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## TUBERCULOSIS ASSOCIATIONS AND DOMICILIARY SERVICES

The salient points with regard to tuberculosis control in India were given in the last issue of this Journal (Vol. IX, No. 3). The two important items in the National Tuberculosis Control Programme are preventive vaccination with BCG of uninfected susceptible population in the community, and treatment of all cases, or at least of infective cases, with anti-bacterial drugs. This latter is intended more to reduce the pool of infection

Effective treatment of all tuberculous patients in the country as a whole is not easy. Present day emphasis is on domiciliary treatment. This may appear simple at first sight, but it is not really so. To make it fool-proof district tuberculosis control programmes visualise securing the assistance of all the health agencies in the area. The provision of drugs for administration to every detected case however, is not adequate. Even if the drugs are made available by government there is still the problem of getting these drugs to individual patients and seeing that they *do take them regularly* during the prescribed period. Such period may extend even to one year in most of the cases. Government agencies alone will not be able to ensure this. Co-operation of non-governmental agencies is therefore essential to make domiciliary service programmes successful in all aspects.

Such agencies are generally represented through Tuberculosis Associations. It is recognised that these Associations have to play their part in carrying out an intensive educative propaganda and enlist the co-operation of the community in all anti-tuberculosis measures. They should properly organise their district and sub-divisional branches and see that they actively participate in the National Tuberculosis Programme. Any appeal the non-official organisations make would have force and demand adequate response if they have constructive programmes which the people can actually see being implemented, and some tangible results achieved. For example, the Tuberculosis Seals Campaign that is being conducted every year by the Associations could make an appeal if the money

raised by the campaign is used properly, usefully and expeditiously. Helping the district control programme could be an item of such expenditure. Each district should have a set of workers, either voluntary or paid, who could assist the district authorities in distributing the drugs and seeing that *patients do take the prescribed quantity of drugs regularly and for sufficiently long periods*. This demands sustained enthusiasm and constant effort. This also pre-supposes active co-operation and partnership between the official organisations and their staff and non-official organisations and their workers. The various Tuberculosis Associations in the country should reorientate their programme and work to fit in with the scheme for domiciliary treatment of tubercular patients.

**CHANGES IN TUBERCULOSIS PREVALENCE IN A SOUTH INDIAN RURAL  
COMMUNITY FOLLOWING A TUBERCULOSIS CONTROL PROGRAMME  
OVER A SEVEN YEARS' PERIOD (A preliminary report)**

J. FRIMODT-MOLLER\*

A tuberculosis programme based upon detection of bacillary cases of pulmonary tuberculosis, isolation and treatment in hospital as well as on BCG vaccination of non-infected persons was introduced in Madanapalle in 1948 and in the surrounding villages in 1950. The total study population was about 50,000, later increasing to about 60,000. The present report deals with the results obtained after a period of seven years in a population of about 40,000 living in nearly 200 villages within a radius of about ten miles of Madanapalle but excludes the town population.

In 1950-51 an X-ray survey by a mobile unit was carried out and about 21,000 persons were photographed. Between 1951 and 1954 another three rounds of X-ray examinations were done bringing the total of persons X-rayed up to nearly 32,000 and many of these had repeat X-rays. At the same time an intensive examination by tuberculin tests was done, about 25,000 persons being tested at least once. Details of these activities have been given in a previous report (Frimodt-Moller, 1960).

In 1957-58 the same population was again X-rayed. This time about 32,000 were X-rayed, the coverage being better than during the first survey. Tuberculin examinations were not done.

At all surveys, cases showing significant pulmonary pathology on X-ray were selected for further examination by large X-ray and bacteriology. The present report, however, deals only with the prevalence of tuberculosis based upon the radiological findings.

METHOD USED

In order to ensure that the X-ray films obtained at the first and the last X-ray examinations were studied alike, the whole material of films from both surveys was submitted to a new independent reading—the former readings and their results being wholly ignored. The material comprised about 21,000 films from

the first and about 32,000 from the last survey, in all about 53,000 films. In order to reduce the work load the task was divided equally between two readers. As there were 50 exposures per roll of X-ray film, 420 rolls from the first and 640 from the last survey had to be studied. One reader was given all the rolls with even serial numbers and the other the rolls with odd numbers. In order to avoid that any possible change in interpretation of the X-ray pictures on the part of the two readers during the period of studying the two series of films might introduce some bias, it was arranged that the two readers read alternately two rolls from the first and three rolls from the last survey. Subsequent analysis showed that both readers had been very consistent with themselves throughout the whole period of reading, although they differed considerably from each other.

Pulmonary pathology seen on the X-ray photographs was classified according to the code used by the Indian sample survey ('Tuberculosis in India', 1959). For the purpose of the present analysis all cases designated as 'Probably tuberculous, possibly active' and 'Probably tuberculous and probably active', irrespective of the extent of the lesions or presence of cavities, have been accepted as indication of pulmonary tuberculosis. The prevalence is based upon the average found by the two readers.

RESULTS

*Coverage.* In 1950-51, 64.3 per cent of all persons over 4 years of age were X-rayed. In 1957-58 the coverage was as high as 89.4 per cent. The coverage for males and females was almost the same—in 1950-51, 64.7 and 63.9 per cent and in 1957-58, 89.9 and 89.3 per cent respectively. The distribution of persons X-rayed according to age is shown in Fig. 1. In both surveys the coverage of males over 50 years was better than that of females at the same age.

\* From the Madanapalle Tuberculosis Research Unit, Indian Council of Medical Research. Paper read at the Eighteenth Tuberculosis and Chest Diseases Workers' Conference, Bangalore, January 1962.

TABLE I  
*Distribution of cases radiologically suggestive of probably or possibly active pulmonary tuberculosis according to readers, each reader having read half the material*

Age	Number X-rayed	MALES			Number X-rayed	FEMALES		
		Cases		X+Y Per 1000		Cases		X+Y Per 1000
		Reader X No.	Reader Y No.			Reader X No.	Reader Y No.	
I. SURVEY 1950-51								
5-9	2009	4	2	3.0	1862	12	3	8.1
10-	2859	4	2	2.1	2081	6	5	5.3
20-	1956	6	12	9.2	2165	7	3	4.6
30-	1683	11	10	12.5	1620	10	5	9.3
40-	1227	20	17	30.1	1077	9	4	12.1
50-	938	15	16	33.0	597	9	5	23.4
60+	628	20	17	58.0	273	5	3	29.3
II. SURVEY 1957-58								
5-9	2596	7	0	2.7	2487	3	0	1.2
10-	4615	10	3	2.8	3996	10	5	3.7
20-	2500	16	13	11.6	2534	15	7	8.7
30-	2500	25	14	15.6	2776	27	15	15.1
40-	1936	44	25	35.6	1653	22	7	17.5
50-	1428	41	36	53.9	1218	22	14	29.6
60+								

*Prevalence of tuberculosis in males.* The original finding of a close association between age and prevalence (Frimodt-Møller, 1960) was also found in the last survey. The prevalence was lowest in children, less than 3 per 1000, rose to 12 at 25 years, was 16 at 35 years, 36 at 45 years and reached 78 per 1000 in old people over 60 years (Table 1). The shape of the curve is very much the same as found previously (Fig. 2), but there is a difference in position corresponding to a higher prevalence in 1957-58 than in 1950-51. The difference is small and statistically insignificant, yet it is noted at all ages except in children below 10.

*Prevalence in females.* The observation made in 1950-51 that females had a much lower prevalence of tuberculosis than males is also confirmed by the last survey. This applies mainly to women over 35 years of age. Below the age of 35 the prevalence for men and women is almost the same but after the age of 35, the rate for women is nearly half that of men (Table 1). As for the difference between 1950-51 and 1957-58 we find some increase in prevalence in women over 20 but a decrease in

children and adolescents (Fig. 3). Whereas the increase is not statistically significant, the decrease in girls below the age of 10 years is significant.

*Difference between readers.* The results given above were based upon the average as obtained by the two readers. There was, however, some difference between the two. This is borne out by the graphs presented in Figures 4 and 5. These show the findings for males and females respectively according to each reader. In both graphs the prevalence for 1950-51 for each age group has been considered as 100, and the prevalence for 1957-58 has been calculated in relation to that of 1950-51. The difference between the two prevalences can, therefore, be read in percent directly from the graphs.

The two readers have been remarkably close in case of the females. Both found a decrease of more than 80 per cent in girls below 10 and an increase of almost the same extent in women at 20-29 years while at higher ages the increase is less pronounced. As mentioned earlier, it is only the decrease in girls below 10 years which is statistically significant.

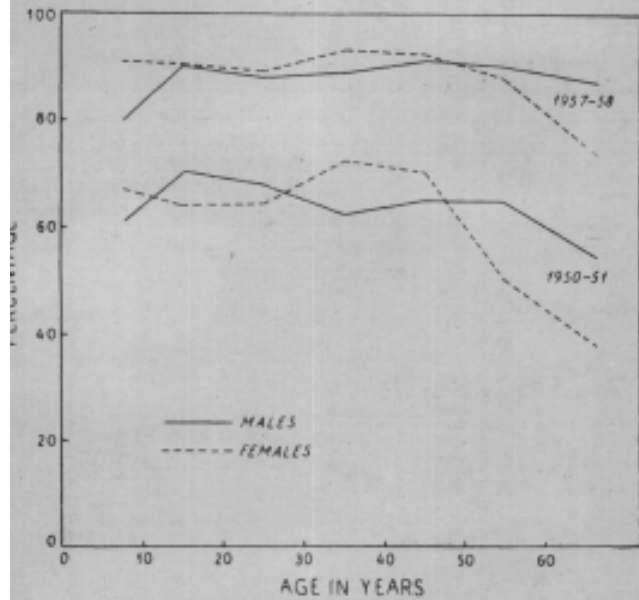


FIG. 1

Coverage by X-ray examination of the Madanapalle village population at the two surveys in 1950-51 and 1957-58 respectively.

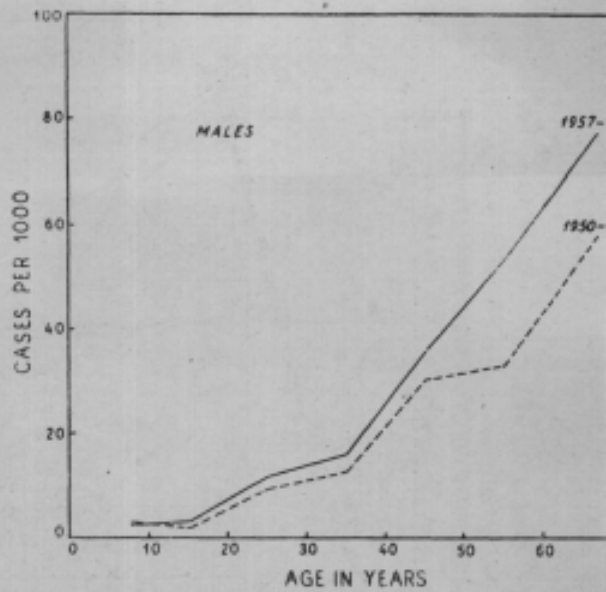


FIG. 2

Prevalence of tuberculosis in males according to cases classified as possibly or probably active on basis of mass miniature X-ray photographs.

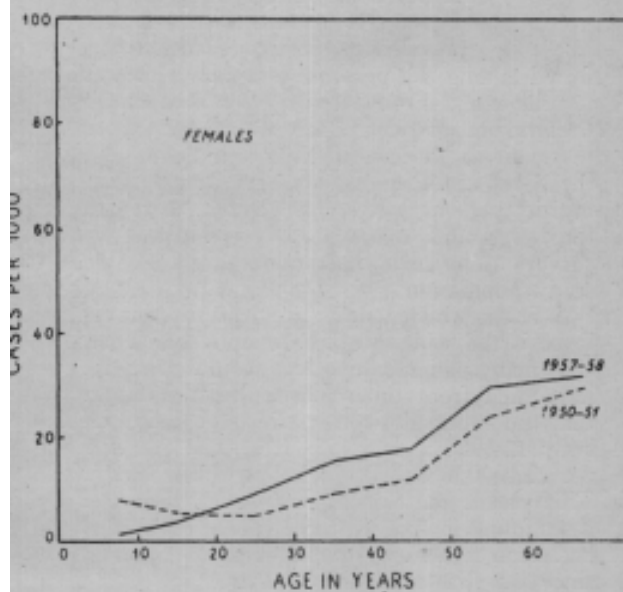


FIG. 3

Prevalence of tuberculosis in females according to cases classified as possibly or probably active on basis of mass miniature X-ray photographs.

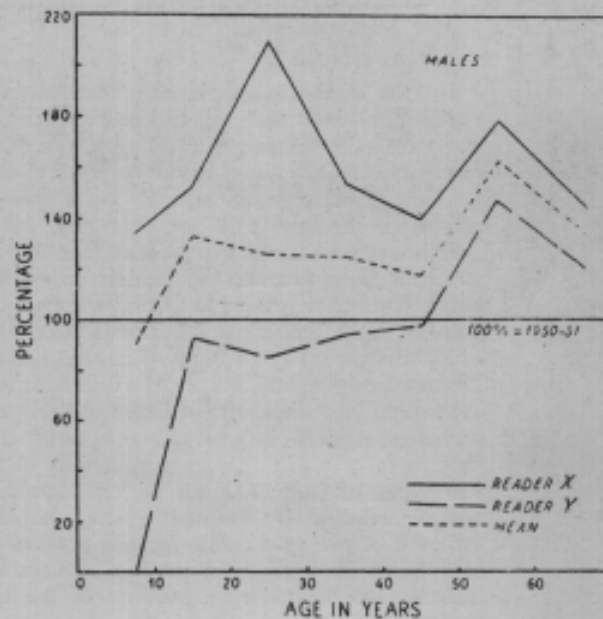


FIG. 4

The prevalence of tuberculosis in males at the 1957-58 survey in relation to that of the 1950-51 survey, the latter calculated as 100 for each age group and X-ray reader.

from which the relative prevalence could be compared. An estimate of the prevalence less open to personal vagaries would be findings based upon the bacteriological follow-up. This analysis has not yet been completed. However, there would be other difficulties such as difference in technique as well as in number of examinations made.

#### DISCUSSION

It is quite remarkable that in spite of a fairly intensive effort to control tuberculosis by all existing means during a period of seven years, it is not possible to demonstrate any obvious general decrease in the prevalence. What could be the reason for this?

In case of the males the two readers differ much more from each other. Reader X found an increase in prevalence at all ages whereas Y found a decrease in boys below 10 years, almost no change between 15 and 45 years and an increase in men above 50.

It is not possible at the present time to give an explanation why the two readers differed so much from each other, and why they should do so in case of males but not in case of females. Since the two materials read by the two readers are not likely to be inherently different from each other, the difference is likely to lie in the way the readers interpreted the films. As there is no way of judging the reliability of the two types of interpretation without applying another reading by a third reader, the best estimate of the prevalence for the purpose of comparing the findings of the two surveys has been to take the average findings of the two readers.

