, Director-General of Health Services, Government of India.

Bombay Obstetric and Gynaecological Society

The 9th intensive Refresher Course in Obstetric and Gynaecology will be held under the auspices of the Bombay Obstetric and Gynaecological Society from 7th November to 12th November, 1960.

A nominal fee of Rs. 15/- has to be paid in advance for registration of the names for this course.

Candidates will have to make their own arrangements for boarding and lodging. Applicants wishing to join the course should give in English their full names full postal addresses and the degrees or diplomas they hold. If candidates require any special subjects to be treated during the course, the same should be intimated in advance.

Those desirous of joining the course should write to the Joint Secretaries, Bombay Obstetric and Gynaecological Societies, Purandara Griha, Chowpatty Sea Face, Bombay-7.

Funds for Isolation Beds

The Tuberculosis Association of Andhra Pradesh at a meeting of its central committee resolved to raise 328 isolation beds for TB patients with the central assistance given by Government of India @ Rs. 1,250/- per bed. The total cost of proposed beds will amount to Rs. 8,20,080/- out of which the Tuberculosis Association of Andhra Pradesh will contribute Rs. 4,10,000/- from the Seal Sale collection and donation from State government. Each centre will consist of 20 beds located at district headquarters. These beds will be maintained by the district TB Association and government. The concerned Medical Officer of the TB Clinic/District Medical Officer will supervise the treatment of patients.

1961 Tuberculosis Health Visitors' Course

The next Tuberculosis Health Visitors' Course will be organised by the Tuberculosis Association of India from January 1961. The duration of the course is one year of which one month will be in the College of Nursing, seven months in the New Delhi TB Centre and one month in the Lady Linlithgow Sanatorium, Kasauli.

The candidates will be examined at the end of this nine months' training and those who are successful will be required to do practical work in home visiting for three months at the New Delhi TB Centre. Certificates will be awarded at the end of one year after satisfactory completion of practical training in the field. The minimum qualification for admission to this course is Intermediate with Science/or Hygiene and Physiology in the Matriculation.

Applications for admission to this course should reach the Secretary, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-2, on the prescribed form on or before November 15, 1960.

New Seal Design

Design for the T.B. Seal for the Eleventh Seal Sale Campaign has now been selected. Out of 292 entries received from 157 artists, design depicting "mother feeding the little one" submitted by Shri B. B. Banerji of Delhi has been selected as the best. Mr. Jal Cooper, the well-known Philatelic commentator wrote in Illustrated weekly as follows :

"The motif is very simple—a mother feeding the little—and the artist B. B. Binerjee of Delhi is to be congratulated on his presentation, particularly his choice selection of harmonising colours for this simple but attractive design. With the increasing number of stamp collectors going in for "thematic" or "Topical" collections, this year's TB Seal will be given a warm welcome by collectors of "Birds on Stamps" in all parts of the world. And there cannot be a better X'mas Gift for overseas philatelic friends than a sheet of these attractive seals".

Standing Technical Committee

Dr. J. Frimodt-Moller, Director, Madanapalle Research Unit, has been appointed by the Tuberculosis Association of India as the Chairman of the Standing Technical Committee of the Association and also President of the Seventeenth Conference of Tuberculosis and Chest Diseases Workers' in India.

XVII Workers' Conference

The Seventeenth Conference of Tuberculosis and Chest Diseases Workers' in India will be held in Cuttack, Orissa, from 31st January, 1961 to 3rd February, 1961.

As usual rail travel concession is admissible to those delegates whose travelling expenses are not met by either their government, Central or State or any local or statutory authority.

XVI International Tuberculosis Conference, Toronto

Under the auspices of the International Union Against Tuberculosis the next Tuberculosis Conference will be held in Toronto, Canada, from September 10th—14th, 1961 under the presidency of Dr. G. J. Wherrett.

There will be academic and scientific conferences as well as visits to hospitals and clinics. Tours in the city of Toronto and nearby places will give an opportunity to come into contact with various aspects of Canadian life. There will be a full-day trip to Niagara Falls and pre-and-post convention tours in Canada and the United States. Special arrangements for travel with reduced fares for Chartered aircraft will be made through national travel agents.

Full details of the Conference can be obtained from the General Secretary Dr. C. W. L. Jeans, 265, Elgin Street, Ottawa, Canada or Dr. W. Gellner, Executive Director, International Union Against Tuberculosis, 15, Pomerue Street, Paris-16, France.

The Indian Journal of Tuberculosis

ABSTRACTS

Vol. VII

September, 1960

Abst. No. 4

A rapid Mouse Test for the Diagnosis of Pulmonary Tuberculosis

III. Validation of the with specimens from test 1000 patients.

The mouse test is both more rapid and sensitive than the usual culture procedure for the detection of tubercle bacilli.

Of the 362 patients, 145 patients (40 per cent) yielded specimens which were positive by the mouse test in twenty days, whereas the specimens from 75 patients (20 per cent) were positive by culture in fifty two days. Of the 75 patients, whose specimens were positive by culture, 84 per cent gave positive results by mouse test in five days and 96 per cent in ten days, whereas no. cultures were positive in ten days.