It has not been the purpose of the present analysis to estimate the absolute prevalence at the two surveys but only to provide a material

In 1950-51 about 36 per cent were absent from the X-ray examination, in 1957-58 only 11 per cent; perhaps a number of cases were missed in the first survey but picked up in the last. This might be true if the absentees represented a group of persons with a higher prevalence of tuberculosis than was found among the persons X-rayed. This was not the case. From the surveys subsequent to the first one in 1950-51 there was no evidence that patients with manifest tuberculosis evaded the X-ray examination in a higher degree than healthy persons. It seems justified to regard the two groups of persons X-rayed in the two surveys under review as random samples of the study population.

A factor which tends to increase the prevalence is the wide use of antibiotics which has kept many patients alive who would otherwise have died from tuberculosis. It was found that the tuberculosis mortality had decreased between 1950-51 and 1954 from well over 200 per 100,000 to only 21 (Frimodt-Moller, 1960). This means that among the X-ray abnormal cases found in 1957-58 there will be many who had been treated by ourselves in the interval since the first survey.

As the prevalence at the last survey is a result of various factors such as the survival of the cases which were present at the first survey plus fresh cases arising in the population

plus new ones who would have moved in, minus those who died or moved out, each of these groups would have to be studied carefully. The most important is the group of fresh cases occurring since 1950-51. Going over their records with respect to their status of tuberculin sensitivity at the initial Mantoux tests given, we find that over 80 per cent were already tuberculin positive when examined the first time. It is clear that this group which forms the great majority of cases contributing to the prevalence in 1957-58 has been unaffected by the result of our control measures as they were already infected before we began our present control project.

We must therefore look to those who were not yet infected in 1950-51, if we shall demonstrate a result of our control measures. It must therefore be mainly among the children. It is very significant that it is just in that group that we have been able to find a decrease in prevalence. Our observation that girls below the age of ten in 1957-58 had a significantly lower prevalence than girls of the same age in 1950-51 is a pointer that our efforts have not been without a result. Given a longer period of observation we may expect to find a reduction in prevalence among the older age groups, first in the group 10-19, then later on among those still older.

With the type of tuberculosis found in this population which is mainly characterized by its slow development from the time of primary infection till the first lesion is seen on the

X-ray film or clinical symptoms bring the patient to the clinic, it is necessary to have long periods of observation before it is possible to demonstrate the beneficial effect of a control programme.

#### SUMMARY

A South Indian village population of about 40,000 was examined by X-ray in 1950-51 at the start of an intensive tuberculosis control campaign. By comparing the prevalence of X-ray positive cases suggestive of active or probably active pulmonary tuberculosis as found by a new and independent reading of the 1950-51 films with that obtained by a survey done in 1957-58, children below the age of 10 showed a decrease whereas there was no change, or a small but statistically insignificant increase in the rest of the population. The absence of a decrease in the adults is ascribed to the result of keeping patients alive who would have died if they had not been treated with antibiotics and the fact that the great majority of fresh cases arising since 1950-51 were already infected with tubercle bacilli before the control campaign began.

#### ACKNOWLEDGEMENT

The assistance given by Dr P. Chandrasekhar, M.B., B.S., T.D.D. and Dr V. Emmanuel, M.B., B.S., T.D.D. in carrying out the comparative readings of the many X-ray films is gratefully acknowledged.

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## POST-VACCINATION ALLERGY ELEVEN YEARS AFTER BCG VACCINATION

J. FRIMODT-MOLLER, R. PARTHASARATHY AND PHILIP BENJAMIN

In South India the risk of being infected with tubercle bacilli is greatest at the age of 10 to 19 years. If BCG vaccination is given in the pre-school or during the first school years, the post-vaccination allergy should be maintained at a fairly high level for a period of up to 10 to 15 years. Is it possible that BCG-induced allergy can last that long? In Danish children BCG allergy has been maintained at a high level for 5 years (WHO Tub. Res. Office 1956). The two BCG assessment teams which carried out retests in India in 1954 and 1955 respectively found also BCG induced allergy at a moderate level in children vaccinated 4 years earlier (WHO Tub. Res. Office, 1955 and 1957). At Madanapalle, presence of BCG allergy could be demonstrated after an interval of 4 years (Frimodt-Moller, 1960). Kul Bushan (1960) examined between August 1955 and October 1958 the post-vaccination allergy in school children in 129 different localities throughout India. The interval between vaccination and retests ranged from 1J months to 3J years, the average being 13 months. The mean size of indurations during the first 6 months was 13.0mm., during the second half year 11.5mm., during the third half year 11.2 mm., during the fourth half year 12.8 mm., and after 2-3 J years 12.1 mm.

Our experience with BCG vaccination at Madanapalle dates back to 1948 when a high proportion of the town population was tuberculin tested and nearly all tuberculin negative persons vaccinated (Frimodt-Moller, 1949). In 1950 the village population of 37,000 within 10 miles of Madanapalle was submitted to a community-wide survey by tuberculin tests and X-ray.

The first place to be surveyed was Vayalpad, a small town of 5,500 inhabitants. During the summer of 1950 all persons reacting with less than 6 mm., to 1 and 10 TU were offered BCG vaccination. In 1961, i.e., 11 years later, a series of tuberculin tests was carried out in the Board High School at Vayalpad. Fifty-five per cent of the school children were found to have been vaccinated earlier, and many of these as far back as 1950. The present report describes the results of these retests.

### THE MATERIAL

The main purpose of the tuberculin testing of the school children at Vayalpad was to compare the effect of two different tuberculins: the new standard tuberculin, RT 23, issued since 1958 by the State Serum Institute, Copenhagen, and their former standard tuberculin, RT 19-20-21, which had been used all the previous years by the Madanapalle Tuberculosis Field Research Station. The RT 23 was given in doses of 1 TU with Tween 80 and the RT 19-20-21 in doses of 5 TU without Tween 80. The school children were tested simultaneously with both tuberculins, the sites on right and left arms being alternated from child to child. It was found that the RT 23 produced smaller reactions than the RT 19-20-21, particularly in the lower range of reaction sizes (Frimodt-Moller *et al*, 1961).

The findings given here relate only to the reactions following tests with RT 19-20-21.

There were 387 children in the five forms of the school. Their ages ranged from 9 to 22 years (92 per cent ranged between 11 and 18 years), the mean being 13.8 years. In 342 of the 387 children the tests were given and read (at 48 hours). The readings were done independently by three different readers without their knowing which tuberculin had been used at each site of reaction (the readings of the senior reader are given here).

The transverse diameter was measured on a transparent millimeter scale and dictated to an assistant. After the last reader had finished his readings the left shoulder was examined for presence of vaccination scars. The diameters of these in millimeters were also noted. Afterwards the cards with the names of the children and of their father, or guardian, their age and full address were matched against the files of index cards and household registers maintained at the office of the Research Unit.

It was found that 186 children belonged to the Madanapalle Survey Area whereas 156 children belonged to villages outside the Survey Area. Vayalpad lies in the periphery of the Madanapalle Survey Area, so many of the school children are drawn from the neighboring

Villages on that side of Vayalpad which has not been included in the Madanapalle Study Population. It was found that of 165 children showing BCG scars 74 belonged to the villages outside our Survey Area. They had been vaccinated, probably in 1956 or 1957, by the Andhra Government BCG Campaign team and not by ourselves. Three of these children had fresh scars after vaccination done by the Mass Campaign team four months earlier during its second tour of the area, but the rest had been vaccinated 4 or 5 years earlier.

Of the 186 children belonging to the Madanapalle Survey Area, individual records were found in 162 but could not be found in 24, owing to changes of address. The records of the 162 give detailed information of previous tuberculin tests, BCG vaccination and MM X-ray findings. It was found that 98 had been vaccinated by our own teams, 69 of these in 1950 and the rest during 1951-55. Of the 98 vaccinated, 76 showed BCG scars while 22 showed no scars (several had shown scars at the inspections one or two years after vaccination). Of 64 children known not to have been vaccinated none showed BCG scars. Thus 22 (or 22.5 per cent) of the vaccinated would not have been recognized as vaccinated had the records not been available; they would therefore have appeared among the children presumed not to have been vaccinated.

Of the 156 children belonging to villages outside our Survey Area, 74 showed typical BCG scars and 82 no scars. It must be assumed that some children previously vaccinated but showing no scars must be among the 82 presumed not to have been vaccinated. As these children had been vaccinated only 4-5 years earlier the proportion who had lost their scars might not be so high as found in the group vaccinated 10-11 years earlier.

#### RESULTS

Sixty-nine of the children tested in 1961 had been vaccinated in 1950. The frequency distribution of the diameter of their indurations is shown in Fig. 1. Ignoring some 20 per cent of the children showing reactions of less than 4 mm., the rest are grouped according to a normal distribution around a mode of 11 mm, or so. This suggests that the majority of the children vaccinated eleven years earlier possess a moderately high level of allergy. Whether all this can be ascribed to the BCG vaccination or can be due to other sources of tuberculin

sensitivity can be studied by comparing their reactions with those found in children who were not vaccinated.

In Fig. 2 the results in all the children belonging to the Madanapalle Survey Area have been shown. In the distribution shown in the upper part of the graph, besides the 69 vaccinated in 1950 another 29 who were vaccinated between 1951 and 1955 have been included, as well as 15 with BCG scars whose records could not be found. The mean interval between vaccination and retest for those for whom the date of vaccination is known was 10.6 years. The lower part of the graph shows the distribution of 73 persons of which 64 had not been vaccinated and 9 whose records could not be found but who showed no scars.

The findings in the non-vaccinated children show that their reactions can clearly be divided into two groups, one with reactions ranging from 10 to 26 mm., forming a normal distribution around a mode of 17 or 18 mm., and another with reactions ranging from 2 to 10 mm. Evidently, the group with large reactions represents children with a specific sensitivity caused by infection with tubercle bacilli while the other group with small reactions have a low degree of sensitivity which probably is caused not by tubercle bacilli but by some other type of bacilli. The non-vaccinated children show therefore a pattern of tuberculin sensitivity which is in conformity to what has been found many times before in many places of India and other tropical and semi-tropical areas.

The vaccinated have reactions which correspond to a level of allergy midway between the 'specific' and the 'non-specific' levels and is different from either two. It is, therefore, reasonable to ascribe this sensitivity to the allergy produced by the BCG vaccination. It can therefore be concluded that the effect of the vaccination ten to eleven years earlier is still in existence.

Before discussing whether other factors have modified the pattern on tuberculin sensitivity in the vaccinated group, the results obtained in the children from the villages outside the Madanapalle Survey Area may be studied. Fig. 3 shows the distribution of reactions in 74 children with typical scars and 82 without scars. As mentioned, these children had been vaccinated by the Government BCG vaccination team in the Mass Campaign in 1956-57,

TABLE I  
Results of 342 Mantoux Tests in Vayalpad Board High School, March 1961

Indurations to 5 TU in mm	Children from Madanapalle Survey Area						Children from villages outside the Survey Area	
	Vaccinated (98)		Not vaccinated (64)		No data (24)		Vaccination scars	
	Present	Absent	Present	Absent	Present	Absent	Present	Absent
0	6	4	.	14	3	2	9	18
1	.	.	.	3	.	.	1	4
2	4	2	.	11	1	.	6	12
3	7	1	.	2	3	1	9	8
4	1	1	.	6	1	.	3	4
5	5	2	.	3	.	.	5	4
6	1	.	.	.	.	1	5	1
7	6	2	.	3	.	.	5	2
8	7	2	.	1	1	.	6	.
9	2	1	.	1	1	.	4	2
10	3	.	.	.	1	.	4	.
11	5	1	.	.	1	1	1	2
12	3	2	.	3	1	.	2	3
13	6	.	.	.	.	.	4	3
14	4	.	.	1	.	.	3*	2
15	3	1	.	3	.	.	2*	1
16	4	1	.	2	.	.	2	1
17	3	2	.	3	.	1	1	6
18	1	.	.	2	.	1	1*	2
19	2	.	.	2	1	.	.	2
20	1	.	.	1	1	2	.	1
21	.	.	.	1	.	.	.	1
22	.	.	.	.	.	.	1	.
23	.	.	.	1	.	.	.	2
24	2	.	.	1	.	.	.	1(30 mm)
Total	76	22	0	64	15	9	74	82
	186						156	

One child in each group had been vaccinated only 4 months earlier.

i.e., only 4-5 years earlier. The pattern of reactions in both groups is very similar to that found in the children from the Survey Area just described. The children, presumably not vaccinated, have also two types of reactions—one with large reactions and another with small or no reactions. The vaccinated show reactions intermediary in size between the other two. Compared with the children belonging to the Madanapalle Survey Area the level of post-vaccination allergy seems to be very much of the same order—if anything, perhaps slightly lower. There does not appear to be any essential difference between the type of allergy produced by the vaccination done by the Madanapalle Research team and that produced

in the Mass Campaign. As the Madanapalle material is supported by previous data, it forms the basis for the further analysis.

#### DISCUSSION

In his report on retests done between 1955 and 1958 Kul Bhushan presents a diagram showing the frequency distribution of reactions in well over 18,000 school children. It shows a normal distribution with a mode around 13 mm. It differs from the present findings by showing very few children with really small reactions. His distribution for the children classified as 'positive' has a mode of about 19 mm. The reactions in the vaccinated are, therefore, in general about 6 mm. smaller than

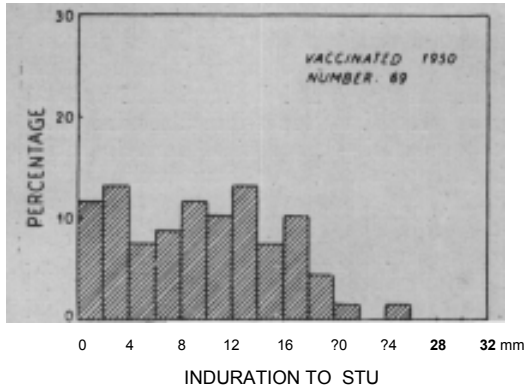


FIG. 1

1. Frequency distributions of diameters of indurations to 5 TU at retests in 1961 of children vaccinated in 1950.
2. Frequency distributions of diameters of indurations to 5 TU at retests in 1961 of children tested initially in 1950-55 by the Madanapalle Research Unit.
3. Frequency distributions of diameters of indurations to 5 TU at tuberculin tests in Vayalpad 1961 of children belonging to villages outside the Madanapalle Study Area. Previous vaccinations done by the Andhra Government BCG Mass Campaign Teams in 1956-57.
4. Hypothetical distributions of children vaccinated by the Madanapalle Research Unit 1950-55 according to size of their indurations to 5 TU at retests in 1961.

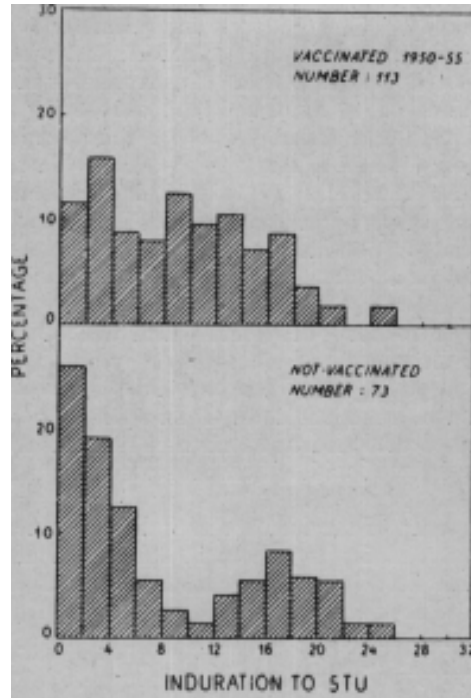


FIG. 2

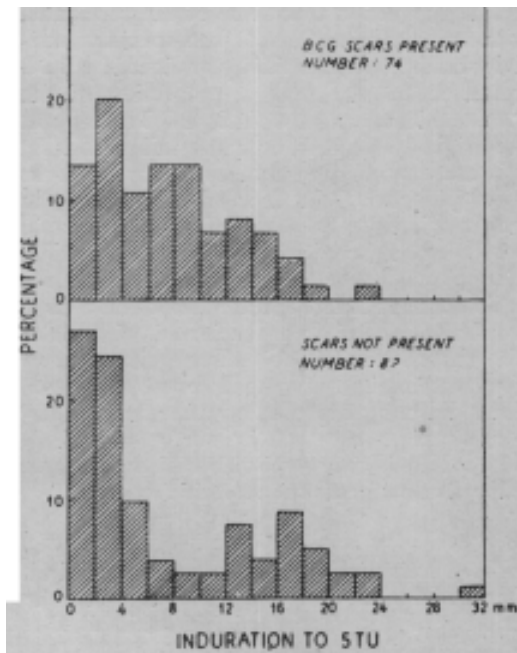


FIG. 3

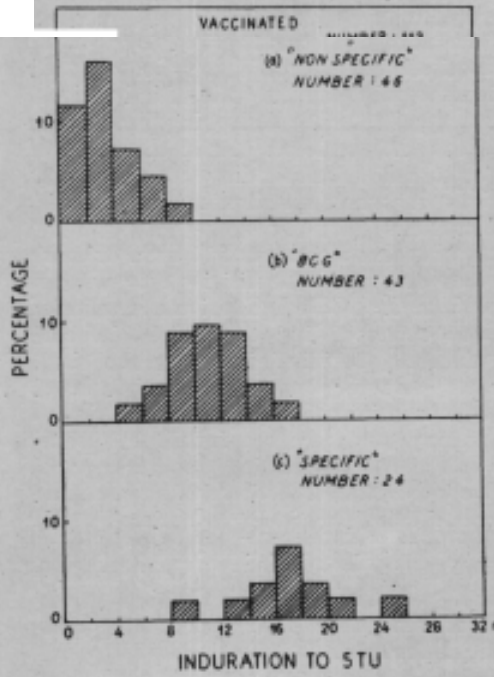


FIG. 4

those observed in the children with specific sensitivity. The corresponding diameter for the present material are 11 and 17 mm. with a difference of also 6 mm. The reason for the reactions in the Madanapalle material being a little smaller is probably due to a difference in reading between the two readers. There appears, however, to be a significant difference in the shape of the distributions in the two materials. Considering that Kul Bushan's retests took place much sooner after vaccination—in 72 per cent of his examinations within the first 12 months—than ours which were done after an interval of ten to eleven years, it is not surprising that there are differences. It would be strange if during such a long period some of the children in our material had not been infected with tubercle bacilli and some had lost some of their allergy by waning.

A study of the findings in India and other Asian countries as well as in Africa and the Middle East by the BCG assessment teams of the WHO Tuberculosis Research Office, Kul Bushan's and our own findings leads to the conclusion that the allergy induced by BCG vaccination in India is generally not so high as found in naturally infected persons. In terms of tuberculin reactions the BCG allergy is usually found midway between that obtained in naturally infected and that found in persons with 'non-specific' low-grade allergy. Each type of allergy is characterized by normal distributions, of tuberculin reactions placed at different points on the scale of indurations. There may be some overlapping but not so much that they coalesce. From the shape of the right tail corresponding to the larger reactions the whole distribution can often be reconstructed.

Assuming that reactions of 17 mm. or more represent the specific sensitivity only we can isolate from the BCG distribution a number of reactions corresponding to children infected with tubercle bacilli (Fig. 4, group *(c)*). Similarly, assuming that the new right hand tail of the remaining bulk of reactions is due to BCG allergy only, we can isolate the 'pure' BCG reactions by forming another normal distribution around a mode of 11 mm. Such a distribution is shown in Fig. 4 under *(b)*. We are now left with a third distribution of small reactions as shown under *(a)* in Fig. 4. They resemble very much the distribution among the unvaccinated (Fig. 2) attributed to the 'non-specific' allergy,

By this kind of reasoning it is not our aim to estimate the exact number of children possessing this or that sort of allergy, but to stress that the allergy found in vaccinated persons may be affected by super-infection with other types of bacilli—the classical tubercle bacilli which step up the degree of tuberculin sensitivity and the unknown bacilli responsible for 'non-specific' allergy. This 'non-specific' allergy may be found in persons who either never did acquire any allergy after BCG or if they did had lost it all, or most of it, so that they could get a low-grade allergy if subsequently infected with the unknown type of bacilli.

As for the incidence of children presumably infected with tubercle bacilli, it was found that among 64 non-vaccinated whose records are available 53 had been tuberculin tested when the vaccinated had their pre-vaccination test. Nine of the 53 showed large reactions at the initial test. Of the other 44 who would be classified as 'tuberculin-negative', 8 showed now large reactions, i.e., a conversion rate of 18 per cent. In comparison we have estimated above that about 24, or 21 per cent, of the vaccinated had acquired so high an allergy that it could be due to an infection with tubercle bacilli (group *(c)* in Fig. 4). It is therefore quite probable that the rate of infection has been about 20 per cent over a period of 10-11 years, or roughly 2 per cent per year.

The suggestion that some of the vaccinated with small reactions have a 'non-specific' sensitivity rather than a sensitivity produced by BCG would mean that only a proportion of the vaccinated still possess their BCG allergy at the original level. How many this would be, it is not easy to say—perhaps it may be about 60-70 per cent. The lack of BCG allergy in the remainder has been offset to a certain extent by the acquisition of the 'non-specific' allergy.

To sum up: There is little doubt that a large proportion of children vaccinated with BCG still possess their BCG allergy eleven years after vaccination. A small proportion who either did not get any allergy after the vaccination, or might have lost it later on, may have been infected with atypical bacilli which have induced a low-grade 'non-specific' allergy.

#### SUMMARY

Post-vaccination retests in school children after an interval of eleven years show that the majority of the vaccinated has maintained a

level of allergy comparable to that found one year after vaccination. It is possible that some of the children whose allergy has waned have been reinfected with atypical bacilli

setting up a low-grade, 'non-specific' sensitivity. Other children show levels of allergy suggesting - that they have been infected with tubercle bacilli setting up a high degree of allergy.

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## EXPERIENCE WITH A SINGLE-DAILY-DOSE OF ISONIAZID

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Since the introduction of Isoniazid as a successful antitubercular drug, the question of the dosage has been discussed in many papers. Doses from one to ten mg/kg. body weight have been recommended. Lately even thirty mg/kg. body weight have been given<sup>5</sup>, often with considerable side-effects. As pointed out by the Tuberculosis Chemotherapy Centre, Madras, in 1960<sup>18</sup>, Isoniazid is used in India as mass-therapy at an ever increasing rate, partly in combination with other anti-tubercular drugs, partly alone as it is, in the usual dosage, being the cheapest and the easiest in administration. Already in 1956<sup>11</sup> it was stated, that the resistance to a single drug (I.N.H., PAS, or STREPTOMYCIN) could be prevented for a long time by combining 2 drugs. In view of this fact it is not astonishing, that in India<sup>16</sup> and Africa 1960<sup>1</sup> the combination of I.N.H. and PAS, proved more satisfactory than I.N.H. alone in long trials, as resistance developed often with the latter therapy<sup>6,9</sup>. In this combination only relative small doses of I.N.H. were given (average 4-6 mg/kg. body weight) and the side-effects were minimal. In the other regimes where I.N.H. was given alone, the higher dosage (8-9.8 mg/kg. body weight) was more effective in controlling the disease, than the lower dosage (4-7.3 mg/kg. body weight). In an editorial of The Lancet 1961<sup>15</sup> it was emphasized that the single dose treatment of I.N.H. could have much attraction for the patient. If this regime is more effective than the multidosage regime, it would be advisable to accept it in all centres undertaking anti-tubercular mass treatment.

The unpleasant side-effects of I.N.H. are well known. The British Medical Journal published in 1958<sup>4</sup> an editorial 'The neurotoxic effect of Isoniazid', which ranges from twitching of muscles to convulsions and real encephalopathias<sup>5, 12, 14</sup>. Apart from these neurotoxic symptoms the gastro-intestinal side-effects of I.N.H. can be quite considerable: it may cause slight nausea, but also violent vomiting, diarrhoea, constipation, anorexia and polyphagia<sup>13, 17</sup>. All these symptoms have been described as

consequences of I.N.H. administration. It is not yet proved if the high doses of I.N.H. are responsible for these side-effects. Mitchell and Bell found 1957<sup>10</sup> that in each patient the serum-I.N.H.-level is different even when the same amount of the drug was administered. They proposed to do serum-I.N.H.-studies in each patient, a suggestion however impossible to carry out in practice. Rather strong side-effects of the one dose regime were described by the Madras Centre. The incidence of peripheral neuritis as consequence of I.N.H. administration was 18 per cent in the one-dose-regime, as compared with only 8 per cent when the same amount of I.N.H. was given in two daily doses<sup>8</sup>. The peripheral neuritis can start quite early during the treatment<sup>3</sup>, which we could confirm in our studies. These side-effects have a great importance in ambulant treatment of patients in underdeveloped areas. From the purely medical point of view the patients under constant medical supervision (for instance in a hospital) can be reassured about the harmlessness of a sudden complaint during the course of treatment. Whereas an ambulant patient spends a long time thinking of a new symptom without having occasion to complain to the nurse or the doctor. He can be reassured only during his next visit to the ambulant centre. In this respect the psychological side-effects of I.N.H. have a special importance. Mental depressions, psychotic episodes, other emotional states<sup>2, 7</sup> etc., which have been described will put such patients easily into a panic and induce them to stop any kind of treatment. But even if patients with mild objective side-effects of the drug like vertigo, nausea, difficulty in urination<sup>13</sup> have no occasion to talk to the doctor, there is always the danger that they will stop the treatment if they think that the present complaint is caused by one of the medicines. Everybody who has done mass treatment in underdeveloped countries knows that there is always the danger that the patients disappear and under these circumstances the treatment cannot be completed until the disease is controlled. In cities like Bombay these patients

go to their native places and cannot be traced any more. The patient is much more likely to stop the treatment if he notices any kind of discomfort, which he attributes to the medicine.

This study has been conducted to find out, if our routine administration of Isoniazid in a daily dose of 300 mg. (divided in 3 daily doses) per adult is inferior to the dose of 400 mg. (given in one daily dose) per adult as suggested by the Tuberculosis Chemotherapy Centre, Madras.<sup>16</sup>

The treatment in our centres is ambulatory. Most of the patients are long-standing cases, and are under our treatment for many months or even years. The standard treatment, consisting of STREPTOMYCIN injections (from 1-6 injections per week), PAS 6-8 gr. (given in 3-4 doses daily) and I.N.H. (daily 3 doses 100 mg. each) is carried out, until the condition of the patient allows to reduce the dose of STREPTOMYCIN, or to discard it completely. PAS is usually given in connection with I.N.H. for a still longer time, until finally PAS is discarded, and the patient finishes the treatment with I.N.H. alone. In exudative cases we add PREDNISOLONE for short periods. Control of the weight, Erythrocytes Sedimentation Rate and Sputum tests, are done at regular intervals. Full size radiographs are taken every 3-4 months, unless there are special circumstances requiring additional X-rays.

*Social Factors:* Our patients are all of the lowest income group. Very often the earning member of the family is ill and forced to go on working during the whole treatment time. Most of the patients are labourers, coolies, construction workers, fishermen, hawkers, all doing hard physical work. The women have mostly housework to do, an average of 3-6 children to look after, and many of them go out of the home for different kind of work to earn money to be able to feed the family. It is not possible to be sure, if a patient takes rest or works, as this depends very often on the offer of work for a few days, and the momentary need to earn more. Every patient gets fortnightly a supply of milk powder, and rice or wheat and cereals. The patients come to our different centres for injections, supply of tablets, additional food and vitamin supply.

Nearly all of the cases in this study are pulmonary tuberculosis cases but a few extrapulmonary cases have been included.

At the beginning of our trial we had 54 cases on the one dose (400 mg. I.N.H.) regime, compared with 53 cases on the three doses (100 mg. each dose) regime.

The body weight of these patients was from 28.3 kg.-49 kg. (62 lb.-108 lb.) with an average of 36.8 kg. The I.N.H. given was in the one dose (400 mg.) group 8.1 to 12.2 mg/kg. body weight and in the three doses (300 mg.) group 6.1 to 10.5 mg/kg. body weight. The average doses are nearly the same in both groups and the minor difference is not likely to influence the result. The age of patients in the one dose group (400 mg.) was from 16-64 years, with an average of 28.7 years, in the three doses group (300 mg.) from 18-58 years with an average of 26.8 years. Not included in the average weight and daily dose are the 2 children (one aged 8 years in the one dose group, one aged 10 years in the three doses group). The child in the one dose group got 200 mg. I.N.H.; the one in the three doses group 150 mg. I.N.H. daily (in 3 doses of 50 mg. each), 6.6 mg. and 4.3 mg/kg. body weight respectively.

The different forms of tuberculosis are listed in Table I, the number of each form of the disease in both groups is nearly the same.

We have tried to match similar patients, case per case in the one dose (400 mg.) group and in the three doses (300 mg.) group. If one of the matched cases dropped out, we cancelled the pair from the trial. As the number of patients would have been reduced too much in this manner, we decided, after the trial was finished, to take the cases for each group together. We got thus approximately the same number of cases in each group. The anti-tubercular treatment besides the I.N.H., consisting in STREPTOMYCIN, PAS AND PREDNISOLONE was carried out without interruption during this I.N.H. trial. Table II.

*The duration of the trial:* At the beginning we had decided to run the experiment for 3 months without interruption. Already during the first 2 weeks the complaints about the side-effects in the one dose (400 mg.) group were more and more pronounced every time we saw these patients in the centre. The mode of treatment had to be changed, otherwise these patients would have stopped the treatment on their own. Therefore we abandoned the trial in the one dose (400 mg.) group in eight patients after 3-4 weeks, most of them went on for 6

TABLE I

Treatment	No.	Sex		Bi-Lateral	Uni-lateral	Infiltration without Cavities	Infiltration with Cavities	Exudative pleurisy	Tb-adenitis	Bone-Tb	Haemoptysis	Positive sputum
		M	F									
<i>One dose</i> (400 mg. I.N.H.)	54	31	23	39	14	31	20	4	1		3	9
<i>Three doses</i> (300 mg. I.N.H.)	53	29	24 e	40	11	24 ng of	26	4	1	1	3	9

TABLE II

Treatment	No.	Streptomycin	Pas	Predni-solone
<i>One dose</i> (400 mg. I.N.H.)	54	49	52	5
<i>Three doses</i> (300 mg. I.N.H.)	53	47	51	5
Treatment besides isoniazid.				