(David Gale and Lock Hart, Elizabeth A. Amer. Rev. Resp. Dis., Vol. 81, No. 5; May, 1960)

Comparative morbidity and mortality of Anti-microbially treated and untreated Idiopathic Effusion in the Negroes

Of the 47 patients with idiopathic pleural effusion treated with bed rest and therapeutic aspiration, 64 % developed tuberculosis during a five years, follow up. 21% died.

Of the 45 patients, treated with Chemotherapy, 17.7% developed tuberculosis and 4.4% died.

Pleural and thoracic complications were few and less severe following antimicrobial therapy.

(John H. Seabury; John, B. Bobear and M. Jack Liberman, Dis. Chest, Vol. XXXVII, May, 1960; No. 5.)

Cycloserine-Isoniazid in the treatment of Chronic Resistant Pulmonary Tuberculosis.

Fortysix Negro patients who were treatment failures with combination of SM, P.A.S. and I. N. H were treated with cycloserine and I.N.H. 54 per cent showed bacterial conversion after 6 months of therapy, 27 per cent at 12 months, and 26 per cent relapsed. X-ray improvement occurred in 3 per cent. Treatment was discontinued in 6 per cent because of toxicity (convulsion), one for hyperreflexion and tremors and one due to emotional change.

The optimal duration of treatment with CH—I.N.H. in resistant cases should be six months.

There was no significant difference between the two different doses of CS 750 mgm and 500 mgm daily in therapeutic efficacy and drug toxicity.

(Hijo Keun Lee; Dis. Chest, Vol. XXXVII, No. 4, April, 1960.)

Drug Treatment of Pulmonary Tuberculosis : An interim Report by the Committee on Therapy—Single Drug Therapy with Isoniazid

Isoniazid alone is as effective as Isoniazid plus P.A.S. in the treatment of minimal and moderately advanced non-cavitary disease.

Combination of three drugs versus two : In resected lesions fewer tubercle bacilli resistant to drug were found when a triple drug combination has been used than when a two drug regimen has been followed. The addition of a third drug to two drug regimen increases the toxicity.

Isoniazid in high dosage : In the rapid inactivator group higher dosage of Isoniazid improves its efficacy. With increased dosage of Isoniazid a minimum dosage of 50 mgm of Pyridoxine should be given to protect against Isoniazid toxicity.

Pyrazinamide : Has a limited effect, but is a serious hepatotoxic. The oral dose is 1 gm. three times daily. Dosage lower than this reduces its toxic effect but are not therapeutically effective.

Streptomycin-pantothenate : The use of Streptomycin pantothenate as a substitute for streptomycin sulphate does not reduce toxicity to the eighth cranial nerve. Similarly dihydrostreptomycin-pantothenate is not advantageous over other streptomycin or dihydrostreptomycin drugs.

Strepto Varicin alone or in combination with Isoniazid has no therapeutic advantage over Isoniazid alone.

Cycloserine : In combination with Isoniazid, cycloserine in dosage of 0.25 gm twice daily is as effective as Isoniazid plus P. A. S. except in patients with advanced cavitary disease. As

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

such cycloserine may be used as a substitute for P.A.S.

Under certain circumstances the toxic effects of high doses of cycloserine on the central nervous system have been controlled by concomitant administration of sedatives, anticonvulsants, tranquillizing agents and pyridoxine singly or in combination.

Thio Carbantdin : It is poorly absorbed from human gastrointestinal tract. In man a single oral dose of 1 gm of thiocarbinidin per day is less effective than P.A.S. in delaying resistance to Isoniazid and probably to Streptomycin.

Kanamycin : It is related to neomycin and resistance to it is fairly rapid. Auditory and renal toxicity is fairly common.

Adreno Corticosteroids and Cortico Tropin : Beneficial effects from the addition of adreno Corticosteroids and Cortico tropin have been reported in the treatment of tuberculous meningitis, miliary tuberculosis, pleurisy with effusion and hyper-sensitivity to antitubercular agents.

(*Amer. Rev. Resp. Dis. Vol. 81, No. 3; March, 1960.*)

Treatment of Adult Tuberculin Converter—A Statement of Committee on Therapy

Every individual in whom tuberculin hyper-sensitivity appears should be studied by means of complete medical history and physical examination, a roentgenogram of the chest and cultures of three specimens of sputum on gastric content, for evidence of clinical infection. If there is evidence of clinical infection, it should be treated. But if there is no evidence of any clinical tuberculosis, before considering the individual for antimicrobials, we must determine:

- (1) The risk to the individual without antimicrobial therapy.
- (2) The effect of therapy.
- (3) Undesirable effects of therapy.

The risk of developing tuberculosis following conversion of the tuberculin reaction is between five and 15 per cent with high figures in certain groups; but it is variable. The reasons for such variations are nature and frequency of exposure and susceptibility of the individual to tuberculosis.

The administration of antitubercular drugs following tuberculin conversion significantly reduces the incidence of tuberculosis disease.