TABLE III

Treatment	No.	3-4 weeks	6 weeks	8 weeks	Stopped on his own	Remaining for assessment
<i>Owe dose</i> (400 mg. I.N.H.)	54	7	37	5	5	49
<i>Three doses</i> (300 mg. I.N.H.)	53	6	29	16	2	50

Duration of the trial.

weeks, and 18 of these patients completed 2 months. As mentioned above, we cancelled in the beginning of the trial always the pair of patients, if one had changed to another kind of treatment. Therefore the number of cases in both groups remained practically equal. Table III.

*Self administration:* No objective control of medicine taking was possible in our centres. Urine examinations, pill-counting, surprise visits at the home of the patient cannot be carried out in our organisation due to shortage of staff. But, as each patient is well known to at least one member of the staff, (mostly the centre supervisor) we are in almost all cases sure, that the medicine has been taken, if the patient says so. Our patients receive only 3-4 days supply of oral medicines to be taken at home and they have to come to the centre for new supply even if they do not come for injection. Since a few months we give to

many of our patients once or twice weekly a Vitamin injection, so that they have to come to the centre, even if they are taking oral anti-tubercular treatment. As we will see later on in this report, patients on the one dose (400 mg.) I.N.H. regime complained nearly from the beginning of the treatment and we could be fairly sure, that they had taken the big 400 mg. tablet of I.N.H.

*Changes during the trial:* We started this study with 110 cases, 55 in the one dose (400 mg.) group, 55 in the three doses (300 mg.) group. This number of cases could not be assessed for the result, as eight cases stopped the treatment on their own, six threatened to do so, if the treatment was not changed and two went to hospital on account of deterioration of the disease. Therefore only 49 cases in the one dose (400 mg.) group could be compared with 50 cases in the three doses (300 mg.) group. The results are shown in Table IV.

TABLE IV

Treatment	Results at the end of the trial.													
	No.	Weight up	Weight down	Weight same	Weight not done	E.S.R. up	E.S.R. down	E.S.R. same	E.S.R. not done	X-ray improved	X-ray same	X-ray deteriorated	X-ray not done	
One dose (400 mg. I.N.H.)	49	21 42.8%	19 38.7%	4 8.2%	5 10.2%	22 44.9%	16 32.6%	4 8.2%	7 14.3%	16 32.6%	21 42.8%	5 10.2%	7 14.3%	
Three doses (300 mg. I.N.H.)	50	24 48%	13 26%	8 16%	5 10%	18 36%	18 36%	8 16%	6 12%	22 44%	12 24%	2 4%	14 28%	

Results at the end of the trial.

Weight could not be taken (before or after treatment) of patients who were too ill to come to the centre. (10 per cent in each group). E.S.R. was not taken in cases of pregnancy, of the two children or if there were technical difficulties (14 per cent resp. 12 per cent). X-rays were not taken immediately before the trial or after the trial in 14 per cent in the one dose (400 mg.) group and in 28 per cent of the three doses (300 mg.) group. We do not think that these differences have any bearing on the over-all result.

The therapeutic results in both groups were approximately the same.

#### Weight

1 dose (400 mg.) group: Increased: 42.8 per cent, Stationary: 8.2 per cent, and Decreased: 38.7 per cent.

3 dose (300 mg.) group: Increased: 48 per cent, Stationary: 16 per cent, and Decreased: 25 per cent.

#### E.S.R.

1 dose (400 mg.) group: Increased: 44.9 per cent, Stationary: 8.2 per cent, and Decreased: 32.6 per cent.

3 dose (300 mg.) group: Increased: 36 per cent, Stationary: 16 per cent, and Decreased: 36 per cent.

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#### X-ray

1 dose (400 mg.) group: Improved: 32.6 per cent, No change: 42.8 per cent, and Deteriorated: 10.8 per cent.

3 dose (300 mg.) group: Improved: 44 per cent, No change: 24 per cent, and Deteriorated: 4 per cent.

*Sputum Conversion:* There were 9 cases with positive sputum findings in each group at the beginning. After the trial 2 in the one dose (400 mg.) group, and 3 in the three doses (300 mg.) group were negative, the rest (i.e. 7 in the one dose, and 6 in the three doses group) were still positive. (These figures are too small to be conclusive).

*Haemoptysis:* At the beginning of the trial 3 patients in each group had had an haemoptysis not longer than one week before the beginning of the trial. All cases recovered but one, in the three doses (300 mg.) group, who had a serious re-occurrence of the haemoptysis and was sent to a hospital, shortly after the beginning of the trial and was therefore cancelled for the assessment.

Concluding we can therefore state that there are no clinical or radiological significant differences in the results between the one dose (400 mg.) group and the three doses (300 mg.) group.

TABLE V

Treatment	No.	Mild complaints	Considerable side-effects
One dose (400 mg. I.N.H.)	49	30	17
Three doses (300 mg. I.N.H.)	50	20	3

Complaints and side-effects during the trial.

In our experience however the most important difference between the two groups is the considerable side-effects of the I.N.H. dose, given once daily as compared to the three times daily regime.

In the classification (Table V) all complaints of the patients which did *not* force us to change the medication, are considered as mild complaints. Complaints and side-effects, for which we had to change the chemotherapy are listed as considerable side-effects. Included in this category are all patients who had stopped their treatment on their own. In most cases this happened, because the patient felt some subjective discomfort which he attributed to the treatment. Actually nearly all cases complained to us on the day before disappearing.

#### *We had*

In the one dose (400 mg.) group: 31.4 per cent cases with considerable side-effects.

In the three doses (300 mg.) group: 5.6 per cent cases with considerable side-effects.

In the one dose (400 mg.) group: 55.5 per cent cases with mild complaints.

In the three doses (300 mg.) group: 37.5 per cent cases with mild complaints.

In our opinion there is no doubt, that in the one dose (400 mg.) group patient's complaints occur much more frequently. The considerable side-effects which are the important ones for the treating physician are nearly 6 times higher in the one dose (400 mg.) group.

In Table VI we have listed the different complaints we have heard from the patients and the side-effects noted by us. Only patients from the one dose (400 mg.) group have been

TABLE VI

Stopped on their own	Giddiness	Urinary trouble	General malaise	Peripheral neuritis	Nausea and intestinal complaints
5	15	12	6	1	8

Complaints and side-effects in the one dose (400 mg.) group.

included without distinction of mild complaints or considerable side-effects.

There were 47 cases (from 54) who had some or the other complaint. 5 patients stopped the treatment on their own in this group (compared with only 2 patients in the three doses group). The urinary trouble consisted in difficulty in starting micturation<sup>13</sup> without any pathological findings in urine examination. In most of these cases this complaint could be eliminated with more liquid-intake, Coconut or Barley water administration, and only in two cases, we had to change the treatment. The one case of peripheral neuritis occurred in the 4th week of the trial. The clinical picture was exactly as described by the Madras Centre<sup>8</sup>, Paraesthesia, burning sensation, tenderness of calf-muscles, as subjective complaints. As regards objective findings: muscular weakness, loss of knee and ankle reflexes and loss of position sense but no foot drop. The I.N.H. administration was stopped immediately and daily an injection of 200 mg. B6 was given. The recovery was very slow and even today, after 3 months the patient still complains of paraesthesias. We continue now with Vitamin B complex injections three times per week.

As we stopped the trial after a relatively short time, we did not encounter more cases of peripheral neuritis. But even this one (statistically insignificant) case is a handicap for ambulatory treatment specially in under-developed areas. It was extremely difficult for us to continue any kind of treatment in this patient and also the contacts of this case had to be persuaded with difficulty to continue their treatment and examinations. From the psychological point of view also the others partly minor complaints are very important. If one of our patients has only the faint suspicion, that his discomfort is caused by any of the administered

medicines he or she stops taking this medicine. We tried to persuade the patient to go on with the treatment, but in many cases without success.- In this respect, even the harmless micturation trouble, which usually responds well to increased fluid-intake, has importance. This complaint is often not even mentioned to the physician, specially by the female patient, but it is uncomfortable enough to induce the patient to discontinue the treatment. We could ascertain in over 50 per cent of the patients, who stopped the treatment on their own, that they did so on account of micturation difficulties. The other listed complaints, like giddiness, general weakness, nausea and intestinal irregularities are definitely not in all cases due to the one dose treatment with I.N.H. they may have been caused by STREPTOMYCIN, PAS or not at all by any of the administered drugs.

## SUMMARY

I. 107 patients, under ambulant treatment for Tuberculosis (mostly pulmonary) were subjected to 2 different regimes of Isoniazid administration.

- (a) 54 patients were given 400 mg. of I.N.H. in a single daily dose.
- (b) 53 patients were given 300 mg. of I.N.H. in three daily doses of 100 mg. each.

II. All patients continued with their anti-tuberculous treatment besides the I.N.H. i.e., STREPTOMYCIN, PAS, PREDNISOLONE (one, two or all three of these drugs).

III. The clinical results of both groups could only be assessed for 49 patients of the one dose (400 mg.) group, and 50 patients of three doses (300 mg.) group, due to change of treatment. There was no significant difference in the results of both groups, but definitely no better results in the one dose (400 mg.) group.

IV. The side-effects of the one dose (400 mg.) group were so high, that in many cases the treatment had to be changed, and a considerable number of patients refused to continue this treatment further.

V. There was one case of serious peripheral neuritis after 4 weeks of 400 mg. I.N.H. in a single dose.

VI. The single daily dose treatment of Isoniazid administration is in our opinion not advisable for ambulant anti-tubercular treatment in underdeveloped areas, as the frequent disturbing side-effects induce the patient to carry out the treatment insufficiently or to stop it altogether.

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# TREATMENT OF CHRONIC NON-CO-OPERATIVE PATIENTS WITH ISONICOTINIC HYDRAZIDE p-AMINOSALICYLATE

## A Co-operative Study by the Tuberculosis Institutions\* in Delhi

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In the absence of organized case-finding programmes, a large number of patients reporting at the TB Clinics are found to be fairly advanced at the initial visit. Many of such advanced cases fail to achieve quiescence in spite of regular treatment with the 3 standard antimicrobial drugs viz., Streptomycin, INH and PAS. Surgery may not be possible or they may refuse surgical treatment when advised. There is still another class of patients who in spite of repeated advice, take treatment irregularly and interruptedly. The result is that every clinic has got on its hands a considerable number of such chronic patients with fairly extensive disease; and even though sensitivity tests are not carried out, clinically at least they have ceased to show any improvement with the available standard drugs. Almost all of them are infectious.

From time to time, manufacturing concerns put on the market new preparations for the treatment of TB patients. Claims are often made that these preparations are effective even when the bacterial resistance to the standard drugs has emerged. Isonicotinic Hydrazide p-Aminosalicylate (hereinafter called the new salt) is one such preparation and sufficient quantity of this salt was offered to us by two manufacturing concerns! for trial on such cases.

A co-operative trial was planned and five Tuberculosis Institutions\* in Delhi agreed to join.

Criteria for the selection of cases and other relevant procedures like randomization and issue of drugs etc., were decided at a joint meeting of the Chiefs of all the institutions who continued to meet periodically to discuss and co-ordinate the progress of the trial.

The following drug schedules were decided:

Drug Schedule	A—INH 100 gm. twice a day
„ „	B—Pasinht† 5 tablets twice a day† (500 mgm. daily)
„ „	C—Isopart† 3 tablets twice a day (600 mgm. daily)
„ „	D—Calcium Lactate 1 tablet twice a day (Placebo)

It was decided that drugs B, C and D would be issued from one central place—New Delhi Tuberculosis Centre—to each unit according to requirements and the patients in each co-ordinating unit would be serially allocated to the four schedules i.e., first patient selected for the study to be allocated to Drug Schedule A, second to Drug Schedule B, third to Drug Schedule C, fourth to Drug Schedule D, and fifth to Drug Schedule A again and so on. It was also decided that special steps like frequent visits by the Health Visitors, counting of tablets, urine examination for PAS etc., should be taken to ensure regularity and co-operation as far as possible and to prevent patients dropping off from the study. The trial was started in October 1957 and terminated in March 1959. Skiagrams and sputum examinations were carried out at three monthly intervals.

Some of the institutions did not have facilities for culture of sputum or laryngeal swab. The Director, Vallabhbai Patel Chest Institute was requested to afford culture facilities to the Silver Jubilee TB Hospital and the Municipal

\* 1. Silver Jubilee TB Hospital (Dr P. U. Rao). 2. TB Hospital, Mehrauli Road (Dr H. B. Dingley). 3. R.K. Mission TB Clinic (Dr I. B. Majumdar). 4. Municipal TB Clinic (Dr M. M. Singh). 5. New Delhi Tuberculosis Centre (Dr B. K. Sikand).

† Isopar from Messrs Cadilla Laboratories and Pasinh from Messrs Zandu Pharmaceutical Works Ltd., Bombay.

J Proprietary names of the new salt,

TB Clinic, and the Director, New Delhi Tuberculosis Centre to arrange for culture of patients from R.K. Mission TB Clinic. The former arrangement, however, did not work satisfactorily and the results of sputum conversion from Silver Jubilee TB Hospital and Municipal TB Clinic, therefore, are based on Direct Smear examination of sputum only.

A scheme for resistance studies against the drugs to be tried was worked out by the bacteriologists of the Vallabhbhai Patel Chest Institute, TB Hospital, Mehrauli and New Delhi Tuberculosis Centre. The routine sensitivity tests were carried out against the standard antimicrobials and the new salt whenever a culture was found positive. The following strengths were used:

Pasinh & Isopar	1, 2&5 $\mu$ per ml
INH	2 $\mu$ per ml 5 p, per ml
PAS	5 $\mu$ per ml
Streptomycin	

Strains were judged as resistant to a concentration, if the growth in that particular tube equalled or exceeded the growth in the control tube. Equal growth in the tube with 2 $\mu$  per ml of the new salt was taken to indicate definite resistance (Clegg, 1955).

Initial and last X-rays of all patients included in the study were read centrally by a panel consisting of Doctors B. K. Sikand, H. B. Dingley and M. M. Singh and their reading was taken as final.

The results were compiled centrally by the author of this report with the help of Mr. G. P. Mathur, Statistical Officer of the New Delhi Tuberculosis Centre.

*Material.* A total of 231 cases were included in the trial and the sources of these cases are shown below:

New Delhi Tuberculosis Centre R.K.	86
Mission Tuberculosis Clinic Mehrauli	60
TB Hospital Municipal TB Clinic	39
Silver Jubilee TB Hospital	26
	20
Total	231

All patients from New Delhi Tuberculosis Centre, R.K. Mission TB Clinic and Municipal TB Clinic were treated as out-patients while in the other two institutions, some were indoor patients and some out-patients. The results

however did not differ with the place of treatment and all cases, whether in-patients or out-patients have been considered together.

Of the total 231 cases, 175 were considered unsuitable for surgery and the remaining 56 had refused surgery. As the results of both the sub-groups were more or less similar, they have been combined. Out of these 231 patients, 200 or nearly 87 percent patients took treatment for six months or more and the reasons for the remaining 31 not completing 6 months' treatment are given below:

Study terminated	7
Died	5
Stopped treatment against advice	13
Left Locality	2
Admitted to other Hospitals	2
Treatment changed because of complications	2

The background data for the 200 cases whose results are being reported is given in Table 1. It may be pointed out that 31 patients were negative by culture and another 7 were negative by direct smear (culture not available). In every one of these cases, one or more sputum examinations had however been positive earlier.

Treatment was, by and large, regular and the percentage of non-co-operators in spite of absence of clinical improvement was lower than the usual figure obtaining in routine domiciliary treatment. Urine examination for PAS was not possible as a routine measure but whenever done, it indicated a fair degree of regularity in the taking of drugs.

*Results.* Results of 200 patients who completed at least 6 months treatment are given below. Of these, 133 completed the stipulated 12 months' treatment and the remaining 67 stopped treatment at some period between 6 and 12 months. As continuation of the drug beyond six months did not materially affect the results, these have been analysed irrespective of the length of treatment, provided it was more than 6 months. The results have been analysed in respect of sputum conversion, cavity closure, radiological change and changes in weight in all cases and shown in Tables 2 to 7 respectively. It would be seen that there are no statistically significant differences in the results of the various schedules. The rate of cavity closure and of radiological improvement was practically negligible in all the schedules.

TABLE I  
Background Information on Cases included in the Trial who completed  
at least 6 months' Treatment

		Drug Schedule								Total	
		A		B		C		D			
		No.	%	No.	%	No.	%	No.	%	No.	%
Sex Distribution	Males	33	62.3	38	67.9	29	61.7	33	75.0	133	66.5
	Females	20	37.7	18	32.1	18	38.3	11	25.0	67	33.5
Age Distribution	Under 15 years ...	1	1.9		0.0		0.0		0.0	1	0.5
	15-34 years	24	45.3	24	42.9	24	51.1	19	43.2	91	45.5
	35-44 years	15	28.3	17	30.4	11	23.4	12	27.3	55	27.5
	45 years and over...	13	24.5	15	26.8	12	25.5	13	29.5	53	26.5
Length of Treatment	6-8 months	158	28.3	7	12.5	4	8.5	8	18.2	34	17.0
	9-11 months		15.1	10	17.9	8	17.0	7	15.9	33	16.5
	12 months	30	56.6	39	69.6	35	74.5	29	65.9	133	66.5
Total		53	100.0	56	100.0	47	100.0	44	100.0	200	100.0

There were 16 deaths, after six months' treatment and these were almost evenly distributed amongst various schedules viz., 4, 6, 3, 3 in Schedules A, B, C and D respectively.

Table 8 shows the pre-treatment sensitivity

results of 130 patients, where these tests were possible. At the end of treatment, two of the 15 patients showing initial resistance became negative and the resistance pattern in the remaining 13 was practically unchanged. Further, out of the 52 patients whose culture was

TABLE II

Latest sputum conversion among patients completing at least 6 months' treatment (where culture examination was possible)

Schedule	Number sputum positive at start	Converted at last observation	
		Number	Per cent
A	29	4	13.8
B	38	9	23.7
C	36	8	22.2
D	29	5	17.2
Total	132	26	20.0

TABLE II (a)

Latest known sputum conversion results among patients completing at least 6 months' treatment (where only sputum D.S. examination was possible)

Schedule	Number sputum positive at start	Converted at last observation	
		Number	Per cent
A	10	1	10.0
B	9	1	11.1
C	4	...	...
D	5	...	...
Total	28*	2	7.0

\* Excluding 2 cases whose sputum status at end of six months could not be ascertained.

TABLE III

Sputum reversion among patients completing at least 6 months' treatment (where culture examination was possible)

Schedule	Number Sputum Negative at start	Number reverted at last observation	
		Number	Per cent
A	11	1	9.1
B	6	...	
C	5	1	20.0
D	9	1	11.1
Total	31	3	9.7

TABLE III (a)

Sputum reversion among patients completing at least 6 months' treatment (where only sputum D.S. examination was possible)

Schedule	Number Sputum Negative at start	Number reverted at last observation
A	2	
B	2	...
C	1	1
D	1	1
Total	6*	2

\* Excluding 1 case whose sputum status at end of six months could not be ascertained.

TABLE IV

Cavity closure among patients completing at least 6 months' treatment

Schedule	Cavitory cases at start	Cavity/cavities closed at last observation	
		Number	Per cent
A	41	2	4.9
B	48	4	8.3
C	38	4	10.5
D	35	4	11.4
Total	162*	14	8.6

\* Excluding 9 cases whose skiagrams at end of 6 months' treatment were not available.

sensitive to all drugs at start of trial (Table IX), 32 subsequently showed resistance during the course of treatment. It may, however, be pointed out that 9 out of these 25 resistant cases, (records of 7 cases were incomplete in this respect) had shown resistant bacilli some time prior to inclusion in the trial.

#### DISCUSSIONS

It has been claimed that this new salt has *in vitro* and *in vivo* anti-tuberculosis activity

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TABLE V

Cavitory worsenings among patients completing at least 6 months' treatment

Schedule	Cases with no cavitation at start	Cavitory cases at last observation	
		Number	Per cent
A	7	1	14.3
B	6	1	16.7
C	8	4	50.0
D	8	5	62.5
Total	29	11	37.9

which is independent of its I.N.H. and PAS constituents; it is active against bacilli resistant to I.N.H. and PAS and bacillary resistance to I.N.H. and PAS is unlikely to emerge as a result of treatment with this salt. Several Continental workers (quoted by Williams *et al.*, 1958) reported favourable results in 1953-55. Clegg (1955) corroborated the favourable results, using 'Dipasic' brand of the salt. Subsequent English workers (Walker *et al.*, 1957, Cuthbert *et al.*, 1958 and Williams *et al.*, 1958) however,

TABLE VI  
Latest known radiological changes among patients completing at least 6 months' treatment

Schedule	Total cases	Last known Radiological Status					
		Better		No change		Worse	
		No.	%	No.	%	No.	%
A	48	1	2.1	42	87.5	5	10.4
B	54	4	7.4	43	79.6	7	13.0
C	46	1	2.2	39	84.8	6	13.0
D	43		0.0	39	90.7	4	9.3
Total	191*	6	3.1	163	85.3	22	11.5

\* Skiagrams at end of 6" months' treatment were not available for 9 patients.

TABLE VII  
Weight changes among patients completing at least 6 months' treatment

Schedule	Total cases	Weight changes at end of treatment					
		Increase 5lb.		No change ±5 lb.		Decrease over 5 lb.	
		No.	%	No.	%	No.	%
A	52	4	7.7	36	69.2	12	23.1
B	54	11	20.4	31	57.4	12	22.2
C	45	6	13.3	28	62.2	11	24.4
D	44	8	18.2	21	47.7	15	34.1
Total	195*	29	14.9	116	59.5	50	25.6

\* Weight records were not available for 5 persons.

failed to confirm the conclusions of Clegg and other Continental workers. Trying the 'Dipasic' brand on chronic cases, almost similar to our material and using nearly the same dosage, English workers could not substantiate any of the above claims for the new salt.

It may be argued that the type of cases selected for this trial precluded any possibility of improvement. Allen *et al* (1957) did in fact report cavity closure in 4 out of 9 patients and sputum conversion in 9 out of 17 after 6 months of treatment, of not so advanced cases

but the authors themselves concluded 'that its *in vivo* action is just like that of I.N.H.'. Our study would tend to prove that whatever its intrinsic activity, *in vitro* and *in vivo*, this salt is not in any way superior to I.N.H. and there would seem hardly any justification for using it in early cases.

The sensitivity tests were not available for all the cases as stated earlier; but since these cases in respect of other criteria did not behave differently from those, where sensitivity tests were not possible, it may be assumed that if

TABLE VIII  
Results of Sensitivity Studies at start of Trial

Drug Schedule	Total Cases in N.D.TB. Centre and R. K. Clinic completing six months' treatment	Culture Negative at start of trial	Sensitive to all drugs at start of trial	Initially Resistant to at least one drug	Initial Resistance to Individual Drugs			
					Isopar	Pasinh	INK	SM
A	32	19	13	...	...		...	
B	37	13	18	6	1	2	4	4
C	31	14	11	6	1	1	4	6
D	30	17	10	3	1	1	2	3
Total	130	63	52	15	3	4	10	13

TABLE IX

Results of Subsequent Sensitivity Studies among cases Culture Negative or Sensitive to all drugs at start of Trial

Drug Schedule	Initially Sensitive or Culture Negative			Resistant to at least one drug during Treatment	Resistance to individual Drugs			
	Culture Negative	Sensitive	Total		Isopar	Pasinh	INH	SM
A	19	13	32	11	3	2	6	2
B	13	18	31	10	4	4	7	4
C	14	11	25	7	3	3	5	5
D	17	10	27	4	1	2	4	2
Total ...	63	52	115	32	11	11	22	13

sensitivity tests were possible for all the cases, the results would not have been any different. The results would tend to show:

- (a) The new salt has no action on bacilli resistant to I.N.H.,
- (b) Resistance to the salt develops fairly quickly,
- (c) Patients treated with the salt develop resistance to I.N.H. even though all previous cultures may be sensitive to I.N.H.; and
- (d) Resistance to the new salt more or less closely follows the resistance to I.N.H. even though this salt was not administered to the patients.

Dunbar and Ritchie (1957) after extensive sensitivity studies came to the conclusion that resistance to this salt closely mirrors that of I.N.H. If this salt had any action independent of its I.N.H. and PAS constituents, resistance patterns would have been expected to be different. Probably the salt breaks down into I.N.H. and PAS—its constituents—*in vivo* and the PAS content being so low would be ineffective to prevent I.N.H. resistance developing rapidly as opposed to standard drug treatment with I.N.H. and PAS separately, where adequate dosage of PAS delays resistance developing to I.N.H.

It seems reasonable to assume that whether in respect of clinical and radiological improvements or sputum conversions and bacillary

resistance, this salt is practically speaking, no better than I.N.H.

A noteworthy point that emerges is that patients included in the study continued the treatment for one year far more regularly than the usual run of patients on Domiciliary treatment, in spite of the fact that they were not benefited. Only 13 patients failed to complete 12 months treatment. This regularity could be due to the attraction of an apparently new drug and the special personal attention and more concentrated Home Visiting which these patients had.

#### SUMMARY

A co-operative trial was conducted by the five Tuberculosis institutions in Delhi to assess the activity of Isonicotinic Hydrazide-p-Aminosalicylate in treatment of pulmonary tuberculosis. Two hundred and thirty-one chronic patients were included in the trial. Nearly one-fourth were left untreated, another one-fourth were given I.N.H. and the remaining had two different brands of the salt viz., Pasinh and Isopar. Results of 200 patients who had more than six months' treatment were analysed in respect of sputum conversion, cavity closure, radiological and weight changes, and sensitivity of bacilli (latter in 130 patients only). All groups behaved almost similarly in these respects and Isonicotinic Hydrazide-p-Aminosalicylate appeared in no way superior to I.N.H. in the type of cases included in the trial.

## ACKNOWLEDGEMENT

The organizers of the study are grateful to Messrs Zandu Pharmaceutical Works Limited, Bombay and Messrs Cadilla Laboratories, Ahmedabad for placing generous supplies of their products Pasinh and Isopar respectively at our disposal for this trial.

Thanks are due to the Doctors and Health Visitors of all the institutions without whose efforts this study would not have been a success.

Thanks are also due to the Director and Dr De Monte, Bacteriologist of Vallabhbhai Patel Chest Institute for kindly agreeing to do the sensitivity tests for patients from Silver Jubilee TB Hospital and Municipal TB Clinic.

Lastly the compiler is very grateful to Mr. G. P. Mathur, Statistical Officer of New Delhi Tuberculosis Centre for his invaluable help in collecting and analyzing the data.

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# HIGH DOSAGE OF ISONIAZID IN CHRONIC ACTIVE PULMONARY TUBERCULOSIS WITH RESISTANT STRAINS

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## OBJECT OF STUDY

Tuberculous patients suffering from chronic active Pulmonary Tuberculosis, whose Tubercle Bacilli have become resistant to Isonicotinic acid hydrazide and to another standard anti-tuberculous drug, present a major problem. Even though the laboratory tests show drug resistance, it has been my usual practice to try the standard drugs together in adequate dosage, sometimes with encouraging results but most of them deteriorated. Thirty such patients who deteriorated after treatment for six months with standard drugs given in adequate dosage (I.N.A.H. 3-5 mgm/Kgm., P.A.S. 5 Gm. B.D., S.M. 1 Gm. daily or on alternate days) after the drug-resistance was declared were selected for trial with Isonicotinic acid hydrazide 15 to 20 mgm/kgm Body weight (i.e., four times the usual dosage) used alone in two divided doses daily. The purpose of this trial was :

- (i) To find out the clinical, bacteriological and radiological effect of the above treatment.
- (ii) To find out whether the 'dangerously ill patients can tolerate this treatment over a period not less than one year.

## MATERIAL AND METHOD

### (A) Condition of Entry into trial

1. All patients have far-advanced Pulmonary Tuberculosis.
2. Sputum positive both in smear and culture examinations.
3. Resistance to Isonicotinic acid hydrazide (more than 50 colonies in L.J. media laden with 1.0 microgram of I.N.A.H. per c.c.), and at least one other drug — e.g., Streptomycin or PAS (Innumerable colonies, at least above 100, at L.J. media laden with 100 µg/ml is interpreted as definite resistance and 10 doubtful resistance).

4. All three drugs in standard dosage tried for six months or more after resistance has been declared bacteriologically.

### (B) Dosage Scheme

- (a) I.N.A.H. 15 to 20 mgm/Kgm Body weight calculated to the nearest multiple of 50 mgm (i.e. strength of tablet) given in two equal doses daily. (b) Pyridoxine 40 to 100 mgm daily depending on dosage of I.N.A.H.

### Sensitivity Test of Mycobacterium Tuberculosis done in L.J. media read in four weeks (Indirect Method).

#### Against Isoniazid

- Sensitive*—No growth\* in 0.2 microgram per ml.  
*Doubtfully Resistant*—growth in 0.2 microgram per ml.  
No growth in 1.0 microgram per ml.  
*Resistant*—Growth in 1.0 microgram per ml.  
(Strengths of 5.0, 10.0, 50.0 microgram per ml. were also used to assess degree of resistance).

#### Against P.A.S.

- Sensitive*—No growth in 1.0 microgram per ml. and/or  
Growth in 1.0 microgram per ml.  
No growth in 10.0 microgram per ml.  
*Doubtfully Resistant*—Growth in 10.0 microgram per ml.  
No growth in 100.0 microgram per ml.  
*Resistant*—Growth in 100.0 microgram per ml.

#### Against Streptomycin

- Sensitive*—No growth in 2.0 microgram per ml. and/or  
Growth in 2.0 microgram per ml.  
No growth in 10.0 microgram per ml.  
*Doubtfully Resistant*—Growth in 10.0 microgram per ml.  
No growth in 100.0 microgram per ml.  
*Resistant*—Growth in 100.0 microgram per ml.

\* No growth—No colonies or colonies below the member of fifty in four weeks. Less than twenty colonies are ignored. Below a hundred colonies they are counted.