The incidence and type of drug toxicity would depend upon the therapeutic agent used; but this seldom raises serious problems. The indica-

tions for the use of antimicrobials in the recent converter are:—

- (1) those who are unusually susceptible to tuberculosis such as adolescents and persons with diabetes or silicosis,
- (2) Heavy or prolonged exposure to tuberculosis,
- (3) those in whom unusual circumstances would indicate every precaution in preventing clinical tuberculosis.

Multiple Drug Therapy as for established cases of tuberculosis might be expected to afford maximal assurance of preventing clinical tuberculosis.

If two drugs are used, Isoniazid P.A.S. is the combination of choice. In early months Isoniazid alone might be a satisfactory alternative therapeutic regimen because it is convenient, inexpensive and free from side effects.

The treatment should be continued for one year without interruption on an ambulatory basis.

The use of antimicrobials in the case of recent tuberculin-converter is designed as a measure to prevent clinical tuberculosis and does not mean that the patient has a disabling disease.

(*Amer. Rev. Resp. Dis., Vol. 81, No. 3; March, 1960.*)

Chemotherapy of Extra-Pulmonary Tuberculosis in Adults

1. Antimicrobial Chemotherapy is recommended for all patients with active tuberculous infection.

2. The treatment should be continued, intensive and uninterrupted. P.A.S. if tolerated is recommended as it can be easily given.

The dosage of Isoniazid is 100 mgm three times daily (3-5 mgm per Kg. of body weight). Larger doses are still recommended and this should be combined with pyridoxine to minimise the risk of neurologic complications.

Para-amino-salicylic acid is given in maximal dose of 150-200 mgm per Kg. of body weight.

Daily Streptomycin is given in serious cases; injection every 2nd or 3rd day appeared quite satisfactory.

3. Chemotherapy is continued for a prolonged period for at least two years and at least one year after tuberculosis has become inactive as determined by roentgenographic, bacteriologic and clinical diagnostic method.

4. Surgical Treatment :—

Skeletal Tuberculosis: A weight bearing joint requires surgical fixation more than a non-weight bearing joint.

Tuberculosis of the synovial membrane heals much more rapidly with Chemotherapy. Early diagnosis requires biopsy. The fusion of a tuberculous joint is delayed until medical treatment has diminished soft tissue reaction, closed of any draining sinuses present and stabilized the pathologic process. Tuberculous abscesses should be evacuated to facilitate healing.

Tuberculous Lymphadenites:—Heals but rather slowly with antibiotics. Abscesses associated with lymph nodes should be evacuated.

Genito-Urinary Tuberculosis:—More prolonged treatment is required in renal tuberculosis than in pulmonary tuberculosis.

Tuberculous cystitis responds promptly when infection is recent and superficial, but prolonged treatment is indicated.

Tuberculous epididimitis, seminal Vesiculitis and orostatitis responds slowly but definitely to adequate and prolonged Chemotherapy.

Tuberculous salpingitis may require surgical interference.

Tuberculous endometritis is generally secondary, but responds to medical treatment.

Miliary Tuberculosis and tuberculous meningitis:—

Isoniazid is the most potent drug. Intensive and prolonged therapy is indicated. Corticosteroids are beneficial. Intra thecal therapy is rarely used.

(*Amer. Rev. Resp. Dis., Vol. 81, No. 3; March, 1960.*)

Centre Therapy in Pulmonary Tuberculosis A Study of 100 Cases by 100 participating Physicians with Analysis of their Opinions

A Report of the Committee on Non-Surgical and Drug Therapy, American College Chest Physicians.

All of the 100 physicians answered that they

would use Chemotherapy immediately upon diagnosis in addition to bed rest.

Double combination using 300 mgm of INH and 12 gms. of PAS was the drug of choice.

Where SM was used, it was given 1 gm daily during acute period and thereafter two times weekly.

In failures with the ordinary drugs, use of pyrazinamide, viomycin or serocycline was recommended. In acute febrile cases, use of Corticosteroids during the period of high fever and acute symptoms was recommended.

A minimum of 24 months, duration was recommended for drug therapy. The indications for non-surgical collapse therapy were less, and pneumoperitonem was almost exclusively used.

Pneumothorax was rarely recommended. Phrenic operations, extra pleural pneumothorax and oleothorax have become obsolete.

When collapse therapy was used, the time for initiation varied usually from immediately to three months. The duration of pneumoperitonem ranged from one to five years.

Surgery has been considered more useful in the attack upon active tuberculosis. The procedure of choice was excisional surgery. Thoracoplasty has largely fallen into disuse. In cases with extensive disease and diminished pulmonary functions, extra periosial lucite plombage was recommended.

Decrptication was done in cases with pleural thickening. The favourite time for initiation of surgery was after 6 months of Chemotherapy and bed rest. Post-surgical bed rest varied upto a period of six months.

Regarding the time of complete bed rest and duration of sanatorium stay, there is trend to decrease both because of intensive Chemotherapy and increased tendency for surgical intervention and of good home conditions.

(*Dis. Chest, Vol. XXXVII, No. 4; April, 1960.*)

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