**(C) Plan of trial**

- (a) Thorough investigations prior to trial.
- (b) Weekly—Clinical status, quality and quantity of sputum.
- (c) Monthly Sputum Smear Examinations, E.S.R., Body weight, Clinical Examination.
- (d) Three Monthly—Reviews with X-ray Chest.
- (e) Six monthly—Culture and Sensitivity Tests.

Three and six monthly reviews with Chest X-rays were placed before a medical conference with Tuberculosis specialists, radiologists and bacteriologists. X-ray improvement and deterioration by a near unanimous decision was shown as + + +, or —, — —, where it was given by a majority opinion it was shown as ? +, or ?-.

**Findings at start of trial**

1. Twenty-nine patients had far advanced Pulmonary Tuberculosis. Two patients had Pneumonectomy done and the other lung was attacked with Tuberculosis and hence classed in this category.  
All thirty patients had over three years of chemotherapy against P.TB (Both inside and outside the hospital) and over six months on all three drugs together, after the resistance test had been declared.

3. 24 Patients (80 per cent) had Tubercle Bacilli growing.

More than 50 colonies at 5.0 } of I.N.A.H.  
4 Patients (13.3%) at 1.0 µg/ml }  
2 Patients (6.7%) at 0.2 µg/ml }

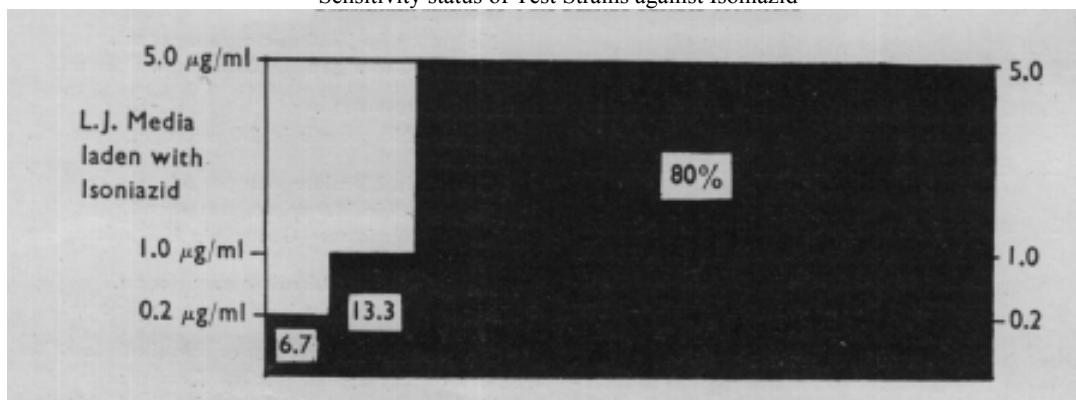
of these last two patients, in one's case (A.B.) the sensitivity report was three year old, and as the patient during that period was tried with a course of Pasinide (an I.N.H. combination), I.N.H. sensitivity was not repeated and Pasinide sensitivity carried out. The other case was the post-pneumonectomy case and two reports repeated at six monthly intervals showed similar figures. (FIGURE 1).

4. 21 patients (70 per cent) showed definite resistance to P.A.S., 7 patients (23.3 per cent) showed doubtful resistance to P.A.S. and only 2 patients (6.7 per cent) showed doubtful sensitivity to P.A.S. (FIGURE 2).

12 patients (40 per cent) showed definite Streptomycin resistance, 5 patients (16.6 per cent) doubtful resistance. It is important to note that all patients had Streptomycin for six months or more after the sensitivity report and had failed to improve. As such it is likely that by the time they come on trial they had lost sensitivity to Streptomycin too.

5. All patients were sputum positive—continuously for a very longtime.

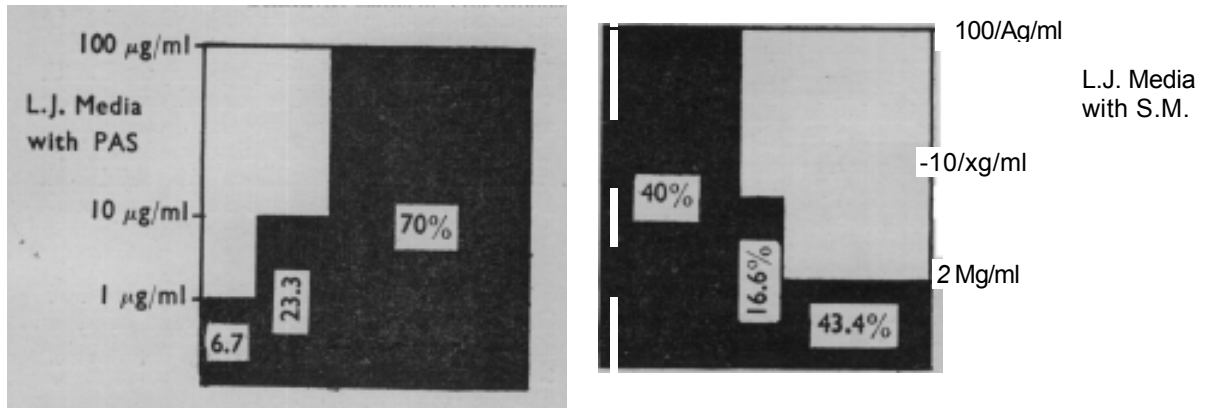
Sensitivity status of Test Strains against Isoniazid



(Positive=growth of 50 colonies or more) i.e. 80% grew more than 50 colonies in all three strengths, 0.2, 1.0, and 5.0

**Fig. 1**

HIGH DOSAGE OF ISONIAZID IN CHRONIC ACTIVE PULMONARY TUBERCULOSIS  
Sensitivity status of Test Strains against P.A.S. and Streptomycin



(Positive growth=many colonies well above 50; interpretation as in Fig. 1)  
FIG.2. (Growth 100 µg/ml as above interpreted as definite and growth in 10/µg/ml as above interpreted as doubtful resistance)

Grouping according to Resistant Status

A Resistant to I.N.H. alone	3.3%
B Resistant to I.N.H., Resistant to P.A.S.	40%
C Resistant to I.N.H., Resistant to P.A.S., S.M. Doubtful	16.6%
D Resistant to I.N.H., Resistant to P.A.S., Resistant to S.M.	23.4%
E Resistant to I.N.H., Resistant to S.M., P.A.S. Doubtful	13.4%
F Resistant to I.N.H., Resistant to S.M.	3.3%

FIG. 3.

[Note that these sensitivity tests were not done immediately on start of trial. These patients had all three drugs together for six months at least after these tests and failed to improve, proving that they are 'clinically' resistant too]

6. Four patients were too weak to get up and record the body weight. The rest had an average body weight of 93 lb. Almost all patients had mucopurulent expectorations more than two ounces /24 hours. Their E.S.R. varied very much but was mostly above 50 mm.

Observations made during first six months

It took a few weeks before all the patients could take the desired dosage. There was an  
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immediate rise in appetite and their average evening temperature came down by roughly one degree (F). In about half of the cases the sputum turned mucoid and expectoration was less in amount.

Headache, giddiness, heaviness in head, tingling sensation in hands and feet and a 'hot' feeling in the body were immediate side effects. Patients were urged to continue the treatment and in some cases antistine was prescribed or Pyridoxine dosage stepped up. Having suffered for quite a few years and almost on the verge

of death, these patients were naturally irritable but they behaved remarkably well and none of them refused treatment throughout the whole period of observation.

At end of three months, 12 cases (40 per cent) showed radiological improvement (+), 5 cases (16.6 per cent) showed radiological deterioration, 13 cases (43.4 per cent) were either ? +, ?— or no change.

18 patients (60 per cent) were sputum positive on direct smear examination, 12 patients (40 per cent) sputum negative. 16 patients (53.3 per cent) were culture positive and 14 patients (46.6 per cent) were culture negative. 7 patients (23.3 per cent) were sputum negative both in smear and cultural examinations. 7 patients with positive smears yielded negative cultures while 5 patients with negative smear yielded positive cultures.

### Sensitivity status

It is regretted\*that the positive sputum culture of one patient was lost at the stage of subculture, of the remaining 15 cultures, 6 patients (40 per cent) showed sensitivity reports similar to pre-trial ones, 6 patients (40 per cent) showed reversal to Streptomycin and 3 patients (20 per cent) reversal to P.A.S. As P. A.S. sensitivity reports are always looked upon with caution, it was decided not to put much significance on these. 6 patients who were Streptomycin resistant before the start of trial and reverted during the trial were given 1.0 gm. of Streptomycin on alternate days along with the trial dosage of I.N.A.H. for a period varying from three to six months. It was however found that these patients did not materially behave in a different way to those having I.N.H. alone. One interesting point to note here is that in repeat sensitivity tests (at 6 months) two patients showed resistance even at 50 mg/ml of I.N.A.H. concentrations, the highest tried in our laboratory.

### Observations made at end of Eighteen months

(a) *Toxicity*: 3 patients (10 per cent) developed overt toxic effects all after one year of therapy. One (B.D.) developed peripheral neuritis which went downhill very slowly in spite of Vitamins B<sub>6</sub>, B<sub>1</sub> and Pantothenic acid. The therapy was continued, however, for over eighteen months with dosage slightly reduced

and given in one dosage daily (to have the required blood concentration). One (A.M.) developed mental derangement in 16 months. I.N.A.H. was stopped and Streptomycin, P.A.S. were prescribed. He deteriorated very rapidly and died after two months. One (B.S.) developed epileptic fits. History elicited that he had several 'convulsions' in childhood. Dosage was reduced, anti-consultants prescribed, and the reduced dosage was given in one dosage daily.

(b) *Death*: 8 patients (26.6 per cent) died. One (A.M.) patient after stoppage of drug after toxicity, one (S.D.) following post-operative spread after rib-resection drainage of chronic post-pneumonic my empyema. Three patients (R.D., D.D. & A.K.) were all above 50 years of age and deteriorated slowly and died. Two patients (B.D. & K.G.) died of choking the remaining healthy portion of lung following brisk haemoptysis from the destroyed side. One (P.D.) died of continued pyrexia.

Of these 8 patients two reverted to Streptomycin sensitivity after six months and had Streptomycin thereafter. Four others also received Streptomycin and Terrifying during their terminal stages.

(c) Of the other 22 patients (73.4 per cent) two discharged themselves from hospital after one year of treatment. One (G.N.) was negative, progressing well at the time and the other (T.) was positive and weak.

3 patients (10 per cent) (A.D., P.H., SB.) were negative, over one year, and were discharged with some amount of radiological clearing but not up to the degree of clinical and bacteriological improvement.

Three other patients (10 per cent) (P.P., B.S., A.K.M.) were negative over nine months or more and were fit for discharge but were kept inside the hospital for other considerations. Their general condition was fair, X-ray improved to some extent.

Four patients (13.3 per cent) had radiological improvement and remained negative on the whole. (K.D.) had left lower lobotomy, remained positive and later converted. She is fit for discharge but has been classed in this group as there was surgical intervention on top of I.N.A.H. therapy. One (P.N.) was earmarked for surgical treatment and two (N.K. & S.D.) produced stray positive sputa.

Bacteriological Status (sputum tests for a.f.b.)

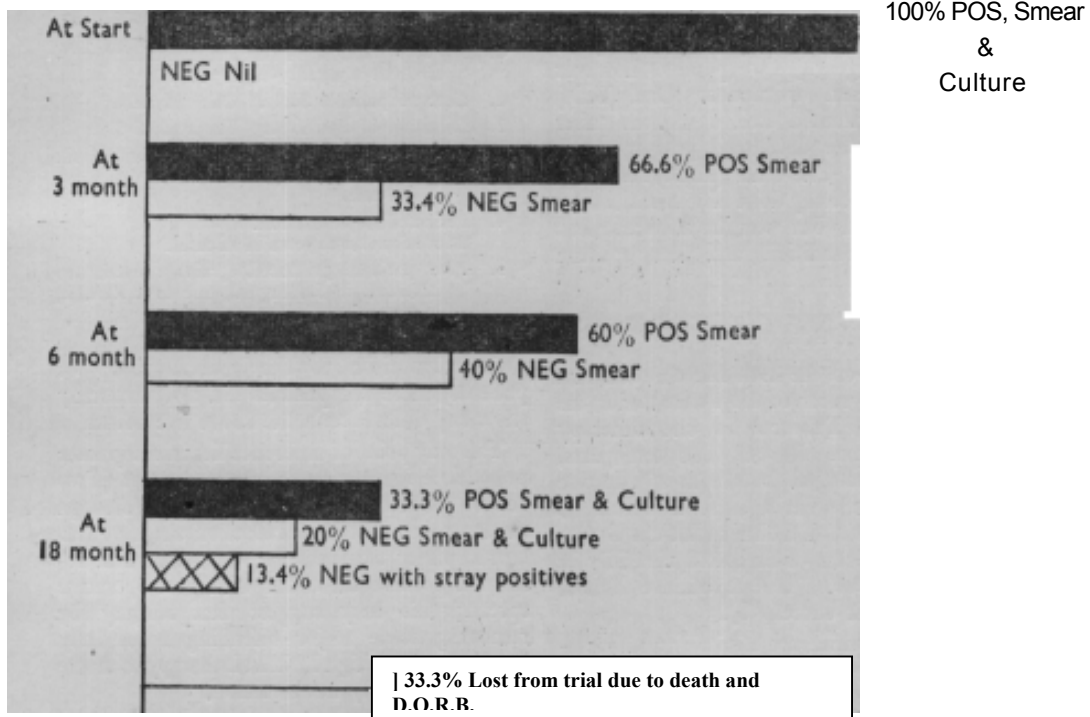


FIG. 4

Table showing result at 18 months of ISONIAZID therapy used alone in high dosage (15-2 in cases of active Pulmonary Tuberculosis with resistant strains who failed to improve after at least three years of previous chemotherapy and were nearly moribund

- A Bacteriologically quiescent & fit for light work
- B Little change or slightly improved
- C No improvement or slight deterioration
- D Death
- E Discharged on Risk Bond

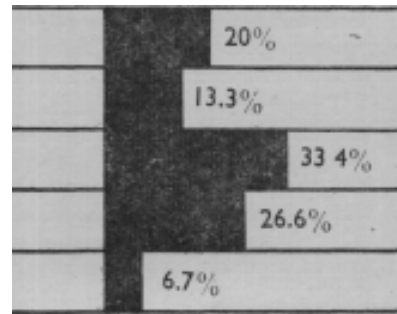


FIG. 5

Ten patients (33.3 per cent) remained sputum positive, radiologically deteriorated or not improved and general condition weak.

Most of the patients were too ill and their respiratory reserves were too poor to contemplate any form of surgery. Two patients however underwent surgical operations. One (S.D.) had emphysema drained twelve months after start of trial. She developed post-operative spread and died. The other (K.D.) remained positive after lobotomy done nine months after the start of trial but continued treatment improved her condition and her sputum became negative.

#### DISCUSSION

(1) (2) It was on the 29th March 1952 that the first patients received I.N.A.H. under the auspices of the Tuberculosis chemotherapy Trials Committee. In the last ten years, I.N.A.H. has emerged as the most effective chemotherapeutic agent against Tuberculosis and used in combination either with ten Grams of PAS or one Gram of Streptomycin daily in drug sensitive cases, it can achieve almost hundred per cent success (3).

But the cases which are clinically and bacteriological drug resistant to I.N.A.H. and at least to another standard drug present a serious problem. In thirty such patients with chronic far-advanced Pulmonary Tuberculosis of over three years' duration, I.N.A.H. was tried in 15-20 mgm/kgm dosage over one year. At eighteen months six patients (20 per cent) showed improvement with sputum conversion and were made fit for light work, two patients took their own discharge at twelve months or more, eight patients (26.6 per cent) died, four patients (13.3 per cent) had remained almost stationary with some measure of improvement and ten patients (33.3 per cent) stationary with some measure of deterioration. (FIGURE 6).

These thirty patients during the eighteen months of trial had, strictly speaking, no control group of patients. However, these patients had themselves eighteen months of standard chemotherapy inside the hospital prior to coming to trial and at the onset it was decided to use these records as control. However while reporting this paper it was considered superfluous to compare the present paper with the records in the 'control' time of 18 months prior to trial, as none of these patients according to

protocol improved during that time and all remained sputum positive and 'dangerously ill'. Further analysis of six patients (20 per cent) that improved and became fit for discharge:

1. *Age:* 4 patients in thirties, 1 patient forty-five and other fifty-eight years.
2. *Sex:* 5 patients Male. One female.
3. *Duration of Pulmonary Tuberculosis:*  
Over ten years in one, seven years in one, six years in two, five years in one, three years in one case.
4. *Period of hospitalization.*  
More than three years in all cases.
5. *Five patients produced strains resistant to I.N.A.H. in 5.0 mg/ml, one to I.N.A.H., 1.0 mg/ml.*

In comparison to the general group of patients, these six patients did not materially show any difference in the above five points.

The only point of difference lies in the greater prevalence in previously operated cases (Two out of six) in the improved group. Though these two patients had resection surgery with thoracoplasty two years prior to trial and remained positive thereafter with post-operative spread; this may suggest that surgery by removing some major offending focus may have helped the high I.N.A.H. therapy to tackle the comparatively newer lesion.

It is further noted that the seventh (K.D.) who also is fit for discharge had resection surgery while on trial, remained sputum positive after operation but later converted. As such she is not grouped among the improved patients on high I.N.A.H. alone. However in her case also the major offending focus was removed leaving the high I.N.A.H. therapy to tackle bilateral scattered lesions.

It is the author's impression that I.N.A.H. in high dosage should be given a trial in all cases clinically and bacteriologically resistant to standard chemotherapy. It is reasonably safe and used in less chronic cases than the present series or in moderately advanced Pulmonary Tuberculosis it should achieve even greater success.

(4) Role of surgery has been stressed in the drug-resistant cases. There is a very high incidence of operative complications in sputum positive patients (5). The information gathered in this respect from the trial, is too meagre to come to any definite conclusion but it can be said that I.N.A.H. in high dosage failed

Further analysis of Table V in light of Table III

	R to I.N.H.	R to I.N.H. R to P.A.S.	R to I.N.H. R to P.A.S. Doubt S.M.	R to I.N.H. R to P.A.S. R to S.M.	R to I.N.H. R to S.M. Doubt P.A.S.	R to I.N.H. R to S.M.
A. Bacteriologically quiescent and fit for light work	...	3	1	1	1	
B. Little change or slightly improved		2	...	2		...
C. No improvement or slight Deterioration	...	4	3	2	1	...
D. Death	1	2	1	2	>	1
E. Discharged on Risk Bond	...	1			1	
	I.N.H.	R I.N.H. P.A.S.	RESISTANT I.N.H. P.A.S. Doubtful S.M.	TO I.N.H. P.A.S. S.M.	I.N.H. S.M. Doubtful P.A.S.	I.N.H. S.M.
Total cases in each group...	1	12	5	7	4	1

FIG. 6

to effectively cover the operation from spread and other complications.

In the 14th Conference of the International Union against Tuberculosis (6) the problems and the prospects of 'Isoniazid alone\*' were reviewed. The isoniazid resistant Bacilli are usually catalase-negative and possess a low degree of virulence to experimental animals. But isoniazid resistance is more than a bacteriologist's puzzle (7). It has been suggested that highly resistant mutants have a reduced degree of pathogen city in man (8). This is one basis for the use of large doses of Isoniazid. However it seems wise to assume that the highly isoniazid-resistant bacilli may be harmful to man (9). Isoniazid-resistant Bacilli continue to multiply freely in lung cavities (10). In the extensive East African trial carried out by the

Medical Research Council the patients with pre-treatment Isoniazid resistance treated with Isoniazid in high dosage fared much less favorably than the sensitive group (11). In the author's series even very highly resistant strains (10 mg/ml or even 50 mg/ml) showed every sign of being virulent to human being.

In an article (12) published in 1959, the world literature on I.N.A.H. toxicity was reviewed. Peripheral neuritis (or more correctly neuropathy with subjective symptoms predominating) tops the list and pyridoxine has been regarded as the effective prophylactic. Psychosis (Vitamin B complex and barbiturates used as prophylactics), epileptic convulsions, pellagra-state, optic atrophy, occasional agranulocytosis and watery diarrhea are other recorded toxic symptoms. In the author's series the patients were

'dangerously ill' and emaciated to start with. They had pyridoxine approximately 1/8th the dosage of I.N.A.H. and two Vitamin B Complex tablets daily. Only three patients (10 per cent) developed toxic symptoms of note. One developed mental derangement (psychosis) for which treatment had to be stopped. The other two patients developed peripheral neuritis and epileptic convulsions respectively, for which dosage of I.N.A.H. was reduced to half (given once daily), Pyridoxine was given in heavy doses with calcium pantothenate and anti-convulsants prescribed. These two patients thereafter continued the treatment with I.N.A.H. with no further adverse effects. It can be concluded that the very high dosage of

I.N.A.H. given over a prolonged period of time is reasonably safe.

Opinions differ regarding the fall of effective blood level of I.N.A.H. on simultaneous administration of Pyridoxine. However at least in some of these patients, subjective symptoms of peripheral neuropathy increased on temporary discontinuance of Pyridoxine and it was decided to continue Pyridoxine as outlined in protocol.

Lastly I must offer my sincere and heart-felt thanks to Prof. P. K. Sen for his kind advice and Dr B. Mukherjee, Superintendent, Kanchrapara T.B. Hospital for giving me the necessary permission to report this paper.

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## A SIMPLE PAPER TEST FOR ISONIAZID IN URINE\*

P. R. J. GANGADHARAM, C. NARAYANAN NAIR AND T. V. SUBBAIAH

### INTRODUCTION

Tests for the presence of chemotherapeutic drugs or their metabolites in urine play an important part in the management of the treatment of tuberculosis (Dixon *et al.*, 1957; Fox, 1958). A previous report from this Centre (Gangadharam *et al.*, 1958) presentee\* a comparison of a number of methods for detecting isoniazid in urine including the direct naphthoquinone-mercuric chloride (N-M) test (Short and Case, 1957), and also a modification of this test which employed alkaline hydrolysis to liberate isoniazid from its conjugated forms. The direct and hydrolysis N-M tests have been employed in this Centre for the past four years to control the self-administration of isoniazid used in the domiciliary treatment of pulmonary tuberculosis. The effect of irregularity in taking isoniazid as detected by these tests on the response to treatment has been reported elsewhere (Tuberculosis Chemotherapy Centre, 1960). Since this method has the disadvantage that it requires a certain amount of equipment and trained personnel, it is not suitable for routine use in all chest clinics or under field conditions.

An attempt was therefore made in this Centre to simplify the direct N-M test by incorporating the reagents in absorbent papers. Though impregnation of the paper with the pHIO buffer and naphthoquinone reagent was successful, impregnation with the aqueous solution of the mercuric chloride was unsatisfactory. In 1960, Cattaneo, Fantoli and Belasio published details of a paper test modification of the N-M test in which this difficulty was overcome by impregnating absorbent papers with a solution of mercuric chloride in ether. Since then this modification has been adopted for the preparation of the test-paper developed in this Centre.

Since a lower concentration of the naphthoquinone reagent and a shorter period of exposure was used in the preparation of the test-paper developed in this Centre than described

by Cattaneo *et al.* (1960), both the paper tests have been compared with the direct and combined N-M tests described previously (Gangadharam *et al.*, 1958). This paper presents the results of the comparison and of an investigation of the specificity of the paper test.

### MATERIALS AND METHODS

#### Specimens of urine from patients

In all, 1455 specimens of urine, collected from patients who were receiving isoniazid in a daily dosage that ranged from approximately 4 to 16 mg/kg. body-weight were tested in a series of 32 experiments, 18 to 64 urine specimens being tested in each experiment.

#### Control urine specimens

A total of 116 specimens of urine, 84 collected from among 28 staff members and 32 collected from patients who were not receiving isoniazid or PAS, were tested in 28 of the 32 experiments as a check on the occurrence of false positive results.

### REAGENTS

#### Direct and hydrolysis naphthoquinone-mercuric chloride tests (Direct and hydrolysis N-M tests)

(i) *Borate buffer pH10*: 12.369 g. of boric acid and 14.991 g. of potassium chloride were dissolved in 1000 ml. of distilled water and the solution was added to 860 ml. of 0.2 N sodium hydroxide.

(it) *Sodium 1:2 naphthoquinone-4-sulphonate*: 0.1 per cent (w/v) aqueous solution. This was stored in a dark bottle at 6°C for up to one month.

(Hi) *Mercuric chloride*: 5.0 per cent (w/v) aqueous solution.

(iv) *Sodium hydroxide*: 40 per cent (w/v) aqueous solution.

(v) *Hydrochloric acid*: 1.5 per cent (w/v) aqueous solution.

\* From the Tuberculosis Chemotherapy Centre, Madras, India. This Centre is under the joint auspices of the Indian Council of Medical Research, the Madras State Government, the World Health Organization, and the Medical Research Council of Great Britain.

### Naphthoquinone-mercuric chloride paper tests

#### (a) Tuberculosis Chemotherapy Centre (TCC) method

- (f) *Borate buffer pH10*: Same as above.  
 (it) *Sodium 1:2 naphthoquinone-4-sulphonate*: Same as above.  
 (Hi) *Mercuric chloride*: 0.5 per cent (w/v) solution in ether.

#### PREPARATION OF THE PAPER

A mixture (5:1) of the pH10 borate buffer and the 0.1 per cent (w/v) aqueous solution of naphthoquinone reagent was prepared and thoroughly mixed. Sheets of locally obtained blotting paper (this was found to be as suitable for this purpose as the more expensive filter papers) 30 cm X 15 cm in size, were soaked in this mixture for one to two minutes and air-dried overnight in a darkened room at approximately 23°C. When dry, they were dipped into the solution of mercuric chloride for 10-15 seconds, and then air-dried at approximately 23 °C for 10 minutes. They were then cut into small squares (4 cm X 4 cm) and stored in a light-proof box at 6°C.

#### (b) Cattaneo et al. (1960) (Cattaneo) method

- (i) *Borate buffer pH10*: Same as above.  
 (it) *Sodium 1:2 naphthoquinone sulphonate*: 0.3 per cent (w/v) aqueous solution.  
 (Hi) *Mercuric chloride*: 0.5 per cent (w/v) solution in ether.

#### PREPARATION OF THE PAPER

Sheets of locally obtained blotting paper were immersed for 1 hour in a mixture of equal volumes (1:1) of the pH10 borate buffer and the 0.3 per cent (w/v) aqueous solution of the naphthoquinone reagent. The subsequent stages in the preparation of the paper were the same as described for the TCC paper.

#### URINE TESTS

##### (i) Direct naphthoquinone-mercuric chloride test (Direct N-M test)

To 5.0 ml. of urine in a large test-tube (150mm X20 mm), 2.5 ml. of borate buffer and 0.5 ml. of the naphthoquinone reagent were added with thorough shaking after each addition. After 5 to 10 minutes, 1.0 ml. of mercuric chloride

solution was added. The tube was centrifuged for one minute at 1000 r.p.m. to allow the precipitate formed to settle at the bottom. The test was read by observing the colour of the precipitate; a purple colour indicated the presence of free isoniazid.

(ii) **Hydrolysis naphthoquinone-mercuric chloride test (Hydrolysis N-M test)** To 5.0 ml. of urine in a large test-tube (150 mm X 20 mm) exactly 1.0 ml. of the sodium hydroxide was added with a 2.0 ml. syringe fitted with a long needle. The tube was placed in a boiling water bath for exactly 10 minutes after which it was cooled under the tap and about 95 per cent of the volume of hydrochloric acid necessary to neutralise the 1.0 ml. of sodium hydroxide was added. The urine sample was then tested for the presence of free isoniazid as in the direct N-M test. The use of the direct followed by the hydrolysis N-M test if the former gave a negative result is referred to as the combined N-M test.

##### (iii) Naphthoquinone-mercuric chloride paper test (N-M paper test)

Test papers prepared by the Tuberculosis Chemotherapy Centre (TCC) method and by the method of Cattaneo *et al.* (1960), were used in the same way. With a Pasteur pipette, three drops of the urine were added to the test paper placed on a glazed tile. The development of a purple ring when the urine had dried (5-10 minutes) indicated the presence of isoniazid.

#### Reading of tests

The tests were read independently by two observers who were unaware of the source of the specimens of urine. The result of each test was recorded as negative, trace, 1-plus positive or 2-plus positive. If one observer read a trace and the other a trace or a positive, the test was regarded as positive; if the other observer recorded a negative result, the test was regarded as negative. For purposes of calculating the observer error, scores of 0, 1, 2 and 3 were given for the negative, trace, 1-plus positive and 2-plus positive readings, respectively.

#### RESULTS

##### Control urines

A total of 116 control urine specimens from volunteers and patients who had not taken

isoniazid or PAS were included in 28 of the 32 experiments in which the urine specimens from patients under treatment with isoniazid were tested. Both the TCC paper test and the direct N-M test gave positive results with three specimens, one specimen from a volunteer being positive by both tests. Nineteen of these control specimens of urine were tested by the Cattaneo paper test; none gave positive results.

#### **Specificity of the tests for isoniazid**

The specificity of the TCC and Cattaneo paper tests and the direct N-M test for isoniazid was studied by performing these tests on specimens of urine obtained from staff members at 0, 2 and 6 hours after they had taken one of the following drugs: 'Aspirin' (acetyl salicylic acid 500 mg.); 'Anacin' (acetyl salicylic acid 194 mg, phenacetin 194 mg, caffeine 16 mg, and quinine 15 mg); 'Saridon' (phenyl-dimethyl isopropyl pyrazolon 150 mg); 'Codopyrine' (acetyl salicylic acid 260 mg, codeine phosphate 10 mg); pyrazinamide 500 mg; cycloserine 250 mg; thiacetazone 50 mg; ethionamide 250 mg;  $\beta$ -amino salicylic acid (PAS) 1000 mg; phthalylsulpha thiazole 500 mg; sulphadiazine 500 mg; chlorpromazine 25 mg, or ephedrine 32 mg.

Of these drugs only PAS gave any reaction and this only with the Cattaneo test-papers which became pink with the two-hour specimen. The effect of a higher dose of PAS on the efficiency of the three tests in detecting isoniazid was therefore studied in six volunteers who were given 5 g. of PAS and 100 mg. of isoniazid in cachets. Specimens of urine were collected at zero and six hours after taking the cachets. None of the specimens collected before the drugs were taken gave a positive result with any of the tests. The TCC paper and the direct N-M test detected isoniazid in all the six-hour specimens of urine. On the other hand, with the Cattaneo papers all the six-hour specimens gave a deep pink colour and no purple ring could be detected. In summary, of all the drugs tested, only PAS produced a colour and this only with the Cattaneo test papers; the pink colour which was produced interfered with the detection of the purple colour produced by isoniazid.

#### **Stability of the TCC test-paper on storage**

The stability of the TCC test-papers on storage at room temperature (30° C) and at 6° C was studied by comparing the number of

positive results obtained with test-papers after they had been stored for different periods of time.

It was found that TCC test-papers which had been stored protected from light at 6° C for up to eight weeks, detected as positive all of six urines which were positive for isoniazid by the direct N-M test. On the other hand, when the test-papers were stored protected from light at room temperature (30° C) they rapidly deteriorated. Thus, the proportion of positive results was 10 out of 10 after two days of storage, 8 of 10 after four days, 5 of 6 after one week, 2 of 7 after two weeks and none of 6 after four weeks.

#### **Stability of the colour developed by the test papers**

The stability of the colour developed by the test papers was studied by reading test papers from tests carried out on 20 specimens of urine, as soon as they were dry and 1, 3, 5 and 24 hours later. To avoid bias, the papers were arranged in a different random order for each reading.

It was found that the purple ring produced with the TCC papers could be read with equal precision up to 24 hours. On the other hand the colour of the Cattaneo papers darkened progressively and it was very difficult to differentiate a positive from a negative after one hour. The colour of the precipitate in the direct N-M test also persisted unchanged for at least 24 hours.

#### **Comparison of the TCC paper test with the Direct and Combined N-M test**

Table I presents the results obtained with the TCC paper and the direct and combined N-M tests on a total of 1455 urine specimens obtained from patients who were receiving isoniazid. The specimens were tested in 32 experiments. Of the 1455 urine specimens, 1070 (73.5 per cent) gave a positive result for isoniazid with the TCC paper test compared with 1030 (70.8 per cent) with the direct N-M test and 1335 (91.8 per cent) with the combined N-M test. (Of the 120 urine specimens which were negative by the combined N-M test 6 were positive by the TCC paper test.) The TCC paper test was thus, if anything, slightly more sensitive than the direct N-M test but considerably less sensitive than the combined N-M test. The difference between the results obtained with

TABLE I  
Comparison of the TCC paper test with the direct and combined N-M tests

Method	Total number of specimens tested	Specimens positive for isoniazid*	
		No.	%
TCC Paper	1455	1070	73.5
Direct N-M	1455	1030	70.8
Combined N-M ...	1455	1335	91.8

\* For definition of positivity see text.

the TCC paper test and the combined N-M test attains statistical significance ( $P < 0.01$ ).

The TCC and Cattaneo paper tests compared with the Direct and Combined N-M tests

The TCC paper test was compared with the Cattaneo paper test using test-papers prepared in this laboratory according to the method described by Cattaneo *et al.* (1960) and with the direct and combined N-M tests in 305 of the 1455 urine specimens obtained from patients who were receiving isoniazid. These 305 specimens were those tested in the 19th, 20th, 29th, 30th, 31st and 32nd experiments. Of these 305 specimens, 231 (75.7 per cent) were positive by the TCC paper test, 213 (70.0 per cent) by the Cattaneo paper test, 222 (70.3 per cent) by the direct N-M test and 281 (92.1 per cent) by the combined N-M test. Two of the 36 specimens that were negative by the combined N-M test were positive by both the TCC and the Cattaneo paper tests. Thus, the TCC paper test detected slightly more positives than either the Cattaneo paper test or the Direct N-M test. However, only the differences between the combined N-M test and the other tests attain statistical significance.

#### Observer error in reading the tests

The error between observers was studied from the results of two experiments in which 103 urine specimens were tested by the TCC

paper test, the Cattaneo paper test and the direct N-M test, and read independently by two observers. After converting the results into numerical values using the scoring system described on page 220, they were examined by analysis of variance; in none of the three tests was there a significant difference between the reading of the two observers.

Duration urine remained positive after a single dose of isoniazid

The period for which urine specimens were positive by the TCC paper test after a single oral dose of approximately 6.7 mg. isoniazid per kg. body-weight (300 mg. for a volunteer weighing 100 lb.) was studied in 20 volunteers. Urine specimens were collected before the isoniazid was taken and at 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours thereafter. All the specimens were tested together in a randomised order. None of the specimens collected from the 20 volunteers before they had taken the isoniazid was positive. The numbers of positive specimens were 20 of 20 from one to six hours inclusive, 17 of 20 at seven hours, 15 of 20 at eight hours, 14 of 20 at ten hours and 13 of 20 at twelve hours.

#### DISCUSSION

The investigations reported here have shown that the paper modification of the naphthoquinone-mercuric chloride (N-M) test developed in this Centre (TCC paper test) was of about the same sensitivity as the direct N-M test previously described by Short & Case (1957) and Gangadharam *et al.* (1958). However, the TCC paper test was considerably less sensitive than the combined N-M test (Gangadharam *et al.*, 1958), but this was to be expected since the TCC paper test was performed only on unhydrolysed urine.

Both the TCC paper and the direct N-M tests gave false positive results in three (2.6 per cent) of the 116 control specimens of urine tested concurrently with the urine specimens from patients who were receiving isoniazid. In addition, the TCC paper test gave positive results in 6 of the 120 specimens obtained from patients which were negative by the combined N-M test. Corresponding figures for the direct N-M test are not available since specimens were not retested after hydrolysis if they gave positive results in this test. In

consequence the two tests cannot be compared in this respect.

This study has shown that the TCC paper test was slightly more sensitive than the Cattaneo paper test and had 2 minor advantages. The Cattaneo test-papers darkened progressively after use and this masked the purple ring produced by the isoniazid. In consequence the accuracy of reading the Cattaneo papers decreased if they were read after 1 hour. This could be of importance in a domiciliary chemotherapy service under which condition it might be desirable to test the patients' urine in the home, and read or check the results some hours later in a central clinic. Secondly, PAS was found to interfere with the detection of isoniazid by the Cattaneo test-papers, but not by the TCC test-papers. Since essentially similar findings to those found with the Cattaneo test-papers prepared in this laboratory with locally bought blotting paper were obtained with test-papers kindly supplied by Prof. Cattaneo, it is most likely that these differences between the TCC and Cattaneo test-papers were due to the only other important dissimilarity between them, namely, the higher concentration of naphthoquinone reagent used in the preparation of the Cattaneo test-papers.

Since our attempts to simplify the hydrolysis procedure have so far been unsuccessful, the only practical approach under field conditions seems to be to examine urine specimens by the paper test during the period in which they could be expected to be positive if the isoniazid had been taken. Under the climatic conditions of Madras, this period has been shown to be from about one to six hours following a dose of approximately 6.7 mg. of isoniazid per kg. body-weight. In chest clinics where facilities to carry out the hydrolysis procedure are available it is suggested that the paper test could be used to replace the direct N-M test with a consequent saving in time and expense.

#### SUMMARY

A paper test modification of the direct naphthoquinone-mercuric chloride (N-M) test developed in this Centre has been compared with a similar paper test described by Cattaneo *etal.* (1960), and with the previously described direct and combined N-M tests. The paper test was, if anything, slightly more sensitive than the Cattaneo paper test and the direct N-M test but considerably less sensitive than the combined N-M test. However, the paper test detected isoniazid in all the urine specimens obtained from one to six hours from 20 volunteers who had taken a single dose of approximately 6.7 mg. isoniazid per kg. body-weight. The application of the paper test for use in chest clinics and under field conditions has been discussed.

#### ACKNOWLEDGEMENTS

We are grateful to Mr. R. Srinivasan and Mr K. L. Thomas for their assistance in carrying out this study, to the nursing staff of this Centre for the collection of specimens of urine and to Prof. C. Cattaneo for supplying us with test papers made in the Carlo Forlanini Institute.

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## NEWS AND NOTES

Shri B. M. Cariappa, Secretary, Tuberculosis Association of India and Secretary and Treasurer, Eastern Regional Committee of the International Union Against Tuberculosis visited Ceylon from the 27th June, to 7th July, 1962 to study the Health Education Programme of the Ceylon National Association for the Prevention of Tuberculosis and make a report to the International Union.

### **XIXth Tuberculosis and Chest Diseases Workers' Conference**

The 19th conference of Tuberculosis and Chest Diseases Workers\* will be held in Hyderabad in January next. Dr L. R. Dongrey will preside over the conference.

The following are some of the important subjects to be discussed at the conference:

1. Symposium on 'Problems connected with the Home Treatment of TB patients'—Dr B. K. Sikand will act as the Moderator.
2. Results of one year drug taking on the pool of infection in a community.
3. Effects of BCG vaccination in reducing incidence of TB—A second report from Madanapalle.
4. Tuberculosis and Pregnancy.
5. Distribution of infection and disease in different categories of household.
6. Freeze-dried vaccine, post vaccination allergy and some other aspects of vaccine.
7. Limitations of a single sputum in spot collection and overnight collection in a survey and in a case finding programme.

8. Bacterial resistance (tubercle), as observed in a community.

### **1963 Tuberculosis Health Visitors' Course**

The next Tuberculosis Health Visitors' Course will be held from January, 1963. 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.

### **XIII Seal Sale Campaign**

The annual TB Seal Sale Campaign will commence on October, 2 and terminate on 26th January, 1963. TB Seals cost 10 naye paise each and are available all over India.

### **Chest and Heart Association Scholarship**

Dr B. C. Arora, Medical Officer, V. M. Hospital, Agartala (Tripura) has been awarded the Chest and Heart Association Scholarship during 1962-63 by the Tuberculosis Association of India.

### **Eastern Regional Committee Meeting at Bangkok**

The next regular meeting of the Eastern Regional Committee be held in Bangkok from 21st to 23rd November, 1962 at the invitation of the National Tuberculosis Association of Thailand. The meeting is expected to be inaugurated by H.M. the King of Thailand and the inaugural session will be addressed by the President of the Anti-Tuberculosis Association of Thailand and the Health Minister of Thailand.

Dr P. V. Benjamin, President of the Regional Committee and Mr B. M. Cariappa, its Secretary and Treasurer will attend the meeting.

# The Indian Journal of Tuberculosis

## ABSTRACTS

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Abst No. 4

### **Tuberculosis Morbidity in a Controlled Trial of the Prophylactic use of Isoniazid among House hold Contacts.**

A total of 25,512 contacts in 6,219 households were examined soon after diagnosis of an Index case for each house hold.

Of the 479 contacts found to have active tuberculosis, 343 were children with primary tuberculosis and 136 adults with pulmonary disease, thus showing a rate of 19 new cases per 1,000 contacts examined.

The remaining 25,033 contacts were enrolled in the trial. Half of the House holds were randomly assigned isoniazid and half placebo.

They were asked to take unidentified pills daily for one year. The average dose of Isoniazid was 5 mgm per kilo.

Both the groups were almost identical as regards age, race, sex, tuberculin sensitivity and other characteristics.

Side effects were slightly more frequent with Isoniazid than with placebo. Indirect method of pill taking indicates that approximately two thirds of both groups took their pills quite regularly for the entire year while less than 10 per cent took pills for only a short time or irregularly.

Isoniazid markedly reduces the incidence of tuberculosis among contacts while they were taking pills.

16 cases had primary tuberculosis in the placebo group and 5 in the Isoniazid group.

16 cases had extra pulmonary tuberculosis in the placebo group and 4 in the Isoniazid group.

Adult Pulmonary Tuberculosis appeared in 62 persons in the placebo group in 14 in the Isoniazid group.

After the medication year in the placebo group there were 6 cases of primary diseases, 2 extra pulmonary, and 17 pulmonary compared with 6 primary, 1 extra pulmonary and 10 pulmonary cases in the Isoniazid group.

Isoniazid prophylaxis is an effective and practical measure to add to existing programmes of contact supervision.

(Shirley H. Ferebec and Frank W. Mount: *American Review of Respiratory Diseases*, Vol. 85, No. 4, April 1962.)

### **Management of Non-Tuberculous Empyema**

The problem of empyema is increasing probably due to bacterial changes associated with use and misuse of antimicrobials as well as alterations in the host associated with increased longevity and chronic diseases.

*Etiology:* The causative organisms may be pneumococci, streptococci, the mixed group of mouth organisms, staphylococci and enterococci.

*Pathogenesis:* The pleura may become infected by direct extension of an inflammatory process such as by haematogenous or lymphogenous as in pneumonia, lung abscess or subphrenic routes or by direct inoculations as from penetrating wounds.

*Pathology:* Pathologic response is divided into three phases:

I. *Exudative:* In it the cellular content is relatively low, fluid is thin and lung is readily re-expandable.

II. *Fibrino-Purulent:* There is accumulation of frank pus with large number of polymorpho nuclear leucocytes and fibrin may deposit on the visceral or parietal pleura and then a tendency for loculation and formation of limiting membrane prevents extension of empyema and fixes the lung.

III. *Organizing:* Fibroblasts grow into the exudation on both the visceral and parietal pleura surface producing an inelastic membrane. With increasing fibroses, the process becomes chronic and lungs are firmly fixed.

If untreated it may drain through the chest (Empyema necessitatus) or into lung (Broncho pleural fistula).

*Treatment* consists of:

- (a) Antimicrobial drug therapy.
- (b) Adequate dependant drainage.
- (c) Obliteration of pleural space.

At the onset of empyema, antimicrobial treatment is primary and drainage is an adjunct; after empyema is established this is reversed and surgical drainage is primary.

*Exudative Phase:* Intermittent closed drainage by repeated thoracocentesis may constitute adequate drainage.

If fluid re-accumulates rapidly or patient is toxic, thoracocentesis may be supplemented with continuous drainage with intercostal catheter. Open drainage may cause collapse of lung.

*Fibrous Purulent Phase:* Closed intercostal drainage with suction is the treatment of choice. (Thoracocentesis may not allow complete removal of thick exudate).

Drainage tubes used in the treatment of empyema should not be removed until the cavity is totally obliterated by expansion of lung

Enzymatic treatment of empyema in conjunction with systematic antimicrobials may be used.

*Organizing Phase:* Closed intercostal drainage may be adequate or rib resection and open drainage with removal of coagulated exudate and fixing of loculation is necessary.

Decortications may be done in cases in which dependant drainage has failed or failure is anticipated.

(*A Report of Sub-Committee on Surgery. Am. Rev. Resp. Dis., June, 62; Vol. 85: No. 6.*)

### **Pleural Tumours**

The clinical behaviour of pleural metastases in 274 cases has been compared with in 16 cases of tumours believed to be primarily pleural.

The only primary pleural tumour is a sarcoma, which may be circumscribed or may involve the pleura diffusely.

Pleural *Sarcoma* is a slow-growing tumour associated with long survival and differs from metastatic pleural tumour which usually results in death within a year.

(*B. T. LeRoux. Thorax (1962) 17, 111.*)